Report on the Deliberation Results

September 5, 2024

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

Brand Name	Rybrevant Intravenous Infusion 350 mg
Non-proprietary Name	Amivantamab (Genetical Recombination) (JAN*)
Applicant	Janssen Pharmaceutical K.K.
Date of Application	November 17, 2023

Results of Deliberation

In its meeting held on August 30, 2024, the Second Committee on New Drugs concluded that the product may be approved and that this result should be presented to the Pharmaceutical Affairs Council.

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

Approval Condition

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

**Japanese Accepted Name (modified INN)*

Review Report

August 14, 2024
Pharmaceuticals and Medical Devices Agency

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

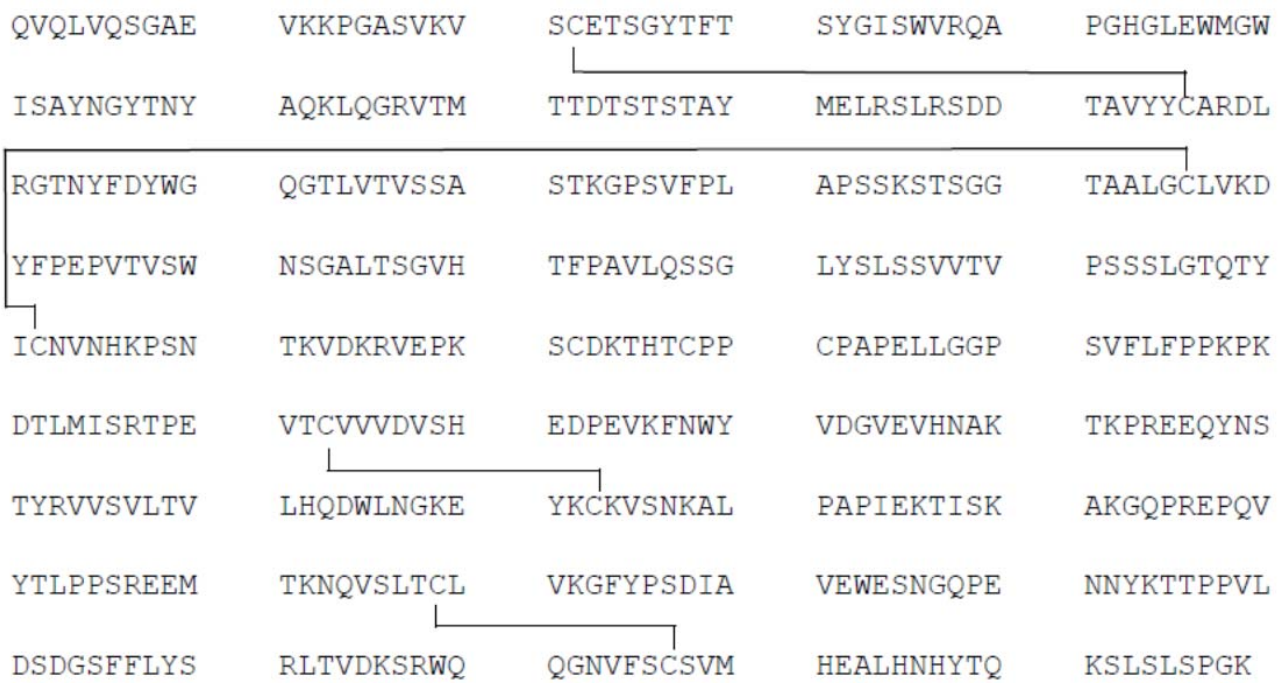
Brand Name	Rybrevant Intravenous Infusion 350 mg
Non-proprietary Name	Amivantamab (Genetical Recombination)
Applicant	Janssen Pharmaceutical K.K.
Date of Application	November 17, 2023
Dosage Form/Strength	Injection: Each vial contains 350 mg of amivantamab (genetical recombination).
Application Classification	Prescription drug, (1) Drug with a new active ingredient
Definition	Amivantamab is a recombinant bispecific human IgG1 monoclonal antibody against human epidermal growth factor receptor (EGFR) and human hepatocyte growth factor receptor (MET) whose amino acid residues at positions 413 in the anti-EGFR-H-chain and 411 in the anti-MET-H-chain are substituted by Leu and Arg, respectively. Amivantamab is produced in Chinese hamster ovary cells that express antibody with low-fucosylated glycans. Amivantamab is a glycoprotein (molecular weight: ca. 148,000) composed of an anti-EGFR-H-chain (γ1-chain) consisting of 455 amino acid residues, an anti-MET-H-chain (γ1-chain) consisting of 449 amino acid residues, an anti-EGFR-L-chain (κ-chain) consisting of 214 amino acid residues and an anti-MET-L-chain (κ-chain) consisting of 214 amino acid residues each.

Structure

Amino acid sequence:

Anti-EGFR-H-chain

Anti-MET-H-chain



Anti-EGFR-L-chain

```
AIQLTQSPSS    LSASVGDRVT    ITCRASQDIS    SALVWYQQKP    GKAPKLLIYD
ASSLESGVPS    RFSGSESGTD    FTLTISSLQP    EDFATYYCQQ    FNSYPLTFGG
GTKVEIKRTV    AAPSVFIFPP    SDEQLKSGTA    SVVCLLNNFY    PREAKVQWKV
DNALQSGNSQ    ESVTEQDSKD    STYSLSSTLT    LSKADYEKHK    VYACEVTHQG
LSSPVTKSFN    RGEC
```

Anti-MET-L-chain

```
DIQMTQSPSS    VSASVGDRVT    ITCRASQGIS    NWLAWFQHKP    GKAPKLLIYA
ASSLLSGVPS    RFSGSGSGTD    FTLTISSLQP    EDFATYYCQQ    ANSFPITFGQ
GTRLEIKRTV    AAPSVFIFPP    SDEQLKSGTA    SVVCLLNNFY    PREAKVQWKV
DNALQSGNSQ    ESVTEQDSKD    STYSLSSTLT    LSKADYEKHK    VYACEVTHQG
LSSPVTKSFN    RGEC
```

Pyroglutamic acid (partial): anti-EGFR-H-chain Q1, anti-MET-H-chain Q1

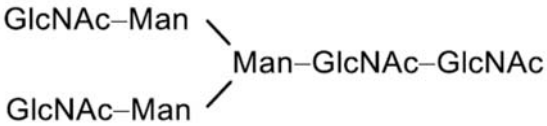
Glycosylation sites: anti-EGFR-H-chain N305, anti-MET-H-chain N299

Partial processing: anti-EGFR-H-chain K455, anti-MET-H-chain K449

Disulfide bonds:

anti-EGFR-H-chain C228-anti-EGFR-L-chain C214, anti-MET-H-chain C222-anti-MET-L-chain C214, anti-EGFR-H-chain C234-anti-MET-H-chain C228, anti-EGFR-H-chain C237-anti-MET-H-chain C231

Main proposed carbohydrate structure



Molecular formula: $C_{6472}H_{10014}N_{1730}O_{2023}S_{46}$ (protein moiety, 4 chains)

Molecular weight: ca. 148,000

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 has efficacy in the treatment of *EGFR* exon 20 insertion mutation-positive unresectable advanced or recurrent non-small cell lung cancer, and that the product has acceptable safety in view of its benefits (see Attachment).

As a result of its review, PMDA has concluded that the product may be approved for the indication and dosage and administration shown below, with the following condition. A further investigation for venous thromboembolism via post-marketing surveillance is needed.

Indication

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

Dosage and Administration

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

Approval Condition

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

Attachment

Review Report (1)

July 3, 2024

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

Product Submitted for Approval

Brand Name Rybrevant Intravenous Infusion 350 mg

Non-proprietary Name Amivantamab (Genetical Recombination)

Applicant Janssen Pharmaceutical K.K.

Date of Application November 17, 2023

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

Proposed Indication

Inoperable or recurrent non-small cell lung cancer with EGFR exon 20 insertion mutations

Proposed Dosage and Administration

Usually for adults, amivantamab (genetical recombination) should be administered by intravenous infusion in combination with carboplatin and pemetrexed in 3-week cycles, as per the table below. 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	1050 mg
		Day 8, Day 15	1400 mg
	Cycle 2	Day 1	1400 mg
	Cycle 3 onwards	Day 1	1750 mg
Greater than or equal to 80 kg	Cycle 1	Day 1	350 mg
		Day 2	1400 mg
		Day 8, Day 15	1750 mg
	Cycle 2	Day 1	1750 mg
	Cycle 3 onwards	Day 1	2100 mg

Table of Contents

List of Abbreviations

See Appendix.

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

1.1 Outline of the proposed product

Upon binding of its ligands, such as epidermal growth factor [EGF], the epidermal growth factor receptor (EGFR) dimerizes, resulting in the activation of downstream signaling pathways involved in cell proliferation, survival, and other cellular activities (*Nature*. 2018; 553: 446-54). In non-small cell lung cancer (NSCLC) with *EGFR* exon 20 (EGFRex20) insertion mutations, a conformational change in EGFR results in the activation of downstream signaling pathways, thereby promoting the proliferation of tumor cells (*Signal Transduct Target Ther*. 2019; 4: 5).

Mesenchymal epithelial transition factor (MET) and EGFR share the downstream signaling pathways. Upon binding of its ligand, such as hepatocyte growth factor [HGF], MET dimerizes, resulting in the activation of downstream signaling pathways involved in cell proliferation, survival, and other cellular activities *(Pathol Oncol Res*. 2009; 15:651-8).

Amivantamab (genetical recombination) (hereinafter referred to as amivantamab) is a recombinant protein (a bispecific antibody) with antigen-binding fragments targeting human EGFR and MET, discovered by Genmab (Denmark) and Janssen Research & Development, LLC (the US).

Amivantamab binds to EGFR and MET and inhibits EGFR- and MET-mediated signaling. In addition, it induces antibody-dependent cellular cytotoxicity (ADCC) activity. Through these mechanisms, among others, amivantamab is considered to inhibit tumor growth.

1.2 Development history, etc.

The applicant initiated a global phase I study in patients with unresectable advanced or recurrent NSCLC (Study EDI1001) in May 2016 and a global phase III study in patients with EGFRex20 insertion mutation-positive unresectable advanced or recurrent NSCLC previously untreated with chemotherapy (PAPILLON study) in December 2020.

US and EU applications were submitted based mainly on the results from the PAPILLON study in September and October 2023, respectively. Amivantamab was approved for the following indication in the US in March 2024: "RYBREVANT is indicated in combination with carboplatin and pemetrexed 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 20 insertion mutations, as detected by an FDA-approved test." Amivantamab was approved for the following indication in the EU in June 2024: "RYBREVANT is indicated in combination with carboplatin and pemetrexed for the first-line treatment of adult patients with advanced non-small cell lung cancer (NSCLC) with activating epidermal growth factor receptor (EGFR) Exon 20 insertion mutations."

As of June 2024, amivantamab has been approved for the indication of EGFRex20 insertion mutation-positive unresectable advanced or recurrent NSCLC previously untreated with chemotherapy in 4 countries or regions.

In Japan, the applicant initiated patient enrollment in Study EDI1001 and the PAPILLON study in March 2019 and February 2021, respectively.

The applicant has now filed a marketing application for amivantamab, based mainly on the results from the PAPILLON study.

2. Quality and Outline of the Review Conducted by PMDA

2.1 Drug substance

Amivantamab is a bispecific antibody that binds to EGFR and MET. In the drug substance manufacturing process, it is prepared by controlled reduction and oxidation of the inter-heavy chain disulfide bonds of the parental anti-EGFR (a human IgG1 antibody targeting EGFR) and anti-MET (a human IgG1 antibody targeting MET) antibodies resulting in an exchange of the Fab arms.

2.1.1 Generation and control of cell substrate

The cell substrate for production of the parental anti-EGFR antibody is generated as follows:
Hybridomas were generated by the fusion of [redacted] cells with [redacted] cells, both from transgenic mice engineered to express human IgG immunized with a human epidermoid carcinoma cell line and soluble human EGFR, and the most suitable clone was selected from the hybridoma cells based on EGFR binding activity. Based on (1) the anti-EGFR antibody heavy chain expression plasmid constructed by inserting the heavy chain variable region sequence obtained from this clone into a vector containing the constant region sequence of IgG1 and (2) the anti-EGFR antibody light chain expression plasmid constructed by inserting the light chain variable region sequence obtained from this clone into a vector containing [redacted] sequence, the expression construct for the parental anti-EGFR antibody was generated. One amino acid substitution in the heavy chain constant region is for bispecific formation. The expression construct was transfected into a Chinese hamster ovary (CHO) cell line, and a clone most suitable for the manufacture of amivantamab was selected and used to prepare a master cell bank (MCB) and a working cell bank (WCB).

The cell substrate for production of the parental anti-MET antibody is generated as follows:
Hybridomas were generated by the fusion of [redacted] cells and [redacted] cells with [redacted] cells, all from transgenic mice engineered to express human IgG immunized with CHO cells expressing the extracellular domain of MET and MET, and the most suitable clone was selected based on MET binding activity, etc. Based on (1) the anti-MET antibody heavy chain expression plasmid constructed by inserting the heavy chain variable region sequence obtained from this clone into a vector containing the constant region sequence of IgG1 and (2) the anti-MET antibody light chain expression plasmid constructed by inserting the light chain variable region sequence obtained from this clone into a vector containing [redacted] sequence, the expression construct for the parental anti-MET antibody was generated. One amino acid substitution in the heavy chain constant region is for bispecific formation. The expression construct was transfected into a CHO cell line, and a clone most suitable for the manufacture of amivantamab was selected

from the CHO cell line producing low-fucose antibodies obtained by screening and used to prepare MCB and WCB.

The MCBs, WCBs, and end of production cells (EOP) for the parental anti-EGFR and anti-MET antibodies were characterized and subjected to purity tests in accordance with the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) Q5A (R1), Q5B, and Q5D guidelines. The test results demonstrated genetic stability during production, and no viral or non-viral adventitious agents were detected other than endogenous retrovirus-like particles, which are generally known to be present in rodent cell lines, in any of the tests conducted.

The MCBs and WCBs for the parental anti-EGFR and anti-MET antibodies are stored in the vapor phase of liquid nitrogen. There is no plan for generating a new MCB, but a new WCB will be generated as needed.

2.1.2 Manufacturing process

The manufacturing processes for the parental anti-EGFR and anti-MET antibodies consist of preculture/expansion, production culture, clarification of the harvest, [redacted] chromatography, and concentration/filling.

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

The manufacturing process for the drug substance consists of thawing/pooling, [redacted], [redacted], virus inactivation at low pH, [redacted] chromatography, [redacted] chromatography, virus removal filtration, [redacted], and formulation/filling/testing/cryopreservation.

[redacted] for the drug substance has been defined as a critical step. Process validation of the commercial-scale manufacturing processes for the parental anti-EGFR and anti-MET antibodies and the drug substance has been performed.

2.1.3 Safety evaluation of adventitious agents

Except for the host CHO cell line, no raw materials of biological origin are used in the manufacturing processes for the parental anti-EGFR and anti-MET antibodies and the drug substance.

The MCBs, WCBs, and EOPs for the parental anti-EGFR and anti-MET antibodies were subjected to purity tests [see Section 2.1.1]. Pre-harvest unprocessed bulk at commercial scale for the parental anti-EGFR and anti-MET antibodies was subjected to tests for bioburden and mycoplasma, *in vitro* test for adventitious viruses, and observation of retrovirus-like particles by transmission electron microscopy. No viral or non-viral adventitious agents were detected in any of the tests conducted. Among the above tests for pre-harvest

unprocessed bulk, tests for bioburden and mycoplasma and test for adventitious viruses are defined as in-process controls.

Viral clearance studies of the purification process for the parental anti-EGFR and anti-MET antibodies and the drug substance were performed with model viruses. The results demonstrated a certain robustness of the purification process (Table 1).

Table 1. Results of viral clearance studies

Process step		Virus reduction factor (log_{10})		
	Xenotropic murine leukemia virus	Minute virus of mice	Pseudorabies virus	Reovirus type 3
[redacted] chromatography[*1]	[redacted]	[redacted]	[redacted]	[redacted]
Virus inactivation at low pH	[redacted]	[redacted]	[redacted]	[redacted]
[redacted] chromatography	[redacted]	[redacted]	[redacted]	[redacted]
Virus removal filtration	[redacted]	[redacted]	[redacted]	[redacted]
Overall reduction factor	>20.0[*2]	>12.1	>18.5[*2]	>14.8[*2]

*1 The study results for [redacted] process step showing lower values than those for [redacted] process step are presented.
*2 Calculated using the results of [redacted] representing a worst-case condition as the virus reduction factor of the virus removal filtration step.

2.1.4 Manufacturing process development

The major changes made to the drug substance manufacturing process during development were manufacturing site and scale changes (the manufacturing processes before and after the changes were made are referred to as the pre-change process and the proposed commercial process, respectively). The drug product produced from the drug substance manufactured by the pre-change process was used in [redacted]. The drug product produced from the drug substance manufactured by the proposed commercial process was used in [redacted].

For process changes, the comparability of pre-change and post-change drug substances has been demonstrated in accordance with the ICH Q5E guideline.

2.1.5 Characterization

2.1.5.1 Structure and properties

Characterization of the drug substance was performed as shown in Table 2.

Table 2. Characterization attributes of drug substance

Primary/higher-order structure	Amino acid sequence, molecular weight, post-translational modifications ([redacted], [redacted], deamidated variants, oxidized variants, isomerized variants, glycated variants, aglycosylated variants, sequence variants), disulfide bonds, free thiol group, higher-order structure, thermal stability
Physicochemical properties	Size variants, charge variants
Carbohydrate structure	Glycosylation sites, N-glycan profile
Biological properties	EGFR binding activity, MET binding activity
	Inhibition of EGFR-mediated signaling, inhibition of MET-mediated signaling, inhibition of downstream extracellular signal-regulated kinase (ERK) and protein kinase B (AKT) phosphorylation signaling [see Section 3.1.5.1]
	FcγR (FcγRI, FcγRIIa, FcγRIIIa) binding activity, FcRn binding activity
	Trogocytosis activity, ADCC activity

Main study results on biological properties are as follows:

- Trogocytosis activity[1)] was demonstrated in the following test systems.
  (1) In the presence of amivantamab, [redacted] cell line or [redacted] cell line expressing EGFR and MET was co-cultured with [redacted], [redacted], or [redacted], and EGFR, phosphorylated EGFR, and MET protein levels were measured by [redacted].
  (2) EGFR- and MET-expressing [redacted] cell line opsonized with [redacted] amivantamab was co-cultured with [redacted] or [redacted] and then was subject to [redacted].
- The ADCC activity of amivantamab is primarily driven by the EGFR arm, and ADCC activity by binding to EGFR and/or MET was demonstrated in the test systems shown below.
  (1) A luciferase reporter assay: [redacted] cell line expressing high levels of EGFR was co-cultured with [redacted] cell line expressing FcγRIIIa and luciferase under the control of [redacted] promoter, and the luciferase activity was quantified.
  (2) Co-culture of EGFR-expressing cell line with FcγRIIIa-expressing [redacted] cell line induced cell death, and [redacted] activity was measured based on [redacted] released in the co-culture supernatant.

2.1.5.2 Product-related substances/Product-related impurities

Based on the results of characterization in Section "2.1.5.1 Structure and properties," Related Substance A ([redacted], [redacted]), [redacted], [redacted], Related Substance B ([redacted], [redacted], Related Substance C ([redacted], [redacted], [redacted], [redacted], [redacted], [redacted], [redacted], [redacted], [redacted], [redacted]), Related Substance D, and Related Substance E were identified as product-related substances.

Impurity A ([redacted], [redacted], [redacted], [redacted], [redacted]), Impurity B ([redacted]), [redacted] ([redacted]), high molecular weight forms (HMW), low molecular weight forms (LMW), and aglycosylated variants ([redacted] were identified as product-related impurities. Among the product-related impurities, oxidized variants are controlled by the drug substance specification, and isomerized variants, deamidated variants, aglycosylated variants, HMW, and LMW are controlled by the drug substance and drug product specifications.

2.1.5.3 Process-related impurities

Host cell protein (HCP), host cell DNA, endogenous retrovirus-like particles, protein A, 2-mercaptoethylamine (MEA), and the parental anti-EGFR and anti-MET antibodies were considered process-related impurities. HCP, host cell DNA, endogenous retrovirus-like particles, protein A, and 2-MEA have been demonstrated to be

[1)] When immune cells such as monocytes and macrophages are in direct contact with tumor cells, the intercellular transfer of membrane fragments occurs (trogocytosis). It is inferred that amivantamab inhibits tumor growth by binding to EGFR and MET on the tumor cell surface and downmodulating EGFR and MET through a trogocytosis mechanism (*Blood*. 2015; 125: 762-6).

adequately removed by the manufacturing process. The parental anti-EGFR and anti-MET antibodies are controlled by the drug substance specification.

2.1.6 Control of drug substance

The proposed specifications for the drug substance consist of quantity, appearance, identity (dot blot, peptide map), pH, purity (non-reduced/reduced capillary electrophoresis sodium dodecyl sulfate [CE-SDS], size exclusion liquid chromatography [SEC]), [redacted] ([redacted] and [redacted], hydrophobic interaction high performance liquid chromatography [HI-HPLC]), post-translational modifications (peptide map), oligosaccharide analysis (hydrophobic interaction liquid chromatography [HILIC]), charge heterogeneity (capillary isoelectric focusing), endotoxins, microbial limits, potency (EGFR ADCC activity, MET binding activity), and assay (ultraviolet-visible spectrophotometry).

2.1.7 Stability of drug substance

The primary stability studies on the drug substance are shown in Table 3.

Table 3. Overview of primary stability studies on drug substance

Study	No. of batches*1	Storage conditions	Testing period	Storage package
Long-term	6	−[redacted]±[redacted]°C	[redacted] months*2	[redacted] container and [redacted]
Accelerated		−[redacted]±[redacted]°C	[redacted] months	
Stress		[redacted]±[redacted]°C	[redacted] months	

*1 Drug substance manufactured at [redacted],
*2 The stability study is ongoing up to [redacted] months.

Under the long-term condition, [redacted] tended to decrease, [redacted] tended to increase, [redacted] tended to decrease and [redacted] tended to increase in capillary isoelectric focusing, and [redacted] activity tended to increase.

Under the accelerated and stress conditions, no significant degradation occurred throughout the testing period.

Based on the above, a shelf life of [redacted] months has been proposed for the drug substance stored in [redacted] container and [redacted] at −[redacted]±[redacted]°C.

2.2 Drug product

2.2.1 Description and composition of drug product and formulation development

The drug product is an aqueous injection. Each glass vial (8 mL) contains amivantamab 350 mg/7.0 mL. The drug product contains the following excipients: L-histidine, L-histidine hydrochloride monohydrate, sucrose, polysorbate 80, L-methionine, ethylenediaminetetraacetic acid (EDTA) disodium salt dihydrate, and water for injection.

2.2.2 Manufacturing process

The drug product is manufactured through a process comprised of active substance thawing, compounding, sterile filtration, filling, packaging, and testing/storage.

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

Process validation of the commercial-scale drug product manufacturing process has been performed.

2.2.3 Manufacturing process development

The major changes made to the drug product manufacturing process during development were manufacturing site and scale changes (the manufacturing processes before and after the changes were made are referred to as the pre-change process and the proposed commercial process, respectively). The drug product produced by the proposed commercial process was used in [redacted].

For process changes, the comparability of pre-change and post-change drug products has been demonstrated in accordance with the ICH Q5E guideline.

2.2.4 Control of drug product

The proposed specifications for the drug product consist of quantity, appearance, identity (dot blot), osmolarity, pH, purity (turbidity, non-reduced/reduced CE-SDS, SEC), post-translational modifications (peptide map), charge heterogeneity (capillary isoelectric focusing), endotoxins, extractable volume, foreign insoluble matter, [redacted], insoluble particulate matter, sterility, polysorbate 80 content, potency (EGFR ADCC activity, MET binding activity), and assay (ultraviolet-visible spectrophotometry).

2.2.5 Stability of drug product

The primary stability studies on the drug product are shown in Table 4.

Table 4. Overview of primary stability studies on drug product

Study	Drug substance manufacturing process	Drug product manufacturing process	No. of batches	Storage conditions	Testing period	Storage package
Long-term	Proposed commercial process	Proposed commercial process	5	2°C-8°C	[redacted] months	Glass vial and butyl rubber stopper
Accelerated				25ºC/60%RH	[redacted] months	
Stress				40ºC/75%RH	[redacted] months	
Photostability			1	An overall illumination of ≥1.2 million lux·h and an integrated near ultraviolet energy of 200 W·h/m, 25°C		

Under the long-term condition, [redacted] in non-reduced CE-SDS tended to decrease, [redacted] in reduced CE-SDS tended to decrease, [redacted] tended to decrease, [redacted] tended to increase, [redacted] tended to increase, [redacted] tended to increase, [redacted] tended to decrease and [redacted] and [redacted] tended to increase in capillary isoelectric focusing, [redacted] tended to decrease, and [redacted] tended to decrease.

Under the accelerated condition, [redacted] in non-reduced CE-SDS tended to decrease, [redacted] in reduced CE-SDS tended to decrease, [redacted] tended to decrease, [redacted] tended to increase, [redacted] tended to decrease and [redacted] and

[redacted] tended to increase in capillary isoelectric focusing, and [redacted] tended to decrease.

Under the stress condition, in addition to the changes observed in the accelerated testing, [redacted] tended to increase, and [redacted] tended to increase.

The photostability testing indicated that the drug product is photosensitive.

Based on the above, a shelf life of 36 months has been proposed for the drug product when primary packaged in a glass vial with a butyl rubber stopper and stored in a carton to protect from light, at 2°C to 8°C.

2.3 Quality control strategy

Based on the following studies etc., the method of control of the quality attributes of amivantamab through the combination of the control of process parameters and raw materials, in-process controls, the specifications, etc., was developed [for the control of product-related impurities and process-related impurities, see Sections 2.1.5.2 and 2.1.5.3].

- Identification of critical quality attributes (CQAs)

  The following CQAs were identified based on the information obtained during the development of amivantamab, the relevant knowledge, etc.

  CQAs of the drug substance:

  Color, pH, osmolarity, identification test (identity), protein concentration, MET binding, EGFR binding, EGFR ADCC activity, trogocytosis activity, Fcγ receptor I (FcγRI) binding, FcγRIIa binding, FcγRIIIa binding, neonatal Fc receptor (FcRn) binding, charge heterogeneity, purity (the monomeric form), HMW, LMW, host cell DNA, HCP, protein A, residual homodimer, excipient concentrations (histidine, sucrose, methionine, EDTA), polysorbate 80 content, microbial contamination (bioburden, sterility), endotoxins, pyrogens, adventitious viruses, mycoplasma, endogenous viruses, higher-order protein structure, oxidized variants ([redacted], [redacted], [redacted], [redacted], [redacted]), a deamidated variant ([redacted]), an isomerized variant ([redacted]), a sequence variant ([redacted]), aglycosylated variants, fucosylated variants, galactosylated variants, [redacted], disulfide structure, [redacted]

  CQAs specific to the drug product:

  Appearance of the primary container, extractable volume, turbidity, foreign insoluble matter, translucent particles, insoluble particulate matter

- Process characterization

Based on the data during development, scientific knowledge, and the understanding of the manufacturing process, critical process parameters (CPPs) that may impact CQAs were identified. Among

these potential CPPs, CPPs were identified based on the results of criticality analysis etc. through design of experiments.

2.R Outline of the review conducted by PMDA

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

2.R.1 Control of biological activity

The applicant's explanation about the control of the biological activity of amivantamab:

The primary mechanisms of action of amivantamab are inhibition of ligand binding of EGFR and MET, ADCC activity, and trogocytosis activity. The biological activity of amivantamab, which may contribute to its efficacy, can be controlled with the following measures:

- The binding of amivantamab to EGFR and its ADCC activity are controlled by a potency assay using [redacted] cells expressing high levels of EGFR (EGFR ADCC activity) included in the drug substance and drug product specifications. (1) Oxidized variants ([redacted], [redacted]) and (2) an isomerized variant ([redacted]), which both affect amivantamab binding to EGFR, are controlled by (1) post-translational modifications (peptide map) included in the drug substance specification and (2) post-translational modifications (peptide map) included in the drug substance and drug product specifications.
- The binding of amivantamab to MET is controlled by a potency assay (MET binding activity) included in the drug substance and drug product specifications. An oxidized variant ([redacted]), which affects binding, is controlled by post-translational modifications (peptide map) included in the drug substance specification.
- Since the trogocytosis activity of amivantamab is induced by its binding to EGFR, MET, and Fcγ receptor (FcγR), trogocytosis activity is controlled indirectly through the control of EGFR and MET binding by the above potency assays (EGFR ADCC activity, MET binding activity) and post-translational modifications (peptide map) and through the control of [redacted], which affects FcγR binding, by oligosaccharide analysis included in the drug substance specification and reduced CE-SDS included in the drug substance and drug product specifications.

PMDA concluded that the above method of control of the biological activity of amivantamab is acceptable.

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

3.1 Primary pharmacodynamics

3.1.1 Binding affinity to EGFR (CTD 4.2.1.1.1)

The binding affinity of amivantamab to human EGFR (a recombinant protein) was determined by surface plasmon resonance (SPR). The K_D value of amivantamab for EGFR (mean ± standard deviation [SD], n = 4) was 1.43 ± 0.17 nmol/L.

3.1.2 Binding affinity to MET (CTD 4.2.1.1.1)

The binding affinity of amivantamab to human MET (a recombinant protein) was determined by SPR. The K_D value of amivantamab for MET (mean ± SD, n = 7) was 0.040 ± 0.011 nmol/L.

3.1.3 Blockade of ligand (EGF) binding of EGFR (CTD 4.2.1.1.1)

The inhibitory effect of amivantamab on ligand (human EGF) binding of human EGFR was determined in a competitive binding assay using fluorescently labelled human EGF. The IC_{50} value of amivantamab for inhibition of human EGF binding of human EGFR (n = 1) was 10 nmol/L.

3.1.4 Blockade of ligand (HGF) binding of MET (CTD 4.2.1.1.1)

The inhibitory effect of amivantamab on ligand (human HGF) binding of human MET was determined in a competitive binding assay using fluorescently labelled human HGF. The IC_{50} value of amivantamab for inhibition of human HGF binding of human MET (n = 1) was 30 nmol/L.

3.1.5 Inhibition of EGFR- and MET-mediated signaling

3.1.5.1 *In vitro* (CTD 4.2.1.1.2, 4.2.1.1.4, 4.2.1.1.6, 4.2.1.1.39)

Using various human NSCLC cell lines, the inhibition of EGFR and MET phosphorylation by amivantamab in the presence of EGF and HGF was evaluated based on chemiluminescence of anti-phosphorylated EGFR or anti-phosphorylated MET antibody. The IC_{50} values of amivantamab are shown in Table 5.

Table 5. Inhibition of EGFR and MET phosphorylation by amivantamab in various human NSCLC cell lines

Cell line	Gene mutation or amplification		EGFR		MET	
	EGFR	MET	n	IC_{50} value (nmol/L)	n	IC_{50} value (nmol/L)
H292	Wild-type	Wild-type	1	29	1	0.74
SKMES-1	Wild-type	Wild-type	1	—	1	0.49
H1993	Wild-type	Amplified*6	1	4.2	1	13
H1975	L858R*1/T790M*2	Wild-type	1	1.5	1	0.64
H3255	L858R and amplified*3	Wild-type	1	85	1	1.2
H1650	E746_A750del*4	Wild-type	—	—	1	0.86
HCC2935	E746_A750del	Wild-type	—	—	1	0.97
HCC827	E746_A750del and amplified*3	Wild-type	2	28, 84	3	1.7 ± 0.36
H820	E746_A750del, T790M	Amplified*7	1	2.9	1	3.8
HCC4006	L747_S752del*5	Wild-type	1	13	1	1.7

Mean ± SD (Individual values are listed for n = 1 or 2); —, Not calculated
*1 Leucine (L) at position 858 in exon 21 substituted with arginine (R)
*2 Threonine (T) at position 790 in exon 20 substituted with methionine (M)
*3 According to the CCLE database, the log2 ratios of the signal intensities are 4.1 (HCC3255) and 4.9 (HCC827).
*4 Deletions of glutamic acid (E) at position 746 to alanine (A) at position 750 in exon 19
*5 Deletions of leucine (L) at position 747 to serine (S) at position 752 in exon 19
*6 According to the CCLE database, the log2 ratio of the signal intensity is 3.8.
*7 The gene copy number is 6.1 (*Int J Cancer*. 2009; 124: 1778-84, etc.).

Using various human NSCLC cell lines, the inhibition of phosphorylation of EGFR and MET downstream signal transducers (ERK and AKT) by amivantamab was evaluated using anti-phosphorylated ERK or anti-phosphorylated AKT antibody, based on chemiluminescence. The IC_{50} values of amivantamab are shown in Table 6.

Table 6. Inhibition of phosphorylation of EGFR and MET downstream signal transducers (ERK and AKT) by amivantamab in various human NSCLC cell lines

Cell line	Gene mutation or amplification		ERK		AKT	
	EGFR	MET	n	IC_{50} value (nmol/L)	n	IC_{50} value (nmol/L)
H292	Wild-type	Wild-type	1	0.64	1	0.27
SKMES-1	Wild-type	Wild-type	1	0.54	—	—
H1975	L858R/T790M	Wild-type	3	1.63 ± 0.21	3	0.82 ± 0.12
H3255	L858R and amplified	Wild-type	1	0.74	1	0.8
H1650	E746_A750del	Wild-type	1	0.53	1	0.41
HCC2935	E746_A750del	Wild-type	1	1.5	1	0.65
HCC827	E746_A750del and amplified	Wild-type	3	0.92 ± 0.27	3	0.53 ± 0.10
H820	E746_A750del, T790M	Amplified	1	76	1	22
HCC4006	L747_S752del	Wild-type	1	2.5	1	1.3

Mean ± SD (Individual values are listed for n = 1); —, Not calculated

Using EGFRex20 insertion mutation-positive human NSCLC-derived (1) DFCI-127 (P772_H773insPNP[2)]), (2) DFCI-58 (H773_V774insNPH[3)]), and (3) YU-1163 (S768_D770dup[4)]) cell lines, the inhibition of phosphorylation of EGFR and MET and their downstream signal transducers (ERK and AKT) by amivantamab was evaluated by Western blotting. Amivantamab inhibited (i) the phosphorylation of EGFR, MET, and AKT in all cell lines and (ii) the phosphorylation of ERK in the DFCI-127 and DFCI-58 cell lines.

3.1.5.2 *In vivo* (CTD 4.2.1.1.15, 4.2.1.1.16, 4.2.1.1.39)

(1) NOG mice[5)] were subcutaneously implanted with DFCI-127 cell line, and (2) nude mice were subcutaneously implanted with YU-1163 cell line (5/group). The expression levels of EGFR and MET and the inhibition of EGFR and MET phosphorylation by amivantamab were determined. When tumors reached an average of 150 to 200 mm^3, intraperitoneal amivantamab 30 mg/kg was administered twice weekly. The expression levels of EGFR, MET, phosphorylated EGFR, and phosphorylated MET in tumor tissues were determined by Western blotting. In both cell lines, amivantamab treatment led to decreases in EGFR and MET levels and inhibition of EGFR and MET phosphorylation.

Nude mice (7/group) were subcutaneously implanted with EGFRex20 insertion mutation-positive NSCLC patient-derived YHIM-1029 xenograft tumors (D770_N771insG[6)]). The expression levels of EGFR, MET, and downstream signal transducers (ERK, AKT, S6) and the inhibition of phosphorylation by amivantamab were determined. When tumors reached an average of 150 to 200 mm^3, intraperitoneal amivantamab 10 mg/kg was administered twice weekly. The expression levels of EGFR, MET, and downstream signal transducers (ERK, AKT, S6) in tumor tissues and the inhibition of phosphorylation of each protein by amivantamab were determined by Western blotting. Amivantamab treatment resulted in decreased expression of MET and inhibition of the phosphorylation of EGFR, ERK, AKT, and S6.

[2)] Insertion of proline (P), asparagine (N), and proline (P) between proline (P) at position 772 and histidine (H) at position 773 in exon 20
[3)] Insertion of asparagine (N), proline (P), and histidine (H) between histidine (H) at position 773 and valine (V) at position 774 in exon 20
[4)] Duplication of serine (S) at position 768 to aspartic acid (D) at position 770 in exon 20
[5)] Non-obese diabetic/severe combined immunodeficient (NOD/SCID) mice lacking IL-2 receptor γ chain extracellular domain
[6)] Insertion of glycine (G) between aspartic acid (D) at position 770 and asparagine (N) at position 771 in exon 20

Nude mice (4/group) were subcutaneously implanted with H1975-HGF[7] cell line, and the expression levels of EGFR, MET, and downstream signal transducers (ERK and AKT) and the inhibition of phosphorylation by amivantamab were determined by Western blotting. The day when tumors reached an average of 150 to 200 mm^3 was designated as Study Day 1. Amivantamab 10 mg/kg was administered on Days 1 and 4, and the expression levels of EGFR, MET, and downstream signal transducers (ERK and AKT) in tumor tissues on Day 5 and the inhibition of phosphorylation of each protein by amivantamab were determined by Western blotting. Compared to vehicle control (phosphate buffer saline [PBS]), administration of amivantamab resulted in statistically significant decreases in EGFR and MET expression and statistically significant inhibition of phosphorylation of EGFR, MET, and AKT ($P < 0.05$, Sidak's multiple comparison test).

3.1.6 Effects on internalization/degradation of EGFR and MET (CTD 4.2.1.1.39)

Using (1) DFCI-127 cell line, (2) DFCI-58 cell line, and (3) EGFRex20 insertion mutation (D770delinsGY[8] or H773_V774insH[9])-positive mouse pro-B cell-derived Ba/F3 cell lines, the effect of amivantamab on the internalization of EGFR and MET [the above (1) and (2)] and the effect of amivantamab on the internalization of EGFR [the above (3)] were evaluated by flow cytometry. Amivantamab reduced EGFR and MET [the above (1) and (2)] and EGFR [the above (3)] on the cell surface.

Using DFCI-127 cell line, the effect of amivantamab on the internalization of EGFR and MET was evaluated by immunofluorescence staining for EGFR and MET in the cells followed by microscopy. Treatment with amivantamab led to the redistribution of EGFR and MET into internal compartments.

Using Ba/F3 cell line, the effect of amivantamab on EGFR degradation was evaluated by Western blotting. The total EGFR levels were reduced following treatment with amivantamab, and an autophagy inhibitor (bafilomycin [unapproved in Japan])[10] inhibited EGFR degradation triggered by amivantamab.

The applicant's explanation:
The above results suggested that amivantamab induces the internalization and lysosomal degradation of EGFR and MET.

3.1.7 Effect on trogocytosis activity (CTD 4.2.1.1.11, 4.2.1.1.12)

The trogocytosis[1] activity of amivantamab in the presence of peripheral blood mononuclear cells (PBMCs) or macrophages, was evaluated in H1975 cell line by Western blotting. In the presence of either PBMCs or macrophages, treatment with amivantamab resulted in a reduction in the levels of EGFR, MET, and phosphorylated EGFR in tumor cells. The trogocytosis activity of amivantamab in the presence of macrophages was evaluated using confocal time-lapse microscopy in H1975 cell line opsonized with

[7] H1975 cell line engineered to express human HGF
[8] Deletion of aspartic acid (D) at position 770 and insertion of glycine (G) and tyrosine (Y) at this position in exon 20
[9] Insertion of histidine (H) between histidine (H) at position 773 and valine (V) at position 774 in exon 20
[10] Bafilomycin inhibits lysosomal degradation (autophagy) by inhibiting vacuolar ATPase/the endoplasmic reticulum calcium pump (Ca-P60A/SERCA) and autophagosome-lysosome fusion (*Autophagy*. 2015; 11: 1437-8).

fluorescently labeled amivantamab. While no appreciable phagocytosis was observed, an accumulation of amivantamab was observed within the macrophages.

The applicant's explanation:
The above results suggested that amivantamab induces trogocytosis.

3.1.8 Effect on ADCC activity (CTD 4.2.1.1.39, 4.2.1.1.41, 4.2.1.1.42)

The binding of amivantamab in YU-1163 cell line or EGFRex20 insertion mutation (H773_V774 ins NPH[11])-positive human NSCLC-derived LU-0387 cell line was evaluated by flow cytometry. Amivantamab bound to the YU-1163 and LU-0387 cell lines.

The ADCC activity of amivantamab against DFCI-127, YU-1163, and LU-0387 cell lines was evaluated using human PBMCs as effector cells by measuring lactate dehydrogenase (LDH) activity. Amivantamab induced ADCC activity against all cell lines.

The ADCC activity of amivantamab against YU-1163 cell line was evaluated using human PBMCs as effector cells by time-resolved fluorescence resonance energy transfer (TR-FRET). Amivantamab induced ADCC activity.

In mice subcutaneously implanted with YHIM-1029 xenograft tumors, the effect of amivantamab on apoptosis was evaluated using terminal deoxynucleotidyl transferase-mediated dUTP nick end labeling (TUNEL) staining. Amivantamab induced apoptosis.

3.1.9 Effect on cell migration and invasion induced by HGF (CTD 4.2.1.1.43)

Using LU-0387 cell line, the effect of amivantamab on cell migration and invasion stimulated by HGF was evaluated by microscopy of migrated cells and invaded cells. Amivantamab inhibited cell migration and invasion.

3.1.10 Growth inhibition of malignant tumor cell lines etc.

3.1.10.1 *In vitro* (CTD 4.2.1.1.2, 4.2.1.1.39)

The anti-proliferative activity of amivantamab against DFCI-127 and DFCI-58 cell lines was evaluated based on the amount of ATP from viable cells. Amivantamab inhibited the proliferation of all cell lines ($P < 0.0001$, Student’s t-test).

The anti-proliferative activity of amivantamab against various human NSCLC cell lines was evaluated based on the amount of ATP from viable cells. Maximal percentage tumor growth inhibition after treatment with amivantamab is shown in Table 7.

[11] Insertion of asparagine (N), proline (P), and histidine (H) between histidine (H) at position 773 and valine (V) at position 774 in exon 20

Table 7. Anti-proliferative activity of amivantamab against various human NSCLC cell lines

Cell line	Gene mutation or amplification		n	Maximal tumor growth inhibition (%)
	EGFR	MET		
H292	Wild-type	Wild-type	6	81 ± 1.8
SKMES-1	Wild-type	Wild-type	6	87 ± 1.2
H1993	Wild-type	Amplified	4	11 ± 3.8
H1975	L858R/T790M	Wild-type	7	64 ± 0.9
H3255	L858R and amplified	Wild-type	8	66 ± 4.4
H1650	E746_A750del	Wild-type	6	44 ± 1.8
HCC2935	E746_A750del	Wild-type	6	33 ± 1.3
HCC827	E746_A750del and amplified	Wild-type	6	53 ± 2.1
H820	E746_A750del, T790M	Amplified	9	46 ± 3.1
HCC4006	L747_S752del	Wild-type	4	14 ± 5.6

Mean ± SE

3.1.10.2 *In vivo*

3.1.10.2.1 NSCLC cell lines and NSCLC patient-derived xenograft tumors (CTD 4.2.1.1.13, 4.2.1.1.20, 4.2.1.1.21, 4.2.1.1.22, 4.2.1.1.24, 4.2.1.1.25, 4.2.1.1.26, 4.2.1.1.39, 4.2.1.1.42, 4.2.1.1.44)

The anti-tumor activity of amivantamab was evaluated in (1) NOG mice subcutaneously implanted with DFCI-127 cell line and (2) nude mice subcutaneously implanted with YU-1163 cell line (5/group). The day when tumors reached an average of (1) 111 or (2) 150 to 200 mm^3 was designated as Study Day 1. Intraperitoneal amivantamab 30 mg/kg was administered twice weekly for (1) 11 or (2) 15 days, beginning at Day 1, and tumor volumes were calculated. On (1) Day 11 or (2) Day 15, amivantamab statistically significantly inhibited tumor growth compared to vehicle control (PBS) (Figure 1).

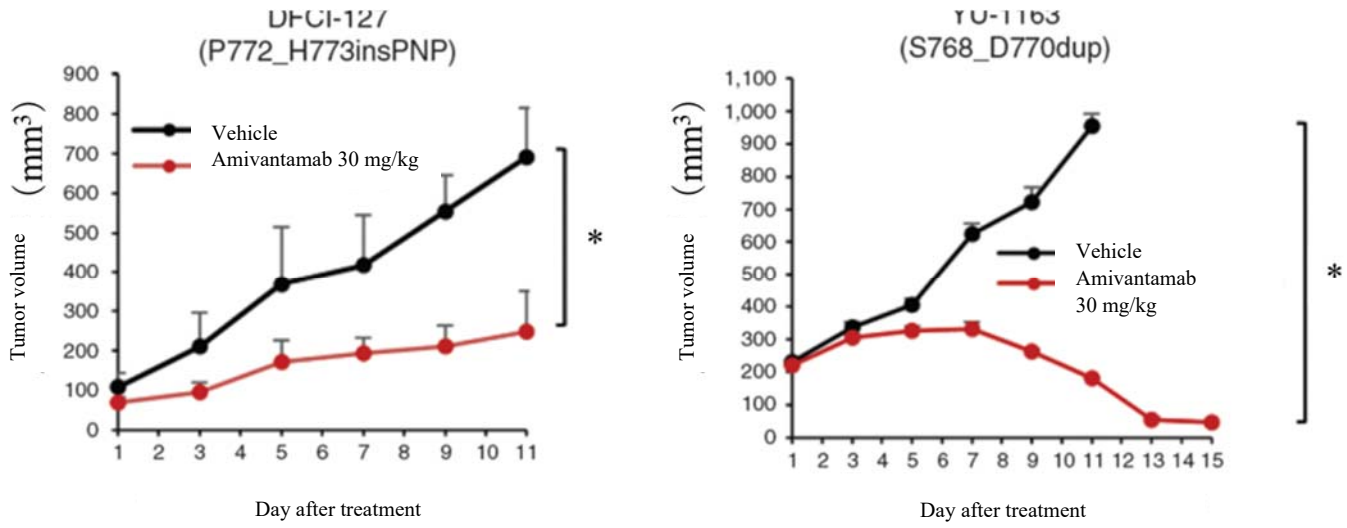


Figure 1. Anti-tumor activity of amivantamab in mice subcutaneously implanted with DFCI-127 or YU-1163 cell line
n = 5, Mean ± SE, *$P < 0.0001$ vs. vehicle control (Dunnett's multiple comparison test)

The anti-tumor activity of amivantamab was evaluated in nude mice subcutaneously implanted with (1) YHIM-1029 xenograft tumors or (2) EGFRex20 insertion mutation-positive NSCLC patient-derived LXFE2478 xenograft tumors (M766_A767insASV[12)]) [(1) 7/group and (2) 10/group]. The day when tumors reached an average of 100 to 200 mm^3 was designated as Study Day 1. Amivantamab or other drugs were administered

[12)] Insertion of alanine (A), serine (S), and valine (V) between methionine (M) at position 766 and alanine (A) at position 767 in exon 20

intraperitoneally at the following doses from Day 1 through Day 21, and tumor volumes were calculated. On (1) Day 31 or (2) Day 27, amivantamab statistically significantly inhibited tumor growth compared to vehicle control (PBS) (Figure 2).

(1) Amivantamab or cetuximab 10 mg/kg twice weekly, or poziotinib (unapproved in Japan) 1 mg/kg daily
(2) Amivantamab or cetuximab 10 mg/kg twice weekly, or erlotinib 25 mg/kg or osimertinib 30 mg/kg daily

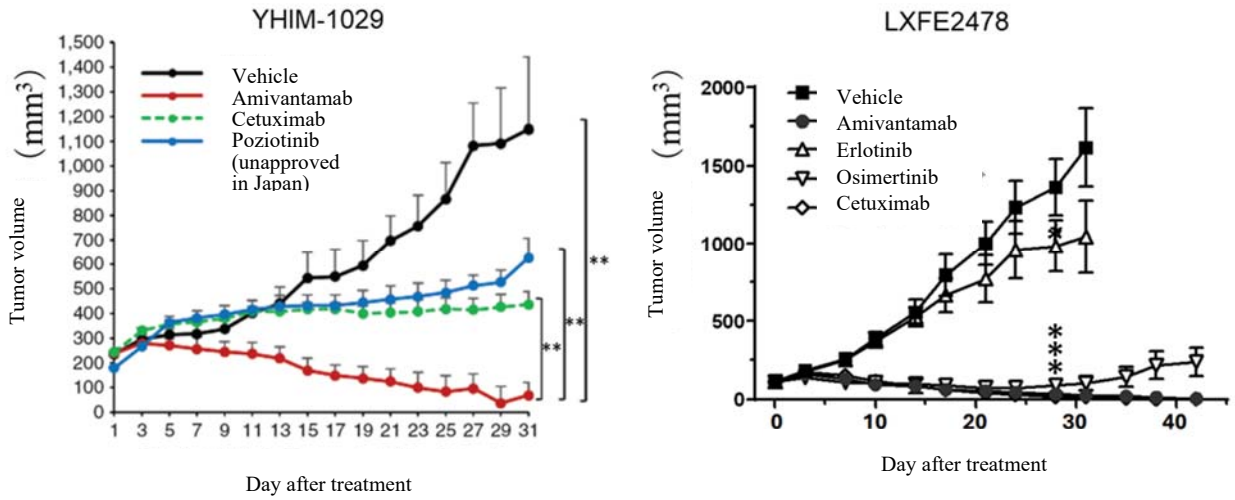


Figure 2. Anti-tumor activity of amivantamab
in nude mice subcutaneously implanted with YHIM-1029 or LXFE2478 xenograft tumors
N = 7 or 10, mean ± SE
*$P \leq 0.05$ vs. vehicle control (Benjamini-Hochberg's multiple comparison test)
**$P < 0.0001$ vs. vehicle control, cetuximab, or poziotinib (Dunnett's multiple comparison test)

The anti-tumor activity of amivantamab was evaluated in mice subcutaneously implanted with various human NSCLC cell lines. The day when the tumor volume reached 140 to 210 mm^3 (14 days post-tumor cell implant for H1975 and H1975-HGF cell lines only) was designated as Study Day 1. Beginning at Day 1, amivantamab 10 mg/kg (5 mg/kg for SKMES-HGF cell line only) was administered intraperitoneally twice weekly for 12 to 28 days, [13] and tumor volumes were calculated. Percentage tumor growth inhibition [14] in the amivantamab group is shown in Table 8.

[13] 28 days for SKMES-HGF, 16 days for H1975 and H1975-HGF, 21 days for LU858, H1993, HCC827, and HCC827-HGF, 12 days for LU1901, 17 days for LU1868, 20 days for EBC-1, 28 days for HCC827, 25 days for HCC827-ER1
[14] Tumor growth inhibition (%) = [1 −{(mean tumor volume at the last time point in the amivantamab group) − (mean tumor volume on Day 0 in the amivantamab group)}/ {(mean tumor volume at the last time point in the control group) − (mean tumor volume on Day 0 in the control group)}]×100

Table 8. Anti-tumor activity of amivantamab in mice subcutaneously implanted with various human NSCLC cell lines

Cell line	Gene mutation or amplification		Mouse	Tumor volume calculation (Day)	n	Tumor growth inhibition (%)
	EGFR	MET				
SKMES-HGF[*1]	Wild-type	Wild-type	SCID mouse	36	8	100[*9]
H1975	L858R/T790M	Wild-type	Nude mouse	16	9	82[*8]
H1975-HGF[*1]	L858R/T790M	Wild-type		16	9	89[*8]
LU858	L858R	Amplified[*4]		22	12	68[*7]
LU1901	G719A[*3]	Amplified[*4]		12	8	42[*8]
LU1868	L858R/T790M	Wild-type		17	10	81[*9]
H1993	Wild-type	Amplified		23	12	11
EBC-1	Wild-type	Amplified[*5]		20	12	20
HCC827	E746_A750del and amplified	Wild-type		39	9	89[*8]
HCC827-ER1[*2]	E746_A750del and amplified	Amplified[*6]		31	9	92[*8]
HCC827	E746_A750del and amplified	Wild-type	SCID-beige mouse	24	9	92[*7]
HCC827-HGF[*1]	E746_A750del and amplified	Wild-type		37	9	100[*7]

*1 Cell line engineered to express human HGF, *2 HCC827 cell line with acquired resistance to erlotinib
*3 Glycine (G) at position 719 in exon 18 substituted with alanine (A)
*4 The gene copy numbers based on sequencing are 15.68 (LU858) and 35.59 (LU1901).
*5 According to the CCLE database, the log2 ratio of the signal intensity is 3.1.
*6 The gene copy number based on quantitative PCR is approximately 12.
*7 $P < 0.05$ vs. vehicle control (PBS) (Student's t-test), *8 $P < 0.05$ vs. vehicle control (PBS) (Tukey-Kramer's multiple comparison test)
*9 $P < 0.001$ vs. vehicle control (PBS) (Tukey-Kramer's multiple comparison test)

3.1.10.2.2 Non-NSCLC malignant tumor cell lines (CTD 4.2.1.1.28, 4.2.1.1.29, 4.2.1.1.30, 4.2.1.1.32, 4.2.1.1.33)

The anti-tumor activity of amivantamab was evaluated in mice subcutaneously implanted with various malignant tumor cell lines.[15)] The day when tumors reached a specified volume[16)] was designated as Study Day 1. Beginning at Day 1, amivantamab 10 mg/kg (5 mg/kg for SNU-5 cell line only) was administered intraperitoneally twice weekly for 13 to 42 days,[17)] and tumor volumes were calculated. Percentage tumor growth inhibition in the amivantamab group is shown in Table 9.

[15)] SCID mice for SG16 and SNU-5 cell lines, severe combined immunodeficient hairless outbred (SHO) mice for Ba/F3 (Ba/F3-EGFR-TDC) cell line, and nude mice for others were used.
[16)] 400-600 mm^3 for CRC0196, 250-300 mm^3 for SG16, 150-250 mm^3 for others
[17)] 21 days for CR0012, CR0029, CR0588, CR1197, MHCC97H, LI0801, and LI1646, 19 days for CR0146, CR1574, and GA0046, 13 days for CRC0196, 25 days for SNU-5, 42 days for SG16, 14 days for Ba/F3-EGFR-TDC

Table 9. Anti-tumor activity of amivantamab in mice subcutaneously implanted with various malignant tumor cell lines

Cell line	Origin	Gene mutation or amplification		Tumor volume calculation (Day)	n	Tumor growth inhibition (%)
		EGFR	MET			
CR0012	Human CRC	Wild-type	Wild-type	24	10	21
CR0029		Wild-type	Wild-type	22	10	-12
CR0146		Wild-type	Wild-type	19	10	8
CR0588		Wild-type	Wild-type	21	10	59[*6]
CR1197		Amplified	Wild-type	21	10	10
CR1574		R776H[*1]	Wild-type	19	10	-10
CRC0196		Wild-type	Amplified[*3]	13	6	0
MHCC97H	Human HCC	Wild-type	Unknown[*4]	29	10	30
LI0801		Wild-type	Wild-type	21	8	81[*7]
LI1646		Wild-type	Wild-type	21	8	4
GA0046	Human gastric cancer	Wild-type	Wild-type	19	10	67[*8]
SNU-5		Wild-type	Amplified[*5]	25	10	98[*9]
SG16	Human esophageal cancer	Wild-type	Amplified[*3]	49	6	88
Ba/F3-EGFR-TDC	Mouse pro-B cells	E746_A750del, T790M/C797S[*2]	Wild-type	14	8	78[*10]

*1 Arginine (R) at position 776 in exon 20 substituted with histidine (H), *2 Cysteine (C) at position 797 in exon 20 substituted with serine (S)
*3 The gene copy numbers are 23 (CRC0196) and 28 (SG16). *4 No gene mutation or amplification was found.
*5 According to the CCLE database, the log2 ratio of the signal intensity is 3.2.
*6 $P < 0.05$ vs. vehicle control (PBS) (Fisher's LSD multiple comparison test), *7 $P < 0.05$ vs. vehicle control (PBS) (Student's t-test)
*8 $P < 0.001$ vs. vehicle control (PBS) (Tukey-Kramer's multiple comparison test)
*9 $P < 0.001$ vs. vehicle control (PBS) (Games Howell's multiple comparison test)
*10 $P < 0.0001$ vs. vehicle control (PBS) (Dunnett's multiple comparison test)

The anti-tumor activity of amivantamab was evaluated in NOG mice subcutaneously implanted with mouse pro-B cell-derived Ba/F3 cell lines expressing mutant EGFR (D770delinsGY [18)] or H773_V774insH[19)]) (5/group). The day when tumors reached an average of 150 to 200 mm^3 was designated as Study Day 1. Beginning at Day 1, amivantamab 30 mg/kg was administered intraperitoneally twice weekly for 15 days, and tumor volumes on Day 15 were calculated. Amivantamab statistically significantly inhibited tumor growth ($P < 0.0001$ for both, Dunnett's multiple comparison test or Student's t-test).

3.2 Safety pharmacology

3.2.1 Effects on central nervous, cardiovascular, and respiratory systems

The effects of amivantamab on the central nervous, cardiovascular, and respiratory systems were evaluated in 1-month, 6-week, and 3-month intravenous dose toxicity studies in cynomolgus monkeys [see Section 5.2]. There were no amivantamab-related effects.

3.R Outline of the review conducted by PMDA

On the basis of the submitted data, PMDA concluded that the applicant's explanation about the non-clinical pharmacology of amivantamab is acceptable, except for the considerations in the following section.

[18)] Deletion of aspartic acid (D) at position 770 and insertion of glycine (G) and tyrosine (Y) at this position in exon 20
[19)] Insertion of histidine (H) between histidine (H) at position 773 and valine (V) at position 774 in exon 20

3.R.1 Mechanism of action and efficacy of amivantamab

The applicant's explanation about the mechanism of action of amivantamab and its efficacy in the treatment of EGFRex20 insertion mutation-positive NSCLC:

(1) Activating mutations (Ex19del and L858R) account for approximately 90% and (2) EGFRex20 insertion mutations account for approximately 5.8% of all *EGFR* mutations in NSCLC, and both mutations are mutually exclusive (*Cancer Sci*. 2016; 107: 1179-86). While the existing epidermal growth factor receptor-tyrosine kinase inhibitors (EGFR-TKIs) (gefitinib, erlotinib, afatinib, dacomitinib, osimertinib) are expected to be effective in the above patients (1), the above patients (2) are resistant to the existing EGFR-TKIs (*Cancer Sci*. 2016; 107: 1179-86, etc.). EGFRex20 insertion mutations (an amino acid residue insertion in a portion of the tyrosine kinase domain of EGFR) induce a structural alteration in the loop of the tyrosine kinase domain, resulting in steric hindrance of the binding of the existing EGFR-TKIs and constitutive activation of EGFR-mediated signaling (*Sig Transduct Target Ther*. 2019; 4: 5 and *Nat Med*. 2018; 24: 638-46).

Amivantamab binds to the extracellular domains of EGFR and MET [see Sections 3.1.1 and 3.1.2] and inhibits EGFR- and MET-mediated signaling. In addition, it induces ADCC activity [see Section 3.1.8]. Amivantamab is considered to show anti-tumor activity against EGFRex20 insertion mutation-positive NSCLC through these mechanisms. Although the degree of contribution of MET to the proliferation of EGFRex20 insertion mutation-positive NSCLC, etc. (constitutive activation of signaling, etc.) is unknown, the activation of MET-mediated signaling has been reported as an acquired resistance mechanism to drugs targeting EGFR in patients with *EGFR* activating mutation-positive NSCLC (*Br J Cancer*. 2019; 121: 725-37, etc.). Given this finding etc., binding to both EGFR and MET and inhibition of MET-mediated signaling may be of significance. The internalization/degradation of EGFR and MET [see Section 3.1.6] and trogocytosis [see Section 3.1.7] induced by amivantamab may also contribute to its anti-tumor activity against EGFRex20 insertion mutation-positive NSCLC.

Given the above mechanism of action, the following results obtained from non-clinical pharmacology studies that evaluated the anti-tumor activity of amivantamab [see Section 3.1.10.2.1], etc., amivantamab is expected to have efficacy in the treatment of EGFRex20 insertion mutation-positive NSCLC.

- Amivantamab inhibited tumor growth in mice subcutaneously implanted with EGFRex20 insertion mutation-positive NSCLC patient-derived LXFE2478 or YHIM-1029 xenograft tumors.
- Amivantamab showed greater anti-tumor activity than an anti-EGFR antibody (cetuximab) in mice subcutaneously implanted with YHIM-1029 xenograft tumors.

PMDA’s view:

PMDA largely accepted the applicant's explanation. However, the significance of amivantamab binding to both EGFR and MET in inhibiting tumor growth of EGFRex20 insertion mutation-positive NSCLC is not fully understood at present. In addition, the degree of contribution of the internalization/degradation of EGFR and MET and trogocytosis to tumor growth inhibition by amivantamab, and the effect of MET expression levels etc. remain unknown to date. Since these points may be beneficial information in terms of selecting patients eligible for the use of amivantamab in clinical practice, information collection should be continued. If any new

findings become 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

The non-clinical PK of amivantamab were determined in monkeys.

Amivantamab in monkey serum was quantified by electrochemiluminescence (ECL) (lower limit of quantification [LLOQ], 0.20 μg/mL). Anti-amivantamab antibodies in monkey serum were detected by ECL.

4.1 Absorption

4.1.1 Single-dose studies

Following a single intravenous injection of amivantamab 3, 10, or 30 mg/kg in male and female monkeys, serum amivantamab concentrations were determined (Table 10). There were no clear sex-related differences in amivantamab exposure. While the C_{max} of amivantamab increased in an approximately dose-proportional manner over the dose range tested, the AUC_{inf} of amivantamab increased in a greater than dose-proportional manner. The applicant explained that the AUC_{inf} of amivantamab increased in a greater than dose-proportional manner because target-mediated CL of amivantamab decreased with increasing dose.

Anti-amivantamab antibodies were detected in 9 of 12 animals dosed with amivantamab.

Table 10. PK parameters of amivantamab (male and female monkeys, single IV injection)

Dose (mg/kg)	Sex	C_{max} (μg/mL)	AUC_{inf} (μg·day/mL)	$t_{1/2}$ (day)	CL (mL/day/kg)	V_z (mL/kg)
3	M	24.42,* 52.78	154.5,* 153.2	2.08,* 1.84	19.42,* 19.58	58.17,* 51.89
	F	43.65, 76.21	147.7, 150.8	1.78, 2.02	19.89, 20.31	51.06, 59.19
10	M	176.6, 241.5	774.3, 865.5	3.55, 3.59	11.55, 12.91	59.10, 66.85
	F	214.2, 217.3	744.4, 781.5	2.58, 3.31	12.80, 13.43	50.01, 61.12
30	M	545.7, 640.4	3,051, 3,443	3.47, 3.55	8.71, 9.83	44.66, 49.25
	F	611.5, 614.9	2,961, 3,844	4.26, 4.43	7.80, 10.13	49.86, 62.29

Individual values, n = 2
* Outlying serum amivantamab concentration at 1 hour time point was excluded from calculation of PK parameters.

4.1.2 Repeated-dose studies

Amivantamab 20, 60, or 120 mg/kg quaque 1 week or once every week (QW) was administered intravenously to male and female monkeys for 5 weeks, and serum amivantamab concentrations were determined (Table 11). There were no clear sex-related differences in amivantamab exposure. Amivantamab exposure increased in an approximately dose-proportional manner over the dose range tested. Amivantamab exposure on Day 29 was higher than that on Day 1.

Anti-amivantamab antibodies were detected in 6 of 30 animals dosed with amivantamab.

Table 11. PK parameters of amivantamab (male and female monkeys, 5-week intravenous administration)

Sampling day (Day)	Dose (mg/kg)	Sex	C_{max} (μg/mL)	AUC_{7day} (μg·day/mL)	$t_{1/2}$ (day)
1	20	M	580.6 ± 70.22	1,620 ± 174.3	—
		F	516.2 ± 108.8	1,485 ± 359.1	—
	60	M	1,669 ± 98.51	5,139 ± 777.9	—
		F	1,528 ± 445.6	5,051 ± 2,083	—
	120	M	2,423 ± 342.0	8,916 ± 503.0	—
		F	3,203 ± 645.0	10,343 ± 2,837	—
29	20	M	768.2 ± 132.3	2,498 ± 973.1	2.01, 3.38
		F	858.8 ± 182.6	3,313 ± 715.0	2.81, 3.81
	60	M	2,633 ± 464.1	10,722 ± 2,179	5.49, 5.52
		F	2,532 ± 553.5	10,050 ± 2,810	3.27, 4.74
	120	M	4,691 ± 1,187	19,025 ± 5,053	2.47, 9.57
		F	5,389 ± 1,720	21,981 ± 8,558	8.55, 12.3

Mean ± SD (Individual values are listed for n = 2); n = 5; —, Not calculated

4.2 Distribution

The applicant's explanation about the tissue distribution of amivantamab:

Given the volume of distribution of amivantamab in a single intravenous dose study in monkeys [see Section 4.1.1] and the plasma volume (44.8 mL/kg) and extracellular fluid volume (208 mL/kg) in monkeys (*Pharm Res.* 1993; 10: 1093-5), amivantamab is considered to have low tissue distribution and be distributed predominantly into extracellular fluids including plasma.

Since human IgG crosses the placenta into the fetus, amivantamab, which is a human IgG1-based antibody, also has the potential to cross the placenta into the fetus.

4.3 Metabolism and excretion

The applicant's explanation about the metabolism and excretion of amivantamab:

Amivantamab is an antibody drug and is expected to be catabolized into small peptides and amino acids and cleared.

Since human IgG is excreted in milk, amivantamab, which is a human IgG1-based antibody, also has the potential to be excreted in milk.

4.R Outline of the review conducted by PMDA

On the basis of the submitted data, PMDA concluded that the applicant's explanation about the non-clinical pharmacokinetics of amivantamab is acceptable.

5. Toxicology and Outline of the Review Conducted by PMDA

5.1 Single-dose toxicity

No single-dose toxicity studies were conducted with amivantamab. The acute toxicity and approximate lethal dose of amivantamab were assessed in repeated-dose toxicity studies in cynomolgus monkeys (Table 12). Since no mortality or acute symptoms occurred at the highest dose of 120 mg/kg, the approximate lethal dose of amivantamab was determined to be >120 mg/kg.

5.2 Repeated-dose toxicity

Repeated-dose toxicity studies in cynomolgus monkeys (6 weeks and 3 months) were conducted (Table 12). The no observed-adverse-effect level (NOAEL) of amivantamab following 3-month administration was determined to be 120 mg/kg/week. The noteworthy abnormal findings were increased leukocyte parameters, changes in blood albumin and globulin, decreased blood calcium, increases in blood alanine aminotransferase (ALT) and aspartate aminotransferase (AST), decreased adrenal gland weights, tubular degeneration and interstitial mixed cell infiltration in the kidney, Kupffer cell pigmentation in the liver, mucosal degeneration and regeneration and hemorrhage in the lamina propria in the stomach, and increased incidence and severity of mononuclear cell infiltration in the lamina propria and muscular layer. Among these findings, increased leukocyte parameters were considered secondary to physiological stress (*Toxicol Pathol*. 2013; 41: 560-614), Kupffer cell pigmentation in the liver was considered related to amivantamab clearance (*Toxicol Pathol*. 2014; 42: 725-64), and changes in blood albumin and globulin, decreased blood calcium, increases in blood ALT and AST, and decreased adrenal gland weights were not associated with abnormal findings. Thus, all of those findings were considered of little toxicological significance. Amivantamab systemic exposure (21,936 μg·day/mL) following 3-month administration at the NOAEL (120 mg/kg/week) in cynomolgus monkeys was approximately 4.7-fold the maximum systemic exposure[20] (4,685 μg·day/mL) in Japanese patients treated with amivantamab at the proposed dosing regimen.

Table 12. Repeated-dose toxicity studies

Test system	Route of administration	Duration of dosing	Dose (mg/kg/week)	Noteworthy findings	NOAEL (mg/kg/week)	Attached document CTD
Male and female cynomolgus monkeys	IV	6 weeks (QW)	0,*1 20, 60, 120	≥20: increased blood ALT,*3 decreased blood albumin (male and female), decreased adrenal gland weights (male), increased blood AST (female), ≥60: increased blood globulin, decreases in blood A/G ratio/calcium (male and female) 120: increases in white blood cell count/neutrophil count,*3 decreased eosinophil count*3 (male and female), decreased lymphocyte count*3 (female)	120	4.2.3.2.2
Male and female cynomolgus monkeys	IV	3 months (QW)	0,*2 60, 120	≥60: decreased blood albumin, increased blood globulin, tubular regeneration in the kidney, Kupffer cell hypertrophy/cytoplasmic pigment in the liver, glandular/mucosal epithelial degeneration/regeneration in the stomach, acute hemorrhage in the mucosa/lamina propria of the stomach*4 (male and female) 120: interstitial mixed cell infiltration in the kidney, mononuclear cell infiltration in the mucosa/lamina propria*5/muscular layer in the stomach (male)	120	4.2.3.2.3

*1 Saline, *2 5% dextrose injection, *3 Day 2, *4 Excluding 120 mg/kg females, *5 Increased severity of the finding

5.3 Genotoxicity

No genotoxicity studies were conducted because amivantamab is an antibody drug, and it is not expected that amivantamab would interact directly with DNA or other chromosomal material.

[20] Amivantamab exposure ($AUC_{0\text{-}168h}$) on Cycle 2 Day 1 in Japanese patients treated with amivantamab at the proposed dosing regimen in a global phase I study (Study EDI1001)

5.4 Carcinogenicity

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

5.5 Reproductive and developmental toxicity

In repeated-dose toxicity studies in cynomolgus monkeys, no effects on male or female reproductive organs were observed (Table 12). A weight-of-evidence assessment of the potential for amivantamab to cause reproductive and developmental toxicity was performed. Based on the results of phenotypic analyses of (1) EGFR and (2) MET knockout mice [(1) *Science*.1995; 269: 234-8, *Nature*. 1995; 376: 337-41, *EMBO J.* 1998; 17: 719-31, etc., and (2) *Nature*. 1995; 376: 768-71, *Nature.* 1995; 373: 702-5, *Nature*. 1995; 373: 669-702, etc.], fertility and early embryonic development (FEED) and embryo-fetal development (EFD) studies with [redacted] that inhibits EGFR in rats, an EFD study with [redacted] that neutralizes EGFR in cynomolgus monkeys, and an enhanced pre- and postnatal developmental (ePPND) study with onartuzumab that neutralizes MET/HGF in cynomolgus monkeys (*Toxicol Sci.* 2018; 165: 186-97), inhibition of EGFR- or MET-mediated signaling by amivantamab is likely to cause serious adverse effects on the development and growth of the placenta, embryo, lung, skin, heart, nervous system, etc., and the maintenance of pregnancy.

Based on the above, the applicant explained that the following precautionary statements will be included in the package insert:

(1) Advise women of reproductive potential to use effective contraception during treatment and for 3 months[21)] after the last dose of amivantamab.

(2) Amivantamab may be administered to pregnant women or women who may be pregnant only if the expected therapeutic benefits outweigh the possible risks.

(3) The decision to continue or discontinue breastfeeding should be made taking account of the therapeutic benefits of amivantamab and the benefits of breastfeeding nutrition.

5.6 Other toxicity studies

5.6.1 Local tolerance

Local tolerance to intravenous administration of amivantamab was assessed in a 3-month intravenous toxicity study in cynomolgus monkeys (CTD4.2.3.2.3). There was no amivantamab-related irritation at the administration sites following administration of amivantamab at a concentration (50 mg/mL) higher than the maximum concentration in clinical use (8.4 mg/mL) (Table 12). Local tolerance to subcutaneous administration of amivantamab with or without recombinant human hyaluronidase PH20 (rHuPH20) was assessed in cynomolgus monkeys (Table 13), and no local irritation was observed.

[21)] Based on "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) and the reproductive and developmental toxicity of amivantamab, this contraception period was recommended taking account of the $t_{1/2}$ (13.7 days) of amivantamab in humans [see Section 6.2.2].

Table 13. Local tolerance study

Type of study	Test system	Test method	Noteworthy findings	Attached document CTD
Dermal irritation study	Male cynomolgus monkey	Two weekly subcutaneous doses of amivantamab (125 mg/kg) with or without rHuPH20 (2,000 IU/mL) were administered, and dermal irritation was evaluated by the Draize method.	Amivantamab alone group Score 0, No irritation Amivantamab + rHuPH20 group Score 0, No irritation	4.2.3.6.1

5.6.2 Tissue cross-reactivity

Tissue cross-reactivity studies using normal human tissues were conducted. Amivantamab membrane staining was observed in the epithelium of multiple tissues, perineural sheath cells, and placental decidual cells (Table 14). Amivantamab was cross-reactive with the cytoplasm, cytoplasmic processes, cytoplasmic granules, and/or cytoplasmic globules in multiple tissue elements. The applicant explained that the binding of amivantamab in these tissues is of little toxicological significance because amivantamab is not expected to access the cytoplasm of the cells.

Table 14. Tissue cross-reactivity study

Test system	Test method	Membrane staining	Attached document CTD
Normal human tissues	Amivantamab (5 and 25 μg/mL) was applied to cryosections of normal human tissues and mixed with biotinylate F(ab')2 donkey anti-human IgG Fcγ fragment specific antibody as the secondary antibody. Then tissue binding was evaluated.	<u>Epithelium</u> Urinary bladder, breast, eye (cornea, conjunctiva, ciliary body), esophagus (mucosa, submucosal glands), kidney (tubules, parietal), liver (hepatocytes, bile ducts), lung (pneumocytes, bronchioles), pancreas (ducts), pituitary (Rathke's), placenta (trophoblasts), prostate, salivary gland (ducts), skin (epidermis, hair follicles, sweat glands, sebaceous glands), thymus (reticular), tonsil (squamous), ureter (mucosa), and uterus-cervix (mucosa, external ostium) <u>Neural elements</u> Perineural sheath cells in the urinary bladder, eye (ocular nerves), fallopian tube, esophagus, small intestine (myenteric plexus and peripheral nerve), heart, liver, lymph node, pancreas, peripheral nerve, prostate, salivary gland, skin, spinal cord (nerve roots), skeletal muscle, testis, thyroid, tonsil, ureter, and uterus-cervix <u>Other cells</u> Placental decidual cells	4.2.3.7.7.2

5.6.3 Cytokine release assay

The cytokine release profile for amivantamab was evaluated using human whole blood (Table 15), and no increases in cytokine concentrations were observed.

Table 15. Cytokine release assay

Test system	Test method	Noteworthy findings	Attached document CTD
Human whole blood	Amivantamab (approximately 148.3 μg/mL) was incubated with human whole blood for 48 hours, and concentrations of cytokines (IL-1β, IL-2, IL-4, IL-6, IL-8, IL-10, IL-12p70, IL-17, IL-18, IFN-γ, TNF-α [the monomer and trimer]) were determined.	No increases in cytokine concentrations	4.2.3.7.7.3 (Reference data)

5.6.4 Hemocompatibility/hemolytic potential study

The hemocompatibility and hemolytic potential of amivantamab were evaluated using human serum and human blood, respectively (Table 16), and no serum agglutination/precipitation or relevant hemolysis occurred.

Table 16. Hemocompatibility/hemolytic potential study

Test system	Test method	Noteworthy findings	Attached document CTD
Human serum	Amivantamab (0.025-25 mg/mL) was incubated with human serum for 40 minutes, and serum compatibility of amivantamab was evaluated.	No precipitation	4.2.3.7.7.4 (Reference data)
Human blood	Amivantamab (0.025-25 mg/mL) was incubated with diluted human blood for 40 minutes, and hemolytic potential of amivantamab was evaluated.	No hemolysis	4.2.3.7.7.5 (Reference data)

5.R Outline of the review conducted by PMDA

On the basis of the submitted data and the considerations in the following sections, PMDA concluded that the applicant's explanation about the toxicity of amivantamab is acceptable.

5.R.1 Effects on gastric mucosa

In a repeated-dose toxicity study in cynomolgus monkeys (3 months), abnormal findings related to mucosal degeneration and regeneration in the stomach occurred at both the low and high doses of amivantamab. These findings were observed in the amivantamab group only, and the incidence of these findings was higher than the historical control range of the laboratory.

The applicant's explanation:
Since both EGFR and MET are expressed in human gastric mucosa (*Anticancer Res*. 2003; 23: 3639-50 and *Int J Cancer*. 1991; 49: 323-8), and inhibition of EGFR or MET in the gastric mucosa may cause epithelial degeneration, a relationship between amivantamab and the above findings cannot be ruled out. However, given that the above findings were of minimal severity, and that there were no effects on food consumption or body weight or no associated clinical signs or clinical pathological changes, these findings were less adverse, and the effects of amivantamab on the gastric mucosa are unlikely to become a safety problem in the clinical use of amivantamab.

PMDA accepted the applicant's explanation.

5.R.2 Effects on renal tubules

In a repeated-dose toxicity study in cynomolgus monkeys (3 months), tubular regeneration in the kidney occurred at both the low and high doses of amivantamab. This finding was observed in the amivantamab group only, and its incidence was higher than the historical control range of the laboratory.

The applicant's explanation:
Since both EGFR and MET are expressed in human renal tubular cells (*Anticancer Res*. 2003; 23: 3639-50, *Int J Cancer*. 1991; 49: 323-8, *J Urol*. 2004; 171: 2166-70), and inhibition of EGFR or MET in the renal tubules may cause epithelial degeneration, a relationship between amivantamab and the above finding cannot be ruled out. However, given that the above finding was of minimal severity, and that there were no abnormal renal function parameters, the finding was less adverse, and the effects of amivantamab on the renal tubules are unlikely to become a safety problem in the clinical use of amivantamab.

PMDA accepted the applicant's explanation.

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

6.1 Summary of biopharmaceutic studies and associated analytical methods

Amivantamab in human serum was quantified by ECL (LLOQ, 0.32 μg/mL). Anti-amivantamab antibodies in human serum were detected by ECL.

6.2 Clinical pharmacology

6.2.1 Global studies

6.2.1.1 Global phase I study (CTD5.3.5.2.2, Study EDI1001 Amivantamab monotherapy cohorts [ongoing since May 2016 (data cutoff date of February 26, 2021[22])])

An open-label, uncontrolled study was conducted in 489 patients with unresectable advanced or recurrent NSCLC (326 included in the PK analysis) to evaluate the PK and other aspects of amivantamab. The dosing regimens are shown below, and serum amivantamab concentrations were determined.

- Part 1

  Subjects were to receive amivantamab intravenously at the starting dose of 140 mg QW for the first 4 weeks during the 4-week cycle, then the same dose quaque 2 weeks or every 2 weeks (Q2W) during subsequent cycles. Dose escalation was to progress from 140 mg to 350, 700, 1050, 1400, and 1750 mg. In the ≥700 mg dose cohorts, 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).[23)]

- Part 2

  Subjects were to receive amivantamab intravenously (1) at 1,050 or 1,400 mg regardless of body weight or (2) at 1,050 mg for patients weighing <80 kg or 1,400 mg for patients weighing ≥80 kg QW for the first 4 weeks (Cycle 1) and Q2W in all subsequent 4-week cycles.[24)]

  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).

Table 17 shows the PK parameters of amivantamab in patients enrolled in Part 1 and patients who were enrolled in Part 2 and received amivantamab at the above dosing regimen (1). Amivantamab exposure increased in an approximately dose-proportional manner over a dose range from 350 to 1,750 mg.

[22)] The data cutoff date for the assessment of PK and the impact of anti-amivantamab antibodies on the PK of amivantamab

[23)] At the time of starting Part 1, splitting the first dose in Cycle 1 over Days 1 and 2 was not required. However, given that if an infusion was interrupted due to an infusion reaction associated with amivantamab, it would be difficult to complete the infusion within the in-use storage time after dilution, splitting the first dose in Cycle 1 over Days 1 and 2 was required after the start of Part 1 (Protocol Amendment 4 [as of March 9, 2018]).

[24)] At the time of starting Part 2, the 1,050 mg dose of amivantamab was identified as the first RP2D regardless of body weight. After the start of Part 2, weight-based dosing was adopted because the weight-based RP2D was selected (Protocol Amendment 7 [as of November 17, 2019]).

Table 17. PK parameters of amivantamab

Dosing day	Dose (mg)	n	Pre-dose concentration (μg/mL)	C_{max} (μg/mL)	t_{max} [*1] (h)	AUC[*2] (μg·h/mL)
Cycle 1 Day 1	140	2	—	45.1, 55.7	—	2,361, 2,722
	350	3	—	142 ± 23.7	—	11,316 ± 1,925
	700	10	—	276 ± 41.7[*3, 4]	—	24,133 ± 3,928
	1,050	27	—	367 ± 93.9[*3]	—	32,475 ± 9,585
	1,400	20	—	474 ± 160[*3]	—	38,691 ± 11,306
	1,750	4	—	605 ± 180[*3]	—	51,612 ± 19,115
Cycle 2 Day 1	140	3	7.56 ± 6.58	64.5 ± 13.6	5.92 (2.20, 8.67)	5,583 ± 2,230
	350	3	84.3 ± 8.96	244 ± 18.0	3.92 (2.33, 7.58)	36,084 ± 5,191
	700	9	212 ± 49.7	528 ± 122	3.97 (2.33, 8.90)	92,576 ± 22,491
	1,050	70	326 ± 114	811 ± 260[*5]	4.12 (2.03, 8.33)[*5]	147,861 ± 60,244[*6]
	1,400	22	378 ± 131	938 ± 269[*7]	3.87 (2.08, 26.6)[*7]	164,738 ± 47,993[*8]
	1,750	4	604 ± 276	1,482 ± 172[*9]	7.73 (6.28, 25.4)[*9]	296,411 ± 69,557[*9]

Mean ± SD (Individual values are listed for n = 2); —, Not calculated
*1 Median (Min., Max.), *2 AUC_{168h} on Cycle 1 Day 1, AUC_{tau} on Cycle 2 Day 1
*3 C_{max} after dosing on Day 2 because the first dose was split (350 mg on Cycle 1 Day1 and the remainder on Cycle 1 Day 2)
*4 n = 5, *5 n = 29, *6 n = 27, *7 n = 21, *8 n = 19, *9 n = 3

Table 18 shows serum amivantamab concentrations in patients who were enrolled in Part 2 and received amivantamab at the above dosing regimen (2).

Table 18. Serum amivantamab concentrations

Body weight	Dosing day	n	Pre-dose concentration (μg/mL)
<80 kg	Cycle 1 Day 8	89	124 ± 31.6
	Cycle 2 Day 1	72	343 ± 103
	Cycle 3 Day 1	57	220 ± 90.9
	Cycle 4 Day 1	38	178 ± 71.3
≥80 kg	Cycle 1 Day 8	23	138 ± 35.0
	Cycle 2 Day 1	24	349 ± 101
	Cycle 3 Day 1	18	216 ± 70.6
	Cycle 4 Day 1	12	170 ± 44.7

Mean ± SD

6.2.1.2 Global phase I study (CTD5.3.5.2.3, Study EDI1001 Amivantamab/CP cohort [ongoing since May 2016 (data cutoff date of November 15, 2022)])

An open-label, uncontrolled study was conducted in 20 patients with unresectable advanced or recurrent NSCLC (20 included in the PK analysis) to evaluate the PK and other aspects of amivantamab. Amivantamab was to be administered in combination with carboplatin and pemetrexed (CP) in 3-week cycles as shown below, and serum amivantamab concentrations were determined.

- Patients weighing <80 kg

  Patients were to receive amivantamab intravenously at 350 mg on Cycle 1 Day 1, 1,050 mg on Cycle 1 Day 2, 1,400 mg on Cycle 1 Days 8 and 15 and Cycle 2 Day 1, and 1,750 mg on Day 1 of Cycle 3 onwards.
- Patients weighing ≥80 kg

  Patients were to receive amivantamab intravenously at 350 mg on Cycle 1 Day 1, 1,400 mg on Cycle 1 Day 2, 1,750 mg on Cycle 1 Days 8 and 15 and Cycle 2 Day 1, and 2,100 mg on Day 1 of Cycle 3 onwards.

Table 19 shows the PK parameters of amivantamab.

Table 19. PK parameters of amivantamab

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 Days 1 and 2	10	—	416 ± 75.6[*3]	—	39,731 ± 7,759[*4]
	Cycle 2 Day 1	11	343 ± 94.4	939 ± 198	4.03 (2.17, 26.0)	219,835 ± 59,301[*5]
	Cycle 3 Day 1	10	211 ± 71.1	876 ± 245	3.34 (2.17, 25.4)	179,639 ± 51,605[*4]
	Cycle 6 Day 1	10	158 ± 90.0	912 ± 275	5.83 (2.27, 26.6)	179,553 ± 59,878[*4]
≥80 kg	Cycle 1 Days 1 and 2	2	—	359, 447[*3]	—	35,498, 36,370
	Cycle 2 Day 1	4	298 ± 98.2	865 ± 58.7[*6]	2.27 (2.03, 4.25)[*6]	192,714, 214,543
	Cycle 3 Day 1	3	146 ± 62.7	824 ± 32.3	4.20 (2.42, 7.63)	148,069 ± 35,237
	Cycle 6 Day 1	3	96.4 ± 22.2	642 ± 192	2.28 (2.08, 4.17)	127,464 ± 21,151

Mean ± SD (Individual values are listed for n = 2); —, Not calculated
*1 Median (Min., Max.), *2 AUC_{168h} on Cycle 1 Day1, AUC_{tau} for Cycle 2 onwards, *3 C_{max} after dosing on Cycle 1 Day 2
*4 n = 9, *5 n = 10, *6 n = 3

6.2.1.3 Global phase III study (CTD5.3.5.1.1, PAPILLON study [ongoing since December 2020 (data cutoff date of May 3, 2023)])

A randomized, open-label study was conducted in 306 patients with EGFRex20 insertion mutation-positive unresectable advanced or recurrent NSCLC previously untreated with chemotherapy (151 in the amivantamab/CP group, 155 in the CP group) (151 included in the PK analysis) to assess the efficacy and safety of amivantamab/CP as compared with CP. Amivantamab was to be administered in combination with CP in 3-week cycles as shown below, and serum amivantamab concentrations were determined.

- Patients weighing <80 kg

  Patients were to receive amivantamab intravenously at 350 mg on Cycle 1 Day 1, 1,050 mg on Cycle 1 Day 2, 1,400 mg on Cycle 1 Days 8 and 15 and Cycle 2 Day 1, and 1,750 mg on Day 1 of Cycle 3 onwards.
- Patients weighing ≥80 kg

  Patients were to receive amivantamab intravenously at 350 mg on Cycle 1 Day 1, 1,400 mg on Cycle 1 Day 2, 1,750 mg on Cycle 1 Days 8 and 15 and Cycle 2 Day 1, and 2,100 mg on Day 1 of Cycle 3 onwards.

Table 20 shows the PK parameters of amivantamab.

Table 20. Serum amivantamab concentrations

Body weight	Dosing day	n	Pre-dose concentration (μg/mL)	n	End of infusion concentration (μg/mL)
<80 kg	Cycle 1 Day 2	82	105 ± 76.8	105	421 ± 130
	Cycle 2 Day 1	91	371 ± 110	78	902 ± 222
	Cycle 3 Day 1	79	186 ± 119	83	816 ± 233
	Cycle 5 Day 1	62	175 ± 169	47	723 ± 237
	Cycle 7 Day 1	53	160 ± 89.2	50	827 ± 194
≥80 kg	Cycle 1 Day 2	15	66.7 ± 24.6	17	442 ± 113
	Cycle 2 Day 1	11	332 ± 95.3	10	847 ± 291
	Cycle 3 Day 1	9	154 ± 71.2	10	827 ± 222
	Cycle 5 Day 1	8	134 ± 56.0	6	677 ± 136
	Cycle 7 Day 1	8	132 ± 75.3	9	669 ± 339

Mean ± SD

6.2.2 PPK analysis

Using the pooled data from Study EDI1001 and the PAPILLON study, the PPK model developed based on the amivantamab PK data[25] obtained from Study EDI1001 was updated. Analyses using the updated PPK model are summarized below.

Based on the amivantamab PK data (639 subjects, 16,321 sampling points),[26] PPK analysis was performed using the nonlinear mixed-effects modelling (software used: NONMEM Version 7.5.0). The PK of amivantamab were described by a 2-compartment model with parallel linear and nonlinear Michaelis-Menten eliminations.

In this analysis, using the model including (1) body weight and sex as covariates on CL and (2) body weight as a covariate on V1, age, body weight, sex, race, albumin, and coadministration with chemotherapy were tested as covariates on the CL, V1, and V2 of amivantamab. (i) Age, body weight, sex, and albumin, (ii) body weight and sex, and (iii) body weight were identified as significant covariates on (i) CL, (ii) V1, and (iii) V2 of amivantamab.

The applicant's explanation about the results of this analysis:

- Body weight

  Given that a weight-based dosing regimen (a cutoff of 80 kg) was selected for the PAPILLON study based on the PK data obtained from Study EDI1001 [see Sections 7.1.1.1, 7.1.1.3, etc.], a weight-based dosing regimen (a cutoff of 80 kg) was proposed. The estimated geometric mean ratio of the $AUC_{3weeks,\ ss}$ at the proposed dosing regimen for (2) patients weighing ≥80 kg vs. (1) patients weighing <80 kg [90% confidence interval (CI)] was 0.94 [0.85, 1.04], showing no clear differences in amivantamab exposure between the above (1) and (2) patients. Thus, the proposed weight-based dosing regimen (a cutoff of 80 kg) is appropriate.
- Sex

  Although the estimated geometric mean ratio of the $AUC_{3weeks,\ ss}$ at the proposed dosing regimen for female patients vs. male patients [90% CI] was 1.32 [1.25, 1.40], there was no clear relationship between amivantamab exposure and efficacy [see Section 6.2.3.1], nor was there any trend towards a higher incidence of adverse events in female patients than in male patients.[27] Given these findings, sex is unlikely to have a clinically relevant effect on the PK of amivantamab.
- Age and albumin

  Since the following results indicate that age and albumin have no clear effect on amivantamab exposure, age and albumin are unlikely to have a clinically relevant effect on the PK of amivantamab.

[25] 439 subjects, 13,440 sampling points (data cutoff date of February 26, 2021)

[26] For the patients included in the analysis, patient demographics [median (min., max.)] or the number of patients in each category are shown below. Age, 62.0 (27.0, 87.0) years; body weight, 61.1 (35.4, 140) kg; sex, 252 men and 387 women; race, 205 white patients, 387 Asian patients, and 47 patients with other race; albumin, 40.0 (23.0, 52.8) g/L; 171 patients with coadministered chemotherapy and 468 patients without coadministered chemotherapy

[27] In the amivantamab/CP group of the PAPILLON study, the incidences of (1) adverse events of any grade, (2) Grade ≥3 adverse events, (3) adverse events leading to death, and (4) serious adverse events were (1) 100% in male patients and 100% in female patients, (2) 74.6% in male patients and 76.2% in female patients, (3) 7.5% in male patients and 2.4% in female patients, and (4) 44.8% in male patients and 31.0% in female patients. For adverse events whose incidences tended to increase with increasing amivantamab exposure [see Section 6.2.3.2], there was no trend towards a higher incidence in female patients than in male patients.

- The estimated geometric mean ratios of the $AUC_{3weeks, ss}$ of amivantamab for (1) patients aged ≥65 and <75 years and (2) patients aged ≥75 years vs. patients aged <65 years [90% CI] were (1) 1.11 [1.04, 1.19] and (2) 1.09 [0.96, 1.24].
- The estimated geometric mean ratio of the $AUC_{3weeks, ss}$ of amivantamab for patients with albumin <40.0 g/L vs. patients with albumin ≥40.0 g/L [90% CI] was 0.97 [0.91, 1.04].

Based on the results of the above PPK analysis, following administration of amivantamab at the proposed dosing regimen, (1) the $t_{1/2}$ was estimated at 13.7 days, and (2) steady-state amivantamab exposure was predicted to be reached by Week 13.

6.2.3 Exposure-efficacy/safety relationship

Based on the results from the amivantamab/CP group in the PAPILLON study, the relationships between amivantamab exposure and efficacy/safety were explored. Amivantamab exposure was predicted from the PPK analysis [see Section 6.2.2].

6.2.3.1 Exposure-efficacy relationship

The relationship between amivantamab exposure (the pre-dose concentration on Cycle 1 Day 8, the maximum C_{trough}, C_{avg} in Cycle 1) and progression-free survival (PFS) as assessed by blinded independent central review (BICR) according to Response Evaluation Criteria in Solid Tumors (RECIST) ver.1.1 was explored. There was no clear relationship between amivantamab exposure and the above PFS.

6.2.3.2 Exposure-safety relationship

The relationship between amivantamab exposure (the maximum C_{eoi}, C_{avg} in Cycle 1) and rash of any grade, Grade ≥3 rash, or paronychia, hypoalbuminaemia, nausea, or constipation of any grade was explored. The incidences of rash, paronychia, hypoalbuminaemia, and constipation of any grade tended to increase with increasing amivantamab exposure. On the other hand, there was no clear relationship between amivantamab exposure and the incidence of Grade ≥3 rash or nausea of any grade.

6.2.4 Effect of decreased renal or hepatic function on PK of amivantamab

No clinical studies to evaluate the PK of amivantamab in patients with renal or hepatic impairment have been conducted. The applicant explained that given the following points etc., decreased renal or hepatic function is unlikely to affect the PK of amivantamab.

- Since amivantamab is an antibody drug, it is expected to be catabolized into small peptides and amino acids and cleared.
- In the PPK analysis,[28)] creatinine clearance (CrCL) or hepatic impairment[29)] was not identified as a significant covariate on the PK of amivantamab.

[28)] The PPK analysis was performed based on amivantamab PK data obtained from Study EDI1001 (362 subjects, 8,756 sampling points, data cutoff date of March 31, 2020) (software used, NONMEM Version 7.3.0).
[29)] Classified by the National Cancer Institute Organ Dysfunction Working Group (NCI-ODWG) criteria.

6.2.5 Differences in PK of amivantamab between Japanese and non-Japanese populations

The applicant's explanation:

Since there were no clear differences in pre-dose and end of infusion serum amivantamab concentrations between Japanese and non-Japanese patients in the amivantamab/CP group of the PAPILLON study (Table 21), there should be no clear differences in the PK of amivantamab between Japanese and non-Japanese populations.

Table 21. Serum amivantamab concentrations

Dosing day	Japanese patients				Non-Japanese patients			
	n	Pre-dose concentration (μg/mL)	n	End of infusion concentration (μg/mL)	n	Pre-dose concentration (μg/mL)	n	End of infusion concentration (μg/mL)
Cycle 1 Day 2	18	89.6 ± 26.5	18	434 ± 143	79	101 ± 79.4	104	423 ± 126
Cycle 2 Day 1	14	393 ± 104	13	1,002 ± 243	88	363 ± 110	75	877 ± 223
Cycle 3 Day 1	13	224 ± 62.3	14	936 ± 177	75	175 ± 121	79	796 ± 234
Cycle 5 Day 1	6	168 ± 96.4	5	757 ± 211	64	170 ± 166	48	714 ± 230
Cycle 7 Day 1	4	223 ± 15.5	5	886 ± 269	57	152 ± 88.6	54	795 ± 223

Mean ± SD

6.R Outline of the review conducted by PMDA

On the basis of the submitted data and the considerations in the following section, PMDA concluded that the applicant's explanation about the clinical pharmacology etc. of amivantamab is acceptable.

6.R.1 Impact of anti-amivantamab antibodies on PK of amivantamab

The applicant's explanation about the impact of anti-amivantamab antibodies on the PK of amivantamab:

The incidence of anti-amivantamab antibodies was determined in Study EDI1001 and the PAPILLON study. Since >400 μg/mL of amivantamab was considered to interfere with the anti-amivantamab antibody assay, patients with ≥1 post-dose sample having an amivantamab concentration ≤400 μg/mL were classified as evaluable subjects (465 subjects in Study EDI1001, 198 subjects in the PAPILLON study), and patients with all analyzed samples after receiving amivantamab having an amivantamab concentration >400 μg/mL were classified as unevaluable subjects (25 subjects in Study EDI1001, 1 subject in the PAPILLON study). Anti-amivantamab antibodies were detected in 3 subjects[30] (0.6%) in Study EDI1001 among the evaluable subjects. At least 1 sample had an amivantamab concentration >400 μg/mL in 158 evaluable subjects (99 subjects in Study EDI1001, 59 subjects in the PAPILLON study).

Table 22 shows serum amivantamab concentrations in (1) an anti-amivantamab antibody-positive patient and (2) antibody-negative patients among patients who received 1,400 mg amivantamab with time-matched PK/anti-amivantamab antibody assay data in the amivantamab monotherapy cohort of Study EDI1001. There was no trend towards clear differences in serum amivantamab concentrations between the above patients (1) and (2). However, given that the limited number of patients tested positive for anti-amivantamab antibodies, it is difficult at present to draw a definitive conclusion on the impact of anti-amivantamab antibodies on the PK of amivantamab.

[30] Anti-amivantamab antibodies were detected in a sample obtained during the amivantamab treatment period in 1 subject who received 1,400 mg amivantamab among the 3 subjects who tested positive for anti-amivantamab antibodies.

Table 22. Serum amivantamab concentrations in anti-amivantamab antibody-positive or negative patients

Dosing day	Antibody-positive patient		Antibody-negative patients	
	N	Pre-dose concentration (μg/mL)	N	Pre-dose concentration (μg/mL)
Cycle 2 Day 1	1	443	75	414 ± 133
Cycle 3 Day 1	1	257	66	257 ± 100
Cycle 4 Day 1	1	204	51	221 ± 92.9

Mean ± SD or individual values

PMDA's view:

Given that some or all of the samples had an amivantamab concentration above a threshold that interferes with the anti-amivantamab antibody assay in 184 of 689 patients assessed for anti-amivantamab antibodies after receiving amivantamab in Study EDI1001 and the PAPILLON study, it is difficult to draw a definitive conclusion on the impact of anti-amivantamab antibodies on the PK of amivantamab, with the anti-amivantamab antibody assay used in these studies. Thus, the applicant should continue to collect information on the impact of anti-amivantamab antibodies on the PK of amivantamab, and if any new findings become available, the information should be provided appropriately to healthcare professionals in clinical practice.

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 23.

Table 23. Listing of efficacy and safety clinical studies

Data category	Geographical location	Study ID	Phase	Study population	Number of patients enrolled		Dosing regimen	Main endpoints
Evaluation	Global	EDI1001	I	Patients with unresectable advanced or recurrent NSCLC	Amivantamab monotherapy cohorts	Part 1: 80 Part 2: 409	[Part 1] Amivantamab 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,[*1] 1,050,[*1] 1,400,[*1] and 1,750[*1] mg. [Part 2] Amivantamab[*1, 2] administered intravenously QW in the first 4-week cycle and Q2W for subsequent cycles.	Tolerability Safety Efficacy PK
					Combination cohorts	[Amivantamab/ CP cohort] 20	Amivantamab[*3]/CP[*3]	
						[Amivantamab/ lazertinib cohort] Part 1: 63 Part 2: 45	[Part 1] Amivantamab [*1, 4] administered intravenously QW in the first 4-week cycle and Q2W for subsequent cycles, in combination with lazertinib (unapproved in Japan) 240 mg QD. [Part 2] Amivantamab[*1, 2] administered intravenously QW in the first 4-week cycle and Q2W for subsequent cycles, in combination with lazertinib (unapproved in Japan) 240 mg QD.	
		PAPILLON	III	Patients with EGFR ex20 insertion mutation-positive unresectable advanced or recurrent NSCLC previously untreated with chemotherapy	308 (1) 153 (2) 155		(1) Amivantamab[*3]/CP[*3] (2) CP[*3]	Efficacy Safety

*1 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).
*2 1,050 mg for patients weighing <80 kg and 1,400 mg for patients weighing ≥80 kg
*3 See Table 24 for the dosing regimens of amivantamab and CP.
*4 (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

These clinical studies are summarized below. Table 24 shows the dosing regimens of amivantamab and CP used in the amivantamab/CP cohort of Study EDI1001 and the PAPILLON study. The main adverse events other than deaths observed in the clinical studies are described in Section "7.2 Adverse events etc. observed in clinical studies."

Table 24. Dosing regimens of amivantamab and CP used in amivantamab/CP cohort of Study EDI1001 and PAPILLON study

Amivantamab	Amivantamab was to be administered intravenously in 3-week cycles according to the following dosing regimen. ● Patients weighing <80 kg Amivantamab 350 mg on Cycle 1 Day 1, 1,050 mg on Cycle 1 Day 2, 1,400 mg on Cycle 1 Days 8 and 15, 1,400 mg on Cycle 2 Day 1, and 1,750 mg on Day 1 of Cycle 3 onwards ● Patients weighing ≥80 kg Amivantamab 350 mg on Cycle 1 Day 1, 1,400 mg on Cycle 1 Day 2, 1,750 mg on Cycle 1 Days 8 and 15, 1,750 mg on Cycle 2 Day 1, and 2,100 mg on Day 1 of Cycle 3 onwards
CP	Carboplatin at an AUC of 5 mg·mL/min and pemetrexed at a dose of 500 mg/m^2 were to be administered intravenously on Day 1 of each 3-week cycle for 4 cycles, and then pemetrexed at a dose of 500 mg/m^2 was to be administered intravenously on Day 1 of each 3-week cycle.

7.1 Evaluation data

7.1.1 Global studies

7.1.1.1 Global phase I study (CTD5.3.5.2.1, 5.3.5.2.2, Study EDI1001 Amivantamab monotherapy cohorts [ongoing since May 2016 (data cutoff date of March 30, 2021)])

An open-label, uncontrolled study was conducted at 53 sites in 10 countries or regions including Japan to evaluate the tolerability, safety, efficacy, etc. of amivantamab in patients with unresectable advanced or recurrent NSCLC (target sample size, ≥3 subjects/dose cohort in Part 1, up to 460 subjects[31)] in Part 2).

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

- Part 1

  Subjects were to receive amivantamab intravenously at the starting dose of 140 mg QW[32)] for the first 4 weeks during the 4-week cycle, then Q2W during subsequent cycles. Dose escalation was to progress from 140 mg to 350, 700, 1050, 1400, and 1750 mg.

  In the ≥700 mg dose cohorts, 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).[23)]

- Part 2

  Subjects were to receive amivantamab (1,050 mg for patients weighing <80 kg, 1,400 mg for patients weighing ≥80 kg)[24)] intravenously QW for the first 4 weeks (Cycle 1) and Q2W in all subsequent 4-week cycles.

  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 489 subjects enrolled in the study (80 in Part 1, 409 in Part 2) received amivantamab and were included in the safety population (including 18 Japanese patients in Part 1 and 19 Japanese patients in Part 2).

In Part 1 of this study, the dose-limiting toxicity (DLT) evaluation period lasted until 28 days after the start of amivantamab treatment. In non-Japanese patients, (1) the tolerability of amivantamab 140 to 1,400 mg was

[31)] Part 2 consisted of the following 6 cohorts.

A	Patients who had progressed following treatment with an EGFR inhibitor and had an identified EGFR-based mechanism of resistance (target sample size, 40 subjects)
B	Patients who had progressed following treatment with an EGFR inhibitor and did not have EGFR-based mechanism of resistance (target sample size, 20 subjects)
C	Patients with primary *EGFR* mutated disease, with a documented *EGFR* alteration (e.g., C797S) mediating resistance to previous treatment with a third generation EGFR-TKI (e.g., osimertinib) (target sample size, up to 100 subjects)
D	Patients with EGFRex20 insertion disease who had not previously been treated with an EGFR-TKI with known activity against EGFRex20 insertion mutation-positive NSCLC (e.g., poziotinib [unapproved in Japan]) and had progressed on or intolerant to prior platinum-based chemotherapy (target sample size, up to 100 subjects)
MET-1	Patients with documented primary EGFR mutated disease and documented *MET* amplification or *MET* mutation after progression on any EGFR-TKI. Patients had progressed on or intolerant to prior platinum-based chemotherapy (target sample size, up to 100 subjects)
MET-2	Patients with *MET* exon 14 skipping disease (target sample size, up to 100 subjects)

[32)] For early achievement of the preclinically established target serum amivantamab concentration for efficacy, the dosing interval in Cycle 1 was shorter than that in subsequent cycles. According to the results of PPK analysis based on amivantamab PK data obtained from Part 1 of Study EDI1001 (15 subjects, 336 sampling points), the proportions of patients achieving the target serum amivantamab concentration after dosing on Cycle 1 Day 8 when administered QW and after dosing on Cycle 1 Day 15 when administered Q2W were estimated at ≥95% and 71%, respectively.

evaluated, and no DLTs were observed.[33)] Taking account of (1) and (2) amivantamab PK data[34)] etc., the recommended Phase II dose (RP2D) of amivantamab monotherapy was determined to be 1,050 mg. During Part 2, based on amivantamab PK data[35)] etc. obtained from patients enrolled in Part 1 and Part 2, the RP2D of amivantamab monotherapy was modified to 1,050 mg for patients weighing <80 kg and 1,400 mg for patients weighing ≥80 kg.

Regarding safety, 1 of 14 subjects (7.1%) in the 700 mg cohort and 2 of 25 subjects (8.0%) in the 1,050 mg cohort of Part 1 and 23 of 406 subjects (5.7%) in Part 2 died during the amivantamab treatment period or within 30 days after the last dose of amivantamab, and there were no deaths in other dose cohorts of Part 1 (No Japanese patients died). The causes of deaths other than progressive disease (1 subject in the 1,050 mg cohort of Part 1, 7 subjects in Part 2) were pneumonia (1 subject in the 700 mg cohort) and respiratory failure (1 subject in the 1,050 mg cohort) in Part 1 and pneumonia (4 subjects); respiratory failure (2 subjects); and pneumonia aspiration; sudden death; pulmonary sepsis; adenovirus infection; sepsis; atypical pneumonia; aspiration; acute respiratory failure; cardiac arrest; and others (respiratory failure) (1 subject each) in Part 2. A causal relationship to study drug was denied for all causes of deaths classified as adverse events.[36)]

7.1.1.2 Global phase I study (CTD5.3.5.2.3, Study EDI1001 Combination cohorts (amivantamab/CP cohort and amivantamab/lazertinib 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 amivantamab in patients with unresectable advanced or recurrent NSCLC (target sample size, up to 20 subjects in the amivantamab/CP cohort, 6 subjects per dose level in Part 1 of the amivantamab/lazertinib cohort, up to 100 subjects in Part 2 of the amivantamab/lazertinib cohort). The amivantamab/CP cohort was conducted at 13 sites in 4 countries including Japan, and Part 1 and Part 2 of the amivantamab/lazertinib cohort were conducted at 12 and 28 sites overseas, respectively. In this review report, the results from the amivantamab/CP cohort are described.

Table 24 shows the dosing regimens of amivantamab and CP[37)] in the amivantamab/CP cohort. Treatment was to continue until disease progression or any criterion for treatment discontinuation was met.

[33)] After tolerability in non-Japanese patients was demonstrated, the tolerability of amivantamab in Japanese patients enrolled in Part 1 of Study EDI1001 (3 subjects in the 700 mg cohort, 4 subjects in the 1,050 mg cohort, 5 subjects in the 1,400 mg cohort, 3 subjects in the 1,750 mg cohort) was evaluated. No DLTs were observed.

[34)] According to the results of PPK analysis based on PK data following administration of amivantamab 140 to 1,050 mg obtained from Part 1 of Study EDI1001 (15 subjects, 336 sampling points), the proportions of patients achieving the preclinically established target serum amivantamab concentration for efficacy were estimated at approximately 50% at a dose of 700 mg and approximately 95% at a dose of 1,050 mg.

[35)] According to the results of PPK analysis based on amivantamab PK data obtained from Part 1 and Part 2 of Study EDI1001 (80 subjects, 1,758 sampling points), (1) body weight and sex, (2) body weight, and (3) body weight and sex were identified as covariates on (1) CL, (2) V1, and (3) V2 of amivantamab. The PPK analysis predicted that there would be no clear differences in amivantamab exposure (C_{avg} at steady state) between the dose of 1,050 mg in patients weighing <80 kg and the dose of 1,400 mg in patients weighing ≥80 kg. The PPK analysis based on amivantamab PK data obtained from Study EDI1001 and the PAPILLON study also predicted that there would be no clear differences in amivantamab exposure ($AUC_{3weeks, ss}$) between the dose of 1,050 mg in patients weighing <80 kg and the dose of 1,400 mg in patients weighing ≥80 kg [see Section 6.2.2].

[36)] 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.

[37)] Given that CP to be combined with amivantamab was to be administered in 3-week cycles, a dosing regimen of amivantamab using a 3-week cycle was selected to achieve comparable amivantamab exposures (pre-dose concentrations on Cycle 2 Day 1 and at steady state) to the RP2D regimen of amivantamab monotherapy using a 4-week cycle, which was determined in the amivantamab monotherapy cohorts of Study EDI1001. There were no clear differences in serum amivantamab concentrations between the amivantamab/CP and amivantamab monotherapy cohorts of Study EDI1001 [see Table 18 and Table 19].

All of 20 subjects enrolled in the amivantamab/CP cohort received amivantamab and were included in the safety population (including 4 Japanese patients).

In the amivantamab/CP cohort, the DLT evaluation period lasted until 21 days after the start of amivantamab treatment. No DLTs were observed, and the tolerability of amivantamab/CP at the dosing regimens used in this study was demonstrated.[38)]

Regarding safety, 1 of 20 subjects (5.0%) in the amivantamab/CP cohort died during the amivantamab treatment period or within 30 days after the last dose of amivantamab (No Japanese patients died). The cause of death was pneumonia, and its causal relationship to study drug was denied.

7.1.1.3 Global phase III study (CTD5.3.5.1.1, PAPILLON study [ongoing since December 2020 (data cutoff date of May 3, 2023)])

A randomized, open-label study was conducted at 131 sites in 24 countries or regions including Japan to assess the efficacy and safety of amivantamab/CP compared with CP in patients with EGFRex20 insertion mutation-positive[39)] unresectable advanced or recurrent non-squamous non-small cell lung cancer (NSQ-NSCLC)[40)] previously untreated with chemotherapy[41)] (target sample size, 300 subjects[42)]).

Table 24 shows the dosing regimens of amivantamab and CP in this study. Treatment was to continue until disease progression or any criterion for treatment discontinuation was met. Patients in the CP group who had disease progression were allowed to crossover to receive amivantamab monotherapy.[43)]

All of 308 subjects who were enrolled in the study and randomized (153 in the amivantamab/CP group, 155 in the CP group) were included in the full analysis set (FAS), which was used for efficacy analyses (including 19 Japanese patients in the amivantamab/CP group and 15 Japanese patients in the CP group). After excluding 2 subjects who did not receive study drug (both in the amivantamab/CP group), 306 subjects (151 in the amivantamab/CP group, 155 in the CP group) were included in the safety population (including 19 Japanese patients in the amivantamab/CP group and 15 Japanese patients in the CP group).

The primary endpoint for the study was PFS as assessed by BICR according to RECIST ver.1.1. The primary analysis was to be performed when approximately 200 PFS events had been observed.

---

38) After tolerability in non-Japanese patients was demonstrated, the tolerability of amivantamab/CP in 4 Japanese patients enrolled in the amivantamab/CP cohort of Study EDI1001 was evaluated. No DLTs were observed.

39) Patients with a documented EGFRex20 insertion mutation by testing of (1) tumor tissue or (2) blood sample performed by a certified or accredited local laboratory were enrolled in the study. The numbers of patients by type of sample used for testing at enrollment in the amivantamab/CP and CP groups were (1) 145 and 139, respectively, and (2) 8 and 16, respectively.

40) Patients with untreated brain metastases were excluded.

41) Prior monotherapy with an EGFR-TKI (gefitinib, erlotinib, afatinib, dacomitinib, osimertinib) was allowed if all of the following criteria (1) to (4) were met.
(1) treatment duration did not exceed 8 weeks; (2) an increase in tumor burden; (3) associated toxicities had resolved to baseline; and (4) the EGFR-TKI was discontinued at least 2 weeks or 4 half-lives prior to randomization, whichever was longer.

42) A total of 200 events would provide approximately 90% power to detect a hazard ratio of the primary endpoint of PFS as assessed by BICR according to RECIST ver.1.1 for amivantamab/CP vs. CP of 0.625 at a two-sided alpha level of 0.05. Thus, a sample size was chosen taking account of the observation period etc.

43) The dosing regimen of amivantamab is shown in Table 24, and 65 subjects (including 11 Japanese patients) received amivantamab.

The results of the primary analysis of the primary efficacy endpoint of PFS as assessed by BICR according to RECIST ver.1.1 (data cutoff date of May 3, 2023) and the Kaplan-Meier curves are shown in Table 25 and Figure 3, respectively. The superiority of amivantamab/CP to CP was demonstrated.

Table 25. Results of primary analysis of PFS (BICR, FAS, data cutoff date of May 3, 2023)

	Amivantamab/CP	CP
N	153	155
No. of events (%)	84 (54.9)	132 (85.2)
Median [95% CI] (months)	11.4 [9.79, 13.7]	6.70 [5.59, 7.33]
Hazard ratio [95% CI]*1	0.395 [0.296, 0.528]	
P-value (two-sided)*2	<0.0001	

*1 A Cox proportional-hazards model stratified by ECOG PS (0, 1) and brain metastases (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

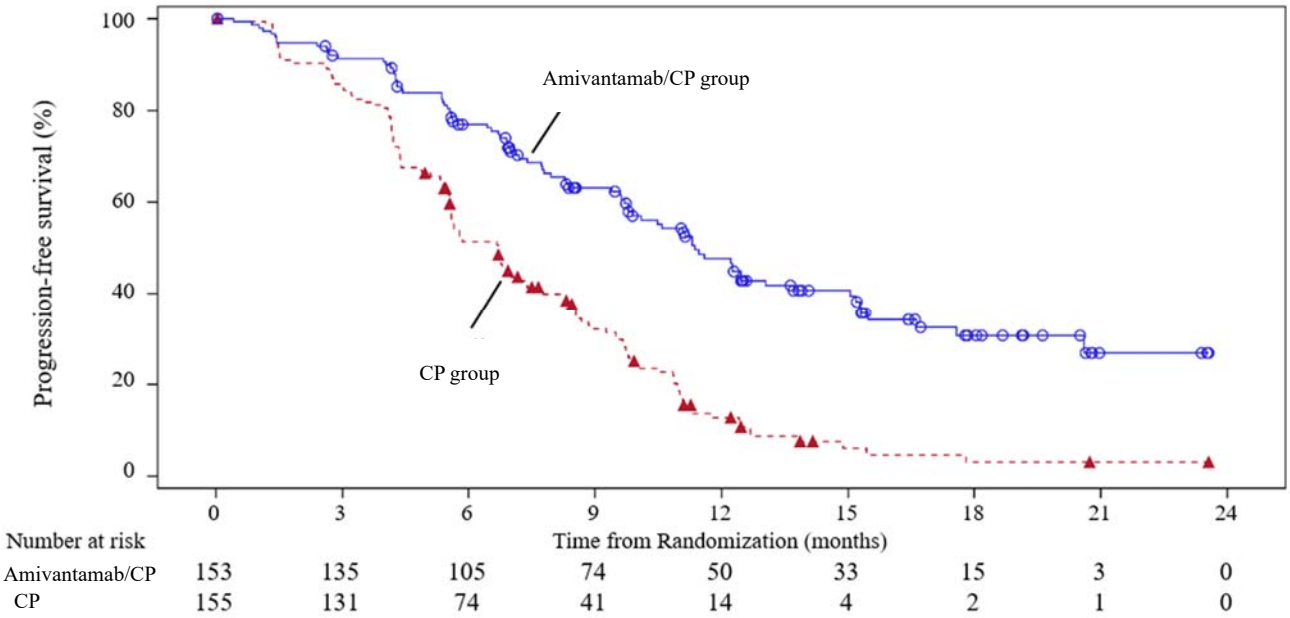


Figure 3. Kaplan-Meier curves of PFS at the time of primary analysis (BICR, FAS, data cutoff date of May 3, 2023)

Regarding safety, 7 of 151 subjects (4.6%) in the amivantamab/CP group and 4 of 155 subjects (2.6%) in the CP group died during the study treatment period or within 30 days after the last dose of study drug[44] (No Japanese patients died). The causes of deaths other than progressive disease (1 in the amivantamab/CP group, 1 in the CP group) were pneumonia; cerebrovascular accident; sepsis; COVID-19 pneumonia; COVID-19; and others (disease exacerbation) (1 subject each) in the amivantamab/CP group and acute myocardial infarction; febrile neutropenia and sepsis; and others (progressive disease and adverse reactions to chemotherapy) (1 subject each) in the CP group. A causal relationship to study drug could not be ruled out for sepsis; and COVID-19 pneumonia (1 subject each) in the amivantamab/CP group and febrile neutropenia and sepsis (1 subject) in the CP group.[36]

[44] Among patients in the CP group who had disease progression and crossed over to receive amivantamab, those who died during the crossover phase are excluded. In the CP group, 3 of 65 subjects (4.6%) died during amivantamab treatment period or within 30 days after the last dose of amivantamab (No Japanese patients died). The causes of deaths other than progressive disease (1 subject) were pneumonia; and pleural effusion (1 subject each), and a causal relationship to amivantamab was denied for both events.

7.R Outline of the review conducted by PMDA

7.R.1 Review strategy

PMDA review strategy:

Among the evaluation data submitted, the pivotal clinical study to evaluate the efficacy and safety of amivantamab is a global phase III study in patients with EGFRex20 insertion mutation-positive unresectable advanced or recurrent NSCLC previously untreated with chemotherapy (PAPILLON study). PMDA decided to focus its review on this study. The efficacy of amivantamab in Japanese patients is evaluated systematically based on the PAPILLON 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 amivantamab/CP in patients with EGFRex20 insertion mutation-positive unresectable advanced or recurrent NSQ-NSCLC previously untreated with chemotherapy was demonstrated.

7.R.2.1 Choice of control group

The applicant's explanation about the reason for selecting patients treated with CP as a control group in the PAPILLON study:

Based on the following points, patients treated with CP were selected as a control group in the PAPILLON study.

- Japanese clinical practice guidelines (Clinical Practice Guideline for Lung Cancer, the Japan Lung Cancer Society ed. [2019]) and foreign clinical practice guidelines (National Comprehensive Cancer Network Clinical Practice Guidelines in Oncology, Non-Small Cell Lung Cancer [hereinafter referred to as NCCN guidelines] [v.1.2020], etc.) used at the time of planning the PAPILLON study recommended CP as a treatment option for patients with unresectable advanced or recurrent NSQ-NSCLC previously untreated with chemotherapy.
- Patients with EGFRex20 insertions were described as follows in the Japanese and foreign clinical practice guidelines at the time of planning the PAPILLON study.
  - Japanese clinical practice guideline (2019)
    The guideline recommends against treatment with an EGFR-TKI in patients with EGFRex20 insertion mutation-positive NSCLC.
  - NCCN guidelines (v.1.2020)
    EGFRex20 insertion mutation-positive NSCLC is resistant to EGFR-TKI therapy, except for a rare variant, p.A763_Y764insFQEA.
- Although immune checkpoint inhibitor (ICI) monotherapy or ICI in combination with chemotherapy was a treatment option for patients with EGFRex20 insertion mutation-positive unresectable advanced or

recurrent NSCLC previously untreated with chemotherapy, these were not considered appropriate as a comparator in the PAPILLON study for the following reasons.

- A global phase III study assessed the efficacy and safety of ICI monotherapy. Subgroup analyses of PFS and overall survival (OS) in the study failed to demonstrate the efficacy of ICI in patients with *EGFR* mutation-positive unresectable advanced or recurrent NSCLC (*Lancet*. 2016; 387: 1540-50, *N Engl J Med*. 2015; 373: 1627-39).
- According to the Japanese clinical practice guideline (2019) at the time of planning the PAPILLON study, there is no definite evidence for recommending ICIs for patients with *EGFR* mutation-positive unresectable advanced or recurrent NSCLC.
- According to the NCCN guidelines (v.1.2020) at the time of planning the PAPILLON study, ICIs are less effective in patients with *EGFR* mutation-positive unresectable advanced or recurrent NSCLC.

PMDA accepted the applicant's explanation.

7.R.2.2 Efficacy endpoint

The applicant's explanation about the appropriateness of selecting PFS as the primary endpoint for the PAPILLON study:

In patients with EGFRex20 insertion mutation-positive unresectable advanced or recurrent NSCLC previously untreated with chemotherapy, longer PFS is expected to delay worsening of clinical symptoms associated with disease progression and is considered clinically meaningful. Thus, PFS was selected as the primary endpoint for the PAPILLON study.

PMDA's view:

Since the patient population of the PAPILLON study was to be treated with an expectation of survival benefit, OS should have been selected as the primary endpoint for the PAPILLON study. However, as the above explanation by the applicant (longer PFS in these patients is clinically meaningful) is understandable, the efficacy of amivantamab/CP can be evaluated based on the results of the primary endpoint of PFS after reviewing the results of OS in the PAPILLON study.

7.R.2.3 Results of efficacy assessment

The PAPILLON study demonstrated the superiority of amivantamab/CP to CP in the primary endpoint of PFS as assessed by BICR according to RECIST ver.1.1 [see Section 7.1.1.3].

The results of an interim analysis of OS[45)] conducted at the time of the primary analysis of PFS (data cutoff date of May 3, 2023) and the Kaplan-Meier curves are shown in Table 26 and Figure 4, respectively. Although the incidence of death within 3 months after randomization was higher in the amivantamab/CP group than in the CP group,[46)] the causes of deaths during this period (6 in the amivantamab/CP group, 1 in the CP group)

[45)] The final analysis of OS is planned to be conducted approximately 48 months after the first patient was randomized.

[46)] The incidences of death (%) (1) within 3 months, (2) from >3 months to 6 months, and (3) from >6 months to 9 months after randomization in the amivantamab/CP and CP groups were (1) 3.9 and 0.6, respectively, (2) 2.0 and 2.6, respectively, and (3) 1.3 and 7.7, respectively.

were progressive disease; cerebrovascular accident; sepsis; COVID-19; COVID-19 pneumonia; and others (disease exacerbation) (1 subject each) in the amivantamab/CP group and progressive disease in the CP group. There were no causes of deaths for which a causal relationship to amivantamab could not be ruled out in the amivantamab/CP group.[36)]

Table 26. Results of interim analysis of OS (FAS, data cutoff date of May 3, 2023)

	Amivantamab/CP	CP
N	153	155
No. of events (%)	28 (18.3)	42 (27.1)
Median [95% CI] (months)	－ [－, －]	24.38 [22.08, －]
Hazard ratio [95% CI]*	0.717 [0.441, 1.165]	

－, Not estimable, * A Cox proportional-hazards model stratified by ECOG PS (0, 1) and brain metastases (yes, no)

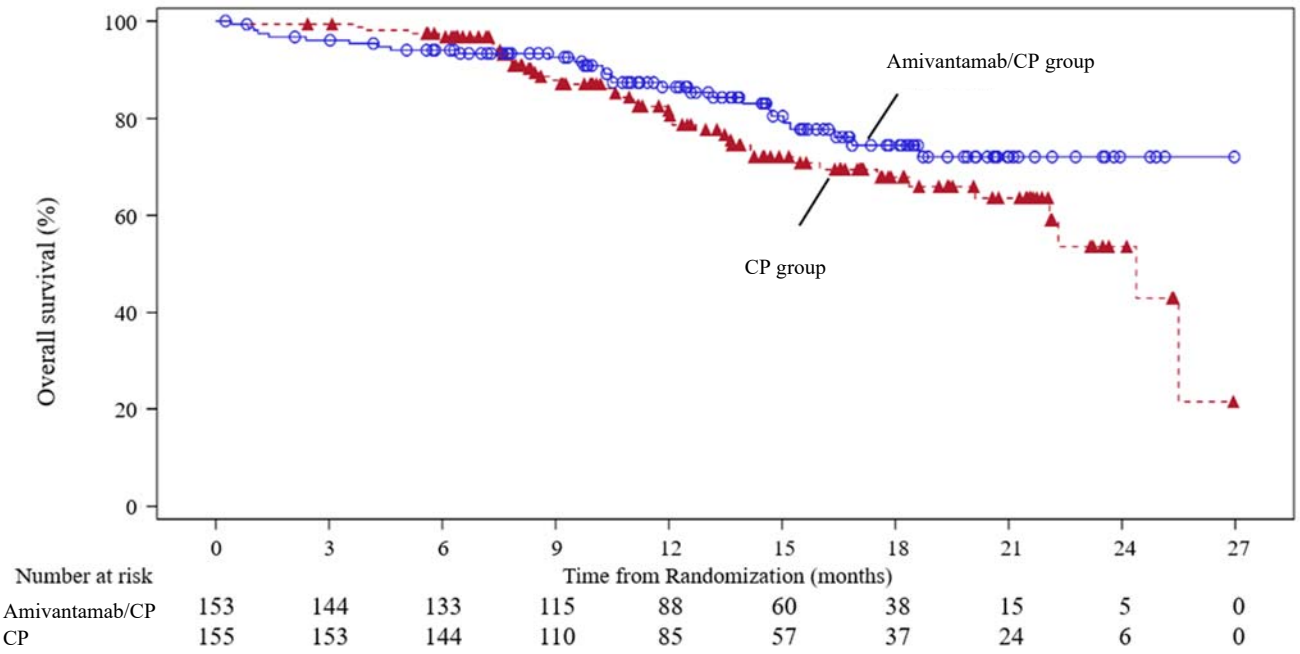


Figure 4. Kaplan-Meier curves of OS at the time of interim analysis (FAS, data cutoff date of May 3, 2023)

The results of the primary analysis of PFS and the Kaplan-Meier curves in the Japanese subgroup of the PAPILLON study are shown in Table 27 and Figure 5, respectively.

Table 27. Results of primary analysis of PFS in Japanese subgroup (BICR, FAS, data cutoff date of May 3, 2023)

	Amivantamab/CP	CP
N	19	15
No. of events (%)	10 (52.6)	15 (100)
Median [95% CI] (months)	15.47 [7.95, －]	5.59 [3.02, 7.00]
Hazard ratio [95% CI]*	0.218 [0.090, 0.529]	

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

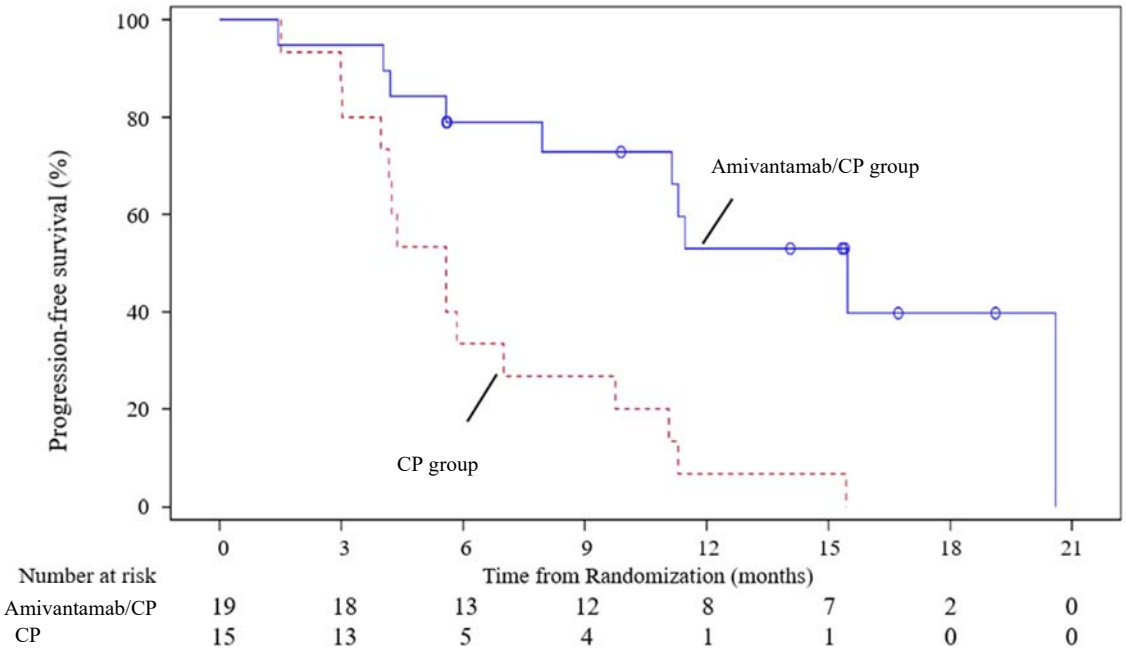


Figure 5. Kaplan-Meier curves of PFS at the time of primary analysis in Japanese subgroup (BICR, FAS, data cutoff date of May 3, 2023)

PMDA's view:

For the following reasons etc., the efficacy of amivantamab/CP was demonstrated in patients with EGFRex20 insertion mutation-positive unresectable advanced or recurrent NSCLC previously untreated with chemotherapy.

- The PAPILLON study demonstrated the superiority of amivantamab/CP to CP in the primary endpoint of PFS as assessed by BICR, and the PFS benefit derived from amivantamab/CP was clinically meaningful.
- The PAPILLON study showed no trend towards shorter OS in the amivantamab/CP group than in the CP group.
- The results of PFS in the Japanese subgroup showed a similar trend to those of the overall population. For this reason, among others, the efficacy of amivantamab/CP is expected also in Japanese patients.

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

PMDA's conclusion:

Based on the following considerations, adverse events that require particular attention following administration of amivantamab/CP are infusion reactions, interstitial lung disease (ILD), skin disorders (including paronychia), venous thromboembolism, fluid retention (including oedema and hypoalbuminemia), and diarrhoea.

Although attention should be paid to the possible occurrence of the above adverse events during the use of amivantamab, amivantamab/CP 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 amivantamab or the concomitant anti-neoplastic drugs.

7.R.3.1 Safety profile

The applicant's explanation about the safety profile of amivantamab/CP based on the safety information from the PAPILLON study:

Safety data from the PAPILLON study are summarized in Table 28. Table 29 shows adverse events reported at a higher incidence in the amivantamab/CP group than in the CP group. There were no adverse events leading to death that were reported at a ≥1% higher incidence in the amivantamab/CP group than in the CP group.

Table 28. Summary of safety data (PAPILLON study, data cutoff date of May 3, 2023)

	n (%)	
	Amivantamab/CP N = 151	CP N = 155
All adverse events	151 (100)	152 (98.1)
Grade ≥3 adverse events	114 (75.5)	83 (53.5)
Adverse events leading to death	7 (4.6)	4 (2.6)
Serious adverse events	56 (37.1)	48 (31.0)
Adverse events leading to treatment discontinuation*	36 (23.8)	16 (10.3)
Amivantamab	17 (11.3)	—
Carboplatin or pemetrexed	31 (20.5)	16 (10.3)
Adverse events leading to dose or infusion interruption*	122 (80.8)	56 (36.1)
Amivantamab	117 (77.5)	—
Carboplatin or pemetrexed	88 (58.3)	56 (36.1)
Adverse events leading to dose reduction*	73 (48.3)	35 (22.6)
Amivantamab	54 (35.8)	—
Carboplatin or pemetrexed	43 (28.5)	35 (22.6)
Adverse events leading to reduction in infusion rate of amivantamab	41 (27.2)	—

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

Table 29. Adverse events reported at a higher incidence[*1] in the amivantamab/CP group than in the CP group (PAPILLON study, data cutoff date of May 3, 2023)

PT (MedDRA ver.25.0)	n (%)	
	Amivantamab/CP N = 151	CP N = 155
All adverse events		
Paronychia	85 (56.3)	0
Rash	81 (53.6)	12 (7.7)
Infusion related reaction	63 (41.7)	2 (1.3)
Hypoalbuminaemia	62 (41.1)	15 (9.7)
Dermatitis acneiform	47 (31.1)	5 (3.2)
Grade ≥3 adverse events		
Neutropenia	50 (33.1)	35 (22.6)
Rash	17 (11.3)	0
Serious adverse events		
Pneumonitis	4 (2.6)	0
Adverse events leading to treatment discontinuation[*2]		
Pneumonitis	4 (2.6)	0
Infusion related reaction	3 (2.0)	0
Decreased appetite	3 (2.0)	0
Adverse events leading to dose or infusion interruption[*2]		
Infusion related reaction	57 (37.7)	0
Neutropenia	25 (16.6)	11 (7.1)
Rash	18 (11.9)	0
Paronychia	13 (8.6)	0
Hypokalaemia	10 (6.6)	0
Dermatitis acneiform	8 (5.3)	0
Adverse events leading to dose reduction[*2]		
Rash	14 (9.3)	0
Paronychia	12 (7.9)	0

*1 All adverse events reported at a ≥20% higher incidence, Grade ≥3 adverse events reported at a ≥10% higher incidence, serious adverse events reported at a ≥2% higher incidence, adverse events leading to treatment discontinuation reported at a ≥2% higher incidence, adverse events leading to dose or infusion interruption reported at a ≥5% higher incidence, and adverse events leading to dose reduction reported at a ≥5% higher incidence are listed.
*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 higher incidence in the amivantamab/CP group than in the CP group in the PAPILLON study may occur following administration of amivantamab, the patient's condition should be monitored closely for these events during treatment with amivantamab/CP, considering their possible relationship to amivantamab. Meanwhile, most of these events were non-serious and manageable with dose interruption of amivantamab or CP, etc. Given the above points, amivantamab/CP 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 amivantamab or the concomitant anti-neoplastic drugs.

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

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

Safety data from Japanese and non-Japanese patients in the amivantamab/CP group of the PAPILLON study are summarized in Table 30. Table 31 shows adverse events reported at a higher incidence in Japanese patients than in non-Japanese patients. Among serious adverse events, adverse events leading to treatment discontinuation, and adverse events leading to a reduction in the infusion rate of amivantamab that

were reported at a ≥5% higher incidence in Japanese patients than in non-Japanese patients, none were reported by ≥2 Japanese patients.

Table 30. Summary of safety data (Amivantamab/CP group of PAPILLON study, data cutoff date of May 3, 2023)

	n (%)	
	Japanese patients N = 19	Non-Japanese patients N = 132
All adverse events	19 (100)	132 (100)
Grade ≥3 adverse events	17 (89.5)	97 (73.5)
Adverse events leading to death	0	7 (5.3)
Serious adverse events	9 (47.4)	47 (35.6)
Adverse events leading to treatment discontinuation*1	6 (31.6)	30 (22.7)
Amivantamab	5 (26.3)	12 (9.1)
Carboplatin or pemetrexed	3 (15.8)	28 (21.2)
Adverse events leading to dose or infusion interruption*1	17 (89.5)	105 (79.5)
Amivantamab	14 (73.7)	103 (78.0)
Carboplatin or pemetrexed	16 (84.2)	72 (54.5)
Adverse events leading to dose reduction*1	12 (63.2)	61 (46.2)
Amivantamab	8 (42.1)	46 (34.8)
Carboplatin or pemetrexed	10 (52.6)	33 (25.0)
Adverse events leading to reduction in infusion rate of amivantamab	3 (15.8)	38 (28.8)

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

Table 31. Adverse events reported at a higher incidence in Japanese patients than in non-Japanese patients [*1] (Amivantamab/CP group of PAPILLON study, data cutoff date of May 3, 2023)

PT (MedDRA ver.25.0)	n (%)	
	Japanese patients N = 19	Non-Japanese patients N = 132
All adverse events		
Decreased appetite	13 (68.4)	41 (31.1)
Leukopenia	13 (68.4)	44 (33.3)
Oedema peripheral	11 (57.9)	34 (25.8)
Constipation	11 (57.9)	49 (37.1)
Stomatitis	10 (52.6)	28 (21.2)
Dermatitis acneiform	10 (52.6)	37 (28.0)
AST increased	10 (52.6)	37 (28.0)
ALT increased	10 (52.6)	40 (30.3)
Malaise	6 (31.6)	10 (7.6)
Grade ≥3 adverse events		
Neutropenia	10 (52.6)	40 (30.3)
Leukopenia	6 (31.6)	11 (8.3)
ALT increased	3 (15.8)	3 (2.3)
Dermatitis acneiform	3 (15.8)	3 (2.3)
Adverse events leading to dose or infusion interruption[*2]		
Neutropenia	8 (42.1)	17 (12.9)
Oedema peripheral	4 (21.1)	2 (1.5)
Dermatitis acneiform	3 (15.8)	5 (3.8)
Skin ulcer	2 (10.5)	3 (2.3)
Hypoalbuminaemia	2 (10.5)	3 (2.3)
Adverse events leading to dose reduction[*2]		
ALT increased	3 (15.8)	3 (2.3)
Dermatitis acneiform	3 (15.8)	4 (3.0)
Thrombocytopenia	3 (15.8)	7 (5.3)
Paronychia	3 (15.8)	9 (6.8)
Neutropenia	3 (15.8)	11 (8.3)
Skin ulcer	2 (10.5)	1 (0.8)
Decreased appetite	2 (10.5)	2 (1.5)

*1 All adverse events reported at a ≥20% higher incidence, Grade ≥3 adverse events reported at a ≥10% higher incidence, and other adverse events that were reported at a ≥5% higher incidence and by ≥2 Japanese patients are listed.
*2 Adverse events leading to dose or infusion interruption or dose reduction of any study drug

PMDA's view:

Although there are limitations to rigorous comparison of safety between Japanese and non-Japanese populations due to the limited number of Japanese patients treated with amivantamab/CP in the PAPILLON study, some adverse events were reported at a higher incidence in Japanese patients than in non-Japanese patients in the PAPILLON study, and attention should be paid to the possible occurrence of these events following administration of amivantamab. However, most events were non-serious, and the reported events were possibly related to the concomitant anti-neoplastic drugs. Amivantamab will be used under the supervision of physicians with sufficient knowledge of and experience in cancer chemotherapy. For these and other reasons, amivantamab/CP is tolerable also in Japanese patients as long as appropriate measures, e.g., dose interruption of amivantamab or the concomitant anti-neoplastic drugs, are taken.

In the following subsections, PMDA conducted its safety review, focusing on adverse events reported at a higher incidence with amivantamab/CP in the PAPILLON study and other studies, and adverse events that require attention following administration of other drugs targeting EGFR or MET.

7.R.3.3 Infusion reactions

The applicant's explanation about infusion reactions associated with amivantamab:

Events coded to the following MedDRA PTs that occurred on the day of or the day after infusion of amivantamab in the amivantamab/CP group or on the day of or the day after infusion of carboplatin or pemetrexed in the CP group were counted as infusion reactions: "infusion related reaction," "urticaria," "infusion site urticaria," "allergy to immunoglobulin therapy," "anaphylactic reaction," "anaphylactic shock," "anaphylactoid reaction," "anaphylactoid shock," "cross sensitivity reaction," "drug hypersensitivity," "hypersensitivity," "serum sickness," "serum sickness-like reaction," "systemic immune activation," "type I hypersensitivity," "type II hypersensitivity," "type IV hypersensitivity reaction," "type III immune complex mediated reaction," "drug eruption," and "infusion related hypersensitivity reaction."

The incidence of infusion reactions in the PAPILLON study is shown in Table 32 and Table 33. In the amivantamab/CP group of the PAPILLON study, the median time to the first onset of infusion reaction (min., max.) (days) was 1 (1, 337).

Table 32. Incidence of infusion reactions (PAPILLON study)

PT (MedDRA ver.25.0)	n (%)			
	Amivantamab/CP N = 151		CP N = 155	
	All Grades	Grade ≥3	All Grades	Grade ≥3
Infusion reactions*	61 (40.4)	1 (0.7)	3 (1.9)	0
Infusion related reaction	61 (40.4)	1 (0.7)	2 (1.3)	0
Urticaria	0	0	1 (0.6)	0

* Any event of infusion reaction

Table 33. Incidence of serious infusion reactions etc. (PAPILLON study)

PT (MedDRA ver.25.0)	n (%)	
	Amivantamab/CP N = 151	CP N = 155
Infusion reactions leading to death	0	0
Serious infusion reactions	1 (0.7)	0
Infusion related reaction	1 (0.7)	0
Infusion reactions leading to treatment discontinuation*	1 (0.7)	0
Infusion related reaction	1 (0.7)	0
Infusion reactions leading to dose or infusion interruption*	56 (37.1)	0
Infusion related reaction	56 (37.1)	0
Infusion reactions leading to dose reduction*	1 (0.7)	0
Infusion related reaction	1 (0.7)	0
Infusion reactions leading to reduction in infusion rate of amivantamab	38 (25.2)	—
Infusion related reaction	38 (25.2)	—

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

Table 34 shows the details of patients with serious infusion reactions for which a causal relationship to amivantamab could not be ruled out in the clinical studies of amivantamab including the PAPILLON study.[47)]

[47)] The PAPILLON study, Study EDI1001, a global phase I/Ib study in patients with unresectable advanced or recurrent NSCLC (CHRYSALIS-2 study), a global phase III study in patients with *EGFR*-mutated unresectable advanced or recurrent NSCLC after disease progression on osimertinib (MARIPOSA-2 study), and a global phase III study in patients with *EGFR*-mutated unresectable advanced or recurrent NSCLC previously untreated with chemotherapy (MARIPOSA study)

Table 34. Listing of patients with serious infusion reactions for which a causal relationship to amivantamab could not be ruled out

Study ID	Age	Sex	Concomitant medications	PT (MedDRA ver.25.0)	Grade	Time to onset (days)	Duration (days)	Action taken with amivantamab*	Outcome
PAPILLON	7[redacted]	M	CP	Infusion related reaction	3	1	3	Discontinued	Resolved
EDI1001	4[redacted]	F	None	Infusion related reaction	3	1	4	None	Resolved
	4[redacted]	M	None	Infusion related reaction	2	1	1	Dose interrupted	Resolved
	7[redacted]	M	None	Infusion related reaction	4	1	1	Discontinued	Resolved
	7[redacted]	F	None	Infusion related reaction	3	1	1	Discontinued	Resolved
				Infusion related reaction	2	1	1	Discontinued	Resolved
				Infusion related reaction	1	1	4	Discontinued	Resolved
CHRYSALIS-2	8[redacted]	F	Lazertinib	Infusion related reaction	3	1	6	Dose interrupted	Resolved
	6[redacted]	F	Lazertinib	Infusion related reaction	3	1	2	Dose interrupted	Resolved
	7[redacted]	M	Lazertinib	Infusion related reaction	3	1	1	Discontinued	Resolved
	3[redacted]	F	Lazertinib	Infusion related reaction	2	1	1	Infusion interrupted	Resolved
	6[redacted]	F	Lazertinib	Infusion related reaction	3	1	1	Discontinued	Resolved
	6[redacted]	F	Lazertinib	Infusion related reaction	3	1	2	Discontinued	Resolved
	6[redacted]	F	Lazertinib	Infusion related reaction	3	1	2	Discontinued	Resolved
	6[redacted]	F	Lazertinib	Infusion related reaction	3	1	1	Discontinued	Resolved
	6[redacted]	F	Lazertinib	Infusion related reaction	2	1	3	Dose interrupted	Resolving
	6[redacted]	M	Lazertinib	Infusion related reaction	4	1	1	Discontinued	Resolved
	6[redacted]	F	Lazertinib	Infusion related reaction	3	1	1	Dose interrupted	Resolved
	7[redacted]	F	Lazertinib	Infusion related reaction	3	1	1	Discontinued	Not resolved
MARIPOSA-2	6[redacted]	F	CP	Infusion related reaction	3	1	1	Discontinued	Resolved
	5[redacted]	M	CP	Infusion related reaction	3	1	2	Discontinued	Resolved
MARIPOSA	6[redacted]	M	Lazertinib	Infusion related reaction	4	1	1	Discontinued	Resolved
	5[redacted]	F	Lazertinib	Infusion related reaction	3	1	2	Discontinued	Resolved
	6[redacted]	F	Lazertinib	Infusion related reaction	3	1	2	Dose interrupted	Resolved
				Infusion related reaction	4	9	1	Discontinued	Resolved
	5[redacted]	F	Lazertinib	Infusion related reaction	4	1	1	Discontinued	Resolved
				Infusion related reaction	1	1	7	Not applicable	Resolved
	6[redacted]	F	Lazertinib	Infusion related reaction	3	1	2	Discontinued	Resolved
	7[redacted]	M	Lazertinib	Infusion related reaction	4	1	2	Discontinued	Resolved

* Also in the case where the Cycle 1 Day 1 infusion was aborted, and the infusion was resumed on Cycle 1 Day 2, an action taken of "dose interrupted" was stated.

In the PAPILLON study, premedications were administered as described in the table below to reduce the risk of infusion reactions with amivantamab. In the amivantamab/CP group, the proportions of patients premediated (1) on Day 1 Cycle 1 (the majority of infusion reactions occurred) and (2) on Cycle 1 Day 2 were (1) 94.0% and (2) 97.4% for glucocorticoids, (1) 98.7% and (2) 97.4% for antihistamines, (1) 87.4% and (2) 88.1% for antipyretics, (1) 27.8% and (2) 18.5% for H_2 receptor antagonists, and (1) 98.0% and (2) 9.9% for antiemetics.

Amivantamab administration	Required	Optional
Cycle 1 Days 1 and 2	Glucocorticoid Antihistamine Antipyretic	H_2 receptor antagonist Antiemetic
Cycle 1 Day 8 onwards	Antihistamine Antipyretic	Glucocorticoid H_2 receptor antagonist Antiemetic

PMDA's view:

Given that the incidence of infusion reactions was higher in the amivantamab/CP group than in the CP group in the PAPILLON study, and that multiple cases of serious infusion reactions for which a causal relationship to amivantamab could not be ruled out were reported in the clinical studies of amivantamab including the

PAPILLON study, etc., attention should be paid to the possible occurrence of infusion reactions following administration of amivantamab. Thus, the package insert and other materials should appropriately advise healthcare professionals in clinical practice about the incidence and infusion reactions in the clinical studies and the management of such event.

7.R.3.4 ILD

The applicant's explanation about ILD associated with amivantamab:
Events in the MedDRA SMQ "interstitial lung disease (narrow)" were counted as ILD.

The incidence of ILD in the PAPILLON study is shown in Table 35 and Table 36. In the amivantamab/CP group of the PAPILLON study, the median time to the first onset of ILD (min., max.) (days) was 128 (13, 188).

Table 35. Incidence of ILD (PAPILLON study)

PT (MedDRA ver.25.0)	n (%)			
	Amivantamab/CP N = 151		CP N = 155	
	All Grades	Grade ≥3	All Grades	Grade ≥3
Pneumonitis	4 (2.6)	4 (2.6)	0	0

Table 36. Incidence of serious ILD etc. (PAPILLON study)

PT (MedDRA ver.25.0)	n (%)			
	Amivantamab/CP N = 151		CP N = 155	
	All Grades	Grade ≥3	All Grades	Grade ≥3
ILD leading to death	0	0	0	0
Serious ILD	4 (2.6)	4 (2.6)	0	0
ILD leading to treatment discontinuation*	4 (2.6)	4 (2.6)	0	0
ILD leading to dose or infusion interruption*	0	0	0	0
ILD leading to dose reduction*	0	0	0	0

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

Table 37 shows the details of patients with serious ILD for which a causal relationship to amivantamab could not be ruled out (patients treated with amivantamab/CP or amivantamab monotherapy) in the clinical studies of amivantamab including the PAPILLON study.[47)]

Table 37. Listing of patients with serious ILD for which a causal relationship to amivantamab could not be ruled out (Patients treated with amivantamab/CP or amivantamab monotherapy)

Study ID	Age	Sex	Race	Concomitant medications	PT (MedDRA ver.25.0)	Grade	Time to onset (days)	Duration (days)	Action taken with amivantamab	Outcome
PAPILLON	7[redacted]	F	Non-Japanese	CP	Pneumonitis	3	98	44	Discontinued	Resolved
	6[redacted]	M	Non-Japanese	CP	Pneumonitis	3	160	14	Discontinued	Resolved
	8[redacted]	M	Japanese	CP	Pneumonitis	3	14	10	Discontinued	Resolving
					Pneumonitis	2	23	63	Not applicable	Resolved
	5[redacted]	M	Non-Japanese	CP	Pneumonitis	3	189	9	Discontinued	Resolving
					Pneumonitis	2	197	180	Not applicable	Resolved
EDI1001	6[redacted]	M	Non-Japanese	None	Pneumonitis	1	57	30	Not applicable	Resolved
	6[redacted]	F	Non-Japanese	None	Pneumonitis	2	73	57	Discontinued	Resolved
	7[redacted]	M	Non-Japanese	None	Interstitial lung disease	2	57	Unknown	Dose or infusion interrupted	Not resolved
	7[redacted]	F	Non-Japanese	None	Pneumonitis	3	95	14	Discontinued	Resolved
MARIPOSA-2	6[redacted]	F	Non-Japanese	CP	Interstitial lung disease	3	39	14	Discontinued	Resolved
	8[redacted]	M	Non-Japanese	CP	Pneumonitis	2	215	26	Discontinued	Not resolved

PMDA's view:

Although the number of patients with ILD in the PAPILLON study was limited, given that multiple cases of serious ILD for which a causal relationship to amivantamab could not be ruled out were reported in the clinical studies of amivantamab including the PAPILLON study, and that ILD is a known risk associated with other drugs targeting EGFR or MET, etc., attention should be paid to the possible occurrence of ILD following administration of amivantamab. Thus, the package insert and other materials should appropriately advise healthcare professionals in clinical practice about the incidence of ILD in the clinical studies and the management of such event.

7.R.3.5 Skin disorders (including paronychia)

The applicant's explanation about skin disorders (including paronychia) associated with amivantamab:

Events in the MedDRA SOC "skin and subcutaneous tissue disorders" and events coded to the MedDRA PT "paronychia" were counted as skin disorders (including paronychia).

The incidence of skin disorders (including paronychia) in the PAPILLON study is shown in Table 38 and Table 39. In the amivantamab/CP group of the PAPILLON study, the median time to the first onset of skin disorder (including paronychia) (min., max.) (days) was 12 (2, 572).

Table 38. Incidence of skin disorders (including paronychia)[*1] (PAPILLON study)

PT (MedDRA ver.25.0)	n (%)			
	Amivantamab/CP N = 151		CP N = 155	
	All Grades	Grade ≥3	All Grades	Grade ≥3
Skin disorders (including paronychia)[*2]	142 (94.0)	36 (23.8)	53 (34.2)	0
Paronychia	85 (56.3)	10 (6.6)	0	0
Rash	81 (53.6)	17 (11.3)	12 (7.7)	0
Dermatitis acneiform	47 (31.1)	6 (4.0)	5 (3.2)	0
Dry skin	16 (10.6)	0	6 (3.9)	0
Alopecia	13 (8.6)	0	8 (5.2)	0
Skin ulcer	10 (6.6)	2 (1.3)	1 (0.6)	0
Pruritus	10 (6.6)	0	12 (7.7)	0
Dermatitis	6 (4.0)	1 (0.7)	3 (1.9)	0
Skin fissures	6 (4.0)	0	1 (0.6)	0
Acne	5 (3.3)	0	0	0
Nail disorder	4 (2.6)	0	3 (1.9)	0
Rash maculo-papular	4 (2.6)	0	2 (1.3)	0
Penile ulceration	3 (2.0)	1 (0.7)	0	0
Seborrhoeic dermatitis	3 (2.0)	1 (0.7)	0	0
Skin hyperpigmentation	3 (2.0)	0	2 (1.3)	0
Palmar-plantar erythrodysaesthesia syndrome	3 (2.0)	0	1 (0.6)	0
Ingrowing nail	3 (2.0)	0	0	0
Erythema	1 (0.7)	0	8 (5.2)	0

*1 Adverse events reported by ≥2% of subjects in either group are listed. *2 Any event of skin disorder (including paronychia)

Table 39. Incidence of serious skin disorders (including paronychia) etc.[*1] (PAPILLON study)

PT (MedDRA ver.25.0)	n (%)	
	Amivantamab/CP N = 151	CP N = 155
Skin disorders (including paronychia) leading to death	0	0
Serious skin disorders (including paronychia)	5 (3.3)	0
Dermatitis acneiform	2 (1.3)	0
Rash	2 (1.3)	0
Skin disorders (including paronychia) leading to treatment discontinuation[*2]	6 (4.0)	1 (0.6)
Dermatitis acneiform	2 (1.3)	0
Rash	2 (1.3)	1 (0.6)
Skin ulcer	2 (1.3)	0
Skin disorders (including paronychia) leading to dose or infusion interruption[*2]	46 (30.5)	1 (0.6)
Rash	18 (11.9)	0
Paronychia	13 (8.6)	0
Dermatitis acneiform	8 (5.3)	0
Skin ulcer	5 (3.3)	0
Dry skin	2 (1.3)	0
Penile ulceration	2 (1.3)	0
Rash maculo-papular	2 (1.3)	0
Skin disorders (including paronychia) leading to dose reduction[*2]	33 (21.9)	0
Rash	14 (9.3)	0
Paronychia	12 (7.9)	0
Dermatitis acneiform	7 (4.6)	0
Skin ulcer	3 (2.0)	0

*1 Adverse events reported by ≥2 subjects in either group are listed. *2 Adverse events leading to discontinuation, dose or infusion interruption, or dose reduction of any study drug

Table 40 shows the details of patients with serious skin disorders (including paronychia) for which a causal relationship to amivantamab could not be ruled out in the clinical studies of amivantamab including the PAPILLON study.[47)]

Table 40. Listing of patients with serious skin disorders (including paronychia) for which a causal relationship to amivantamab could not be ruled out (Patients treated with amivantamab/CP or amivantamab monotherapy)

Study ID	Age	Sex	Concomitant medications	PT (MedDRA ver.25.0)	Grade	Time to onset (days)	Duration (days)	Action taken with amivantamab	Outcome
PAPILLON	5[redacted]	M	CP	Dermatitis acneiform	1	16	138	None	Not resolved
	5[redacted]	M	CP	Rash	3	118	10	Dose or infusion interrupted	Resolving
				Rash	2	127	9	Dose or infusion interrupted	Resolved
	5[redacted]	F	CP	Rash	2	351	7	Dose or infusion interrupted	Resolving
	6[redacted]	F	CP	Rash maculo-papular	2	14	198	Dose or infusion interrupted	Resolving
	4[redacted]	F	CP	Dermatitis acneiform	3	57	36	Discontinued	Resolving
EDI1001	5[redacted]	M	None	Dermatitis acneiform	3	184	19	Dose or infusion interrupted	Resolved
				Dermatitis acneiform	3	251	10	Dose or infusion interrupted	Resolved
	6[redacted]	F	None	Rash	3	37	3	Dose or infusion interrupted	Sequelae
				Toxic epidermal necrolysis	3	48	60	Discontinued	Resolved
	5[redacted]	M	None	Rash	3	232	8	Dose or infusion interrupted	Resolved

In the PAPILLON study, the following measures were recommended for the prophylaxis of skin disorders (including paronychia):

- 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.

PMDA's view:

The incidence of skin disorders was higher in the amivantamab/CP group than in the CP group in the PAPILLON study. Multiple cases of serious skin disorders including toxic epidermal necrolysis for which a causal relationship to amivantamab could not be ruled out were reported in the clinical studies of amivantamab including the PAPILLON study. Multiple cases of serious infections potentially associated with skin disorders caused by amivantamab were reported [see Section 7.R.3.7]. Skin disorders are a known risk associated with other drugs targeting EGFR. Given these points etc., attention should be paid to the possible occurrence of skin disorders following administration of amivantamab. Thus, the package insert and other materials should appropriately advise healthcare professionals in clinical practice about the incidence and skin disorders (including serious infections potentially associated with skin disorders caused by amivantamab) in the clinical studies and the management of such events.

7.R.3.6 Venous thromboembolism

The applicant's explanation about venous thromboembolism associated with amivantamab:

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

The incidence of venous thromboembolism in the PAPILLON study is shown in Table 41 and Table 42. In the amivantamab/CP group of the PAPILLON study, the median time to the first onset of venous thromboembolism (min., max.) (days) was 112 (6, 535).

Table 41. Incidence of venous thromboembolism (PAPILLON study)

PT (MedDRA ver.25.0)	n (%)			
	Amivantamab/CP N = 151		CP N = 155	
	All Grade	Grade ≥3	All Grades	Grade ≥3
Venous thromboembolism*	24 (15.9)	5 (3.3)	14 (9.0)	6 (3.9)
Pulmonary embolism	12 (7.9)	5 (3.3)	7 (4.5)	6 (3.9)
Retinal vein occlusion	0	0	1 (0.6)	0
Deep vein thrombosis	10 (6.6)	0	3 (1.9)	0
Embolism	1 (0.7)	0	1 (0.6)	0
Superior vena cava syndrome	0	0	1 (0.6)	0
Thrombophlebitis	0	0	1 (0.6)	0
Thrombosis	1 (0.7)	0	0	0
Venous thrombosis limb	2 (1.3)	0	1 (0.6)	0

* Any event of venous thromboembolism

Table 42. Incidence of serious venous thromboembolism etc. (PAPILLON study)

PT (MedDRA ver.25.0)	n (%)	
	Amivantamab/CP N = 151	CP N = 155
Venous thromboembolism leading to death	0	0
Serious venous thromboembolism	4 (2.6)	4 (2.6)
Pulmonary embolism	4 (2.6)	4 (2.6)
Venous thromboembolism leading to treatment discontinuation*	0	1 (0.6)
Pulmonary embolism	0	1 (0.6)
Venous thromboembolism leading to dose or infusion interruption*	5 (3.3)	1 (0.6)
Pulmonary embolism	4 (2.6)	1 (0.6)
Deep vein thrombosis	1 (0.7)	0
Venous thromboembolism leading to dose reduction*	1 (0.7)	0
Pulmonary embolism	1 (0.7)	0

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

Table 43 shows the details of patients with serious venous thromboembolism for which a causal relationship to amivantamab could not be ruled out in the clinical studies of amivantamab including the PAPILLON study.[47)]

Table 43. Listing of patients with serious venous thromboembolism for which a causal relationship to amivantamab could not be ruled out

Study ID	Age	Sex	Concomitant medications	PT (MedDRA ver.25.0)	Grade	Time to onset (days)	Duration (days)	Action taken with amivantamab	Outcome
PAPILLON	6[redacted]	M	CP	Pulmonary embolism	2	160	14	Dose or infusion interrupted	Resolved
	3[redacted]	M	CP	Pulmonary embolism	3	6	6	Dose or infusion interrupted	Resolved
EDI1001	7[redacted]	F	None	Pulmonary embolism	3	95	14	Discontinued	Resolved
	6[redacted]	M	Lazertinib	Pulmonary embolism	3	483	16	Dose or infusion interrupted	Resolved
	5[redacted]	M	Lazertinib	Pulmonary embolism	3	209	14	Discontinued	Resolving
CHRYSALIS-2	6[redacted]	M	Lazertinib	Pulmonary embolism	3	42	9	Dose or infusion interrupted	Resolved
	6[redacted]	M	Lazertinib	Pulmonary embolism	3	25	5	Dose or infusion interrupted	Resolving
				Pulmonary embolism	2	29	Unknown	None	Not resolved
	6[redacted]	M	Lazertinib	Deep vein thrombosis	2	215	53	Dose or infusion interrupted	Resolved
	5[redacted]	M	Lazertinib	Embolism	3	58	7	None	Resolving
	8[redacted]	F	Lazertinib	Pulmonary embolism	3	96	20	None	Not resolved
	7[redacted]	M	Lazertinib	Pulmonary embolism	2	56	Unknown	Dose or infusion interrupted	Not resolved
MARIPOSA-2	4[redacted]	F	CP	Deep vein thrombosis	2	71	Unknown	Dose or infusion interrupted	Not resolved
				Pulmonary embolism	3	72	7	Dose or infusion interrupted	Resolved
	7[redacted]	F	CP	Pulmonary embolism	3	169	8	Dose or infusion interrupted	Sequelae
	6[redacted]	M	CP	Pulmonary embolism	3	90	9	None	Resolving
				Deep vein thrombosis	3	97	2	None	Resolving

MARIPOSA	6[redacted]	M	Lazertinib	Pulmonary embolism	3	112	19	Discontinued	Resolving
	6[redacted]	F	Lazertinib	Pulmonary embolism	4	217	10	Dose or infusion interrupted	Resolving
	6[redacted]	M	Lazertinib	Pulmonary embolism	3	43	7	None	Resolving
	7[redacted]	F	Lazertinib	Deep vein thrombosis	2	30	3	Dose or infusion interrupted	Not resolved
				Deep vein thrombosis	3	33	10	Dose or infusion interrupted	Resolving
	3[redacted]	F	Lazertinib	Venous thrombosis	3	631	5	None	Resolved
	6[redacted]	F	Lazertinib	Deep vein thrombosis	2	44	29	Dose or infusion interrupted	Resolved
				Venous thrombosis limb	2	674	4	None	Resolving
	5[redacted]	M	Lazertinib	Pulmonary embolism	2	450	6	None	Resolved
	7[redacted]	F	Lazertinib	Deep vein thrombosis	3	320	6	Dose or infusion interrupted	Resolved
	8[redacted]	F	Lazertinib	Pulmonary embolism	3	175	8	Dose or infusion interrupted	Sequelae
	6[redacted]	F	Lazertinib	Pulmonary embolism	3	95	9	Dose or infusion interrupted	Resolving
				Venous thrombosis	2	128	7	None	Resolving
	5[redacted]	F	Lazertinib	Pulmonary embolism	3	54	11	Dose or infusion interrupted	Resolving
	8[redacted]	F	Lazertinib	Pulmonary embolism	3	283	13	Dose or infusion interrupted	Resolving
	4[redacted]	F	Lazertinib	Pulmonary embolism	3	332	5	Dose or infusion interrupted	Resolving
	6[redacted]	F	Lazertinib	Pulmonary embolism	3	12	Unknown	None	Not resolved
	5[redacted]	F	Lazertinib	Deep vein thrombosis	3	61	9	Dose or infusion interrupted	Resolving
				Deep vein thrombosis	2	70	Unknown	None	Not resolved
	6[redacted]	M	Lazertinib	Pulmonary embolism	3	335	17	Dose or infusion interrupted	Resolving
	5[redacted]	F	Lazertinib	Pulmonary embolism	3	112	22	Dose or infusion interrupted	Resolved
				Deep vein thrombosis	2	134	Unknown	Dose or infusion interrupted	Not resolved
	6[redacted]	M	Lazertinib	Pulmonary embolism	2	70	45	None	Resolved
	5[redacted]	F	Lazertinib	Jugular vein thrombosis	2	148	2	None	Resolved
	6[redacted]	F	Lazertinib	Pulmonary embolism	3	301	Unknown	None	Not resolved
	7[redacted]	F	Lazertinib	Embolism venous	3	43	5	Dose or infusion interrupted	Resolved
	5[redacted]	F	Lazertinib	Venous thrombosis limb	2	75	Unknown	None	Not resolved
	7[redacted]	M	Lazertinib	Pulmonary embolism	3	51	90	Dose or infusion interrupted	Resolved
	7[redacted]	M	Lazertinib	Venous thrombosis limb	3	260	28	Dose or infusion interrupted	Resolving
				Venous thrombosis limb	2	287	51	Dose or infusion interrupted	Resolving
				Venous thrombosis limb	1	337	Unknown	None	Not resolved
	7[redacted]	M	Lazertinib	Pulmonary embolism	3	96	11	Discontinued	Resolved

PMDA's view:

Given that there were no clear differences in the incidence of serious venous thromboembolism between the amivantamab/CP and CP groups in the PAPILLON study, etc., it is difficult at present to draw a definitive conclusion on the risk of serious venous thromboembolism associated with amivantamab. However, venous thromboembolism may lead to a serious outcome. Given the following points etc., the package insert and

other materials should appropriately advise healthcare professionals in clinical practice about the incidence of venous thromboembolism in the clinical studies and the management of such event. In addition, post-marketing information should be collected. If new information becomes available, the information should be provided appropriately to healthcare professionals in clinical practice.

- The incidence of venous thromboembolism of any grade was higher in the amivantamab/CP group than in the CP group in the PAPILLON study.
- While a causal relationship to concomitant medications also could not be ruled out for most cases in the clinical studies of amivantamab including the PAPILLON study, a certain number of cases of serious venous thromboembolism for which a causal relationship to amivantamab could not be ruled out have been accrued.
- Venous thromboembolism has been reported also with other drugs targeting EGFR.

7.R.3.7 Fluid retention (including oedema and hypoalbuminemia)

The applicant's explanation about fluid retention (including oedema and hypoalbuminemia) associated with amivantamab:

Events in the MedDRA HLT "total fluid volume increased" and events coded to the MedDRA PTs "hypoalbuminaemia," "blood albumin decreased," "oedema," "pleural effusion," "pericardial effusion," and "ascites" were counted as fluid retention (including oedema and hypoalbuminemia).

The incidence of fluid retention (including oedema and hypoalbuminemia) in the PAPILLON study is shown in

Table 44 and Table 45. In the amivantamab/CP group of the PAPILLON study, the median time to the first onset of fluid retention (including oedema and hypoalbuminemia) (min., max.) (days) was 50.5 (1, 526).

Table 44. Incidence of fluid retention (including oedema and hypoalbuminemia) (PAPILLON study)

PT (MedDRA ver.25.0)	n (%)			
	Amivantamab/CP N = 151		CP N = 155	
	All Grades	Grade ≥3	All Grades	Grade ≥3
Fluid retention (including oedema and hypoalbuminemia)*	94 (62.3)	9 (6.0)	39 (25.2)	7 (4.5)
Hypoalbuminaemia	62 (41.1)	6 (4.0)	15 (9.7)	0
Oedema peripheral	45 (29.8)	2 (1.3)	16 (10.3)	0
Oedema	10 (6.6)	0	2 (1.3)	0
Pleural effusion	5 (3.3)	1 (0.7)	8 (5.2)	6 (3.9)
Localised oedema	2 (1.3)	0	3 (1.9)	0
Ascites	1 (0.7)	0	1 (0.6)	1 (0.6)
Generalised oedema	1 (0.7)	0	0	0
Pericardial effusion	0	0	1 (0.6)	1 (0.6)

*Any event of fluid retention (including oedema and hypoalbuminemia)

Table 45. Incidence of serious fluid retention (including oedema and hypoalbuminemia) etc. (PAPILLON study)

PT (MedDRA ver.25.0)	n (%)	
	Amivantamab/CP N = 151	CP N = 155
Fluid retention (including oedema and hypoalbuminemia) leading to death	0	0
Serious fluid retention (including oedema and hypoalbuminemia)	1 (0.7)	6 (3.9)
Pleural effusion	1 (0.7)	5 (3.2)
Pericardial effusion	0	1 (0.6)
Ascites	0	1 (0.6)
Fluid retention (including oedema and hypoalbuminemia) leading to treatment discontinuation*	0	1 (0.6)
Oedema peripheral	0	1 (0.6)
Fluid retention (including oedema and hypoalbuminemia) leading to dose or infusion interruption*	12 (7.9)	2 (1.3)
Oedema peripheral	6 (4.0)	0
Hypoalbuminaemia	5 (3.3)	0
Pleural effusion	2 (1.3)	2 (1.3)
Pericardial effusion	0	1 (0.6)
Fluid retention (including oedema and hypoalbuminemia) leading to dose reduction*	5 (3.3)	1 (0.6)
Oedema peripheral	3 (2.0)	0
Hypoalbuminaemia	2 (1.3)	0
Oedema	0	1 (0.6)

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

Table 46 shows the details of patients with serious fluid retention (including oedema and hypoalbuminemia) for which a causal relationship to amivantamab could not be ruled out in the clinical studies of amivantamab including the PAPILLON study.[47)]

Table 46. Listing of patients with serious fluid retention (including oedema and hypoalbuminemia) for which a causal relationship to amivantamab could not be ruled out

Study ID	Age	Sex	Concomitant medications	PT (MedDRA ver.25.0)	Grade	Time to onset (days)	Duration (days)	Action taken with amivantamab	Outcome
CHRYSALIS-2	7[redacted]	F	Lazertinib	Oedema peripheral	3	127	11	Dose or infusion interrupted	Resolved
	5[redacted]	M	Lazertinib	Hypoalbuminaemia	3	60	37	Not applicable	Resolved
	7[redacted]	M	Lazertinib	Oedema peripheral	3	156	15	Dose or infusion interrupted	Resolving
	8[redacted]	F	Lazertinib	Oedema peripheral	3	32	13	Dose or infusion interrupted	Resolved
	7[redacted]	F	Lazertinib	Oedema peripheral	3	97	10	Dose or infusion interrupted	Resolving
MARIPOSA	6[redacted]	F	Lazertinib	Pleural effusion	2	162	Unknown	None	Not resolved
	8[redacted]	F	Lazertinib	Oedema	3	464	12	Dose or infusion interrupted	Resolving
	5[redacted]	M	Lazertinib	Hypoalbuminaemia	2	83	85	None	Resolving
	7[redacted]	M	Lazertinib	Oedema peripheral	2	30	3	None	Resolved
	7[redacted]	M	Lazertinib	Oedema peripheral	3	43	13	Dose or infusion interrupted	Resolved
	6[redacted]	M	Lazertinib	Hypoalbuminaemia	2	28	21	Dose or infusion interrupted	Resolving
	6[redacted]	M	Lazertinib	Generalised oedema	3	176	7	Dose or infusion interrupted	Resolving
				Generalised oedema	2	182	44	Dose or infusion interrupted	Resolved
	5[redacted]	F	Lazertinib	Hypoalbuminaemia	2	42	7	None	Resolving
				Pericardial effusion	2	56	36	None	Resolved
				Pleural effusion	2	56	36	Discontinued	Resolved
	7[redacted]	M	Lazertinib	Hypoalbuminaemia	2	42	19	None	Resolving
				Hypoalbuminaemia	1	60	25	None	Not resolved
				Hypoalbuminaemia	2	84	57	Dose or infusion interrupted	Resolving
				Hypoalbuminaemia	1	140	134	Dose reduced	Resolved

PMDA's view:

There were no clear differences in the incidence of serious fluid retention between the amivantamab/CP and CP groups in the PAPILLON study. Most of the events of serious fluid retention for which a causal relationship to amivantamab could not be ruled out observed in the clinical studies of amivantamab including the PAPILLON study were peripheral oedema or hypoalbuminaemia, and some of these events resolved or were resolving with continued treatment with amivantamab. Given these points etc., it is difficult at present to draw a definitive conclusion on the risk of serious fluid retention associated with amivantamab. However, the incidence of fluid retention of any grade was higher in the amivantamab/CP group than in the CP group in the PAPILLON study, and fluid retention is a known risk associated with other drugs targeting MET. For these reasons, among others, the applicant should provide information on the incidence of fluid retention in the clinical studies to healthcare professionals in clinical practice, using the 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.

7.R.3.8 Diarrhoea

The applicant's explanation about diarrhoea associated with amivantamab:

Events coded to the MedDRA PT "diarrhoea" were counted as diarrhoea.

The incidence of diarrhoea in the PAPILLON study is shown in Table 47 and Table 48. In the amivantamab/CP group of the PAPILLON study, the median time to the first onset of diarrhoea (min., max.) (days) was 9 (2, 428).

Table 47. Incidence of diarrhoea (PAPILLON study)

PT (MedDRA ver.25.0)	n (%)			
	Amivantamab/CP N = 151		CP N = 155	
	All Grades	Grade ≥3	All Grades	Grade ≥3
Diarrhoea	31 (20.5)	5 (3.3)	20 (12.9)	2 (1.3)

Table 48. Incidence of serious diarrhoea etc. (PAPILLON study)

PT (MedDRAver.25.0)	n (%)	
	Amivantamab/CP N = 151	CP N = 155
Diarrhoea leading to death	0	0
Serious diarrhoea	2 (1.3)	1 (0.6)
Diarrhoea leading to treatment discontinuation*	0	0
Diarrhoea leading to dose or infusion interruption*	3 (2.0)	1 (0.6)
Diarrhoea leading to dose reduction*	1 (0.7)	1 (0.6)

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

Table 49 shows the details of patients with serious diarrhoea for which a causal relationship to amivantamab could not be ruled out in the clinical studies of amivantamab including the PAPILLON study.[47)]

Table 49. Listing of patients with serious diarrhoea for which a causal relationship to amivantamab could not be ruled out

Study ID	Age	Sex	Concomitant medications	PT (MedDRA ver.25.0)	Grade	Time to onset (days)	Duration (days)	Action taken with amivantamab	Outcome
PAPILLON	7[redacted]	M	CP	Diarrhea	3	48	28	Dose or infusion interrupted	Resolved
EDI1001	7[redacted]	F	None	Diarrhoea	3	47	Unknown	Dose or infusion interrupted	Not resolved
	7[redacted]	F	None	Diarrhoea	3	408	15	Dose or infusion interrupted	Resolved
	6[redacted]	M	CP	Diarrhoea	3	43	24	Discontinued	Resolved
CHRYSALIS-2	7[redacted]	F	Lazertinib	Diarrhoea	3	260	7	Discontinued	Resolved
MARIPOSA-2	6[redacted]	M	CP	Diarrhoea	3	55	10	None	Resolved
MARIPOSA	6[redacted]	M	Lazertinib	Diarrhoea	3	12	5	None	Resolved
				Diarrhoea	3	27	4	Dose or infusion interrupted	Resolving
	6[redacted]	F	Lazertinib	Diarrhoea	3	147	18	Dose or infusion interrupted	Resolved
	8[redacted]	F	Lazertinib	Diarrhoea	3	72	2	None	Resolved
				Diarrhoea	3	87	5	Discontinued	Resolved
	7[redacted]	F	Lazertinib	Diarrhoea	3	23	13	Dose reduced	Resolving

PMDA's view:

Given that there were no clear differences in the incidence of serious diarrhoea between the amivantamab/CP and CP groups in the PAPILLON study, and that a causal relationship to concomitant medications also could not be ruled out for most of the events of serious diarrhoea for which a causal relationship to amivantamab could not be ruled out observed in the clinical studies of amivantamab including the PAPILLON study, it

is difficult at present to draw a definitive conclusion on the risk of serious diarrhoea associated with amivantamab. However, the incidence of diarrhoea of any grade was higher in the amivantamab/CP group than in the CP group in the PAPILLON study, and diarrhoea is a known risk associated with other drugs targeting EGFR. For these reasons, among others, the applicant should provide information on the incidence of diarrhoea in the clinical studies to healthcare professionals in clinical practice, using the 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.

7.R.3.9 Infections

The applicant's explanation about infections associated with amivantamab:
Events in the MedDRA SOC "infections and infestations" were counted as infections.

The incidence of infections in the PAPILLON study is shown in Table 50 and Table 51. In the amivantamab/CP group of the PAPILLON study, the median time to the first onset of infection (min., max.) (days) was 53 (3, 521).

Table 50. Incidence of infections[*1] (PAPILLON study)

PT (MedDRA ver.25.0)	n (%)			
	Amivantamab/CP N = 151		CP N = 155	
	All Grades	Grade ≥3	All Grades	Grade ≥3
Infections[*2]	120 (79.5)	31 (20.5)	65 (41.9)	11 (7.1)
Paronychia	85 (56.3)	10 (6.6)	0	0
COVID-19	36 (23.8)	3 (2.0)	21 (13.5)	1 (0.6)
Pneumonia	17 (11.3)	7 (4.6)	10 (6.5)	3 (1.9)
Conjunctivitis	9 (6.0)	0	7 (4.5)	0
Upper respiratory tract infection	9 (6.0)	0	6 (3.9)	0
Herpes zoster	7 (4.6)	0	4 (2.6)	0
Rash pustular	6 (4.0)	4 (2.6)	0	0
Urinary tract infection	6 (4.0)	1 (0.7)	8 (5.2)	1 (0.6)
Cellulitis	5 (3.3)	2 (1.3)	3 (1.9)	1 (0.6)
Folliculitis	5 (3.3)	1 (0.7)	1 (0.6)	0
Suspected COVID-19	5 (3.3)	0	1 (0.6)	0
Skin infection	4 (2.6)	3 (2.0)	0	0
Oral candidiasis	4 (2.6)	0	2 (1.3)	0
Tinea pedis	4 (2.6)	0	0	0
Otitis media	4 (2.6)	0	0	0
Infection	3 (2.0)	1 (0.7)	1 (0.6)	0
Otitis externa	3 (2.0)	0	0	0
COVID-19 pneumonia	2 (1.3)	1 (0.7)	0	0
Candida infection	2 (1.3)	0	0	0
Sepsis	1 (0.7)	1 (0.7)	2 (1.3)	1 (0.6)
Asymptomatic COVID-19	1 (0.7)	0	2 (1.3)	0
Gastroenteritis	0	0	2 (1.3)	0
Herpes virus infection	2 (1.3)	0	0	0
Hordeolum	2 (1.3)	0	1 (0.6)	0
Nasopharyngitis	2 (1.3)	0	3 (1.9)	0
Parotitis	2 (1.3)	0	0	0
Periodontitis	2 (1.3)	0	2 (1.3)	0
Pneumonia bacterial	2 (1.3)	0	0	0
Pustule	2 (1.3)	0	0	0
Respiratory tract infection	2 (1.3)	0	2 (1.3)	0
Rhinitis	1 (0.7)	0	2 (1.3)	0
Sialoadenitis	2 (1.3)	0	0	0
Sinusitis	2 (1.3)	0	1 (0.6)	0

*1 Adverse events reported by ≥2 subjects in either group are listed. *2 Any event of infection

Table 51. Incidence of serious infections etc. (PAPILLON study)

PT (MedDRA ver.25.0)	n (%)	
	Amivantamab/CP N = 151	CP N = 155
Infections leading to death	4 (2.6)	1 (0.6)
Sepsis	1 (0.7)	1 (0.6)
COVID-19	1 (0.7)	0
COVID-19 pneumonia	1 (0.7)	0
Pneumonia	1 (0.7)	0
Infections leading to death for which a causal relationship to study drug could not be ruled out	2 (1.3)	1 (0.6)
Sepsis	1 (0.7)	1 (0.6)
COVID-19 pneumonia	1 (0.7)	0
Serious infections	18 (11.9)	10 (6.5)
Pneumonia	6 (4.0)	4 (2.6)
COVID-19	3 (2.0)	1 (0.6)
Cellulitis	2 (1.3)	1 (0.6)
Rash pustular	2 (1.3)	0
Skin infection	2 (1.3)	0
Postoperative wound infection	1 (0.7)	1 (0.6)
Sepsis	1 (0.7)	1 (0.6)
COVID-19 pneumonia	1 (0.7)	0
Infection	1 (0.7)	0
Viral pneumonia	1 (0.7)	0
Appendicitis	0	1 (0.6)
Enterocolitis infectious	0	1 (0.6)
Serious infections for which a causal relationship to study drug could not be ruled out	9 (6.0)	4 (2.6)
Pneumonia	2 (1.3)	1 (0.6)
Rash pustular	2 (1.3)	0
Skin infection	2 (1.3)	0
Cellulitis	1 (0.7)	1 (0.6)
Sepsis	1 (0.7)	1 (0.6)
Postoperative wound infection	1 (0.7)	0
COVID-19 pneumonia	1 (0.7)	0
Infection	1 (0.7)	0
Infections leading to treatment discontinuation[*1, 2]	8 (5.3)	2 (1.3)
Pneumonia	2 (1.3)	0
Skin infection	2 (1.3)	0
Infections leading to dose or infusion interruption[*1, 2]	40 (26.5)	21 (13.5)
Paronychia	13 (8.6)	0
COVID-19	12 (7.9)	12 (7.7)
Pneumonia	6 (4.0)	2 (1.3)
Cellulitis	3 (2.0)	1 (0.6)
Rash pustular	2 (1.3)	0
Respiratory tract infection	2 (1.3)	1 (0.6)
Skin infection	2 (1.3)	0
Infections leading to dose reduction [*1, 2]	20 (13.2)	4 (2.6)
Paronychia	12 (7.9)	0
Rash pustular	5 (3.3)	0
Folliculitis	2 (1.3)	0
Urinary tract infection	0	2 (1.3)

*1 Infections reported by ≥2 subjects in either group are listed.
*2 Adverse events leading to discontinuation, dose or infusion interruption, or dose reduction of any study drug

Table 52 shows the details of patients with a serious infection for which a causal relationship to amivantamab could not be ruled out in the clinical studies of amivantamab including the PAPILLON study.[47)]

Table 52. Listing of patients with a serious infection for which a causal relationship to amivantamab could not be ruled out

Study ID	Age	Sex	Concomitant medications	PT (MedDRA ver.25.0)	Grade	Time to onset (days)	Duration (days)	Action taken with amivantamab	Outcome
PAPILLON	4[redacted]	M	CP	Postoperative wound infection	3	30	5	Dose reduced	Resolved
	7[redacted]	F	CP	Cellulitis	3	411	3	Dose reduced	Resolved
				Cellulitis	3	438	6	Dose or infusion interrupted	Resolving
	5[redacted]	F	CP	Rash pustular	3	16	9	Dose reduced	Resolving
	6[redacted]	M	CP	Pneumonia	3	147	36	None	Resolved
	3[redacted]	M	CP	Rash pustular	3	241	5	Not applicable	Sequelae
EDI1001	6[redacted]	M	None	Infected dermal cyst	3	70	3	None	Resolved
	5[redacted]	F	None	Cellulitis	2	105	11	Dose or infusion interrupted	Resolved
	7[redacted]	F	None	Impetigo	3	102	Unknown	Dose or infusion interrupted	Not resolved
	6[redacted]	F	CP	Cellulitis	3	136	7	Dose or infusion interrupted	Resolving
CHRYSALIS-2	6[redacted]	F	Lazertinib	Skin infection	3	500	17	Dose or infusion interrupted	Resolving
	5[redacted]	F	Lazertinib	Dacryocystitis	3	419	1	None	Resolving
				Dacryocystitis	2	419	96	None	Resolved
	7[redacted]	F	Lazertinib	Paronychia	2	26	Unknown	None	Not resolved
	6[redacted]	F	Lazertinib	Skin infection	3	104	12	Dose or infusion interrupted	Resolving
	5[redacted]	M	Lazertinib	Paronychia	3	84	15	Dose or infusion interrupted	Resolved
	5[redacted]	F	Lazertinib	Folliculitis	3	72	29	Dose or infusion interrupted	Resolving
	6[redacted]	F	Lazertinib	Paronychia	2	352	110	Dose or infusion interrupted	Not resolved
	6[redacted]	F	Lazertinib	Cytomegaloviral pneumonia	3	122	24	Dose or infusion interrupted	Resolving
	3[redacted]	M	Lazertinib	Pneumonia	3	38	20	None	Resolving
MARIPOSA-2	6[redacted]	F	CP	Soft tissue infection	3	322	11	None	Resolving
	5[redacted]	M	CP	Skin infection	2	23	24	None	Resolved
	5[redacted]	F	CP	Herpes virus infection	3	116	9	Dose reduced	Resolving
	7[redacted]	F	CP	Skin infection	3	73	9	None	Resolved
MARIPOSA	6[redacted]	F	Lazertinib	Subcutaneous abscess	3	372	21	Dose or infusion interrupted	Resolved
	6[redacted]	F	Lazertinib	Pustule	2	77	5	None	Resolving
	6[redacted]	F	Lazertinib	Achromobacter infection	3	223	9	Dose or infusion interrupted	Resolving
	4[redacted]	M	Lazertinib	Dermatitis infected	3	104	35	Dose or infusion interrupted	Resolving
	3[redacted]	M	Lazertinib	Sepsis	3	212	3	None	Resolved
	5[redacted]	F	Lazertinib	Dermatitis infected	3	51	41	Discontinued	Resolved
	8[redacted]	F	Lazertinib	Sepsis	3	50	8	Discontinued	Resolved

PMDA's view:

In the PAPILLON study, the incidence of infections was higher in the amivantamab/CP group than in the CP group, and the incidence of infections excluding MedDRA PT "paronychia," which was assessed as a skin disorder [see Section 7.R.3.3], was also higher in the amivantamab/CP group than in the CP group.[48)] However, most of serious infections for which a causal relationship to amivantamab could not be ruled out were potentially associated with skin disorders caused by amivantamab or the primary disease. Also as to serious infections for which a causal relationship to amivantamab could not be ruled out observed in the clinical studies of amivantamab other than the PAPILLON study, most cases were potentially associated with skin disorders caused by amivantamab or the primary disease. In addition, a causal relationship to

[48)] The incidences of infections of any grade excluding paronychia were 67.5% (102 of 151 subjects) in the amivantamab/CP group and 41.9% (65 of 155 subjects) in the CP group, and the incidences of Grade ≥3 infections excluding paronychia were 15.9% (24 of 151 subjects) in the amivantamab/CP group and 7.1% (11 of 155 subjects) in the CP group.

concomitant medications also could not be ruled out. Given these points etc., it is difficult at present to draw a definitive conclusion on the risk of infections associated with amivantamab. Thus, no particular precautionary statement is needed at present, on the premise that information on the incidence of infections in the clinical studies will be provided using the package insert and other materials. However, the applicant should provide precautions about serious infections potentially associated with skin disorders caused by amivantamab together with skin disorders associated with amivantamab [see Section 7.R.3.3].

7.R.3.10 Cardiac disorders

The applicant's explanation about cardiac disorders associated with amivantamab:
Events in the MedDRA SOC "cardiac disorders" were counted as cardiac disorders.

The incidence of cardiac disorders in the PAPILLON study is shown in Table 53 and Table 54. In the amivantamab/CP group of the PAPILLON study, the median time to the first onset of cardiac disorder (min., max.) (days) was 25 (2, 515).

Table 53. Incidence of cardiac disorders (PAPILLON study)

PT (MedDRA ver.25.0)	n (%)			
	Amivantamab/CP N = 151		CP N = 155	
	All Grades	Grade ≥3	All Grades	Grade ≥3
Cardiac disorders*	19 (12.6)	1 (0.7)	9 (5.8)	2 (1.3)
Sinus tachycardia	5 (3.3)	0	2 (1.3)	0
Palpitations	5 (3.3)	0	1 (0.6)	0
Tachycardia	3 (2.0)	0	0	0
Arrhythmia	2 (1.3)	0	0	0
Supraventricular extrasystoles	2 (1.3)	0	0	0
Cardio-respiratory arrest	1 (0.7)	1 (0.7)	0	0
Atrial fibrillation	1 (0.7)	0	1 (0.6)	0
Atrial tachycardia	1 (0.7)	0	0	0
Cardiac amyloidosis	1 (0.7)	0	0	0
Chronic left ventricular failure	1 (0.7)	0	0	0
Right ventricular dysfunction	1 (0.7)	0	0	0
Sinus bradycardia	1 (0.7)	0	0	0
Supraventricular tachycardia	1 (0.7)	0	0	0
Ventricular extrasystoles	1 (0.7)	0	0	0
Acute myocardial infarction	0	0	1 (0.6)	1 (0.6)
Pericardial effusion	0	0	1 (0.6)	1 (0.6)
Atrioventricular block first degree	0	0	1 (0.6)	0
Cardiac failure	0	0	1 (0.6)	0
Extrasystoles	0	0	1 (0.6)	0

*Any event of cardiac disorder

Table 54. Incidence of serious cardiac disorders etc. (PAPILLON study)

PT (MedDRA ver.25.0)	n (%)	
	Amivantamab/CP N = 151	CP N = 155
Cardiac disorders leading to death	1 (0.7)	1 (0.6)
Cardio-respiratory arrest	1 (0.7)	0
Acute myocardial infarction	0	1 (0.6)
Serious cardiac disorders	1 (0.7)	2 (1.3)
Cardio-respiratory arrest	1 (0.7)	0
Acute myocardial infarction	0	1 (0.6)
Pericardial effusion	0	1 (0.6)
Cardiac disorders leading to treatment discontinuation*	0	1 (0.6)
Acute myocardial infarction	0	1 (0.6)
Cardiac disorders leading to dose or infusion interruption*	1 (0.7)	1 (0.6)
Right ventricular dysfunction	1 (0.7)	0
Pericardial effusion	0	1 (0.6)
Cardiac disorders leading to dose reduction*	0	0

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

Table 55 shows the details of patients with serious cardiac disorders for which a causal relationship to amivantamab could not be ruled out in the clinical studies of amivantamab including the PAPILLON study.[47)]

Table 55. Listing of patients with serious cardiac disorders for which a causal relationship to amivantamab could not be ruled out

Study ID	Age	Sex	Concomitant medications	PT (MedDRA ver.25.0)	Grade	Time to onset (days)	Duration (days)	Action taken with amivantamab	Outcome
PAPILLON	3[redacted]	F	CP	Cardio-respiratory arrest	5	26	1	None	Fatal
EDI1001	7[redacted]	F	None	Atrial flutter	3	7	5	Dose or infusion interrupted	Resolved
CHRYSALIS-2	8[redacted]	F	Lazertinib	Myocardial infarction	3	6	10	Discontinued	Resolving
MARIPOSA-2	4[redacted]	F	CP	Ventricular fibrillation	5	357	1	Discontinued	Fatal
MARIPOSA	8[redacted]	F	Lazertinib	Myocardial infarction	5	524	1	Discontinued	Fatal
	6[redacted]	F	Lazertinib	Myocardial infarction	3	285	5	None	Not resolved
				Coronary artery disease	4	286	4	Discontinued	Not resolved
				Coronary artery disease	5	289	1	Discontinued	Fatal
				Myocardial infarction	5	289	1	Discontinued	Fatal
	5[redacted]	F	Lazertinib	Pericardial effusion	2	56	36	None	Resolved
	7[redacted]	M	Lazertinib	Cardiac failure	4	78	Unknown	Discontinued	Not resolved

PMDA's view:

In the PAPILLON study, the incidence of cardiac disorders of any grade was higher in the amivantamab/CP group than in the CP group, but there were no clear differences in the incidence of serious cardiac disorders etc. For most of serious cardiac disorders for which a causal relationship to amivantamab could not be ruled out observed in the clinical studies of amivantamab including the PAPILLON study, a causal relationship to concomitant medications also could not be ruled out. In addition, some of these cases were potentially associated with complications. Given these points etc., it is difficult at present to draw a definitive conclusion on the risk of cardiac disorders associated with amivantamab. Thus, no particular precautionary statement is needed at present, on the premise that information on the incidence of

cardiac disorders in the clinical studies will be provided using the package insert and other materials [for arterial thromboembolism such as myocardial infarction, see also Section 7.R.3.13].

7.R.3.11 Hepatic dysfunction

The applicant's explanation about hepatic dysfunction associated with amivantamab:
Events in the MedDRA Sub-SMQs "cholestasis and jaundice of hepatic origin (broad)," "hepatic failure, fibrosis and cirrhosis and other liver damage-related conditions (broad)," "hepatitis, non-infectious (broad)," and "liver related investigations, signs and symptoms (broad)" were counted as hepatic dysfunction.

The incidence of hepatic dysfunction in the PAPILLON study is shown in Table 56 and Table 57. In the amivantamab/CP group of the PAPILLON study, the median time to the first onset of hepatic dysfunction (min., max.) (days) was 15 (1, 536).

Table 56. Incidence of hepatic dysfunction (PAPILLON study)

PT (MedDRA ver.25.0)	n (%)			
	Amivantamab/CP N = 151		CP N = 155	
	All Grades	Grade ≥3	All Grades	Grade ≥3
Hepatic dysfunction*	97 (64.2)	14 (9.3)	83 (53.5)	9 (5.8)
Hypoalbuminaemia	62 (41.1)	6 (4.0)	15 (9.7)	0
ALT increased	50 (33.1)	6 (4.0)	56 (36.1)	2 (1.3)
AST increased	47 (31.1)	1 (0.7)	51 (32.9)	1 (0.6)
GGT increased	21 (13.9)	4 (2.6)	26 (16.8)	6 (3.9)
Blood ALP increased	19 (12.6)	1 (0.7)	12 (7.7)	0
Hyperbilirubinaemia	15 (9.9)	1 (0.7)	6 (3.9)	0
Hypertransaminasaemia	2 (1.3)	0	1 (0.6)	0
Bilirubin conjugated increased	2 (1.3)	0	0	0
Ascites	1 (0.7)	0	1 (0.6)	1 (0.6)
Transaminases increased	1 (0.7)	0	1 (0.6)	0
Cholestasis	1 (0.7)	0	0	0
Hepatitis	1 (0.7)	0	0	0
Liver injury	1 (0.7)	0	0	0
Blood bilirubin increased	0	0	2 (1.3)	0
Hepatic cytolysis	0	0	1 (0.6)	0
Hepatic function abnormal	0	0	1 (0.6)	0
Hepatic steatosis	0	0	1 (0.6)	0
Jaundice cholestatic	0	0	1 (0.6)	1 (0.6)
Liver disorder	0	0	1 (0.6)	0

*Any event of hepatic dysfunction

Table 57. Incidence of serious hepatic dysfunction etc. (PAPILLON study)

PT (MedDRA ver.25.0)	n (%)	
	Amivantamab/CP N = 151	CP N = 155
Hepatic dysfunction leading to death	0	0
Serious hepatic dysfunction	1 (0.7)	3 (1.9)
ALT increased	1 (0.7)	1 (0.6)
AST increased	0	1 (0.6)
Ascites	0	1 (0.6)
Jaundice cholestatic	0	1 (0.6)
Hepatic dysfunction leading to treatment discontinuation*	2 (1.3)	0
ALT increased	1 (0.7)	0
AST increased	1 (0.7)	0
GGT increased	1 (0.7)	0
Hepatic dysfunction leading to dose or infusion interruption*	13 (8.6)	9 (5.8)
ALT increased	6 (4.0)	6 (3.9)
Hypoalbuminaemia	5 (3.3)	0
AST increased	2 (1.3)	5 (3.2)
GGT increased	1 (0.7)	1 (0.6)
Hepatitis	1 (0.7)	0
Transaminases increased	0	1 (0.6)
Jaundice cholestatic	0	1 (0.6)
Hepatic dysfunction leading to dose reduction*	10 (6.6)	2 (1.3)
ALT increased	6 (4.0)	2 (1.3)
AST increased	4 (2.6)	2 (1.3)
Blood ALP increased	2 (1.3)	1 (0.6)
Hypoalbuminaemia	2 (1.3)	0
GGT increased	1 (0.7)	2 (1.3)
Hyperbilirubinaemia	1 (0.7)	0
Liver injury	1 (0.7)	0

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

Table 58 shows the details of patients with serious hepatic dysfunction for which a causal relationship to amivantamab could not be ruled out in the clinical studies of amivantamab including the PAPILLON study.[47)]

Table 58. Listing of patients with serious hepatic dysfunction for which a causal relationship amivantamab could not be ruled out

Study ID	Age	Sex	Concomitant medications	PT (MedDRA ver.25.0)	Grade	Time to onset (days)	Duration (days)	Action taken with amivantamab	Outcome
PAPILLON	6[redacted]	M	CP	ALT increased	3	14	3	Dose reduced	Resolving
CHRYSALIS-2	5[redacted]	M	Lazertinib	Hypoalbuminaemia	3	60	37	Not applicable	Resolved
MARIPOSA	4[redacted]	M	Lazertinib	ALT increased	2	8	1	Dose or infusion interrupted	Resolving
	7[redacted]	F	Lazertinib	ALT increased	2	99	8	None	Resolving
	3[redacted]	F	Lazertinib	ALT increased	2	8	7	Dose or infusion interrupted	Resolved
	5[redacted]	M	Lazertinib	Hypoalbuminaemia	2	83	85	None	Resolving
				ALT increased	3	126	4	Dose or infusion interrupted	Resolving
	6[redacted]	M	Lazertinib	Hypoalbuminaemia	2	28	21	Dose or infusion interrupted	Resolving
	4[redacted]	M	Lazertinib	AST increased	4	239	1	Dose or infusion interrupted	Resolving
	5[redacted]	F	Lazertinib	Hypoalbuminaemia	2	42	7	None	Resolving
	7[redacted]	M	Lazertinib	Hypoalbuminaemia	2	42	19	None	Resolving
				Hypoalbuminaemia	1	60	25	None	Not resolved
				Hypoalbuminaemia	2	84	57	Dose or infusion interrupted	Resolving
				Hypoalbuminaemia	1	140	134	Dose reduced	Resolved
	5[redacted]	M	Lazertinib	ALT increased	3	225	8	Dose or infusion interrupted	Resolving

Of patients experiencing serious hepatic dysfunction in the clinical studies of amivantamab including the PAPILLON study, 1 patient in the MARIPOSA study had hepatic dysfunction meeting 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), but this event was potentially associated with concomitant medications.

PMDA's view:

Among the events of hepatic dysfunction observed in the PAPILLON study, the incidence of hypoalbuminaemia was higher in the amivantamab/CP group than in the CP group, but no serious hypoalbuminaemia was reported. Hypoalbuminaemia may also occur by causes other than hepatic dysfunction, e.g., fluid retention [see Section 7.R.3.5]. For most of the events of serious hepatic dysfunction for which a causal relationship to amivantamab could not be ruled out observed in the clinical studies of amivantamab including the PAPILLON study, a causal relationship to concomitant medications also could not be ruled out. Given these points etc., it is difficult at present to draw a definitive conclusion on the risk of hepatic dysfunction associated with amivantamab. Thus, no particular precautionary statement is needed, on the premise that information on the incidence of hepatic dysfunction in the clinical studies will be provided using the package insert and other materials.

7.R.3.12 Myelosuppression

The applicant's explanation about myelosuppression associated with amivantamab:

Events in the MedDRA SMQ "haematopoietic cytopenias (narrow)" were counted as myelosuppression.

The incidence of myelosuppression in the PAPILLON study is shown in Table 59 and Table 60. In the amivantamab/CP group of the PAPILLON study, the median time to the first onset of myelosuppression (min., max.) (days) was 8 (1, 392).

Table 59. Incidence of myelosuppression (PAPILLON study)

PT (MedDRA ver.25.0)	n (%)			
	Amivantamab/CP N = 151		CP N = 155	
	All Grades	Grade ≥3	All Grades	Grade ≥3
Myelosuppression*	101 (66.9)	56 (37.1)	89 (57.4)	44 (28.4)
Neutropenia	89 (58.9)	50 (33.1)	70 (45.2)	35 (22.6)
Leukopenia	57 (37.7)	17 (11.3)	50 (32.3)	5 (3.2)
Thrombocytopenia	55 (36.4)	15 (9.9)	46 (29.7)	16 (10.3)
Lymphopenia	7 (4.6)	4 (2.6)	11 (7.1)	4 (2.6)
Febrile neutropenia	4 (2.6)	4 (2.6)	3 (1.9)	3 (1.9)
Lymphocyte count decreased	3 (2.0)	2 (1.3)	3 (1.9)	0
Platelet count decreased	2 (1.3)	0	0	0
White blood cell count decreased	2 (1.3)	0	0	0
Pancytopenia	1 (0.7)	1 (0.7)	0	0
Neutrophil count decreased	1 (0.7)	0	1 (0.6)	0
Myelosuppression	0	0	1 (0.6)	1 (0.6)
Erythropenia	0	0	1 (0.6)	0

* Any event of myelosuppression

Table 60. Incidence of serious myelosuppression etc. (PAPILLON study)

PT (MedDRA ver.25.0)	n (%)	
	Amivantamab/CP N = 151	CP N = 155
Myelosuppression leading to death	0	0
Serious myelosuppression	4 (2.6)	7 (4.5)
Thrombocytopenia	3 (2.0)	5 (3.2)
Neutropenia	2 (1.3)	0
Febrile neutropenia	1 (0.7)	3 (1.9)
Leukopenia	1 (0.7)	0
Myelosuppression	0	1 (0.6)
Myelosuppression leading to treatment discontinuation*	3 (2.0)	4 (2.6)
Neutropenia	3 (2.0)	2 (1.3)
Thrombocytopenia	1 (0.7)	3 (1.9)
Myelosuppression leading to dose or infusion interruption*	32 (21.2)	17 (11.0)
Neutropenia	25 (16.6)	11 (7.1)
Thrombocytopenia	9 (6.0)	8 (5.2)
Leukopenia	6 (4.0)	3 (1.9)
Febrile neutropenia	0	1 (0.6)
Lymphocyte count decreased	1 (0.7)	0
Neutrophil count decreased	1 (0.7)	0
White blood cell count decreased	1 (0.7)	0
Myelosuppression leading to dose reduction*	20 (13.2)	21 (13.5)
Neutropenia	14 (9.3)	8 (5.2)
Thrombocytopenia	10 (6.6)	13 (8.4)
Leukopenia	2 (1.3)	5 (3.2)
Febrile neutropenia	2 (1.3)	1 (0.6)
Myelosuppression	0	1 (0.6)

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

Table 61 shows the details of patients with serious myelosuppression for which a causal relationship to amivantamab could not be ruled out in the clinical studies of amivantamab including the PAPILLON study.[47)]

Table 61. Listing of patients with serious myelosuppression for which a causal relationship to amivantamab could not be ruled out

Study ID	Age	Sex	Concomitant medications	PT (MedDRA ver.25.0)	Grade	Time to onset (days)	Duration (days)	Action taken with amivantamab	Outcome
PAPILLON	5[redacted]	M	CP	Thrombocytopenia	3	52	10	None	Resolving
MARIPOSA-2	6[redacted]	F	CP	Thrombocytopenia	3	10	3	Dose or infusion interrupted	Resolving
				Thrombocytopenia	4	12	3	Dose or infusion interrupted	Resolving
				Thrombocytopenia	3	14	3	Dose or infusion interrupted	Resolving
				Thrombocytopenia	2	16	3	Dose or infusion interrupted	Resolving
				Thrombocytopenia	1	18	4	Dose or infusion interrupted	Resolved
MARIPOSA	6[redacted]	F	Lazertinib	Bone marrow failure	4	112	55	Dose or infusion interrupted	Not resolved

PMDA's view:

Among the events of myelosuppression observed in the PAPILLON study, the incidences of neutropenia, leukopenia, etc. were higher in the amivantamab/CP group than in the CP group, but there were no clear differences in the incidence of serious myelosuppression. The events of serious myelosuppression for which a causal relationship to amivantamab could not be ruled out observed in the clinical studies of amivantamab including the PAPILLON study were limited, and a causal relationship to concomitant medications also could not be ruled out for all those events. Given these points etc., it is difficult at present to draw a definitive conclusion on the risk of myelosuppression associated with amivantamab. Thus, no particular precautionary statement is needed at present, on the premise that information on the incidence of myelosuppression in the clinical studies will be provided using the package insert and other materials.

7.R.3.13 Others

(1) Gastrointestinal disorders (excluding diarrhoea)

The applicant's explanation about gastrointestinal disorders (excluding diarrhoea) associated with amivantamab:

Events in the MedDRA SOC "gastrointestinal disorders" (excluding MedDRA PT "diarrhoea") were counted as gastrointestinal disorders (excluding diarrhoea).

The incidence of gastrointestinal disorders (excluding diarrhoea) in the PAPILLON study is shown in Table 62 and Table 63. In the amivantamab/CP group of the PAPILLON study, the median time to the first onset of gastrointestinal disorder (excluding diarrhoea) (min., max.) (days) was 5 (1, 633).

Table 62. Incidence of gastrointestinal disorders (excluding diarrhoea)[*1] (PAPILLON study)

PT (MedDRA ver.25.0)	n (%)			
	Amivantamab/CP N = 151		CP N = 155	
	All Grades	Grade ≥3	All Grades	Grade ≥3
Gastrointestinal disorders (excluding diarrhoea)[*2]	125 (82.8)	13 (8.6)	108 (69.7)	5 (3.2)
Constipation	60 (39.7)	0	47 (30.3)	1 (0.6)
Nausea	55 (36.4)	1 (0.7)	65 (41.9)	0
Stomatitis	38 (25.2)	2 (1.3)	9 (5.8)	0
Vomiting	32 (21.2)	5 (3.3)	29 (18.7)	1 (0.6)
Haemorrhoids	18 (11.9)	2 (1.3)	2 (1.3)	0
Mouth ulceration	12 (7.9)	0	4 (2.6)	0
Abdominal pain	11 (7.3)	1 (0.7)	4 (2.6)	0
Gingival bleeding	8 (5.3)	0	2 (1.3)	0
Abdominal distension	7 (4.6)	0	10 (6.5)	0
Anal fissure	7 (4.6)	0	1 (0.6)	0
Dry mouth	5 (3.3)	0	2 (1.3)	0
Cheilitis	4 (2.6)	1 (0.7)	0	0
Abdominal pain upper	4 (2.6)	0	8 (5.2)	0
Dyspepsia	4 (2.6)	0	6 (3.9)	0
Gastrooesophageal reflux disease	4 (2.6)	0	1 (0.6)	0
Dysphagia	3 (2.0)	0	1 (0.6)	0
Angular cheilitis	3 (2.0)	0	0	0
Anal inflammation	2 (1.3)	0	0	0
Abdominal discomfort	1 (0.7)	0	2 (1.3)	0
Eructation	2 (1.3)	0	0	0
Gastritis	1 (0.7)	0	2 (1.3)	0
Gastrointestinal haemorrhage	0	0	2 (1.3)	2 (1.3)
Odynophagia	2 (1.3)	0	0	0
Proctalgia	2 (1.3)	0	0	0
Rectal haemorrhage	2 (1.3)	0	1 (0.6)	0
Toothache	2 (1.3)	0	1 (0.6)	0

*1 Adverse events reported by ≥2 subjects in either group are listed.
*2 Any event of gastrointestinal disorder (excluding diarrhoea)

Table 63. Incidence of serious gastrointestinal disorders (excluding diarrhoea) etc. (PAPILLON study)

PT (MedDRA ver.25.0)	n (%)	
	Amivantamab/CP N = 151	CP N = 155
Gastrointestinal disorders (excluding diarrhoea) leading to death	0	0
Serious gastrointestinal disorders (excluding diarrhoea)	8 (5.3)	3 (1.9)
Vomiting	3 (2.0)	1 (0.6)
Abdominal pain	1 (0.7)	0
Cheilitis	1 (0.7)	0
Duodenitis	1 (0.7)	0
Enterocolitis	1 (0.7)	0
Lower gastrointestinal haemorrhage	1 (0.7)	0
Ascites	0	1 (0.6)
Gastrointestinal haemorrhage	0	1 (0.6)
Gastrointestinal disorders (excluding diarrhoea) leading to treatment discontinuation*	0	0
Gastrointestinal disorders (excluding diarrhoea) leading to dose or infusion interruption*	7 (4.6)	1 (0.6)
Nausea	2 (1.3)	1 (0.6)
Vomiting	2 (1.3)	0
Abdominal pain	1 (0.7)	0
Duodenitis	1 (0.7)	0
Rectal haemorrhage	1 (0.7)	0
Stomatitis	1 (0.7)	0
Gastrointestinal disorders (excluding diarrhoea) leading to dose reduction*	6 (4.0)	4 (2.6)
Vomiting	2 (1.3)	1 (0.6)
Stomatitis	2 (1.3)	0
Cheilitis	1 (0.7)	0
Enterocolitis	1 (0.7)	0
Nausea	1 (0.7)	4 (2.6)
Constipation	0	1 (0.6)

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

Table 64 shows the details of patients with serious gastrointestinal disorders (excluding diarrhoea) for which a causal relationship to amivantamab could not be ruled out in the clinical studies of amivantamab including the PAPILLON study.[47)]

Table 64. Listing of patients with serious gastrointestinal disorders (excluding diarrhoea) for which a causal relationship to amivantamab could not be ruled out

Study ID	Age	Sex	Concomitant medications	PT (MedDRA ver.25.0)	Grade	Time to onset (days)	Duration (days)	Action taken with amivantamab	Outcome
PAPILLON	6[redacted]	F	CP	Cheilitis	3	273	7	Dose reduced	Resolving
	3[redacted]	F	CP	Vomiting	3	24	3	None	Resolved
	5[redacted]	F	CP	Vomiting	3	8	7	Dose reduced	Resolved
	8[redacted]	M	CP	Duodenitis	2	6	18	Dose or infusion interrupted	Resolved
EDI1001	3[redacted]	F	Lazertinib	Vomiting	2	177	4	None	Resolved
	6[redacted]	M	Lazertinib	Stomatitis	2	12	39	Dose or infusion interrupted	Resolving
	6[redacted]	M	CP	Nausea	3	29	15	None	Resolving
				Nausea	2	44	20	Dose or infusion interrupted	Resolved
CHRYSALIS-2	6[redacted]	F	Lazertinib	Gastric perforation	4	51	120	Dose or infusion interrupted	Not resolved
	6[redacted]	F	Lazertinib	Pancreatitis acute	4	23	7	None	Resolved
	4[redacted]	M	Lazertinib	Nausea	2	9	3	None	Resolving
				Nausea	1	11	Unknown	None	Not resolved
	7[redacted]	F	Lazertinib	Stomatitis	3	40	56	Dose or infusion interrupted	Resolving
	6[redacted]	F	Lazertinib	Nausea	3	29	6	Dose or infusion interrupted	Resolving
MARIPOSA	6[redacted]	F	Lazertinib	Gastritis	3	158	Unknown	None	Not resolved
	6[redacted]	F	Lazertinib	Nausea	3	15	7	Dose or infusion interrupted	Resolved
	6[redacted]	M	Lazertinib	Vomiting	3	162	25	Dose or infusion interrupted	Resolving
				Colitis	4	171	17	Dose or infusion interrupted	Resolved

PMDA's view:

In the PAPILLON study, although the incidence of gastrointestinal disorders (excluding diarrhoea) was higher in the amivantamab/CP group than in the CP group, serious gastrointestinal disorders (excluding diarrhoea) reported by more than 1 subject were vomiting, which was unlikely to lead to a serious outcome. For all of serious gastrointestinal disorders (excluding diarrhoea) for which a causal relationship to amivantamab could not be ruled out observed in the clinical studies of amivantamab including the PAPILLON study, a causal relationship to concomitant medications also could not be ruled out. Given these points etc., no particular precautionary statement concerning gastrointestinal disorders (excluding diarrhoea) associated with amivantamab is needed at present.

(2) Renal dysfunction

The applicant's explanation about renal dysfunction associated with amivantamab:

Events in the MedDRA SMQ "acute renal failure (broad)" were counted as renal dysfunction.

The incidence of renal dysfunction in the PAPILLON study is shown in Table 65 and Table 66. In the amivantamab/CP group of the PAPILLON study, the median time to the first onset of renal dysfunction (min., max.) (days) was 162 (7, 541).

Table 65. Incidence of renal dysfunction (PAPILLON study)

PT (MedDRA ver.25.0)	n (%)			
	Amivantamab/CP N = 151		CP N = 155	
	All Grades	Grade ≥3	All Grades	Grade ≥3
Renal dysfunction*	21 (13.9)	4 (2.6)	20 (12.9)	0
Blood creatinine increased	11 (7.3)	2 (1.3)	15 (9.7)	0
Blood urea increased	2 (1.3)	0	3 (1.9)	0
Creatinine renal clearance decreased	1 (0.7)	0	1 (0.6)	0
Acute kidney injury	1 (0.7)	1 (0.7)	0	0
Renal impairment	4 (2.6)	1 (0.7)	2 (1.3)	0
Nephropathy toxic	1 (0.7)	0	0	0
Proteinuria	2 (1.3)	0	0	0
Renal failure	2 (1.3)	0	0	0

* Any event of renal dysfunction

Table 66. Incidence of serious renal dysfunction etc. (PAPILLON study)

PT (MedDRA ver.25.0)	n (%)	
	Amivantamab/CP N = 151	CP N = 155
Renal dysfunction leading to death	0	0
Serious renal dysfunction	2 (1.3)	1 (0.6)
Blood creatinine increased	1 (0.7)	1 (0.6)
Acute kidney injury	1 (0.7)	0
Renal dysfunction leading to treatment discontinuation*	2 (1.3)	2 (1.3)
Nephropathy toxic	1 (0.7)	0
Renal impairment	1 (0.7)	1 (0.6)
Blood creatinine increased	0	1 (0.6)
Renal dysfunction leading to dose or infusion interruption*	2 (1.3)	5 (3.2)
Blood creatinine increased	1 (0.7)	3 (1.9)
Creatinine renal clearance decreased	0	1 (0.6)
Renal impairment	1 (0.7)	1 (0.6)
Renal dysfunction leading to dose reduction*	2 (1.3)	1 (0.6)
Creatinine renal clearance decreased	1 (0.7)	0
Blood creatinine increased	0	1 (0.6)
Renal impairment	1 (0.7)	0

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

Table 67 shows the details of patients with serious renal dysfunction for which a causal relationship to amivantamab could not be ruled out in the clinical studies of amivantamab including the PAPILLON study.[47)]

Table 67. Listing of patients with serious renal dysfunction for which a causal relationship to amivantamab could not be ruled out

Study ID	Age	Sex	Concomitant medications	PT (MedDRA ver.25.0)	Grade	Time to onset (days)	Duration (days)	Action taken with amivantamab	Outcome
PAPILLON	6[redacted]	F	CP	Blood creatinine increased	3	253	5	None	Resolved
CHRYSALIS-2	4[redacted]	F	Lazertinib	Acute kidney injury	3	8	9	Dose or infusion interrupted	Sequelae
MARIPOSA-2	5[redacted]	F	CP	Blood creatinine increased	3	176	Unknown	Dose or infusion interrupted	Not resolved

PMDA's view:

There were no clear differences in the incidence of renal dysfunction between the amivantamab/CP and CP groups in the PAPILLON study. The events of serious renal dysfunction for which a causal relationship to amivantamab could not be ruled out observed in the clinical studies of amivantamab including the PAPILLON study were limited, and a causal relationship to concomitant medications also could not be ruled out for all

those events. Given these points etc., no particular precautionary statement concerning renal dysfunction associated with amivantamab is needed at present.

(3) Arterial thromboembolism

The applicant's explanation about arterial thromboembolism associated with amivantamab:

Events in the MedDRA SMQ "embolic and thrombotic events, arterial (narrow)" were counted as arterial thromboembolism.

The incidence of arterial thromboembolism in the PAPILLON study is shown in Table 68 and Table 69. In the amivantamab/CP group of the PAPILLON study, the median time to the first onset of arterial thromboembolism (min., max.) (days) was 232.5 (8, 457).

Table 68. Incidence of arterial thromboembolism (PAPILLON study)

PT (MedDRAver.25.0)	n (%)			
	Amivantamab/CP N = 151		CP N = 155	
	All Grades	Grade ≥3	All Grades	Grade ≥3
Arterial thromboembolism*	2 (1.3)	0	3 (1.9)	2 (1.3)
Acute myocardial infarction	0	0	1 (0.6)	1 (0.6)
Lacunar infarction	0	0	1 (0.6)	1 (0.6)
Transient ischaemic attack	1 (0.7)	0	0	0
Arterial thrombosis	0	0	1 (0.6)	0
Peripheral arterial occlusive disease	1 (0.7)	0	0	0

*Any event of arterial thromboembolism

Table 69. Incidence of serious arterial thromboembolism etc. (PAPILLON study)

PT (MedDRAver.25.0)	n (%)	
	Amivantamab/CP N = 151	CP N = 155
Arterial thromboembolism leading to death	0	1 (0.6)
Acute myocardial infarction	0	1 (0.6)
Serious arterial thromboembolism	1 (0.7)	2 (1.3)
Acute myocardial infarction	0	1 (0.6)
Lacunar infarction	0	1 (0.6)
Transient ischaemic attack	1 (0.7)	0
Arterial thromboembolism leading to treatment discontinuation*	0	1 (0.6)
Acute myocardial infarction	0	1 (0.6)
Arterial thromboembolism leading to dose or infusion interruption*	1 (0.7)	0
Transient ischaemic attack	1 (0.7)	0
Arterial thromboembolism leading to dose reduction*	0	0

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

Table 70 shows the details of patients with serious arterial thromboembolism for which a causal relationship to amivantamab could not be ruled out in the clinical studies of amivantamab including the PAPILLON study.[47)]

Table 70. Listing of patients with serious arterial thromboembolism for which a causal relationship to amivantamab could not be ruled out

Study ID	Age	Sex	Concomitant medications	PT (MedDRA ver.25.0)	Grade	Time to onset (days)	Duration (days)	Action taken with amivantamab	Outcome
CHRYSALIS-2	8[redacted]	F	Lazertinib	Myocardial infarction	3	6	10	Discontinued	Resolving
MARIPOSA	8[redacted]	F	Lazertinib	Myocardial infarction	5	524	1	Discontinued	Fatal
	6[redacted]	F	Lazertinib	Myocardial infarction	3	285	5	None	Not resolved
				Myocardial infarction	5	289	1	Discontinued	Fatal

PMDA's view:

There were no clear differences in the incidence of arterial thromboembolism between the amivantamab/CP and CP groups in the PAPILLON study. The events of serious arterial thromboembolism for which a causal relationship to amivantamab could not be ruled out observed in the clinical studies of amivantamab including the PAPILLON study were limited, and a causal relationship to concomitant medications also could not be ruled out for all those events. Some of these cases were potentially associated with complications etc. Given these points etc., no particular precautionary statement concerning arterial thromboembolism associated with amivantamab is needed at present.

(4) Eye disorders

The applicant's explanation about eye disorders associated with amivantamab:

Events in the MedDRA SOC "eye disorders" were counted as eye disorders.

The incidence of eye disorders in the PAPILLON study is shown in Table 71 and Table 72. In the amivantamab/CP group of the PAPILLON study, the median time to the first onset of eye disorder (min., max.) (days) was 97.5 (1, 547).

Table 71. Incidence of eye disorders[*1] (PAPILLON study)

PT (MedDRA ver.25.0)	n (%)			
	Amivantamab/CP N = 151		CP N = 155	
	All Grades	Grade ≥3	All Grades	Grade ≥3
Eye disorders[*2]	28 (18.5)	0	28 (18.1)	0
Dry eye	7 (4.6)	0	5 (3.2)	0
Xerophthalmia	4 (2.6)	0	2 (1.3)	0
Lacrimation increased	3 (2.0)	0	8 (5.2)	0
Blepharitis	3 (2.0)	0	2 (1.3)	0
Cataract	3 (2.0)	0	1 (0.6)	0
Conjunctival haemorrhage	3 (2.0)	0	0	0
Vision blurred	2 (1.3)	0	2 (1.3)	0
Eye irritation	2 (1.3)	0	1 (0.6)	0
Eyelid oedema	2 (1.3)	0	1 (0.6)	0
Visual impairment	0	0	3 (1.9)	0
Conjunctivitis allergic	0	0	2 (1.3)	0

*1 Adverse events reported by ≥2 subjects in either group are listed.
*2 Any event of eye disorder

Table 72. Incidence of serious eye disorders etc. (PAPILLON study)

PT (MedDRA ver.25.0)	n (%)	
	Amivantamab/CP N = 151	CP N = 155
Eye disorders leading to death	0	0
Serious eye disorders	0	0
Eye disorders leading to treatment discontinuation*	0	0
Eye disorders leading to dose or infusion interruption*	1 (0.7)	0
Eye pain	1 (0.7)	0
Eye disorders leading to dose reduction*	1 (0.7)	2 (1.3)
Eyelid oedema	1 (0.7)	0
Blepharitis	0	1 (0.6)
Periorbital oedema	0	1 (0.6)

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

Table 73 shows the details of patients with serious eye disorders for which a causal relationship to amivantamab could not be ruled out in the clinical studies of amivantamab including the PAPILLON study.[47)]

Table 73. Listing of patients with serious eye disorders for which a causal relationship to amivantamab could not be ruled out

Study ID	Age	Sex	Concomitant medications	PT (MedDRA ver.25.0)	Grade	Time to onset (days)	Duration (days)	Action taken with amivantamab	Outcome
CHRYSALIS-2	7[redacted]	F	Lazertinib	Corneal erosion	3	127	3	Dose or infusion interrupted	Resolving
				Corneal erosion	3	179	3	Dose or infusion interrupted	Resolved
				Corneal erosion	3	277	42	Dose or infusion interrupted	Resolved
	7[redacted]	F	Lazertinib	Ulcerative keratitis	3	72	14	Dose or infusion interrupted	Not resolved
MARIPOSA	7[redacted]	M	Lazertinib	Keratitis	3	463	33	Dose or infusion interrupted	Resolving
				Giant papillary conjunctivitis	3	485	11	Dose or infusion interrupted	Resolving

PMDA's view:

There were no clear differences in the incidence of eye disorders between the amivantamab/CP and CP groups in the PAPILLON study. The events of serious eye disorders for which a causal relationship to amivantamab could not be ruled out observed in the clinical studies of amivantamab including the PAPILLON study were limited, and a causal relationship to concomitant medications also could not be ruled out for most of these events. Given these points etc., no particular precautionary statement concerning eye disorders associated with amivantamab is needed at present.

7.R.4 Clinical positioning and indication

The proposed indication for amivantamab is shown in the table below. After the submission of the present application, the applicant explained that the statements in the table below would be included in the PRECAUTIONS CONCERNING INDICATION section.

Indication	Precautions Concerning Indication
Inoperable or recurrent non-small cell lung cancer with EGFR exon 20 insertion mutations	● 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 amivantamab. ● The efficacy and safety of amivantamab in the neoadjuvant or adjuvant setting have not been established. ● Amivantamab 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.

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 INDICATION and PRECAUTIONS CONCERNING INDICATION sections.

Indication	Precautions Concerning Indication
EGFR exon 20 insertion mutation-positive unresectable advanced or recurrent non-small cell lung cancer	● Eligible patients must be selected by physicians with a full understanding of the information presented in the CLINICAL STUDIES section concerning the histology, type of genetic mutation, etc., in patients enrolled in the clinical study and of the efficacy and safety of amivantamab. ● The efficacy and safety of amivantamab in the neoadjuvant or adjuvant setting have not been established. ● Amivantamab 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.

7.R.4.1 Clinical positioning and indication of amivantamab

Amivantamab/CP for patients with EGFRex20 insertion mutation-positive unresectable advanced or recurrent NSCLC previously untreated with chemotherapy is described as follows in the major Japanese/foreign clinical practice guidelines and textbook of clinical oncology:

[Clinical practice guidelines]

- NCCN guidelines (v.5.2024)
  - Amivantamab/CP is recommended as the preferred first-line therapy option for EGFRex20 insertion mutation-positive unresectable advanced or recurrent NSQ-NSCLC.

The applicant's explanation about the clinical positioning and indication of amivantamab:

Since the PAPILLON study in patients with EGFRex20 insertion mutation-positive unresectable advanced or recurrent NSQ-NSCLC previously untreated with chemotherapy demonstrated the clinical usefulness of amivantamab/CP [see Sections 7.R.2 and 7.R.3], amivantamab/CP should be positioned as a treatment option for these patients.

Since no clinical studies have evaluated the efficacy and safety of amivantamab in the neoadjuvant or adjuvant setting for NSCLC, the use of amivantamab in the neoadjuvant or adjuvant setting is not recommended.

In addition, (i) while the frequency of *EGFR* mutations is 10% to 40% in NSCLC adenocarcinoma, *EGFR* mutations are very rare in patients with SQ-NSCLC (*N Engl J Med*. 2008; 359: 1367-80) and (ii) EGFRex20 insertion mutations account for 4% to 12% of all *EGFR* mutations in NSCLC patients (*Sci Rep*. 2021; 11: 18762). Given these reports, the number of patients with EGFRex20 insertion mutation-positive SQ-NSCLC was considered very limited. Thus, these patients were not included in the PAPILLON study. Although

there are no data from clinical studies intended to evaluate the efficacy of amivantamab/CP in patients with EGFRex20 insertion mutation-positive SQ-NSCLC, the Japanese and foreign clinical practice guidelines recommend drugs targeting EGFR for unresectable advanced or recurrent NSCLC, based on *EGFR* mutation status, regardless of histology. Given the recommendation, amivantamab will be used properly, provided that the following information is included in the CLINICAL STUDIES section of the package insert: "Patients with NSQ-NSCLC were included in the PAPILLON study," and that the following statement is included in the PRECAUTIONS CONCERNING INDICATION section: "Eligible patients must be selected by physicians with a full understanding of the information presented in the CLINICAL STUDIES section, etc."

Based on the above, after providing the information on the histology of patients enrolled in the clinical study in the CLINICAL STUDIES section of the package insert and including the following statements in the PRECAUTIONS CONCERNING INDICATION section, the indication of "inoperable or recurrent non-small cell lung cancer with EGFR exon 20 insertion mutations" was proposed.

- 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 amivantamab.
- The efficacy and safety of amivantamab in the neoadjuvant or adjuvant setting have not been established.

The applicant's view on when to use (1) EGFR-TKIs approved for the indication of *EGFR* mutation-positive unresectable advanced or recurrent NSCLC or (2) ICI in combination with chemotherapy approved for the indication of unresectable advanced or recurrent NSCLC and when to use amivantamab/CP in Japan:

(1) EGFR-TKIs

Given the following descriptions on EGFR-TKIs in the Japanese and foreign clinical practice guidelines, etc., amivantamab should be preferred over EGFR-TKIs.

- Japanese clinical practice guideline (2023)

  The guideline recommends against treatment with an EGFR-TKI in patients with EGFRex20 insertion mutation-positive NSCLC.
- NCCN guidelines (v.5.2024)

  EGFRex20 insertion mutation-positive NSCLC, except for p.A763_Y764insFQEA and p.A763_Y764insLQEA, is resistant to EGFR-TKI therapy.
- ESMO guideline (2023)

  The majority of patients with EGFRex20 insertion mutation-positive NSCLC are resistant to the existing EGFR-TKIs.

(2) ICI in combination with chemotherapy

Given the following descriptions on ICI in combination with chemotherapy in the foreign clinical practice guidelines, amivantamab should be preferred over ICI in combination with chemotherapy:

- NCCN guidelines (v.5.2024)

  Although ICI in combination with chemotherapy is a first-line therapy option for EGFRex20 insertion mutation-positive NSCLC, amivantamab/CP is the preferred option.
- ESMO guideline (2023)

EGFRex20 insertion mutation-positive NSCLC shows limited sensitivity to ICIs.

PMDA's view:
PMDA largely accepted the above explanation by the applicant. As to the precautionary statement in the package insert (i.e., "Eligible patients must be selected by physicians with a full understanding of the information presented in the CLINICAL STUDIES section of the package insert"), "concerning the histology etc. of patients enrolled in the clinical study" should be added to convey clear intention of the precautionary statement.

Based on the above, PMDA concluded that the proposed statements in the INDICATION and PRECAUTIONS CONCERNING INDICATION sections should be modified as follows:

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

Precautions Concerning Indication
- Eligible patients must be selected by physicians with a full understanding of the information presented in the CLINICAL STUDIES section concerning the histology etc. of patients enrolled in the clinical study and of the efficacy and safety of amivantamab.
- The efficacy and safety of amivantamab in the neoadjuvant or adjuvant setting have not been established.

7.R.4.2 Testing for EGFRex20 insertion mutations
The applicant's explanation about testing for EGFRex20 insertion mutations to be used for selection of eligible patients:
Patients with a documented EGFRex20 insertion mutation by testing of tumor tissue or blood samples performed by a certified or accredited local laboratory were enrolled in the PAPILLON study, which demonstrated the clinical usefulness of amivantamab/CP in this patient population [see Sections 7.R.2 and 7.R.3]. The hazard ratios for PFS as assessed by BICR according to RECIST ver.1.1 for amivantamab/CP vs. CP [95% CI] by (1) type of sample (tumor tissue and blood) and (2) test method (polymerase chain reaction [PCR] and next generation sequencing [NGS]) used for testing at enrollment were (1) 0.395 [0.295, 0.529] and 0.308 [0.095, 0.997], respectively, and (2) 0.489 [0.329, 0.727] and 0.313 [0.208, 0.471], respectively.[49)]

As companion diagnostics etc. for amivantamab, "Oncomine Dx Target Test Multi-CDx system" using tumor tissue samples was submitted by Life Technologies Japan Ltd. for marketing approval, and "Guardant360 CDx Cancer Gene Panel" using blood samples was submitted by Guardant Health Japan Corp. for marketing approval. A high degree of concordance was observed between these CDx tests and the local tests used in the PAPILLON study. For this reason, among others, a group of patients who are expected to clinically benefit from amivantamab/CP can be identified appropriately.

[49)] (1) Tumor tissue samples (145 subjects in the amivantamab/CP group and 139 subjects in the CP group) and blood samples (8 subjects and 16 subjects, respectively), (2) PCR test (71 subjects and 66 subjects, respectively) and NGS test (82 subjects and 89 subjects, respectively)

After patient enrollment in the PAPILLON study based on the results of testing performed by a certified or accredited local laboratory, central testing was performed for 153 tumor tissue samples using "Oncomine Dx Target Test Multi-CDx system"[50] and 209 plasma samples using "Guardant360 CDx Cancer Gene Panel."[51] The types of EGFRex20 insertion mutations detected by central testing ("Oncomine Dx Target Test Multi-CDx system" and "Guardant360 CDx Cancer Gene Panel") and the results of PFS by type of mutation are shown in Table 74 and Table 75, respectively.

Table 74. Types of EGFRex20 insertion mutations detected by central testing with "Oncomine Dx Target Test Multi-CDx system" or "Guardant360 CDx Cancer Gene Panel" in the PAPILLON study

Type of mutation	Number of subjects	
	Oncomine Dx Target Test Multi-CDx system	Guardant360 CDx Cancer Gene Panel
A763_Y764insFQEA	2	3
A767_V769dup	47	50
S768_V769delinsIL	1	－
S768_V769insVGT	1	－
S768_D770dup	22	31
V769_D770insCV	1	1
V769_D770insGG	－	1
D770delinsANPP	1	1
D770delinsGP	1	1
D770delinsGY	1	1
D770dup	－	1
D770_N771insG	4	10
D770_N771insGF	1	1
D770_N771insGN	1	1
D770_N771insNPG	1	－
D770_P772dup	1	1
D770_V774dup	－	1
N771delinsGF	2	1
N771delinsGY	3	2
N771_P772insH	1	3
N771_P772insPHH	1	－
N771_H773dup	13	18
P772delinsRHNR	－	1
P772_H773dup	4	5
P772_H773insQ	1	1
H773delinsPNPY	2	－
H773delinsYNPY	2	2
H773dup	8	6
H773_V774insAH	1	2
H773_V774insGHPH	－	1
H773_V774insTH	－	2
H773_V774insY	1	1
H773_V774dup	3	2
V774_C775insHV	1	4

－, Not applicable

[50] Of 308 subjects enrolled in the PAPILLON study, 87 subjects enrolled in China, 60 subjects with insufficient tumor content or DNA quantity, and 8 subjects with unavailable tumor issue sample were excluded from testing. The samples from the remaining 153 subjects were tested. Of the 153 tumor tissue samples, 128 were positive for EGFRex20 insertion mutations, 3 were negative for EGFRex20 insertion mutations, and 22 failed analysis.

[51] Of 308 subjects enrolled in the PAPILLON study, 87 subjects enrolled in China and 12 subjects with missing sample or poor sample quality etc. were excluded from testing. The samples from the remaining 209 subjects were tested. Among the 209 subjects, 155 were identified as EGFRex20 insertion mutation-positive, 50 were identified as EGFRex20 insertion mutation-negative, and 4 failed analysis.

Table 75. Results of PFS analysis by type of EGFRex20 insertion mutation detected by central testing with "Oncomine Dx Target Test Multi-CDx system" or "Guardant360 CDx Cancer Gene Panel" in the PAPILLON study (BICR, FAS, data cutoff date of May 3, 2023)

Test	Amino acid insertion site	Treatment group	N	No. of events (%)	Median [95% CI] (months)	Hazard ratio[*2] [95% CI]
Oncomine Dx Target Test Multi-CDx system	Any insertion site	Amivantamab/CP	66	35 (53.0)	11.14 [8.38, 17.58]	0.311 [0.194, 0.495]
		CP	62	56 (90.3)	6.67 [5.55, 8.51]	
	(1) A767_S768	Amivantamab/CP	24	12 (50.0)	11.37 [7.72, not reached]	0.283 [0.136, 0.588]
		CP	23	23 (100)	5.59 [4.80, 8.51]	
	(2) S768_V769	Amivantamab/CP	10	6 (60.0)	11.07 [0.85, not reached]	0.436 [0.155, 1.232]
		CP	14	11 (78.6)	8.84 [2.69, 9.49]	
	(3) Others	Amivantamab/CP	32	17 (53.1)	11.14 [7.20, not reached]	0.300 [0.149, 0.606]
		CP	25	22 (88.0)	6.67 [4.21, 8.54]	
Guardant360 CDx Cancer Gene Panel	Any insertion site	Amivantamab/CP	82	50 (61.0)	11.14 [8.31, 12.45]	0.374 [0.253, 0.554]
		CP	73	67 (91.8)	5.65 [5.49, 7.00]	
	(1) A767_S768	Amivantamab/CP	28	18 (64.3)	11.30 [7.75, 15.18]	0.231 [0.113, 0.469]
		CP	22	22 (100)	5.44 [4.21, 6.70]	
	(2) S768_V769	Amivantamab/CP	16	10 (62.5)	8.28 [4.30, not reached]	0.623 [0.270, 1.433]
		CP	15	14 (93.3)	7.69 [4.37, 9.56]	
	(3) N771_P772	Amivantamab/CP	14	6 (42.9)	11.47 [5.36, not reached]	0.308 [0.104, 0.908]
		CP	10	10 (100)	6.70 [3.25, 11.07]	
	(4) Others	Amivantamab/CP	24	16 (66.7)	12.22 [6.74, 17.58]	0.414 [0.208, 0.824]
		CP	26	21 (80.8)	5.65 [4.14, 8.67]	

Table 76 shows EGFRex20 insertion mutations eligible for enrollment in the PAPILLON study and EGFRex20 insertion mutations eligible for treatment with amivantamab as assessed by testing with "Oncomine Dx Target Test Multi-CDx system" or "Guardant360 CDx Cancer Gene Panel."

Table 76. EGFRex20 insertion mutations eligible for enrollment in the PAPILLON study and EGFRex20 insertion mutations detected by testing with "Oncomine Dx Target Test Multi-CDx system" or "Guardant360 CDx Cancer Gene Panel" to identify eligibility for treatment with amivantamab

PAPILLON study	Oncomine Dx Target Test Multi-CDx system	Guardant360 CDx Cancer Gene Panel
All EGFRex20 insertion mutations (Mutations that could be detected by testing performed by a certified or accredited local laboratory)	A763_Y764insFQEA	In-frame EGFRex20 insertion mutations (Information on the type of specific mutations to be detected is not available to the applicant.)
	Y764_D770dup	
	M766_A767insAI, M766_A767insATL	
	A767_S768insSVG, A767_S768insYVM, A767_V769dup	
	S768_V769delinsIL, S768_V769insVAN, S768_V769insVDN, S768_V769insVDNP, S768_V769insVC, S768_V769insVGT, S768_V769insVGV	
	D769insASV	
	V769_D770insASV, V769_D770insGG, V769_D770insDNP, V769_D770insDG, V769_D770insDK, V769_D770insERG, V769_D770insMASVD, V769dup	
	D770_N771delinsAGH, D770_N771insNP, D770_N771insNPG, D770_N771insNPHG, D770_N771insNPP, D770_N771insQRG, D770_N771insGN, D770_N771insP, D770_N771insSVE, D770_N771insT, D770_N771insY, D770delinsANPP, D770delinsGP, D770delinsGTH, D770_N771delinsAGG, D770_N771insAPW, D770_N771insG, D770_N771insGF, D770_N771insGL, D770_N771insGT, D770_N771insH, D770_N771insMATP, D770_N771insSVD, D770>GY, D770delinsNNPH	
	N771_H773dup, N771_P772insRH, N771_P772insHH, N771_P772insL, N771_P772insPHH, N771_P772insPHV, N771_P772insPTH, N771_P772insT, N771_P772insV, N771delinsGF, N771delinsGY, N771delinsKG, N771delinsKL, N771delinsSGH, N771delinsSH, N771delinsSTH, N771delinsVH, N771dup, N771_P772insH, N771_P772insHN, N771delinsKH, N771delinsPH, N771delinsTH	
	P772_H773insGT, P772_H773insHV, P772_H773insTP, P772_H773insV, P772_H773insR, P772_H773insQ, P772_H773insGNP, P772_H773insHA, P772_H773insHN, P772_H773insTPNP	
	H773_V774insH, H773_V774insNPH, H773_V774insPH, H773_V774insPHPH, H773_V774insQ, H773_V774insTQPP, H773delinsPNPY, H773delinsRY, H773_V774dup, H773_V774insY, H773delinsNPY, H773delinsYNPY, H773delinsYDPNPY	
	V774_C775insHV, V774_C775insPR	

Based on the above, "Oncomine Dx Target Test Multi-CDx system" or "Guardant360 CDx Cancer Gene Panel" should be used for the selection of patients for treatment with amivantamab, and the following statement will be included in the PRECAUTIONS CONCERNING INDICATION section.

- Amivantamab 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.

PMDA asked the applicant to explain the relationship between the type of EGFRex20 insertion mutation and the efficacy of amivantamab.

The applicant's response:

As EGFRex20 insertion mutations, insertions of at least 1 amino acid in the C-helix or the loop following the C-helix domain (D761 to C775) of the EGFRex20 have been reported (*Sig Transduct Target Ther*. 2019; 4: 5 and *Nat Med*. 2018; 24: 638-46). Like EGFRex19 deletions, which are known as EGFR activating mutations, amino acid insertions in the above domains destabilize the inactive form of EGFR, i.e., a C-helix out conformation, causing a shift towards its active form, a C-helix in conformation, which results in activation of EGFR-mediated signaling (*Sig Transduct Target Ther*. 2019; 4: 5).

The majority of the mutations of amino acid insertions in the above domains[52)] have been reported to confer poor response to the existing EGFR-TKIs due to steric hindrance of their binding sites resulting from a structural alteration in the loop of the EGFR tyrosine kinase domain (*Sig Transduct Target Ther*. 2019; 4: 5, *Cancer Sci.* 2016; 107: 1179-86, etc.). In contrast, amivantamab binds to the extracellular domain of EGFR and therefore is not affected by this structural alteration. Thus, the efficacy of amivantamab is expected in the treatment of NSCLC with activated EGFR-mediated signaling, including NSCLC with mutations causing this structural alteration. No mutations of amino acid insertions in other regions of the EGFRex20 have been reported so far. Although the possibility of activation of EGFR-mediated signaling is unknown, the efficacy of amivantamab is expected in the treatment of NSCLC with activated EGFR-mediated signaling caused by these mutations.

PMDA's view:
PMDA accepted the applicant's explanation about the efficacy of amivantamab in the treatment of NSCLC with amino acid insertions in the C-helix or the loop following the C-helix domain (D761 to C775) of the EGFRex20.

Nevertheless, based on the currently available information, it is difficult to draw a conclusion on the efficacy of amivantamab in the treatment of NSCLC with amino acid insertions in other regions of the EGFRex20. However, given that amivantamab will be used by physicians with sufficient knowledge of and experience in cancer chemotherapy, eligible patients will be selected appropriately, provided that "Oncomine Dx Target Test Multi-CDx system" or "Guardant360 CDx Cancer Gene Panel" is used to identify EGFRex20 insertion mutations and that the physicians are informed of the following information: (1) At present, insertions of at least 1 amino acid in the C-helix or the loop following the C-helix domain (D761 to C775) of the EGFRex20 have been reported to result in activation of EGFR-mediated signaling and (2) the type of EGFRex20 insertion mutations detected in patients enrolled in the PAPILLON study.

Thus, the above information (1) and (2) should be provided appropriately to healthcare professionals in clinical practice, using information materials, and the CLINICAL STUDIES section of the package insert should present the following information: "The mutations detected in patients enrolled in the PAPILLON study were insertions of at least 1 amino acid in the C-helix or the loop following the C-helix domain (D761 to C775) of the EGFRex20." In addition, the following statements should be included in the PRECAUTIONS CONCERNING INDICATION section. However, the applicant should collect post-marketing information on the efficacy of amivantamab in the treatment of NSCLC with amino acid insertions in other regions of the EGFRex20, and if any new information becomes available, the information should be provided appropriately to healthcare professionals in clinical practice.

- Amivantamab 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.

[52)] An amino acid insertion between A763 and Y764 does not cause a structural alteration in the loop of the EGFR tyrosine kinase domain (*Sig Transduct Target Ther*. 2019; 4: 5).

- 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 amivantamab.

7.R.5 Dosage and administration

The proposed dosage and administration statement is shown below. After the submission of the present application, the applicant explained that the following statements will be included in the PRECAUTIONS CONCERNING DOSAGE AND ADMINISTRATION section.

Dosage and Administration

Usually for adults, amivantamab (genetical recombination) should be administered by intravenous infusion in combination with carboplatin and pemetrexed in 3-week cycles, as per the table below. 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

Precautions Concerning Dosage and Administration

- Prior to the initial and second doses of amivantamab, antihistamines, antipyretics, and glucocorticoids should be administered to reduce the risk of infusion-related reactions. For subsequent doses, antihistamines and antipyretics are required to be administered, and glucocorticoids should also be administered as needed. Prior to all doses of amivantamab, antiemetics should be administered as needed.
- It is recommended that the first dose should be prepared as close to administration as possible. The diluted solution should be administered within 10 hours (including infusion time). It is necessary to ensure sufficient time to allow for extended infusion time for the first dose and management of symptoms in the event of an infusion-related reaction.
- Administer amivantamab according to the infusion rates in the table below. Due to the frequency of infusion-related reactions at the first dose, amivantamab infusion via a peripheral vein at Week 1 and Week 2 should be considered so that the infusion can be interrupted immediately in the event of an infusion-related reaction. Amivantamab may be administered via central line for subsequent weeks.

Doses and infusion rates of amivantamab

Cycle	Dosing schedule	Dose (/250 mL)	Infusion rate	
			Initial infusion rate	Subsequent infusion rate[Note1)]
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[Note2)]	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[Note2)]	Day 1	2,100 mg	125 mL/h	

Note 1) Increase the initial infusion rate to the subsequent infusion rate after 2 hours in the absence of infusion-related reactions.
Note 2) Starting at Cycle 3, administer amivantamab every 3 weeks.

- Recommended amivantamab dosage modifications for adverse reactions [see Section 7.R.5.2]

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

Dosage and Administration

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

Precautions Concerning Dosage and Administration

- Prior to the initial infusion of amivantamab (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.

- Administer the diluted solution according to the infusion rates in the table below.

Doses and infusion rates of amivantamab

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.

- Recommended amivantamab dosage modifications for adverse reactions

7.R.5.1 Dosage and administration of amivantamab

The applicant's explanation about the basis for the proposed dosing regimen of amivantamab:

The dosing regimen for the amivantamab/CP cohort of Study EDI1001 was selected taking account of the following points etc., and the tolerability of amivantamab/CP was demonstrated in the study. For this reason, among others, the PAPILLON study was conducted using the same dosing regimen as in this cohort. Since the study demonstrated the efficacy and clinical usefulness of amivantamab/CP in patients with EGFRex20 insertion mutation-positive unresectable advanced or recurrent NSCLC previously untreated with chemotherapy [see Sections 7.R.2 and 7.R.3], the dosing regimen of amivantamab was proposed based on this study.

- Splitting the first dose in Cycle 1 over Days 1 and 2[23)]; a shorter dosing interval in Cycle 1 [32)]; a weight-based dosing regimen[35)]; and a dosing regimen using a 3-week cycle[37)]
- Given that the majority of infusion reactions on Cycle 1 Day 1 occurred within 2 hours after the start of infusion in the amivantamab 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.

Based on the requirements in the PAPILLON study, the following information was included in the PRECAUTIONS CONCERNING DOSAGE AND ADMINISTRATION section: premedications to reduce the risk of infusion reactions with amivantamab; precautions for preparation of the diluted solution; and the infusion rate and the route of administration. An H_2 receptor antagonist was listed as a premedication in the PAPILLON study [see Section 7.R.3.1], but it was optional for all doses. Thus, a precautionary statement regarding H_2 receptor antagonists is unnecessary.

Based on the above, the following statements were included in the PRECAUTIONS CONCERNING DOSAGE AND ADMINISTRATION section, and then the following dosage and administration statement was proposed.

Dosage and Administration

Usually for adults, amivantamab (genetical recombination) should be administered by intravenous infusion in combination with carboplatin and pemetrexed in 3-week cycles, as per the table below. The dosage should be reduced, as appropriate, according to the patient's condition.

Precautions Concerning Dosage and Administration

- Prior to the initial and second doses of amivantamab, antihistamines, antipyretics, and glucocorticoids should be administered to reduce the risk of infusion-related reactions. For subsequent doses, antihistamines and antipyretics are required to be administered, and glucocorticoids should also be administered as needed. Prior to all doses of amivantamab, antiemetics should be administered as needed.
- It is recommended that the first dose should be prepared as close to administration as possible. The diluted solution should be administered within 10 hours (including infusion time). It is necessary to ensure sufficient time to allow for extended infusion time for the first dose and management of symptoms in the event of an infusion-related reaction.
- Administer amivantamab according to the infusion rates in the table below. Due to the frequency of infusion-related reactions at the first dose, amivantamab infusion via a peripheral vein at Week 1 and Week 2 should be considered so that the infusion can be interrupted immediately in the event of an infusion-related reaction. Amivantamab may be administered via central line for subsequent weeks.

Doses and infusion rates of amivantamab

Cycle	Dosing schedule	Dose (/250 mL)	Infusion rate	
			Initial infusion rate	Subsequent infusion rate[Note1)]
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[Note2)]	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[Note2)]	Day 1	2,100 mg	125 mL/h	

Note 1) Increase the initial infusion rate to the subsequent infusion rate after 2 hours in the absence of infusion-related reactions.
Note 2) Starting at Cycle 3, administer amivantamab every 3 weeks.

PMDA's view:

PMDA largely accepted the applicant's explanation. Meanwhile, the PAPILLON study conducted in accordance with the premedication instructions for infusion reactions demonstrated the clinical usefulness of amivantamab/CP, and some patients were premedicated also with an H_2 receptor antagonist in the PAPILLON study [see Section 7.R.3.1]. Taking also account of these points, the same premedication instructions as those employed in the PAPILLON study should be used. In addition, based on the following points, there is no need to include (1) precautions for preparation of the diluted solution and (2) the route of administration in the PRECAUTIONS CONCERNING DOSAGE AND ADMINISTRATION section.

(1) Precautions for preparation of the diluted solution should be included in the PRECAUTIONS CONCERNING USE section of the package insert.
(2) The route of administration is not a matter that should be specifically noted in the package insert.

Based on the above, PMDA concluded that the following statements should be included in the DOSAGE AND ADMINISTRATION and PRECAUTIONS CONCERNING DOSAGE AND ADMINISTRATION sections.

Dosage and Administration

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

Precautions Concerning Dosage and Administration

- Prior to the initial infusion of amivantamab (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.
- Administer the diluted solution according to the infusion rates in the table below.

Doses and infusion rates of amivantamab

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.

7.R.5.2 Recommended dosage modifications

The applicant's explanation about the recommended amivantamab dosage modifications:

The PAPILLON study was conducted according to the amivantamab dosage modification guidelines for adverse events, and the study demonstrated the clinical usefulness of amivantamab/CP. Thus, the PRECAUTIONS CONCERNING DOSAGE AND ADMINISTRATION section included a revised version of these guidelines as shown in the table below.

	Details of revision to the guidelines used in the PAPILLON study
Infusion reactions	● In the PAPILLON study, the infusion rate etc. when resuming the infusion after interruption for Grade 1 infusion reaction were not specified. Revised version For safety considerations, as in the case of Grade 2 infusion reactions, the infusion should be resumed at 50% of the rate at the time of interruption, and then the physician should decide the procedure for adjusting the infusion rate (the timing of increasing the infusion rate and the infusion rate). ● In the PAPILLON study, if the infusion was resumed after interruption for Grade 2 infusion reaction, and there was no further evidence of infusion reaction after 30 minutes, the rate could be increased to 100% of the infusion rate at the time of interruption. In the case of second interruption for Grade 2 infusion reaction, discontinuation of further study treatment at that visit was to be considered. Revised version The physician should decide the procedure for adjusting the infusion rate (the timing of increasing the infusion rate and the infusion rate) after resumption of the infusion. ● In the PAPILLON study, in the event of Grade 3 infusion reaction, further treatment at that visit was to be discontinued as a rule, and discussion with medical monitor was required before continuing with subsequent dosing. The infusion rate etc. when resuming the infusion after interruption for Grade 3 infusion reaction were not specified. Revised version Given that for the first occurrence of Grade 3 infusion reaction, there was room for resuming the infusion depending on the patient's condition even in the PAPILLON study, "further treatment at that visit should be discontinued as a rule, etc." was omitted. For recurrent Grade 3 infusion reactions, for safety considerations, treatment should be permanently discontinued. Moreover, since the infusion rate when resuming the infusion after interruption for infusion reaction is important, based on the guidance for Grade 2 infusion reactions in the PAPILLON study, etc., the infusion should be resumed at 50% of the rate at the time of interruption for the first occurrence of Grade 3 infusion reaction, and then the physician should decide the procedure for adjusting the infusion rate (the timing of increasing the infusion rate and the infusion rate).
Skin and nail reactions	● In the PAPILLON study, patients who developed Grade 1 or 2 skin or nail reaction were to be reassessed after 2 weeks, but no guidance for dose reduction was provided. Revised version Among patients with Grade 1 or 2 skin or nail reactions in the PAPILLON study, many of patients who were reassessed after 2 weeks and had a dose reduction were those with Grade 2 skin or mail reactions. Thus, if Grade 2 skin or nail reaction does not improve after 2 weeks, dose reduction should be considered. ● In the PAPILLON study, study treatment was to be withheld temporarily until Grade 3 skin reaction improved to Grade ≤2, whereas similar guidance was not provided for nail reactions. Revised version Treatment should be withheld until Grade 3 nail reaction as well as Grade 3 skin reaction improves to Grade ≤2.
Other adverse reactions (other than infusion reactions, ILD, pneumonitis, and skin and nail reactions)	● In the PAPILLON study, in the event of Grade 2 other adverse events, (1) dose interruption was to be considered, and (2) resuming at a reduced dose was to be considered for interruptions of >7 days. Revised version This guidance was omitted because both the above (1) and (2) can be left up to the physician's discretion. ● In the PAPILLON study, treatment was to be resumed at a reduced dose for subjects whose dose had been withheld due to Grade 3 other adverse events for >4 weeks. Revised version Given that Grade 3 adverse events persisting for >4 weeks may be irreversible, permanent discontinuation of treatment should be considered. ● In the PAPILLON study, amivantamab dosing was to be interrupted in the event of Grade 4 other adverse events and then (1) resumed at a reduced dose for interruptions of ≤7 days and (2) permanently discontinued as a rule for interruptions of >7 days. Revised version Given that there was room for resuming at a reduced dose depending on the patient's condition also for the above patients (2) in the PAPILLON study, this guidance (treatment should be permanently discontinued as a rule) was omitted. ● In the PAPILLON study, if dose reduction of amivantamab was required during dosing with carboplatin and pemetrexed, the dose of amivantamab could be re-escalated, starting at Cycle 5 (when dosed with pemetrexed or as monotherapy). Revised version Given that such re-escalation occurred in a limited number of patients, etc., this guidance was omitted.

PMDA's view:

PMDA largely accepted the applicant's explanation. However, the following guidance should be included as the recommended dosage modifications.

- The following guidance based on the guidelines etc. used in the PAPILLON study
  - The specific procedure for adjusting the infusion rate (the timing of increasing the infusion rate and the infusion rate) after the infusion is interrupted for Grade 1 or 2 infusion reaction and resumed

- For the first occurrence of Grade 3 infusion reaction, further treatment on that day should be discontinued. Whether to continue with subsequent dosing and the infusion rate should be decided according to the patient's condition.
- In the event of Grade 2 other adverse reactions, dose interruption should be considered. Resuming at a reduced dose should be considered for interruptions of >1 week.

- Given that even some patients with Grade 1 skin or nail reaction were reassessed after 2 weeks and had a dose reduction in the PAPILLON study, as in the case of Grade 2 skin or nail reactions, dose reduction should be considered if Grade 1 skin or nail reaction does not improve after 2 weeks.
- In the PAPILLON study, amivantamab dosing was interrupted in the event of Grade 4 other adverse reactions and then resumed in a limited number of patients, and most of Grade 4 other adverse reactions leading to dose interruption in these patients were cytopenia and abnormal electrolytes that could be managed by supportive measures. Given these points, in the event of Grade 4 other adverse reactions, treatment should be permanently discontinued as a rule, regardless of the length of interruption.

After the above changes are made, the following guidance should be included as the recommended dosage modifications for amivantamab in the PRECAUTIONS CONCERNING DOSAGE AND ADMINISTRATION section.

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

Amivantamab 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 amivantamab
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 amivantamab dosage modifications for adverse reactions

Infusion reactions

Severity*	Dosage Modifications
Grade 1 or 2	● Interrupt amivantamab 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 amivantamab.
Grade 4	Permanently discontinue amivantamab.

Interstitial lung disease

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

Skin or nail reactions

Severity*	Dosage Modifications
Grade 1 or 2	If there is no improvement after 2 weeks, consider dose reduction.
Grade 3	● Withhold amivantamab until recovery to Grade ≤2. ● Resume amivantamab at a reduced dose.
Grade 4	Permanently discontinue amivantamab.
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 recovery occurs after 1 week.
Grade 3	● Withhold amivantamab 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 amivantamab if recovery does not occur within 4 weeks.
Grade 4	Permanently discontinue as a rule.

*Severity grade based on NCI-CTCAE v4.03

7.R.6 Post-marketing investigations

The applicant's explanation about post-marketing surveillance plan:

The applicant plans to conduct all-case post-marketing surveillance, covering all patients treated with amivantamab, to assess the safety of amivantamab in clinical practice after marketing.

Based on adverse events reported in the PAPILLON study, etc., the safety specification for the surveillance includes infusion-related reactions, ILD, and hepatotoxicity, because these events require particular attention during treatment with amivantamab.

Taking account of the incidences of the events that are included in the safety specification for the surveillance in the PAPILLON study, the target sample size is 114 patients, and the observation period is 52 weeks.

PMDA’s view:

Based on the considerations etc. in Section "7.R.3 Safety," it is necessary to conduct post-marketing surveillance to collect safety information in clinical practice for venous thromboembolism, because its causal relationship to amivantamab is unknown at present, and venous thromboembolism may lead to a serious outcome.

However, given the following points etc., there is little need to conduct all-case post-marketing surveillance.

- Certain safety information on amivantamab has been obtained from the clinical studies etc. of amivantamab including the PAPILLON study (a global study), and no concerns that warrant information collection via all-case post-marketing surveillance in Japan have been identified.
- There are no clear differences in the nature etc. of adverse events that require attention during treatment between amivantamab and the currently approved drugs targeting EGFR or MET in Japan.

In addition, given that useful information for assessment of a causal relationship between amivantamab and venous thromboembolism may be obtained from a study that has a control group, one idea is to conduct

a post-marketing database survey.

7.2 Adverse events etc. observed in clinical studies

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

7.2.1 Global phase I study (Study EDI1001) Amivantamab monotherapy cohorts (Part 1)

Adverse events occurred in 3 of 3 subjects (100%) in the 140 mg cohort, 3 of 3 subjects (100%) in the 350 mg cohort, 14 of 14 subjects (100%) in the 700 mg cohort, 25 of 25 subjects (100%) in the 1,050 mg cohort, 26 of 26 subjects (100%) in the 1,400 mg cohort, and 9 of 9 subjects (100%) in the 1,750 mg cohort, and those for which a causal relationship to study drug could not be ruled out occurred in 3 of 3 subjects (100%) in the 140 mg cohort, 3 of 3 subjects (100%) in the 350 mg cohort, 13 of 14 subjects (92.9%) in the 700 mg cohort, 25 of 25 subjects (100%) in the 1,050 mg cohort, 25 of 26 subjects (96.2%) in the 1,400 mg cohort, and 9 of 9 subjects (100%) in the 1,750 mg cohort. Table 77 shows adverse events reported by ≥20% of subjects and ≥3 subjects in any of the ≥1,050 mg dose cohorts.

Table 77. Adverse events reported by ≥20% of subjects and ≥3 subjects in any of the ≥1,050 mg dose cohorts

SOC PT (MedDRA ver.23.0)	n (%)					
	140 mg N = 3		350 mg N = 3		700 mg N = 14	
	All adverse events	Grade ≥3	All adverse events	Grade ≥3	All adverse events	Grade ≥3
Any adverse event	3 (100)	0	3 (100)	0	14 (100)	5 (35.7)
Injury, poisoning and procedural complications						
Infusion related reaction	3 (100)	0	2 (66.7)	0	11 (78.6)	0
Gastrointestinal disorders						
Constipation	1 (33.3)	0	1 (33.3)	0	2 (14.3)	0
Diarrhoea	1 (33.3)	0	0	0	2 (14.3)	0
Dyspepsia	1 (33.3)	0	0	0	0	0
Nausea	1 (33.3)	0	0	0	3 (21.4)	0
Stomatitis	0	0	0	0	1 (7.1)	0
General disorders and administration site conditions						
Fatigue	0	0	1 (33.3)	0	2 (14.3)	0
Metabolism and nutrition disorders						
Hyponatraemia	0	0	0	0	0	0
Decreased appetite	2 (66.7)	0	0	0	2 (14.3)	0
Hypoalbuminaemia	1 (33.3)	0	0	0	0	0
Hypocalcaemia	1 (33.3)	0	0	0	0	0
Skin and subcutaneous tissue disorders						
Dermatitis acneiform	0	0	2 (66.7)	0	3 (21.4)	0
Infections and infestations						
Paronychia	0	0	1 (33.3)	0	2 (14.3)	0
Investigations						
AST increased	1 (33.3)	0	0	0	0	0
Respiratory, thoracic and mediastinal disorders						
Dyspnoea	0	0	0	0	2 (14.3)	0
Musculoskeletal and connective tissue disorders						
Arthralgia	0	0	0	0	0	0
Back pain	0	0	0	0	1 (7.1)	0
Vascular disorders						
Hypotension	0	0	0	0	0	0

SOC PT (MedDRA ver.23.0)	n (%)					
	1,050 mg N = 25		1,400 mg N = 26		1,750 mg N = 9	
	All adverse events	Grade ≥3	All adverse events	Grade ≥3	All adverse events	Grade ≥3
Any adverse event	25 (100)	15 (60.0)	26 (100)	12 (46.2)	9 (100)	4 (44.4)
Injury, poisoning and procedural complications						
Infusion related reaction	17 (68.0)	0	15 (57.7)	0	6 (66.7)	0
Gastrointestinal disorders						
Constipation	5 (20.0)	0	6 (23.1)	0	3 (33.3)	0
Diarrhoea	6 (24.0)	1 (4.0)	1 (3.8)	0	2 (22.2)	1 (11.1)
Dyspepsia	5 (20.0)	0	2 (7.7)	0	0	0
Nausea	5 (20.0)	0	6 (23.1)	0	2 (22.2)	0
Stomatitis	4 (16.0)	0	7 (26.9)	1 (3.8)	2 (22.2)	0
General disorders and administration site conditions						
Fatigue	9 (36.0)	0	10 (38.5)	0	4 (44.4)	1 (11.1)
Metabolism and nutrition disorders						
Hyponatraemia	6 (24.0)	3 (12.0)	2 (7.7)	0	1 (11.1)	0
Decreased appetite	5 (20.0)	0	4 (15.4)	0	2 (22.2)	1 (11.1)
Hypoalbuminaemia	5 (20.0)	0	11 (42.3)	0	4 (44.4)	0
Hypocalcaemia	4 (16.0)	0	7 (26.9)	0	2 (22.2)	0
Skin and subcutaneous tissue disorders						
Dermatitis acneiform	13 (52.0)	0	12 (46.2)	0	5 (55.6)	1 (11.1)
Infections and infestations						
Paronychia	10 (40.0)	1 (4.0)	9 (34.6)	0	5 (55.6)	0
Investigations						
AST increased	2 (8.0)	0	6 (23.1)	0	0	0
Respiratory, thoracic and mediastinal disorders						
Dyspnoea	11 (44.0)	4 (16.0)	5 (19.2)	0	3 (33.3)	2 (22.2)
Musculoskeletal and connective tissue disorders						
Arthralgia	6 (24.0)	0	1 (3.8)	0	1 (11.1)	0
Back pain	6 (24.0)	0	5 (19.2)	1 (3.8)	1 (11.1)	0
Vascular disorders						
Hypotension	5 (20.0)	1 (4.0)	3 (11.5)	1 (3.8)	1 (11.1)	0

Serious adverse events occurred in 3 of 14 subjects (21.4%) in the 700 mg cohort, 11 of 25 subjects (44.0%) in the 1,050 mg cohort, 7 of 26 subjects (26.9%) in the 1,400 mg cohort, and 5 of 9 subjects (55.6%) in the 1,750 mg cohort, but not in the 140 mg or 350 mg cohort. Table 78 shows serious adverse events reported by ≥5% of subjects and ≥2 subjects in any dose cohort.

Table 78. Serious adverse events reported by ≥5% of subjects and ≥2 subjects in any dose cohort

SOC PT (MedDRA ver.23.0)	n (%)							
	700 mg N = 14		1,050 mg N = 25		1,400 mg N = 26		1,750 mg N = 9	
	All adverse events	Adverse events for which a causal relationship to study drug could not be ruled out	All adverse events	Adverse events for which a causal relationship to study drug could not be ruled out	All adverse events	Adverse events for which a causal relationship to study drug could not be ruled out	All adverse events	Adverse events for which a causal relationship to study drug could not be ruled out
Any adverse event	3 (21.4)	2 (14.3)	11 (44.0)	1 (4.0)	7 (26.9)	0	5 (55.6)	1 (11.1)
Infections and infestations								
Pneumonia	1 (7.1)	0	0	0	2 (7.7)	0	0	0
Respiratory, thoracic and mediastinal disorders								
Dyspnoea	0	0	4 (16.0)	0	0	0	1 (11.1)	0

Adverse events leading to study drug discontinuation occurred in 1 of 14 subjects (7.1%) in the 700 mg cohort, 2 of 25 subjects (8.0%) in the 1,050 mg cohort, and 4 of 26 subjects (15.4%) in the 1,400 mg cohort, but not in the 140 mg, 350 mg, or 1,750 mg cohort. There were no adverse events leading to study drug discontinuation reported by ≥5% of subjects and ≥2 subjects in any dose cohort.

7.2.2 Global phase I study (Study EDI1001) Amivantamab monotherapy cohort (Part 2)

Adverse events occurred in 404 of 406 subjects (99.5%), and those for which a causal relationship to study drug could not be ruled out occurred in 390 of 406 subjects (96.1%). Table 79 shows adverse events reported by ≥20% of subjects.

Table 79. Adverse events reported by ≥20% of subjects

SOC PT (MedDRA ver.23.0)	n (%) N = 406	
	All Grades	Grade ≥3
Any adverse event	404 (99.5)	162 (39.9)
Skin and subcutaneous tissue disorders		
Rash	157 (38.7)	6 (1.5)
Dermatitis acneiform	134 (33.0)	7 (1.7)
Gastrointestinal disorders		
Nausea	93 (22.9)	2 (0.5)
Constipation	92 (22.7)	0
Stomatitis	81 (20.0)	2 (0.5)
Injury, poisoning and procedural complications		
Infusion related reaction	271 (66.7)	11 (2.7)
Infections and infestations		
Paronychia	178 (43.8)	9 (2.2)
Metabolism and nutrition disorders		
Hypoalbuminaemia	125 (30.8)	9 (2.2)
General disorders and administration site conditions		
Oedema peripheral	87 (21.4)	3 (0.7)

Serious adverse events occurred in 113 of 406 subjects (27.8%). Table 80 shows serious adverse events reported by ≥2% of subjects.

Table 80. Serious adverse events reported by ≥2% of subjects

SOC PT (MedDRA ver.23.0)	n (%) N = 406	
	All adverse events	Adverse events for which a causal relationship to study drug could not be ruled out
Any adverse event	113 (27.8)	22 (5.4)
Respiratory, thoracic and mediastinal disorders		
Dyspnoea	10 (2.5)	0
Pulmonary embolism	9 (2.2)	1 (0.2)
Pneumonitis	6 (1.5)	5 (1.2)
Infections and infestations		
Pneumonia	19 (4.7)	0

Adverse events leading to study drug discontinuation occurred in 32 of 406 subjects (7.9%). There were no adverse events leading to study drug discontinuation reported by ≥2% of subjects.

7.2.3 Global phase I study (Study EDI1001) Combination cohort (amivantamab/CP cohort)

Adverse events occurred in 20 of 20 subjects (100%), and those for which a causal relationship to study drug could not be ruled out occurred in 20 of 20 subjects (100%). Table 81 shows adverse events reported by ≥20% of subjects.

Table 81. Adverse events reported by ≥20% of subjects

SOC PT (MedDRA ver.25.0)	n (%) N = 20	
	All Grades	Grade ≥3
Any adverse event	20 (100)	15 (75.0)
Gastrointestinal disorders		
Nausea	16 (80.0)	1 (5.0)
Constipation	10 (50.0)	0
Diarrhoea	7 (35.0)	1 (5.0)
Stomatitis	6 (30.0)	0
Skin and subcutaneous tissue disorders		
Dermatitis acneiform	12 (60.0)	0
Dry skin	4 (20.0)	0
Rash	6 (30.0)	0
General disorders and administration site conditions		
Fatigue	11 (55.0)	0
Oedema peripheral	10 (50.0)	0
Infections and infestations		
Paronychia	7 (35.0)	0
Cellulitis	4 (20.0)	1 (5.0)
Blood and lymphatic system disorders		
Neutropenia	9 (45.0)	7 (35.0)
Thrombocytopenia	9 (45.0)	3 (15.0)
Anaemia	5 (25.0)	3 (15.0)
Injury, poisoning and procedural complications		
Infusion related reaction	13 (65.0)	0
Respiratory, thoracic and mediastinal disorders		
Dyspnoea	5 (25.0)	0
Metabolism and nutrition disorders		
Decreased appetite	6 (30.0)	0
Hypoalbuminaemia	5 (25.0)	2 (10.0)
Hypokalaemia	5 (25.0)	1 (5.0)
Musculoskeletal and connective tissue disorders		
Pain in extremity	5 (25.0)	0
Nervous system disorders		
Headache	5 (25.0)	1 (5.0)

Serious adverse events occurred in 10 of 20 subjects (50.0%), and those reported by ≥10% of subjects were pneumonia (2 subjects [10.0%]).

Adverse events leading to study drug discontinuation occurred in 9 of 20 subjects (45.0%), and those reported by ≥10% of subjects were anaemia; and pneumonia (2 subjects each [10.0%]).

7.2.4 Global phase III study (PAPILLON study)

Adverse events occurred in 151 of 151 subjects (100%) in the amivantamab/CP group and 152 of 155 subjects (98.1%) in the CP group, and those for which a causal relationship to study drug could not be ruled out occurred

in 151 of 151 subjects (100%) in the amivantamab/CP group and 146 of 155 subjects (94.2%) in the CP group. Table 82 shows adverse events reported by ≥20% of subjects in either group.

Table 82. Adverse events reported by ≥20% of subjects in either group

SOC PT (MedDRA ver.25.0)	n (%)			
	Amivantamab/CP N = 151		CP N = 155	
	All Grades	Grade ≥3	All Grades	Grade ≥3
Any adverse event	151 (100)	114 (75.5)	152 (98.1)	83 (53.5)
Blood and lymphatic system disorders				
Neutropenia	89 (58.9)	50 (33.1)	70 (45.2)	35 (22.6)
Anaemia	76 (50.3)	16 (10.6)	85 (54.8)	19 (12.3)
Leukopenia	57 (37.7)	17 (11.3)	50 (32.3)	5 (3.2)
Thrombocytopenia	55 (36.4)	15 (9.9)	46 (29.7)	16 (10.3)
Infections and infestations				
Paronychia	85 (56.3)	10 (6.6)	0	0
COVID-19	36 (23.8)	3 (2.0)	21 (13.5)	1 (0.6)
General disorders and administration site conditions				
Oedema peripheral	45 (29.8)	2 (1.3)	16 (10.3)	0
Fatigue	23 (15.2)	1 (0.7)	32 (20.6)	2 (1.3)
Gastrointestinal disorders				
Constipation	60 (39.7)	0	47 (30.3)	1 (0.6)
Nausea	55 (36.4)	1 (0.7)	65 (41.9)	0
Stomatitis	38 (25.2)	2 (1.3)	9 (5.8)	0
Vomiting	32 (21.2)	5 (3.3)	29 (18.7)	1 (0.6)
Diarrhoea	31 (20.5)	5 (3.3)	20 (12.9)	2 (1.3)
Investigations				
ALT increased	50 (33.1)	6 (4.0)	56 (36.1)	2 (1.3)
AST increased	47 (31.1)	1 (0.7)	51 (32.9)	1 (0.6)
Metabolism and nutrition disorders				
Hypoalbuminaemia	62 (41.1)	6 (4.0)	15 (9.7)	0
Decreased appetite	54 (35.8)	4 (2.6)	43 (27.7)	2 (1.3)
Hypokalaemia	32 (21.2)	13 (8.6)	13 (8.4)	2 (1.3)
Injury, poisoning and procedural complications				
Infusion related reaction	63 (41.7)	2 (1.3)	2 (1.3)	0
Skin and subcutaneous tissue disorders				
Rash	81 (53.6)	17 (11.3)	12 (7.7)	0
Dermatitis acneiform	47 (31.1)	6 (4.0)	5 (3.2)	0

Serious adverse events occurred in 56 of 151 subjects (37.1%) in the amivantamab/CP group and 48 of 155 subjects (31.0%) in the CP group. Table 83 shows serious adverse events reported by ≥2% of subjects in either group.

Table 83. Serious adverse events reported by ≥2% of subjects in either group

SOC PT (MedDRA ver.25.0)	n (%)			
	Amivantamab/CP N = 151		CP N = 155	
	All adverse events	Adverse events for which a causal relationship to study drug could not be ruled out	All adverse events	Adverse events for which a causal relationship to study drug could not be ruled out
Any adverse event	56 (37.1)	36 (23.8)	48 (31.0)	16 (10.3)
Blood and lymphatic system disorders				
Thrombocytopenia	3 (2.0)	3 (2.0)	5 (3.2)	5 (3.2)
Anaemia	1 (0.7)	1 (0.7)	6 (3.9)	5 (3.2)
Infections and infestations				
Pneumonia	6 (4.0)	2 (1.3)	4 (2.6)	1 (0.6)
Respiratory, thoracic and mediastinal disorders				
Pneumonitis	4 (2.6)	4 (2.6)	0	0
Pulmonary embolism	4 (2.6)	2 (1.3)	4 (2.6)	0
Dyspnoea	1 (0.7)	0	5 (3.2)	0
Pleural effusion	1 (0.7)	0	5 (3.2)	0

Adverse events leading to study drug discontinuation occurred in 36 of 151 subjects (23.8%) in the amivantamab/CP group and 16 of 155 subjects (10.3%) in the CP group. Table 84 shows adverse events leading to study drug discontinuation reported by ≥2% of subjects in either group.

Table 84. Adverse events leading to study drug discontinuation reported by ≥2% of subjects in either group

SOC PT (MedDRA ver.25.0)	n (%)			
	Amivantamab/CP N = 151		CP N = 155	
	All adverse events	Adverse events for which a causal relationship to study drug could not be ruled out	All adverse events	Adverse events for which a causal relationship to study drug could not be ruled out
Any adverse event	36 (23.8)	31 (20.5)	16 (10.3)	13 (8.4)
Blood and lymphatic system disorders				
Neutropenia	3 (2.0)	3 (2.0)	2 (1.3)	2 (1.3)
Anaemia	3 (2.0)	2 (1.3)	1 (0.6)	0
Injury, poisoning and procedural complications				
Infusion related reaction	3 (2.0)	3 (2.0)	0	0
Metabolism and nutrition disorders				
Decreased appetite	3 (2.0)	3 (2.0)	0	0
Respiratory, thoracic and mediastinal disorders				
Pneumonitis	4 (2.6)	4 (2.6)	0	0

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 amivantamab has efficacy in the treatment of EGFRex20 insertion mutation-positive unresectable advanced or recurrent non-small cell lung cancer, and that amivantamab has acceptable safety in view of its benefits. Amivantamab is a drug with a new active ingredient, which is considered to inhibit tumor growth, for example by binding to EGFR and MET and inhibiting EGFR- and MET-mediated signaling. Amivantamab is clinically meaningful as a treatment option for patients with EGFRex20 insertion mutation-positive unresectable advanced or recurrent non-small cell lung cancer. PMDA considers that testing for EGFRex20 insertion mutations for selection of eligible patients should be further discussed.

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

Review Report (2)

August 13, 2024

Product Submitted for Approval

Brand Name	Rybrevant Intravenous Infusion 350 mg
Non-proprietary Name	Amivantamab (Genetical Recombination)
Applicant	Janssen Pharmaceutical K.K.
Date of Application	November 17, 2023

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 amivantamab/CP in patients with EGFRex20 insertion mutation-positive unresectable advanced or recurrent NSQ-NSCLC previously untreated with chemotherapy, because a global phase III study in this patient population (PAPILLON study) demonstrated the superiority of amivantamab/CP to CP in the primary endpoint of PFS as assessed by BICR according to RECIST ver.1.1.

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 amivantamab/CP are infusion reactions, ILD, skin disorders (including paronychia), venous thromboembolism, fluid retention (including oedema and hypoalbuminemia), and diarrhoea.

Although patients should be monitored for the above adverse events during the use of amivantamab, amivantamab/CP 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 amivantamab or the concomitant anti-neoplastic drugs.

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

1.3 Clinical positioning and indication

PMDA's conclusion:

On the basis of the considerations in Section "7.R.4 Clinical positioning and indication" in the Review Report (1), the statements in the table below should be included in the INDICATION and PRECAUTIONS CONCERNING INDICATION sections.

Indication	Precautions Concerning Indication
EGFR exon 20 insertion mutation-positive unresectable advanced or recurrent non-small cell lung cancer	● Eligible patients must be selected by physicians with a full understanding of the information presented in the CLINICAL STUDIES section concerning the histology, type of genetic mutation and other characteristics of patients enrolled in the clinical study and of the efficacy and safety of amivantamab. ● The efficacy and safety of amivantamab in the neoadjuvant or adjuvant setting have not been established. ● Amivantamab 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.

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

- Given that the Japanese clinical practice guideline recommends pemetrexed, which is used in combination with amivantamab, for patients with non-squamous NSCLC, and that amivantamab will be used by physicians with sufficient knowledge of and experience in cancer chemotherapy, there is little need to advise in the PRECAUTIONS CONCERNING INDICATION section that eligible patients must be selected by physicians with a full understanding of the information presented in the CLINICAL STUDIES section concerning the histology of patients enrolled in the clinical study.

In view of the discussion above, PMDA concluded that the statements in the table below should be included in the INDICATION and PRECAUTIONS CONCERNING INDICATION sections.

Indication	Precautions Concerning Indication
EGFR exon 20 insertion mutation-positive unresectable advanced, or recurrent non-small cell lung cancer	● 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 amivantamab. ● The efficacy and safety of amivantamab in the neoadjuvant or adjuvant setting have not been established. ● Amivantamab 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.

Based on the above, PMDA instructed the applicant to include the above statements in the INDICATION and PRECAUTIONS CONCERNING INDICATION sections. The applicant agreed to do so.

1.4 Dosage and administration

On the basis of the considerations in Section "7.R.5 Dosage and administration" in the Review Report (1), PMDA concluded that the following statements should be included in the DOSAGE AND ADMINISTRATION and PRECAUTIONS CONCERNING DOSAGE AND ADMINISTRATION sections.

Dosage and Administration

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

Precautions Concerning Dosage and Administration

- Prior to the initial infusion of amivantamab (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.
- Administer the diluted solution according to the infusion rates in the table below.

Doses and infusion rates of amivantamab

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.

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

Amivantamab 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 amivantamab
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 amivantamab dosage modifications for adverse reactions

Infusion reactions

Severity*	Dosage Modifications
Grade 1 or 2	● Interrupt amivantamab 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 amivantamab.
Grade 4	Permanently discontinue amivantamab.

Interstitial lung disease

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

Skin or nail reactions

Severity*	Dosage Modifications
Grade 1 or 2	If there is no improvement after 2 weeks, consider dose reduction.
Grade 3	● Withhold amivantamab until recovery to Grade ≤2. ● Resume amivantamab at a reduced dose.
Grade 4	Permanently discontinue amivantamab.
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 recovery occurs after 1 week.
Grade 3	● Withhold amivantamab 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 amivantamab if recovery does not occur within 4 weeks.
Grade 4	Permanently discontinue as a rule.

*Severity grade based on NCI-CTCAE v4.03

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. The applicant agreed to do so.

1.5 Risk management plan (draft)

The applicant plans to conduct post-marketing surveillance, covering all patients treated with amivantamab, to assess the safety of amivantamab in clinical practice after marketing. The safety specification for the surveillance includes infusion-related reactions, ILD, and hepatotoxicity. The planned sample size is 114 patients, and the observation period is 52 weeks.

PMDA's conclusion:

On the basis of the considerations in Section "7.R.6 Post-marketing investigations" in the Review Report (1), the applicant should conduct post-marketing surveillance to collect safety information concerning venous thromboembolism in clinical practice, because its causal relationship to amivantamab remains unknown to date, and venous thromboembolism may lead to a serious outcome.

Given that useful information for assessment of a causal relationship between amivantamab and venous thromboembolism may be obtained from a study that has a control group, a post-marketing database survey should be conducted.

Given the following points etc., there is little need to conduct all-case post-marketing surveillance.

- Certain safety information on amivantamab has been obtained from the clinical studies etc. of amivantamab including the PAPILLON study (a global study), and no concerns that warrant information collection via all-case post-marketing surveillance in Japan have been identified.
- There are no clear differences in the nature etc. of adverse events that require attention during treatment

between amivantamab and the currently approved drugs targeting EGFR or MET in Japan.

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

On the basis of the above considerations, PMDA instructed the applicant to reconsider the post-marketing surveillance plan.

The applicant's response:

- The safety specification for the surveillance will include venous thromboembolism.
- Non-all-case post-marketing surveillance will be conducted. Since the database from which information on venous thromboembolism can be retrieved exists, the feasibility of a survey using this database will be confirmed first. Then, a post-marketing database survey will be conducted to assess the causal relationship between amivantamab and venous thromboembolism in patients with EGFRex20 insertion mutation-positive unresectable advanced or recurrent NSCLC.

PMDA accepted the applicant's response.

In view of the discussion above, PMDA has concluded that the risk management plan (draft) for amivantamab should include the safety specification presented in Table 85, and that the applicant should conduct additional pharmacovigilance activities and risk minimization activities presented in Table 86.

Table 85. Safety and efficacy specifications in the risk management plan (draft)

Safety specification		
Important identified risks	Important potential risks	Important missing information
● Infusion reactions ● ILD ● Severe skin disorders	● Venous thromboembolism ● Fluid retention ● Severe diarrhoea ● Embryo-fetal toxicity	None
Efficacy specification		
None		

Table 86. Summary of additional pharmacovigilance activities, efficacy survey and studies, and additional risk minimization activities included under the risk management plan (draft)

Additional pharmacovigilance activities	Efficacy survey and studies	Additional risk minimization activities
● Early post-marketing phase vigilance ● Post-marketing database survey (venous thromboembolism)	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

2. Overall Evaluation

As a result of the above review, PMDA has concluded that the product may be approved for the indication and dosage and administration 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 the product 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. Since the product is a drug with a new active ingredient, the re-examination period is 8 years. The product is classified as a biological product, and the drug product and its drug substance are both classified as powerful drugs.

Indication

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

Dosage and Administration

The usual adult dosage of Rybrevant [as 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

Approval Condition

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

Warnings

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.

Contraindication

Patients with a history of hypersensitivity to any of the ingredients of Rybrevant

Precautions Concerning Indication

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.

Precautions Concerning Dosage and Administration

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

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.

3. In the event of adverse reactions to Rybrevant, reduce the dose or 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.

Skin or nail reactions

Severity*	Dosage Modifications
Grade 1 or 2	If there is no improvement after 2 weeks, consider dose reduction.
Grade 3	● Withhold Rybrevant until recovery to Grade ≤2. ● Resume Rybrevant at a reduced dose.
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 recovery occurs after 1 week.
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 v4.03

Appendix

List of Abbreviations

ADCC	antibody dependent cellular cytotoxicity
afatinib	afatinib maleate
A/G ratio	albumin/globulin ratio
ALP	alkaline phosphatase
ALT	alanine aminotransferase
AKT	protein kinase B
amivantamab	Amivantamab (Genetical Recombination)
amivantamab/CP	the combination of amivantamab and CP
amivantamab/lazertinib	the combination of amivantamab and lazertinib
application	marketing application
AST	aspartate aminotransferase
AUC	area under the serum concentration-time curve
BICR	blinded independent central review
C_{avg}	average serum concentration
C_{eoi}	serum concentration at the end of infusion
CE-SDS	capillary electrophoresis sodium dodecyl sulfate
cetuximab	Cetuximab (Genetical Recombination)
CHO cells	Chinese hamster ovary cells
CHRYSALIS-2 study	Study 73841937NSC1001
CI	confidence interval
COVID-19	coronavirus disease
CP	the combination of carboplatin and pemetrexed
CPP	critical process parameter
CQA	critical quality attribute
CRC	colorectal cancer
CrCL	creatinine clearance
dacomitinib	dacomitinib hydrate
DF	diafiltration
DLT	dose-limiting toxicity
DNA	deoxyribonucleic acid
ECL	electrochemiluminescence
ECOG	Eastern Cooperative Oncology Group
EDTA	ethylenediaminetetraacetic acid
EFD	embryo-fetal development
EGF	epidermal growth factor
EGFR	epidermal growth factor receptor
EGFRex19	*EGFR* exon 19
EGFRex20	*EGFR* exon 20
EGFR-TKI	epidermal growth factor receptor-tyrosine kinase inhibitor
ELISA	enzyme-linked immunosorbent assay
EOP	End of Production
ERK	extracellular signal-regulated kinase
ePPND	enhanced pre- and postnatal developmental
ERK	extracellular signal-regulated kinase
erlotinib	erlotinib hydrochloride
FAS	full analysis set
FcRn	neonatal Fc receptor
FcγR	Fcγ receptor
FEED	fertility and early embryonic development
FRET	fluorescence resonance energy transfer

GGT	γ-glutamyl transferase
HCC	hepatocellular carcinoma
HCP	host cell protein
HGF	hepatocyte growth factor
HI-HPLC	hydrophobic interaction high performance liquid chromatography
HILIC	hydrophobic interaction liquid chromatography
HMW	high molecular weight forms
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
ICH Q5A (R1) guideline	Viral Safety Evaluation of Biotechnology Products Derived From Cell Lines of Human or Animal Origin (PMSB/ELD Notification No. 329 dated February 22, 2000)
ICH Q5B guideline	Analysis of the Expression Construct in Cells Used for Production of r-DNA Derived Protein Products (PMSB/ELD Notification No. 3 dated January 6, 1998)
ICH-Q5D guideline	Derivation and Characterisation of Cell Substrates Used for Production of Biotechnological/Biological Products (PMSB/ELD Notification No. 873 dated July 14, 2000)
ICI	immune checkpoint inhibitor
IFN	Interferon
Ig	Immunoglobulin
IL	interleukin
ILD	interstitial lung disease
Japanese clinical practice guideline	Clinical Practice Guideline for Lung Cancer, the Japan Lung Cancer Society ed.
LC-MS/MS	liquid chromatography/tandem mass spectrometry
LDH	lactate dehydrogenase
LMW	low molecular weight forms
MARIPOSA study	Study 73841937NSC3003
MARIPOSA-2 study	Study 61186372NSC3002
MCB	master cell bank
MEA	mercaptoethylamine
MedDRA	Medical Dictionary for Regulatory Activities
MET	mesenchymal epithelial transition factor
NCCN guidelines	National Comprehensive Cancer Network Clinical Practice Guidelines in Oncology, Non-Small Cell Lung Cancer
NCI-ODWG	National Cancer Institute Organ Dysfunction Working Group
NGS	next generation sequencing
NFAT	nuclear factor of activated T-cells
NOD/SCID mouse	non-obese diabetic/severe combined immunodeficient mouse
NSCLC	non-small cell lung cancer
NSQ	non-squamous
NSQ-NSCLC	non-squamous non-small cell lung cancer
OS	overall survival
osimertinib	osimertinib mesylate
PAPILLON study	Study 61186372NSC3001
PBMC	peripheral blood mononuclear cell
PBS	phosphate buffer saline
PCR	polymerase chain reaction
PD	pharmacodynamics
pemetrexed	pemetrexed sodium
PFS	progression-free survival
PK	pharmacokinetics

PMDA	Pharmaceuticals and Medical Devices Agency
PPK	population pharmacokinetics
PS	performance status
PT	preferred term
QD	quaque die
QOL	quality of life
QW	quaque 1 week
Q2W	quaque 2 weeks
RECIST	Response Evaluation Criteria in Solid Tumors
rHuPH20	recombinant human hyaluronidase PH20
RNA	ribonucleic acid
RP2D	recommended Phase II dose
SCID mouse	severe combined immunodeficient mouse
SEC	size exclusion liquid chromatography
SHO mouse	severe combined immunodeficient hairless outbred mouse
SMQ	standardized MedDRA queries
SOC	system organ class
SPF	sun protection factor
SPR	surface plasmon resonance
Study EDI1001	Study 61186372EDI1001
TNF	tumor necrosis factor
TR-FRET	Time-Resolved Fluorescence Resonance Energy Transfer
TUNEL	terminal deoxynucleotidyl transferase-mediated dUTP nick end labeling
WCB	working cell bank
UF	ultrafiltration
V1	central volume of distribution
V2	peripheral volume of distribution