Report on the Deliberation Results

March 3, 2020

Pharmaceutical Evaluation Division, Pharmaceutical Safety and Environmental Health Bureau

Ministry of Health, Labour and Welfare

Brand Name	Tepmetko Tablets 250 mg
Non-proprietary Name	Tepotinib Hydrochloride Hydrate (JAN*)
Applicant	Merck Biopharma Co., Ltd.
Date of Application	November 12, 2019

Results of Deliberation

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

The product is not classified as a biological product or a specified biological product. The re-examination period is 10 years. The drug product and its drug substance are both classified as powerful drugs.

Approval Conditions

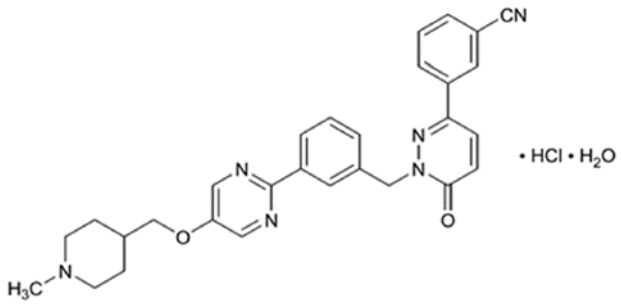
1. The applicant is required to develop and appropriately implement a risk management plan.
2. Because the number of patients studied in Japan is very limited, the applicant is required to conduct a post-marketing use-results survey covering all patients treated with the product, until data from a specified number of patients will be collected, in order to obtain information on the characteristics of patients treated with the product, to collect data on the safety and efficacy of the product as soon as possible, and to take necessary measures to ensure proper use of the product.

**Japanese Accepted Name (modified INN)*

Review Report

February 10, 2020
Pharmaceuticals and Medical Devices Agency

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

Brand Name	Tepmetko Tablets 250 mg
Non-proprietary Name	Tepotinib Hydrochloride Hydrate
Applicant	Merck Biopharma Co., Ltd.
Date of Application	November 12, 2019[1)]
Dosage Form/Strength	Each tablet contains 250 mg of Tepotinib Hydrochloride Hydrate
Application Classification	Prescription drug, (1) Drug with a new active ingredient
Chemical Structure	
Molecular formula:	$C_{29}H_{28}N_6O_2 \cdot HCl \cdot H_2O$
Molecular weight:	547.05
Chemical name:	3-{1-[(3-{5-[(1-Methylpiperidin-4-yl)methoxy]pyrimidin-2-yl}phenyl)methyl]-6-oxo-1,6-dihydropyridazin-3-yl}benzonitrile monohydrochloride monohydrate

Items Warranting Special Mention

SAKIGAKE designation drug (SAKIGAKE Drug Designation No. 4 of 2018 [*30 yaku*]; PSEHB/PED Notification No. 0327-1 dated March 27, 2018, by the Pharmaceutical Evaluation Division, Pharmaceutical Safety and Environmental Health Bureau, Ministry of Health, Labour and Welfare)

Orphan drug (Orphan Drug Designation No. 449 of 2019 [*31 yaku*]; PSEHB/PED Notification No. 1119-1 dated November 19, 2019, by the

1) An application for marketing approval was filed for the 100 mg formulation in addition to the 250 mg formulation; however, it was later withdrawn.

	Pharmaceutical Evaluation Division, Pharmaceutical Safety and Environmental Health Bureau, Ministry of Health, Labour and Welfare)
Reviewing Office	Office of New Drug V

Results of Review

On the basis of the data submitted, PMDA has concluded that the product has a certain degree of efficacy in the treatment of unresectable, advanced or recurrent *MET* exon 14 skipping mutation-positive 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 conditions. Interstitial lung disease, fluid retention, hepatic dysfunction, renal dysfunction, and QT interval prolongation should be further evaluated.

Indication	Unresectable, advanced or recurrent *MET* exon 14 skipping mutation-positive non-small cell lung cancer
Dosage and Administration	The usual adult dosage is 500 mg of tepotinib hydrochloride hydrate administered orally once daily after a meal. The dose may be reduced according to the patient's condition.

Approval Conditions

1. The applicant is required to develop and appropriately implement a risk management plan.
2. Because the number of patients studied in Japan is very limited, the applicant is required to conduct a post-marketing use-results survey covering all patients treated with the product, until data from a specified number of patients will be collected, in order to obtain information on the characteristics of patients treated with the product, to collect data on the safety and efficacy of the product as soon as possible, and to take necessary measures to ensure proper use of the product.

Attachment

Review Report (1)

January 10, 2020

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

Product Submitted for Approval

Brand Name	Tepmetko Tablets 100 mg, Tepmetko Tablets 250 mg
Non-proprietary Name	Tepotinib Hydrochloride Hydrate
Applicant	Merck Biopharma Co., Ltd.
Date of Application	November 12, 2019
Dosage Form/Strength	Each tablet contains 100 mg or 250 mg of Tepotinib Hydrochloride Hydrate
Proposed Indication	Unresectable, advanced or recurrent *MET* exon 14 skipping mutation-positive non-small cell lung cancer

Proposed Dosage and Administration

The usual adult dosage is 500 mg of tepotinib hydrochloride hydrate administered orally once daily after a meal. The dose may be reduced according to the patient's condition.

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

Abnormalities in splicing of messenger ribonucleic acid (mRNA) for the gene that encodes mesenchymal-epithelial transition factor (MET), a receptor tyrosine kinase, cause exon 14 skipping alterations, producing a mutant protein of MET, which prevents MET protein degradation, etc. Decreased MET degradation is thought to cause activation of downstream signaling pathway in a ligand-independent manner, leading to accelerated cell proliferation and other changes (*J Natl Cancer Inst.* 2017;109:1-12, etc.). The mutant protein, which plays a key role in driving oncogenesis, is reported to contribute to the proliferation and survival of tumor cells, and tumorigenesis of normal cells (*Cancer Res.* 2017;77:4498-505, etc.).

Tepotinib Hydrochloride Hydrate (hereinafter referred to as "tepotinib") is a low molecular weight tyrosine kinase inhibitor of MET discovered by Merck KGaA (Germany). Tepotinib is considered to inhibit phosphorylation of MET, inhibiting phosphorylation of downstream signaling molecules, thereby suppressing tumor growth in non-small cell lung cancer (NSCLC) with MET exon 14 (METex14) skipping alterations.

1.2 Development history etc.

A phase I study (Study EMR200095-001 [Study 01]) was conducted in patients with advanced solid tumors outside Japan by Merck KGaA and EMD Serono (the US) from [redacted] 20[redacted]. Then, a global phase II study (Study MS200095-0022 [VISION study]) was conducted from [redacted] 20[redacted] in patients with unresectable, advanced or recurrent METex14 skipping mutation-positive NSCLC by Merck KGaA, EMD Serono, and the applicant.

As of November 2019, tepotinib has not been approved in any country or region.

In Japan, a phase I study (Study EMR200095-003 [Study 03]) was conducted by the applicant in patients with advanced solid tumors from [redacted] 20[redacted]. Patient enrollment in the VISION study began in [redacted] 20[redacted].

The application for tepotinib was filed with the findings from the VISION study as the main study results.

Tepotinib was designated as a SAKIGAKE designation drug (SAKIGAKE Drug Designation No. 4 of 2018 [*30 yaku*]) for the intended indication of "advanced (stage IIIB/IV) non-small cell lung cancer with MET exon 14 skipping alterations" in March 2018, and as an orphan drug (Orphan Drug Designation No. 449 of 2019 [*31 yaku*]) for the intended indication of "*MET* gene mutation-positive non-small cell lung cancer" in November 2019.

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

2.1 Drug substance

2.1.1 Characterization

The drug substance is a white powder. Its description, melting point, solubility, hygroscopicity, acid dissociation constant, distribution coefficient, and particle diameter have been determined. A total of 3 crystalline forms ([redacted], [redacted], and [redacted]) of the drug substance have been identified. Among these forms, crystalline form [redacted] has been demonstrated to be produced during the manufacturing process at commercial scale and to be stable in stability tests.

The chemical structure of the drug substance has been elucidated by ^{1}H- and ^{13}C- nuclear magnetic resonance spectrometry (^{1}H- and ^{13}C-NMR), mass spectrometry, infrared spectrophotometry (IR), ultraviolet and visible absorption spectra, single crystal X-ray structure analysis, [redacted], water content, and elemental analysis.

2.1.2 Manufacturing process

The drug substance is synthesized using [redacted], [redacted], [redacted], [redacted], and [redacted] as the starting materials.

A quality by design (QbD) approach has been applied to the following to formulate the quality control strategy (Table 1).

- Identification of critical quality attributes (CQAs).
- Identification of critical process parameters (CPPs) through quality risk assessment, etc., and determination of acceptable ranges for manufacturing process parameters.

Table 1. Outline of control strategies for the drug substance

CQA	Control method
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]

The [redacted] step for [redacted] and the [redacted] step for [redacted] have been defined as critical steps in the manufacture of the drug substance.

The [redacted], [redacted], [redacted], [redacted], and [redacted] are controlled as critical intermediates.

2.1.3 Control of drug substance

The proposed specifications for the drug substance include content, description, identification ([redacted], IR, and X-ray powder diffraction), purity (organic impurities [liquid chromatography (LC)], and [redacted] [redacted]), water content, residue on ignition, microbial limit test, [redacted], and assay (LC).

2.1.4 Stability of drug substance

Table 2 shows main stability studies that have been conducted on the drug substance. The results of the photostability studies show that the drug substance is photostable.

Table 2. Stability studies on the drug substance

Study	Primary batch	Temperature	Humidity	Storage package	Storage period
Long-term	3 commercial-scale batches	25°C	60%RH	[redacted] polyethylene bags (double-layer) + [redacted] polyethylene drum	12 months
Accelerated		40°C	75%RH		6 months

Based on the above results, a retest period of [redacted] months was proposed for the drug substance when placed in double-layer [redacted] polyethylene bags and stored in a [redacted] polyethylene drum at room temperature according to the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) Q1E Guidelines. Long-term testing will be continued up to [redacted] months.

2.2 Drug product

2.2.1 Description and composition of drug product and formulation development

The drug product is an immediate-release film-coated tablet, with each tablet containing 100 mg or 250 mg of the drug substance. The drug product contains D-mannitol, microcrystalline cellulose, crospovidone, magnesium stearate, colloidal silicon dioxide, and Opadry II yellow [redacted] (100 mg tablet), or Opadry II pink [redacted] (250 mg tablet) as excipients.

2.2.2 Manufacturing process

The drug product is manufactured through a process comprising first mixing, [redacted], second mixing, tableting, film-coating, and packaging and labeling steps.

A QbD approach has been applied to the following to formulate the quality control strategy (Table 3).

- Identification of CQAs.

- Identification of CPPs and determination of acceptable ranges for manufacturing process parameters through quality risk assessment and experimental results of the effects on quality attributes.

Table 3. Outline of control strategies for the drug product

CQA	Control method
Strength	Specifications
[redacted]	[redacted], [redacted]
[redacted]	[redacted]
[redacted]	[redacted], [redacted]
[redacted]	[redacted]
[redacted]	[redacted]
Uniformity of dosage units	[redacted], specifications
Dissolution	[redacted], specifications
[redacted]	[redacted]
[redacted]	[redacted]

[redacted] have been defined as critical process steps, and process control items and their action limits have been established for steps [redacted], [redacted], and [redacted].

2.2.3 Control of drug product

The proposed specifications for the drug product include strength, description, identification (LC and ultraviolet absorption spectra), purity (degradation product [LC]), uniformity of dosage units (mass variation test), dissolution (ultraviolet-visible spectrophotometry), and assay (LC).

2.2.4 Stability of drug product

Table 4 shows main stability studies that have been conducted on the drug product. The results of the photostability studies show that the drug product is photostable.

Table 4. Stability studies on the drug product

Strength	Study	Primary batch	Temperature	Humidity	Storage package	Storage period
100 mg	Long-term	3 commercial-scale batches	25°C	60%RH	Blister pack ([redacted] and aluminum foil)	12 months
	Accelerated		40°C	75%RH		
250 mg	Long-term		25°C	60%RH		
	Accelerated		40°C	75%RH		

Based on the above results, a shelf life of 24 months was proposed for the drug product when packaged in a blister pack ([redacted] and aluminum foil), and stored at room temperature according to the ICH Q1E Guidelines. Long-term testing will be continued up to [redacted] months.

2.R Outline of the review conducted by PMDA

Based on the submitted data, PMDA concluded that the quality of the drug substances and the drug product is adequately controlled.

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

In this section, unless otherwise stated, the dose and concentration of tepotinib and its metabolite are expressed as the dose and concentration of hydrochloride hydrate.

3.1 Primary pharmacodynamics

3.1.1 Binding site of tepotinib on MET (CTD 4.2.1.1.1)

An X-ray crystallographic analysis of the cocrystal of MET and tepotinib was performed to investigate the binding site of tepotinib on MET. The results of the analysis indicated that tepotinib binds at the adenosine triphosphate (ATP)-binding site of MET.

3.1.2 Inhibition of phosphorylation of kinases by tepotinib (CTD 4.2.1.1.2, 4.2.1.1.5, 4.2.1.1.6, 4.2.1.1.7, and 4.2.1.1.27)

Inhibition of the phosphorylation of MET (recombinant protein) by tepotinib was investigated by monitoring the incorporation of ^{33}P-ATP into the substrate. The IC_{50} values of tepotinib (n = 2, individual values) were 1.7 and 1.8 nmol/L.

The inhibition of phosphorylation of 305 different kinases (recombinant proteins) by tepotinib was investigated by monitoring the incorporation of ^{33}P-ATP into the substrate. Of these kinases, MET, MET^{M1250T}, and MET^{Y1230H} had an inhibition percentage[2)] of ≥50% at tepotinib 0.1 μmol/L. Table 5 shows percentage inhibition of phosphorylation of these kinases by tepotinib.

Table 5. Inhibition of phosphorylation of kinases by tepotinib

Kinase	Inhibition (%) (individual value)	
	Tepotinib 0.1 μmol/L	Tepotinib 1 μmol/L
MET	100, 99	100, 100
MET^{M1250T} *1	99, 99	>100, >100
MET^{Y1230H} *2	53, 54	96, 96

n = 2; *1, methionine at residue 1,250 is replaced by threonine; *2, tyrosine at residue 1,230 is replaced by histidine

Inhibition of the phosphorylation of 399 different kinases (recombinant proteins) by tepotinib was investigated by monitoring the incorporation of ^{33}P-ATP into the substrate. Of these kinases, MET, interleukin-1 receptor-associated kinase (IRAK)1, IRAK4, tropomyosin receptor kinase (TRK)C, MET^{F1200I}, MET^{M1250T}, MET^{P991S}, MET^{T992I}, MET^{T1173I}, MET^{V1092I}, and MET^{Y1235D} had an inhibition percentage[2)] of ≥50% at tepotinib 1 μmol/L. Table 6 shows percentage inhibition of phosphorylation of these kinases by tepotinib.

2) Inhibition (%) = 100 − [(mean for the tepotinib group) − (mean for the non-intervention group)] / [(mean for the control [DMSO] group) − (mean for the non-intervention group)] × 100.

Table 6. Inhibition of phosphorylation of kinases by tepotinib

Kinase	Inhibition (%)	Kinase	Inhibition (%)	Kinase	Inhibition (%)
MET	99.7	MET^{F1200I} *1	72.4	MET^{T1173I} *4	91.5
IRAK1	56.6	MET^{M1250T}	86.0	MET^{V1092I} *5	90.1
IRAK4	76.5	MET^{P991S} *2	71.9	MET^{Y1235D} *6	99.9
TRKC	90.8	MET^{T992I} *3	84.2		

n = 1; *1, phenylalanine at residue 1,200 is replaced by isoleucine; *2, proline at residue 991 is replaced by serine; *3, threonine at residue 992 is replaced by isoleucine; *4, threonine at residue 1,173 is replaced by isoleucine; *5, valine at residue 1,092 is replaced by isoleucine; *6, tyrosine at residue 1,235 is replaced by aspartic acid

Using human NSCLC cell lines A549 and EBC-1, and the human gastric carcinoma cell line GTL-16 and Hs746T, inhibition of the phosphorylation of MET by tepotinib was examined by enzyme-linked immunosorbent assay (ELISA). Table 7 shows IC_{50} values of tepotinib for cell lines A549, EBC-1, GTL-16, and Hs746T.

Table 7. Inhibition of the phosphorylation of MET in different cell lines by tepotinib

Cell line	Derived from	n	IC_{50} (nmol/L)
A549	NSCLC	3	5.4 ± 0.15
EBC-1		4	1.1 ± 0.38
GTL-16	Gastric carcinoma	2	3.3, 2.5
Hs746T		4	2.1 ± 0.098

Geometric mean ± standard deviation; individual values if n = 2

Using cell line A549, inhibition of the phosphorylation of MET by MSC2571109A, a major metabolite of tepotinib, was examined by ELISA. The IC_{50} values of MSC2571109A (n = 2) were 13 and 26 nmol/L.

3.1.3 Inhibition of MET signal transduction (CTD 4.2.1.1.7)

Using cell lines EBC-1, GTL-16, and Hs746T, inhibition of the phosphorylation of MET and its downstream signaling molecules (growth factor receptor bound protein 2-associated protein [GAB]1, AKT, and extracellular signal-regulated kinase 1 and 2 [ERK1/2]) was examined by Western blot. Table 8 shows IC_{50} values of tepotinib.

Table 8. Inhibition of the phosphorylation of MET and its downstream signaling molecules

Cell line	IC_{50} (nmol/L)			
	MET	GAB1	AKT	ERK1/2
EBC-1	9.2	3.4	1.6	0.75
GTL-16	4.8	1.9	—	—
Hs746T	1.0	0.40	0.042	0.018

n = 1; —, not calculated

3.1.4 Anti-proliferative activity against malignant tumor-derived cell lines

3.1.4.1 *In vivo*

3.1.4.1.1 NSCLC-derived cell lines (CTD 4.2.1.1.9)

The *in vivo* anti-tumor effect of tepotinib was studied in severe combined immunodeficient (SCID) mice (n = 10/group) that had been subcutaneously xenografted with the human NSCLC cell line H596 harboring METex14 skipping alterations. Tepotinib was administered to the mice at 100 mg/kg QD

orally for 23 days starting from Day 0 when tumor volume reached 100 to 150 mm^3. On Day 23, the T/C value[3)] was 30%, indicating that a statistically significant anti-tumor effect was observed in the tepotinib group compared with the control (sodium acetate buffer containing 20% polyethylene glycol 15 hydroxystearate) group (Figure 1)

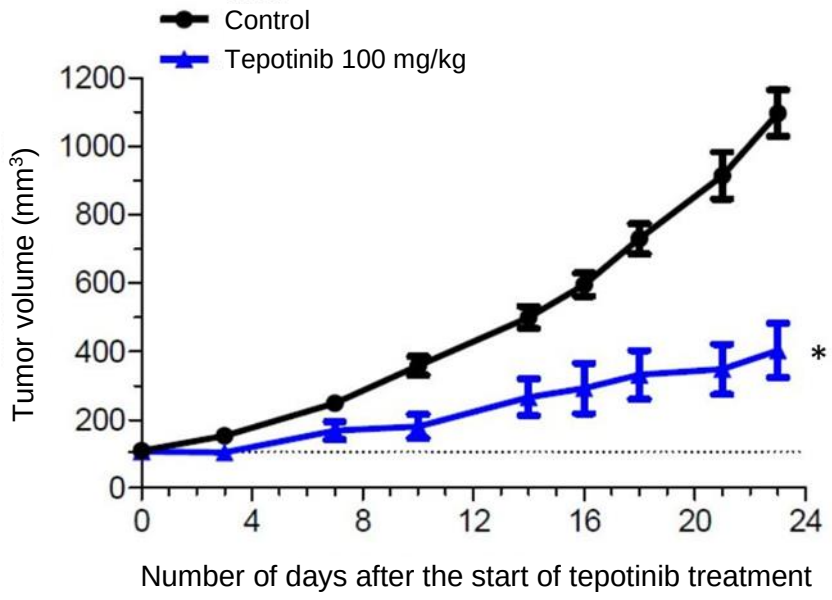


Figure 1. Anti-tumor effect of tepotinib in SCID mice subcutaneously xenografted with cell line H596
n = 10; mean ± standard error; *, $P \leq 0.05$ versus the control group (Mann-Whitney test)

3.1.4.1.2 Cell lines derived from malignant tumors other than NSCLC (CTD 4.2.1.1.10)

The anti-tumor effect of tepotinib was studied in nude mice (n = 10/group) subcutaneously xenografted with cell line Hs746T harboring METex14 skipping alterations and *MET* amplifications. Tepotinib (free base) was administered to the mice at 3 or 6 mg/kg QD orally for 14 days starting from Day 0 when tumor volume reached 100 mm^3. On Day 14, complete tumor regression[4)] was observed in 5 of 10 animals in the tepotinib (free base) 3 mg/kg group, and 10 of 10 animals in the tepotinib (free base) 6 mg/kg group.

3.2 Secondary pharmacodynamics

3.2.1 Effects on wound healing (CTD 4.2.1.2.1)

Using mice (n = 10/group), tepotinib 25 or 50 mg/kg was administered QD orally for 3 or 10 days to mice after full-thickness skin incision (5 mm) to assess the effect on skin wound healing. No effects of tepotinib were observed.

3) T/C (%) = [(mean tumor volume of the tepotinib group at the end of treatment − mean tumor volume of the tepotinib group at the start of treatment) / (mean tumor volume of the control group at the end of treatment − mean tumor volume of the control group at the start of treatment)] × 100.

4) Complete tumor regression was defined as absence of visible or palpable tumors.

3.3 Safety pharmacology

3.3.1 Effects on the central nervous system (CTD 4.2.1.3.15)

A single oral dose of tepotinib 25, 75, or 200 mg/kg was administered to rats (n = 10/group) to assess the effects of tepotinib on clinical signs and behavior by the functional observational battery. There were no effects associated with tepotinib treatment.

3.3.2 Effects on the cardiovascular system

3.3.2.1 Effects on hERG potassium current (CTD 4.2.1.3.7, 4.2.1.3.17)

The effects of tepotinib 0.2, 1, 3, and 10 μmol/L on the human *ether-a-go-go*-related gene (hERG) potassium current were assessed using the human embryonic kidney cell line HEK293 transfected with hERG. The percentage inhibition of hERG potassium current (mean ± standard deviation; n = 3) was 15.7 ± 0.8% (0.2 μmol/L), 42.3 ± 4.3% (1 μmol/L), 73.3 ± 1.4% (3 μmol/L), and 92.7 ± 0.6% (10 μmol/L) with an IC_{50} value of 1.2 μmol/L. Statistically significant inhibition was observed in all tepotinib groups compared with the control (HEPES buffered saline solution[5)] containing 0.3% dimethyl sulfoxide [DMSO]) group ($P < 0.05$; Dunnett's multiple comparison test).

The effects of MSC2571109A at 0.1, 0.3, 1, 3, and 10 μmol/L on hERG potassium current were assessed using cell line HEK293 transfected with hERG. The percentage inhibition of hERG potassium current (mean ± standard deviation; n = 3 or 4) was 5.3 ± 4.7% (0.1 μmol/L), 4.5 ± 1.9% (0.3 μmol/L), 14.6 ± 8.5% (1 μmol/L), 18.5 ± 10.8% (3 μmol/L), and 24.9 ± 8.9% (10 μmol/L). Statistically significant inhibition was observed in the MSC2571109A 10 μmol/L group compared with the control (extracellular buffer solution[6)] containing 0.1% or 0.5% DMSO) group ($P < 0.05$; Dunnett's multiple comparison test).

3.3.2.2 Effects on myocardial ion channels (CTD 4.2.1.3.9, 4.2.1.3.18)

The effects of tepotinib (free base) 3 and 10 μmol/L, and MSC2571109A 10 and 30 μmol/L on myocardial ion channels (hKCNQ1/hminK, hKv1.5, hNav1.5, hHCN4, hKv4.3/hKChIP2, hCav1.2, and hKir2.1) were assessed. Neither tepotinib (free base) nor MSC2571109A inhibited any of the myocardial ion channels by ≥50%.

3.3.2.3 Effects on blood pressure, heart rate, and ECG (CTD 4.2.1.3.12)

A single oral dose of tepotinib 30 or 70 mg/kg was administered to dogs (n = 5/group), and the effects of tepotinib on blood pressure (systolic, diastolic, and mean blood pressure), heart rate, and electrocardiograms (ECGs; QT, RR, and QTc intervals) were assessed. There were no effects associated with tepotinib treatment.

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5) 137 mmol/L sodium chloride, 4.0 mmol/L potassium chloride, 1.8 mmol/L calcium chloride, 1 mmol/L magnesium chloride, 10 mmol/L HEPES, and 10 mmol/L glucose.

6) 140 mmol/L sodium chloride, 2.5 mmol/L potassium chloride, 2 mmol/L calcium chloride, 2 mmol/L magnesium chloride, 10 mmol/L HEPES, 10 mmol/L glucose, and 19 mmol/L sucrose.

3.3.3 Effects on the respiratory system (CTD 4.2.1.3.14)

A single oral dose of tepotinib 25, 75, or 200 mg/kg was administered to rats (n = 8/group), and the effects of tepotinib on respiratory rate, respiratory volume, tidal volume, and other parameters were assessed. There were no effects associated with tepotinib treatment.

3.R Outline of the review conducted by PMDA

Based on the submitted data, and discussions in the following sections, PMDA concluded that the applicant's explanation about the non-clinical pharmacology of tepotinib is acceptable. The inhibitory effect of tepotinib on the hERG potassium current demonstrated in the safety pharmacology study is included in the "7.R.3.7 Others" section, while taking into consideration the efficacy and safety data for tepotinib from clinical studies.

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

The applicant's explanation about the mechanism of action and efficacy of tepotinib in the treatment of NSCLC with METex14 skipping alterations:

Exon 14 of the *MET* gene encodes an important site involved in ubiquitination (protein degradation) of MET (*J Natl Cancer Inst.* 2017;109:1-12). When exon 14 skipping alterations (METex14 skipping alterations) occur, MET protein degradation is inhibited, causing MET mutant protein to accumulate within the cell. Decreased MET degradation is considered to cause activation of downstream signaling pathway in a ligand-independent manner, leading to accelerated cell proliferation and other changes (*J Natl Cancer Inst.* 2017;109:1-12, etc.). Findings including the following suggest that METex14 skipping alteration is involved in tumor cell growth, acting as an oncogenic driver:

- METex14 skipping alterations accelerate MET-mediated signaling pathways. In addition, the alteration and deficiency of a tumor-suppressor *p53* cause lung adenocarcinoma. Based on this and other findings, it has been suggested that METex14 skipping alterations play significant roles in the survival and proliferation of tumor cells (*Cancer Res.* 2017;77:4498-505, etc.).

Tepotinib, a low molecular weight compound that binds at the ATP-binding site of MET [see Section 3.1.1], inhibited the phosphorylation of MET and other kinases [see Section 3.1.2] and of downstream signaling molecules (e.g., AKT and ERK1/2) [see Section 3.1.3], and showed anti-tumor effects in NSCLC with METex14 skipping alterations [See Section 3.1.4.1.1].

Based on the above findings, tepotinib is expected to be effective in the treatment of NSCLC with METex14 skipping alterations.

PMDA accepted the applicant's explanation.

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

The non-clinical pharmacokinetics of tepotinib were evaluated mainly in rats. The plasma protein binding, drug metabolizing enzymes, transporters, and other pharmacokinetic properties of tepotinib were investigated using biological samples derived from humans or animals.

4.1 Absorption

4.1.1 Single-dose studies

A single dose of tepotinib 3 mg/kg (intravenous), or 6 mg/kg (oral) was administered to male and female rats, and plasma tepotinib concentrations were investigated (Table 9). The bioavailability (BA) of tepotinib following oral dose administration was 21.4% in males, and 55.3% in females. The C_{max} and AUC_{last} were higher in females than in males.

Table 9. Pharmacokinetic parameters of tepotinib (male and female rats; single intravenous or oral administration)

Dose (Route of administration)	n	C_{max} (ng/mL)		t_{max}* (h)		AUC_{last} (ng·h/mL)	
		Male	Female	Male	Female	Male	Female
3 mg/kg (Intravenous)	3	198 (13.4)	249 (9.12)	0.100 (0.100, 0.100)	0.100 (0.100, 0.100)	276 (14.2)	579 (14.5)
6 mg/kg (Oral)	3	21.8 (25.5)	66.0 (19.0)	4.00 (4.00, 8.00)	4.00 (4.00, 4.00)	121 (22.0)	637 (13.9)

Mean (coefficient of variation [%]); *, median (range)

4.1.2 Repeated-dose studies

Repeated doses of tepotinib 3, 10, 30, or 90 mg/kg was administered QD orally to male and female rats for 4 weeks, and plasma tepotinib concentrations were investigated (Table 10). The C_{max} and AUC_{24h} were higher in females than in males. The C_{max} and AUC_{24h} on Day 28 were higher than those on Day 1.

Table 10. Pharmacokinetic parameters of tepotinib (male and female rats; 4-week repeated oral administration)

Day of measurement (Day)	Dose (mg/kg)	n	C_{max} (ng/mL)		t_{max}* (h)		AUC_{24h} (ng·h/mL)	
			Male	Female	Male	Female	Male	Female
1	3	3	12.0 ± 4.86	15.0 ± 4.28	3 (3, 3)	3 (1, 6)	122 ± 24.9	131 ± 40.6
	10	3	48.0 ± 2.04	101 ± 19.9	3 (3, 3)	3 (3, 3)	358 ± 6.04	725 ± 185
	30	3	132 ± 37.14	214 ± 52.0	3 (3, 3)	3 (3, 3)	987 ± 165	1,650 ± 172
	90	3	252 ± 33.75	421 ± 41.1	3 (3, 3)	3 (3, 6)	2,130 ± 118	5,970 ± 1,270
28	3	3	17.7 ± 4.96	27.9 ± 2.39	6 (3, 6)	1 (1, 1)	158 ± 36.8	223 ± 64.9
	10	3	53.8 ± 5.98	114 ± 45.9	3 (3, 6)	6 (6, 6)	468 ± 173	1,010 ± 201
	30	3	184 ± 87.71	394 ± 61.26	3 (3, 3)	6 (3, 6)	1,600 ± 576	3,320 ± 308
	90	3	459 ± 22.27	834 ± 46.99	6 (3, 6)	6 (6, 6)	5,130 ± 131	11,100 ± 2,770

Mean ± standard deviation; *, median (range)

There were differences in C_{max} and AUC between the sexes in the rat single dose study [see Section 4.1.1] and the repeated-dose study above. The applicant explained that the differences may have been associated with factors including sex differences in the expression of cytochrome P450 (CYP) isozymes

in rats (*Mol Pharmacol.* 2009;76:215-28, etc.), taking into consideration that tepotinib is eliminated by metabolism [see Section 4.3.1].

4.1.3 *In vitro* membrane permeability

The membrane permeability of tepotinib was investigated using the human colon cancer-derived Caco-2 cell line. The apparent permeability in apical to basal direction ($P_{app\ A \rightarrow B}$) for ^{14}C-tepotinib 100 μmol/L was 157 nm/sec in the presence of a non-specific inhibitor[7)] for the transporters. In addition, the $P_{app\ A \rightarrow B}$ for metoprolol (10 μmol/L), a known highly permeable compound, was 321 nm/sec. The applicant explained that these results indicate tepotinib has an intermediate permeability.

4.2 Distribution

4.2.1 Tissue distribution

A single oral dose of ^{14}C-tepotinib 4 mg/kg was administered to male and female albino rats and male pigmented rats to investigate tissue distribution of radioactivity.

In male albino rats, radioactivity was widely distributed across the tissues. Tissue radioactivity levels reached their maximum within 6 hours post-dose in the majority of tissues. Compared with the AUC_{last} of plasma radioactivity (80 ng Eq.·h/g), the AUC_{last} of tissue radioactivity was particularly high in the small intestinal wall (114,000 ng Eq.·h/g), gastric wall (53,700 ng Eq.·h/g), liver (48,900 ng Eq.·h/g), large intestinal wall (28,400 ng Eq.·h/g), kidney (28,400 ng Eq.·h/g), lung (23,800 ng Eq.·h/g), lymph nodes (21,500 ng Eq.·h/g), pancreas (12,900 ng Eq.·h/g), and spleen (12,900 ng Eq.·h/g) [see Section 5.2]. There were no clear differences in the tissue distribution of radioactivity between the sexes in albino rats. In male pigmented rats, tissue distribution of radioactivity was similar to that of male albino rats except for the eye. The radioactivity level in the eye fell below the lower limit of quantification at 48 hours post-dose in male albino rats; in contrast, the radioactivity level was 1,370 ng Eq./g at 96 hours post-dose in male pigmented rats. The applicant explained that these results suggest the binding of tepotinib and its metabolites to melanin.

4.2.2 Plasma protein binding

Mouse, rat, rabbit, dog, monkey, and human plasma was incubated with ^{14}C-tepotinib (0.3-10 μmol/L) at 37°C for 1 hour, and the plasma protein binding of tepotinib was investigated using equilibrium dialysis. The unbound fraction of tepotinib was roughly constant in the concentration range studied in mouse, rat, rabbit, and dog plasma: 2.7% to 2.9% (mouse), 4.0% to 4.2% (rat), 4.2% to 4.5% (rabbit), and 6.3% to 6.5% (dog). In contrast, the unbound fraction of tepotinib in plasma tended to increase with increasing concentrations in monkey and human plasma in the concentration range studied: 4.4% to 6.2% (monkey), and 1.6% to 3.4% (human). The applicant explained that the concentration-dependent increase in the unbound fraction of tepotinib in monkey and human plasma may be attributable to a large

7) Non-specific inhibitor contains PSC833 (1 μmol/L), Ko143 (1 μmol/L), and cyclosporin A (20 μmol/L).

contribution of α1-acid glycoprotein to the protein binding of tepotinib in monkey and human plasmas compared with that in mouse, rat, rabbit, and dog plasma.

Mouse, rat, dog, and human plasma was incubated with MSC2571109A (0.2-10 μmol/L) at 37°C for 3 hours, and the plasma protein binding of MSC2571109A was investigated using equilibrium dialysis. The unbound fraction of MSC2571109A was roughly constant in the concentration range studied in mouse, rat, dog, and human plasma: 1.2% to 1.3% (mouse), 0.88% to 1.3% (rat), 2.4% to 2.5% (dog), and 1.1% to 1.2% (human).

Human serum albumin (600 μmol/L), human α1-acid glycoprotein (20 μmol/L), human ceruloplasmin (3 μmol/L), human complement C4 (2 μmol/L) or human transferrin (38 μmol/L) was incubated with ^{14}C-tepotinib (1 μmol/L) at 37°C for 1 hour, and the plasma protein binding of tepotinib was investigated using equilibrium dialysis. The unbound fraction[8)] of tepotinib to plasma proteins was 6.5% to 8.2% (human serum albumin), 17% to 25% (human α1-acid glycoprotein), 84% (human ceruloplasmin), 75% (human complement C4), and 74% (human transferrin). The applicant explained that the results suggest that tepotinib binds primarily to serum albumin and α1-acid glycoprotein in human plasma.

4.2.3 Distribution in blood cells

Mouse, rat, rabbit, dog, monkey, and human blood was incubated with ^{14}C-tepotinib (0.1-1 μmol/L) at 37°C for 10 minutes, and the distribution of tepotinib in blood cells was investigated. The blood-to-plasma ratios for radioactivity ranged from 1.9 to 2.1 (mouse), 2.1 to 2.2 (rat), 2.5 to 2.6 (rabbit), 2.5 (dog), 1.9 to 2.2 (monkey), and 0.6 to 1.0 (human) in the concentration range studied. The applicant explained that the results indicated that tepotinib is distributed primarily in plasma in human.

Human blood was incubated with MSC2571109A (0.2-2 μmol/L) at 37°C for 15 minutes, and the distribution of MSC2571109A in blood cells was investigated. The blood-to-plasma concentration ratio ranged from 0.75 to 0.78 in the concentration range studied. The applicant explained that the results indicated that MSC2571109A is distributed primarily in plasma in human.

4.2.4 Placental and fetal transfer

Neither the placental nor fetal transfer of tepotinib has been studied. The applicant explained that tepotinib may cross the placenta and to the fetus since toxicities including fetal skeletal anomalies have been noted in a rabbit embryo-fetal development study [see Section 5.5].

8) The unbound fraction in human serum albumin and human α1-acid glycoprotein was measured twice, and data are therefore presented in ranges.

4.3 Metabolism

4.3.1 *In vitro*

Mouse, rat, rabbit, dog, monkey, and human hepatocytes were incubated with ^{14}C-tepotinib (0.8-1.5 μmol/L[9)]) at 37°C for 24 hours, and the metabolites of tepotinib were determined. In all animal and human hepatocytes, M508 (*N*-oxide) was detected. In addition, M668 (glucuronide conjugate) was detected in human hepatocytes.

The applicant's explanation about the enzymes involved in the metabolism of tepotinib in humans:
Recombinant human CYP isoforms (CYP1A2, CYP2A6, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, CYP2E1, CYP3A4, and CYP3A5) were incubated with ^{14}C-tepotinib (10 μmol/L) in the presence of nicotinamide adenine dinucleotide phosphate hydrogen (NADPH) at 37°C for 1 hour, and CYP isoforms involved in the metabolism of tepotinib were determined. The proportion of unchanged tepotinib decreased to 87.1% at most when incubated with CYP2C8, and 77.3% at most when incubated with CYP3A4. When incubated with other CYP isoforms studied, the proportion of unchanged tepotinib was 100%.

Based on the above results and other factors, it is considered that CYP3A4 and CYP2C8 are involved in the metabolism of tepotinib; however, given that their contribution to the metabolism of tepotinib is limited, it is unlikely that when tepotinib is used clinically, co-administration with an inhibitor or inducer of CYP3A or CYP2C8 will pose a problem.

4.3.2 *In vivo*

A single oral dose of ^{14}C-tepotinib 50 mg/kg was administered to male and female rats to investigate the metabolites of tepotinib in plasma, urine, and feces, and the following results were obtained:

- Mainly, unchanged tepotinib and M508 were detected in plasma at 10 hours post-dose (60% [unchanged tepotinib] and 40% [M508] of the total plasma radioactivity in male rats; 66% [unchanged tepotinib] and 35% [M508] of the total plasma radioactivity in female rats).
- Mainly, unchanged tepotinib and M508 were detected in urine up to 24 hours post-dose (2% [unchanged tepotinib] and 2% [M508] to the total radioactivity administered in male rats; 6% [unchanged tepotinib] and 4% [M508] to the total radioactivity administered in female rats).
- Mainly, unchanged tepotinib was detected in feces up to 48 hours post-dose (85% to the total radioactivity administered in male rats; and 77% to the total radioactivity administered in female rats).

9) The hepatocytes were studied at the following concentrations: mouse and rat at 0.8 μmol/L, dog and monkey at 1.2 μmol/L, rabbit at 0.9 μmol/L, and human at 1.5 μmol/L.

4.4 Excretion

4.4.1 Urinary, fecal, and biliary excretion

The applicant's explanation:

Based on the study results below, tepotinib and its metabolites are expected to be excreted mainly in feces via bile.

- In bile duct-uncannulated male and female rats, the urinary and fecal excretion rates (relative to the administered radioactivity) at 120 hours after a single oral dose of ^{14}C-tepotinib at 4 mg/kg were 2.06% and 96.8%, respectively, in male rats; and 7.33% and 89.8%, respectively, in female rats.
- In bile duct-cannulated male and female rats, the urinary, fecal, and biliary excretion rates (relative to the administered radioactivity) up to 24 hours after a single oral dose of ^{14}C-tepotinib at 4 mg/kg were 1.54%, 58.2%, and 23.0%, respectively, in male rats; and 5.34%, 36.5%, and 32.6%, respectively, in female rats.

4.4.2 Excretion into milk

The excretion of tepotinib into milk has not been investigated. The applicant explains that tepotinib may be excreted into milk on the basis of several factors including the physicochemical properties of tepotinib (i.e., molecular weight [free base], 492.58; polar surface area, 94.7 Å^2; logP, 4.6; and logD, 2.3).

4.5 Pharmacokinetic interactions

4.5.1 Enzyme inhibition

The applicant's explanation about the pharmacokinetic interactions of tepotinib and MSC2571109A through the inhibition of metabolizing enzymes:

Based on the study results shown below, in addition to the $C_{max,ss}$ values of tepotinib and MSC2571109A (7.17 μmol/L[10] and 2.05 μmol/L[11], respectively) and the estimated maximum tepotinib concentration in the gastrointestinal tract of 4,060 μmol/L observed when tepotinib was administered according to the proposed dosage and administration, tepotinib during clinical use is unlikely to cause pharmacokinetic interactions through the inhibition of CYP1A2, CYP2A6, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, CYP2E1, uridine diphosphate glucuronosyl transferase (UGT)1A1, UGT1A3, UGT1A4, UGT1A6, UGT1A9, UGT2B7, UGT2B15, or UGT2B17 by tepotinib; or the inhibition of CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, CYP3A, UGT1A3, UGT1A4, UGT1A6, UGT1A9, UGT2B7, UGT2B15, or UGT2B17 by MSC2571109A. However, pharmacokinetic interactions are likely to be caused by tepotinib via inhibition of CYP3A expressed in the gastrointestinal tract, or by MSC2571109A via inhibition of UGT1A1.

- Human liver microsomes were incubated with tepotinib (0.03-49.5 μmol/L) in the presence of substrate for CYP isoforms (CYP1A2, CYP2A6, CYP2B6, CYP2C8, CYP2C9, CYP2C19,

10) The $C_{max,ss}$ value following administration of tepotinib 500 mg QD orally in the foreign phase I study (Study 01)
11) The $C_{max,ss}$ value following administration of tepotinib 500 mg QD orally in the global phase Ib/II study (Study 06)

CYP2D6, CYP2E1, or CYP3A)[12] and NADPH to evaluate the inhibitory effects of tepotinib on these CYP isoforms. Tepotinib inhibited the metabolism of the substrates for CYP2C8 (IC_{50} = 16 μmol/L), CYP2C9 (IC_{50} = 27 μmol/L), CYP2C19 (IC_{50} = 30 μmol/L), and CYP3A (IC_{50} = 25 μmol/L[13]). However, tepotinib did not show a clear inhibitory effect on the metabolism of the other CYP substrates tested. Tepotinib displayed no clear time-dependent inhibitory effect on the metabolism of the CYP substrates.

- Human liver microsomes were incubated with MSC2571109A (0.02-15 μmol/L) in the presence of substrate for CYP isoforms (CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, or CYP3A)[14] and NADPH to evaluate the inhibitory effects of MSC2571109A on these CYP isoforms. MSC2571109A inhibited the metabolism of the substrate for CYP2C9 with an IC_{50} value of 8.8 μmol/L. However, MSC2571109A did not show a clear inhibitory effect on the metabolism of other CYP substrates tested.
- Human liver microsomes were incubated with tepotinib (0.015-15 μmol/L) or MSC2571109A (0.008-15 μmol/L[15]) in the presence of substrate for UGT isoforms (UGT1A1, UGT1A3, UGT1A4, UGT1A6, UGT1A9, UGT2B7, UGT2B15, or UGT2B17)[16] and uridine diphosphate glucuronic acid (UDPGA) to evaluate the inhibitory effects of tepotinib or MSC2571109A on these UGT isoforms. Tepotinib inhibited the metabolism of the substrates for UGT1A9 (IC_{50} = 3.8 μmol/L) and UGT2B17 (IC_{50} = 6.1 μmol/L). MSC2571109A inhibited the metabolism of the substrates for UGT1A1 (IC_{50} = 1.1 μmol/L), UGT1A3 (IC_{50} = 5.8 μmol/L), UGT1A4 (IC_{50} = 6.2 μmol/L), UGT1A9 (IC_{50} = 3.6 μmol/L), UGT2B15 (IC_{50} = 9.6 μmol/L), and UGT2B17 (IC_{50} = 2.2 μmol/L). However, neither tepotinib nor MSC2571109A showed a clear inhibitory effect on the metabolism of other UGT substrates tested.

4.5.2 Enzyme induction

The applicant's explanation about the pharmacokinetic interactions of tepotinib and MSC2571109A through the induction of metabolizing enzymes:

Based on the study results shown below, together with the $C_{max,ss}$ of tepotinib and MSC2571109A (7.17 μmol/L[10] and 2.05 μmol/L[11], respectively) observed when tepotinib was administered according to the proposed dosage and administration, tepotinib and MSC2571109A during clinical use are unlikely to cause pharmacokinetic interactions through the induction of CYP1A2 or CYP2B6. However, tepotinib and MSC2571109A are likely to cause pharmacokinetic interactions through the induction of CYP3A4.

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12) The following compounds were used as substrates for the CYP isoforms: phenacetin (CYP1A2), coumarin (CYP2A6), efavirenz (CYP2B6), amodiaquine (CYP2C8), diclofenac (CYP2C9), *S*-mephenytoin (CYP2C19), dextromethorphan (CYP2D6), chlorzoxazone (CYP2E1). As substrates for CYP3A, testosterone, midazolam, and nifedipine were used.

13) The IC_{50} value obtained when midazolam was used as the substrate. The IC_{50} values were 31 μmol/L and 26 μmol/L, respectively, when testosterone and nifedipine were used as the substrate.

14) The following compounds were used as substrates for the CYP isoforms: phenacetin (CYP1A2), efavirenz (CYP2B6), amodiaquine (CYP2C8), diclofenac (CYP2C9), *S*-mephenytoin (CYP2C19), and dextromethorphan (CYP2D6). As substrates for CYP3A, testosterone, midazolam, and nifedipine were used.

15) The assays were performed at the following concentrations: 0.012 to 15 μmol/L for the substrates of UGT1A1, UGT2B7, UGT2B15, and UGT2B17; and 0.015 to 15 μmol/L for the substrates of UGT1A3, UGT1A6, and UGT1A9.

16) The following compounds were used as substrates for the UGT isoforms: estradiol (UGT1A1), chenodeoxycholic acid (UGT1A3), trifluoperazine (UGT1A4), naphthol (UGT1A6), propofol (UGT1A9), morphine (UGT2B7), oxazepam (UGT2B15), and testosterone (UGT2B17).

- Primary human hepatocytes were incubated in the presence of tepotinib (0.01-5 μmol/L) for 3 days to determine the mRNA expression of CYP isoforms (CYP1A2, CYP2B6, and CYP3A4). Tepotinib induced the mRNA expression of CYP3A4 at a maximum of 13.2% of that of the positive control rifampicin (20 μmol/L). The half maximal effective concentration (EC_{50}) value for the induction of CYP3A4 mRNA expression by tepotinib was 1.64 μmol/L, and the maximum effect (E_{max}) was 7.35-fold. In contrast, tepotinib showed no obvious inductive effect on the mRNA expression levels of CYP1A2 or CYP2B6.
- Primary human hepatocytes were incubated in the presence of MSC2571109A (0.003-5 μmol/L) for 3 days to determine the mRNA expression of CYP isoforms (CYP1A2, CYP2B6, and CYP3A4). MSC2571109A induced the mRNA expression of CYP2B6 at a maximum of 56.9% of that of the positive control phenobarbital (750 μmol/L), and the mRNA expression of CYP3A4 at a maximum of 40.1% of the positive control rifampicin (20 μmol/L). The EC_{50} values for the induction of mRNA expression by MSC2571109A was 1.86 μmol/L (CYP2B6) and 1.10 μmol/L (CYP3A4), and the E_{max} was 6.98-fold (CYP2B6) and 22.7-fold (CYP3A4). In contrast, MSC2571109A showed no obvious inductive effect on the mRNA expression levels of CYP1A2.

4.5.3 Transporters

The applicant's explanation about pharmacokinetic interactions by tepotinib and MSC2571109A through transporters:

Based on the following study results and other available data, tepotinib was demonstrated not to be a substrate of breast cancer resistance protein (BCRP), multidrug resistance associated protein (MRP)2, organic anion transporting polypeptide (OATP)1B1, OATP1B3, organic cation transporter (OCT)1, OCT2, multidrug and toxin extrusion (MATE)1, or MATE2-K, but to be substrate for P-glycoprotein (P-gp). MSC2571109A was also demonstrated not to be a substrate of OATP1B1, OATP1B3, OCT1, OCT2, MATE1, or MATE2-K.

- Various transporters-mediated transport of ^{14}C-tepotinib (1.0-15 μmol/L[17)]) was investigated in porcine kidney-derived LLC-PK1 cells expressing human P-gp, or canine kidney-derived MDCK II cells expressing human BCRP or MRP2. The efflux ratios of ^{14}C-tepotinib without and with a P-gp inhibitor (PSC833, 3 μmol/L) were 8.9 to 9.3 and 1.6 to 2.1, respectively; those without and with BCRP inhibitor (Ko143, 1 μmol/L) were 1.3 to 1.8 and 0.84 to 1.1, respectively; and those without and with MRP2 inhibitor (MK-571, 50 μmol/L) were 1.4 to 2.1 and 1.2 to 1.7, respectively, over the concentration ranges studied.
- Various transporters-mediated intracellular uptake of ^{14}C-tepotinib (0.51-32 μmol/L[18)]) and MSC2571109A (0.03-3.0 μmol/L) was investigated in HEK293 cells expressing human OATP1B1, OATP1B3, OCT1, OCT2, MATE1, or MATE2-K. The ratios of the uptake of ^{14}C-tepotinib and

17) The assays were performed at the following concentrations: 0.3 to 1.0 μmol/L for P-gp, and 0.1 to 1.0 μmol/L for MRP2.
18) The assays were performed at the following concentrations: 0.2 to 10 μmol/L for OATP1B1, OATP1B3, OCT1, OCT2, and MATE2-K.

MSC2571109A into transporter-expressing cells to that into transporter unexpressed cells[19] were ≤2, over the concentration ranges studied.

Given the following study results, as well as the $C_{max,ss}$ values of tepotinib and MSC2571109A (7.17[10] and 2.05 μmol/L[11], respectively), and the estimated gastrointestinal concentrations (up to 4,060 μmol/L) of tepotinib administered with the proposed dosage and administration, tepotinib in clinical use is unlikely to cause pharmacokinetic interactions through the inhibition of OAT1, OAT3, OCT2, OATP1B1, OATP1B3, or bile salt export pump (BSEP). Similarly, MSC2571109A is unlikely to cause pharmacokinetic inhibition of OAT1, OAT3, OATP1B3, or MATE1. On the other hand, tepotinib is likely to cause pharmacokinetic interactions through the inhibition of P-gp, BCRP, OCT1, MATE1, or MATE2-K, while MSC2571109A is likely to cause pharmacokinetic interactions through the inhibition of OATP1B1, OCT1, OCT2, or MATE2-K.

- The inhibitory effects of tepotinib (0.03-300 μmol/L[20]) on the transport of substrates[21] for various transporters through P-gp, BCRP, OCT1, OATP1B1, OATP1B3, OAT1, OAT3, OCT2, MATE1, MATE2-K, and BSEP were investigated in Caco-2 cells, HEK293 cells expressing human OCT1, OATP1B1, OATP1B3, OAT1, OAT3, OCT2, MATE1, or MATE2-K, and membrane vesicles prepared from insect cell-derived Sf9 cells expressing human BSEP. Tepotinib inhibited the transport of substrate for P-gp (IC_{50} = 0.41 μmol/L), BCRP (IC_{50} = 1.9 μmol/L), OCT1 (IC_{50} = 2.3 μmol/L), OATP1B1 (IC_{50} = 177 μmol/L), OATP1B3 (IC_{50} = 35 μmol/L), OAT1 (IC_{50} = 271 μmol/L), OCT2 (IC_{50} = 67 μmol/L), MATE1 (IC_{50} = 3.6 μmol/L), and MATE2-K (IC_{50} = 1.1 μmol/L). Tepotinib had no evident inhibitory effects on the transport of the substrates for OAT3 and BSEP.
- The inhibitory effects of MSC2571109A (0.05-5 μmol/L[22]) on the transport of substrates[23] for various transporters through OATP1B1, OATP1B3, OCT1, OAT1, OAT3, or OCT2 were investigated in HEK293 cells expressing human OATP1B1, OATP1B3, OCT1, OAT1, OAT3, or OCT2. MSC2571109A inhibited the transport of substrate for OATP1B1 (IC_{50} = 0.79 μmol/L), OCT1 (IC_{50} = 0.60 μmol/L), OAT3 (IC_{50} = 3.3 μmol/L), OCT2 (IC_{50} = 0.04 μmol/L). MSC2571109A had no evident inhibitory effect on the transport of the substrates for OATP1B3 and OAT1.

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19) The ratios of the uptake of tepotinib and MSC2571109A into transporter-expressing cells to that into non-expressing cells.
20) The assays were performed at the following concentrations: 0.1 to 10 μmol/L for P-gp, 0.03 to 30 μmol/L for BCRP, 0.25 to 9.76 μmol/L for OCT1, 1 to 500 μmol/L for OCT2, 0.05 to 150 μmol/L for MATE1, 0.005 to 150 μmol/L for MATE2-K, and 2.6 to 12.8 μmol/L for BSEP.
21) The following radiolabeled compounds were used as the substrates for the transporters: ^{3}H-digoxin (5 μmol/L) for P-gp, ^{14}C-2-Amino-1-methyl-6-phenylimidazo[4,5-b]pyridine (2 μmol/L) for BCRP, ^{3}H-N-methyl-4-phenylpyridinium (37 μmol/L) for OCT1, ^{3}H-sulfobromophthalein (0.86 μmol/L) for OATP1B3, ^{3}H-*para*-aminohippuric acid (90 μmol/L) for OAT1, ^{3}H-1-methyl-4-phenylpyridinium (57 μmol/L) for OCT2, and ^{3}H-taurocholic acid (2 μmol/L) for BSEP; ^{3}H-estrone sulfate salt (0.26 μmol/L) for OATP1B1, and (20 μmol/L) for OAT3; ^{14}C-metformin (274 μmol/L) for MATE1, and (934 μmol/L) for MATE2-K.
22) The assays were performed at 1 and 5 μmol/L for OATP1B3.
23) The following radiolabeled compounds were used as the substrates for the transporters: ^{3}H-estradiol-17β-glucuronide (1 μmol/L) for OATP1B1 and OATP1B3; ^{14}C-tetraethylammonium chloride (10 μmol/L) for OCT1; ^{3}H-*para*-aminohippuric acid (2 μmol/L) for OAT1, ^{3}H-estrone-3-sulfate salt (2 μmol/L) for OAT3, and ^{14}C-metformin hydrochloride (5 μmol/L) for OCT2.

- The inhibitory effects of MSC2571109A (0.03-4.0 μmol/L[24]) on the transport of substrates[25] for various transporters through MATE1 or MATE2-K were investigated in HEK293 cells expressing human MATE1 or MATE2-K. MSC2571109A inhibited the transport of substrate for MATE2-K with an IC_{50} of 0.36 μmol/L. MSC2571109A had no evident inhibitory effect on the transport of the substrates for MATE1.

4.R Outline of the review conducted by PMDA

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

4.R.1 Tissue distribution

The study results suggested that tepotinib and its metabolites bind to melanin [see Section 4.2.1]. PMDA asked the applicant to explain the safety of tepotinib in melanin-containing tissues.

The applicant's explanation:

In view of the following study outcomes and other data, the distribution of tepotinib and its metabolites in melanin-containing tissues is unlikely to pose a safety concern for its clinical use.

- The results of a 39-week repeated dose toxicity study in dogs provided no toxicity findings in melanin-containing tissues such as skin and eyes [see Section 5.2].
- In the global phase II study (VISION study), rash (6.2%, 8 of 130 subjects) and lacrimation increased (8.5%, 11 of 130 subjects), etc. were reported as adverse events related to skin and subcutaneous tissue disorders, and eye disorders. However, many of the adverse events were Grade ≤2 in severity, and there were no particular clinical concerns.

PMDA accepted the applicant's explanation.

4.R.2 Pharmacokinetic interactions

The following *in vitro* data suggested that tepotinib may cause pharmacokinetic interactions through some metabolizing enzymes or transporters in human:

- Tepotinib inhibits BCRP, OCT1, MATE1, and MATE2-K while MSC2571109A inhibits UGT1A1, OATP1B1, OCT1, OCT2, and MATE2-K [see Sections 4.5.1 and 4.5.3].
- Tepotinib serves as the substrate of P-gp [see Section 4.5.3].

The applicant's explanation about the pharmacokinetic interactions mediated by the metabolizing enzymes and transporters of tepotinib and MSC2571109A shown above:

Because only a limited number of patients received tepotinib in combination with the substrates or inhibitors of the metabolizing enzymes or transporters shown above, such interactions are difficult to

24) The assays were performed at concentrations of 0.04 to 4.1 μmol/L for MATE1.
25) ^{14}C-metformin was used as the substrates for the following: MATE1 (at 274 μmol/L) and MATE2-K (at 934 μmol/L).

evaluate. However, based on the findings, including the study results listed below, such interactions are unlikely to cause problems in the clinical use of tepotinib.

- In the foreign phase I study (Study 01), Japanese phase I study (Study 03), foreign phase Ib/II studies (Studies EMR200095-004 and -005 [Studies 04 and 05]), and global phase II study (VISION study), no clinically significant increase in the blood concentrations of bilirubin, a substrate of UGT1A1 (*J Biol Chem.* 1994;269:17960-4), was observed.
- In the foreign phase I study (Study 01), Japanese phase I study (Study 03), foreign phase Ib/II studies (Studies 04 and 05), and global phase II study (VISION study), no particular safety concerns were noted when tepotinib was co-administered with a substrate[26)] of BCRP, OATP1B1, OCT1, OCT2, MATE1, or MATE2-K, or with a P-gp inhibitor.

PMDA's discussion:
PMDA accepted the applicant's explanation in general. However, information on the pharmacokinetic interactions of tepotinib through UGT1A1, P-gp, BCRP, OATP1B1, OCT1, OCT2, MATE1, and MATE2-K is important for the proper use of tepotinib. Therefore, currently available information should be appropriately communicated to healthcare professionals, and relevant information should continue to be collected.

The following findings are detailed in Section "6.2.2 Foreign clinical studies."

- Tepotinib inhibits CYP3A, and both tepotinib and MSC2571109A induce CYP3A4 [see Section 4.5.2].
- Tepotinib inhibits P-gp [see Section 4.5.3].

5. Toxicity and Outline of the Review Conducted by PMDA

The results of the following toxicity studies of tepotinib were submitted: single-dose toxicity, repeated-dose toxicity, genotoxicity, reproductive and developmental toxicity, metabolite toxicity, impurity toxicity, and phototoxicity.

The amount of tepotinib administered is expressed as tepotinib hydrochloride hydrate. Finely powdered tepotinib was used in the dog 14-day repeated-dose toxicity study, dog 39-week repeated-dose toxicity study, rat 4-week repeated-dose toxicity study (Study [redacted]-DA0061-0), rat phototoxicity study, and rabbit embryo-fetal development toxicity study, while non-powdered tepotinib was used in the rest of the studies. In these studies, 0.25% hydroxypropyl methylcellulose was administered to rats and rabbits in the control groups, and empty capsules were administered to dogs in the control groups.

26) Co-administration was evaluated using rosuvastatin as the substrate of BCRP and OATP, and metformin as the substrate of OCT and MATE.

5.1 Single-dose toxicity

Single oral dose toxicity studies were conducted in mice and rats (Table 11). Although no single-dose toxicity studies were conducted in dogs, the results from the 13-day oral dose escalation study (Study T8240) suggest that the maximum tolerated dose (MTD) is 45 mg/kg.

Table 11. Single-dose toxicity study

Test system	Route of administration	Dose (mg/kg)	Major findings	Approximate lethal dose (mg/kg)	Attached document CTD
Male/female mice (NMRI)	Oral	2,000	No noteworthy findings	>2,000	4.2.3.1.1
Male/female rats (Wistar)	Oral	2,000	No noteworthy findings	>2,000	4.2.3.1.2

5.2 Repeated-dose toxicity

Repeated oral dose toxicity studies in rats (4 and 26 weeks) and dogs (13 days to 39 weeks) were conducted (Table 12). The hepatobiliary system is considered to be the primary target organ [see Section 4.2.1], and a high incidence of digestive symptoms such as vomiting and change in stool properties were noted in dogs. In the 26-week repeated oral-dose toxicity study in rats, tepotinib exposures at the no-observed adverse effect level (NOAEL) (45 mg/kg/day) were as follows: the C_{max} was 90.1 ng/mL (male) and 135.5 ng/mL (female), 0.07 and 0.1 times the clinical exposures,[27)] respectively; the $AUC_{0\text{-}24}$ was 809.9 ng·h/mL (male) and 1,312.1 ng·h/mL (female), 0.03 and 0.05 times the clinical exposures, respectively. In the 39-week repeated oral-dose toxicity study in dogs, tepotinib exposures at the NOAEL (10 mg/kg/day) were as follows: the C_{max} was 76.9 ng/mL (male) and 105 ng/mL (female), 0.06 and 0.08 times the clinical exposures, respectively; the $AUC_{0\text{-}24}$ was 898 ng·h/mL (male) and 1,370 ng·h/mL (female), 0.03 and 0.05 times the clinical exposures, respectively.

27) The C_{max} and AUC values on Day 14 in humans receiving repeated oral doses of tepotinib 500 mg QD were 1,291 ng/mL and 27,438 ng·h/mL, respectively.

Table 12. Repeated-dose toxicity studies

Test system	Route of admini-stration	Duration of dosing	Dose (mg/kg/day)	Major findings	NOAEL (mg/kg/day)	Attached document CTD
Male/ female rats (Wistar)	Oral	4 weeks + 4-week recovery period	0, 3, 10, 30, and 90	Died, at 30 (female, 1 of 15 animals)[a)] 90, salivation, high B cell number (female), low T cell total number and helper T cell number (female), high suppressor T cell number (male), urine occult blood (female), high spleen weight (female), alveolar foam cell aggregation (female) ≥30, burrowing in cage floor covering, low cholesterol, high ALT, high ALP, alveolar macrophage aggregation, macrophages increased in mesenteric lymph node paracortical area The findings were reversible.	90	4.2.3.2.1
Male/ female rats (Wistar)	Oral	4 weeks + 4-week recovery period	0, 30, 90, and 270	270, burrowing in cage floor covering, low hemoglobin (female), low red blood cell count and low platelet count (female), high reticulocyte count (female), high total white blood cell count (female), low eosinophil percentage (male), high creatinine, high thymus gland weight (female), alveolar macrophage aggregation ≥90, high SDH, high glucose level, high liver weight (female), high ovary weight (female), high adrenal gland weight (female), high spleen weight, histiocytic infiltration of submandibular lymph node ≥30, low cholesterol, low triglycerides, low total protein, low albumin, high ALT, high AST, high ALP, histiocytic infiltration of mesenteric lymph node The findings were reversible[b)].	90	4.2.3.2.2

Test system	Route of admini-stration	Duration of dosing	Dose (mg/kg/day)	Major findings	NOAEL (mg/kg/day)	Attached document CTD
Male/ female rats (Wistar)	Oral	4 weeks	0, 30, 90, 450, and 2,000	Sacrificed moribund, at 2,000 (male, 14 of 14 animals; female, 14 of 14 animals) 2,000, gasping respiration, piloerection, generalized pallor, eye and nasal discharge, eyelid ptosis, change in stool properties, weight decreased, high red blood cell count, high hemoglobin, high hematocrit, high white blood cell count, high monocyte count, high neutrophil count, high potassium, high inorganic phosphorus (female), high urea, high ALT, high AST, high ALP, low sodium, low cholesterol, low total protein, low albumin, stomach distention, mucus in the large intestine, adrenal gland (cell hypertrophy, increase in number of vacuoles, and mild single cell necrosis in zona fasciculata), aorta (atrophy of perivascular adipose tissue), large intestine (single cell necrosis of epithelial cells and mild granulocyte infiltration in lamina propria mucosae), liver (hepatocyte necrosis and multifocal mononuclear infiltration), lung (alveolar foam cells), lymphatic system (decrease in number of cells accompanied by lymphocyte necrosis in mandibular and mesenteric lymph nodes, Peyer's patch, spleen, and thymus), mammary gland (apoptotic single cell necrosis, atrophy of acinar epithelium), pancreas (decreased zymogen content in acinar cells), seminal vesicle (decreased discharge, epithelial atrophy), salivary gland (multifocal apoptosis of acinar cells), skin (subcutaneous fat atrophy), stomach (mild multifocal ulcers in glandular stomach mucosa) 450, low weight gain (male), low food consumption, high monocyte count, high white blood cell count (male), high lymphocyte count (male), high ALT, high AST, mucus in the large intestine, white spots in the lung, decreased size of the seminal vesicles, red discoloration of gastric fundic mucosa, adrenal gland (cell hypertrophy, increase in number of vacuoles, and mild single cell necrosis in zona fasciculata), large intestine (single cell necrosis of epithelial cells and mild granulocyte infiltration in lamina propria mucosae), liver (hepatocyte necrosis, multifocal mononuclear infiltration), lung (alveolar foam cells), lymphatic system (decrease in number of cells accompanied by lymphocyte necrosis in mandibular and mesenteric lymph nodes, Peyer's patch, spleen, and thymus), pancreas (autophagosomes in acinar cells), seminal vesicle (decreased discharge), stomach (ulcers in non-glandular stomach mucosa), thyroid gland (hypertrophy of cortex) ≥90, salivation, burrowing in cage floor covering, high ALP, low cholesterol, high spleen weight, high adrenal gland weight, high thyroid gland weight (male)	90	4.2.3.2.3

Test system	Route of admini-stration	Duration of dosing	Dose (mg/kg/day)	Major findings	NOAEL (mg/kg/day)	Attached document CTD
Male/ female rats (Wistar)	Oral	26 weeks + 8-week recovery period	0, 15, 45, and 135	Died, at 15 (male, 1 of 20 animals),[a)] at 135 (female, 2 of 20 animals)[a)] 135, high white blood cell count (female), low cholesterol, low triglycerides, high AST, high ALT, high ALP, localized white discoloration of the lung (female), high liver weight (female), high adrenal gland weight (female), high ovary weight (female), macrophage aggregation in mesenteric lymph node, and histiocytosis in lymph sinus ≥45, alveolar foam cell aggregation ≥15, low total protein, low albumin, activation of thyroid follicular epithelium The findings were reversible[c)].	45	4.2.3.2.4
Male/ female dogs (Beagle)	Oral	13-day dose escalation	1-180	≥90, repeated vomiting, accelerated erythrocyte sedimentation rate, high hepatic enzymes ≥45, loose stool ≥30, continuous tongue moving behavior, decrease in food consumption	N/A (MTD = 45)	4.2.3.2.5
Male/ female dogs (Beagle)	Oral	4 weeks + 8-week recovery period	0, 2.5, 10, and 40	40, inclusion of white substance in feces and vomitus, diarrhea containing mucus/blood, decrease in food consumption (female), weight decreased (female), low platelet count (male), high reticulocyte count (female), accelerated erythrocyte sedimentation rate (female), high AST, high ALT, high ALP, high total bilirubin, high direct bilirubin, high indirect bilirubin, bile duct dilation (female), cholangitis, pericholangitis, inflammatory cell infiltration in the liver (female), fibrosis in peripheral bile duct (female), bile duct proliferation (female), bile duct epithelial hyperplasia (female), hepatocyte necrosis in peripheral bile duct (male), bile duct necrosis (male), thymic atrophy (female) ≥10, vomiting, diarrhea, bloody stool, high GLDH ≥2.5, loose stool, mucous stool The findings were reversible.	10	4.2.3.2.6
Male/ female dogs (Beagle)	Oral	13 weeks + 12-week recovery period	0, 3, 10, and 30	30, high AST (male), high ALT (male), high SDH (male), small A/G ratio ≥10, high GLDH (male), low albumin ≥3, loose stool, mucus-containing stool, sporadic diarrhea and vomiting, high liver weight (female), lymphocyte infiltration in the large intestine The findings were reversible[d)].	30	4.2.3.2.7

Test system	Route of admini-stration	Duration of dosing	Dose (mg/kg/day)	Major findings	NOAEL (mg/kg/day)	Attached document CTD
Male/ female dogs (Beagle)	Oral	14 days	10, 40, and 160/120[e)]	160/120, repeated vomiting (at 160 mg), low food consumption, high neutrophil count, high white blood cell count, low lymphocyte count, spotty depigmentation of the liver, pericholangitis in the liver ≥40, sporadic vomiting, loose stool, diarrhea, high ALT, high ALP, high GLDH, high GGT, high bile acid levels, bile duct proliferation in the liver, inflammatory cell infiltration in the gallbladder	N/A	4.2.3.2.8
Male/ female dogs (Beagle)	Oral	39 weeks + 12-week recovery period	0, 3, 10, and 30	30, high AST, high ALT, high ALP, high GLDH, high GGT, high SDH, high bile acid levels, high total bilirubin, high direct bilirubin, high indirect bilirubin, low albumin, small A/G ratio, high liver weight (female), gray discoloration of the adrenal gland (female), white discoloration of the intrahepatic bile duct, decrease in vacuoles in the adrenal cortex, hepatocyte focal necrosis, increase in periportal bile ductules, hemosiderin deposition in periportal area, bile pigment retention in the intrahepatic bile duct, papillary hyperplasia of the bile duct epithelium accompanied by fibrosis in peripheral bile duct, lymphoplasmacytic infiltration in the bile duct ≥10, lacrimation, low food consumption, some animals showed weight decrease ≥3, sporadic vomiting, loose stool, diarrhea The findings were reversible[f)]	10	4.2.3.2.9

a) The deaths were concluded to be unrelated to tepotinib administration; b) histiocytic infiltration of mesenteric lymph node persisted; c) high ALT, high GLDH (male), macrophage aggregation in mesenteric lymph node, and activation of thyroid follicular epithelium persisted; d) loose stool, and lymphocyte infiltration in the large intestine persisted; e) tepotinib was administered at 160 mg/kg/day up to Day 3, followed by a rest period between Day 4 to 6, and administration resumed from Day 7 at 120 mg/kg/day; f) white discoloration of the intrahepatic bile duct, and fibrosis in peripheral bile duct persisted

5.3 Genotoxicity

Genotoxicity studies consisted of an *in vitro* bacterial reverse mutation assay, an *in vitro* gene mutation assay in mammalian cells, and an *in vivo* micronucleus assay using rat bone marrow cells (Table 13). All the genotoxicity studies tested negative, and indicated that tepotinib is unlikely to be genotoxic in the body.

Table 13. Genotoxicity studies

Type of study		Test system	Metabolic activation (treatment)	Concentration (μg/plate or μg/mL) or dose (mg/kg/day)	Test result	Attached document CTD
In vitro	Bacterial reverse mutation assay (Ames)	*Salmonella typhimurium*: TA98, TA100, TA102, TA1535, TA1537 *Escherichia coli*: WP2 *uvrA*	S9−	0,[a] 5, 15.8, 50, 158, 500, 1580, 5000 (first) 0,[a] 1.58, 5, 15.8, 50, 158, 500 (second)	Negative	4.2.3.3.1.1
			S9+	0,[a] 5, 15.8, 50, 158, 500, 1580, 5000 (first) 0,[a] 1.58, 5, 15.8, 50, 158, 500 (second)		
	Gene mutation assay in mammalian cells	Mouse lymphoma L5178Y cells	S9− (24 hours)	0,[a] 0.158, 0.5, 1.58, 5, 15.8, 50	Negative	4.2.3.3.1.2
			S9− (3 hours)	0,[a] 0.158, 0.5, 1.58, 5, 15.8	Negative	
			S9 (3%) + (3 hours)	0,[a] 0.158, 0.5, 1.58, 5, 15.8, 50	Negative	
			S9 (1%) + (3 hours)	0,[a] 0.158, 0.5, 1.58, 5, 15.8	Negative	
In vivo	Rat micronucleus assay	Male rats (Wistar) Bone marrow		0, 667, 1,333, 2,000[b] (single-dose/oral)	Negative	4.2.3.3.2.1

a) DMSO; b) Specimens were prepared at 2 timepoints, 24 hours and 48 hours post-dose, for the 2,000 mg/kg group.

5.4 Carcinogenicity

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

5.5 Reproductive and developmental toxicity

Two preliminary embryo-fetal development studies in rabbits were conducted (Table 14). The results of these studies suggested that tepotinib was teratogenic (e.g., skeletal anomalies), and therefore additional studies have not been conducted. The NOAEL for embryo-fetal development has been determined to be 0.5 mg/kg/day, at which tepotinib exposures are 0.27 ng/mL (C_{max}) and 3.1 ng·h/mL (AUC_{0-24}), 0.0002-times and 0.0001-times the clinical exposure,[27] respectively.

Table 14. Reproductive and developmental toxicity studies

Type of study	Test system	Route of admini-stration	Duration of dosing	Dose (mg/kg/day)	Major findings	NOAEL (mg/kg/day)	Attached document CTD
Preliminary embryo-fetal development study	Female rabbits (NZW)	Oral	Gestation days 6-18 Cesarean section on gestation day 29	0, 50, 150, and 450	Dams: Died, 150 (1 of 8 animals), 450 (4 of 8 animals)[a)] 450, diarrhea, loose stool, low food consumption, low weight gain 150, abortion, low food consumption, low weight gain ≥50, kidney calcification, basophilic tubule, tubular dilation Fetuses: 150, low weight ≥50, high skeletal anomalies	The study was unable to determine neither the NOAEL for dams, nor that for embryo-fetal development	4.2.3.5.2.2
	Female rabbits (NZW)	Oral	Gestation days 6-18 Cesarean section on gestation day 29	0, 0.5, 5, and 25	Dams: Died, 0 (1 of 8 animals) ≥0.5, low food consumption, low weight gain, low weight Fetuses: ≥5, high skeletal anomalies, malrotated hindlimbs, hindlimb hyperextension	Dams: 25 Embryo-fetal development: 0.5	4.2.3.5.2.3

a) Surviving animals in the 450 mg/kg/day group were excluded from the study

5.6 Local tolerance

No local tolerance studies were conducted because tepotinib is an oral formulation.

5.7 Other toxicity studies

5.7.1 Immunotoxicology evaluation

The effect of tepotinib on the immune system was evaluated based on data from repeated-dose toxicity studies (including results of flow cytometric analyses). The results suggested that tepotinib is unlikely to cause immunotoxic effects.

5.7.2 Toxicity studies on metabolite

An *in vitro* safety pharmacology study [see Section 3.3.2] and an *in vitro* genotoxicity study were conducted on MSC2571109A, a major metabolite in humans (Table 15). The results indicated no significant concerns regarding the safety pharmacology and genotoxicity of MSC2571109A.

Table 15. Genotoxicity studies of the metabolite

Type of study	Concentration (μg/plate or μg/mL)	Test result	Attached document CTD
Ames	0[a)]-1,580	Negative	4.2.3.7.5.1
Mouse lymphoma assay for gene mutation	0[a)]-88.9	Negative	4.2.3.7.5.2

a) DMSO

5.7.3 Toxicity studies on impurities

Of impurities contained in the drug substance, MSC2157042B, MSC2200106A, MSC2200552B, MSC2209428A, and MSC2270983A are contained at levels greater than the qualification threshold specified in the ICH Q3A Guidelines. Therefore, the safety of these impurities at the upper limits of specifications was evaluated based on the results from 4-week repeated-dose toxicity studies in rats (CTD 4.2.3.2.2 and 4.2.3.2.3), in which these impurities were spiked. In addition, *in vitro* genotoxicity studies of these impurities were conducted, and the results indicated no genotoxic concerns (Table 16).

Table 16. Genotoxicity studies of impurities

Impurity	Type of study	Concentration (μg/plate or μg/mL)	Test result	Attached document CTD
MSC2157042B	Ames	0.3-5,000	Negative	4.2.3.7.6.1
	Chromosomal aberration assay in human lymphocytes	0.5-5	Negative	4.2.3.7.6.2
MSC2200106A	Ames	3-5,000	Negative	4.2.3.7.6.3
	Chromosomal aberration assay in human lymphocytes	0.244-250	Negative	4.2.3.7.6.4
MSC2200552B	Ames	3-5,000	Negative	4.2.3.7.6.5
	Chromosomal aberration assay in human lymphocytes	0.975-15.6	Negative	4.2.3.7.6.6
MSC2209428A	Ames	3-5,000	Negative	4.2.3.7.6.7
	Chromosomal aberration assay in human lymphocytes	0.25-30	Negative	4.2.3.7.6.8
MSC2270983A	Ames	1.58-1,580	Negative	4.2.3.7.6.9
	In vitro micronucleus assay	1.58-50	Negative	4.2.3.7.6.10
	In vivo comet assay (rats)	0,[a)] 125, 250, 500, and 1,000	Negative	4.2.3.7.6.11

a) Polyethylene glycol

5.7.4 Phototoxicity

Since the molar extinction coefficient of tepotinib at 290 nm was 19,300 L/mol·cm, an *in vitro* 3T3 neutral red uptake (3T3 NRU) phototoxicity test was conducted. Because the *in vitro* study tested positive, an *in vivo* phototoxicity study was conducted using pigmented rats, with all tested negative (Table 17). It was therefore concluded that tepotinib is unlikely to cause phototoxic effects.

Table 17. Phototoxicity studies

Type of test	Test system	Test method	Result	Attached document CTD
In vitro	3T3 NRU	Add tepotinib 0-100 μg/mL to the cells. One hour later, irradiate the cells with a UV-A dose of 5 J/cm^2	Positive	4.2.3.7.7.1.2
In vivo	Pigmented rats (LE)	Rats receiving a single oral dose of tepotinib at 0, 500, 1,000, or 1,500 mg/kg were exposed to ultraviolet light 3 hours post-dose.	Negative	4.2.3.7.7.1.3

5.R Outline of the review conducted by PMDA

Based on the submitted data and discussions in the following sections, PMDA concluded that the applicant's explanation about the toxicity of tepotinib is acceptable.

5.R.1 Papillary hyperplasia of the bile duct epithelium

The applicant's explanation about papillary hyperplasia of the bile duct epithelium observed in the 39-week repeated-dose study in dogs:

This finding was also noted in the 4-week repeated-dose study in dogs. In addition, the cells were positive for proliferation markers, Ki-67 and phospho-histone H3, by immunohistochemistry (IHC). However, the observed papillary hyperplasia is considered to be a change associated with the regeneration/repair process of an inflammatory change in the bile duct because (1) neoplastic transformation was not observed as a result of the prolonged treatment period; and that (2) the finding was reversible. Although a high level of aspartate aminotransferase (AST) or alanine aminotransferase (ALT) was observed in clinical studies, it is unlikely that papillary hyperplasia of the bile duct epithelium will become a safety concern in the clinical use of tepotinib, considering no bile duct disorder indicating a definitive causal relationship with tepotinib has been reported.

In contrast to the above, if bile duct inflammation persists in patients on long-term tepotinib treatment, the possibility of the above-mentioned finding progressing into neoplastic lesions due to promotion effect associated with inflammation cannot be ruled out. Therefore, the finding of papillary hyperplasia of the bile duct epithelium will be included in the package insert to provide caution.

PMDA accepted the applicant's explanation.

5.R.2 Use of tepotinib in pregnant women or in women who may possibly be pregnant

The applicant's explanation about the use of tepotinib in pregnant women or in women who may possibly be pregnant:

The results of the embryo-fetal development studies in rabbits suggested that tepotinib was teratogenic [see Section 5.5]. However, given the poor prognosis of NSCLC, it is considered acceptable to administer tepotinib with caution to pregnant women or to women who may possibly be pregnant if the expected therapeutic benefits outweigh the risks, provided that the patient is fully informed of the potential risks to the fetus associated with tepotinib. The package insert will include the test results of the embryo-fetal development studies in rabbits, and a cautionary statement to the effect that treatment with tepotinib may have adverse effects on the fetus.

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

The available oral formulations of tepotinib are liquid, capsules, and tablets, and the formulations were used to investigate the PK and other aspects of tepotinib (Table 18). The proposed commercial formulation of tepotinib is tablet formulation (TF)3.

Table 18. Oral formulations used in clinical studies

Oral formulation		Study
Liquid		Foreign phase I study (Study 07)
Capsules	CF1 (15, 50, and 100 mg)	Foreign phase I study (Study 01)
	CF2 (15 and 100 mg)	Japanese phase I study (Study 03), foreign phase I study (Studies 01 and 02[*2])
	CF3 (100 mg[*1])	Foreign phase I study (Study 07)
Tablets	TF1 (25, 30, and 100 mg)	Global phase Ib/II study (Study 06[*3]), foreign phase I study (Studies 01,[*3] 02,[*4] 07,[*5] and 012[*5]), foreign phase Ib/II study (Studies 04[*3] and 05[*3])
	TF2 (100 and 500 mg)	Global phase II study (Cohort A of VISION study), foreign phase I studies (Studies 012, 028, 030, 032, 039, and 044[*6])
	TF3 (100 and 250 mg)	Foreign phase I study (Study 044[*7])

*1, Expressed as the content of ^{14}C-tepotinib; *2, the 15 mg capsules were used; *3, the 25 and 100 mg tablets were used; *4, the 30 mg tablets were used; *5, the 100 mg tablets were used; *6, the 500 mg tablets were used; *7, the 250 mg tablets were used

6.1.1 Analytical methods

In Cohort A of the VISION study, METex14 skipping alterations were assessed by the following testing methods: "Guardant360," a next-generation sequencing (NGS) assay from Guardant Health, Inc. for liquid biopsy testing (LBx); and "Oncomine Focus Assay," an NGS assay from Thermo Fisher Scientific Inc. for tissue biopsy testing (TBx).[28)] On December 12, 2019, ArcherDx, Inc. filed an application for "ArcherMET companion diagnostic," an *in vitro* diagnostic intended to be used as an aid to identify patients eligible for treatment with tepotinib.

6.1.2 Assay

Tepotinib in human plasma was determined by liquid chromatography/tandem mass spectrometry (LC-MS/MS), and the lower limit of quantification was 5.00 ng/mL.[29)]

6.1.3 Foreign clinical studies

6.1.3.1 Foreign phase I study (CTD 5.3.1.2.1, Study 044, Part A [August 2018 to January 2019])

A 2-treatment, 2-period crossover study was conducted in 40 healthy adults (38 subjects were included in the PK analysis) to evaluate bioequivalence of Formulations TF2 and TF3. A single oral dose of tepotinib 500 mg was administered under fasting conditions,[30)] and there was a ≥21-day washout period between tepotinib treatments.

The geometric mean ratio of TF3 to TF2 [90% CI] was 1.14 [1.08, 1.20] for C_{max} and 1.15 [1.09, 1.23] for AUC_t, indicating that both values were within the range of criteria for bioequivalence (0.80-1.25). The applicant explained that the results demonstrated bioequivalence of Formulations TF2 and TF3.

28) In the testing of Japanese patients, use of reverse transcription polymerase chain reaction (RT-PCR) was also allowed.
29) In Study 01, plasma specimens were measured by analytical methods with a lower limit of quantification of 0.186 ng/mL (initial phase) and 20.0 ng/mL (late phase). Plasma specimens were measured by analytical methods with a lower limit of quantification of 0.186 ng/mL in Study 02, and 20.0 ng/mL in Study 03.
30) Subjects received tepotinib after fasting for ≥10 hours (overnight), and refrained from eating for ≥4 hours post-dose.

6.1.3.2 Foreign phase I study (CTD 5.3.1.2.1, Study 044, Part C [August 2018 to January 2019])

A 2-treatment, 2-period crossover study was conducted in 12 healthy adults (all 12 subjects were included in the PK analysis) to assess the effects of food on the PK of tepotinib. A single oral dose of tepotinib 500 mg was administered under fasting conditions, or 30 minutes after a high-fat meal,[31)] and there was a ≥21-day washout period between tepotinib treatments.

The geometric mean ratio of high-fat-fed to fasted conditions [90% CI] was 2.00 [1.76, 2.26] for C_{max} and 1.63 [1.46, 1.82] for AUC_{inf}. The applicant explained that based on several factors including the solubility of tepotinib in artificial intestinal juice that simulated human intestinal fluids under fasting (0.0779 mg/mL) and fed conditions (0.324 mg/mL), the solubility of tepotinib may have increased after the meal, increasing the amount of tepotinib absorbed by the digestive tract, perhaps resulting in the increased exposure.

6.1.3.3 Foreign phase I study (CTD 5.3.3.4.3, Study 039 [May to July 2018])

A 6-treatment, 3-period crossover study was conducted in 12 healthy adults (all 12 subjects were included in the PK analysis) to assess the effects of a proton pump inhibitor (omeprazole) on the PK of tepotinib. In each treatment period, subjects received a single oral dose of tepotinib 500 mg alone under fed conditions, or oral doses of omeprazole 40 mg QD for 5 days plus a single oral dose of tepotinib 500 mg on Day 5 under fasting[30)] or fed conditions. There was a ≥14-day washout period between tepotinib treatments.

The geometric mean ratio of tepotinib plus omeprazole to tepotinib alone under fed conditions [90% CI] was 1.04 [0.929, 1.17] for C_{max} and 1.10 [1.02, 1.19] for AUC_{inf}. Based on the results, the applicant explained that it is unlikely that an increase in gastric pH associated with administration of a proton pump inhibitor or other factors will cause a marked effect on the PK of tepotinib.

6.2 Clinical pharmacology

The PK of tepotinib in healthy adults and patients with cancer following administration of tepotinib alone was studied. The effects of tepotinib on the PK of midazolam or dabigatran etexilate (DABE) were also investigated.

6.2.1 Japanese clinical studies

6.2.1.1 Japanese phase I study (CTD 5.3.3.2.2, Study 03 [[redacted] 20[redacted] to [redacted] 20[redacted]])

An open-label, uncontrolled study was conducted in 12 patients with advanced solid tumors (all 12 subjects were included in the PK analysis) to investigate the PK and other aspects of tepotinib. Oral doses of tepotinib 215, 300, or 500 mg were administered QD under fed conditions, and parameters including plasma tepotinib concentrations were assessed.

31) Approximately a total of 800 to 1,000 kcal, in which fat accounted for approximately 50%

Table 19 shows the PK parameters of tepotinib. The geometric mean (geometric coefficient of variation [%]) of C_{ave} on Day 14 following oral administration of tepotinib 500 mg QD was 0.899 μg/mL (16.4%) and the accumulation rate[32)] was 2.45.

Table 19. PK parameters of tepotinib

Dose (mg)	Day of measurement (Day)	n	C_{max} (μg/mL)	t_{max}* (h)	AUC_{24h} (μg·h/mL)
215	1	3	0.244 (29.9)	8.00 (7.92, 8.03)	4.06 (30.7)
	14	3	0.808 (11.5)	8.00 (7.98, 8.02)	16.1 (12.2)
300	1	3	0.301 (42.6)	8.02 (8.00, 10.0)	5.41 (45.0)
	14	3	0.610 (84.8)	9.92 (1.95, 10.2)	13.3 (82.5)
500	1	6	0.442 (27.5)	10.0 (3.97, 23.9)	8.24 (30.9)
	14	5	0.997 (17.5)	4.13 (3.87, 9.87)	21.5 (16.7)

Geometric mean (geometric coefficient of variation [%]); *, median (range)

6.2.2 Foreign clinical studies

6.2.2.1 Foreign phase I study (CTD 5.3.3.2.1, Study 01, Regimen 3 [[redacted] 20[redacted] to [redacted] 20[redacted]])

An open-label, uncontrolled study was conducted in 62 patients with advanced solid tumors (all 62 subjects were included in the PK analysis) to investigate the PK and other aspects of tepotinib. Oral doses of tepotinib (capsule formulation [CF]2) 300, 500, 700, 1,000, or 1,400 mg, or tepotinib (TF1) 500 mg were administered QD under fed conditions, and parameters including plasma tepotinib concentrations were assessed.

Table 20 shows the PK parameters of tepotinib (CF2). The accumulation rate[32)] of tepotinib following oral administration of tepotinib (CF2) 500 mg QD was 3.42.

Table 20. PK parameters of tepotinib (Formulation CF2)

Dose (mg)	Day of measurement (Day)	n	C_{max} (μg/mL)	t_{max}*1 (h)	AUC_{24h} (μg·h/mL)
300	1	3	0.247 (32.7)	8.00 (8.00, 24.0)	4.21 (33.5)
	14	3	0.742 (45.7)	10.0 (0.50, 10.0)	15.6 (50.0)
500	1	19	0.330 (72.4)	10.0 (4.00, 24.0)	5.92 (74.8)*2
	14	17	0.943 (34.6)	8.00 (0, 24.0)	20.2 (33.5)
700	1	3	0.434 (27.6)	10.0 (4.00, 24.0)	7.58 (24.6)
	14	3	1.01 (39.4)	3.18 (0.25, 8.00)	22.0 (42.9)
1,000	1	7	0.666 (46.0)	10.0 (4.00, 10.2)	11.8 (48.1)*3
	14	6	1.22 (59.2)	8.83 (0, 24.0)	27.2 (59.4)
1,400	1	6	0.863 (37.4)	24.0 (8.00, 24.0)	15.5 (41.9)
	14	4	1.81 (31.2)	9.08 (2.83, 24.0)	39.3 (28.0)

Geometric mean (geometric coefficient of variation [%]); *1, median (range); *2, n = 18; *3, n = 6

In the Japanese phase I study (Study 03) [see Section 6.2.1.1] and this study (Study 01), the C_{max} and AUC_{24h} of tepotinib increased in a less than dose proportional manner within the dose range studied.

32) Ratios of AUC_{24h} on Day 14 to that after Day 1

The applicant explained that decreases in solubility and absorption in the digestive tract with increasing dose may have had an effect on dose proportionality.

6.2.2.2 Foreign phase I study (CTD 5.3.1.1.1, Study 07, Part A [[redacted] 20[redacted] to [redacted] 20[redacted]])

An open-label, uncontrolled study was conducted in 6 healthy adults (all 6 subjects were included in the PK analysis) to investigate the mass balance and other aspects of tepotinib. Radioactivity levels, etc. in blood, plasma, urine, and feces following administration of a single oral dose of ^{14}C-tepotinib 500 mg were assessed.

Up to 240 hours post-dose, MSC2571109A was the major metabolite detected in plasma (the AUC_{240h} represents 40.4% of total radioactivity in plasma, and 74.9% of unchanged tepotinib).

The recovery of radioactivity up to 360 hours post-dose was 13.6% (urine) and 77.9% (feces) of the radioactivity administered. In urine, up to 360 hours post-dose, the *N*-oxide metabolites M508-2 and M508-1, which are major metabolites detected, accounted for 3% and 2% of the radioactivity administered, respectively, and unchanged tepotinib accounted for 7% of the radioactivity administered. In feces, up to 360 hours post-dose, the main compound detected was unchanged tepotinib, which accounted for 45% of the total radioactivity administered, while major metabolites detected were a des-methyl metabolite M478 (9% of the radioactivity administered) and an *N*-glucuronide M668 (6% of the radioactivity administered).

6.2.3 Drug interactions

6.2.3.1 Drug interaction study with midazolam (CTD 5.3.3.4.1, Study 030 [[redacted] to [redacted] 20[redacted]])

An open-label, uncontrolled study was conducted in 12 healthy adults (all 12 subjects were included in the PK analysis) to investigate the effects of tepotinib on the PK of midazolam (a substrate for CYP3A). Subjects received a single oral dose of midazolam 7.5 mg alone, or oral doses of tepotinib 500 mg QD under fed conditions for 11 days plus a single oral dose of midazolam 7.5 mg on Day 11, and there was a 2-day washout period between the treatments.

The midazolam geometric mean ratio of midazolam plus tepotinib to midazolam alone [90% CI] was 1.04 [0.869, 1.24] for C_{max} and 1.01 [0.892, 1.15] for AUC_{inf}. The applicant explained that the results suggest that no cautionary statements on co-administration with CYP3A substrates will be necessary.

6.2.3.2 Drug interaction study with DABE (CTD 5.3.3.4.2, Study 032 [[redacted] to [redacted] 20[redacted]])

An open-label, uncontrolled study was conducted in 20 healthy adults (all 20 subjects were included in the PK analysis) to investigate the effects of tepotinib on the PK of DABE (P-gp substrate). Subjects received a single oral dose of DABE 75 mg alone under fed conditions, or oral doses of tepotinib 500 mg QD under fed conditions for 8 days plus a single oral dose of DABE 75 mg on Day 8 under fed conditions, and there was a ≥72-hour washout period between the treatments.

The DABE geometric mean ratio of DABE plus tepotinib to DABE alone [90% CI] was 1.38 [1.22, 1.58] for C_{max} and 1.45 [1.23, 1.70] for AUC_{inf}. The applicant explained that the results suggest that co-administration with tepotinib may increase the exposure of P-gp substrates, and therefore, cautionary statements to that effect will be provided.

6.2.4 Foreign phase I study to assess the effects of hepatic impairment on the PK of tepotinib (CTD 5.3.3.3.1, Study 028 [[redacted] to [redacted]])

An open-label, uncontrolled study was conducted in 12 patients with mild hepatic impairment (Child-Pugh class A) or moderate hepatic impairment (Child-Pugh class B) (n = 6/class; n = 6/class were included in the PK analysis), and 6 healthy adults (all 6 subjects were included in the PK analysis), whose baseline characteristics (i.e., age, weight, and sex) were matched with those of the patients with moderate hepatic impairment to assess the effects of hepatic impairment on the PK of tepotinib. Subjects received a single oral dose of tepotinib 500 mg under fed conditions, and plasma tepotinib concentrations and other parameters were investigated.

The tepotinib geometric mean ratio of the patients with mild hepatic impairment to the healthy adults whose baseline characteristics were matched with those of the moderate patients [90% CI] was 1.02 [0.809, 1.30] for C_{max} and 0.950 [0.648, 1.39] for AUC_{inf}. The tepotinib geometric mean ratio of the patients with moderate hepatic impairment to the characteristics-matched healthy adults [90% CI] was 0.710 [0.561, 0.899] for C_{max} and 0.879 [0.599, 1.29] for AUC_{inf}.

The applicant's explanation about the use of tepotinib in patients with hepatic impairment based on the above results and other information:
Since mild and moderate hepatic impairment is not considered to cause a significant effect on the PK, dose adjustment of tepotinib is not necessary for patients with mild or moderate hepatic impairment. However, given that tepotinib is eliminated via biliary excretion [see Section 6.2.2.2], the information will be provided by including a statement in the package insert to the effect that tepotinib has not been used in patients with severe hepatic impairment.

6.2.5 Use of tepotinib in patients with renal impairment

The applicant explained that no dose adjustment is required when using tepotinib in patients with renal impairment taking factors including the following into consideration:

- It was shown that renal excretion is not a significant elimination pathway of tepotinib [see Section 6.2.2.2].
- The population pharmacokinetic (PPK) analysis [see Section 6.2.7] indicated that the AUC of tepotinib at steady state in patients with renal impairment (an estimated glomerular filtration rate [eGFR] of ≤59 mL/min/1.73 m^3) increased by 2% compared with patients without renal impairment (an eGFR of 99.8 mL/min/1.73 m^3). However, a pooled analysis of data from the Japanese phase I study (Study 03), global phase II study (Cohort A of VISION study), foreign phase I study (Study 01), and foreign phase Ib/II studies (Studies 04 and 05) indicated the following results. In patients

with normal renal function[33] (n = 105), mild renal impairment (n = 142), and moderate renal impairment (n = 58), the incidence of serious adverse events was 42.9% (normal), 43.7% (mild), and 46.6% (moderate); the incidence of Grade ≥3 adverse events was 50.5% (normal), 53.5% (mild), and 62.1% (moderate); the incidence of adverse events leading to dose reduction was 13.3% (normal), 20.4% (mild), and 24.1% (moderate); and the incidence of adverse events leading to treatment discontinuation was 13.3% (normal), 22.5% (mild), and 34.5% (moderate). These findings indicate no clear relationship between renal impairment and the incidence of adverse events.

6.2.6 Relationship between exposure and change in QT/QTc interval

The relationship between plasma tepotinib concentrations and change from baseline in QT interval corrected by Fridericia's formula (ΔQTcF) was investigated using a linear mixed effects model based on the data from 285 subjects enrolled in the Japanese phase I study (Study 03), foreign phase I study (Study 01), and foreign phase Ib/II studies (Studies 04 and 05), whose plasma tepotinib concentration and electrocardiogram (ECG) measurements were able to be taken at the same timepoint. The upper limits of ΔQTcF 90% CI at the mean C_{max} at steady state after oral administration of tepotinib 500 or 1,400 mg QD were estimated to be 3.57 ms (500 mg) and 7.54 ms (1,400 mg).

Based on the above, the applicant explained that tepotinib administered at the proposed dosage and administration is unlikely to cause prolongation of QT/QTc intervals.

6.2.7 PPK analyses

Population pharmacokinetic analyses of tepotinib were conducted based on tepotinib PK data (n = 613; 10,788 timepoints) from the Japanese study (Study 03), global studies (Study EMR200095-006 [Study 06] and Cohort A of VISION study), foreign studies (Studies EMR200095-001, -002, -004, -005, -007, MS200095-0012, -028, -039, and -044 [Studies 01, 02, 04, 05, 07, 012, 028, 039, and 044]) using a non-linear mixed effects model (software, NONMEM Version 7.3.0). The PK of tepotinib was described by a 2-compartment model with sequential zero-order and first-order processes, and first-order elimination from the V_c.

In the analyses, the following covariates were tested using the base model[34] for their effect on the PK parameters of tepotinib: (1) eGFR, carcinoma (colorectal cancer, hepatocellular carcinoma), and opioid administration on CL; (2) body weight and National Cancer Institute organ dysfunction group (NCI ODG) classification on F; (3) serum albumin and international normalized ratio (INR) on Q; (4) carcinoma (NSCLC) and age on V_c; (5) presence of disease (patients with cancer) on V_p; and (6) NCI

33) The patients were classified based on CrCL or eGFR (mL/min): normal, ≥90; mild, ≥60 and <90; moderate, ≥30 and <60; severe, <30. Patients with severe renal impairment were not enrolled in the following studies: Japanese phase I study (Study 03), global phase II study (Cohort A of VISION study), foreign phase I study (Study 01), and foreign phase Ib/II studies (Studies 04 and 05).

34) A PPK model incorporating the effects of the following covariates on the parameters of tepotinib: food conditions (fasting) on D1; dose, food conditions (fasting or after high-fat meal), and formulations (CF1 and TF3) on F; and food conditions (fasting) and formulations (CF1 and TF1) on the first-order absorption rate constant.

ODG classification and presence of disease (patients with cancer) on D1. The following significant covariates were chosen from the results: (1) eGFR, carcinoma (hepatocellular carcinoma, colorectal cancer), and opioid administration on CL; (2) body weight and NCI ODG classification on F; (3) serum albumin and INR on Q; (4) carcinoma (NSCLC) and age on V_c; (5) presence of disease (patients with cancer) on V_p; and (6) NCI ODG classification on D1. The covariates showed only limited effects on tepotinib exposures (AUC at steady state). The applicant explained that findings including the above suggest that the covariates are unlikely to have a significant effect on the PK of tepotinib that could potentially lead to clinical problems.

6.2.8 Exposure-efficacy/safety relationship

6.2.8.1 Exposure-efficacy relationship

Using data from the global phase II study (Cohort A of VISION study), the exposure data on tepotinib in patients with METex14 skipping mutation-positive NSCLC (AUC_{24h} on Day 1 and mean daily AUC [$mAUC_{24h}$][35),36)]) were divided at the quartile points,[37)] and the objective response rate (ORR) for each of the exposure groups (Q1 through Q4) was estimated. The ORR was roughly constant in each exposure group (Figure 2).

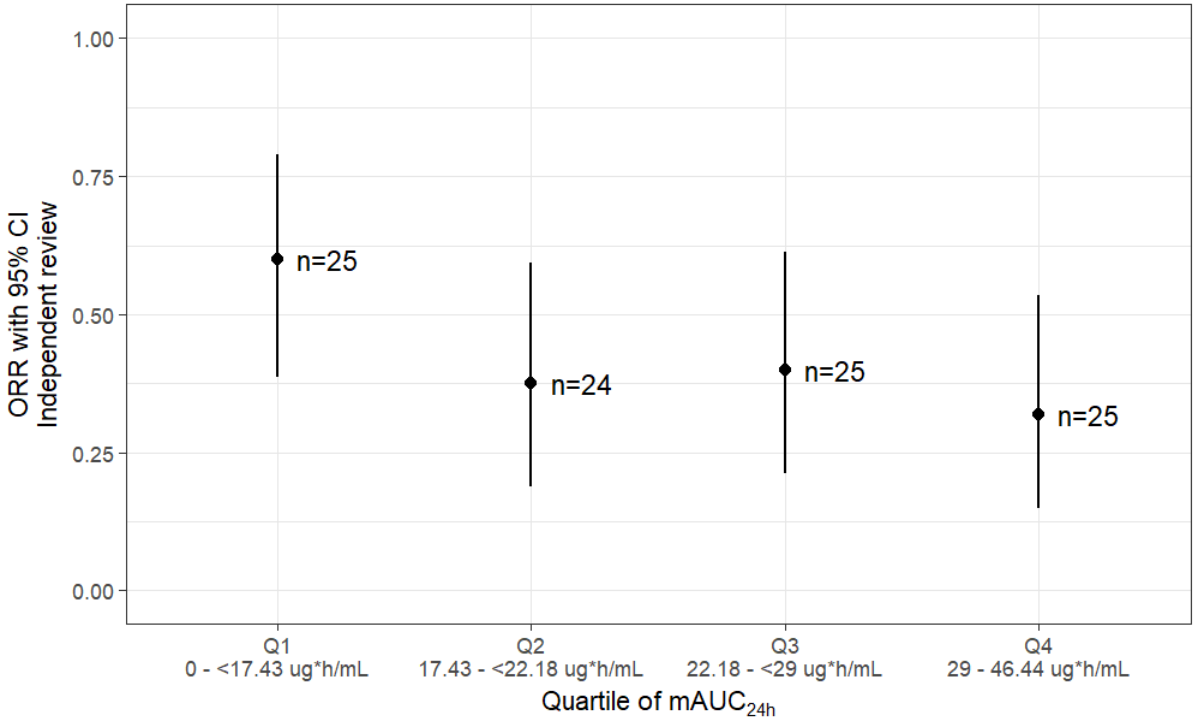

Figure 2. Objective response rate (ORR) [95% CI] of each exposure group (Q1 through Q4) divided at quartile points for the mean daily AUC ($mAUC_{24h}$) (RECIST ver.1.1, independent review, data cut-off date on [redacted])

35) The mean daily AUC for the period from the first dose to the day the response was confirmed, last dose was administered, or treatment was discontinued, whichever occurs first.

36) The exposures were estimated based on the PPK analyses [see Section 6.2.7].

37) The quartile ranges based on the AUC_{24h} of Day 1 were ≥0 and <7.24 μg·h/mL; ≥7.24 and <8.97 μg·h/mL; ≥8.97 and <11.0 μg·h/mL; ≥11.0 and ≤20.7 μg·h/mL. The quartile ranges based on the mean daily AUC [$mAUC_{24h}$] were ≥0 and <17.4 μg·h/mL; ≥17.4 and <22.2 μg·h/mL; ≥22.2 and <29.0 μg·h/mL; ≥29.0 and ≤46.4 μg·h/mL.

6.2.8.2 Exposure-safety relationship

Using data from the Japanese phase I study (Study 03), global phase II study (Cohort A of VISION study), foreign phase I study (Study 01), and foreign phase Ib/II studies (Studies 04 and 05), the relationship between the exposures of tepotinib (AUC_{24h}[36)]) in patients with METex14 skipping mutation-positive NSCLC and adverse events (oedema peripheral, amylase increased, and lipase increased) was assessed.

There was a relationship between the exposure quartiles[38)] based on exposure (mean daily AUC [$mAUC_{24h}$][39)]) and the risk of developing oedema peripheral for the first time, and the results suggested that the risk of first occurrence of oedema peripheral increases with increasing exposure.

The hazard ratios [90% CI] of the incidence of oedema peripheral following administration of tepotinib at 200, 250, or 300 mg to that at 500 mg[40)] were 0.895 [0.683, 1.22] (200 mg), 0.921 [0.687, 1.28] (250 mg), and 0.942 [0.691, 1.34] (300 mg), indicating that the hazard ratio for oedema peripheral tended to increase with increasing exposure.

6.2.9 Differences in PK between Japanese and non-Japanese populations

There were no clear differences in tepotinib exposures (C_{max} and AUC_{24h}) following oral administration of tepotinib 300 or 500 mg QD in the Japanese phase I study [Study 03, see Section 6.2.1.1] and foreign phase I study [Study 01, see Section 6.2.2.1]. The applicant explained that results including the above show that there are no clear differences in the PK of tepotinib between Japanese and non-Japanese populations.

6.R Outline of the review conducted by PMDA

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

6.R.1 Food effects

The applicant's explanation about the effect of food on the PK of tepotinib:

The results of the foreign phase I study (Study 044) showed increased tepotinib exposures under fed conditions compared with fasting conditions [see Section 6.1.3.2]. The results of the global phase II study (Cohort A of VISION study) demonstrated the clinical benefits of tepotinib by defining the timing of dosing tepotinib in the study as "after a meal."

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38) The quartile ranges based on the mean daily AUC ($mAUC_{24h}$) were 0 to 10.9 μg·h/mL; 10.9 to 18.7 μg·h/mL; 18.7 to 26.4 μg·h/mL; and 26.4 to 69.9 μg·h/mL.

39) The mean daily AUC ($mAUC_{24h}$) for the period from the first dose to the onset date of oedema peripheral or the day of treatment discontinuation, whichever occurs first.

40) The AUC_{24h} values at steady state following administration of different doses of tepotinib were 11.4 μg·h/mL (200 mg), 14.0 μg·h/mL (250 mg), 16.5 μg·h/mL (300 mg), and 25.4 μg·h/mL (500 mg).

Therefore, it was specified in the proposed dosage and administration that tepotinib should be administered after a meal [see Section 7.R.5].

PMDA's discussion:
PMDA accepted the applicant's explanation above. The dosage and administration of tepotinib will be described in Section "7.R.5 Dosage and administration" after examining clinical study results regarding the efficacy and safety of tepotinib.

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

The applicant submitted efficacy and safety evaluation data, in the form of results data from 14 studies summarized in Table 21: 1 Japanese phase I study, 1 global phase Ib/II study, 1 global phase II study, 9 foreign phase I studies, and 2 foreign phase Ib/II studies.

Table 21. List of clinical studies on efficacy and safety

Data category	Geographical location	Study identifier	Phase	Study population	No. of subjects enrolled	Summary of dosage regimen	Main endpoints
Evaluation data	Japan	03	I	Patients with advanced solid tumors	12	Oral administration of tepotinib 215, 300, or 500 mg QD (Formulation CF2)	PK Tolerability Safety
	Global	06	Ib	Patients with unresectable, advanced or recurrent *MET* amplification-positive NSCLC, previously treated with gefitinib	18	Oral administration of tepotinib 300 or 500 mg (Formulation TF1) QD in combination with gefitinib	PK Tolerability Safety
			II	Randomized part: Patients with unresectable, advanced or recurrent EGFR T790M mutation-negative, and *MET* amplification-positive NSCLC, aggravated after the first-line EGFR-TKI therapy Non-randomized part: Patients with unresectable, advanced or recurrent EGFR T790M mutation-positive, and *MET* amplification-positive NSCLC, with disease progression after the first-line EGFR-TKI therapy	Randomized part: 55 (a) 31 (b) 24 Non-randomized part: (a) 15	(a) Oral administration of tepotinib 500 mg (Formulation TF1) QD in combination with gefitinib (b) CDDP 75 mg/m^2 or CBDCA at a dose of AUC 5 mg·mL/min, plus PEM 500 mg/m^2 were administered intravenously Q3W in 3-week cycles.	Efficacy Safety

Data category	Geographi-cal location	Study identifier	Phase	Study population	No. of subjects enrolled	Summary of dosage regimen	Main endpoints
		VISION	II	Cohort A: Patients with unresectable, advanced or recurrent METex14 skipping mutation-positive NSCLC	130	Oral administration of tepotinib 500 mg (Formulation TF2) QD	Efficacy Safety
	Foreign	01	I	Patients with advanced solid tumors	149 (a) 42 (b) 45 (c) 62	(a) Oral administration of tepotinib 30, 60, 100, 115, 145, 215, 230, 300, or 400 mg (Formulation CF1 or CF2) QD in 3-week cycles, 2 weeks on, 1 week off (b) Oral administration of tepotinib 30, 60, 100, 115, 130, 175, or 315 mg (Formulation CF1 or CF2) 3 times per week (Days 1, 3, and 5) in 3-week cycles (c) Oral administration of tepotinib 300, 500, 700, 1,000, or 1,400 mg (Formulation TF1 or CF2) QD	PK Tolerability Safety
		02	I	Healthy adults	28	Using a single oral-dose, crossover design, either of the 2 formulations of tepotinib 30 mg (Formulation TF1 or CF2) administered in each treatment period under fed or fasting conditions	PK
		07	I	Healthy adults	27 Part A 6 Part B 6 Part C 15	A Single oral dose of ^{14}C-tepotinib 500 mg (Formulation CF3) B Single oral dose of ^{14}C-tepotinib 500 mg (Formulation TF1) C Single oral-dose, in a crossover fashion, of 2 tepotinib 100-mg formulations (Formulation TF1, or a tablet formulation with a particle size distribution being smaller than TF1), and 1 tepotinib 100-mg liquid formulation	PK
		012	I	Healthy adults	24	Using a single oral-dose, crossover design, either of the 2 formulations of tepotinib 500 mg (Formulations TF1 and TF2) administered in each treatment period	PK
		028	I	Healthy adults and patients with hepatic impairment	18	Single oral-dose administration of tepotinib 500 mg (Formulation TF2)	PK

Data category	Geographi-cal location	Study identifier	Phase	Study population	No. of subjects enrolled	Summary of dosage regimen	Main endpoints
		030	I	Healthy adults	12	Oral doses of tepotinib 500 mg (Formulation TF2) administered QD in combination with midazolam	PK
		032	I	Healthy adults	20	Oral doses of tepotinib 500 mg (Formulation TF2) administered QD in combination with DABE	PK
		039	I	Healthy adults	12	Oral doses of tepotinib 500 mg (Formulation TF2) administered QD in combination with omeprazole	PK
		044	I	Healthy adults	66 Part A: 40 Part B: 14 Part C: 12	A Using a crossover design, a single oral dose of one of the formulations of tepotinib 500 mg (Formulations TF2 and TF3) administered under fasting conditions in each period B Using a crossover design, a single oral dose of tepotinib 500 mg (Formulation TF2) administered under fasting or fed conditions in each period C Using a crossover design, a single oral dose of tepotinib 500 mg (Formulation TF3) administered under fasting or fed conditions in each period	PK
		04	Ib/II	Patients with MET-positive advanced hepatocellular carcinoma	Phase Ib part: 27 Phase II part: 90 (a) 45 (b) 45	Phase Ib part: Oral administration of tepotinib 300, 500, or 1,000 mg QD (Formulation TF1) Phase II part: (a) Oral administration of tepotinib 500 mg QD (Formulation TF1) (b) Oral administration of sorafenib 400 mg BID	PK Efficacy Safety
		05	Ib/II	Patients with MET-positive advanced hepatocellular carcinoma, previously treated with sorafenib	Phase Ib part: 17 Phase II part: 49	Phase Ib part: Oral administration of tepotinib 300 or 500 mg QD (Formulation TF1) Phase II part: Oral administration of tepotinib 500 mg QD (Formulation TF1)	PK Efficacy Safety

The following sections provide an outline of the clinical studies. Main adverse events other than deaths reported in the clinical studies are detailed in Section “7.2 Adverse events and other findings reported in clinical studies.”

7.1 Evaluation data

7.1.1 Clinical pharmacology studies

The applicant submitted the results from the following 8 clinical pharmacology studies in healthy adults or patients with hepatic impairment [see Sections 6.1 and 6.2]. In these studies, no deaths were reported during the study drug treatment period.

7.1.1.1 Foreign phase I study (CTD 5.3.1.2.2, Study 02 [[redacted] to [redacted] 20[redacted]])

7.1.1.2 Foreign phase I study (CTD 5.3.1.1.1, Study 07 [[redacted] 20[redacted] to [redacted] 20[redacted]])

7.1.1.3 Foreign phase I study (CTD 5.3.1.2.3, Study 012 [[redacted] to [redacted] 20[redacted]])

7.1.1.4 Foreign phase I study (CTD 5.3.3.3.1, Study 028 [June 2018 to February 2019])

7.1.1.5 Foreign phase I study (CTD 5.3.3.4.1, Study 030 [August to October 2018])

7.1.1.6 Foreign phase I study (CTD 5.3.3.4.2, Study 032 [May to August 2018])

7.1.1.7 Foreign phase I study (CTD 5.3.3.4.3, Study 039 [May to July 2018])

7.1.1.8 Foreign phase I study (CTD 5.3.1.2.1, Study 044 [August 2018 to January 2019])

7.1.2 Japanese studies

7.1.2.1 Japanese phase I study (CTD 5.3.3.2.2, Study 03 [[redacted] 20[redacted] to [redacted] 20[redacted]])

An open-label, uncontrolled study was conducted at 2 study centers in Japan to evaluate the tolerability and other aspects of tepotinib in patients with advanced solid tumors (target sample size, 18 subjects maximum).

Tepotinib 215, 300, or 500 mg (Formulation CF2) QD was orally administered in 21-day cycles, and treatment was to be continued until disease progression or the discontinuation criteria were met.

All 12 subjects enrolled in the study (215 mg cohort, 3 subjects; 300 mg cohort, 3 subjects; and 500 mg cohort, 6 subjects) received tepotinib, and were included in the safety analyses.

In the first 21-day cycle, which was predefined as the dose-limiting toxicity (DLT) assessment period, no DLTs were observed, and therefore the recommended Phase II dose (RP2D) was determined to be 500 mg QD.

During the tepotinib treatment period and within 30 days of the last dose, 1 of the 6 subjects (16.7%) in the 500 mg group died. The cause of death was dyspnoea, and a causal relationship to tepotinib was denied.

7.1.3 Global studies

7.1.3.1 Global phase Ib/II study (CTD 5.3.5.4.3, Study 06 [ongoing since December 2013, data cut-off date on December 12, 2018])

A global phase Ib/II study consisting of (a) phase Ib part, (b) phase II randomized part, and (c) non-randomized part was conducted as follows:

(a) An open-label, uncontrolled study was conducted at 7 study centers outside Japan to assess the safety and other aspects of tepotinib when administered in combination with gefitinib in patients with unresectable, advanced or recurrent NSCLC harboring *MET* amplification[41)] previously treated with gefitinib (target sample size, 21 subjects maximum). Tepotinib 300 or 500 mg (Formulation TF1) was orally administered QD in combination with oral doses of gefitinib 250 mg QD. The administration was to be continued until disease progression or the discontinuation criteria were met.

(b) An open-label, randomized, controlled study was conducted at 51 study centers in 10 countries and regions including Japan to assess the efficacy and safety of tepotinib plus gefitinib versus platinum-based plus pemetrexed sodium hydrate (PEM) chemotherapy in patients with unresectable, advanced or recurrent epidermal growth factor receptor (EGFR) T790M mutation-negative, *MET* amplification-positive[42)] NSCLC which aggravated after the first-line EGFR- tyrosine kinase inhibitor (TKI) therapy (target sample size, 156 subjects). In the tepotinib/gefitinib group, tepotinib 500 mg (Formulation TF1) was orally administered QD in combination with gefitinib 250 mg orally QD. In the platinum-based/PEM chemotherapy group, cisplatin (CDDP) 75 mg/m^2 plus PEM 500 mg/m^2 Q3W intravenously, or carboplatin (CBDCA) at a dose of AUC 5 mg·mL/min plus PEM 500 mg/m^2 Q3W intravenously was administered in 3-week cycles. The administration was to be continued until disease progression or the discontinuation criteria were met.

(c) An open-label, uncontrolled study was conducted at 15 study centers in China to assess the efficacy and safety of tepotinib plus gefitinib in patients with unresectable, advanced or recurrent EGFR T790M mutation-positive, *MET* amplification-positive[41)] NSCLC which aggravated after the first-line EGFR-TKI therapy (target sample size, 15 subjects). Tepotinib 500 mg (Formulation TF1) was administered orally QD in combination with gefitinib 250 mg orally QD. The administration was to be continued until disease progression or the discontinuation criteria were met.

Of the 88 subjects enrolled in this study (phase Ib, 18 subjects; phase II randomized, 55 subjects[43)] [tepotinib/gefitinib (31); platinum-based/PEM (24)], and non-randomized, 15 subjects), 87 subjects (phase Ib, 18 subjects; phase II randomized, 54 subjects [tepotinib/gefitinib (31); platinum-based/PEM

41) *MET* amplification was determined by IHC.
42) *MET* amplification-positive was determined by IHC alone, or IHC plus *in situ* hybridization.
43) Due to difficulties in enrolling patients who met the inclusion criteria, patient enrollment ended early in June 2017.

(23)], and non-randomized, 15 subjects) were included in the safety analyses after excluding 1 subject who did not receive the study drug (platinum-based/PEM in phase II randomized). Of these subjects, Japanese patients were as follows: phase Ib, 0 subjects; phase II randomized, 1 subject (tepotinib/gefitinib [1]; platinum-based/PEM [0]); and non-randomized, 0 subjects.

During the study drug treatment period and within 30 days of the last dose, deaths occurred in 1 of 6 subjects (16.7%) in the 300 mg group and 1 of 12 subjects (8.3%) in the 500 mg group in the phase Ib part; 1 of 31 subjects (3.2%) in the tepotinib/gefitinib group in the phase II randomized part; and 1 of 15 subjects (6.7%) in the non-randomized part. There were no deaths among Japanese patients. Two subjects died from disease progression (1 subject in the 500 mg group in the phase Ib part and 1 subject in the phase II non-randomized part). Other causes of death were dyspnoea in 1 subject in the 300 mg group in the phase Ib part, and ascites in 1 subject in the tepotinib/gefitinib group in the phase II randomized part. A causal relationship to the study drug was denied for the both events.

7.1.3.2 Global phase II study (CTD 5.3.5.1.1, Cohort A of VISION study [ongoing since September 2016, data cut-off date on [redacted], 20[redacted]])

An open-label, uncontrolled study was conducted at 123 study centers in 11 countries and regions including Japan to assess the efficacy and safety of tepotinib in patients with unresectable, advanced or recurrent METex14 skipping mutation-positive[44] NSCLC[45] (target sample size, ≥60 subjects in the LBx group and ≥60 subjects in the TBx group). At the start of the study, only patients whose biopsy specimen tested positive for METex14 skipping alterations by TBx were enrolled in the study. Later, it was considered possible to use LBx to appropriately select patients eligible for tepotinib treatment; therefore, patients who were assessed as having METex14 skipping alterations by LBx were also allowed to be enrolled in the study (Protocol, 4th amendment version, dated March 15, 2017).

Tepotinib 500 mg (Formulation TF2) was orally administered QD, and the treatment was to be continued until disease progression or the discontinuation criteria were met.

Of the 130 subjects enrolled in the study (including 17 Japanese patients), all subjects were included in the safety analyses. By setting a data cut-off date of [redacted], 20[redacted], both the number of patients with METex14 skipping alterations assessed by LBx and that by TBx reached ≥60, a number at which objective response rates can be evaluated. Of 100 subjects who received tepotinib by the cut-off date (patients who had started receiving tepotinib on or prior to April 2, 2019), 1 subject[46] was excluded because the testing of METex14 skipping did not meet the protocol criteria, and the remaining 99 subjects (including 15 Japanese patients) were included in the efficacy analyses.

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44) METex14 skipping alterations were assessed by LBx or TBx or both.
45) *EGFR* mutation-positive patients and anaplastic lymphoma kinase (*ALK*) fusion gene-positive patients were excluded.
46) The subject was excluded from efficacy analyses because the data on the METex14 skipping mutation were insufficient.

The primary endpoint for the study was the objective response rate as assessed by an independent review committee according to Response Evaluation Criteria in Solid Tumors (RECIST) ver.1.1 (Protocol, 4th amendment version, dated March 15, 2017). A threshold response rate of 20%[47] was specified for the 3 efficacy analysis sets for LBx group, TBx group, and LBx/TBx group of this study (Protocol, 4th amendment version, dated March 15, 2017).

Originally, the primary analysis of this study was to be performed when every patient in the LBx and TBx groups either (1) has received ≥6 months of tepotinib treatment; (2) has died; or (3) tepotinib treatment has ended for some reason. However, since the amount of data were considered to be sufficient to determine whether the primary objective had been achieved when the number of patients enrolled in the LBx and TBx groups totaled ≥60, which was required for the evaluation of the objective response rates in Cohort A, one of the primary objectives of this study, as specified in Protocol 4th amendment version (March 15, 2017), and a follow-up period of the last enrolled patient was ≥3.5 months. Accordingly, prior to database lock (August 15, 2019), an implementation of a key analysis of objective response rate with a data cut-off date of [redacted], 20[redacted], was specified in Statistical Analysis Plan, 3rd amendment (dated August 13, 2019).

Table 22 shows the objective response rate assessed by an independent review committee according to RECIST ver.1.1, the primary endpoint (data cut-off date on [redacted], 20[redacted]).

Table 22. Best overall response and objective response rate (RECIST ver.1.1, efficacy analysis set, independent review, data cut-off date on [redacted], 20[redacted])

Best overall response	n (%)					
	Total study population			Japanese subpopulation		
	LBx group (N = 66)	TBx group (N = 60)	LBx/TBx group (N = 99)	LBx group (N = 8)	TBx group (N = 12)	LBx/TBx group (N = 15)
CR	0	0	0	0	0	0
PR	30 (45.5)	26 (43.3)	42 (42.4)	6 (75.0)	4 (33.3)	7 (46.7)
SD	13 (19.7)	15 (25.0)	23 (23.2)	1 (12.5)	4 (33.3)	4 (26.7)
PD	11 (16.7)	11 (18.3)	17 (17.2)	1 (12.5)	3 (25.0)	3 (20.0)
NE	12 (18.2)	8 (13.3)	17 (17.2)	0	1 (8.3)	1 (6.7)
Objective response[*1] (Objective response rate [95%CI[*2]], %)	30 (45.5 [33.1, 58.2])	26 (43.3 [30.6, 56.8])	42 (42.4 [32.5, 52.8])	6 (75.0 [34.9, 96.8])	4 (33.3 [9.9, 65.1])	7 (46.7 [21.3, 73.4])

*1, CR + PR; *2 Clopper-Pearson method

During the study drug treatment period and within 30 days of the last dose, deaths occurred in 18 of 130 subjects (13.8%), including 1 death among Japanese patients. Two of the 18 subjects died from disease progression. Other causes of death were general physical health deterioration in 4 subjects, death in 2 subjects, dyspnoea/acute respiratory failure, ileus/sepsis, pneumonia, sudden death, bacterial infection, cardiac failure, pneumonia aspiration, pulmonary haemorrhage, respiratory tract infection, and spinal

47) A threshold response rate was based on data including the mean objective response rate of nivolumab being 20% for the 2 foreign phase III studies which were conducted to compare the efficacy and safety of nivolumab versus docetaxel in patients with advanced/recurrent squamous or non-squamous NSCLC previously treated with platinum-based chemotherapy (*J Clin Oncol.* 2017;35:3924-33).

fracture in 1 subject each. Among these events, a causal relationship to the study drug could not be ruled out for dyspnoea/acute respiratory failure in 1 subject (the cause of death for the Japanese patient was pulmonary haemorrhage, and a causal relationship to the study drug was denied for the event).

7.1.4 Foreign studies

7.1.4.1 Foreign phase I study (CTD 5.3.3.2.1, Study 01 [November 2009 to October 2015])

An open-label, uncontrolled study was conducted at 4 study centers outside Japan to evaluate tolerability and other aspects in patients with advanced solid tumors (target sample size, 108 subjects [dose escalation cohort] and 24 subjects [expansion cohort]).

The study was conducted with the following dosage administration, and the treatment was to be continued until disease progression or the discontinuation criteria were met.

- Regimen 1: tepotinib 30, 60, 100, 115,[48)] 145, 215, 230, 300, or 400 mg (Formulation CF1 or CF2) administered orally QD in 3-week cycles, 2 weeks on, 1 week off.
- Regimen 2: tepotinib 30, 60, 100, 115,[48)] 130, 175, or 315 mg (Formulation CF1 or CF2) administered orally 3 times per week (Days 1, 3, and 5) in 3-week cycles.
- Regimen 3: tepotinib 300, 500, 700, 1,000, or 1,400 mg (Formulation TF1 or CF2) administered orally QD continuously over the entire cycle (no rest period).

All 149 subjects enrolled in the study (Regimen 1, 42 subjects; Regimen 2, 45 subjects; and Regimen 3, 62 subjects) received tepotinib, and were included in the safety analyses.

In all the 3 regimens, DLTs were evaluated in the first 21-day cycle. While DLTs were observed as follows, no MTD was reached: in Regimen 1, 1 of 12 subjects in the 115 mg group (Grade 4 lipase increased and Grade 3 amylase increased); in Regimen 2, 1 of 10 subjects in the 60 mg group (Grade 3 lipase increased), 1 of 6 subjects in the 100 mg group (Grade 3 lipase increased), and 1 of 6 subjects in the 130 mg group (Grade 3 nausea and vomiting); and in Regimen 3, 1 of 7 subjects in the 1,000 mg group (Grade 3 ALT increased), and 1 of 7 subjects in the 1,400 mg group (Grade 3 fatigue). The results of DLT evaluation suggested that the once-daily dosing of tepotinib in Regimen 3 was considered tolerable. Furthermore, the pharmacokinetic/pharmacodynamic simulation results suggested that the 500-mg QD regimen (Regimen 3) would sustain ≥95% phosphorylated MET inhibition at steady state. Therefore, the RP2D of tepotinib and the dosage and administration for the expansion cohort was determined to be tepotinib 500 mg orally administered daily over the entire cycle (no rest period).

During the tepotinib treatment period and within 30 days of the last dose, 1 of the 42 subjects (2.4%) in the 500 mg group of Regimen 3 died. The cause of death was hepatic failure, and a causal relationship to tepotinib was denied.

48) The regimen under fasting vs. fed conditions was studied in separate cohorts.

7.1.4.2 Foreign phase Ib/II study (CTD 5.3.5.4.1, Study 04 [ongoing since February 2014, data cut-off date on February 5, 2018])

An open-label, randomized, controlled study was conducted at 43 study centers outside Japan to assess the efficacy and safety of tepotinib versus sorafenib in patients with MET-positive advanced hepatocellular carcinoma (target sample size, 21 subjects [phase Ib] and 140 subjects [phase II]).

The study was conducted with the following dosage administration: tepotinib 300, 500, or 1,000 mg (Formulation TF1) was administered orally QD in the phase Ib part; tepotinib 500 mg (Formulation TF1) was administered orally QD in the tepotinib group, and sorafenib 400 mg was administered orally BID in the sorafenib group in the phase II part. The treatment was to be continued until disease progression or the discontinuation criteria were met.

All 117 subjects enrolled in this study (27 subjects in the phase Ib part; 90 subjects in the phase II part [45 each in the tepotinib and sorafenib groups]) received the study drug, and were included in the safety analyses.

The first 21-day cycle of the phase Ib part was predefined as the DLT assessment period. No DLTs were observed, and 500 mg QD was determined to be the RP2D.

During the study drug treatment period and within 30 days of the last dose, deaths occurred in 1 of 7 subjects (14.3%) in the 300 mg group in the phase Ib part; 6 of 45 subjects (13.3%) in the tepotinib group and 1 of 44 subjects (2.3%) in the sorafenib group in the phase II part. Five subjects died from disease progression (1 subject in the 300 mg group in the phase Ib part; 3 subjects in the tepotinib group and 1 subject in the sorafenib group in the phase II part). Other causes of death were hepatic failure, systemic infection, and upper gastrointestinal haemorrhage in 1 subject each (2.2%) in the tepotinib group in the phase II part. A causal relationship to the study drug could not be ruled out for the event of upper gastrointestinal haemorrhage in 1 subject in the tepotinib group.

7.1.4.3 Foreign phase Ib/II study (CTD 5.3.5.4.2, Study 05 [May 2014 to February 2018])

An open-label, uncontrolled study was conducted at 30 study centers outside Japan to assess the efficacy and safety of tepotinib in patients with MET-positive, advanced hepatocellular carcinoma previously treated with sorafenib (target sample size, 18 subjects [phase Ib] and 48 subjects [phase II]).

The study was conducted with the following dosage administration: tepotinib 300 or 500 mg (Formulation TF1) was administered orally QD in the phase Ib part; and tepotinib 500 mg (Formulation TF1) was administered orally QD in the phase II part. The treatment was to be continued until disease progression or the discontinuation criteria were met.

All 66 subjects enrolled in the study (17 subjects in the phase Ib part and 49 subjects in the phase II part) received tepotinib, and were included in the safety analyses.

During the study drug treatment period and within 30 days of the last dose, deaths occurred in 1 of 4 subjects (25.0%) in the 300 mg group, and 2 of 13 subjects (15.4%) in the 500 mg group in the phase Ib part; and 8 of 49 subjects (16.3%) in the phase II part. Six subjects died from disease progression (1 subject each in the 300 and 500 mg groups in the phase Ib part; and 4 subjects in the phase II part). Other causes of death were coma in 1 subject (7.7%) at tepotinib 500 mg QD in the phase I part; gastrointestinal haemorrhage, general physical health deterioration, hypoglycaemic coma, and sepsis in 1 subject each in the phase II part. A causal relationship to tepotinib could not be ruled out for the event of hypoglycaemic coma in 1 subject in the phase II part.

7.R Outline of the review conducted by PMDA

7.R.1 Review strategy

Of the evaluation data submitted, PMDA concluded that Cohort A of the global phase II study (VISION study), which was conducted to assess the efficacy and safety of tepotinib in patients with unresectable, advanced or recurrent METex14 skipping mutation-positive NSCLC, is the pivotal clinical study in evaluating the efficacy and safety of tepotinib, and therefore decided to conduct a review primarily focusing on this study.

7.R.2 Efficacy

Based on the following discussions, PMDA concluded that tepotinib has a certain level of efficacy in the treatment of patients with unresectable, advanced or recurrent METex14 skipping mutation-positive NSCLC.

7.R.2.1 Efficacy endpoints and evaluation results

The applicant's explanation about the primary endpoint for Cohort A of the VISION study and the efficacy of tepotinib in patients with unresectable, advanced or recurrent METex 14 skipping mutation-positive NSCLC:

Some studies have reported that clinical symptoms associated with disease progression are expected to improve as a result of achieving response in patients with unresectable, advanced or recurrent METex 14 skipping mutation-positive NSCLC (*JAMA.* 2003;290:2149-58, etc.), which is the patient population of Cohort A of the VISION study. Achieving response is therefore considered clinically meaningful. Based on this and other factors, objective response rate was selected as the primary endpoint for Cohort A of the study.

In Cohort A of the VISION study, the objective response rate for the total study population [95% CI] was 45.5% [33.1, 58.2] for subjects in the LBx group, 43.3% [30.6, 56.8] for subjects in the TBx group, and 42.4% [32.5, 52.8] for subjects in the LBx/TBx group, indicating that the objective response rate was greater than the threshold of 20% in all groups [see Section 7.1.3.2]. For the Japanese subpopulation in Cohort A of the VISION study, the objective response rate [95% CI] was 75.0% [34.9, 96.8] for

subjects in the LBx group, 33.3% [9.9, 65.1] for subjects in the TBx group, and 46.7% [21.3, 73.4] for subjects in the LBx/TBx group [see Section 7.1.3.2].

In addition to the above, taking into account the factors including the following, the efficacy of tepotinib is expected in patients with unresectable, advanced or recurrent METex14 skipping mutation-positive NSCLC.

- METex14 skipping is suggested to be an oncogenic driver, playing a key role in oncogenesis in patients with unresectable, advanced or recurrent METex14 skipping mutation-positive NSCLC [see Section 3.R.1].
- The objective response rate obtained from the results of Cohort A in the VISION study is considered to be clinically meaningful.

PMDA's discussion:

The changes in the schedule of the primary analysis [see Section 7.1.3.2] should have been specified in the protocol and other relevant documents prior to the data cut-off date, after a thorough discussion on possible impacts of the changes on the interpretation of results. However, given that the number of patients required by the protocol for the assessment of objective response rates in Cohort A of the VISION study, which is ≥60, had already been enrolled in each of the LBx and TBx groups before the data cut-off date, it is acceptable to evaluate the efficacy of tepotinib based on the data from Cohort A of the VISION study, submitted for the present application.

Furthermore, the relationship between objective response rate and overall survival (OS), a true endpoint for patients with unresectable, advanced or recurrent METex14 skipping mutation-positive NSCLC, is not clear. Therefore, the effect of tepotinib on prolongation of life in the patient population is difficult to evaluate based on the objective response rate results, the primary endpoint for Cohort A of the VISION study. Nevertheless, the applicant's explanation about the efficacy of tepotinib above is still understandable, and it was concluded that objective response rates and other data from Cohort A of the VISION study demonstrated that tepotinib has a certain level of efficacy in the treatment of patients with unresectable, advanced or recurrent METex14 skipping mutation-positive NSCLC.

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

Based on the discussions in the following sections, PMDA considered that adverse events that require particular attention when tepotinib is used in patients with unresectable, advanced or recurrent METex14 skipping mutation-positive NSCLC are interstitial lung disease (ILD), fluid retention (including hypoalbuminaemia), hepatic dysfunction, renal dysfunction, and QT/QTc interval prolongation, and that attention should be paid to the possible development of these adverse events during treatment with tepotinib.

Although the use of tepotinib requires particular caution for the onset of adverse events mentioned above, PMDA concluded that tepotinib is tolerable as long as appropriate steps, including monitoring and management of adverse events, and dose interruption, are taken by physicians with sufficient knowledge of and experience with cancer chemotherapy.

7.R.3.1 Safety profile

The applicant's explanation about the safety profile of tepotinib based on the safety data from Cohort A of VISION study:

Table 23 summarizes the safety data from Cohort A of the VISION study.

Table 23. Summary of safety data (Cohort A of VISION study)

	n (%) N = 130
All adverse events	124 (95.4)
Grade ≥3 adverse events	66 (50.8)
Adverse events leading to death	18 (13.8)
Serious adverse events	60 (46.2)
Adverse events leading to treatment discontinuation	27 (20.8)
Adverse events leading to dose interruption	55 (42.3)
Adverse events leading to dose reduction	33 (25.4)

In Cohort A of the VISION study, adverse events of any grade with an incidence of ≥10% were oedema peripheral (77 subjects, 59.2%); diarrhoea (40 subjects, 30.8%); nausea (39 subjects, 30.0%); blood creatinine increased (31 subjects, 23.8%); dyspnoea (27 subjects, 20.8%); hypoalbuminaemia (23 subjects, 17.7%); asthenia, constipation, and decreased appetite (19 subjects each, 14.6%); cough (18 subjects, 13.8%); pleural effusion (16 subjects, 12.3%); back pain, fatigue, and amylase increased (15 subjects each, 11.5%); and ALT increased (14 subjects, 10.8%). Grade ≥3 adverse events with an incidence of ≥2% were oedema peripheral (11 subjects, 8.5%); pleural effusion (9 subjects, 6.9%); ALT increased and general physical health deterioration (6 subjects each, 4.6%); anaemia, pneumonia, pulmonary embolism, and generalised oedema (5 subjects each, 3.8%); hypoalbuminaemia and amylase increased (4 subjects each, 3.1%); and disease progression, AST increased, gamma-glutamyltransferase (GGT) increased, and oedema genital (3 subjects each, 2.3%). An adverse event leading to death with an incidence of ≥2% was general physical health deterioration (4 subjects, 3.1%). Serious adverse events with an incidence of ≥2% were pleural effusion (10 subjects, 7.7%); general physical health deterioration (7 subjects, 5.4%); generalised oedema and pneumonia (5 subjects each, 3.8%); dyspnoea (4 subjects, 3.1%); and disease progression, asthenia, oedema peripheral, pulmonary embolism, and back pain (3 subjects each, 2.3%). Adverse events leading to treatment discontinuation with an incidence of ≥2% were oedema peripheral (5 subjects, 3.1%); and oedema genital (3 subjects, 2.3%). Adverse events leading to dose interruption with an incidence of ≥2% were oedema peripheral (19 subjects, 14.6%); blood creatinine increased and ALT increased (6 subjects each, 4.6%); pleural effusion (4 subjects, 3.1%); and AST increased, nausea, asthenia, diarrhoea, amylase increased, generalised oedema, oedema, and oedema genital (3 subjects each, 2.3%). Adverse events leading to dose reduction with an incidence

of ≥2% were oedema peripheral (17 subjects, 13.1%); and blood creatinine increased and oedema (3 subjects each, 2.3%).

PMDA's discussion:
Adverse events that occurred with a higher incidence, serious adverse events, adverse events leading to death, and Grade ≥3 adverse events in Cohort A of the VISION study are likely to occur in treatment with tepotinib. While patients on tepotinib should be monitored for these events while being aware of the relationship with tepotinib, the majority of the events were manageable by dose interruption, reduction, or other measures. Based on these and other findings, it was concluded that tepotinib is tolerable as long as appropriate steps, including monitoring and management of adverse events, and dose interruption or reduction, are taken by physicians with sufficient knowledge of and experience with cancer chemotherapy.

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

The applicant's explanation about differences in the safety of tepotinib between Japanese and non-Japanese subjects based on the safety data from Cohort A of the VISION study:
Table 24 summarizes the safety data in Japanese and non-Japanese patients from Cohort A of the VISION study.

Table 24. Summary of safety data (Cohort A of VISION study)

	n (%)	
	Japanese subjects N = 17	Non-Japanese subjects N = 113
All adverse events	16 (94.1)	108 (95.6)
Grade ≥3 adverse events	10 (58.8)	56 (49.6)
Adverse events leading to death	1 (5.9)	17 (15.0)
Serious adverse events	7 (41.2)	53 (46.9)
Adverse events leading to treatment discontinuation	5 (29.4)	22 (19.5)
Adverse events leading to dose interruption	14 (82.4)	41 (36.3)
Adverse events leading to dose reduction	10 (58.8)	23 (20.4)

In Cohort A of the VISION study, adverse events of any grade with an incidence higher in the Japanese subjects than in the non-Japanese subjects by ≥20% were blood creatinine increased (9 subjects, 52.9% [Japanese]; 22 subjects, 19.5% [non-Japanese]), hypoalbuminaemia (6 subjects, 35.3% [Japanese]; 17 subjects, 15.0% [non-Japanese]), and amylase increased (5 subjects, 29.4% [Japanese]; 10 subjects, 8.8% [non-Japanese]). Grade ≥3 adverse events with an incidence higher in the Japanese subjects than in the non-Japanese subjects by ≥ 10% were hypoalbuminaemia (3 subjects, 17.6% [Japanese]; 1 subject, 0.9% [non-Japanese]), GGT increased (2 subjects, 11.8% [Japanese]; 1 subject, 0.9% [non-Japanese]), and lung infection (2 subjects, 11.8% [Japanese]; 0 subjects [non-Japanese]). A serious adverse event with an incidence higher in the Japanese subjects than in the non-Japanese subjects by ≥10% was lung infection (2 subjects, 11.8% [Japanese]; 0 subjects [non-Japanese]). Adverse events leading to dose interruption with an incidence higher in the Japanese subjects than in the non-Japanese subjects by ≥10% were ILD (2 subjects, 11.8% [Japanese]; 0 subjects [non-Japanese]) and lung infection (2 subjects,

11.8% [Japanese]; 0 subjects [non-Japanese]). An adverse event leading to dose reduction with an incidence higher in the Japanese subjects than in the non-Japanese subjects by ≥10% was hypoalbuminaemia (2 subjects, 11.8% [Japanese]; 0 subjects [non-Japanese]). No adverse events led to death or treatment discontinuation with an incidence higher in the Japanese subjects than in the non-Japanese subjects by ≥10%.

PMDA's discussion:
Although it is difficult to rigorously compare the safety profiles between Japanese and non-Japanese subjects due to the limited number of Japanese subjects who have received tepotinib, blood creatinine increased, hypoalbuminaemia, GGT increased, and other adverse events occurred at a higher incidence in Japanese subjects than in non-Japanese subjects in Cohort A of the VISION study. Therefore, adequate caution should be exercised against the possible occurrence of these events when using tepotinib. However, given that there were no clear trends towards increasing incidence of adverse events leading to death or serious adverse events in the Japanese subjects compared with the non-Japanese subjects, and that tepotinib is to be administered by a physician with sufficient knowledge of and experience with cancer chemotherapy, it was concluded that tepotinib is tolerable in Japanese patients.

In the following sections, PMDA reviewed adverse events based on the safety results from Cohort A of the VISION study, primarily focusing on events occurring with a high incidence in tepotinib-treated patients, and those requiring particular caution in Japanese patients.

7.R.3.3 Interstitial lung disease

The applicant's explanation about ILD associated with tepotinib:
For all patients who experienced any of the following ILD events, a medical review was performed regarding the patient profile and radiological diagnostic findings at baseline and when the ILD-related event occurred, and patients[49)] who experienced ILD events as defined by the medical review were analyzed: events classified under Standardised Medical Dictionary for Regulatory Activities (MedDRA) Queries (SMQs) "ILD (broad)" and "respiratory failure (narrow)," and MedDRA PTs "atypical pneumonia," "pneumonia aspiration," and "pulmonary haemorrhage."

Table 25 shows the incidence of ILD in Cohort A of the VISION study.

Table 25. Incidence of ILD (Cohort A of VISION study)

PT (MedDRA ver.22.0)	n (%) N = 130	
	All Grades	Grades ≥3
ILD	5 (3.8)	2 (1.5)
Pneumonitis	2 (1.5)	1 (0.8)
ILD	2 (1.5)	0
Acute respiratory failure	1 (0.8)	1 (0.8)

49) The data included pneumonitis in 1 subject, which developed into Grade ≥3 and serious ILD after the data cut-off date.

In Cohort A of the VISION study, ILD resulted in death in 1 of 130 subjects (0.8%, acute respiratory failure), and a causal relationship to tepotinib could not be ruled out for this event. Serious ILD occurred in 3 of 130 subjects (2.3%; pneumonitis, ILD, and acute respiratory failure in 1 subject each), and a causal relationship to tepotinib could not be ruled out for any of the events. Interstitial lung disease led to discontinuation of tepotinib in 4 of 130 subjects (3.1%; pneumonitis in 2 subjects; acute respiratory failure and ILD in 1 subject each). Interstitial lung disease led to tepotinib dose interruption in 4 of 130 subjects (3.1%; ILD and pneumonitis in 2 subjects each), while ILD led to dose reduction of tepotinib in 1 of 130 subjects (0.8%; ILD in 1 subject).

In Cohort A of the VISION study, the median time to initial onset of ILD was 54 days (range, 21-135 days).

Table 26 shows detailed data on patients who received tepotinib and had serious ILD, or ILD that led to death in all the studies included in the submitted data.

Table 26. List of patients who had serious ILD or ILD that led to death

Study	Age	Sex	Ethnicity	PT (MedDRA ver.22.0)	Grade	Time to onset (days)	Duration (days)	Causal relationship to tepotinib	Tepotinib treatment	Outcome
VISION	79	M	Non-Japanese	Acute respiratory failure	2	21	13	Yes	Discontinued	Not resolved
				Acute respiratory failure	5	33	3	Yes	Discontinued	Died
	76	M	Japanese	ILD	2	21	—	Yes	Dose interrupted	Not resolved
	75	F	Non-Japanese	Pneumonitis	3	54	—	Yes	Discontinued	Resolved
06*	60	M	Non-Japanese	Atypical pneumonia	3	33	—	Yes	Discontinued	Not resolved

*, Gefitinib was co-administered

PMDA's discussion:

In Cohort A of the VISION study, there was an event of ILD that led to death in which a causal relationship to tepotinib could not be ruled out. In addition, a serious ILD occurred in a Japanese patient in which a causal relationship to tepotinib could not be ruled out. These and other findings suggest that attention should be paid to the possible development of ILD during treatment with tepotinib. Therefore, PMDA concluded that the incidence and other data on ILD from the clinical studies should be appropriately cautioned to healthcare professionals through the package insert.

7.R.3.4 Fluid retention (including hypoalbuminaemia)

The applicant's explanation about fluid retention (including hypoalbuminaemia, the same shall apply hereinafter) associated with tepotinib:

Fluid retention events classified under the MedDRA SMQ "haemodynamic oedema, effusions and fluid overload (narrow)" and MedDRA PTs "face oedema," "oedema genital," "periorbital oedema," "scrotal

oedema," "blood albumin abnormal," "blood albumin decreased," and "hypoalbuminaemia" were counted.

Table 27 shows the incidence of fluid retention in Cohort A of the VISION study.

Table 27. Incidence of fluid retention (Cohort A of VISION study)

PT (MedDRA ver.22.0)	n (%) N = 130	
	All Grades	Grades ≥3
Fluid retention	94 (72.3)	23 (17.7)
Oedema peripheral	77 (59.2)	11 (8.5)
Hypoalbuminaemia	23 (17.7)	4 (3.1)
Pleural effusion	16 (12.3)	9 (6.9)
Oedema	7 (5.4)	0
Generalised oedema	6 (4.6)	5 (3.8)
Oedema genital	5 (3.8)	3 (2.3)
Face oedema	3 (2.3)	0
Blood albumin decreased	2 (1.5)	1 (0.8)
Ascites	1 (0.8)	0
Pericardial effusion	1 (0.8)	0
Periorbital oedema	1 (0.8)	0

In Cohort A of the VISION study, no fluid retention events led to death. Serious fluid retention occurred in 15 of 130 subjects (11.5%; pleural effusion in 10 subjects; generalised oedema in 5 subjects; oedema peripheral in 3 subjects; and hypoalbuminaemia in 1 subject [some subjects had more than 1 event]). Among these events, a causal relationship to tepotinib could not be ruled out for generalised oedema in 4 subjects, oedema peripheral in 3 subjects, and pleural effusion in 2 subjects. Fluid retention led to discontinuation of tepotinib in 7 of 130 subjects (5.4%; oedema peripheral in 5 subjects; oedema genital in 3 subjects; and pleural effusion in 1 subject [some subjects had more than 1 event]). Fluid retention led to tepotinib dose interruption in 25 of 130 subjects (19.2%; oedema peripheral in 19 subjects; pleural effusion in 4 subjects; oedema, generalised oedema, and oedema genital in 3 subjects each; hypoalbuminaemia and blood albumin decreased in 1 subject each [some subjects had more than 1 event]). Fluid retention led to tepotinib dose reduction in 21 of 130 subjects (16.2%; oedema peripheral in 17 subjects; oedema in 3 subjects; hypoalbuminaemia in 2 subjects; pleural effusion and generalised oedema in 2 subjects each [some subjects had more than 1 event]).

In Cohort A of the VISION study, the median time to initial onset of fluid retention was 42.5 days (range, 1-208 days).

PMDA asked the applicant to explain the mechanism of the development of and risk factors for fluid retention associated with tepotinib treatment.

The applicant's response:

The mechanism of the development of and risk factors for fluid retention associated with tepotinib treatment still remain somewhat unclear. However, MET is expressed in blood vessels and lymphoid tissues (*Nat Rev Mol Cel Biol.* 2003;4:915-25, etc.), and fluid retention-related adverse events such as oedema have been reported in patients receiving other antineoplastic agents that are tyrosine kinase inhibitors targeting MET (*Oncotarget.* 2014;5:2866-80, etc.). Findings such as these suggest that fluid retention is a group of events likely to be associated with the pharmacological action of tepotinib.

PMDA's discussion:

In Cohort A of the VISION study, a causal relationship to tepotinib could not be ruled out for serious events of fluid retention. Findings including this result suggest that attention should be paid to the possible development of fluid retention during treatment with tepotinib. Therefore, PMDA concluded that the incidence and other data on fluid retention from the clinical studies should be appropriately cautioned to healthcare professionals through the package insert.

Since the relationship between tepotinib treatment and the risk of developing fluid retention has not yet been clarified, PMDA concluded that the applicant should continue to collect information after the market launch, and provide any new useful findings to healthcare professionals in an appropriate manner.

7.R.3.5 Hepatic dysfunction

The applicant's explanation about hepatic dysfunction associated with tepotinib:

Hepatic dysfunction events classified under the MedDRA SMQ "drug related hepatic disorders—comprehensive search (SMQ)" were counted.

Table 28 shows the incidence of hepatic dysfunction in Cohort A of the VISION study.

Table 28. Incidence of hepatic dysfunction (Cohort A of VISION study)

PT (MedDRA ver.22.0)	n (%) N = 130	
	All Grades	Grades ≥3
Hepatic dysfunction	40 (30.8)	13 (10.0)
Hypoalbuminaemia	23 (17.7)	4 (3.1)
ALT increased	14 (10.8)	6 (4.6)
AST increased	12 (9.2)	3 (2.3)
Blood ALP increased	9 (6.9)	0
GGT increased	7 (5.4)	3 (2.3)
Hepatic function abnormal	2 (1.5)	0
International normalised ratio increased	1 (0.8)	1 (0.8)
Ascites	1 (0.8)	0
Blood bilirubin increased	1 (0.8)	0
Hepatic enzyme increased	1 (0.8)	0
Hepatic steatosis	1 (0.8)	0
Hepatocellular injury	1 (0.8)	0

In Cohort A of the VISION study, no hepatic dysfunction events led to death. Serious hepatic dysfunction occurred in 2 of 130 subjects (1.5%; ALT increased, AST increased, and hypoalbuminaemia in 1 subject each [a subject had more than 1 event]). Among these events, a causal relationship to tepotinib could not be ruled out for ALT increased and AST increased in 1 subject each. No events of hepatic dysfunction led to discontinuation of tepotinib. Hepatic dysfunction led to tepotinib dose interruption in 7 of 130 subjects (5.4%; ALT increased in 6 subjects; AST increased in 3 subjects; GGT increased and hypoalbuminaemia in 1 subject each [some subjects had more than 1 event]). Hepatic dysfunction led to tepotinib dose reduction in 4 of 130 subjects (3.1%; ALT increased and hypoalbuminaemia in 2 subjects each; AST increased and GGT increased in 1 subject each [some subjects had more than 1 event]).

In Cohort A of the VISION study, the median time to initial onset of hepatic dysfunction was 42 days (range, 1-337 days).

Table 29 shows detailed data on patients who received tepotinib and had serious hepatic dysfunction, or hepatic dysfunction that led to death, for which a causal relationship to tepotinib could not be ruled out in all the clinical studies included in the submitted data.

Table 29. List of patients who had serious hepatic dysfunction, or hepatic dysfunction that led to death, for which a causal relationship to tepotinib could not be ruled out

Study	Age	Sex	Ethnicity	PT (MedDRA ver.22.0)	Grade	Time to onset (days)	Duration (days)	Tepotinib treatment	Outcome
VISION	88	F	Non-Japanese	ALT increased	3	22	6	Dose reduced/ interrupted	Resolved
				AST increased	3	22	6	Dose reduced/ interrupted	Resolved
04	50	M	Non-Japanese	ALT increased	4	20	7	Dose interrupted	Not resolved
				AST increased	4	20	7	Dose interrupted	Not resolved
				ALT increased	3	26	—	Continued	Not resolved
				AST increased	3	26	—	Continued	Not resolved
	50	M	Non-Japanese	Ascites	3	83	4	Continued	Not resolved
				Ascites	2	126	2	Continued	Not resolved
				Ascites	3	154	—	Discontinued	Not resolved
	65	M	Non-Japanese	Hepatic function abnormal	3	22	14	Dose interrupted	Resolved
	72	M	Non-Japanese	Ascites	3	52	7	Dose interrupted	Not resolved
06	70	M	Non-Japanese	Hypoalbuminaemia	2	267	13	Continued	Resolved

In all the clinical studies included in the submitted data, none of the patients developed hepatic dysfunction based on the laboratory test results according to Hy's law criteria (as defined in the *Guidance for industry. Drug-Induced Liver Injury: Premarketing Clinical Evaluation.* U.S. Department of Health and Human Services, Food and Drug Administration. July 2009).

PMDA's discussion:

In Cohort A of the VISION study, serious hepatic dysfunction for which a causal relationship to tepotinib could not be ruled out was reported. Findings including this result suggest that attention should

be paid to the possible development of hepatic dysfunction during treatment with tepotinib. Therefore, PMDA concluded that the incidence and other data on hepatic dysfunction from the clinical studies should be appropriately cautioned to healthcare professionals through the package insert.

7.R.3.6 Renal dysfunction

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

Renal dysfunction events classified under the MedDRA SMQs "acute renal failure (broad)" and "chronic kidney disease (broad)" were counted.

Table 30 shows the incidence of renal dysfunction in Cohort A of the VISION study.

Table 30. Incidence of renal dysfunction (Cohort A of VISION study)

PT (MedDRA ver.22.0)	n (%) N = 130	
	All Grades	Grades ≥3
Renal impairment	55 (42.3)	11 (8.5)
Blood creatinine increased	31 (23.8)	0
Hypoalbuminaemia	23 (17.7)	4 (3.1)
Renal failure	5 (3.8)	1 (0.8)
Hypocalcaemia	5 (3.8)	0
Hyponatraemia	4 (3.1)	2 (1.5)
Acute kidney injury	4 (3.1)	1 (0.8)
Chronic kidney disease	4 (3.1)	1 (0.8)
Hyperkalaemia	4 (3.1)	1 (0.8)
Blood urea increased	3 (2.3)	0
Renal impairment	3 (2.3)	0
Blood urea increased	3 (2.3)	0
Blood sodium decreased	2 (1.5)	1 (0.8)
Encephalopathy	1 (0.8)	1 (0.8)

In Cohort A of the VISION study, no renal dysfunction events led to death. Serious renal dysfunction occurred in 4 of 130 subjects (3.1%; acute kidney injury in 2 subjects; hypoalbuminaemia and hyponatraemia in 1 subject each), and a causal relationship to tepotinib was denied for both events. No events of renal dysfunction led to discontinuation of tepotinib. Renal dysfunction led to tepotinib dose interruption in 11 of 130 subjects (8.5%; blood creatinine increased in 6 subjects; acute kidney injury in 2 subjects; renal impairment, hypoalbuminaemia, chronic kidney disease, and hyperkalaemia in 1 subject each [some subjects had more than 1 event]). Renal dysfunction led to tepotinib dose reduction in 7 of 130 subjects (5.4%; blood creatinine increased in 3 subjects; hypoalbuminaemia in 2 subjects; acute kidney injury and chronic kidney disease in 1 subject each).

In Cohort A of the VISION study, the median time to initial onset of renal dysfunction was 23 days (range, 4-549 days) for acute renal failure, and 41 days (range, 4-409) for chronic kidney disease.

Table 31 shows detailed data on patients who received tepotinib and had serious renal dysfunction, or renal dysfunction that led to death in all the clinical studies included in the submitted data.

Table 31. List of patients who had serious renal dysfunction, or renal dysfunction that led to death

Study	Age	Sex	Ethnicity	PT (MedDRA ver.22.0)	Grade	Time to onset (days)	Duration (days)	Causal relationship	Tepotinib treatment	Outcome
VISION	80	M	Non-Japanese	Acute kidney injury	2	485	6	No	Interrupted	Resolved
	83	M	Non-Japanese	Acute kidney injury	2	155	17	No	—	Resolved
	94	M	Non-Japanese	Hyponatraemia	3	30	5	No	—	Resolved
	73	M	Japanese	Hypoalbuminaemia	3	147	24	No	Continued	Not resolved
01	48	F	Non-Japanese	Acute kidney injury	3	34	8	No	Withdrawn	Resolved
	59	F	Non-Japanese	Acute kidney injury	3	14	4	No	—	Resolved
	70	M	Non-Japanese	Hyperkalaemia	3	34	—	No	Dose interrupted	Not resolved
05	73	F	Non-Japanese	Acute kidney injury	3	9	9	No	—	Resolved
	70	M	Non-Japanese	Acute kidney injury	2	29	7	Yes	—	Resolved
	68	F	Non-Japanese	Acute kidney injury	2	30	—	No	—	Not resolved
	74	M	Non-Japanese	Acute kidney injury	2	43	8	No	—	Resolved
	75	M	Non-Japanese	Acute kidney injury	3	36	10	Yes	Dose interrupted	Not resolved
	60	M	Non-Japanese	Hypercreatininaemia	2	99	6	No	—	Not resolved
					3	104	—	No	—	Not resolved
	63	M	Non-Japanese	Chronic kidney disease	2	42	4	No	Continued	Resolved
	52	M	Non-Japanese	Hyponatraemia	4	87	13	No	Dose interrupted	Resolved
	60	M	Non-Japanese	Hypercreatininaemia	2	99	6	No	—	Not resolved
					3	104	—	No	—	Not resolved
06	70	M	Non-Japanese	Hypoalbuminaemia	2	67	13	Yes	Continued	Resolved

PMDA's discussion:

In the clinical studies, renal dysfunction for which a causal relationship to tepotinib could not be ruled out was reported. Based on these findings as well as the higher incidence of blood creatinine increased among Japanese patients [see Section 7.R.3.2], attention should be paid to the possible development of renal dysfunction during treatment with tepotinib. Therefore, PMDA concluded that blood creatinine tests should be performed on a regular basis, and that the incidence and other data on renal dysfunction from the clinical studies should be appropriately cautioned to healthcare professionals through the package insert.

7.R.3.7 Other events

Tepotinib inhibited hERG potassium current in the safety pharmacology study [see Section 3.3.2.1]. PMDA asked the applicant to explain the incidence of prolongation of QT/QTc interval.

The applicant's explanation about QT/QTc interval prolongation:

QT/QTc interval prolongation events classified under the MedDRA SMQ "torsade de pointes/QT prolongation (narrow)" were counted.

Table 32 shows the incidence of QT/QTc interval prolongation in Cohort A of the VISION study.

Table 32. Incidence of QT/QTc interval prolongation (Cohort A of VISION study)

PT (MedDRA ver.22.0)	n (%) N = 130	
	All Grades	Grades ≥3
QT/QTc interval prolongation	5 (3.8)	0
Electrocardiogram QT prolonged	4 (3.1)	0
Long QT syndrome	1 (0.8)	0

In Cohort A of the VISION study, no QT/QTc interval prolongation events led to death. None of the QT/QTc interval prolongation events were classified as serious or led to discontinuation of tepotinib. QT/QTc interval prolongation led to tepotinib dose interruption in 1 of 130 subjects (0.8%; electrocardiogram QT prolonged).

In Cohort A of the VISION study, 7 of 130 subjects (5.4%) had >60 ms increase in change from baseline in the QTcF.

In Study 04, no QT/QTc interval prolongation events led to death, and none of the QT/QTc interval prolongation events were classified as serious. However, QT/QTc interval prolongation of Grade ≥3 occurred in 2 of 59 subjects (3.4%), and QT/QTc interval prolongation led to discontinuation of tepotinib in 1 of 59 subjects (1.7%). A causal relationship to tepotinib could not be ruled out for one of the Grade ≥3 QT/QTc interval prolongation events, which also led to discontinuation of tepotinib in the subject.

PMDA's discussion:
In Cohort A of the VISION study, QT/QTc interval prolongation events associated with tepotinib were all classified as Grade ≤2. In addition, in the clinical studies, extremely small number of patients experienced QT/QTc interval prolongation events for which a causal relationship to tepotinib could not be ruled out. It is therefore difficult to reach a definitive conclusion on the QT/QTc interval prolongation associated with tepotinib treatment. However, given that changes were observed in QTcF in some patients in Cohort A of the VISION study, and that in Study 04, QT/QTc interval prolongation led to discontinuation of tepotinib and for this event a causal relationship to tepotinib could not be ruled out, the incidence and other data on QT/QTc interval prolongation from the clinical studies should be appropriately cautioned to healthcare professionals through the package insert. PMDA also concluded that the applicant should continue to collect data on the incidence of QT/QTc interval prolongation after the market launch, and provide any new findings to healthcare professionals in an appropriate manner.

7.R.4 Clinical positioning and indication

The proposed indication of tepotinib was "unresectable, advanced or recurrent *MET* exon 14 skipping mutation-positive non-small cell lung cancer." The following statements were specified in the "Precautions concerning indication" section:

- The efficacy and safety of tepotinib as an [neo] adjuvant therapy have not been established.
- Tepotinib should only be administered to patients who have been confirmed as having *MET* exon 14 skipping mutation-positive by highly experienced pathologists or laboratories. Approved *in vitro* diagnostics should be used for diagnostic testing.

Based on the discussions in the following sections as well as those in Sections "7.R.2 Efficacy" and "7.R.3 Safety," PMDA concluded that it is appropriate to specify the indication of tepotinib as "unresectable, advanced or recurrent *MET* exon 14 skipping mutation-positive non-small cell lung cancer" as proposed by the applicant, and to include the following cautionary statements in the "Precautions concerning indication" section:

- The efficacy and safety of tepotinib as adjuvant therapy have not been established.
- Tepotinib should only be administered to patients who have been confirmed as having *MET* exon 14 skipping alterations by highly experienced pathologists or testing at laboratories. Approved *in vitro* diagnostics should be used for diagnostic testing.

7.R.4.1 Clinical positioning and patients eligible for tepotinib treatment

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

The applicant's explanation about intended patient population and indication of tepotinib:
Results from Cohort A of the VISION study suggest that tepotinib can be positioned as a treatment option for patients with unresectable, advanced or recurrent METex14 skipping mutation-positive NSCLC.

In Cohort A of the VISION study, patients with different lines of prior therapy were enrolled. The objective response rate in 0 to 2 lines of prior therapy was 39.5% (17 of 43 subjects) in patients receiving no prior therapy; 48.5% (16 of 33 subjects) in patients receiving 1 line of prior therapy; and 39.1% (9 of 23 subjects) in patients receiving 2 lines of prior therapy, indicating that certain level of objective response rate was achieved across the patients groups. These results suggest that tepotinib is expected to be effective in patients with unresectable, advanced or recurrent METex14 skipping mutation-positive NSCLC regardless of the number of lines of prior therapy.

Based on the above, the indication of tepotinib was proposed as "unresectable, advanced or recurrent *MET* exon 14 skipping mutation-positive non-small cell lung cancer." However, so far, there have been no clinical study results demonstrating the clinical benefit of tepotinib in patients with METex14 skipping mutation-positive NSCLC eligible for adjuvant therapy; therefore, the use of tepotinib in such patients is not considered recommended. A cautionary statement to this effect will be included in the "Precautions concerning indication" section.

- The efficacy and safety of tepotinib as [neo] adjuvant therapy have not been established.

PMDA's discussion:

PMDA largely accepted the applicant's explanation and concluded that it is appropriate to specify the indication of tepotinib as "unresectable, advanced or recurrent *MET* exon 14 skipping mutation-positive non-small cell lung cancer" as proposed by the applicant. In the present application, a cautionary statement was specified to the effect that "The efficacy and safety of tepotinib as [neo] adjuvant therapy have not been established" in the "Precautions concerning indication" section. However, according to the clinical practice guidelines published in Japan, adjuvant therapy is the only standard therapy performed as an adjunct to surgery in patients with NSCLC; therefore, it is appropriate to make modifications and specify the statement as follows:

- The efficacy and safety of tepotinib as adjuvant therapy have not been established.

7.R.4.2 Testing for METex14 skipping

The applicant's explanation about testing for METex14 skipping alterations to be used for selection of patients intended for the treatment with tepotinib:

In Cohort A of the VISION study, testing was performed by one of the following methods at the central laboratory or the study center: "Guardant360" from Guardant Health for LBx; and "Oncomine Focus Assay" from Thermo Fisher Scientific for TBx. Patients whose biopsy specimen tested positive for METex14 skipping alterations were included in efficacy and safety analyses [see Section 7.1.3.2]. "ArcherMET companion diagnostic," for which an application for approval was filed by ArcherDx, Inc. as a companion diagnostic, has been verified as capable of adequately identifying patients in whom tepotinib is expected to demonstrate efficacy and safety based on the assessment of equivalence using specimens of patients enrolled in Cohort A of the VISION study.

Based on the above, it is appropriate to identify eligible patients using "ArcherMET companion diagnostic" before treating the patients with tepotinib. The information to this effect will be included in the "Precautions concerning indication" section and caution will be advised.

PMDA's discussion:

PMDA accepted the applicant's explanation above and concluded that it is appropriate to provide the cautionary statement in the "Precautions concerning indication" section, with the modification shown below:

- Tepotinib should only be administered to patients who have been confirmed as having *MET* exon 14 skipping alterations by highly experienced pathologists or testing at laboratories. Approved *in vitro* diagnostics should be used for diagnostic testing.

7.R.5 Dosage and administration

The proposed dosage and administration of tepotinib was "The usual adult dosage is 500 mg of tepotinib hydrochloride hydrate administered orally once daily after a meal. The dose may be reduced according to the patient's condition." In the "Precautions concerning dosage and administration" section, the following statements were specified:

- The efficacy and safety of tepotinib in combination with other antineoplastic agents have not been established.
- Discontinue treatment with tepotinib when the patient has developed ILD.
- If other Grade ≥3 adverse drug reactions occurred following the administration of tepotinib, the dose should be reduced to 250 mg until toxicity resolves to Grade ≤2. Also consider interruption of treatment with tepotinib (up to a maximum of 21 days).

Table 33. Dose level reductions for tepotinib

Dose level	Dose
Normal	500 mg/day
Reduced	250 mg/day

Based on the discussions in the following sections as well as those in Sections "7.R.2 Efficacy" and "7.R.3 Safety," PMDA concluded that it is appropriate to specify the dosage and administration of tepotinib as "The usual adult dosage is 500 mg of tepotinib hydrochloride hydrate administered orally once daily after a meal. The dose may be reduced according to the patient's condition." as proposed by the applicant, and to include the following cautionary statements in the "Precautions concerning dosage and administration" section.

- The efficacy and safety of tepotinib in combination with other antineoplastic agents have not been established.
- If an adverse drug reaction occurred following the administration of tepotinib, the doses of tepotinib must be reduced, or treatment with tepotinib must be interrupted or discontinued based on the following criteria.

Table 34. Dose level reductions

Dose reduction level	Dose
Normal	500 mg once daily
First dose reduction	250 mg once daily
Second dose reduction	Discontinue treatment

Table 35. Dose adjustment criteria of tepotinib for adverse drug reactions

Adverse drug reaction	Severity	Action
ILD	Grade ≥1	Discontinue treatment
All other adverse drug reactions	Grade 3	Dose interruption until recovery to Grade ≤2, or dose reduction by one level and continue treatment. If dose interruption of more than 21 days is required, discontinue treatment.
	Grade 4	Dose interruption until recovery to Grade ≤2. If dose interruption of more than 21 days is required, discontinue treatment.

7.R.5.1 Dosage and administration of tepotinib

The applicant's explanation on the rationale for selecting the dosage and administration of tepotinib for patients with unresectable, advanced or recurrent METex14 skipping mutation-positive NSCLC:

Based on the results from the clinical studies shown below, a dosage and administration was established for Cohort A of the VISION study. The results of this study demonstrated the clinical benefits of tepotinib in patients with unresectable, advanced or recurrent METex14 skipping mutation-positive

NSCLC; therefore, the dosage and administration of tepotinib for this application was proposed based on the regimen of Cohort A of the VISION study.

- In Cohort 3 of the foreign phase I study (Study 01), although DLTs were observed in 1 of 7 subjects in the 1,000 mg QD group (Grade 3 ALT increased) and 1 of 7 subjects in the 1,400 mg QD group (Grade 3 fatigue), no MTD was reached, and tolerability and safety at 500 mg QD were demonstrated [see Section 7.1.4.1].
- In the Japanese phase I study (Study 03), no DLTs were observed at tepotinib 215, 300, or 500 mg, and tolerability and safety in Japanese patients at 500 mg QD were demonstrated [see Section 7.1.2.1].
- In the Japanese phase I study (Study 03), the mean plasma concentrations of tepotinib at 500 mg QD were greater than 390 to 823 ng/mL[50)], the target plasma concentration at which an anti-tumor effect can be expected [see Section 6.2.1.1].

No results have been obtained from clinical studies in patients with NSCLC receiving tepotinib in combination with other antineoplastic agents. Therefore, information on the use of other antineoplastic agents in combination with tepotinib will be provided in the "Clinical Studies" section, and the following cautionary statement will be included in the "Precautions concerning dosage and administration" section:

- The efficacy and safety of tepotinib in combination with other antineoplastic agents have not been established.

PMDA accepted the applicant's explanation.

7.R.5.2 Dose adjustment of tepotinib

The applicant's explanation on the dose adjustment of tepotinib:

Specific criteria for the dose adjustment of tepotinib were specified in Cohort A of the VISION study. Tepotinib was administered in accordance with the dose adjustment criteria, and the results of the study demonstrated the clinical benefit of tepotinib. Therefore, the following adjustments will be added, based on the dose adjustment criteria, and the modified criteria will be included in the "Precautions concerning dosage and administration" section as a guide.

- In Cohort A of the VISION study, 300 mg was specified as the first dose reduction level, and 200 mg as the second dose reduction level; however, the modified criteria will have only one dose reduction level, and a reduced dose level of 250 mg will be specified.

PMDA asked the applicant to explain the reason for the above modification being made to the specifications on dose reduction.

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50) Based on the examination of data including results of a study using mice subcutaneously implanted with human pancreatic cancer cell line KP-4, plasma tepotinib concentrations at which an anti-tumor effect of 90% and 95% can be expected in mice were estimated to be 215 ng/mL and 454 ng/mL, respectively. In addition to these results, taking into account of mouse and human plasma protein binding ratio [see Section 4.2.2], plasma tepotinib concentrations at which an anti-tumor effect of 90% and 95% can be expected were estimated to be 390 ng/mL and 823 ng/mL, respectively.

The applicant's response:

- Findings including the following suggest that tepotinib is expected to demonstrate the efficacy at 250 mg also.
  - Based on the relationship between the exposure and efficacy [see Section 6.2.8.1], the objective response rate is considered to be roughly constant within the ranges of exposure at 250 and 300 mg (i.e., the median of AUC_{24h} at steady state [90% prediction interval (PI)] was 14.7 [8.13, 26.9] μg·h/mL at 250 mg, and 17.3 [9.57, 31.7] μg·h/mL at 300 mg).[36)]
  - In Cohort A of the VISION study, the sum of the longest diameter of tumors in patients who underwent dose reduction to 300 or 200 mg remained roughly constant after the dose reduction (Figure 3).

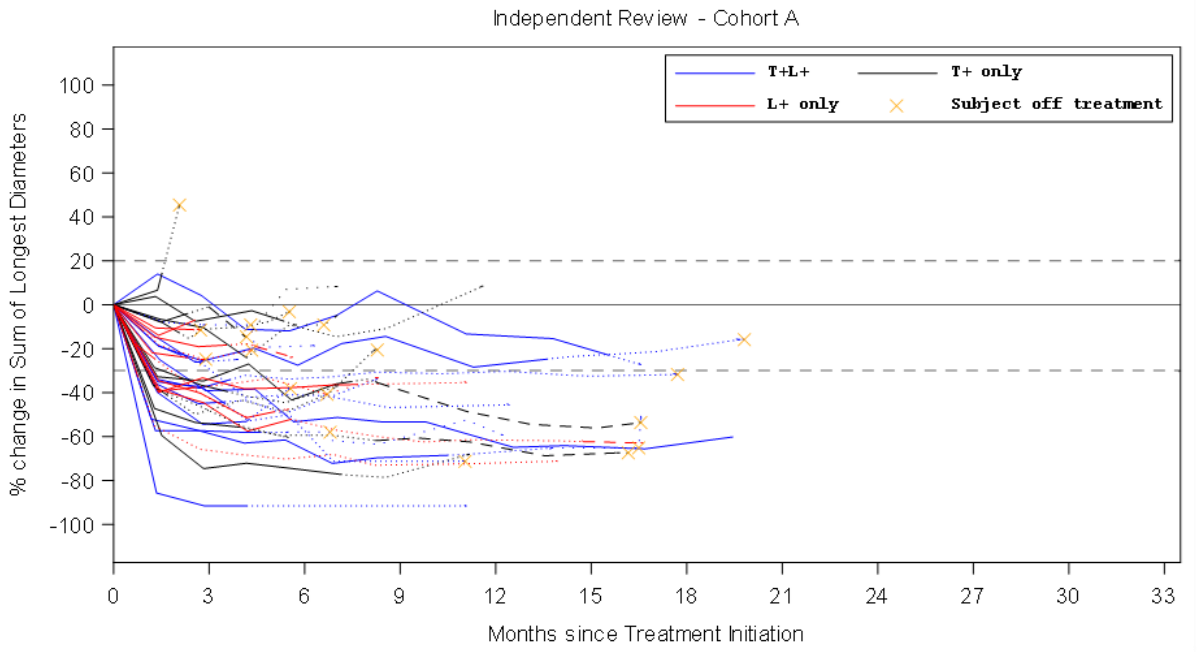

Figure 3. Change in the sum of the longest diameter of tumors over time in patients who underwent dose reduction to 300 or 200 mg
(RECIST ver.1.1, independent review, data cut-off date on [redacted], 20[redacted])

Solid line, the sum of the longest diameter of tumors at 500 mg; dotted line, the sum of the longest diameter of tumors at 300 mg; broken line, the sum of the longest diameter of tumors at 200 mg; T+L+, all patients who were assessed as having METex14 skipping mutation-positive NSCLC by TBx or LBx; T+ only, those assessed as positive by TBx only; L+ only, those assessed as positive by LBx only

- Findings including those below suggest that a reduced dose level of 250 mg is appropriate from a safety standpoint.
  - Based on the relationship between exposure and safety [see Section 6.2.8.2], the risk of developing oedema peripheral is likely to be lower at 250 mg than at 300 mg of tepotinib.
  - In Cohort A of the VISION study, all 8 patients underwent dose reduction to 200 mg due to oedema peripheral, but oedema peripheral persisted in all these patients after the dose reduction, and 4 of these patients discontinued treatment [see Section 7.R.3.4]. Taking this into consideration, a dose reduction level of 200 mg is of little clinical significance.

PMDA's discussion:

PMDA largely accepted the applicant's explanation above, and concluded that it is appropriate to specify the recommended dose adjustments in the "Precautions concerning dosage and administration" section as follows:

- If the patient has developed an adverse drug reaction following administration of tepotinib, the doses of tepotinib must be reduced, or treatment with tepotinib must be interrupted or discontinued based on the following criteria.

Table 36. Dose level reductions

Dose reduction level	Dose
Normal	500 mg once daily
First dose reduction	250 mg once daily
Second dose reduction	Discontinue treatment

Table 37. Dose adjustment criteria of tepotinib for adverse drug reactions

Adverse drug reaction	Severity	Action
ILD	Grade ≥1	Discontinue treatment
All adverse drug reactions except ILD	Grade 3	Dose interruption until recovery to Grade ≤2, or dose reduction by one level and continue treatment. If dose interruption of more than 21 days is required, discontinue treatment.
	Grade 4	Dose interruption until recovery to Grade ≤2. If dose interruption of more than 21 days is required, discontinue treatment.

7.R.6 Post-marketing investigations

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

Given that the incidence of ILD in the Japanese subjects was higher than in the non-Japanese subjects in Cohort A of the VISION study, the applicant has planned to conduct a post-marketing surveillance with ILD as a safety specification to investigate the safety and other aspects of tepotinib in clinical use after the market launch, covering all patients who will be receiving tepotinib.

A planned sample size of 125 patients has been selected in light of unresectable, advanced or recurrent METex14 skipping mutation-positive NSCLC is a very rare disease, and taking into consideration the feasibility of the survey on the basis of the size of patient population in Japan.

An observation period of 1 year from the start of treatment with tepotinib (up to 52 weeks) was selected, taking account of the time to initial onset of ILD and other adverse events in Cohort A of the VISION study.

PMDA's discussion:

As the information on tepotinib in Japanese as well as non-Japanese patients is limited, PMDA concluded that a post-marketing surveillance should be conducted to promptly collect safety data in an unbiased manner, covering all patients who will be receiving tepotinib over a specified period after the

market launch, and the safety data that are obtained should be immediately communicated to healthcare professionals.

Based on the discussions in Section "7.R.3 Safety," the safety specification for the post-marketing surveillance should include fluid retention, hepatic dysfunction, renal dysfunction, and QT interval prolongation, in addition to those specified by the applicant.

PMDA also concluded that the planned sample size and observation period should be reconsidered after examining the incidence of the above-mentioned events to be included in the safety specification for the post-marketing surveillance.

7.2 Adverse events and other findings reported in clinical studies

Deaths reported in clinical studies submitted as the safety evaluation data are presented in Section "7.1 Evaluation data." Other main adverse events are shown below.

7.2.1 Japanese phase I study (Study 03)

Adverse events occurred in 5 of 6 subjects (83.3%) in the 215 and 300 mg cohorts combined, and 6 of 6 subjects (100%) in the 500 mg cohort. Adverse events in which a causal relationship to tepotinib could not be ruled out occurred in 2 of 6 subjects (33.3%) and in 3 of 6 subjects (50.0%), respectively.

Adverse events with an incidence of ≥50% in the 215 and 300 mg cohorts combined were fatigue, constipation, and decreased appetite in 3 subjects each (50.0%); while those in the 500 mg cohort were oedema peripheral and hypoalbuminaemia in 4 subjects each (66.7%), and constipation, nausea, vomiting, and decreased appetite in 3 subjects each (50.0%).

Serious adverse events occurred in 3 of 6 subjects (50.0%) in the 215 and 300 mg cohorts combined, and 1 of 6 subjects (16.7%) in the 500 mg cohort. There were no serious adverse events that occurred in ≥2 subjects in the 215 and 300 mg cohorts combined or in the 500 mg cohort.

No adverse events led to treatment discontinuation of tepotinib.

7.2.2 Global phase Ib/II study (Study 06)

In the phase Ib part of the study, adverse events occurred in 6 of 6 subjects (100%) in the 300 mg group and 12 of 12 subjects (100%) in the 500 mg group. In the phase II randomized part of study, adverse events occurred in 31 of 31 subjects (100%) in the tepotinib/gefitinib group, and 23 of 23 subjects (100%) in the PEM/platinum-based chemotherapy group. In the non-randomized part of the study, adverse events occurred in 13 of 15 subjects (86.7%). Adverse events for which a causal relationship to the study drug could not be ruled out occurred in 6 of 6 subjects (100%) in the phase Ib 300 mg group, 9 of 12 subjects (75.0%) in the phase Ib 500 mg group, 28 of 31 subjects (90.3%) in the

tepotinib/gefitinib group, 23 of 23 subjects (100%) in the PEM/platinum-based chemotherapy group, and 11 of 15 subjects (73.3%) in the non-randomized part.

Adverse events that occurred with an incidence of ≥60% in each of the above groups/part were diarrhoea and amylase increased in 4 subjects each (66.7%) in the 300 mg group in the phase Ib part; diarrhoea in 10 subjects (83.3%) in the 500 mg group in the phase Ib part; anaemia in 16 subjects (69.6%) and nausea in 14 subjects (60.9%) in the PEM/platinum-based chemotherapy group.

Serious adverse events occurred in 4 of 6 subjects (66.7%) in the 300 mg group in the phase Ib part; 7 of 12 subjects (58.3 %) in the 500 mg group in the phase Ib part; 13 of 31 subjects (41.9%) in the tepotinib/gefitinib group in the phase II randomized part; 8 of 23 subjects (34.8%) in the PEM/platinum-based chemotherapy group in the phase II randomized part; and 5 of 15 subjects (33.3%) in the non-randomized part. Serious adverse events that occurred in ≥2 subjects in each group/part were pleural effusion in 3 subjects (9.7%) and oedema peripheral in 2 subjects (6.5%) in the tepotinib/gefitinib group in the phase II randomized part; and anaemia and neutrophil count decreased in 2 subjects each (8.7%) in the PEM/platinum-based chemotherapy group in the phase II randomized part. Among these events, a causal relationship to the study drug could not be ruled out for oedema peripheral in 2 subjects in the tepotinib/gefitinib group, and anaemia and neutrophil count decreased in 2 subjects each in the PEM/platinum-based chemotherapy group in the phase II randomized part.

Adverse events led to treatment discontinuation of the study drug in 2 of 12 subjects (16.7%) in the 500 mg group in the phase Ib part; 3 of 31 subjects (9.7 %) in the tepotinib/gefitinib group and 1 of 23 subjects (4.3%) in the PEM/platinum-based chemotherapy group in the phase II randomized part; and 2 of 15 subjects (13.3%) in the non-randomized part. There were no adverse events that led to study drug discontinuation in ≥2 subjects in any group/part.

7.2.3 Global phase II study (Cohort A of VISION study)

Adverse events occurred in 24 of 130 subjects (95.4%). Adverse events for which a causal relationship to tepotinib could not be ruled out occurred in 110 of 130 subjects (84.6%). Table 38 shows adverse events with an incidence of ≥10% in Cohort A.

Table 38. Adverse events with an incidence of ≥10% (Cohort A of VISION study)

SOC PT (MedDRA/J ver.22.0)	n (%) N = 130	
	All Grades	Grades ≥3
All adverse events	124 (95.4)	66 (50.8)
General disorders and administration site conditions		
Oedema peripheral	77 (59.2)	11 (8.5)
Asthenia	19 (14.6)	2 (1.5)
Fatigue	15 (11.5)	0 (0.0)
Gastrointestinal disorders		
Diarrhoea	40 (30.8)	1 (0.8)
Nausea	39 (30.0)	1 (0.8)
Constipation	19 (14.6)	0 (0.0)
Respiratory, thoracic and mediastinal disorders		
Dyspnoea	27 (20.8)	2 (1.5)
Cough	18 (13.8)	1 (0.8)
Pleural effusion	16 (12.3)	9 (6.9)
Investigations		
Blood creatinine increased	31 (23.8)	0 (0.0)
Amylase increased	15 (11.5)	4 (3.1)
ALT increased	14 (10.8)	6 (4.6)
Metabolism and nutrition disorders		
Hypoalbuminaemia	23 (17.7)	4 (3.1)
Decreased appetite	19 (14.6)	2 (1.5)
Musculoskeletal and connective tissue disorders		
Back pain	15 (11.5)	2 (1.5)

Serious adverse events occurred in 60 of 130 subjects (46.2%). Serious adverse events that occurred in ≥2 subjects were pleural effusion in 10 subjects (7.7%); general physical health deterioration in 7 subjects (5.4%); pneumonia and generalised oedema in 5 subjects each (3.8%); dyspnoea in 4 subjects (3.1%); disease progression, oedema peripheral, asthenia, back pain, and pulmonary embolism in 3 subjects each (2.3%); and death, ileus, lung infection, acute kidney injury, cardiac failure, spinal fracture, confusional state, and embolism in 2 subjects each (1.5%). Among these events, a causal relationship to tepotinib could not be ruled out for generalised oedema in 4 subjects; oedema peripheral in 3 subjects; asthenia and pleural effusion in 2 subjects each; and dyspnoea in 1 subject.

Adverse events led to discontinuation of tepotinib in 27 of 130 subjects (20.8%). Adverse events that led to discontinuation of tepotinib in ≥2 subjects were oedema peripheral in 5 subjects (3.8%); oedema genital in 3 subjects (2.3%); and disease progression, general physical health deterioration, and spinal fracture in 2 subjects each (1.5%). Among these events, a causal relationship to tepotinib could not be ruled out for oedema peripheral in 5 subjects and oedema genital in 2 subjects.

7.2.4 Foreign phase I study (Study 01)

Adverse events occurred in 41 of 42 subjects (97.6%) in Regimen 1; 45 of 45 subjects (100%) in Regimen 2; and 3 of 3 subjects (100%) in the 300 mg group, 39 of 42 subjects (92.9%) in the 500 mg group, 3 of 3 subjects (100%) in the 700 mg group, 7 of 7 subjects (100%) in the 1,000 mg group, and 7 of 7 subjects (100%) in the 1,400 mg group in Regimen 3. Adverse events for which a causal

relationship to tepotinib could not be ruled out occurred in 14 of 42 subjects (33.3%) in Regimen 1; 23 of 45 subjects (51.1%) in Regimen 2; and in Regimen 3, 2 of 3 subjects (66.7%) in the 300 mg group, 27 of 42 subjects (64.3%) in the 500 mg group, 1 of 3 subjects (33.3%) in the 700 mg group, 3 of 7 subjects (42.9%) in the 1,000 mg group, and 6 of 7 subjects (85.7%) in the 1,400 mg group.

Adverse events with an incidence of ≥50% in each of the above regimens/groups occurred in the following groups of Regimen 3: decreased appetite in 2 subjects (66.7%) in the 300 mg group; abdominal pain, constipation, nausea, dehydration, hyponatraemia, and oedema peripheral in 2 subjects each (66.7%) in the 700 mg group; decreased appetite in 4 subjects (57.1%) in the 1,000 mg group; and decreased appetite in 5 subjects (71.4%) and oedema peripheral in 4 subjects (57.1%) in the 1,400 mg group.

Serious adverse events occurred in 14 of 42 subjects (33.3%) in Regimen 1; 17 of 45 subjects (37.8%) in Regimen 2; and in Regimen 3, 1 of 3 subjects (33.3%) in the 300 mg group, 14 of 42 subjects (33.3%) in the 500 mg group, 2 of 3 subjects (66.7%) in the 700 mg group, 4 of 7 subjects (57.1%) in the 1,000 mg group, and 1 of 7 subjects (14.3%) in the 1,400 mg group. Serious adverse events that occurred in ≥2 subjects in each regimen/group were abdominal pain, pleural effusion, and pulmonary embolism in 2 subjects each (4.8%) in Regimen 1; small intestinal obstruction in 4 subjects (8.9%) and acute kidney injury, dehydration, pulmonary embolism, septic shock, and vomiting in 2 subjects each (4.4%) in Regimen 2; and abdominal pain in 3 subjects (7.1%) and ascites, nausea, vomiting, and mental status changes in 2 subjects each (4.8%) in the 500 mg group, and constipation in 2 subjects (28.6%) in the 1,000 mg group in Regimen 3. Among these events, a causal relationship to tepotinib could not be ruled out for vomiting in 1 subject in Regimen 2.

Adverse events led to discontinuation of tepotinib in 3 of 42 subjects (7.1%) in Regimen 1; 4 of 45 subjects (8.9%) in Regimen 2; and 1 of 3 subjects (33.3%) in the 300 mg group, 9 of 42 subjects (21.4%) in the 500 mg group, 1 of 3 subjects (33.3%) in the 700 mg group, 1 of 7 subjects (14.3%) in the 1,000 mg group, and 1 of 7 subjects (14.3%) in the 1,400 mg group in Regimen 3. Adverse events that led to discontinuation of tepotinib in ≥2 subjects in each regimen/group were fatigue, ascites, abdominal pain, and prostatic specific antigen increased in 2 subjects each (4.8%) in the 500 mg group of Regimen 3, and a causal relationship to tepotinib was denied for all these events.

7.2.5 Foreign phase I study (Study 02)

Adverse events occurred in 19 of 28 subjects (67.9%). Adverse events for which a causal relationship to tepotinib could not be ruled out occurred in 6 of 28 subjects (21.4%). Adverse events with an incidence of ≥10% were upper respiratory tract infection in 5 subjects (17.9%); amylase increased and back pain in 4 subjects each (14.3%); and lipase increased and headache in 3 subjects each (10.7%).

There were no serious adverse events, or adverse events leading to treatment discontinuation.

7.2.6 Foreign phase I study (Study 07)

Adverse events occurred in 3 of 6 subjects (50.0%) in Part A, 6 of 6 subjects (100.0%) in Part B, and 14 of 15 subjects (93.3%) in Part C. Adverse events for which a causal relationship to tepotinib could not be ruled out occurred in 0 subjects in Part A, 2 of 6 subjects (33.3%) in Part B, and 5 of 15 subjects (33.3%) in Part C. Adverse events that occurred in ≥2 subjects in each part were abdominal pain and presyncope in 2 subjects each (33.3%) in Part B; and headache in 6 subjects (40.0%), abdominal pain in 4 subjects (26.7%), abdominal distension in 3 subjects (20.0%), and somnolence, diarrhoea, nasopharyngitis, rhinitis, and myalgia in 2 subjects each (13.3%) in Part C.

There were no serious adverse events, or adverse events leading to treatment discontinuation.

7.2.7 Foreign phase I study (Study 012)

Adverse events occurred in 14 of 24 subjects (58.3%). Adverse events for which a causal relationship to tepotinib could not be ruled out occurred in 6 of 24 subjects (25.0%). There were no adverse events that occurred with an incidence of ≥10%.

There were no serious adverse events.

Adverse events led to discontinuation of tepotinib in 2 of 24 subjects (8.3%). There were no adverse events that led to discontinuation of tepotinib in ≥2 subjects.

7.2.8 Foreign phase I study (Study 028)

Adverse events occurred in 1 of 6 healthy adult subjects (16.7%), and 2 of 6 subjects (33.3%) in the moderate hepatic impairment group. Adverse events for which a causal relationship to tepotinib could not be ruled out occurred in 1 of 6 healthy adult subjects (16.7%) and 1 of 6 subjects (16.7%) in the moderate hepatic impairment group.

There were no adverse events that occurred in ≥2 subjects. No serious adverse events occurred, or adverse events leading to discontinuation of tepotinib.

7.2.9 Foreign phase I study (Study 030)

Adverse events occurred in 10 of 12 subjects (83.3%). Adverse events for which a causal relationship to tepotinib could not be ruled out occurred in 8 of 12 subjects (66.7%).

Adverse events with an incidence of ≥30% were headache in 5 subjects (41.7%), abdominal pain upper and diarrhoea in 4 subjects each (33.3%).

There were no serious adverse events, or adverse events leading to discontinuation of tepotinib.

7.2.10 Foreign phase I study (Study 032)

Adverse events occurred in 15 of 20 subjects (75.0%). Adverse events for which a causal relationship to tepotinib could not be ruled out occurred in 14 of 20 subjects (70.0%).

Adverse events with an incidence of ≥30% were diarrhoea in 11 subjects (55.0%), abdominal pain upper in 7 subjects (35.0%), and nausea in 6 subjects (30.0%).

There were no serious adverse events, or adverse events leading to discontinuation of tepotinib.

7.2.11 Foreign phase I study (Study 039)

Adverse events occurred in 4 of 12 subjects (33.3%). Adverse events for which a causal relationship to tepotinib could not be ruled out occurred in 2 of 12 subjects (16.7%).

There were no adverse events that occurred in ≥2 subjects. There were no serious adverse events, or adverse events leading to discontinuation of tepotinib.

7.2.12 Foreign phase I study (Study 044)

Adverse events occurred in 25 of 40 subjects (62.5%) in Part A, 11 of 14 subjects (78.6%) in Part B, and 9 of 12 subjects (75.0%) in Part C. Adverse events for which a causal relationship to tepotinib could not be ruled out occurred in 17 of 40 subjects (42.5%) in Part A, 6 of 14 subjects (42.9%) in Part B, and 7 of 12 subjects (58.3%) in Part C.

Adverse events with an incidence of ≥20% in each part were headache in 10 subjects (25.0%) in Part A; headache in 4 subjects (28.6%) and abdominal pain in 3 subjects (21.4%) in Part B; and headache in 6 subjects (50.0%) and abdominal pain upper and pain in extremity in 3 subjects each (25.0%) in Part C.

Femoral neck fracture in 1 of 14 subjects (7.1%) in Part B was classified as a serious adverse event, but a causal relationship to tepotinib was denied for the event. In Parts A and C, no serious adverse events occurred.

There were no adverse events leading to discontinuation of tepotinib.

7.2.13 Foreign phase Ib/II study (Study 04)

In the phase Ib part, adverse events occurred in 7 of 7 subjects (100%) in the 300 mg group, 14 of 14 subjects (100%) in the 500 mg group, and 6 of 6 subjects (100%) in the 1,000 mg group. In the phase II part, adverse events occurred in 45 of 45 subjects (100%) in the tepotinib group and 43 of 44 subjects (97.7%) in the sorafenib group. Adverse events for which a causal relationship to the study drugs could not be ruled out occurred in 6 of 7 subjects (85.7%) in the 300 mg group, 10 of 14 subjects (71.4%) in the 500 mg group, 6 of 6 subjects (100%) in the 1,000 mg group in phase Ib; 38 of 45 subjects (84.4%) in the tepotinib group and 43 of 44 subjects (97.7%) in the sorafenib group in the phase II part.

Adverse events with an incidence of ≥50% in each of the above groups were as follows: in the phase Ib part, abdominal distension and AST increased in 4 subjects each (57.1%) in the 300 mg group; abdominal pain in 7 subjects (50%) in the 500 mg group; constipation, diarrhoea, AST increased, and hypoalbuminaemia in 4 subjects each (66.7%), and ascites, ALT increased, blood alkaline phosphatase (ALP) increased, and blood creatinine increased in 3 subjects each (50.0%) in the 1,000 mg group; and in the phase II part, palmar-plantar erythrodysaesthesia syndrome in 27 subjects (61.4%) in the sorafenib group.

Serious adverse events occurred, in the phase Ib part, in 2 of 7 subjects (28.6%) in the 300 mg group, 9 of 14 subjects (64.3%) in the 500 mg group, 4 of 6 subjects (6.7%) in the 1,000 mg group; while in the phase II part, in 23 of 45 subjects (51.1%) in the tepotinib group and in 11 of 44 subjects (25.0%) in the sorafenib group. Serious adverse events that occurred in ≥2 subjects in each group were in the following groups in the phase II part: disease progression in 7 subjects (15.6%) and abdominal pain, ascites, hepatic encephalopathy, oedema peripheral, and paraesthesia in 2 subjects each (4.4%) in the tepotinib group; and abdominal pain and disease progression in 2 subjects each (4.5%) in the sorafenib group. Among these events, a causal relationship to tepotinib could not be ruled out for ascites and oedema peripheral in 2 subjects each and disease progression in 1 subject in the tepotinib group in the phase II part.

Adverse events led to study drug discontinuation in 3 of 14 subjects (21.4%) in the 500 mg group in the phase Ib part; 7 of 45 subjects (15.6%) in the tepotinib group, and 6 of 44 subjects (13.6%) in the sorafenib group in the phase II part. Adverse events that led to study drug discontinuation in ≥2 subjects in each group were fatigue in 2 subjects (4.4%) in the tepotinib group, and diarrhoea in 2 subjects (4.5%) in the sorafenib group in the phase II part. Among these events, a causal relationship to the study drugs could not be ruled out for the following events: fatigue in 1 subject in the tepotinib group, and diarrhoea in 2 subjects in the sorafenib group in the phase II part.

7.2.14 Foreign phase Ib/II study (Study 05)

Adverse events occurred in 4 of 4 subjects (100%) in the 300 mg group, and 12 of 13 subjects (92.3%) in the 500 mg group in the phase I part; and 48 of 49 subjects (98.0%) in the phase II part. Adverse events for which a causal relationship to the study drug could not be ruled out occurred in 3 of 4 subjects (75.0%) in the 300 mg group and 11 of 13 subjects (84.6%) in the 500 mg group in the phase I part; and 41 of 49 subjects (83.7%) in the phase II part.

Adverse events with an incidence of ≥50% in each of the above groups/part were as follows: in the phase I part, abdominal pain and oedema peripheral in 3 subjects each (75.0%) and constipation, vomiting, ALT increased, and blood ALP increased in 2 subjects each (50.0%) in the 300 mg group; and oedema peripheral in 10 subjects (76.9%) in the 500 mg group; and in the phase II part, oedema peripheral in 32 subjects (65.3%).

Serious adverse events occurred in 2 of 4 subjects (50.0%) in the 300 mg group and 5 of 13 subjects (38.5%) in the 500 mg group in the phase I part; and 21 of 49 subjects (42.9%) in the phase II part. Serious adverse events that occurred in ≥2 subjects in each group/part were ascites and oedema peripheral in 2 subjects each (15.4%) in the 500 mg group in the phase I part; and disease progression in 7 subjects (14.3%) and acute kidney injury and ascites in 3 subjects each (6.1%) in the phase II part. Among these events, a causal relationship to tepotinib could not be ruled out for oedema peripheral in 2 subjects in the 500 mg group in the phase I part and acute kidney injury in 1 subject in the phase II part.

Adverse events led to discontinuation of tepotinib in 1 of 4 subjects (25.0%) in the 300 mg group and 2 of 13 subjects (15.4%) in the 500 mg group in the phase I part; and 17 of 49 subjects (34.7%) in the phase II part. Adverse events that led to discontinuation of tepotinib in ≥2 subjects in each group/part were ascites in 5 subjects (10.2%), oedema peripheral in 4 subjects (8.2%), and hyponatraemia and localised oedema in 2 subjects each (4.1%) in the phase II part. Among these events, a causal relationship to tepotinib could not be ruled out for oedema peripheral in 4 subjects, localised oedema in 2 subjects, and ascites and hyponatraemia in 1 subject each in the phase II part.

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 compliance inspection and a data integrity assessment in accordance with the provisions of the Act on Securing Quality, Efficacy and Safety of Pharmaceuticals, Medical Devices, Regenerative and Cellular Therapy Products, Gene Therapy Products, and Cosmetics. On the basis of the inspection and assessment, PMDA concluded that there were no obstacles to conducting its review based on the application documents submitted.

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

The new drug application data (CTD 5.3.5.1.1, CTD 5.3.5.4.3) were subjected to an on-site GCP inspection, in accordance with the provisions of the Act on Securing Quality, Efficacy and Safety of Pharmaceuticals, Medical Devices, Regenerative and Cellular Therapy Products, Gene Therapy Products, and Cosmetics. On the basis of the inspection, 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 tepotinib hydrochloride hydrate has a certain level of efficacy in the treatment of unresectable, advanced or recurrent METex14 skipping mutation-positive NSCLC, and that tepotinib has acceptable safety in view of its benefits. Tepotinib hydrochloride hydrate is a drug with a new active ingredient, which is considered to be a MET tyrosine

kinase inhibitor. Tepotinib hydrochloride hydrate is clinically meaningful because it offers a new treatment option for patients with unresectable, advanced or recurrent METex14 skipping mutation-positive NSCLC. PMDA considers that the indication and post-marketing investigations, etc. require further discussions.

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

Review Report (2)

February 6, 2020

Product Submitted for Approval

Brand Name	Tepmetko Tablets 250 mg
Non-proprietary Name	Tepotinib Hydrochloride Hydrate
Applicant	Merck Biopharma Co., Ltd.
Date of Application	November 12, 2019

List of Abbreviations

See Appendix.

1. Content of the Review

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

1.1 Efficacy

In Cohort A of the VISION study, a global phase II study, conducted in patients with unresectable, advanced or recurrent METex14 skipping mutation-positive[51)] NSCLC, the primary endpoint was the objective response rate as assessed by an independent review committee according to RECIST ver.1.1. The objective response rate [95% CI] was 45.5% [33.1, 58.2] (30 of 66 subjects) for LBx- group, 43.3% [30.6, 56.8] (26 of 60 subjects) for TBx- group, and 42.4% [32.5, 52.8] (42 of 99 subjects) for LBx/TBx- group.

In view of the discussions in Section "7.R.2 Efficacy" in Review Report (1), and taking into consideration that tepotinib is an inhibitor targeting METex14 skipping alterations, an oncogenic driver that plays a key role in oncogenesis, findings including the objective response rate shown above demonstrate that tepotinib has a certain level of efficacy for the treatment of patients with such alterations.

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

51) Eligible patients were those who were confirmed as having METex14 skipping alterations by LBx or TBx or both.

1.2 Safety

In view of the discussions in Section "7.R.3 Safety" in Review Report (1), PMDA concluded that adverse events that require particular attention when tepotinib is used in patients with unresectable, advanced or recurrent METex14 skipping mutation-positive NSCLC are ILD, fluid retention (including hypoalbuminaemia), hepatic dysfunction, renal dysfunction, and QT/QTc interval prolongation, and that attention should be paid to the possible development of these adverse events during treatment with tepotinib.

Although the use of tepotinib requires particular caution for the onset of adverse events mentioned above, PMDA concluded that tepotinib is tolerable as long as appropriate steps, including monitoring and management of adverse events, and dose interruption, are taken by physicians with sufficient knowledge of and experience with cancer chemotherapy.

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

1.3 Clinical positioning and indication

In view of the discussion in Section "7.R.4 Clinical positioning and indication" of Review Report (1), PMDA concluded that it is appropriate to specify the indication of tepotinib as "unresectable, advanced or recurrent *MET* exon 14 skipping mutation-positive non-small cell lung cancer," and to include the following cautionary statements in the "Precautions concerning indication" section.

Precautions concerning indications

- The efficacy and safety of tepotinib as adjuvant therapy have not been established.
- Tepotinib should only be administered to patients who have been confirmed as having *MET* exon 14 skipping alterations by highly experienced pathologists or testing at laboratories. Approved *in vitro* diagnostics should be used for diagnostic testing.

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

Based on the above, PMDA instructed the applicant to include the above statements in the "Indication" and "Precautions concerning indication" sections of the package insert, and the applicant agreed with the instruction.

1.4 Dosage and administration

In view of the discussions in Section "7.R.5 Dosage and administration" in Review Report (1), PMDA concluded that it is appropriate to specify the dosage and administration of tepotinib as "The usual adult dosage is 500 mg of tepotinib hydrochloride hydrate administered orally once daily after a meal. The dose may be reduced according to the patient's condition," and to include the following cautionary statement in the "Precautions concerning dosage and administration" section.

Precautions Concerning Dosage and Administration

- The efficacy and safety of tepotinib in combination with other antineoplastic agents have not been established.
- If adverse drug reaction occurred following the administration of tepotinib, the doses of tepotinib must be reduced, or treatment with tepotinib must be interrupted or discontinued based on the following criteria.

Table 39. Dose level reductions

Dose reduction level	Dose
Normal	500 mg once daily
First dose reduction	250 mg once daily
Second dose reduction	Discontinue treatment

Table 40. Dose adjustment criteria of tepotinib for adverse drug reactions

Adverse drug reaction	Severity	Action
ILD	Grade ≥1	Discontinue treatment
All adverse drug reactions except ILD	Grade 3	Dose interruption until recovery to Grade ≤2, or dose reduction by one level and continue treatment. If dose interruption of more than 21 days is required, discontinue treatment.
	Grade 4	Dose interruption until recovery to Grade ≤2. If dose interruption of more than 21 days is required, discontinue treatment.

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

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 of the package insert, and the applicant agreed with the instruction.

1.5 Risk management plan (draft)

The applicant has planned to conduct a post-marketing surveillance to investigate the safety and other aspects of tepotinib in clinical use after the market launch, covering all patients who will be receiving tepotinib with a planned sample size of 125 patients and an observation period of 1 year (up to 52 weeks) from the start of treatment with tepotinib.

In view of the discussions in Section "7.R.6 Post-marketing investigations" in Review Report (1), PMDA concluded that a post-marketing surveillance should be conducted to promptly collect safety data in an unbiased manner, covering all patients who will be receiving tepotinib for a specified period after the market launch, and the safety data that are should be immediately communicated to healthcare professionals.

PMDA also concluded the post-marketing surveillance plan as follows:

- The safety specification for the post-marketing surveillance should include ILD, fluid retention, hepatic dysfunction, renal dysfunction, and QT interval prolongation.

- The planned sample size and observation period should be reconsidered after examining the incidence in the clinical studies for the events to be included in the safety specification for the post-marketing surveillance.

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

Based on the above, PMDA instructed the applicant to reconsider the post-marketing surveillance plan for tepotinib, and the applicant responded as follows:

- The safety specification for the post-marketing surveillance will include ILD, fluid retention, hepatic dysfunction, renal dysfunction, and QT interval prolongation.
- Taking into account the incidence in the clinical studies for the events to be included in the safety specification, the planned sample size will be 100 patients, and the observation period will be 1 year (up to 52 weeks).

PMDA accepted the applicant's response.

Based on the above discussions, PMDA concluded that the risk management plan (draft) for tepotinib should include the safety specification presented in Table 41, and that the applicant should conduct the additional pharmacovigilance activities and risk minimization activities presented in Tables 42 and 43.

Table 41. Safety and efficacy specifications in the risk management plan (draft)

Safety specification		
Important identified risks	Important potential risks	Important missing information
• ILD • Fluid retention • Hepatic dysfunction • Renal dysfunction	• QT interval prolongation	None
Efficacy specification		
None		

Table 42. Summary of additional pharmacovigilance activities, surveillance/studies on efficacy, and risk minimization activities included under the risk management plan (draft)

Additional pharmacovigilance activities	Surveillance/studies on efficacy	Additional risk minimization activities
• Early post-marketing phase vigilance • Use-results survey (all-case surveillance) • Post-marketing clinical study (ongoing VISION study)	None	• Disseminate data from early post-marketing phase vigilance • Develop and disseminate information materials for healthcare professionals • Develop and disseminate information materials for patients

Table 43. Outline of post-marketing surveillance (draft)

Objective	To investigate the safety and other aspects of tepotinib in clinical use
Survey method	All-case surveillance
Population	All patients receiving tepotinib
Observation period	1 year (up to 52 weeks)
Planned sample size	100 patients
Main survey items	Safety specification: ILD, fluid retention, hepatic dysfunction, renal dysfunction, and QT interval prolongation Other main survey items: patient characteristics (e.g., sex, age, disease stage, complications, prior therapy), status of treatment with tepotinib, co-administered drugs, adverse events, and best overall response, etc.

2. Overall Evaluation

As a result of the above review, PMDA has concluded that the product may be approved after modifying the proposed indication and dosage and administration as shown below, with the following conditions for approval, provided that necessary precautionary statements are included in the package insert and information on the proper use of the product is appropriately disseminated after the market launch, and that tepotinib is properly used only under the supervision of physicians with sufficient knowledge of and experience with cancer chemotherapy at medical institutions with adequate facilities to respond to emergencies. Since tepotinib is designated as an orphan drug, the re-examination period is 10 years. The product is not classified as a biological product or a specified biological product. The drug substance and drug product are both classified as powerful drugs.

Indication

Unresectable, advanced or recurrent *MET* exon 14 skipping mutation-positive non-small cell lung cancer

Dosage and Administration

The usual adult dosage is 500 mg of tepotinib hydrochloride hydrate administered orally once daily after a meal. The dose may be reduced according to the patient's condition.

Approval Conditions

1. The applicant is required to develop and appropriately implement a risk management plan.
2. Because the number of patients studied in Japan is very limited, the applicant is required to conduct a post-marketing use-results survey covering all patients treated with the product, until data from a specified number of patients will be collected, in order to obtain information on the characteristics of patients treated with the product, to collect data on the safety and efficacy of the product as soon as possible, and to take necessary measures to ensure proper use of the product.

Warnings

1. Tepotinib should be administered only to patients who are considered eligible for its use under the supervision of physicians with sufficient knowledge of and experience with cancer chemotherapy at medical institutions with adequate facilities to respond to emergencies. Prior to the start of

therapy, the benefits and risks of the therapy should be thoroughly explained to the patient or his/her family members and consent must be obtained.

2. There have been reports of patients who died after experiencing interstitial lung disease.
   Patients should be closely monitored for initial symptoms (e.g., shortness of breath, dyspnoea, coughing, and fever) and examined by regular chest imaging and other tests. In the event of an abnormality being found, the administration of tepotinib should be discontinued and appropriate actions such as the introduction of corticosteroid therapy should be taken.

Contraindication

Patients with a history of hypersensitivity to the ingredients of tepotinib.

Precautions Concerning Indications

1. The efficacy and safety of tepotinib as adjuvant therapy have not been established.
2. Tepotinib should only be administered to patients who have been confirmed as having *MET* exon 14 skipping alterations by highly experienced pathologists or testing at laboratories. Approved *in vitro* diagnostics should be used for diagnostic testing.

Precautions Concerning Dosage and Administration

1. The efficacy and safety of tepotinib in combination with other antineoplastic agents have not been established.
2. If adverse drug reaction occurred following the administration of tepotinib, the doses of tepotinib must be reduced, or treatment with tepotinib must be interrupted or discontinued based on the following criteria.

Dose level reductions

Dose reduction level	Dose
Normal	500 mg once daily
First dose reduction	250 mg once daily
Second dose reduction	Discontinue treatment

Dose adjustment criteria of tepotinib for adverse drug reactions

Adverse drug reaction	Severity[Note)]	Action
Interstitial lung disease	Grade ≥1	Discontinue treatment
All adverse drug reactions except interstitial lung disease	Grade 3	Dose interruption until recovery to Grade ≤2, or dose reduction by one level and continue treatment. If dose interruption of more than 21 days is required, discontinue treatment.
	Grade 4	Dose interruption until recovery to Grade ≤2. If dose interruption of more than 21 days is required, discontinue treatment.

Note) The grade classification is based on Common Terminology Criteria for Adverse Events (CTCAE) version 4.0.

Appendix

List of Abbreviations

A/G	albumin/globulin
ALK	anaplastic lymphoma kinase
ALP	alkaline phosphatase
ALT	alanine aminotransferase
application	marketing application
AST	aspartate aminotransferase
ATP	adenosine triphosphate
BA	bioavailability
BCRP	breast cancer resistance protein
BID	bis in die
BSEP	bile salt export pump
CBDCA	carboplatin
CDDP	cisplatin
CF	capsule formulation
CI	confidence interval
$C_{max,ss}$	maximum plasma concentration at steady state
CPP	critical process parameter
CQA	critical quality attribute
CR	complete response
CYP	cytochrome P450
^{14}C-tepotinib	^{14}C-radiolabeled tepotinib hydrochloride hydrate
DABE	dabigatran etexilate
DLT	dose-limiting toxicity
DMSO	dimethyl sulfoxide
efflux ratio	the ratio of permeability coefficient in the excretion direction to that in the absorption direction
EGFR	epidermal growth factor receptor
EGFR-TKI	epidermal growth factor receptor-tyrosine kinase inhibitor
ELISA	enzyme-linked immunosorbent assay
ERK1/2	extracellular signal-regulated kinase 1 and 2
hERG	human *ether-a-go-go*-related gene
GAB1	growth factor receptor bound protein 2-associated protein 1
GC	gas chromatography
GGT	gamma-glutamyltransferase
GLDH	glutamate dehydrogenase
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
ICH Q1E Guidelines	“Guideline on Evaluation of Stability Data” (PFSB/ELD Notification No. 0603004 dated June 3, 2003)
IHC	immunohistochemistry
ILD	interstitial lung disease
INR	international normalized ratio
IR	infrared absorption spectrum
IRAK	interleukin-1 receptor-associated kinase
LBx	liquid biopsy testing

LBx group	the group comprising patients who were assessed as having *MET* exon 14 skipping alterations by liquid biopsy testing
LBx/TBx group	the group comprising patients who were assessed as having *MET* exon 14 skipping alterations by liquid biopsy testing or tumor biopsy testing or both
LC	liquid chromatography
MATE	multidrug and toxin extrusion
MedDRA	Medical Dictionary for Regulatory Activities
MET	mesenchymal-epithelial transition factor
METex14	exon 14 of *MET* gene
mRNA	messenger ribonucleic acid
MRP	multidrug resistance associated protein
MSC2571109A	a metabolite (ketone) formed by oxidation of tepotinib (R-enantiomer)
MTD	maximum tolerated dose
NADPH	nicotinamide adenine dinucleotide phosphate hydrogen
NCI ODG	National Cancer Institute organ dysfunction group
NE	not evaluable
NMR	nuclear magnetic resonance spectrum
NSCLC	non-small cell lung cancer
OAT	organic anion transporter
OATP	organic anion transporting polypeptide
OCT	organic cation transporter
OS	overall survival
$P_{app\ A \rightarrow B}$	apparent permeability in apical to basal direction
PD	progressive disease
PEM	pemetrexed sodium hydrate
PI	prediction interval
P-gp	P-glycoprotein
PK	pharmacokinetic/pharmacokinetics
platinum-based chemotherapy	CBDCA or CDDP
platinum-based/PEM	pemetrexed combined with platinum-based chemotherapy
PMDA	Pharmaceuticals and Medical Devices Agency
PR	partial response
PT	preferred term
PTP	press through packaging
QbD	quality by design
QD	quaque die
RECIST	Response Evaluation Criteria in Solid Tumors
RP2D	recommended Phase II dose
SCID mouse	severe combined immunodeficient mouse
SD	stable disease
SDH	sorbitol dehydrogenase
sorafenib	sorafenib tosilate
Study 01	Study EMR200095-001
Study 02	Study EMR200095-002
Study 03	Study EMR200095-003
Study 04	Study EMR200095-004

Study 05	Study EMR200095-005
Study 06	Study EMR200095-006
Study 07	Study EMR200095-007
Study 012	Study MS200095-0012
Study 028	Study MS200095-0028
Study 030	Study MS200095-0030
Study 032	Study MS200095-0032
Study 039	Study MS200095-0039
Study 044	Study MS200095-0044
TBx	tissue biopsy testing
TBx group	the group comprising patients who were assessed as having *MET* exon 14 skipping alterations by tumor biopsy testing
tepotinib	tepotinib hydrochloride hydrate
tepotinib/gefitinib	tepotinib administered in combination with gefitinib
TF	tablet formulation
T790M	a mutation of the epidermal growth factor receptor (EGFR) substituting a threonine with methionine at position 790 of exon 20
3T3 NRU	*in vitro* 3T3 neutral red uptake phototoxicity test
TRK	tropomyosin receptor kinase
UDPGA	uridine diphosphate glucuronic acid
UGT	uridine diphosphate glucuronosyl transferase
VISION study	Study MS200095-0022