Report on the Deliberation Results

June 4, 2020
Pharmaceutical Evaluation Division, Pharmaceutical Safety and Environmental Health Bureau
Ministry of Health, Labour and Welfare

Brand Name	Tabrecta Tablets 150 mg, Tabrecta Tablets 200 mg
Non-proprietary Name	Capmatinib Hydrochloride Hydrate (JAN*)
Applicant	Novartis Pharma K.K.
Date of Application	December 12, 2019

Results of Deliberation

In its meeting held on May 28, 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 of extremely limited number of patients participating in clinical studies in Japan, the applicant is required to conduct a post-marketing use-results survey covering all patients treated with the product, until data from a certain number of patients are collected, in order to understand the characteristics of patients treated with the product, promptly collect data on the safety and efficacy of the product, and take necessary measures to ensure the proper use of the product.

**Japanese Accepted Name (modified INN)*

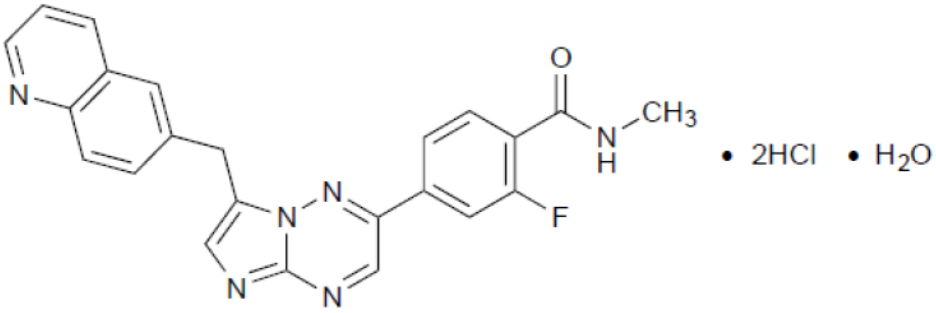
Review Report

May 18, 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	Tabrecta Tablets 150 mg, Tabrecta Tablets 200 mg
Non-proprietary Name	Capmatinib Hydrochloride Hydrate
Applicant	Novartis Pharma K.K.
Date of Application	December 12, 2019
Dosage Form/Strength	Tablets, each containing Capmatinib Hydrochloride Hydrate equivalent to 150 or 200 mg of capmatinib.
Application Classification	Prescription drug, (1) Drug with a new active ingredient

Chemical Structure



Molecular formula: $C_{23}H_{17}FN_6O \cdot 2HCl \cdot H_2O$

Molecular weight: 503.36

Chemical name: 2-Fluoro-*N*-methyl-4-{7-[(quinolin-6-yl)methyl]imidazo[1,2-*b*][1,2,4]triazin-2-yl}benzamide dihydrochloride monohydrate

Items Warranting Special Mention

Orphan drug (Orphan Drug Designation No. 438 of 2019 [*31 yaku*]; PSEHB/PED Notification No. 0530-12 dated May 30, 2019, by the Pharmaceutical Evaluation Division, Pharmaceutical Safety and Environmental Health Bureau, Ministry of Health, Labour and Welfare)

Reviewing Office Office of New Drug V

Results of Review

On the basis of the data submitted, PMDA has concluded that the product has a certain level of efficacy in the treatment of *MET* exon 14 skipping mutation-positive unresectable advanced or recurrent non-small cell lung cancer, and that the product has acceptable safety in view of its benefits (see Attachment).

As a result of its review, PMDA has concluded that the product may be approved for the indication and dosage and administration shown below, with the following conditions. Hepatic dysfunction, interstitial lung disease (ILD), renal dysfunction, fluid retention, acute pancreatitis, and photosensitivity are subject to further investigation.

Indication

MET exon 14 skipping mutation-positive unresectable advanced or recurrent non-small cell lung cancer

Dosage and Administration

The usual adult dosage is 400 mg of capmatinib administered orally twice daily. The dosage should be reduced as appropriate, according to the patient's condition.

Approval Conditions

1. The applicant is required to develop and appropriately implement a risk management plan.
2. Because of extremely limited number of patients participating in clinical studies in Japan, the applicant is required to conduct a post-marketing use-results survey covering all patients treated with the product, until data from a certain number of patients are collected, in order to understand the characteristics of patients treated with the product, promptly collect data on the safety and efficacy of the product, and take necessary measures to ensure the proper use of the product.

Attachment

Review Report (1)

April 3, 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	Tabrecta Tablets 150 mg, Tabrecta Tablets 200 mg
Non-proprietary Name	Capmatinib Hydrochloride Hydrate
Applicant	Novartis Pharma K.K.
Date of Application	December 12, 2019
Dosage Form/Strength	Tablets, each containing 176.55 or 235.40 mg of capmatinib hydrochloride anhydrous (150 or 200 mg of capmatinib).

Proposed Indication

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

Proposed Dosage and Administration

The usual adult dosage is 400 mg of capmatinib administered orally twice daily. The dosage should be reduced as appropriate, 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

The mesenchymal-epithelial transition factor (MET) is a receptor tyrosine kinase that plays a role in embryogenesis, organogenesis, and tissue repair (*Trends Cell Biol*. 1998; 8: 404-10, etc.). Mutation in *MET* (*MET* exon 14 skipping [METex14] mutations) results in aberrant messenger ribonucleic acid (mRNA) splicing, deletion of exon 14 from the mRNA transcript. A MET mutant protein translated from this mRNA is thought to activate downstream signaling pathways and cause increased cell proliferation, etc. through decreased protein degradation and their stabilization on cell surface (*J Natl Cancer Inst*. 2017; 109: 1-12, etc.). This particular mutant variant is one of the principal causes of oncogenesis, etc. and has been reported to contribute to the proliferation/survival of tumor cells and the tumorigenesis of normal cells (*Cancer Res*. 2017; 77: 4498-505, etc.).

Capmatinib Hydrochloride Hydrate (capmatinib) is a low molecular compound discovered by Incyte (the US). Capmatinib is expected to exhibit anti-tumor activity in non-small cell lung cancer (NSCLC) with METex14 mutation by inhibiting the phosphorylation of MET and downstream signaling proteins.

1.2 Development history etc.

Outside Japan, Incyte (the US) initiated a phase I study in patients with advanced solid tumors in January 2010 (Study X2101T). Then, the applicant initiated a global phase II study in patients with METex14 mutation-positive unresectable advanced or recurrent NSCLC, etc. (Study A2201) in June 2015.

In the US, a new drug application for capmatinib was filed based mainly on the results from Study A2201 in December 2019, and is under review.

As of February 2020, capmatinib has not been approved in any country or region.

In Japan, the applicant initiated a phase I study in patients with advanced solid tumors (Study X1101) in February 2012. Patient enrollment in Study A2201 began in [redacted] 20[redacted].

The applicant recently submitted an application for marketing approval of capmatinib based mainly on the results from Study A2201.

Capmatinib was designated as an orphan drug (Orphan Drug Designation No. 438 of 2019 [*31 yaku*]) for the intended indication of "*MET* mutation-positive non-small cell lung cancer" in May 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 yellow powder. Its description, solubility, pH, melting point, dissociation constant, distribution coefficient, hygroscopicity, optical activity, and differential scanning calory were determined. In the drug substance, [redacted] such as [redacted] were identified, but the commercial synthesis yields the crystalline form [redacted] (capmatinib dihydrochloride monohydrate). Stability studies demonstrated no changes in the crystalline form [redacted] (capmatinib dihydrochloride monohydrate).

Its chemical structure was elucidated by elemental analysis, mass spectrometry, ultraviolet-visible spectroscopy, infrared spectroscopy (IR), nuclear magnetic resonance spectroscopy (NMR) (^{1}H-NMR and ^{13}C-NMR), and single-crystal X-ray crystallography.

2.1.2 Manufacturing process

The drug substance is synthesized using (a) [redacted], (b) [redacted], and (c) [redacted] as starting materials.

Quality by design (QbD) approaches were used to determine the proven acceptable ranges for manufacturing process parameters through quality risk assessment, etc., and a quality control strategy was established.

Step (a) to perform [redacted] and Step (b) to obtain [redacted] are defined as critical steps. Process control items and values were established for each reaction step.

2.1.3 Control of drug substance

The proposed specifications for the drug substance consist of content, description, identification (IR and X-ray powder diffraction method), purity (heavy metals [inductively coupled plasma mass spectrometry], related substances [liquid chromatography [LC]], [redacted] [LC], [redacted] [gas chromatography [GC]], [redacted] [GC]), water content, residue on ignition, microbial limits, particle size, and assay (LC).

The hydrochloric acid content was included in the specifications in the course of regulatory review.

2.1.4 Stability of drug substance

The stability studies on the drug substance are shown in Table 1. The photostability data showed that the drug substance is photosensitive.

Table 1. Stability studies on drug substance

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

Based on the above, a re-test period of [redacted] months was proposed for the drug substance when packaged in double polyethylene bags and stored in a metal drum, protected from light [redacted]. The long-term testing is to be continued up to 60 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 containing 176.55 or 235.40 mg of capmatinib hydrochloride anhydrous (150 or 200 mg, respectively, of capmatinib) and the following excipients: microcrystalline cellulose, D-mannitol, crospovidone, povidone, magnesium stearate, colloidal silicon dioxide, sodium lauryl sulfate, [redacted], [redacted], [redacted] ([redacted]-mg tablet only), and [redacted] ([redacted]-mg tablet only).

2.2.2 Manufacturing process

The drug product is manufactured through a process comprised of blending 1, [redacted] granulation, sieving 1, drying, sieving 2, blending 2, final blending, tableting, film coating, and packaging/labeling.

A quality control strategy was established by a QbD approach based on the following studies etc. (Table 2).

- Identification of critical quality attributes (CQAs)
- Identification of critical process parameters (CPPs) through quality risk assessment and design of experiments, and determination of the proven acceptable ranges for manufacturing process parameters
- Use of real time release testing (RTRT) for [redacted] and [redacted]

Table 2. Overview of drug product control strategy

CQA	Method of control
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]

[redacted] was defined as a critical step. In-process controls are included at [redacted], [redacted], [redacted], [redacted], [redacted], and [redacted] steps.

2.2.3 Control of drug product

The proposed specifications for the drug product consist of strength, description, identification (ultraviolet spectrum and LC), purity (related substances [LC]), water content, uniformity of dosage units (content uniformity testing [LC]), dissolution (ultraviolet-visible spectrophotometry), and assay (LC).

RTRT was specified as a release test of the drug product for [redacted] and [redacted], and performed as process control testing according to the following:

- Using [redacted] sampled at the [redacted] step, [redacted] by near-infrared spectrophotometry (NIR), and [redacted]. A decision on [redacted] is made according to the number of samples.

If (a) [redacted], (b) [redacted] and [redacted] cannot be assessed by [redacted] due to apparatus failure etc., or (c) [redacted] etc., [redacted] and [redacted], proposed as specifications, are to be performed to make release decisions.

2.2.4 Stability of drug product

The stability studies on the drug product are shown in Table 3. Bracketing was applied to the long-term testing of the 150-mg tablet. The photostability data showed that the drug product is photostable.

Table 3. Stability studies on drug product

Strength	Study	Primary batches (Scale)	Temperature	Humidity	Storage package	Storage period
[redacted] mg	Long-term	1 batch ([redacted])	25°C	60%RH	Blister packs (polyvinyl chloride/polychlorotrifluoroethylene and aluminum foil)	36 months
	Accelerated	2 batches ([redacted])	40°C	75%RH		6 months
150 mg	Long-term	3 batches ([redacted])	25°C	60%RH		[redacted] months
	Accelerated		40°C	75%RH		6 months
200 mg	Long-term	1 batch ([redacted])	25°C	60%RH		36 months
	Accelerated	2 batches ([redacted])	40°C	75%RH		6 months

Based on the above, a shelf life of 36 months was proposed for the 150- and 200-mg tablets when packaged in blister packs (polyvinyl chloride/polychlorotrifluoroethylene and aluminum foil) and stored at room temperature. The long-term testing of the 150-mg tablet will be continued up to 36 months.

2.R Outline of the review conducted by PMDA

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

2.R.1 Novel excipients

The drug product contains polyethylene glycol, a novel excipient, in an amount higher than the amounts present in existing oral formulations.

2.R.1.1 Specification and stability

PMDA concluded that there are no problems with the specification and stability of polyethylene glycol.

2.R.1.2 Safety

Based on the submitted data, PMDA concluded that there are no safety issues with polyethylene glycol at the amount used in the drug product.

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

In this section, unless otherwise specified, the doses and concentrations of capmatinib and its metabolites are expressed as anhydrous free base.

3.1 Primary pharmacodynamics

3.1.1 Binding affinities to a panel of kinases (CTD 4.2.1.2-4, 4.2.1.2-5)

The binding affinities of capmatinib for a panel of 442 human kinases (recombinant proteins) were determined by a competition binding assay. In the presence of capmatinib 10 μmol/L, <35% of kinase remained bound to the ligand[1)] for MET, MET^{M1250T}, MET^{Y1235D}, abelson murine leukemia virus oncogene 1 $(ABL1)^{H396P}$-nonphosphorylated, AXL, cyclin-dependent kinase 11 (CDK11), interleukin-1 receptor-associated kinase 1 (IRAK1), phosphatidylinositol-5-phosphate 4-kinase, type II, gamma (PIP5K2C), and yeast Sps1/Ste20-related kinase 4 (YSK4). The K_D values of capmatinib for these kinases are shown in Table 4.

Table 4. Binding affinities of capmatinib to a panel of kinases

Kinase	K_D value (nmol/L)	Kinase	K_D value (nmol/L)
MET	0.23, 0.38	CDK11	5,700, 5,700
MET^{M1250T} *1	0.41, 0.97	IRAK1	450, 550
MET^{Y1235D} *2	0.4, 0.67	PIP5K2C	>10,000, >10,000
$ABL1^{H396P}$ *3-nonphosphorylated	3,100, 3,200	YSK4	1,800, 2,400
AXL	840, 1,400		

n = 2 (Individual values are listed.); *1 methionine at position 1,250 substituted with threonine
*2 tyrosine at position 1,235 substituted with aspartic acid; *3 histidine at position 396 substituted with proline

3.1.2 Inhibition of phosphorylation of MET (CTD 4.2.1.1-1, 4.2.1.1-3)

The inhibition of the phosphorylation of MET (recombinant proteins) by capmatinib was determined by a homogeneous time-resolved fluorescence (HTRF) assay using a biotin-labeled substrate. The IC_{50} values of capmatinib are shown in Table 5.

Table 5. Inhibition of phosphorylation of wild type and mutant MET by capmatinib

Kinase	n	IC_{50} value (nmol/L)
MET	17	0.13 ± 0.05
MET^{H1094Y} *1	2	0.28, 0.31
MET^{L1195V} *2	2	664, 808
MET^{Y1230C} *3	2	717, 1651
MET^{Y1235D} *4	2	13, 14

Mean ± SD; Individual values are listed for n = 2; *1, histidine at position 1,094 substituted with tyrosine
*2, leucine at position 1,195 substituted with valine; *3, tyrosine at position 1,230 substituted with cysteine
*4, tyrosine at position 1,235 substituted with aspartic acid

Using human NSCLC A549, H441, H596, and H1437 cell lines, the SNU-5 human gastric carcinoma cell line, and the 786-O human kidney carcinoma cell line, the inhibition of MET phosphorylation by capmatinib was determined by an enzyme-linked immunosorbent assay (ELISA) or Western blotting. The IC_{50} values of capmatinib in these cell lines are shown in Table 6.

1) Reported as % of control, where 100% of kinase remained bound to the ligand in the presence of negative control (100% DMSO) and 0% of kinase remained bound to the ligand in the presence of positive control.

Table 6. Inhibition of MET phosphorylation by capmatinib in various cell lines

Cell line	Tissue type	n	IC_{50} value (nmol/L)
A549	NSCLC	1	0.7
H441		2	0.63, 0.7
H596		2	0.21, 0.56
H1437		1	0.6
SNU-5	Gastric carcinoma	28	1.1 ± 0.4
786-O	Kidney carcinoma	2	0.48, 0.64

Mean ± SD Individual values are listed for n = 1 or 2.

The inhibition of the phosphorylation of human MET (recombinant protein) by capmatinib, M8, M16, or M18 [for the metabolites of capmatinib, see Section 4.3] was determined by a mobility shift assay using a fluorescently-labeled substrate. The IC_{50} values of capmatinib and its metabolites are shown in Table 7.

Table 7. Inhibition of phosphorylation of MET by capmatinib, M8, M16, or M18

	IC_{50} value (nmol/L)
Capmatinib	1.5, 1.8
M8	32, 41
M16	>10,000, >10,000
M18	13, 13

n = 2 (individual values)

3.1.3 Inhibition of MET-mediated signal transduction (CTD 4.2.1.1-1)

Using the SNU-5 cell line, the inhibition of the phosphorylation of MET and downstream signaling proteins (extracellular signal-regulated kinase 1 and 2 [ERK1/2], protein kinase B [AKT], focal adhesion kinase [FAK], growth factor receptor bound protein 2-associated protein 1 [GAB1], signal transducer and activator of transcription 3 and 5 [STAT3/5]) by capmatinib was determined by Western blotting. Capmatinib inhibited the phosphorylation of MET and downstream signaling proteins.

3.1.4 Anti-tumor activity in cancer patient-derived xenograft model

3.1.4.1 *In vivo* (CTD 4.2.1.1-5)

The anti-tumor activity of capmatinib was evaluated in non-obese diabetic/severe combined immunodeficiency (NOD/SCID) mice (5/group) subcutaneously xenografted with LU5381 tumor cells, a patient-derived NSCLC line driven by the METex14 mutation. When the tumor volume reached approximately 168 mm^3 (Day 1), treatment was started. Animals orally received capmatinib 20 mg/kg BID for 6 days. On Day 6, capmatinib treatment resulted in statistically significant anti-tumor activity as compared to the control (0.25% methylcellulose containing 0.05% polysorbate 80) (Figure 1).

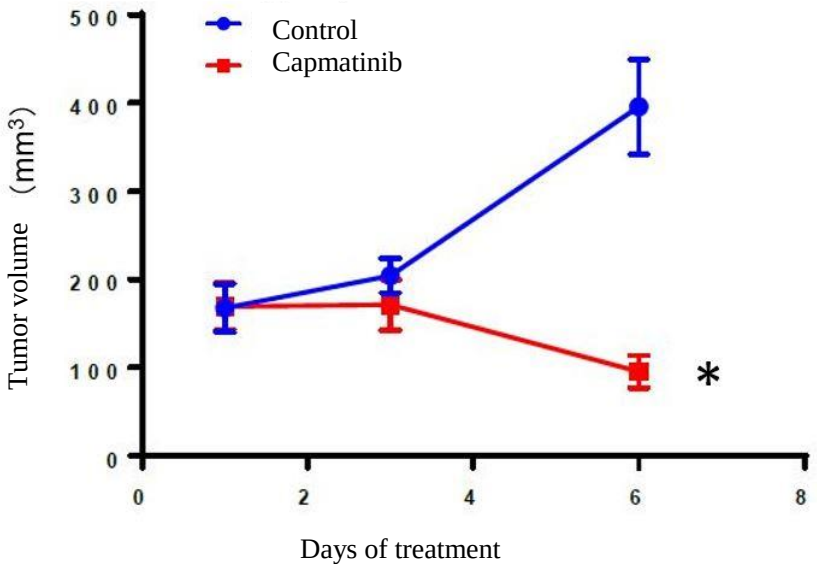


Figure 1. Anti-tumor activity of capmatinib in NOD/SCID mice subcutaneously xenografted with LU5381 cell line
n = 5/group, Mean ± SE, * $P < 0.05$, capmatinib vs. control (multiple t-test)

3.2 Secondary pharmacodynamics

3.2.1 Effects on various receptors, transporters, ion channels, and enzymes (CTD 4.2.1.2-2, 4.2.1.2-6)

Capmatinib was assessed for its inhibitory activity against 156 receptors, transporters, ion channels, and enzymes. The IC_{50} values of capmatinib were <10 μmol/L for vesicular monoamine transporter 2 (VMAT2), angiotensin II type 1 (AT1) receptor, phosphodiesterase 3 (PDE3), PDE4D, and acetylcholineesterase, and these IC_{50} values are shown in Table 8.

Table 8. Inhibitory activity of capmatinib against receptors, transporters, ion channels, and enzymes

	n	IC_{50} value (μmol/L)
VMAT2	1	2.0
AT1 receptor	1	4.4
PDE3	3	4.7
PDE4D	1	5.1
Acetylcholinesterase	1	5.7

Geometric mean; Individual values are listed for n = 1.

The inhibitory activity of M16 was assessed against 127 receptors, transporters, ion channels, and enzymes. The IC_{50} values of M16 were <10 μmol/L for dopamine transporter, bile salt export pump (BSEP), benzodiazepine receptor, phosphodiesterase PDE3A, VMAT2, and serotonin transporter, and these IC_{50} values of M16 (n = 1, individual values) were 0.25, 1.5, 5.7, 4.6, 6.8, and 7.5 μmol/L, respectively.

The applicant's explanation:
Given that the IC_{50} values of capmatinib and M16 for the above receptors etc. were higher than the C_{max} values of capmatinib (unbound) and M16 (unbound) in plasma (0.464 and 0.028 μmol/L, respectively)[2)] at the

[2)] Calculated based on the $C_{max,ss}$ values of capmatinib and M16 (11.6 and 2.80 μmol/L, respectively) following oral administration of capmatinib 400 mg BID in a global phase II study (Study A2201) [see Section 4.5.1].

recommended clinical dose (400 mg BID), etc., the effects of capmatinib or M16 on the above receptors etc. are unlikely to cause safety issues in the clinical use of capmatinib.

3.3 Safety pharmacology

3.3.1 Effects on the central nervous system (CTD 4.2.1.3-3)

Rats (10/group) received a single oral dose of capmatinib 120 mg/kg, and the effects of capmatinib on clinical signs, behavior, etc. were assessed by a functional observation battery. There were no capmatinib-related effects.

3.3.2 Effects on cardiovascular system

3.3.2.1 Effects on hERG potassium current (CTD 4.2.1.3-2)

The effects of capmatinib on the human *ether-a-go-go*-related gene (hERG) potassium current were assessed using the human embryonic kidney HEK293 cell line transfected with hERG. Capmatinib at 3, 10, and 30 μmol/L inhibited the hERG potassium current by 13.7 ± 0.3%, 36.7 ± 0.9%, and 60.6 ± 1.5% (mean ± standard error [SE], n = 3), respectively, with an IC_{50} of 18.7 μmol/L. Statistically significant inhibition occurred in the capmatinib 3, 10, and 30 μmol/L groups as compared to the control (HEPES-buffered saline[3)] containing 0.3% dimethyl sulfoxide [DMSO]) group ($P < 0.05$, Dunnett's multiple comparison test).

3.3.2.2 Effects on blood pressure, heart rate, and ECG (CTD 4.2.1.3-4)

Cynomolgus monkeys (3/group) received a single oral dose of capmatinib 30, 75, or 150 mg/kg, and the effects of capmatinib on blood pressure (mean arterial pressure, systolic blood pressure, diastolic blood pressure, etc.), heart rate, and ECG (PR, RR, QRS, QT, QTc, and QA intervals, etc.) were assessed. There were no effects of capmatinib at any dose level.

3.3.3 Effects on respiratory system (CTD 4.2.1.3-3)

Rats (5/group) received a single oral dose of capmatinib 120 mg/kg, and the effects of capmatinib on the respiratory function (tidal volume, respiratory rate, minute ventilation) were assessed. There were no capmatinib-related effects.

3.R Outline of the review conducted by PMDA

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

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

The applicant's explanation about the action mechanism of capmatinib and its efficacy in the treatment of NSCLC with METex14 mutations:

MET exon 14 encodes a region that plays an important role in MET ubiquitination (*Cancer Res*. 2006; 66: 283-

[3)] 137 mmol/L sodium chloride, 4.0 mmol/L potassium chloride, 1.8 mmol/L calcium chloride, 1.0 mmol/L magnesium chloride, 10 mmol/L HEPES, and 10 mmol/L glucose

9). METex14 mutation reduces ubiquitin-mediated protein degradation, causing the accumulation of MET mutant protein in cells. This is thought to activate the downstream signaling pathways ligand-independently, causing increased cell proliferation, etc. (*Lung Cancer*. 2015; 90: 590-7). Further, the following observation suggest that METex14 mutation is the oncogene driver.

- METex14 mutation not only increases MET-mediated signaling, etc. but also causes lung adenocarcinoma through the mutation and the deficiency of the *p53* gene, an antioncogene. Thus, METex14 mutation is considered to significantly contribute to the survival/proliferation of tumor cells (*Cancer Res*. 2017; 77: 4498-505, etc.).

Capmatinib inhibited the phosphorylation of MET and downstream signaling proteins (ERK1/2, AKT, etc.) [see Sections 3.1.2 and 3.1.3] and exhibited anti-tumor activity against METex14 mutation-driven NSCLC [see Section 3.1.4.1].

Based on the above, the efficacy of capmatinib in the treatment of NSCLC with METex14 mutations is expected.

PMDA accepted the applicant's explanation.

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

The non-clinical PK of capmatinib were investigated in rats, monkeys, etc. Studies on the plasma protein binding, drug metabolizing enzymes, transporters, etc. of capmatinib were conducted using human or animal biomaterials.

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

4.1 Absorption

4.1.1 Single-dose studies

Following single intravenous administration of ^{14}C-capmatinib 3 mg/kg or single oral administration of ^{14}C-capmatinib 10 mg/kg in male rats, plasma capmatinib concentrations were determined (Table 9). The bioavailability (BA) of capmatinib after oral administration was >100%.

Table 9. PK parameters of capmatinib (male rats, single intravenous or oral administration)

Dose (Route of administration)	n	C_{max} (μg/mL)	t_{max}* (h)	AUC_{last} (μg·h/mL)	$t_{1/2}$ (h)	CL (mL/h/kg)	V_{ss} (L/kg)
3 mg/kg (IV)	3	2.27 ± 0.155	0.0830 (0.0830, 0.0830)	1.58 ± 0.111	1.42 ± 0.0929	1.97 ± 0.128	1.73 ± 0.203
10 mg/kg (Oral)	3	0.850 ± 0.173	0.250 (0.250, 0.500)	5.90 ± 1.50	—	—	—

Mean ± SD *Median (range) —, Not calculated

4.1.2 Repeated-dose studies

Male and female monkeys were dosed orally with capmatinib 10, 30, or 75 mg/kg[4)] QD for 13 weeks, and plasma capmatinib concentrations were determined (Table 10). Capmatinib exposure (C_{max} and AUC_{24h}) increased almost dose-proportionally over the dose range tested. There were no clear increases in capmatinib exposure after multiple dosing. There were no clear gender differences in the PK of capmatinib.

Table 10. PK parameters of capmatinib (male and female monkeys, 13-week repeated oral dosing)

Sampling day (Day)	Dose (mg/kg)	n	C_{max} (μg/mL)		t_{max} (h)		AUC_{24h} (μg·h/mL)	
			Male	Female	Male	Female	Male	Female
1	10	4	1.94 ± 0.422	2.43 ± 1.90	0.750 ± 0.500	1.63 ± 1.65	8.77 ± 3.00	5.51 ± 2.06
	30	4	7.36 ± 4.65	7.79 ± 6.07	1.00 ± 0.580	1.25 ± 0.500	32.6 ± 7.93	21.4 ± 5.85
	75	6	19.0 ± 4.87	14.5 ± 4.30	1.33 ± 0.410	1.42 ± 1.36	107 ± 26.6	74.3 ± 24.6
87	10	4	1.56 ± 0.405	2.21 ± 0.597	1.63 ± 1.65	0.500*	7.10 ± 0.866	7.31 ± 0.776
	30	4	7.20 ± 4.22	5.43 ± 2.46	2.88 ± 3.45	0.750 ± 0.500	42.3 ± 10.2	23.4 ± 4.97
	75	6	18.6 ± 6.87	15.1 ± 3.40	1.50*	1.17 ± 0.520	119 ± 17.5	79.3 ± 14.9

Mean ± SD *SD was not calculated.

4.1.3 *In vitro* cell permeability

The cell permeability of capmatinib was evaluated in the human colon carcinoma Caco-2 cell line. The apparent permeability in apical to basal direction ($P_{app\ A \to B}$) of capmatinib 50 μmol/L was 25.1×10^{-6} cm/sec. The applicant explained that capmatinib is highly permeable, given that the $P_{app\ A \to B}$ values of poorly permeable nadolol 50 μmol/L and highly permeable metoprolol 50 μmol/L were 0.61×10^{-6} and 14×10^{-6} cm/sec, respectively.

4.2 Distribution

4.2.1 Tissue distribution

Male pigmented and albino rats received a single oral dose of ^{14}C-capmatinib 10 mg/kg, and the tissue distribution of radioactivity was determined by quantitative whole-body autoradiography. In pigmented rats, extensive tissue distribution of radioactivity was observed, and radioactivity concentrations peaked by 1 hour post-dose in most tissues. In pigmented rats, the maximum concentrations of radioactivity in the stomach mucosa (non-fundic), choroid plexus, meibomian glands, bile ducts, uveal tract/retina, urinary bladder wall, and liver (186, 139, 122, 114, 100, 100, and 59.2 nmol/g, respectively) were particularly higher than the maximum concentration of radioactivity in blood (7.66 nmol/g). The tissue distribution of radioactivity in albino rats was similar to that in pigmented rats, except for the choroid plexus, uveal tract, pigmented fur, meibomian glands, and pigmented skin. The maximum concentration of radioactivity in the choroid plexus of pigmented rats (139 nmol/g) was markedly higher than that of albino rats (≤0.135 nmol/g). The radioactivity concentration in the choroid plexus at 168 hours post-dose was below the lower limit of quantification in albino rats and 31.8 nmol/g in pigmented rats. The applicant explained that the results indicated that capmatinib or its metabolites bind to melanin.

[4)] Doses referring to the dihydrochloride monohydrate salt

4.2.2 Plasma protein binding

The plasma from mouse, rat, dog, or monkey was incubated with capmatinib, or human plasma was incubated with ^{14}C-capmatinib, and the plasma protein binding of capmatinib was determined.[5)] The protein unbound fractions of capmatinib in mouse, rat, dog, monkey, and human plasma were almost constant over the concentration range tested, and were 3.3% to 5.3%, 3.8% to 5.2%, 14% to 20.4%, 2.6% to 3.4%, and 3.71% to 4.42%, respectively.

The plasma from rat, monkey, or human was incubated with M16 (formed via oxidation) (300-3,000 ng/mL) at 37°C for 1 hour, and the plasma protein binding of M16 was determined using an ultrafiltration method. The protein unbound fractions of M16 in rat, monkey, and human plasma were 0.34% to 0.37%, 1.46% to 1.68%, and 0.42% to 0.51%, respectively, over the concentration range tested.

Human serum albumin (40 g/L), human α1-acid glycoprotein (1 g/L), γ-globulin (12 g/L), or lipoproteins[6)] was incubated with capmatinib (10-10,000 ng/mL) at 37°C for 1 hour, and the binding of capmatinib to human serum albumin, human α1-acid glycoprotein, γ-globulin, and lipoproteins was determined using an ultrafiltration method. The binding of capmatinib to human serum albumin, human α1-acid glycoprotein, γ-globulin, and lipoproteins was 91.8% to 93.7%, 44.1% to 55.7%, 58.7% to 65.3%, and 70.5% to 74.2%, respectively. The applicant explained that the results indicated that capmatinib binds primarily to serum albumin in human plasma.

4.2.3 Distribution in blood cells

The blood from rat, dog, or monkey was incubated with capmatinib, or human blood was incubated with ^{14}C-capmatinib, at 37°C for 1 hour, and the distribution of capmatinib in blood cells was determined.[7)] The blood to plasma concentration ratios of capmatinib in rat, dog, and monkey blood were 1.1, 7.9, and 1.4, respectively. On the other hand, the blood to plasma radioactivity concentration ratio in human blood was 1.44 to 1.62 at ^{14}C-capmatinib concentrations of 10 to 1,000 ng/mL. The applicant explained that the above results indicated that capmatinib is mainly distributed in blood cells in all animal species tested.

4.2.4 Placental transfer to fetus

Placental and fetal transfer of capmatinib has not been studied. Because of the fetal teratogenicity etc. of capmatinib shown in embryo-fetal development studies in rats and rabbits [see Section 5.5], the applicant explained that capmatinib may cross the placenta into the fetus.

[5)] Plasma from mice, rats, dogs, or monkeys was incubated with capmatinib (1-10 μmol/L) at 37°C for 2 hours, and plasma protein binding of capmatinib was determined by equilibrium dialysis. Human plasma was incubated with ^{14}C-capmatinib (100-10,000 ng/mL) at 37°C for 1 hour, and plasma protein binding of capmatinib was determined by ultrafiltration.

[6)] HDL (3.9 g/L), LDL (3.6 g/L), and VLDL (1.3 g/L) were used.

[7)] Capmatinib (3 μmol/L) was used for blood from rats, dogs, and monkeys, and ^{14}C-capmatinib (10-10,000 ng/mL) was used for human blood. When human blood was incubated with ^{14}C-capmatinib 10,000 ng/mL, the blood to plasma radioactivity concentration ratio was 0.873.

4.3 Metabolism

4.3.1 *In vitro*

Mouse, rat, dog, monkey, or human hepatocytes were incubated with ^{14}C-capmatinib (10 μmol/L) at 37°C for 6 hours, and the metabolites of capmatinib were identified. In all of mouse, rat, dog, monkey, and human hepatocytes, M4, M5, M8, M16, and M21 (all formed via oxidation), M13 (formed via carboxylic acid formation), M14 (formed via *C*-hydroxylation), and M24 (formed via *N*-oxidation and *C*- hydroxylation) were identified. In human hepatocytes, M1 (formed via *N*-glucuronidation), M10 (formed via hydrogenation and *C*-hydroxylation), M17 (formed via *C*-hydroxylation), M18 (formed via *N*-demethylation), and M26 (formed via hydrogenation) were also identified.

The applicant's explanation:

The following results etc. indicated that capmatinib is primarily metabolized by CYP3A4 and aldehyde oxidase (AO) in humans:

- Recombinant human CYP isoforms (CYP1A1, CYP1A2, CYP2A6, CYP1B1, CYP2B6, CYP2C8, CYP2C9, CYP2C18, CYP2C19, CYP2D6, CYP2E1, CYP2J2, CYP3A4, CYP3A5, CYP4A11, CYP4F2, CYP4F3B, or CYP4F12) or flavin-containing monooxygenase (FMO) isoforms (FMO1, FMO3, or FMO5) were incubated with ^{14}C-capmatinib (5 μmol/L) in the presence of nicotinamide adenine dinucleotide phosphate hydrogen (NADPH) at 37°C for 5 minutes. In the presence of CYP1A1 or CYP3A4, the residual ratio of capmatinib was 76.9% or 72.7%, respectively. In the presence of other CYP isoforms or FMO isoforms tested, the residual ratio of capmatinib was 99% to 100%.
- Human liver microsomes were incubated with ^{14}C-capmatinib (10 μmol/L) and NADPH in the presence or absence of CYP isoform-selective inhibitors[8)] or a nonspecific FMO inhibitor (methimazole) at 37°C for 5 minutes. A CYP3A inhibitor inhibited capmatinib's metabolite formation by 92%.[9)] In the presence of inhibitors of other isoforms tested, capmatinib's metabolite formation was inhibited by up to 9%.
- Human liver cytosol was incubated with ^{14}C-capmatinib (8 μmol/L) in the presence or absence of AO inhibitors[10)] or a xanthine oxidase (XO) inhibitor (allopurinol), at 37°C for 120 minutes. The AO inhibitors and the XO inhibitor inhibited M16 formation by 100%[11)] and 26%, respectively.

4.3.2 *In vivo*

Male rats without bile duct cannulation received (a) a single intravenous dose of ^{14}C-capmatinib 3 mg/kg or (b) a single oral dose of ^{14}C-capmatinib 10 mg/kg, and bile duct-cannulated male rats received a single intravenous dose of ^{14}C-capmatinib 3 mg/kg. ^{14}C-capmatinib metabolites in plasma, urine, feces, and bile were investigated. The following results were obtained.

- In the plasma collected up to (a) 8 hours post-dose and (b) 24 hours post-dose from non-bile duct-cannulated male rats, the unchanged drug, M8, and M16 were mainly identified (the unchanged drug, M8, and M16

[8)] As inhibitors of CYP1A2, CYP2C8, CYP2C9, CYP2C19, CYP2D6, and CYP2E1, furafylline, montelukast, sulfaphenazole, ticlopidine, quinidine, and sodium diethyldithiocarbamate were used, respectively. As CYP3A inhibitors, ketoconazole or azamulin was used.
[9)] Value with azamulin used as a CYP3A inhibitor
[10)] Raloxifene, menadione, isovanillin, or hydralazine was used as AO inhibitors.
[11)] Value with raloxifene used as an AO inhibitor

accounted for (a) 50.6%, 8.54%, and 23.2%, respectively, and (b) 33.4%, 8.09%, and 33.1%, respectively, of the total radioactivity in plasma).

- In the urine collected up to 48 hours post-dose from non-bile duct-cannulated male rats, M8 and M16 were mainly identified (M8 and M16 represented (a) 0.78% and 0.82%, respectively, and (b) 0.93% and 1.77%, respectively, of the administered radioactivity).
- In the feces collected up to 48 hours post-dose from male rats without bile duct cannulation, M8, M13, and M16 were mainly identified (M8, M13, and M16 represented (a) 11.4%, 16.8%, and 20.7%, respectively, and (b) 11.3%, 15.5%, and 17.5%, respectively, of the administered radioactivity).
- In the bile collected up to 8 hours post-dose from bile duct-cannulated male rats, M13, M16, M22, M24, and M25 were mainly identified (M13, M16, M22, M24, and M25 represented 15.8%, 6.58%, 4.07%, 3.71%, and 6.33%, respectively, of the administered radioactivity).

Male monkeys received (a) a single intravenous dose of ^{14}C-capmatinib 3 mg/kg or (b) a single oral dose of ^{14}C-capmatinib 30 mg/kg. ^{14}C-capmatinib metabolites in plasma, urine, and feces were identified. The following results were obtained.

- In the plasma collected up to (a) 7 hours post-dose and (b) 10 hours post-dose, the unchanged drug, M8, and M16 were mainly identified (the unchanged drug, M8, and M16 accounted for (a) 54.3%, 13.7%, and 13.4%, respectively, and (b) 42.5%, 22.8%, and 13.5%, respectively, of the total radioactivity in plasma).
- In the feces collected up to 72 hours post-dose, the unchanged drug, M8, and M16 were mainly identified (the unchanged drug, M8, and M16 represented (a) 5.28%, 6.21%, and 24.8%, respectively, and (b) 6.59%, 12.6%, and 18.8%, respectively, of the administered radioactivity).

4.4 Excretion

4.4.1 Urinary, fecal, and biliary excretion

The applicant explained that the following study results etc. indicated that capmatinib and its metabolites are excreted predominantly in feces via bile.

- Male rats without bile duct cannulation received (a) a single intravenous dose of ^{14}C-capmatinib 3 mg/kg or (b) a single oral dose of ^{14}C-capmatinib 10 mg/kg, and (a) 5.71% and 88.6% and (b) 7.82% and 86.4% of the administered radioactivity were recovered in urine and feces, respectively, over 168 hours.
- Bile duct-cannulated male rats received a single intravenous dose of ^{14}C-capmatinib 3 mg/kg, and 12.1%, 9.23%, and 66.3% of the administered radioactivity were recovered in urine, feces, and bile, respectively, over 24 hours.
- Male monkeys received (a) a single intravenous dose of ^{14}C-capmatinib 3 mg/kg or (b) a single oral dose of ^{14}C-capmatinib 30 mg/kg, and (a) 7.92% and 77.4% and (b) 9.67% and 72.0% of the administered radioactivity were recovered in urine and feces, respectively, over 168 hours.

4.4.2 Excretion into milk

Capmatinib excretion in milk was not studied. The applicant explained that taking account of the physicochemical properties of capmatinib (molecular weight [free base], 412.43; cell permeability [see Section 4.1.3]) etc., capmatinib may be excreted in milk.

4.5 Pharmacokinetic interactions

4.5.1 Enzyme inhibition

The applicant's explanation about pharmacokinetic interactions via the inhibition of metabolizing enzymes by capmatinib and M16:

Given (a) the $C_{max,ss}$ values of capmatinib and M16 (11.6 and 2.80 μmol/L,[12)] respectively) and (b) the estimated capmatinib concentration in the gastrointestinal tract (3,879 μmol/L) following the proposed dosing regimen, and based on the following study results etc., capmatinib is unlikely to cause pharmacokinetic interactions via the inhibition of CYP2A6, CYP2B6, CYP2C9, CYP2C19, CYP2D6, or CYP2E1 by capmatinib, or inhibition of CYP1A2, CYP2A6, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, or CYP2E1 by M16 in clinical use. On the other hand, capmatinib has the potential to cause pharmacokinetic interactions via the inhibition of CYP1A2, CYP2C8, or CYP3A by capmatinib, or inhibition of CYP3A by M16.

- Human liver microsomes were incubated with capmatinib (0.39-100 μmol/L) or M16 (0.23-60 μmol/L) in the presence of the substrates for CYP isoforms (CYP1A2, CYP2A6, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, CYP2E1, or CYP3A)[13)] and NADPH. Capmatinib inhibited the metabolism of the substrates for CYP1A2, CYP2C8, CYP2C9, CYP2C19, and CYP3A with IC_{50} values of 20, 1.7, 7.6, 11.3, and 9.9[14)] μmol/L, respectively. M16 inhibited the metabolism of the substrates for CYP2B6, CYP2C8, CYP2C9, CYP2C19, and CYP3A with IC_{50} values of 48, 3.6, 9.7, 57, and 26[15)] μmol/L, respectively. On the other hand, capmatinib or M16 did not cause evident inhibition of the metabolism of the substrates for other CYP isoforms tested.
- Human liver microsomes were preincubated with capmatinib (1.56-100 μmol/L[16)]) or M16 (0.75-60 μmol/L[17)]) in the presence of NADPH and then incubated with the substrates for CYP isoforms (CYP1A2, CYP2C9, CYP2D6, CYP3A),[18)] and capmatinib was evaluated as a time-dependent inhibitor of these CYP isoforms. Capmatinib caused time-dependent inhibition of the metabolism of the substrates for CYP1A2 and CYP3A, with K_i values of 18.5 and 13.2 μmol/L, respectively. M16 caused time-dependent inhibition of the metabolism of the CYP3A substrate, with a K_i value of 104 μmol/L. On the other hand, capmatinib or M16 did not cause evident time-dependent inhibition of the metabolism of the substrates for other CYP isoforms tested.

4.5.2 Enzyme induction

[12)] The $C_{max,ss}$ values in patients treated orally with capmatinib 400 mg BID in a global phase II study (Study A2201)

[13)] Phenacetin, coumarin, bupropion, diclofenac, *S*-mephenytoin, bufuralol, and chlorzoxazone were used as the substrates of CYP1A2, CYP2A6, CYP2B6, CYP2C9, CYP2C19, CYP2D6, and CYP2E1, respectively, and midazolam and testosterone were used as CYP3A substrates. As CYP2C8 substrates, paclitaxel for testing of capmatinib, and amodiaquine for testing of M16 were used.

[14)] IC_{50} value with midazolam used as a CYP3A substrate

[15)] IC_{50} value with midazolam used as a CYP3A substrate

[16)] The concentrations tested for CYP1A2 and CYP2D6 were 3.13 to 100 μmol/L, and the concentrations tested for CYP2C9 and CYP3A were 1.56 to 50 μmol/L.

[17)] The concentrations tested for CYP1A2, CYP2C9, and CYP2D6 were 0.75 to 24 μmol/L, and the concentrations tested for CYP3A were 1.88 to 60 μmol/L.

[18)] Phenacetin, diclofenac, bufuralol, and midazolam were used as the substrates of CYP1A2, CYP2C9, CYP2D6, and CYP3A, respectively.

The applicant's explanation about pharmacokinetic interactions via the induction of metabolizing enzymes by capmatinib and M16:

Given (a) the following study results and (b) the $C_{max,ss}$ values of capmatinib and M16 following the proposed dosing regimen (11.6 and 2.80 μmol/L,[12)] respectively) etc., capmatinib is unlikely to cause pharmacokinetic interactions via the induction of CYP1A2, CYP2B6, CYP2C9, or CYP3A by capmatinib or M16 in clinical use.

- Primary human hepatocytes were incubated with capmatinib (1-100 μmol/L) or M16 (1-12 μmol/L) for 2 days, and the mRNA expression levels and activities of CYP isoforms (CYP1A2, CYP2B6, CYP2C9, CYP3A4) were determined. The increases in the mRNA expression of CYP2B6, CYP2C9, and CYP3A4 caused by capmatinib were 53% to 111%, 15% to 59%, and 22% to 58%, respectively, of those caused by the respective positive controls.[19)] The increases in the activities of CYP2B6 and CYP2C9 caused by capmatinib were 12% to 69% and 35% to 75%, respectively, of those caused by the respective positive controls.[19)] On the other hand, capmatinib caused no evident increases in the mRNA level or activity of CYP1A2, or the activity of CYP3A. M16 caused no evident increases in the mRNA levels or activities of CYP isoforms tested.

4.5.3 Transporters

The applicant's explanation about transporter-mediated pharmacokinetic interactions of capmatinib and M16:

The following study results etc. indicated that capmatinib is not a substrate of breast cancer resistance protein (BCRP), multidrug resistance associated protein 2 (MRP2), organic anion transporting polypeptide (OATP), organic anion transporter (OAT), or organic cation transporter (OCT), but is a substrate of p-glycoprotein (P-gp).

- P-gp-mediated transport of capmatinib (0.4 μmol/L) was investigated using the pig kidney LLC-PK1 cell line expressing human P-gp. The apparent membrane permeability (PS_{app}) of capmatinib was 0.51 and 1.18[20)] μL/min/mg in the absence and presence of a P-gp inhibitor,[21)] respectively, over the concentration range tested.
- BCRP-mediated transport of capmatinib (0.58-56.0 μmol/L) was investigated using the P-gp/MRP2 double knockout Caco-2 cell line. In the absence and presence of a BCRP inhibitor (Ko143, 1 μmol/L), the efflux ratios of capmatinib were 0.5 to 1.3 and 1.3,[22)] respectively, over the concentration range tested.
- MRP2-mediated transport of capmatinib (1-100 μmol/L) was investigated using the membrane vesicles from the Sf9 insect cell line expressing human MRP2. There were no clear differences in the PS_{app} of capmatinib in the presence of adenosine monophosphate (AMP) or adenosine triphosphate (ATP).
- OATP-, OAT-, and OCT-mediated uptake of capmatinib (1-25 μmol/L) in cells was investigated using human hepatocytes. There were no clear differences in the uptake of capmatinib in cells in the absence or presence of the respective transporter inhibitors[23)] over the concentration range tested.

[19)] Naphthoflavone (10 μmol/L) was used as positive control for CYP1A2, and phenobarbital (1,000 μmol/L) and rifampicin (0.1-20 μmol/L) were used as positive controls for CYP2B6, CYP2C9, and CYP3A.
[20)] Value when using LY335979
[21)] Cyclosporin A (10 μmol/L) and LY335979 (1 μmol/L) were used as P-gp inhibitors.
[22)] Values when using capmatinib 0.74 μmol/L
[23)] Rifampicin (20 μmol/L) as an OATP inhibitor, atorvastatin (10 μmol/L) as an OATP1B1 inhibitor, p-aminohippuric acid (3000 μmol/L) as an OAT inhibitor, and tetraethylammonium (3000 μmol/L) as an OCT inhibitor were used.

Given (a) the $C_{max,ss}$ values of capmatinib and M16 (11.6 and 2.80 μmol/L,[12)] respectively), (b) the estimated capmatinib concentration in the gastrointestinal tract (3,879 μmol/L) following the proposed dosing regimen, and (c) the following study results etc., pharmacokinetic interactions via the inhibition of MRP2, BSEP, OATP1B1, OATP1B3, OATP2B1, OCT1, OCT2, OAT1, or OAT3 by capmatinib or the inhibition of P-gp, BCRP, MRP2, BSEP, OATP1B1, OATP1B3, OCT1, OCT2, OAT1, or OAT3 by M16 is unlikely in the clinical use of capmatinib. On the other hand, pharmacokinetic interactions are possible via the inhibition of P-gp, BCRP, (multidrug and toxin extrusion (MATE) 1, or MATE2-K by capmatinib or the inhibition of MATE1 or MATE2-K by M16.

- Using the LLC-PK1 cell line expressing human P-gp, the MDCKII cell lines expressing human BCRP or MRP2, the membrane vesicles from the Sf9 cell line expressing human BSEP, and the HEK293 cell lines expressing human OATP1B1, OATP1B3, OATP2B1, OCT1, OCT2, OAT1, OAT3, MATE1, or MATE2-K, the potential of capmatinib (0.2-100 μmol/L[24)]) to inhibit P-gp-, BCRP-, MRP2-, BSEP-, OATP1B1-, OATP1B3-, OATP2B1-, OCT1-, OCT2-, OAT1-, OAT3-, MATE1-, or MATE2-K-mediated transport of their substrates[25)] was assessed. Capmatinib inhibited the transport of the substrates of P-gp, BCRP, MRP2, BSEP, OATP1B1, OATP1B3, OATP2B1, OCT1, OAT1, OAT3, MATE1, and MATE2-K with IC_{50} values of 12.0, 16.4, 70.9, 11.4, 6.5, 6.2, 38.5, 20.3, 39.5, 68.2, 0.28, and 0.29 μmol/L, respectively. On the other hand, capmatinib caused no evident inhibition of the transport of the substrate of OCT2.
- Using the LLC-PK1 cell line expressing human P-gp, the MDCKII cell line expressing human BCRP, the membrane vesicles from the Sf9 cell line expressing human MRP2 or BSEP, and the HEK293 cell lines expressing human OATP1B1, OATP1B3, OCT1, OCT2, OAT1, OAT3, MATE1, or MATE2-K, the potential of M16 (0.05-100 μmol/L[26)]) to inhibit P-gp-, BCRP-, MRP2-, BSEP, OATP1B1-, OATP1B3-, OCT1-, OCT2-, OAT1-, OAT3-, MATE1-, or MATE2-K-mediated transport of their substrates[27)] was assessed. M16 inhibited the transport of the substrates of BSEP, OATP1B1, OATP1B3, OCT1, OAT1, MATE1, and MATE2-K with IC_{50} values of 3.3, 3.3, 14.6, 94.7, 28.0, 0.38, and 0.63 μmol/L, respectively. On the other hand, M16 caused no evident inhibition of the transport of the substrates of P-gp, BCRP, MRP2, OCT2, and OAT3.

4.R Outline of the review conducted by PMDA

Based on the submitted data and the considerations in the following sections, PMDA concluded that the applicant's explanation about the non-clinical pharmacokinetics (PK) of capmatinib is acceptable.

[24)] The concentrations tested for BCRP, OATP1B1, and OATP1B3 were 0.2 to 150 μmol/L. The concentrations tested for OATP2B1 were 0.2 to 125 μmol/L. The concentrations tested for MRP2, BSEP, and MATE1 were 5 to 160, 0.5 to 300, and 0.01 to 10.0 μmol/L, respectively. The concentrations tested for OCT1, OCT2, OAT1, OAT3, and MATE2-K were 0.1 to 100 μmol/L.

[25)] ^{3}H-digoxin (1 μmol/L), ^{14}C-2-amino-1-methyl-6-phenylimidazo[4,5-*b*]pyridine (1 μmol/L), ^{14}C-valsartan (5 μmol/L), ^{3}H-taurocholic acid (0.25 μmol/L), and ^{3}H-cidofovir (1 μmol/L) were used as the substrates of P-gp, BCRP, MRP2, BSEP, and OAT1, respectively. ^{3}H-estradiol-17β-glucuronide (1 μmol/L) as a substrate of OATP1B1 and OATP1B3, ^{3}H-estrone sulfate (1 and 5 μmol/L) as a substrate of OAT3 and OATP2B1, and ^{3}H-*N*-methyl-4-phenylpyridinium iodide (0.025 μmol/L) as a substrate of OCT1, OCT2, MATE1 and MATE2-K were used.

[26)] The concentrations tested for BSEP were 0.05 to 200 μmol/L.

[27)] ^{3}H-digoxin (1 μmol/L), ^{14}C-2-amino-1-methyl-6-phenylimidazo[4,5-*b*]pyridine (2 μmol/L), ^{3}H-taurocholic acid (0.25 μmol/L), ^{3}H-cidofovir (1 μmol/L), and ^{3}H-estrone sulfate (1 μmol/L) were used as the substrates of P-gp, BCRP, BSEP, OAT1, and OAT3, respectively. ^{3}H-estradiol-17β-glucuronide (0.1 and 50 μmol/L) was used as a substrate of OATP1B1, OATP1B3, and MRP2. ^{3}H-*N*-methyl-4-phenylpyridinium iodide (0.025 μmol/L) was used as a substrate of OCT1, OCT2, MATE1, and MATE2-K.

4.R.1 Tissue distribution

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

The applicant's response:

Given the following observations, etc., the distribution of capmatinib or its metabolites in melanin-containing tissues is unlikely to cause safety issues in the clinical use of capmatinib.

- In 4- and 13-week repeated-dose toxicity studies in monkeys, no toxicity findings in the eyes or skin (melanin-containing tissues) were observed [see Section 5.2].
- In a global phase II study (Study A2201), lacrimation increased (1.2%, 4 of 334 subjects), pruritus (9.0%, 30 of 334 subjects), etc. were reported as adverse events related to eye disorders or skin and subcutaneous tissue disorders. However, most 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

In vitro studies indicated that capmatinib has the potential to cause pharmacokinetic interactions mediated by the following metabolizing enzymes or transporters in clinical use.

- Capmatinib is a substrate of P-gp [see Section 4.5.3].
- Capmatinib and M16 inhibit MATE1 and MATE2-K [see Section 4.5.3].

The applicant's explanation:

The evaluation of pharmacokinetic interactions of capmatinib and M16 mediated by the above metabolizing enzymes or transporters has limitations because of a limited number of patients receiving capmatinib in combination with the substrates or inhibitors of these metabolizing enzymes or transporters, etc. However, given the following observation, etc., these pharmacokinetic interactions are unlikely to cause a problem in the clinical use of capmatinib.

- In a Japanese phase I study (Study X1101), foreign phase I studies (Studies X2102, A2103, A2105, and A2108), and a global phase II study (Study A2201), the coadministration of capmatinib with a P-gp inhibitor or a substrate of MATE1 or MATE2-K raised no particular safety concerns.

PMDA's discussion:

The applicant's explanation was largely acceptable. However, information on pharmacokinetic interactions mediated by P-gp, MATE1, or MATE2-K is important for the proper use of capmatinib. Currently available information should be appropriately provided to healthcare professionals and continue to collect relevant information.

The following observations are presented in Sections 6.2.3 and 6.R.2.

● Capmatinib is primarily metabolized by CYP3A4 [see Section 4.3.1].
● Capmatinib inhibits CYP1A2 and CYP2C8, and capmatinib and M16 inhibit CYP3A [see Section 4.5.1].
● Capmatinib induces CYP3A [see Section 4.5.2].
● Capmatinib inhibits P-gp and BCRP [see Section 4.5.3].

5. Toxicity and Outline of the Review Conducted by PMDA

The applicant submitted the results from toxicity studies of capmatinib: single-dose toxicity, repeated-dose toxicity, genotoxicity, photosafety, and skin sensitization studies, mechanistic studies of toxicity etc., and toxicity studies on impurities.

In this section, unless otherwise specified, capmatinib dissolved in 0.5% methylcellulose aqueous solution was used in *in vivo* studies, and capmatinib dissolved in DMSO was used in *in vitro* studies. The doses and concentrations of capmatinib are expressed as anhydrous free base.

5.1 Single-dose toxicity

Single oral dose toxicity studies of capmatinib were conducted in mice, rats, and cynomolgus monkeys (Table 11). The approximate lethal doses of capmatinib were >600 mg/kg in mice and cynomolgus monkeys and 50 to 300 mg/kg in female rats.

Table 11. Single-dose toxicity studies

Test system	Route of administration	Dose (mg/kg)	Principal findings	Approximate lethal dose (mg/kg)	Attached document CTD
Male and female mice (CD-1)	Oral	0, 100, 300, 600	≥300: transient decreased activity 600: decreased food consumption	>600	4.2.3.1.1 Reference data
Female rats (Crl:WI (Han))	Oral	0,[a)] 50, 300, 2,000	Deaths or moribund sacrifices: ≥300 ≥50: hunched posture, piloerection ≥300: lethargy, labored respiration, ptosis, etc.	50-300	4.2.3.1.2
Male and female cynomolgus monkeys	Oral	20, 50, 150, 600	None	>600	4.2.3.1.3 Reference data

a) Propyleneglycol only was administered.

5.2 Repeated-dose toxicity

Repeated-dose toxicity studies of capmatinib were conducted in mice (8 days), rats (4 and 13 weeks), and cynomolgus monkeys (4 and 13 weeks) (Table 12). There were capmatinib-related effects on the central nervous system (rats), liver (mice, rats, cynomolgus monkeys), pancreas (rats, cynomolgus monkeys), and kidneys (cynomolgus monkeys).

Capmatinib exposure (C_{max} and $AUC_{0\text{-}24h}$) at the no observed adverse effect levels (NOAELs) in 13-week repeated-dose toxicity studies in rats and cynomolgus monkeys [(a) 40 mg/kg/day in male rats, (b) 20 mg/kg/day in female rats, (c) 30 mg/kg/day in male cynomolgus monkeys, (d) 30 mg/kg/day in female cynomolgus monkeys] were (a) 23.5 μmol/L and 118 μmol/L·h, respectively, (b) 17.1 μmol/L and 94.4

μmol/L·h, respectively, (c) 17.5 μmol/L and 102.6 μmol/L·h, respectively, and (d) 13.2 μmol/L and 56.7 μmol/L·h, respectively, which were (a) 1.6- and 0.9-fold, respectively, (b) 1.2- and 0.7-fold, respectively, (c) 1.2- and 0.8-fold, respectively, and (d) 0.9- and 0.4-fold, respectively, the human exposure.[28)]

Table 12. Repeated-dose toxicity studies

Test system	Route of administration	Duration of dosing	Dose (mg/kg/day)	Principal findings	NOAEL (mg/kg/day)	Attached document CTD
Male and female mice (CD-1)	Oral	8 days (QD)	0, 100, 300, 600	Deaths or moribund sacrifices: 600 (10 of 15 females) ≥100: decreased food consumption, decreases in white blood cell count/lymphocyte count/eosinophil count, increases in AST/ALT/SDH/ALP/bilirubin, yellow material retained in the gastrointestinal tract, decreased spleen weight, acinar cell vacuolation/apoptosis in the pancreas, etc. ≥300: urogenital wetting/staining, lethargy, decreased body temperature, rough hair coat, shivering, decreased body weight gain, decreased reticulocyte count, increased creatinine, decreased total protein, increased liver weight, apoptosis in the lymphoid organs, centrilobular cell hypertrophy in the liver, etc. 600: wetting/staining of facial/periocular/perioral fur, eyelid closure/incomplete eyelid opening, decreased stool output/no-feces, etc.	<100	4.2.3.2.1 Reference data
Male and female rats (Sprague Dawley)	Oral	4 weeks (QD) + 4-week recovery	Males: 0, 20, 60, 120 Females: 0, 10, 30, 60	Deaths or moribund sacrifices: 120 (12 of 15 males),[a)] 60 (8 of 15 females)[a)] ≥20/10[b)]: decreases in serum albumin/total protein, increases in serum ALP/ALT, etc. ≥60/30[b)]: clear material around the mouth, increases in serum bilirubin/AST/cholesterol/triglycerides,[c)] acinar cell vacuolation/apoptosis in the pancreas, etc. 120/60[b)]: yellow/red clear material on fur, decreased skin tone, emaciation, continuous tremors, convulsions, red nasal discharge, decreases in body weight/food consumption,[d)] increases in red blood cell count/hemoglobin/hematocrit,[d)] decreased reticulocyte count,[d)] increases in white blood cell count/monocyte count/basophil count,[c)] increases in serum urea nitrogen/creatinine,[e)] increases in serum phosphorus/amylase/glucose, white matter vacuolation in the brain (thalamus), etc. Reversibility: reversible except for serum bilirubin,[f)]	Males: 60 Females: 30	4.2.3.2.5
Male and female rats (Sprague Dawley)	Oral	13 weeks (QD) + 13-week recovery	Males: 0, 20, 40, 60, 90 Females: 0, 10, 20, 30, 45	Deaths or moribund sacrifices: 20 (1 of 23 males),[g)] 60 (2 of 23 males), 90 (8 of 23 males)[h)]; 30 (2 of 23 females),[i)] 45 (8 of 23 females)[h)] ≥40/20[b)]: salivation, increases in white blood cell count/ lymphocyte count,[d)] decreased serum potassium, etc. ≥60/30[b)]: decreased locomotor activity,[d)] increases in monocyte count/large unstained cells,[j)] increased serum amylase,[d)] white matter vacuolation in the brain/striatum (caudate/putamen), acinar cell apoptosis/vacuolation in the pancreas, etc. 90/45: tremors (intermittent/continuous), convulsions (continuous), decreased body weight, etc. Reversibility: reversible.	Males: 40 Females: 20	4.2.3.2.6

[28)] The C_{max} and $AUC_{0\text{-}24h}$ in Japanese patients treated orally with capmatinib 400 mg BID in Study A2201 were 14.4 μmol/L and 131 μmol/L·h, respectively.

Test system	Route of administration	Duration of dosing	Dose (mg/kg/day)	Principal findings	NOAEL (mg/kg/day)	Attached document CTD
Male and female cynomolgus monkeys	Oral	4 weeks (QD) + 4-week recovery	0, 30, 75, 150	Deaths: 150 (1 of 6 females)[k)] ≥30: abnormal feces colors, increased acinar cell apoptosis in the pancreas, etc. ≥75: discolored urine,[d)] amphophilic deposits with multinucleated giant cells within the renal interstitium/tubule, decreased serum cholesterol,[d)] decreased serum calcium,[c)] etc. 150: increased serum amylase, etc. Reversibility: reversible except for amphophilic deposits with multinucleated giant cells within the renal interstitium/tubule	30	4.2.3.2.8
Male and female cynomolgus monkeys	Oral	13 weeks (QD) + 8-week recovery	0, 10, 30, 75	75: salivation, decreases in serum albumin/total protein,[d)] increases in serum amylase/lipase,[d)] neutrophilic infiltration associated with single cell necrosis in the liver,[d)] etc.	30	4.2.3.2.9

a) Due to high mortalities or moribund sacrifices in the male 120 mg/kg/day and female 60 mg/kg/day groups, all surviving animals in these groups (including recovery animals) were necropsied at the end of the dosing period; b) Dose in males/Dose in females; c) females only; d) males only; e) The applicant discussed that the changes in the male 120 mg/kg/day group may be related to hemoconcentration; f) Although increased serum bilirubin was observed after the recovery period in the male 20 and 60 mg/kg/day groups, there was no clear dose-relationship, and its toxicological significance is unknown; g) Although the cause of death was not identified by histopathological examination, as no death occurred at 40 mg/kg/day, this was considered unrelated to capmatinib; h) Due to high mortalities or moribund sacrifices in the male 90 mg/kg/day and female 45 mg/kg/day groups, an early necropsy was scheduled for half of the surviving animals in these groups at Weeks 4 and 8, respectively. Dosing was suspended for the remaining animals, and the animals proceeded to the 13-week recovery period; i) Including death due to a gavage error (1 of 23 animals); j) Only males in the 60 mg/kg/day group; k) The animal was found dead on the 7th day of the recovery phase. Based on the findings from various examinations, the cause of death was bacterial sepsis, which was considered unrelated to capmatinib.

5.3 Genotoxicity

In vitro studies were conducted using a bacterial reverse mutation assay and a chromosomal aberration assay in human peripheral blood lymphocytes. An *in vivo* study was conducted using a bone marrow micronucleus test in rats (Table 13). These studies all produced negative results, and capmatinib was considered to have little genotoxic potential in the body.

Table 13. Genotoxicity studies

Type of study			Test system	Metabolic activation (Treatment)	Concentration[a)] or dose[b)]	Test result	Attached document CTD
In vitro	Bacterial reverse mutation assay	Plate incorporation (Experiment 1)	*Salmonella typhimurium*: TA98, TA100, TA1535, TA102, TA97a	S9－/＋	0, 1.6, 8, 40, 200, 1,000,[c)] 5,000[c)]	Negative	4.2.3.3.1-1
		Plate incorporation (Experiment 2)	*Salmonella typhimurium*: TA98, TA100, TA1535, TA102, TA97a	S9－	0, 78.13, 156.3, 312.5, 625, 1,250, 2,500,[c)] 5,000[c)]	Negative	
		Pre-incubation (Experiment 2)	*Salmonella typhimurium*: TA98, TA100, TA1535, TA102, TA97a	S9＋	0, 78.13, 156.3, 312.5, 625, 1,250, 2,500,[c)] 5,000[c)]	Negative	
	Chromosomal aberration assay in cultured mammalian cells		Human peripheral blood lymphocytes	S9＋ (3 hours)	0, 50, 75,[c)] 100[c)]	Negative	4.2.3.3.1-2
				S9－ (3 hours)	0, 50, 75, 100[c)]	Negative	
				S9－ (20 hours)	0, 75, 100,[c)] 150[c)]	Negative	
In vivo	Rodent micronucleus assay[c)]		Male and female rats (Sprague Dawley) Bone marrow		Males: 0, 50, 100, 200 Females: 0, 17.5, 35, 70	Negative	4.2.3.2.2-1

a) μg/plate or μg/mL, b) mg/kg/day, c) Precipitation was observed.

5.4 Carcinogenicity

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

5.5 Reproductive and developmental toxicity

Capmatinib is an anti-neoplastic drug intended to treat patients with advanced cancer. A study of fertility and early embryonic development to implantation or a study for effects on pre- and post-natal development, including maternal function, was not conducted.

The applicant explained that because (a) capmatinib is not genotoxic [see Section 5.3] and there were no effects on male or female reproductive organs in repeated-dose toxicity studies [see Section 5.2], capmatinib is unlikely to adversely affect male or female fertility or early embryonic development.

Embryo-fetal development studies of capmatinib were conducted in rats and rabbits, and teratogenicity was observed in rats at ≥10 mg/kg and in rabbits at ≥5 mg/kg (Table 14). Capmatinib exposure (C_{max} and $AUC_{0\text{-}24h}$) at the NOAELs for embryo-fetal developmental toxicity in (a) rats and (b) rabbits (1 mg/kg/day in both rats and rabbits) were (a) 0.4 μmol/L and 4.4 μmol·h/L, respectively, and (b) 0.1 μmol/L and 0.1 μmol·h/L, respectively, which were (a) 0.03- and 0.03-fold, respectively, and (b) 0.001- and 0.007-fold, respectively, the human exposure.[28)]

Table 14. Reproductive and developmental toxicity studies

Type of study	Test system	Route of administration	Duration of dosing	Dose (mg/kg/day)	Principal findings	NOAEL (mg/kg/day)	Attached document CTD
Embryo-fetal development	Female rats (Sprague Dawley)	Oral	Gestation days 6-17 (QD)	0, 1, 10, 30	Dams: 30: reduced body weight gain, reduced food consumption Fetuses: ≥10: reduced fetal weights, increased incidences of fetal malformations, gross external malformations (inward malrotation of forepaws/hindpaws, abnormal flexure of forepaws/hindpaws, entire length of thin forelimbs/hindlimbs, lack of/reduced flexion at the humerus/ulna joints), skeletal variations (incomplete ossification of the hyoid bone/interparietal bone, sternebrae 1 to 4/sternebra 5/xiphisternum variants [unossification, incomplete/irregular ossification, semi-bipartite/bipartite ossification]) 30: gross external malformations (small/narrowed tongue), skeletal malformation (irregular ossification of the fibula)	F_0 females: 10 F_1 litters: 1	4.2.3.5.2-1
	Female rabbits (NZW)	Oral	Gestation days 7-20 (QD)	0, 1, 5, 60	Dams: none Fetuses: 5: visceral malformations (small/fused lung lobes) 60: reduced fetal weights, increased incidences of fetal malformations, gross external malformations (small/narrowed tongue, abnormal flexure of hindpaws, inward malrotation of forepaws/hindpaws, outward malrotation of forepaws, entire length of thin forelimbs/hindlimbs, lack of /reduced flexion at the humerus/ulna joints), visceral malformations (small lung lobes), skeletal malformations (irregular ossification of the ulna, ulna misaligned, irregular ossification of the fibula), gross external variations (abnormal flexure of forepaws), skeletal variations (incomplete ossification of the hyoid bone, sternebrae 1 to 6 variants [unossified/incomplete/semibipartite/bipartite], cervical ribs)	F_0 females: 60 F_1 litters: 1	4.2.3.5.2-3

5.6 Local tolerance

Because capmatinib is an oral formulation, no local tolerance studies were conducted.

5.7 Other toxicity studies

5.7.1 Photosafety

An *in vitro* phototoxicity study using a mouse fibroblast cell line and a photosensitization study in mice were conducted. Capmatinib was considered to have phototoxic and photosensitizing potential (Table 15). Capmatinib exposure (C_{max} and $AUC_{0\text{-}24h}$) at the NOAEL for photosensitization (30 mg/kg/day) was 33.9 μmol/L and 85.3 μmol/L·h, respectively, which were 2.4- and 0.7-fold the human exposure,[28)] respectively.

The applicant explained that because a risk of photosensitivity reaction in clinical use of capmatinib cannot be ruled out, the above phototoxicity results will be communicated via the package insert, etc.

Table 15. Photosafety studies

Type of study	Test system	Test method	Principal findings	Attached document CTD
Phototoxicity	Mouse fibroblast cell line Balb/c 3T3	0.10-6.4 μg/mL (in the presence of UVR[a)]) 5-150 μg/mL (in the absence of UVR[a)])	Phototoxic (Photo irritation factor, 48.2)	4.2.3.7.7-1
Photosensitization	Female mice (BALB/cByJ)	Mice were dosed with oral capmatinib 0, 10, 30, 100, or 300 mg/kg/day for 3 days[b)] and exposed to UVR[c)] 30 minutes after dosing. On Day 4, both ears and lymph nodes were collected and weighed, and then lymph node cell counts were determined. Histopathological examination of the left eye was performed.	100: increased incidence/severity of erythema of the ear/tail, increases in ear/lymph node weights and lymph node cell counts	4.2.3.7.7-2

a) Exposed to UV-A (5 J/cm^2) for 1 hour. b) Animals in the 300 mg/kg/day group with or without UVR were terminated early due to poor general condition, and the 10 mg/kg/group was added for evaluation. c) Exposed to UV-A (10 J/cm^2) for 45 to 75 minutes.

5.7.2 Skin sensitization study

A skin sensitization study in mice was conducted. After application of ≥3% capmatinib, increases in ear weights were observed, but there were no changes in lymph node weights or cell counts. Thus, capmatinib was considered to have no skin sensitizing potential (Table 16).

Table 16. Skin sensitization study

Type of study	Test system	Test method	Principal findings	Attached document CTD
Local lymph node assay	Female mice (BALB/cByJ)	0%,[a)] 0.3%, 3%, or 30% capmatinib was applied onto the dorsal regions of both ears for 3 days. On Day 4, both ears and lymph nodes were collected and weighed, and then lymph node cell counts were determined.	≥3%: Increases in ear weights were observed, but there were no changes in lymph node weights or cell counts.	4.2.3.7.7-1

a) Propylene glycol and water (7:3) only was applied.

5.7.3 Mechanistic studies of toxicity, etc.

5.7.3.1 Mechanistic study of CNS toxicity

Because of clinical signs such as convulsions and tremors and serious toxicities such as white matter vacuolation in the brain or striatum observed in repeated-dose toxicity studies in rats [see Section 5.2], a mechanistic study of the central nervous system (CNS) toxicity was conducted (Table 17). There were no abnormalities in the plasma vitamin B6 concentration or electroencephalogram. Transmission electron microscopy confirmed that the vacuolation in the brain was attributed to swollen myelin sheath characterized by the separation of myelin sheath layers, but its development mechanism remained unidentified. Although strain-related differences in the occurrence of toxicity were observed between rats used in this study (Wistar Hannover strain) and rats used in the repeated-dose toxicity studies (Sprague Dawley strain) [see Section 5.2], there are no differences in the amino acid sequence of MET between the 2 strains, the effects on the CNS were not considered to be related to MET.

Table 17. Mechanistic study of CNS toxicity

Test system	Route of administration	Duration of dosing	Dose (mg/kg/day)	Principal findings	Attached document CTD
Male rats (Wistar Hannover)	Oral	Main study: 4 weeks (QD) Satellite 1: 1, 3, 7, 14, 28 days (QD) Satellite 2: single dose (QD)	Main study: 0, 60, 90 Satellite 1: 0, 90 Satellite 2: 0, 30, 90	≥60: decreases in body weight gain/food consumption 90: Transmission electron microscopy confirmed that vacuolation in the brain was attributed to swollen myelin sheath characterized by separation of myelin sheath layers. On the other hand, downregulation of an *Nrg1/Zeb2*-associated gene signature in the brain was transient and reversible within 24 hours post-dose. No changes in the transcription of the *Nrg1 type I, II,* and *III* isoforms, which are involved in myelination, and no alterations in the protein expression of NRG1 Type III.	4.2.3.7.3-1 Reference data

5.7.3.2 Mechanistic study of ototoxicity

In order to investigate the association between hypoacusis reported in clinical studies and capmatinib, a mechanistic study on the effect of capmatinib on the auditory system was conducted. The study showed no evidence of ototoxicity (Table 18).

Based on the study results, the applicant concluded that capmatinib is unlikely to affect the auditory system in its clinical use.

Table 18. Mechanistic study of ototoxicity

Test system	Route of administration	Duration of dosing	Dose (mg/kg/day)	Principal findings	Attached document CTD
Male rats (Sprague Dawley	Oral	6 weeks (QD) + 8-week recovery	0, 60, 90	Deaths or moribund sacrifices: 60 (5 of 15 animals), 90 (9 of 26 animals) ≥60: White matter vacuolation in the brain was observed. No changes in auditory brainstem response, electroencephalogram, or histopathological examination of the mid- and inner ear.	4.2.3.7.3-2

5.7.3.3 Investigations on crystalline-like material in the kidney

Investigations on the crystalline-like material in the kidney observed in a 4-week repeated oral dose toxicity study in cynomolgus monkeys [see Section 5.2] were conducted, which confirmed that the crystalline-like material consists of an inorganic component containing calcium and phosphate (Table 19).

Table 19. Investigations on crystalline-like material in the kidney

Type of study	Test method	Result	Attached document CTD
Fourier transform infrared (FT-IR) microscopic investigation	FT-IR microscopy was applied to slices of kidney samples collected from cynomolgus monkey of the capmatinib 75 mg/kg group.	The investigation indicated that the crystalline-like material does not consist of an organic component, but consists of an inorganic component, which is considered phosphate.	4.2.3.7.3-3 Reference data
Scanning electron microscopy (SEM)-energy dispersive X-ray spectroscopy (EDS) investigation	To identify the elemental composition of kidney crystals, SEM and EDS were applied to slices of kidney samples collected from cynomolgus monkey of the capmatinib 75 mg/kg group.	The crystalline-like material consists of calcium and phosphorus, and is not related to capmatinib or its metabolites. Its nature and structure are unknown.	4.2.3.7.3-4 Reference data

5.7.4 Toxicity studies on impurities

Among drug substance impurities, the levels of Related Substances A, B, and C are greater than the

qualification threshold given in the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) Q3A and Q3B guidelines. A bacterial reverse mutation assay, a chromosomal aberration assay, a micronucleus test and a comet assay, and a 4-week repeated-dose toxicity study were conducted with the drug substance spiked with Related Substances A and B (Tables 20 and 21). The drug substance spiked with Related Substances A and B induced structural chromosome aberrations etc. in the chromosomal aberration assay, but it did not induce micronuclei in the micronucleus test, nor did it cause DNA strand breaks in the comet assay. Thus, Related Substances A and B are considered to have no genotoxic potential, and are considered free from safety concerns at the upper limit of the specification for the drug substance and the drug product. Related Substance C is a metabolite identified in animals other than the dog and in the human (M16) and has been tested for safety in previous toxicity studies Related Substance C is thus considered free from safety concerns at the upper limit of the specification limit for the drug substance and the drug product.

Table 20. Genotoxicity studies with drug substance spiked with impurities (Related Substances A and B)

Type of study		Test system	Metabolic activation (Treatment)	Concentration (μg/plate)	Test result	Attached document CTD
In vitro a)	Bacterial reverse mutation assay (Ames)	*Salmonella typhimurium*: TA98, TA100, TA1535, TA97a, TA102	S9－/＋	0, 5, 16, 50, 160, 500, 1,600, 5,000	Negative	4.2.3.7.6-1
In vitro a)	Chromosomal aberration assay in cultured mammalian cells	Human peripheral blood lymphocytes	S9－/＋ (3 hours)	0, 50, 70, 80	Negative	4.2.3.7.6-2
			S9－ (20 hours)	0, 5, 10, 15	Positive (15)	
			S9－ (20 hours)	0, 5, 10, 20	Positive (20)	
In vivo b)	Rodent micronucleus test and comet assay	Male and female rats (Sprague Dawley) Bone marrow and liver		0, 17.5, 35, 70	Negative	4.2.3.7.6-3

a) Drug substance containing Related Substance A ([redacted]%) and Related Substance B ([redacted]%) was used. b) Drug substance containing Related Substance A ([redacted]%) and Related Substance B ([redacted]%) was used.

Table 21. Repeated-dose toxicity study with drug substance spiked with impurities (Related Substance A and Related Substance B)

Test system	Route of administration	Duration of dosing	Dose (mg/kg/day)	Principal findings	Attached document CTD
Male and female rats (Sprague Dawley)	Oral	4 weeks (QD)	Males: 0, 20,[a)] 60,[a)] 60[b)] Females: 0, 10,[a)] 30,[a)] 30[b)]	≥20: decreased prostate gland weights, decreased secretion in the lumen of the prostate gland[c)] 60/30[d)]: salivation, wet fur of the lower jaw	4.2.3.7.6.1

a) Drug substance spiked with Related Substance A ([redacted]%) and Related Substance B ([redacted]%) was used. b) Drug substance without spiked impurities was used as a comparator. c) The finding was considered of little toxicological significance because the change was slight and lacked a clear dose-relationship, and there were no changes in prostate epithelial cells or other male reproductive organs, etc. d) Dose in males/Dose in females

5.R Outline of the review conducted by PMDA

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

5.R.1 Effects of capmatinib on central nervous system

The applicant's explanation about the effects of capmatinib on the CNS:

The mechanism of how capmatinib affected the CNS in the 4-week and 13-week repeated-dose toxicity studies in rats is unclear [see Section 5.7.3.1]. However, given the following observations, etc., the effect of capmatinib on the CNS are unlikely to become a problem in its clinical use, requiring no cautionary advice in the package insert, etc.

- Tremors and convulsions observed in rats are changes at lethal doses, and the evaluation of their reversibility was precluded. Meanwhile, white matter vacuolation in the brain or striatum, a histopathological change, is inferred to be reversible because (a) the change was not observed after the recovery period in surviving animals, and (b) transmission electron microscopy revealed that the change was attributed to swollen myelin sheath characterized by separation of myelin sheath layers.
- The relevant adverse events were all manageable in the clinical studies of capmatinib.

PMDA's discussion:

Although it is difficult to draw a definitive conclusion on the effect of capmatinib on the CNS, given the following points etc., the possibility cannot be ruled out that the effect of capmatinib on the CNS become a problem in its clinical use. Thus, the package insert etc. should advise that CNS effect were observed in the toxicity studies of capmatinib.

- Given the systemic exposure of capmatinib at the NOAEL for these changes in the repeated-dose toxicity studies in rats (40 mg/kg/day in male rats, 20 mg/kg/day in female rats), there is no adequate safety margin [see Section 5.2]
- The systemic exposure at the NOAEL for CNS toxicity in the repeated-dose toxicity studies in cynomolgus monkeys (75 mg/kg/day) is approximately 2 times the human exposure.
- The potential of capmatinib to cross the blood brain barrier has been suggested.

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

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

Teratogenicity considered related to MET inhibition by capmatinib was observed in embryo-fetal development studies in rats and rabbits (*BioMed. Rep*. 7: 495-503), and capmatinib exposure at the NOAEL for teratogenicity was lower than the human exposure [see Section 5.5]. Given these points etc., capmatinib can cause fetal harm when administered to pregnant women or women who may be pregnant. Thus, the use of capmatinib in pregnant women or women who may be pregnant is not recommended. However, considering poor prognosis, etc. of NSCLC, capmatinib may be administered with caution to pregnant women or women who may be pregnant if the expected therapeutic benefits outweigh the possible risks, on the premise that patients are fully informed of the potential risk to the fetus. The package insert will disseminate the results from the embryo-fetal development studies in rats and rabbits and advise that capmatinib can cause fetal harm.

PMDA accepted the applicant's explanation.

5.R.3 Use of capmatinib in men with a partner of reproductive potential

The applicant's explanation about the use of capmatinib in men with a partner of reproductive potential:

There was no evidence for the genotoxicity or male reproductive toxicity of capmatinib. Nevertheless, because the embryo-fetal development studies in rats and rabbits showed the teratogenicity of capmatinib related to its pharmacological effects, and capmatinib exposure at the NOAEL for teratogenicity was lower than the human exposure [see Sections 5.5 and 5.R.2], capmatinib exposure via semen in female partners of reproductive potential was estimated. The capmatinib concentration in semen was defined as clinical exposure (C_{max}). Assuming that capmatinib is all absorbed into the circulation through the vaginal wall, the estimated exposure in the female partners is 3.9 times the exposure at the NOAEL for teratogenicity [see Section 5.5]. Based on the estimation, it is difficult to exclude the possibility of teratogenicity via semen. Thus, the package insert etc. will appropriately advise healthcare professionals that men with a partner of reproductive potential must use effective contraception during treatment with capmatinib and for a certain period of time after the last dose.

PMDA's discussion:

The applicant's explanation about the teratogenic risk of capmatinib via semen is acceptable. Men with a partner of reproductive potential need to select a barrier method of contraception (condom) to prevent vaginal absorption of capmatinib in semen.

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 oral formulations of capmatinib is available in capsules and tablets and the PK etc. of capmatinib were studied using the both formulations (Table 22). The proposed commercial formulations are 150- and 200- mg tablets. Although the proposed commercial 150-mg tablet formulation differs from the 150-mg tablet formulation used in Study A2201 in [redacted], a dissolution test performed in accordance with "Guideline for Bioequivalence Studies for Formulation Changes of Oral Solid Dosage Forms" (PMSB/ELD Notification No.67 dated February 14, 2000, the Guideline was partially revised by PFSB/ELD Notification No. 0229-10 dated February 29, 2012) demonstrated the bioequivalence between the 2 formulations. Although the proposed commercial 200-mg tablet formulation differs from the 200-mg tablet formulation used in Study X2107 in [redacted], the results of the proposed dissolution test[29)] showed no clear differences in dissolution profile between the 2 formulations.

Table 22. Oral formulations used in the clinical studies

Formulation	Study ID
Capsules (10 and 50 mg)	Japanese phase I study (Study X1101), foreign phase I studies (Studies X2101T, X2102, X2103,[*1] X2106[*2])
Tablets (50, 100, 150, and 200 mg)	Japanese phase I study (Study X1101[*3]), global phase II study (Study A2201[*4]), foreign phase I studies (Studies A2101,[*5] A2102,[*5] A2103,[*6] A2105,[*6] A2106,[*7] A2108,[*6] A2109,[*8] X2102,[*9] X2103,[*5] X2107[*5])

*1 The 50-mg capsules were used. *2 The 50-mg capsules of ^{14}C-capmatinib were used. *3 The 50- and 200-mg tablets were used. *4 The 100-, 150-, and 200-mg tablets were used. *5 The 200-mg tablets were used. *6 The 100- and 200-mg tablets were used.

[29)] Using 4 different media (pH[redacted], [redacted], [redacted], and [redacted]), the dissolution profile of capmatinib was determined according to [redacted] method ([redacted] rpm).

*7 The 100-mg tablets were used. *8 The 100- and 150-mg tablets were used. *9 The 50-, 100-, and 200-mg tablets were used.

6.1.1 Analytical method

"MET Exon14 Deletion Test," the Novartis Precision Medicine's reverse transcription-polymerase chain reaction (RT-PCR) assay, was used to detect METex14 skipping mutations in Cohorts 4 and 5b of Study A2201. In a meantime, a partial change approval was granted on November 29, 2019 to "FoundationOne CDx Cancer Genomic Profile" produced by Chugai Pharmaceutical Co., Ltd., a companion diagnostics (CDx) that assists the identification of patients eligible for treatment with capmatinib.

6.1.2 Assay

Capmatinib in human plasma was quantified by LC-MS/MS, and the lower limit of quantification was 1.00 ng/mL.[30)]

6.1.3 Foreign clinical studies

6.1.3.1 Foreign phase I study (CTD 5.3.3.4-5, Study X2107 [[redacted] to [redacted]])

A 6-sequence, 3-period, crossover study was conducted in 24 healthy adults (24 subjects included in PK analysis) to assess the effect of food on the PK of capmatinib. Subjects received a single oral dose of capmatinib 600 mg under fasted conditions,[31)] or 30 minutes after a low-fat meal[32)] or a high-fat meal.[33)] A ≥7-day washout period was set between the treatment periods.

The capmatinib C_{max} and AUC_{inf} geometric mean ratios for (a) a low-fat meal and (b) a high-fat meal vs. fasted [90% confidence interval (CI)] were (a) 1.11 [1.01, 1.23] and 1.20 [1.09, 1.31], respectively, and (b) 1.15 [1.04, 1.27] and 1.46 [1.33, 1.60], respectively.

6.1.3.2 Foreign phase I study (CTD 5.3.3.4-1, Study A2101 [[redacted] to [redacted]])

An open-label, uncontrolled study was conducted in 20 healthy adults (20 subjects included in PK analysis) to assess the effect of a proton pump inhibitor (rabeprazole) on the PK of capmatinib. Rabeprazole was administered orally at 20 mg QD on Days 7 to 10,[34)] with a single oral dose of capmatinib 600 mg under fasted conditions on Days 1 and 10.

The geometric mean ratios of C_{max} and AUC_{inf} of capmatinib after capmatinib + rabeprazole treatment to that after capmatinib alone doses [90% CI] were 0.625 [0.533, 0.734] and 0.748 [0.637, 0.878], respectively.

The applicant's explanation:
Based on the above, coadministration with a proton pump inhibitor may decrease capmatinib exposure. This outcome will be communicated.

[30)] The lower limit of quantification for analysis of plasma samples in Studies A2108, A2109, and A2201 was 1.04 ng/mL.
[31)] Subjects were fasted for ≥10 hours (overnight) before administration and for 4 hours after administration.
[32)] Containing approximately 315 kcal and 20% fat
[33)] Containing approximately 1,000 kcal and 50% fat
[34)] Administered after meal on Days 7-9 and under fasted conditions on Day 10.

6.2 Clinical pharmacology

The PK of capmatinib alone or that in combination with itraconazole or rifampicin were studied in healthy adults and patients with cancer. The effect of capmatinib on the PK of caffeine, midazolam, digoxin, and rosuvastatin was assessed.

6.2.1 Japanese clinical study

6.2.1.1 Japanese phase I study (CTD 5.3.5.2-3, Study X1101 [February 2012 to January 2016])

An open-label, uncontrolled study was conducted in 44 patients with advanced solid tumors (44 subjects included in PK analysis) to evaluate the PK etc. of capmatinib. Subjects received capmatinib (tablets) orally at 200 or 400 mg BID under fasted conditions, and plasma capmatinib concentrations etc. were determined.[35)]

The PK parameters of capmatinib (tablets) are shown in Table 23. Following the oral administration of capmatinib (tablets) 400 mg BID, the accumulation ratio of capmatinib[36)] was 1.99.

Table 23. PK parameters of capmatinib (tablets)

Dose (mg)	Sampling day (Day)	n	C_{max} (μg/mL)	t_{max}* (h)	AUC_{12h} (μg·h/mL)	AUC_{last} (μg·h/mL)	$t_{1/2}$ (h)
200	1	3	2.19 (118)	0.950 (0.917, 0.967)	8.17 (61.3)	8.20 (61.0)	2.47 (19.1)
	15	3	2.85 (59.6)	0.967 (0.967, 2.00)	11.0 (56.2)	11.0 (56.2)	2.91 (3.50)
400	1	12	3.23 (80.8)	1.00 (0.467, 3.95)	12.5 (73.8)	12.5 (74.0)	2.73 (26.5)
	15	9	6.45 (67.0)	1.00 (0.500, 2.00)	26.3 (70.2)	26.4 (70.4)	2.69 (24.0)

Geometric mean (% coefficient of variation), *Median (range)

6.2.2 Foreign clinical studies

6.2.2.1 Foreign phase I study (CTD 5.3.5.2-2, Study X2102 [February 2012 to July 2017])

An open-label, uncontrolled study was conducted in 131 patients with *MET* dysregulated[37)] advanced solid tumors (80 subjects included in PK analysis) to evaluate the PK etc. of capmatinib. Subjects orally received capmatinib (capsules) 100, 200, 250, 350, 450, or 600 mg or capmatinib (tablets) 400 mg BID under fasted conditions, and plasma capmatinib concentrations etc. were determined.

The PK parameters of capmatinib are shown in Table 24. The C_{max} and AUC_{12h} of capmatinib increased in a nearly dose-proportional manner over the dose range tested. Following the oral administration of capmatinib (tablets) 400 mg BID, the accumulation ratio[36)] was 1.05.

35) Plasma capmatinib concentrations etc. following the oral administration of capmatinib (capsules) 100, 200, 400, 500, 600, or 800 mg QD, or 400 or 600 mg BID under fasted conditions were also determined.

36) The ratio of AUC_{12h} on Day 15 to AUC_{12h} on Day 1

37) The definitions of *MET* dysregulation (a) For NSCLC, nasopharyngeal cancer, hormone-receptor-negative and HER2-negative breast cancer, gastric cancer, etc.; MET H-score of ≥150, MET/centromere ratio of ≥2.0, MET GCN of ≥5, or ≥50% of tumor cells with IHC score of 2+ or 3+: (b) For hepatocellular carcinoma and glioblastoma; MET H-score of ≥50, MET/centromere ratio of ≥2.0, or MET GCN of ≥5: (c) For papillary renal cell carcinoma (RCC); MET H-score of ≥150, MET/centromere ratio of ≥2.0, MET GCN of ≥5, ≥50% of tumor cells with IHC score of 2+ or 3+, or germline *MET* mutation confirmed at the study site

Table 24. PK parameters of capmatinib

Formulation	Dose (mg)	Sampling day (Day)	n	C_{max} (μg/mL)	t_{max}*1 (h)	AUC_{12h} (μg·h/mL)
Capsule	100	1	4	0.375 (108)	3.02 (1.92, 4.33)	2.51, 3.73
		15	4	0.503 (105)	2.86 (1.88, 4.00)	3.28 (70.3)
	200	1	5	2.32 (41.7)	2.10 (0.500, 4.00)	7.67*2 (50.4)
		15	5	2.37 (39.2)	1.92 (1.85, 8.00)	12.2 (52.4)
	250	1	4	0.902 (99.0)	3.19 (1.00, 5.88)	3.87, 8.10
		15	3	1.27 (114)	1.00 (0.450, 2.02)	6.25 (70.0)
	350	1	3	2.28 (173)	2.05 (0.833, 3.97)	8.75, 26.9
		15	3	3.50 (94.4)	3.93 (1.00, 4.02)	18.9 (26.5)
	450	1	8	2.10 (45.4)	2.25 (1.13, 7.17)	8.15*2 (71.6)
		15	7	2.97 (46.3)	2.00 (1.83, 7.87)	17.9 (32.6)
	600	1	8	3.26 (145)	2.04 (1.00, 7.17)	18.1*2 (135)
		15	45	3.63 (103)	2.00 (0.517, 8.42)	21.2*3 (74.4)
Tablet	400	1	4	4.97 (50.0)	1.88 (0.500, 2.17)	19.0 (33.3)
		15	8	4.35 (57.9)	2.02 (0.500, 4.33)	20.6 (41.9)

Geometric mean (% coefficient of variation) (Individual values are listed for n = 2)
*1 Median (range); *2, n = 4; *3, n = 43

6.2.2.2 Foreign phase I study (CTD 5.3.3.1-1, Study X2106 [to 20)

An open-label, uncontrolled study was conducted in 6 healthy adults (6 subjects included in PK analysis) to evaluate the mass balance, etc. of capmatinib. A single oral dose of ^{14}C-capmatinib 600 mg was administered, and radioactivity concentrations in blood, plasma, urine, and feces etc. were determined.

Unchanged capmatinib and M16 were mainly identified in the plasma collected up to 12 hours post-dose (accounting for 42.9% and 21.5%, respectively, of the total radioactivity AUC_{12h} in plasma).

The recovery of radioactivity in urine and feces (% of the administered radioactivity) up to 168 hours post-dose was 21.8% and 77.9%, respectively. In the urine collected up to 96 hours post-dose, M16 was mainly identified (representing 2.9% of the administered radioactivity). In the feces collected up to 96 hours post-dose, unchanged capmatinib was mainly found (representing 42.1% of the administered radioactivity), and M16, M26, and M20 (formed via oxidation) were identified as the primary metabolites (representing 5.1%, 3.3%, and 2.3%, respectively, of the administered radioactivity).

6.2.3 Drug interaction studies

6.2.3.1 Drug interaction study with itraconazole or rifampicin (CTD 5.3.3.4-2, Study A2102 [to 20])

A 2-arm, 2-period, open-label, uncontrolled study was conducted in 53 healthy adults (51 subjects included in PK analysis)[38)] to assess the effect of itraconazole (a strong CYP3A inhibitor) and rifampicin (a strong CYP3A inducer) on the PK of capmatinib, according to the following regimen.

Inhibition cohort

Oral itraconazole 200 mg QD on Days 5 to 14, with a single oral dose of capmatinib 200 mg on Days 1 and 10

[38)] Inhibition and induction cohorts enrolled 27 and 26 subjects, respectively (26 and 25 subjects included in PK analysis, respectively).

Induction cohort

Oral rifampicin 600 mg QD on Days 5 to 13, with a single oral dose of capmatinib 400 mg on Days 1 and 10

The geometric mean ratios of C_{max} and AUC_{inf} of capmatinib after capmatinib + (a) itraconazole or (b) rifampicin treatment to that after capmatinib alone dose [90% CI] were (a) 1.03 [0.866, 1.22] and 1.42 [1.33, 1.52], respectively, and (b) 0.441 [0.387, 0.502] and 0.335 [0.300, 0.374], respectively.

6.2.3.2 Drug interaction study with caffeine or midazolam (CTD 5.3.3.4-3, Study A2103 [December 2015 to September 2017])

An open-label, uncontrolled study was conducted in 37 patients with *MET* dysregulated[39)] advanced solid tumors (31 subjects included in PK analysis)[40)] to assess the effect of capmatinib on the PK of caffeine (a CYP1A2 substrate) and midazolam (a CYP3A substrate). Capmatinib was administered orally at 400 mg BID on Days 4 to 12, with a single oral dose of caffeine 100 mg and midazolam 2.5 mg on Days 1 and 9.

The geometric mean ratios of C_{max} and AUC_{inf} of (a) caffeine (b) midazolam for caffeine and midazolam + capmatinib to that of caffeine or midazolam alone [90% CI] were (a) 1.04 [0.964, 1.13] and 2.34 [2.08, 2.63], respectively, and (b) 1.22 [1.07, 1.38] and 1.09 [0.976, 1.22], respectively.

The applicant's explanation about the coadministration of capmatinib with a CYP1A2 or CYP3A substrate, based on the above results:

The increase in midazolam exposure due to concomitant capmatinib was limited, and caution against coadministration with a CYP3A substrate is thus unnecessary. On the other hand, coadministration with capmatinib increased caffeine exposure, caution should be exercised against the coadministration of capmatinib with a CYP1A2 substrate. Thus, the relevant cautionary advice will be provided.

6.2.3.3 Drug interaction study with digoxin or rosuvastatin (CTD 5.3.3.4-4, Study A2105 [December 2015 to April 2017])

An open-label, uncontrolled study was conducted in 32 patients with *MET* dysregulated[39)] advanced solid tumors[41)] to assess the effect of capmatinib on the PK of digoxin (a P-gp substrate) and rosuvastatin (a BCRP substrate). Capmatinib was administered orally at 400 mg BID on Days 11 to 32, with a single oral dose of digoxin 0.25 mg and rosuvastatin 10 mg on Days 1 and 22.

The geometric mean ratios of C_{max} and AUC_{inf} of(a) digoxin and (b) rosuvastatin after the digoxin or rosuvastatin + capmatinib treatment to that after the dose of digoxin or rosuvastatin alone [90% CI] were (a) 1.74 [1.43, 2.13] and 1.47 [1.28, 1.68], respectively, and (b) 3.04 [2.36, 3.92] and 2.08 [1.56, 2.76], respectively.

[39)] Defined as MET GCN of ≥4, ≥50% of tumor cells with IHC score of 3+, or METex14 mutation.
[40)] A total of 30 and 31 subjects were included in the caffeine and midazolam PK analyses, respectively.
[41)] A total of 25 and 24 subjects were included in the digoxin and rosuvastatin PK analyses, respectively.

The applicant's explanation:
Based on the above, coadministration with capmatinib may increase P-gp or BCRP substrate exposure. Thus, relevant cautionary advice will be provided.

6.2.4 Foreign phase I study to assess the effect of hepatic impairment on PK of capmatinib (CTD 5.3.3.3-1, Study A2106 [June 2015 to September 2017])

An open-label, uncontrolled study was conducted in 21 patients with mild (Child-Pugh class A), moderate (Child-Pugh class B), or severe (Child-Pugh class C) hepatic impairment (20 subjects included in PK analysis)[42)] and healthy adults (10 subjects) (9 subjects included in PK analysis) of matching age, body weight, and sex with the subjects with hepatic impairment to assess the effect of hepatic impairment on the PK of capmatinib. A single oral dose of capmatinib 200 mg was administered under fasted conditions, and plasma capmatinib concentrations, etc. were determined.

The geometric mean ratios of C_{max} and AUC_{inf} of capmatinib in (a) mild (b) moderate (c) severe hepatic impairment to that in healthy adults [90% CI] were (a) 0.724 [0.476, 1.10] and 0.767 [0.532, 1.11], respectively, (b) 0.828 [0.563, 1.22] and 0.914 [0.652, 1.28], respectively, and (c) 1.02 [0.669, 1.55] and 1.24 [0.858, 1.78], respectively.

The applicant's explanation:
Based on the above, mild, moderate, or severe hepatic impairment is not considered to have evident effect on the PK of capmatinib. No dose adjustment is required for patients with mild, moderate, or severe hepatic impairment.

6.2.5 Use of capmatinib in patients with renal impairment

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

- The results of a foreign phase I study (Study X2106) indicated that contribution of renal excretion to the clearance of capmatinib is negligible [see Section 6.2.2.2].
- According to a pooled analysis of a Japanese phase I study (Study X1101), a global phase II study (Study A2201), and foreign phase I studies (Studies A2103, A2105, A2108, and X2102), in patients with normal renal function[43)] (152 subjects), patients with mild renal impairment (177 subjects) and those with moderate renal impairment (90 subjects), the incidences of (a) Grade ≥3 adverse events, (b) serious adverse events, (c) adverse events leading to dose interruption or reduction, and (d) adverse events leading to discontinuation were (a) 72.4%, 62.7%, and 64.4%, respectively, (b) 55.3%, 49.7%, and 43.3%, respectively, (c) 58.6%, 54.2%, and 70.0%, respectively, and (d) 15.1%, 16.4%, and 18.9%, respectively. There was no clear association between renal impairment and the incidence of adverse events.

[42)] 7, 8, and 6 patients had mild, moderate, and severe hepatic impairment, respectively (6, 8, and 6 patients included in PK analysis, respectively).
[43)] Classified by CrCL (mL/min). Normal renal function, ≥90; mild renal impairment, ≥60 and <90; moderate renal impairment, ≥30 and <60, and severe renal impairment, <30. No patients with severe renal impairment were enrolled in a Japanese phase I study (Study X1101), foreign phase I studies (Studies A2103, A2105, A2108, and X2102), or a global phase II study (Study A2201).

6.2.6 Relationship between exposure and change in QT/QTc interval

The relationship between plasma capmatinib concentration and ΔQTcF was analyzed using a linear mixed effects model, based on pooled time-matched PK and ECG data from 273 patients in a global phase II study (Study A2201) and a foreign phase I study (Study A2108). The upper bound of the 90% confidence interval for the estimated ΔQTcF at the mean steady-state C_{max} following the oral administration of capmatinib 400 mg BID was 2.575 milliseconds.

The applicant's explanation:
Based on the above, capmatinib administered at the proposed dosing regimen is unlikely to cause an increase in QT/QTc interval.

6.2.7 PPK analysis

A population pharmacokinetic analysis (PPK) was performed by non-linear mixed-effects modeling, based on capmatinib PK data from a Japanese phase I study (Study X1101), a global phase II study (Study A2201), and foreign phase I studies (Studies A2108 and X2102) (3,882 PK samples from 501 subjects) (software used, NONMEM Version 7.3). The PK of capmatinib were described by a 2-compartment model with delayed zero-order absorption and first-order elimination from V1.

Using a full model,[44)] (a) race (Japanese or non-Japanese, Asian or non-Asian), sex, age, body weight, hepatic function,[45)] creatinine clearance (CrCL), and serum albumin were tested as potential covariates on the (a) CL of capmatinib, and (b) body weight and serum albumin on the V1 of capmatinib. (a) Race (Asian or non-Asian) and body weight were identified as significant covariates on CL, and (b) body weight on V1.

The applicant's explanation:
Because of limited impact on capmatinib exposure (C_{max} and AUC at steady state), etc., these covariates are unlikely to have clinically significant effects on the PK of capmatinib.

6.2.8 Exposure-efficacy/safety relationship

6.2.8.1 Exposure-efficacy relationship

Based on the data obtained from a global phase II study (Cohorts 4 and 5b of Study A2201), the relationship between capmatinib exposure (C_{max} and C_{ave}[46)])[47)] and best overall response, duration of response, progression-free survival (PFS), and percent change from baseline in tumor size in patients with METex14 mutation-positive NSCLC was explored. There was no clear relationship between capmatinib exposure and these efficacy indicators.

[44)] A PPK model including food status and formulation (capsule or tablet) as covariates on the ALAG1, D1, and F1 of capmatinib
[45)] NCI-Organ Dysfunction Working Group (ODWG) criteria were used to classify hepatic impairment.
[46)](a) Best overall response, the average values per day from the first dose to the day of confirmed response or treatment discontinuation; (b) duration of response, the average values per day from the first dose to disease progression, death, or treatment discontinuation; (c) PFS, the average values per day from the first dose to the day of onset of event or treatment discontinuation, and (d) percent change from baseline in tumor diameter, the average values per day from the first dose to the day of maximum percent reduction in tumor size were used as capmatinib exposure (C_{max} and C_{ave})
[47)] Estimated from PPK analysis [see Section 6.2.7].

6.2.8.2 Exposure-safety relationship

Based on the data obtained from a Japanese phase I study (Study X1101), a global phase II study (Study A2201), and foreign phase I studies (Studies A2108 and X2102), the relationship between capmatinib exposure (C_{max} and C_{ave}[48])[47] and adverse events (peripheral edema, nausea/vomiting, hepatic dysfunction [abnormalities in levels of alanine aminotransferase (ALT), aspartate aminotransferase (AST), and bilirubin], pancreatic dysfunction [abnormalities in levels of amylase and triacylglycerol lipase], Grade ≥3 adverse events, serious adverse events) was explored. There was no clear relationship between capmatinib exposure and the incidence of peripheral edema/hepatic dysfunction (abnormalities in levels of ALT, AST, and bilirubin)/Grade ≥3 adverse events/serious adverse events. On the other hand, the analyses suggested that higher capmatinib exposure was associated with increased incidences of nausea/vomiting and pancreatic dysfunction (abnormalities in levels of amylase and triacylglycerol lipase).

6.2.9 PK differences between Japanese and non-Japanese populations

The applicant's explanation:

Because of no clear differences in capmatinib exposure (C_{max} and AUC_{12h}) following the oral administration of capmatinib 400 mg BID between a Japanese phase I study (Study X1101, see Section 6.2.1.1) and a foreign phase I study (Study X2102, see Section 6.2.2.1), etc., there is no clear differences in the PK of capmatinib between Japanese and non-Japanese populations.

6.R Outline of the review conducted by PMDA

Based on the submitted data and the observations in the following subsections, PMDA concluded that the applicant's explanation about the clinical pharmacology etc. of capmatinib is acceptable.

6.R.1 Food effect

The applicant's explanation:

With respect to the effect of food on the PK of capmatinib, the dosage regimen need not specify meal conditions for the following reasons etc.

- In a foreign phase I study (Study X2107), a high-fat meal increased C_{max} as compared to fasted conditions, but the extent of the increase was limited [see Section 6.1.3.1].
- The changes in exposure (AUC_{inf}) following the administration of capmatinib with food in a foreign phase I study (Study X2107) were within the range of capmatinib exposure[49] in a Japanese phase I study (Study X1101) that demonstrated the tolerable safety profile of capmatinib.
- In the exposure-safety analyses, a trend toward higher incidences of some adverse events such as nausea was observed in subjects with higher capmatinib exposure, but there was no relationship between capmatinib exposure and Grade ≥3 adverse events, serious adverse events, etc. [see Section 6.2.8.2].

[48] The average values per day from the first dose to the day of onset of event or treatment discontinuation

[49] Following the oral administration of capmatinib (capsules) 600 mg BID under fasted conditions, the geometric mean AUC_{last} value (CV %) was (a) 27.6 (56.1) on Day 1 (n = 3) and (b) 62.2 and 63.1 μg·h/mL (individual values) on Day 15 (n = 2).

PMDA's discussion:
PMDA accepted the above explanation by the applicant. The dosing regimen of capmatinib is described in Section "7.R.5 Dosage and administration," taking account of the results from efficacy and safety clinical studies of capmatinib.

6.R.2 Pharmacokinetic interactions mediated by CYP3A or CYP2C8

(1) CYP3A

The applicant's explanation about the coadministration of capmatinib with CYP3A inhibitors or inducers:
Given the concomitant itraconazole (a strong CYP3A inhibitor) or rifampicin (a strong CYP3A inducer) affected capmatinib exposure in a foreign phase I study (Study A2102) [see Section 6.2.3.1], the effect of a moderate CYP3A inhibitor or inducer on the PK of capmatinib was assessed using physiologically-based pharmacokinetic (PBPK) modeling.

The PBPK analyses were performed using Simcyp version 18. A 1st-order absorption model and a minimal PBPK model were chosen to describe the absorption and distribution of capmatinib, respectively. The relative contribution of CYP3A4 to capmatinib clearance was estimated as 35%, based on the results of a foreign phase I study (Study A2102), etc. Based on the following outcomes, etc., the PBPK model used to predict pharmacokinetic interactions of capmatinib mediated by CYP3A is considered adequate.

- There was a reasonable agreement between the observed values in a global phase II study (Study A2201) and the PBPK predicted values for capmatinib exposure following multiple oral doses of capmatinib (tablets) 400 mg BID, and the observed and predicted plasma concentration-time profiles were also close.
- In terms of the geometric mean ratios for the C_{max} and AUC_{inf} of capmatinib after capmatinib + (a) itraconazole or (b) rifampicin treatment to those after capmatinib alone dose, there was a reasonable agreement between the observed values [(a) 1.03 and 1.42, respectively, (b) 0.441 and 0.335, respectively] and the PBPK predicted values [(a) 1.26 and 1.57, respectively, (b) 0.604 and 0.449, respectively]. The observed values were obtained from a foreign phase I study (Study A2102).
- In terms of the geometric mean ratios for the C_{max} and AUC_{inf} of midazolam after midazolam + capmatinib treatment to those after midazolam alone dose, there was a reasonable agreement between the observed values (1.22 and 1.09, respectively) and the PBPK predicted values (1.09 and 1.22, respectively). The observed values were obtained from a foreign phase I study (Study A2103).

Using the above model, capmatinib exposure following the coadministration of a single dose of capmatinib 400 mg with (a) erythromycin (a moderate CYP3A inhibitor) 500 mg TID, (b) fluconazole (a moderate CYP3A inhibitor) 200 mg QD, or (c) efavirenz (a moderate CYP3A inducer) 600 mg QD was predicted. The predicted geometric mean ratios for C_{max} and AUC_{inf} of capmatinib after treatment with capmatinib + the above respective drugs to those after capmatinib alone dose [90% CI] were (a) 1.15 [1.13, 1.16] and 1.27 [1.24, 1.29], respectively, (b) 1.17 [1.16, 1.18] and 1.30 [1.28, 1.32], respectively, and (c) 0.683 [0.661, 0.705] and 0.554 [0.529, 0.579], respectively.

The applicant's view on the coadministration of capmatinib with CYP3A inhibitors or inducers, taking account of a foreign phase I study (Study A2102) and the above PBPK predicted values, etc.:

- A concomitant strong CYP3A inhibitor or inducer may increase or decrease capmatinib exposure, respectively. Caution will be advised.
- The increase in capmatinib exposure due to a concomitant moderate CYP3A inhibitor is considered limited, cautionary advice on the coadministration with moderate CYP3A inhibitors is unnecessary.
- A moderate CYP3A inducer may decrease capmatinib exposure. Caution will be advised.

(2) CYP2C8

The applicant's explanation about the coadministration of capmatinib with CYP2C8 substrates:

Given that capmatinib is an inhibitor of CYP2C8 [see Section 4.5.1], the PBPK model[50)] was used to predict the effect of capmatinib on the PK of repaglinide (a CYP2C8 substrate). The predicted geometric mean ratios for C_{max} and AUC_{last} of repaglinide after a single dose of repaglinide 0.25 mg + capmatinib 400 mg BID to those after a single dose of repaglinide 0.25 mg alone [90% CI] were 1.23 [1.20, 1.25] and 1.39 [1.35, 1.43], respectively. Given these results and the following outcome, cautionary advice on coadministration with CYP2C8 substrates is unnecessary.

- In a Japanese phase I study (Study X1101), a global phase II study (Study A2201), and foreign phase I studies (Studies X2102, A2103, A2105, and A2108), the coadministration of capmatinib with CYP2C8 substrates raised no particular safety concerns.

PMDA's discussion:

PMDA largely accepted the applicant's explanation about the pharmacokinetic interactions mediated by CYP3A based on a foreign phase I study (Study A2102) and the above PBPK predicted values, etc. However, considering the importance of information on pharmacokinetic interactions mediated by CYP3A for assessing the appropriateness of cautionary advice based on the above explanation, relevant information should be further collected, and new findings, once available, should be appropriately communicated to healthcare professionals.

Concerning the pharmacokinetic interactions of capmatinib mediated by CYP2C8, the applicant's explanation that the coadministration of capmatinib with CYP2C8 substrates raised no particular safety concerns in the clinical studies is acceptable at present. Meanwhile, no clinical study was conducted to assess the effect of capmatinib on the PK of CYP2C8 substrates. Given the PBPK predicted values for CYP2C8 substrate exposure, etc., the package insert should mention that capmatinib is an inhibitor of CYP2C8. Information on the pharmacokinetic interactions of capmatinib mediated by CYP2C8 should be further collected, and new findings, once available, should be appropriately communicated to healthcare professionals.

[50)] The PBPK analysis was performed using Simcyp version 17. A 1st order absorption model and a Full PBPK model were chosen to describe the absorption and distribution of the compound, respectively. The contribution of CYP2C8 to repaglinide clearance was assigned as 0.73. The adequacy of the PBPK model was evaluated based on the published articles (*Clin Pharmacol Ther.* 2005; 78: 388-99, etc.).

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

The applicant submitted efficacy and safety evaluation data, in the form of the results from a total of 8 studies presented in Table 25: 1 Japanese phase I study, 1 global phase II study, and 6 foreign phase I studies. The applicant also submitted 6 foreign phase I studies presented in Table 25 as reference data.

Table 25. Listing of efficacy and safety clinical studies

Data category	Geographical location	Study ID	Phase	Study population	Number of subjects enrolled	Dosage regimen	Main endpoints
Evaluation	Japan	X1101	I	Patients with advanced solid tumors	44 (a) 29 (b) 15	(a) Oral capmatinib (capsules) 100, 200, 400, 500, 600, or 800 mg QD or 400 or 600 mg BID (fasted) (b) Oral capmatinib (tablets) 200 or 400 mg BID (fasted)	Safety Tolerability
	Global	A2201	II	Patients with unresectable advanced or recurrent NSCLC [*1] (a) Cohort 1a: MET GCN ≥10 (b) Cohort 1b: MET GCN ≥6 and <10 (c) Cohort 2: MET GCN ≥4 and <6 (d) Cohort 3: MET GCN <4 (e) Cohort 4: METex14 mutation (f) Cohort 5a: MET GCN ≥10 (g) Cohort 5b: METex14 mutation (h) Cohort 6: MET GCN ≥10 or METex14 mutation (i) Cohort 7: METex14 mutation	334 (a) 69 (b) 42 (c) 54 (d) 30 (e) 69 (f) 15 (g) 28 (h) 27 (i) 0	Cohorts 1a-5b: Oral capmatinib (tablets) 400 mg BID (fasted) Cohorts 6 and 7: Oral capmatinib (tablets) 400 mg BID	Efficacy Safety
	Foreign	A2106	I	Healthy adults or patients with hepatic impairment	31	A single oral dose of capmatinib (tablets) 200 mg (fasted)	PK
		A2108	I	Patients with *MET* dysregulated[*2] advanced solid tumors	35 (a) 20 (b) 15	Dose-escalation part: (a) Oral capmatinib (tablets) 300 or 400 mg BID (fed) Dose-expansion part: (b) Oral capmatinib (tablets) 400 mg BID (fed)	PK Safety Tolerability
		A2109	I	Healthy adults	78	Oral capmatinib 300 mg (one of 3 different tablets) administered in a crossover fashion (fasted)	PK
		X2102	I	Patients with *MET* dysregulated[*3] advanced solid tumors	131 (a) 38 (b) 64 (c) 29	Dose-escalation part: (a) Oral capmatinib (capsules) 100, 200, 250, 350, 450, or 600 mg or oral capmatinib (tablets) 400 mg BID (fasted) Dose-expansion part: (b) Capmatinib (capsules) 600 mg BID orally (fasted) (c) Capmatinib (tablets) 400 mg BID orally (fasted)	Safety Tolerability
		X2106	I	Healthy adults	6	A single oral dose of ^{14}C-capmatinib 600 mg (capsules) (fasted)	PK
		X2107	I	Healthy adults	24	Oral capmatinib (tablets) 600 mg (fasted, after a low-fat meal, or after a high-fat meal, administered in a crossover fashion)	PK
Reference	Foreign	A2101	I	Healthy adults	20	Oral rabeprazole 20 mg QD on Days 7-10, with a single oral dose of capmatinib (tablets) 600 mg (fasted) on Days 1 and 10	PK
		A2102	I	Healthy adults	53 (a) 27 (b) 26	Inhibition cohort: (a) Oral itraconazole 200 mg QD (fasted) on Days 5-14, with a single oral dose of capmatinib (tablets) 200 mg (fasted) on Days 1 and 10 Induction cohort: (b) Oral rifampicin 600 mg QD (fasted) on Days 5-13, with a single oral dose of capmatinib (tablets) 400 mg (fasted) on Days 1 and 10	PK
		A2103	I	Patients with *MET* dysregulated[*2] advanced solid tumors	37	Oral capmatinib (tablets) 400 mg BID (fasted) beginning on Day 4, with a single oral dose of midazolam 2.5 mg and caffeine 100 mg (fasted) on Days 1 and 9	PK
		A2105	I	Patients with *MET* dysregulated[*2] advanced solid tumors	32	Oral capmatinib (tablets) 400 mg BID (fasted) beginning on Day 11, with a single oral dose of digoxin 0.25 mg and rosuvastatin 10 mg (fasted) on Days 1 and 22	PK
		X2101T	I	Patients with advanced solid tumors or hematologic malignancies	45	Oral capmatinib (capsules) 10, 20, 50, 70, 150, 200, 300, or 400 mg QD or 50, 200, or 300 mg BID (fasted)	Safety Tolerability
		X2103	I	Healthy adults	24	A single oral dose of capmatinib (tablets) or capmatinib (capsules) 600 mg administered in a crossover fashion (fasted)	PK

*1 (a)-(e), patients who had received 1 or 2 prior lines of chemotherapy; (f)(g)(i) chemotherapy-naïve patients; (h) patients who had received 1 prior line of chemotherapy

*2 Defined as MET GCN of ≥4, ≥50% of tumor cells with IHC score of 3+, or METex14 mutation.

*3 The definitions of *MET* dysregulation (a) For NSCLC, nasopharyngeal cancer, hormone-receptor-negative and HER2-negative breast cancer, gastric cancer, etc.; MET H-score of ≥150, MET/centromere ratio of ≥2.0, MET GCN of ≥5, or ≥50% of tumor cells with IHC score of 2+ or 3+: (b) For hepatocellular carcinoma and glioblastoma; MET H-score of ≥50, MET/centromere ratio of ≥2.0, or MET GCN of ≥5: (c) For papillary RCC, MET H-score of ≥150, MET/centromere a ratio of ≥2.0, MET GCN of ≥5, ≥50% of tumor cells with IHC score of 2+ or 3+, or germline *MET* mutation confirmed at the study site.

The clinical studies are summarized below.

The main adverse events other than deaths observed in the clinical studies are described in Section "7.3 Adverse events etc. observed in clinical studies." PK data are summarized in Section "6.2 Clinical pharmacology."

7.1 Evaluation data

7.1.1 Clinical pharmacology studies

The applicant submitted the following 5 clinical pharmacology studies in healthy adults, patients with hepatic impairment, or patients with *MET* dysregulated[39)] advanced solid tumors [see Sections 6.1 and 6.2]. There were 5 deaths during the study treatment period or within 30 days after the last dose of study drug (5 of 35 subjects [14.3%] in Study A2108), and the causes of deaths were all disease progression.

7.1.1.1 Foreign phase I study (CTD 5.3.3.3-1, Study A2106 [June 2015 to September 2017])

7.1.1.2 Foreign phase I study (CTD 5.3.3.2-1, Study A2108 [December 2016 to May 2018])

7.1.1.3 Foreign phase I study (CTD 5.3.1.2-2, Study A2109 [[redacted] to [redacted]])

7.1.1.4 Foreign phase I study (CTD 5.3.3.1-1, Study X2106 [[redacted] to [redacted]])

7.1.1.5 Foreign phase I study (CTD 5.3.3.4-5, Study X2107 [[redacted] to [redacted]])

7.1.2 Japanese study

7.1.2.1 Japanese phase I study (CTD 5.3.5.2-3, Study X1101 [February 2012 to January 2016])

An open-label, uncontrolled study was conducted at 2 sites in Japan to assess the safety and tolerability of capmatinib in patients with advanced solid tumors (target sample size, 3 subjects/cohort).

Subjects received capmatinib (capsules) orally at 100, 200, 400, 500, 600, or 800 mg QD or at 400 or 600 mg BID under fasted conditions, or capmatinib (tablets) orally at 200 or 400 mg BID under fasted conditions. Subjects were treated in 28-day cycles until disease progression or a discontinuation criterion met.

All of 44 subjects enrolled in the study received capmatinib and were included in the safety set.

The dose-limiting toxicity (DLT) evaluation period started on Cycle 1 Day 1 and ended on Cycle 1 Day 28. DLTs were observed in 1 of 3 subjects (Grade 2 suicidal ideation) in the capmatinib (capsules) 600 mg BID cohort and 1 of 10[51)] subjects (Grade 3 depression) in the capmatinib (tablets) 400 mg BID cohort. Capmatinib (tablets) 400 mg BID was selected as the recommended Phase 2 dose (RP2D).

There were no deaths during the capmatinib treatment period or within 28 days after the last dose of capmatinib.

7.1.3 Global study

[51)] Among 12 subjects in the safety set, 10 subjects who had received capmatinib for ≥21 days during the DLT evaluation period were evaluated for DLT.

7.1.3.1 Global phase II study (CTD 5.3.5.2-1, Study A2201 [ongoing since June 2015 (data cutoff on April 15, 2019)])

An open-label, uncontrolled study was conducted at 152 sites in 25 countries or regions including Japan to evaluate the efficacy and safety of capmatinib in patients with METex14 mutation-positive[52] unresectable advanced or recurrent NSCLC etc.[53] (target samples size, 69 subjects each in Cohorts 1a to 4, 27 subjects each in Cohorts 5a and 5b, 30 subjects in Cohort 6, 27 subjects in Cohort 7) (The efficacy results from Study A2201 refer to those in Cohorts 4 and 5b).

Capmatinib was administered orally at 400 mg (tablets) BID under fasted conditions in Cohorts 1 to 5b and without meal conditions in Cohorts 6 and 7, until disease progression or a discontinuation criterion met.

All of 97 subjects enrolled in Cohorts 4 or 5b of the study (69 in Cohort 4, 28 in Cohort 5b) were included in the efficacy analysis population (including 11 Japanese patients in Cohort 4 and 2 Japanese patients in Cohort 5b). All of 334 subjects enrolled in the study (including 45 Japanese patients) received capmatinib and were included in the safety set.

The primary endpoint of the study was overall response rate determined by a Blinded Independent Review Committee (BIRC) according to Response Evaluation Criteria in Solid Tumors (RECIST) ver.1.1, and the unacceptable overall response rates were determined to be 25%[54] and 35%[55] for Cohorts 4 and 5b, respectively. An interim analysis for futility was planned for Cohort 4. The interim analysis was to be performed when 28 patients had completed ≥18 weeks of treatment with capmatinib or discontinued treatment before Week 18. The primary analyses of Cohorts 4 and 5b were to be performed when all patients enrolled in each cohort had completed ≥18 weeks of treatment with capmatinib or discontinued treatment before Week 18. However, since [redacted]56)[redacted], the primary analyses of Cohorts 4 and 5b were conducted when (a) all patients enrolled in each cohort (i) had completed ≥18 weeks of treatment with capmatinib or (ii) had discontinued treatment before Week 18, and (b) most of the responding patients from Cohort 5b had undergone 12 months follow-up (Statistical Analysis Plan Amendment 3 [as of [redacted], 20[redacted]]).

---

52) Their tumor tissue specimens were tested by Novartis Precision Medicine's RT-PCR assay at the central laboratory.

53) In Study A2201, patients were enrolled in the following cohorts. Patients with *EGFR* mutations and patients with *ALK* rearrangement were excluded.
Cohort 1a: Patients with MET GCN of ≥10 who had received 1 or 2 prior lines of chemotherapy
Cohort 1b: Patients with MET GCN of ≥6 and <10 who had received 1 or 2 prior lines of chemotherapy
Cohort 2: Patients with MET GCN of ≥4 and <6 who had received 1 or 2 prior lines of chemotherapy
Cohort 3: Patients with MET GCN of <4 who had received 1 or 2 prior lines of chemotherapy
Cohort 4: Patients with METex14 mutations who had received 1 or 2 prior lines of chemotherapy
Cohort 5a: Chemotherapy-naïve patients with MET GCN of ≥10
Cohort 5b: Chemotherapy-naïve patients with METex14 mutations
Cohort 6: Patients with MET GCN of ≥10 or METex14 mutations who had received 1 prior line of chemotherapy
Cohort 7: Chemotherapy-naïve patients with METex14 mutations

54) Determined based on the response rates with DOC etc. in multiple foreign phase III studies in patients with unresectable advanced or recurrent NSCLC previously treated with chemotherapy (*Oncologist.* 2008; 13: 14-20), etc.

55) Determined based on the response rates in the CDDP/PEM and CDDP/GEM groups in a foreign phase III study to evaluate the efficacy and safety of CDDP/PEM compared with CDDP/GEM in chemotherapy-naïve patients with unresectable advanced or recurrent NSCLC (*J Clin Oncol*. 2008; 26: 3543-51), etc.

56) [redacted].

57) Time from the first response (CR or PR) to PD or death in patients with a confirmed response (CR or PR)

The primary efficacy analyses of Cohorts 4 and 5b were performed when 17 of 19 responding patients from Cohort 5b had undergone 12 months follow-up (data cutoff date of April 15, 2019). The results of the primary endpoint of the overall response rate per RECIST ver.1.1 assessed by BIRC (data cutoff date of April 15, 2019) are shown in Table 26.

Table 26. Best overall response and overall response rate
(RECIST ver.1.1, Efficacy analysis population, BIRC assessments, data cutoff date of April 15, 2019)

Best overall response	N (%)			
	Entire population		Japanese subgroup	
	Cohort 4 n = 69	Cohort 5b n = 28	Cohort 4 n = 11	Cohort 5b n = 2
CR	0	1 (3.6)	0	0
PR	28 (40.6)	18 (64.3)	4 (36.4)	1 (50.0)
SD	25 (36.2)	8 (28.6)	5 (45.5)	1 (50.0)
PD	6 (8.7)	1 (3.6)	1 (9.1)	0
Non CR/PD	1 (1.4)[*2]	0	0	0
NE	9 (13.0)	0	1 (9.1)	0
Response (CR+PR) (Overall response rate [95% CI[*1]] (%))	28 (40.6 [28.9, 53.1])	19 (67.9 [47.6, 84.1])	4 (36.4 [10.9, 69.2])	1 (50.0 [1.3, 98.7])

*1 Clopper-Pearson method; *2 Measurable lesion was present at baseline as assessed by the investigator, but not by BIRC.

The safety analysis revealed that 53 of 334 subjects (15.9%) died during the capmatinib treatment period or within 30 days after the last dose of capmatinib (10 of 69 [14.5%] in Cohort 1a, 7 of 42 [16.7%] in Cohort 1b, 12 of 54 [22.2%] in Cohort 2, 4 of 30 [13.3%] in Cohort 3, 13 of 69 [18.8%] in Cohort 4, 5 of 28 [17.9%] in Cohort 5b, 2 of 27 [7.4%] in Cohort 6) (including 1 Japanese patient in Cohort 4). The causes of deaths other than disease progression (8 in Cohort 1a, 6 in Cohort 1b, 11 in Cohort 2, 3 in Cohort 3, 11 in Cohort 4, 3 in Cohort 5b, 1 in Cohort 6) were hepatitis; and pneumonia bacterial (1 subject each) in Cohort 1a, sepsis (1) in Cohort 1b, cardiac arrest (1) in Cohort 2, cardiac arrest (1) in Cohort 3, septic shock; and pneumonitis (1 each) in Cohort 4, atrial fibrillation; and respiratory distress (1 each) in Cohort 5b, and organising pneumonia (1) in Cohort 6. A causal relationship to capmatinib could not be ruled out for hepatitis (1) in Cohort 1a, cardiac arrest (1) in Cohort 2, pneumonitis (1) in Cohort 4, and organising pneumonia (1) in Cohort 6 (1 Japanese patient died due to disease progression).

7.1.4 Foreign study

7.1.4.1 Foreign phase I study (CTD 5.3.5.2-2, Study X2102 [February 2012 to July 2017])

An open-label, uncontrolled study was conducted at 33 sites overseas to assess the safety and tolerability of capmatinib in patients with *MET*-dysregulated[37)] advanced solid tumors (target sample size, 15-21 subjects in the dose-escalation part, 30-90 subjects in the dose-expansion part [the original cohort], 20 subjects in the dose-expansion part [the additional cohort[58)]]).

In the dose-escalation part, capmatinib (capsules) was administered orally at 100, 200, 250, 350, 450, or 600 mg BID under fasted conditions or capmatinib (tablets) was administered orally at 400 mg BID under fasted conditions. In the dose-expansion part, capmatinib (capsules) was administered orally at 600 mg BID under

[58)] Patients with *EGFR* wild type NSCLC who had ≥50% of tumor cells with MET IHC score of 3+ were enrolled.

fasted conditions in the original cohort, while capmatinib (tablets) was administered orally at 400 mg BID under fasted conditions in the additional cohort. Subjects were treated until disease progression or a discontinuation criterion met.

All of 131 subjects enrolled in the study (38 in the dose-escalation part, 64 in the original cohort of the dose-expansion part, 29 in the additional cohort of the dose-expansion part) received capmatinib and were included in the safety set.

The DLT evaluation period started on Cycle 1 Day 1 and ended on Cycle 1 Day 28 in the dose-escalation part. DLTs occurred in 1 of 4 subjects (Grade 3 fatigue) in the capmatinib (capsules) 200 mg BID cohort, 1 of 4 subjects (Grade 3 blood bilirubin increased) in the capmatinib (capsules) 250 mg BID cohort, and 1 of 6 subjects (Grade 3 fatigue) in the capmatinib (capsules) 450 mg BID cohort, and capmatinib 600 mg BID capsules were selected as the RP2D. No DLT was observed with capmatinib (tablets), and capmatinib 400 mg BID tablets were selected as the RP2D.

The safety analysis revealed deaths of 2 of 9 subjects (22.2%) in the capsule 450 mg cohort and 1 of 5 subjects (20.0%) in the tablet 400 mg cohort of the dose-escalation part, 9 of 64 subjects (14.1%) in the original expansion cohort, and 3 of 29 subjects (10.3%) in the additional expansion cohort during the capmatinib treatment period or within 30 days after the last dose of capmatinib. The cause of death other than disease progression (2 in the capsule 450 mg cohort and 1 in the tablet 400 mg cohort of the dose-escalation part, 8 in the original expansion cohort, and 3 in the additional expansion cohort) was pneumonia (1 subject) in the original expansion cohort, and its causal relationship to capmatinib was ruled out.

7.2 Reference data

7.2.1 Clinical pharmacology studies

The applicant submitted data from the following 5 clinical pharmacology studies in healthy adults or patients with *MET* dysregulated[39] advanced solid tumors [see Sections 6.1 and 6.2]. There were 18 deaths during the study treatment period or within 30 days after the last dose of study drug (12 of 37 [32.4%] in Study A2103, 6 of 32 [18.8%] in Study A2105). The causes of deaths were general physical condition decreased (5); disease progression (4); respiratory tract infection (2); and pleural effusion; adenocarcinoma; penile cancer; neurological decompensation; cardio-respiratory arrest; adenocarcinoma pancreas; and depressed level of consciousness (1 each), and a causal relationship to study drug was ruled out for all these cases.

7.2.1.1 Foreign phase I study (CTD 5.3.3.4-1, Study A2101 [[redacted] to [redacted] 20[redacted]])

7.2.1.2 Foreign phase I study (CTD 5.3.3.4-2, Study A2102 [[redacted] to [redacted] 20[redacted])

7.2.1.3 Foreign phase I study (CTD 5.3.3.4-3, Study A2103 [December 2015 to September 2017])

7.2.1.4 Foreign phase I study (CTD 5.3.3.4-4, Study A2105 [December 2015 to April 2017])

7.2.1.5 Foreign phase I study (CTD 5.3.1.2-1, Study X2103 [[redacted] 20[redacted] to [redacted] 20[redacted]])

7.2.2 Foreign clinical study

7.2.2.1 Foreign phase I study (CTD 5.3.5.2-4, Study X2101T [January 2010 to January 2013])

An open-label, uncontrolled study was conducted at 2 sites overseas to assess the safety and tolerability of capmatinib in patients with advanced solid tumors or hematologic malignancies (target sample size, 40 subjects).

All of 45 subjects enrolled in the study received capmatinib and were included in the safety set.

The safety analysis revealed 2 deaths of 2 of 45 subjects (4.4%) during the capmatinib treatment period or within 30 days after the last dose of capmatinib. The causes of deaths were hepatic encephalopathy; and staphylococcal sepsis (1 each), and a causal relationship to capmatinib was ruled out for both cases.

7.R Outline of the review conducted by PMDA

7.R.1 Review strategy

PMDA review strategy:

Among the evaluation data submitted, the results from Cohorts 4 and 5b of a global phase II study that evaluated the efficacy and safety of capmatinib in patients with METex14 mutation-positive unresectable advanced or recurrent NSCLC (Study A2201) are the pivotal data to evaluate the efficacy of capmatinib. PMDA decided to focus on these cohorts in its efficacy review and on Study A2201 in safety review.

7.R.2 Efficacy

Based on the following considerations, PMDA concluded that a certain level of efficacy of capmatinib was demonstrated in patients with METex14 mutation-positive unresectable advanced or recurrent NSCLC.

7.R.2.1 Efficacy endpoint and results of evaluation

The applicant's explanation about the primary endpoint for Cohorts 4 and 5b of Study A2201 and the efficacy of capmatinib in patients with METex14 mutation-positive unresectable advanced or recurrent NSCLC:

For patients with METex14 mutation-positive unresectable advanced or recurrent NSCLC (the population eligible for Cohorts 4 and 5b of Study A2201) responding to capmatinib are expected to have improved disease progression-associated clinical symptoms (*JAMA*. 2003; 290: 2149-58, etc.), and having a response to the treatment is clinically significant. Thus, the overall response rate was selected as the primary endpoint for Cohorts 4 and 5b of Study A2201.

In the entire population, the overall response rates [95% CI] in Cohorts 4 and 5b of Study A2201 were 40.6% [28.9, 53.1] and 67.9% [47.6, 84.1], respectively, which exceeded the unacceptable overall response rates of 25% and 35%, respectively [see Section 7.1.3.1].

The overall response rates per RECIST ver.1.1 as assessed by BIRC at the primary analysis time point for Cohorts 4 and 5b prespecified by the protocol of Study A2201 (Cohort 4, data cutoff date of August 9, 2018;

Cohort 5b, data cutoff date of November 8, 2018) [see Section 7.1.3.1] are shown in Table 27, which were similar to the overall response rates at the analysis time point after protocol amendment. Thus, this protocol amendment does not affect the conclusion on the efficacy of capmatinib.

Table 27. Best overall response and overall response rate
(RECIST ver.1.1, Efficacy analysis population, BIRC assessments, data cutoff date of August 9, 2018[*1] or November 8, 2018[*2])

Best overall response	N (%)			
	Entire population		Japanese subgroup	
	Cohort 4 n = 69	Cohort 5b n = 28	Cohort 4 n = 11	Cohort 5b n = 2
CR	0	0	0	0
PR	27 (39.1)[*4]	20 (71.4)	4 (36.4)	1 (50.0)
SD	26 (37.7)	7 (25.0)	5 (45.5)	1 (50.0)
PD	6 (8.7)	1 (3.6)	1 (9.1)	0
Non CR/PD	1 (1.4)[*5]	0	0	0
NE	9 (13.0)	0	1 (9.1)	0
Response (CR + PR) (Overall response rate [95% CI[*3]] (%))	27 (39.1 [27.6, 51.6])	20 (71.4 [51.3, 86.8])	4 (36.4 [10.9, 69.2])	1 (50.0 [1.3, 98.7])

*1 Data cutoff date for Cohort 4; *2 Data cutoff date for Cohort 5b; *3 Clopper-Pearson method
*4 One subject with PR was downgraded to SD at the primary analysis (data cutoff date of April 15, 2019).
*5 Measurable lesion was present at baseline as assessed by the investigator, but not by BIRC.

Given the above results and the following points etc., the efficacy of capmatinib in patients with METex14 mutation-positive unresectable advanced or recurrent NSCLC is promising.

● METex14 mutations are considered oncogene drivers in METex14 mutation-positive unresectable advanced or recurrent NSCLC [see Section 3.R.1].

● The overall response rates with capmatinib in Cohorts 4 and 5b of Study A2201 are considered clinically significant.

PMDA's discussion:

The relationship between overall survival (OS), the true endpoint in patients with METex14 mutation-positive unresectable advanced or recurrent NSCLC, and the overall response rate is unclear, and it is difficult to evaluate the survival benefit of capmatinib in these patients based on the results of the primary endpoint for Cohorts 4 and 5b of Study A2201, i.e. the overall response rate.

However, taking account of the above explanation by the applicant about the efficacy of capmatinib, and given that capmatinib is an inhibitor targeting METex14 mutations as oncogenic drivers, etc., the results from Cohorts 4 and 5b of Study A2201 demonstrated a certain level of efficacy of capmatinib in patients with METex14 mutation-positive unrespectable advanced or recurrent NSCLC, including Japanese patients.

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

PMDA's conclusion:

Based on the following considerations, adverse events that require attention during the treatment with capmatinib in patients with METex14 mutation-positive unresectable advanced or recurrent NSCLC are hepatic dysfunction, ILD, renal dysfunction, fluid retention (including hypoalbuminaemia), acute pancreatitis,

and photosensitivity. Attention should be paid to the possible occurrence of these adverse events during treatment with capmatinib.

Although attention should be paid to the possible occurrence of the above adverse events during treatment with capmatinib, capmatinib is tolerable as long as physicians with adequate knowledge of and experience in cancer chemotherapy take appropriate measures, e.g. monitoring for and management of adverse events and interruption etc. of capmatinib.

7.R.3.1 Safety profile

The applicant's explanation about the safety profile of capmatinib based on safety information from Study A2201:

Safety data from Study A2201 are summarized in Table 28.

Table 28. Summary of safety data (Study A2201)

	N (%) n = 334
All adverse events	328 (98.2)
Grade ≥3 adverse events	219 (65.6)
Adverse events resulting in death	10 (3.0)
Serious adverse events	169 (50.6)
Adverse events leading to treatment discontinuation	54 (16.2)
Adverse events leading to dose interruption	181 (54.2)
Adverse events leading to dose reduction	76 (22.8)

In Study A2201, adverse events of any grade reported by ≥10% of subjects were peripheral oedema (166 [49.7%]); nausea (147 [44.0%]); vomiting (94 [28.1%]); blood creatinine increased (85 [25.4%]); dyspnoea (81 [24.3%]); fatigue (72 [21.6%]); decreased appetite (69 [20.7%]); diarrhoea (61 [18.3%]); constipation (60 [18.0%]); cough (54 [16.2%]); pyrexia; and back pain (47 each [14.1%]); ALT increased (42 [12.6%]); asthenia (41 [12.3%]); and non-cardiac chest pain; and weight decreased (34 each [10.2%]). Grade 3 or higher adverse events reported by ≥2% of subjects were peripheral oedema (28 [8.4%]); dyspnoea (23 [6.9%]); ALT increased (19 [5.7%]); lipase increased (18 [5.4%]); fatigue (16 [4.8%]); asthenia; amylase increased; and general physical health deterioration (12 each [3.6%]); pneumonia; and pulmonary embolism (11 each [3.3%]); AST increased; and hyponatraemia (10 each [3.0%]); nausea; anaemia; and GGT increased (9 each [2.7%]); and vomiting; pleural effusion; and hypophosphataemia (8 each [2.4%]). Serious adverse events reported by ≥2% of subjects were dyspnoea (23 [6.9%]); pneumonia (16 [4.8%]); pleural effusion (12 [3.6%]); general physical health deterioration (10 [3.0%]); vomiting (8 [2.4%]); and nausea (7 [2.1%]). Adverse events leading to dose interruption reported by ≥2% of subjects were peripheral oedema (29 [8.7%]); blood creatinine increased (24 [7.2%]); nausea; and vomiting (18 each [5.4%]); lipase increased (15 [4.5%]); ALT increased; and dyspnoea (13 each [3.9%]); amylase increased (11 [3.3%]); AST increased (10 [3.0%]); and fatigue; pneumonia; and blood bilirubin increased (7 each [2.1%]). Adverse events leading to dose reduction reported by ≥2% of subjects were peripheral oedema (24 [7.2%]); ALT increased (10 [3.0%]); and nausea; and blood creatinine increased (7 each [2.1%]). There were no adverse events resulting in death or treatment discontinuation reported by ≥2% of subjects.

PMDA's discussion:

The adverse events with a high incidence, Grade 3 or higher adverse events, and serious adverse events observed in Study A2201 are likely to occur following administration of capmatinib. Patients should be monitored closely for these events during treatment with capmatinib, considering their possible relationship to capmatinib. However, most of these events were manageable with dose interruption/reduction of capmatinib, etc. Given these, capmatinib is tolerable as long as physicians with adequate knowledge of and experience in cancer chemotherapy take appropriate measures, e.g. management and monitoring for adverse events, and dose interruption/reduction of capmatinib.

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

The applicant's explanation about differences in the safety of capmatinib between Japanese and non-Japanese populations, based on safety information from Study A2201:

Safety data from Japanese and non-Japanese patients in Study A2201 are summarized in Table 29.

Table 29. Summary of safety data from Japanese and non-Japanese patients (Study A2201)

	N (%)	
	Japanese patients n = 45	Non-Japanese patients n = 289
All adverse events	44 (97.8)	284 (98.3)
Grade ≥3 adverse events	32 (71.1)	187 (64.7)
Adverse events resulting in death	0	10 (3.5)
Serious adverse events	21 (46.7)	148 (51.2)
Adverse events leading to treatment discontinuation	8 (17.8)	46 (15.9)
Adverse events leading to dose interruption	29 (64.4)	152 (52.6)
Adverse events leading to dose reduction	13 (28.9)	63 (21.8)

In Study A2201, adverse events of any grade reported at a ≥10% higher incidence in the Japanese subgroup than in the non-Japanese subgroup were blood creatinine increased (25 subjects [55.6%] in the Japanese subgroup, 60 subjects [20.8%] in the non-Japanese subgroup), vomiting (17 subjects [37.8%], 77 subjects [26.6%]), decreased appetite (14 subjects [31.1%], 55 subjects [19.0%]), pyrexia (11 subjects [24.4%], 36 subjects [12.5%]), ALT increased (10 subjects [22.2%], 32 subjects [11.1%]), amylase increased (9 subjects [20.0%], 20 subjects [6.9%]), AST increased (9 subjects [20.0%], 20 subjects [6.9%]), platelet count decreased (8 subjects [17.8%], 6 subjects [2.1%]), and dry skin (7 subjects [15.6%], 8 subjects [2.8%]). Grade 3 or higher adverse events reported at a ≥5% higher incidence in the Japanese subgroup than in the non-Japanese subgroup were neutrophil count decreased (3 subjects [6.7%], 1 subject [0.3%]) and lymphocyte count decreased (3 subjects [6.7%], 0 subjects). Adverse events leading to dose interruption reported at a ≥5% higher incidence in the Japanese subgroup than in the non-Japanese subgroup were decreased appetite (4 subjects [8.9%], 1 subject [0.3%]), diarrhoea (3 subjects [6.7%], 3 subjects [1.0%]), and pyrexia (3 subjects [6.7%], 2 subjects [0.7%]). There were no adverse events resulting in death, serious adverse events, or adverse events leading to dose reduction or treatment discontinuation reported at a ≥5% higher incidence in the Japanese subgroup than in the non-Japanese subgroup.

PMDA's discussion:

Although the number of Japanese patients treated with capmatinib was limited, and there are limitations to comparison of its safety profile between Japanese and non-Japanese populations, some events were reported at a higher incidence in Japanese patients than in non-Japanese patients in Study A2201, and attention should be paid to the possible occurrence of these events during treatment with capmatinib. However, there was no trend towards clearly higher incidence of adverse events resulting in death or serious adverse events in Japanese patients than in non-Japanese patients, and given that capmatinib is used by physicians with adequate knowledge of and experience in cancer chemotherapy, etc., capmatinib is tolerable also in Japanese patients.

In the following sections, based on the safety results from Study A2201, PMDA's safety review focuses on specific adverse events with a high incidence, adverse events that require attention in Japanese patients, adverse events that require attention following administration of another MET inhibitor, tepotinib, etc.

7.R.3.3 Hepatic dysfunction

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

As adverse events of hepatic dysfunction, events in the Medical Dictionary for Regulatory Activities (MedDRA) standardized MedDRA queries (SMQ) of "cholestasis and jaundice of hepatic origin (broad)," "hepatic failure, fibrosis and cirrhosis and other liver damage-related conditions (broad)," "hepatitis, non-infectious (broad)," "liver related investigations, signs and symptoms (broad)," and "liver-related coagulation and bleeding disturbances (broad)" were counted.

The incidence of hepatic dysfunction in Study A2201 is shown in Table 30.

Table 30. Incidence of hepatic dysfunction (Study A2201)

PT (MedDRA ver.22.0)	N (%) n = 334	
	All Grades	Grade ≥3
Hepatic dysfunction	94 (28.1)	32 (9.6)
ALT increased	42 (12.6)	19 (5.7)
AST increased	29 (8.7)	10 (3.0)
Hypoalbuminaemia	29 (8.7)	2 (0.6)
GGT increased	24 (7.2)	9 (2.7)
Blood alkaline phosphatase increased	19 (5.7)	0
Blood bilirubin increased	10 (3.0)	2 (0.6)
Liver function test increased	3 (0.9)	0
Transaminases increased	3 (0.9)	1 (0.3)
Bilirubin conjugated increased	2 (0.6)	0
Hepatic function abnormal	2 (0.6)	1 (0.3)
Liver function test abnormal	2 (0.6)	1 (0.3)
Ascites	1 (0.3)	0
Cholestasis	1 (0.3)	0
Drug-induced liver injury	1 (0.3)	1 (0.3)
Hepatic enzyme increased	1 (0.3)	0
Hepatic steatosis	1 (0.3)	0
Hepatitis	1 (0.3)	1 (0.3)
Hepatotoxicity	1 (0.3)	1 (0.3)
International normalised ratio increased	1 (0.3)	0

In Study A2201, hepatic dysfunction resulting in death occurred in 1 of 334 subjects (0.3%) (hepatitis [1]), and its causal relationship to capmatinib could not be ruled out. Serious hepatic dysfunction occurred in 5 of 334 subjects (1.5%) (hepatotoxicity, hepatitis, liver function test abnormal, hepatic function abnormal, and drug-induced liver injury [1 each]), and a causal relationship to capmatinib could not be ruled out for those events reported by 4 subjects (hepatotoxicity, hepatitis, liver function test abnormal, and hepatic function abnormal [1 each]). Hepatic dysfunction leading to capmatinib discontinuation occurred in 6 of 334 subjects (1.8%) (ALT increased, and AST increased [3 each], blood bilirubin increased [2], and hepatic function abnormal, hepatotoxicity, and liver function test abnormal [1 each] [some subjects had more than 1 event]). Hepatic dysfunction leading to dose interruption occurred in 23 of 334 subjects (6.9%) (ALT increased [13], AST increased [10], blood bilirubin increased [7], GGT increased [4], hypoalbuminaemia [2], and blood alkaline phosphatase increased, hepatic enzyme increased, hepatic steatosis, liver function test abnormal, and transaminases increased [1 each] [some subjects had more than 1 event]). Hepatic dysfunction leading to dose reduction occurred in 12 of 334 subjects (3.6%) (ALT increased [10], AST increased [2], and liver function test abnormal; and transaminases increased [1 each] [some subjects had more than 1 event]).

In Study A2201, the median time to the first onset of hepatic dysfunction (range) was 36.0 (1-694) days.

The details of patients with serious hepatic dysfunction associated with capmatinib (causally related to capmatinib) in all clinical studies submitted are shown in Table 31.

Table 31. Listing of patients with serious hepatic dysfunction (causally related to capmatinib)

Study ID	Age	Sex	Race	Primary disease	PT (MedDRA ver.22.0)	Grade	Time to onset (days)	Duration (days)	Action taken with capmatinib	Outcome
A2201	57	Men	Non-Japanese	NSCLC	Hepatotoxicity	3	22	6	Discontinued	Unresolved
	62	Men	Non-Japanese	NSCLC	Hepatitis	5	52	12	Not applicable	Fatal
	62	Men	Japanese	NSCLC	Liver function test abnormal	4	29	5	Discontinued	Improved
	72	Women	Japanese	NSCLC	Hepatic function abnormal	4	43	6	Discontinued	Improved
	69*	Women	Non-Japanese	NSCLC	Hyperbilirubinaemia	3	43	7	Dose interrupted	Sequelae
					Drug-induced liver injury	3	46	82	Discontinued	Resolved

*Newly reported (data cutoff date of [redacted], 20[redacted]) after the analyses to support the present application (data cutoff date of April 15, 2019).

In all clinical studies submitted, there was 1 case of hepatic dysfunction meeting Hy's law laboratory criteria (defined based on Guidance for industry. Drug-Induced Liver Injury: Premarketing Clinical Evaluation. U.S. Department of Health and Human Services, Food and Drug Administration. July 2009), and its causal relationship to capmatinib could not be ruled out. In this patient, treatment with capmatinib was withheld due to the occurrence of hepatic dysfunction (AST >7 times the upper limit of normal [ULN], ALT >15 times ULN, total bilirubin within the normal range) on Day 43. Since ALT returned to normal on Day 62, capmatinib was resumed at a reduced dose. However, capmatinib was discontinued due to the occurrence of hepatic dysfunction meeting Hy's law laboratory criteria (AST >2 times ULN, ALT >6 times ULN, total bilirubin >2 times ULN) on Day 71.

PMDA's discussion:

Given the reported serious hepatic dysfunction for which a causal relationship to capmatinib could not be ruled out in Study A2201, etc., attention should be paid to the possible occurrence of hepatic dysfunction during treatment with capmatinib. Thus, it is necessary to appropriately advise healthcare professionals about the incidence of hepatic dysfunction in clinical studies, etc. via the package insert, etc.

7.R.3.4 ILD

The applicant's explanation about ILD associated with capmatinib:

As adverse events of ILD, MedDRA preferred terms (PTs) of "acute interstitial pneumonitis," "alveolar lung disease," "alveolar proteinosis," "alveolitis," "alveolitis necrotising," "autoimmune lung disease," "bronchiolitis," "combined pulmonary fibrosis and emphysema," "diffuse alveolar damage," "eosinophilia myalgia syndrome," "eosinophilic granulomatosis with polyangiitis," "eosinophilic pneumonia," "eosinophilic pneumonia acute," "eosinophilic pneumonia chronic," "hypersensitivity pneumonitis," "idiopathic interstitial pneumonia," "idiopathic pneumonia syndrome," "idiopathic pulmonary fibrosis," "immune-mediated pneumonitis," "ILD," "lung infiltration," "necrotising bronchiolitis," "obliterative bronchiolitis," "pneumonitis," "progressive massive fibrosis," "pulmonary fibrosis," "pulmonary necrosis," "pulmonary radiation injury," "pulmonary toxicity," "pulmonary vasculitis," "radiation alveolitis," "radiation fibrosis - lung," "radiation pneumonitis," "small airways disease," and "transfusion-related acute lung injury" were counted.

The incidence of ILD in Study A2201 is shown in Table 32.

Table 32. Incidence of ILD (Study A2201)

PT (MedDRA ver.22.0)	N (%) n = 334	
	All Grades	Grade ≥3
ILD	15 (4.5)	6 (1.8)
Pneumonitis	12 (3.6)	4 (1.2)
ILD	3 (0.9)	2 (0.6)

In Study A2201, ILD resulting in death occurred in 1 of 334 subjects (0.3%) (pneumonitis [1]), and its causal relationship to capmatinib could not be ruled out. Serious ILD occurred in 7 of 334 subjects (2.1%) (pneumonitis [5] and ILD [2]), and a causal relationship to capmatinib could not be ruled out for those events reported by 5 subjects (pneumonitis [3] and ILD [2]). ILD leading to capmatinib discontinuation occurred in 8 of 334 subjects (2.4%) (pneumonitis [6] and ILD [2]). ILD leading to dose interruption occurred in 3 of 334 subjects (0.9%) (pneumonitis [3]). ILD leading to dose reduction occurred in 1 of 334 subjects (0.3%) (pneumonitis [1]).

In Study A2201, the median time to the first onset of ILD (range) was 43.0 (5-451) days.

The details of patients with serious ILD associated with capmatinib (causally related to capmatinib) in all clinical studies submitted are shown in Table 33.

Table 33. Listing of patients with serious ILD (causally related to capmatinib)

Study ID	Age	Sex	Race	Primary disease	PT (MedDRA ver.22.0)	Grade	Time to onset (days)	Duration (days)	Action taken with capmatinib	Outcome
A2201	70	Women	Non-Japanese	NSCLC	ILD	3	55	22	Discontinued	Improved
	69	Men	Japanese	NSCLC	Pneumonitis	3	102	11	Not applicable	Improved
	65	Men	Non-Japanese	NSCLC	Pneumonitis	3	5	29	Discontinued	Fatal
	68	Men	Japanese	NSCLC	ILD	3	29	14	Discontinued	Improved
					ILD	2	43	47	Not applicable	Resolved
	80	Men	Non-Japanese	NSCLC	Pneumonitis	3	451	6	Not applicable	Improved

PMDA asked the applicant to explain the mechanism of development of ILD associated with capmatinib and its risk factors.

The applicant's response:
The mechanism of development of ILD associated with capmatinib is unknown. Although among 15 patients with ILD in Study A2201, 7 were previously treated with an anti-programmed cell death-1 (PD-1) antibody or lung radiation (3 and 5 patients, respectively [1 was previously treated with an anti-PD-1 antibody and lung radiation]), the risk factors for ILD associated with capmatinib are undefined.

PMDA's discussion:
Given the reported ILD resulting in death for which a causal relationship to capmatinib could not be ruled out and Japanese patients experiencing serious ILD for which a causal relationship to capmatinib could not be ruled out in Study A2201, etc., attention should be paid to the possible occurrence of ILD during treatment with capmatinib. Thus, it is necessary to appropriately advise healthcare professionals about the incidence of ILD in clinical studies, etc. via the package insert etc.

7.R.3.5 Renal dysfunction

The applicant's explanation about renal dysfunction associated with capmatinib:
As adverse events of renal dysfunction, events in MedDRA SMQ of "acute renal failure (broad)" were counted.

The incidence of renal dysfunction in Study A2201 is shown in Table 34.

Table 34. Incidence of renal dysfunction (Study A2201)

PT (MedDRA ver.22.0)	N (%) n = 334	
	All Grades	Grade ≥3
Renal dysfunction	89 (26.6)	1 (0.3)
Blood creatinine increased	85 (25.4)	0
Renal failure	4 (1.2)	0
Blood urea increased	2 (0.6)	0
Acute kidney injury	1 (0.3)	1 (0.3)
Azotaemia	1 (0.3)	0
Creatinine renal clearance decreased	1 (0.3)	0
Glomerular filtration rate decreased	1 (0.3)	0
Oliguria	1 (0.3)	0
Renal impairment	1 (0.3)	0

In Study A2201, serious renal dysfunction occurred in 3 of 334 subjects (0.9%) (renal failure [2] and acute kidney injury [1]), and a causal relationship to capmatinib could not be ruled out for all those events. Renal dysfunction leading to capmatinib discontinuation occurred in 2 of 334 subjects (0.6%) (blood creatinine increased [2]). Renal dysfunction leading to dose interruption occurred in 28 of 334 subjects (8.4%) (blood creatinine increased [24], renal failure [3], and acute kidney injury, azotaemia, creatinine renal clearance decreased, and renal impairment [1 each] [some subjects had more than 1 event]). Renal dysfunction leading to dose reduction occurred in 8 of 334 subjects (2.4%) (blood creatinine increased [7] and acute kidney injury [1]). There was no renal dysfunction resulting in death.

In Study A2201, the median time to the first onset of renal dysfunction (range) was 20.0 (1-1040) days.

The details of patients with serious renal dysfunction associated with capmatinib (causally related to capmatinib) in all clinical studies submitted are shown in Table 35.

Table 35. Listing of patients with serious renal dysfunction (causally related to capmatinib)

Study ID	Age	Sex	Race	Primary disease	PT (MedDRA ver.22.0)	Grade	Time to onset (days)	Duration (days)	Action taken with capmatinib	Outcome
A2201	70	Men	Non-Japanese	NSCLC	Renal failure	2	15	2	Dose interrupted	Improved
					Renal failure	1	16	2	Dose interrupted	Resolved
	41	Men	Japanese	NSCLC	Acute kidney injury	3	5	1	Dose interrupted	Improved
	74	Men	Non-Japanese	NSCLC	Renal failure	1	15	2	Dose interrupted	Resolved
X2102	51	Men	Non-Japanese	Hepatocellular carcinoma	Blood creatinine increased	3	5	15	Dose reduced	Resolved
	58	Men	Non-Japanese	NSCLC	Blood creatinine increased	2	8	2	Dose interrupted	Resolved
					Blood creatinine increased	2	22	2	Dose interrupted	Resolved

PMDA asked the applicant to explain the mechanism of development of renal dysfunction associated with capmatinib and its risk factors.

The applicant's explanation:
Although the mechanism of development of renal dysfunction associated with capmatinib and its risk factors are undefined, the possibility is suggested that inhibition of MATE1 and MATE2-K by capmatinib [see Section 4.5.3] blocks creatinine secretion and causes an increase in creatinine.

PMDA's discussion:
In Study A2201, serious renal dysfunction for which a causal relationship to capmatinib could not be ruled out was reported, and blood creatinine increased occurred more frequently in Japanese patients [see Section 7.R.3.2], etc. Given these findings, attention should be paid to the possible occurrence of renal dysfunction during treatment with capmatinib. Thus, it is necessary to appropriately advise healthcare professionals about the incidence of renal dysfunction in clinical studies, etc. via the package insert, etc.

7.R.3.6 Fluid retention (including hypoalbuminaemia)

The applicant's explanation about fluid retention (including hypoalbuminaemia) associated with capmatinib:
As adverse events of fluid retention, MedDRA PTs of "fluid overload," "fluid retention," "oedema peripheral," "peripheral oedema neonatal," "peripheral swelling," "blood albumin decreased," "hypoalbuminaemia," "pleural effusion," "pericardial effusion," and "ascites" were counted.

The incidence of fluid retention in Study A2201 is shown in Table 36.

Table 36. Incidence of fluid retention (Study A2201)

PT (MedDRA ver.22.0)	N (%) n = 334	
	All Grades	Grade ≥3
Fluid retention	190 (56.9)	39 (11.7)
Oedema peripheral	166 (49.7)	28 (8.4)
Hypoalbuminaemia	29 (8.7)	2 (0.6)
Pleural effusion	22 (6.6)	8 (2.4)
Blood albumin decreased	11 (3.3)	2 (0.6)
Peripheral swelling	10 (3.0)	1 (0.3)
Pericardial effusion	2 (0.6)	0
Ascites	1 (0.3)	0
Fluid overload	1 (0.3)	0

In Study A2201, serious fluid retention occurred in 17 of 334 subjects (5.1%) (pleural effusion [12], oedema peripheral [4], and peripheral swelling [3] [some subjects had more than 1 event]), and a causal relationship to capmatinib could not be ruled out for those events reported by 6 subjects (pleural effusion, peripheral oedema [3 each], and peripheral swelling [2] [some subjects had more than 1 event]). Fluid retention leading to capmatinib discontinuation occurred in 7 of 334 subjects (2.1%) (oedema peripheral [6] and pleural effusion [1]). Fluid retention leading to dose interruption occurred in 35 of 334 subjects (10.5%) (oedema peripheral [29]; pleural effusion [3]; hypoalbuminaemia; and peripheral swelling [2 each]; and blood albumin decreased [1] [some subjects had more than 1 event]). Fluid retention leading to dose reduction occurred in 25 of 334 subjects (7.5%) (oedema peripheral [24]; and peripheral swelling [1]). There was no fluid retention resulting in death.

In Study A2201, the median time to the first onset of fluid retention (range) was 43.0 (1-756) days.

The details of patients with serious fluid retention associated with capmatinib (causally related to capmatinib) in all clinical studies submitted are shown in Table 37.

Table 37. Listing of patients with serious fluid retention (causally related to capmatinib)

Study ID	Age	Sex	Race	Primary disease	PT (MedDRA ver.22.0)	Grade	Time to onset (days)	Duration (days)	Action taken with capmatinib	Outcome
A2201	69	Men	Non-Japanese	NSCLC	Oedema peripheral	3	203	14	Dose interrupted	Improved
	57	Men	Non-Japanese	NSCLC	Oedema peripheral	3	5	5	Dose interrupted	Improved
	76	Men	Non-Japanese	NSCLC	Peripheral swelling	2	62	2	Continued	Improved
	63	Men	Non-Japanese	NSCLC	Pleural effusion	2	37	5	Continued	Improved
					Pleural effusion	2	50	2	Continued	Improved
	56	Men	Non-Japanese	NSCLC	Pleural effusion	2	7	10	Not applicable	Resolved
	70	Men	Non-Japanese	NSCLC	Oedema peripheral	2	31	4	Dose interrupted	Resolved
					Peripheral swelling	2	65	2	Not applicable	Resolved
X2102	74	Men	Non-Japanese	Hepatocellular carcinoma	Oedema peripheral	2	85	2	Continued	Resolved
	59	Men	Non-Japanese	NSCLC	Pericardial effusion	3	245	16	Not applicable	Improved

PMDA's discussion:
Because of the reported serious fluid retention for which a causal relationship to capmatinib could not be ruled out in Study A2201, etc., attention should be paid to the possible occurrence of fluid retention during treatment with capmatinib. Thus, it is necessary to appropriately advise healthcare professionals about the incidence of fluid retention in clinical studies, etc. via the package insert, etc.

7.R.3.7 Acute pancreatitis

The applicant's explanation about acute pancreatitis associated with capmatinib:
As adverse events of acute pancreatitis, MedDRA PTs of "amylase abnormal," "amylase creatinine clearance ratio abnormal," "amylase increased," "blood trypsin increased," "Cullen's sign," "Grey Turner's sign," "haemorrhagic necrotic pancreatitis," "hereditary pancreatitis," "hyperamylasaemia," "hyperlipasaemia," "ischaemic pancreatitis," "lipase abnormal," "lipase increased," "lipase urine increased," "obstructive pancreatitis," "oedematous pancreatitis," "pancreatic abscess," "pancreatic duct rupture," "pancreatic enzyme abnormality," "pancreatic enzymes abnormal," "pancreatic enzymes increased," "pancreatic haemorrhage," "pancreatic necrosis," "pancreatic phlegmon," "pancreatic pseudoaneurysm," "pancreatic pseudocyst," "pancreatic pseudocyst drainage," "pancreatitis," "pancreatitis acute," "pancreatitis haemorrhagic," "pancreatitis necrotising," "pancreatitis relapsing," "pancreatorenal syndrome," and "peripancreatic fluid collection" were counted.

The incidence of acute pancreatitis in Study A2201 is shown in Table 38.

Table 38. Incidence of acute pancreatitis (Study A2201)

PT (MedDRA ver.22.0)	N (%) n = 334	
	All Grades	Grade ≥3
Pancreatitis acute	41 (12.3)	26 (7.8)
Amylase increased	29 (8.7)	12 (3.6)
Lipase increased	26 (7.8)	18 (5.4)
Pancreatitis acute	1 (0.3)	1 (0.3)

In Study A2201, serious acute pancreatitis occurred in 2 of 334 subjects (0.6%) (amylase increased and pancreatitis acute [1 each]), and a causal relationship to capmatinib could not be ruled out for both events. Acute pancreatitis leading to capmatinib discontinuation occurred in 2 of 334 subjects (0.6%) (amylase increased and pancreatitis acute [1 each]). Acute pancreatitis leading to dose interruption occurred in 21 of 334 subjects (6.3%) (lipase increased [15] and amylase increased [11] [some subjects had more than 1 event]). Acute pancreatitis leading to dose reduction occurred in 3 of 334 subjects (0.9%) (amylase increased [2] and lipase increased [1]). There was no acute pancreatitis resulting in death.

In Study A2201, the median time to the first onset of acute pancreatitis (range) was 32.0 (1-945) days.

The details of patients with serious acute pancreatitis associated with capmatinib (causally related to capmatinib) in all clinical studies submitted are shown in Table 39.

Table 39. Listing of patients with serious acute pancreatitis (causally related to capmatinib)

Study ID	Age	Sex	Race	Primary disease	PT (MedDRA ver.22.0)	Grade	Time to onset (days)	Duration (days)	Action taken with capmatinib	Outcome
A2201	62	Men	Non-Japanese	NSCLC	Acute pancreatitis	3	43	20	Discontinued	Unresolved
	74	Women	Non-Japanese	NSCLC	Amylase increased	4	43	8	Discontinued	Resolved
X2102	54	Men	Non-Japanese	Hepatocellular carcinoma	Lipase increased	3	10	6	Dose interrupted	Resolved
	84	Men	Non-Japanese	NSCLC	Amylase increased	4	58	12	Continued	Resolved

PMDA's discussion:

Although amylase or lipase increased as clinical laboratory abnormalities and acute pancreatitis were reported in the clinical studies, the number of patients with serious acute pancreatitis was very limited, precluding a definitive conclusion on the relationship between capmatinib and acute pancreatitis. However, given the reported serious acute pancreatitis for which a causal relationship to capmatinib could not be ruled out, etc., acute pancreatitis is likely to occur following the administration of capmatinib, and caution is needed on the use of capmatinib. Thus, healthcare professionals should be appropriately advised of the incidence of acute pancreatitis in the clinical studies, etc. via the package insert, etc.

7.R.3.8 Photosensitivity

The applicant's explanation about photosensitivity associated with capmatinib:

As adverse events of photosensitivity, MedDRA PTs "application site photosensitivity reaction," "chronic actinic dermatitis," "implant site photosensitivity," "infusion site photosensitivity reaction," "injection site photosensitivity reaction," "juvenile spring eruption," "photodermatosis," "photoonycholysis," "photosensitivity reaction," "polymorphic light eruption," "pseudoporphyria," "retinal phototoxicity," "solar dermatitis," "solar urticaria." and "sunburn" were counted.

The incidence of photosensitivity in Study A2201 is shown in Table 40.

Table 40. Incidence of photosensitivity (Study A2201)

PT (MedDRA ver.22.0)	N (%) n = 334	
	All Grades	Grade ≥3
Photosensitivity	1 (0.3)	0
Photosensitivity reaction	1 (0.3)	0

In Study A2201, there was no photosensitivity resulting in death, serious photosensitivity, photosensitivity leading to capmatinib discontinuation, or photosensitivity leading to dose interruption or reduction.

In Study A2201, the time to the first onset of photosensitivity was 65.0 days (1 subject).

In any of the clinical studies submitted, no patients had serious photosensitivity associated with capmatinib.

PMDA's discussion:
The extremely limited number of patients experiencing photosensitivity in the clinical studies precludes a definitive conclusion on the relationship between capmatinib and photosensitivity. However, given that an *in vitro* phototoxicity study using a mouse fibroblast cell line and a photosensitization study in mice indicated that capmatinib has phototoxic potential [see Section 5.7.1], and that the clinical studies were conducted with the recommendation of preventive measures against ultraviolet exposure made in advance, photosensitivity is likely to occur following the administration of capmatinib, and caution is needed on the use of capmatinib. Thus, healthcare professionals should be appropriately advised of the incidence of photosensitivity in clinical studies, etc. via the package insert, etc.

7.R.3.9 Others

Clinical signs and histopathological changes indicative of CNS toxicity were observed in repeated-dose toxicity studies in rats [see Section 5.7.3.1]. PMDA asked the applicant to explain the incidence of CNS toxicity associated with capmatinib.

The applicant's explanation:
CNS toxicity:
As adverse events of CNS toxicity, events in the MedDRA SMQ of "convulsions (broad)," "parkinson-like events (broad)," and "vestibular disorders (broad)," the system organ class (SOC) of "psychiatric disorders," and the high level group term (HLGT) of "mental impairment disorders" were counted.

The incidence of CNS toxicity in Study A2201 is shown in Table 41.

Table 41. CNS toxicity events reported by ≥2 subjects (Study A2201)

PT (MedDRA ver.22.0)	N (%) n = 334	
	All Grades	Grade ≥3
CNS toxicity	108 (32.3)	7 (2.1)
Dizziness	29 (8.7)	1 (0.3)
Insomnia	27 (8.1)	0
Vertigo	15 (4.5)	1 (0.3)
Anxiety	13 (3.9)	0
Depression	9 (2.7)	0
Dysphonia	7 (2.1)	0
Confusional state	5 (1.5)	0
Seizure	5 (1.5)	1 (0.3)
Sleep disorder	5 (1.5)	0
Tremor	4 (1.2)	0
Agitation	3 (0.9)	0
Depressed mood	3 (0.9)	0
Balance disorder	2 (0.6)	0
Delirium	2 (0.6)	1 (0.3)
Epilepsy	2 (0.6)	0
Gait disturbance	2 (0.6)	0
Mental status changes	2 (0.6)	1 (0.3)
Vertigo positional	2 (0.6)	0

In Study A2201, serious CNS toxicity occurred in 10 of 334 subjects (3.0%) (seizure [3], epilepsy, mental status changes [2 each] agitation, confusional state, disorientation, vertigo [1 each] [1 subject had more than 1 event]), and a causal relationship to capmatinib could not be ruled out for 1 case of agitation. CNS toxicity leading to dose interruption occurred in 9 of 334 subjects (2.7%) (epilepsy, seizure [2 each], agitation, behaviour disorder, confusional state, disorientation, dizziness, partial seizures, and tremor [1 each] [some subjects had more than 1 event]). CNS toxicity leading to dose reduction occurred in 2 of 334 subjects (0.6%) (agitation and dizziness [1 each]). There was no CNS toxicity resulting in death or capmatinib discontinuation.

In Study A2201, the median time to the first onset of CNS toxicity (range) was 34.5 (1-589) days.

The details of patients with serious CNS toxicity or CNS toxicity resulting in death associated with capmatinib in all clinical studies submitted are shown in Table 42.

Table 42. Listing of patients with serious CNS toxicity

Study ID	Age	Sex	Race	Primary disease	PT (MedDRA ver.22.0)	Grade	Time to onset (days)	Duration (days)	Causality to capmatinib	Action taken with capmatinib	Outcome
A2201	59	Men	Non-Japanese	NSCLC	Epilepsy	2	16	39	No	Dose interrupted	Resolved
	53	Men	Non-Japanese	NSCLC	Seizure	3	54	3	No	Dose interrupted	Resolved
	65	Men	Non-Japanese	NSCLC	Seizure	2	123	2	No	Continued	Resolved
	53	Men	Non-Japanese	NSCLC	Confusional state	2	54	6	No	Not applicable	Improved
	76	Men	Non-Japanese	NSCLC	Vertigo	3	294	18	No	Continued	Improved
	68	Men	Non-Japanese	NSCLC	Epilepsy	2	1	1	No	Dose interrupted	Resolved
	70	Men	Non-Japanese	NSCLC	Seizure	2	373	12	No	Dose interrupted	Resolved
	64	Men	Non-Japanese	NSCLC	Disorientation	3	5	12	No	Dose interrupted	Unresolved
	73	Men	Japanese	NSCLC	Agitation	2	7	18	Yes	Dose interrupted	Improved
	70	Men	Non-Japanese	NSCLC	Mental status changes	2	65	5	No	Not applicable	Resolved
	71	Women	Non-Japanese	NSCLC	Mental status changes	3	131	17	No	Not applicable	Improved

PMDA's discussion:

Most of CNS toxicity events associated with capmatinib were of Grade ≤2 in Study A2201, and patients experiencing serious CNS toxicity for which a causal relationship to capmatinib could not be ruled out was extremely limited in number in the clinical studies, etc., precluding a definitive conclusion on CNS toxicity. However, given the reported serious CNS toxicity for which a causal relationship to capmatinib could not be ruled out in Study A2201, healthcare professionals should be appropriately advised of the incidence of CNS toxicity in the clinical studies, etc. via the package insert. Post-marketing information on the occurrence of CNS toxicity should be further collected, and new observations should be communicated to healthcare professionals appropriately.

7.R.4 Clinical positioning and indication

The proposed indication for capmatinib is "*MET* mutation-positive unresectable advanced or recurrent non-small cell lung cancer." The following statements are included in the “Precautions for Indication” section of the proposed package insert.

- Capmatinib should be used in patients with a *MET* mutation confirmed through testing by adequately experienced pathologists or at laboratories. Testing should be performed with the approved *in vitro* diagnostic, etc.
- Eligible patients must be selected by physicians with a full understanding of the information presented in the “CLINICAL STUDIES” section and of the efficacy and safety of capmatinib.
- The efficacy and safety of capmatinib in a post-operative adjuvant setting have not been established.

Based on Sections "7.R.2 Efficacy" and "7.R.3 Safety," and the considerations in the following sections, PMDA concluded as follows: The following statements should be presented in the “Precautions for Indication” section. The proposed indication should be modified to "*MET* exon 14 skipping mutation-positive unresectable advanced or recurrent non-small cell lung cancer."

● Capmatinib should be used in patients with a *MET* exon 14 skipping mutation confirmed through testing by adequately experienced pathologists or at laboratories. Testing should be performed with the approved *in vitro* diagnostic or medical device.
● The efficacy and safety of capmatinib in a post-operative adjuvant setting have not been established.

7.R.4.1 Clinical positioning of capmatinib and target population

There is no mention of capmatinib in the latest Japanese and foreign clinical practice guidelines or the major textbooks of clinical oncology.

The applicant's explanation about the target population and indication of capmatinib:
Based on the results from Cohorts 4 and 5b of Study A2201 etc., capmatinib can be recognized as a treatment option for patients with METex14 mutation-positive unresectable advanced or recurrent NSCLC.

In Study A2201, patients who had received 1 or 2 prior lines of chemotherapy and chemotherapy-naïve patients were enrolled in Cohort 4 and Cohort 5b, respectively, and both cohorts achieved certain overall response rates [see Section 7.1.3.1], etc. Thus, capmatinib is expected to have efficacy in patients with METex14 mutation-positive unresectable advanced or recurrent NSCLC, irrespective of number of prior lines of therapy. Because of no clinical data on the efficacy and safety of capmatinib in a post-operative adjuvant setting, the use of capmatinib in a post-operative adjuvant setting is not recommended.

Based on the above, the type of *MET* mutation in patients enrolled in Cohorts 4 and 5b of Study A2201 is mentioned in the “CLINICAL STUDIES” section of the package insert, and the following statements are presented in the “Precautions for Indication” section. Further, the indication of "*MET* mutation-positive unresectable advanced or recurrent non-small cell lung cancer" is proposed.
● Eligible patients must be selected by physicians with a full understanding of the information presented in the “CLINICAL STUDIES” section and of the efficacy and safety of capmatinib.
● The efficacy and safety of capmatinib in a post-operative adjuvant setting have not been established.

PMDA's discussion:
The applicant’s explanation is largely acceptable. However, a certain level of efficacy and safety of capmatinib were demonstrated in Cohorts 4 and 5b of Study A2201, i.e., in patients with METex14 mutations, etc., and this should be clearly mentioned in the “INDICATION” section. As there is no noteworthy findings from the patient population of Study A2201 besides the type of *MET* mutation, the statement of "eligible patients must be selected by physicians with a full understanding of the information presented in the “CLINICAL STUDIES” section and of the efficacy and safety of capmatinib." is unnecessary.

Based on the above, the following statement should be presented in the “Precautions for Indication” section. The proposed indication should be modified to "*MET* exon 14 skipping mutation-positive unresectable advanced or recurrent non-small cell lung cancer."

● The efficacy and safety of capmatinib in a post-operative adjuvant setting have not been established.

7.R.4.2 METex14 testing

The applicant's explanation about METex14 testing, which is used to assess patient eligibility for treatment with capmatinib:

In Cohorts 4 and 5b of Study A2201, the efficacy and safety analyses were performed in patients whose tumor tissue harbored a METex14 mutation detected by Novartis Precision Medicine's RT-PCR assay, "MET Exon14 Deletion Test," at the central laboratory [see Section 7.1.3.1]. Meanwhile, a partial change approval application was submitted for CDx, "FoundationOne CDx Cancer Genomic Profile," as an aid in assessing patient eligibility for treatment with capmatinib. The concordance analysis was performed with tumor tissue specimens, and good agreement between "FoundationOne CDx Cancer Genomic Profile" and "MET Exon14 Deletion Test" was demonstrated. Thus, patients in whom capmatinib is expected to show efficacy and safety can be identified appropriately with "FoundationOne CDx Cancer Genomic Profile."

Based on the above, prior to the use of capmatinib, "FoundationOne CDx Cancer Genomic Profile" should be used to select patients, and the relevant statement will be presented in the “Precautions for Indication” section.

PMDA's discussion:

The applicant’s explanation is acceptable. The proposed description in the “Precautions for Indication” section should be modified as follows so as to clearly indicate that the target population for capmatinib is patients with METex14 mutations.

● Capmatinib should be used in patients with a *MET* exon 14 skipping mutation confirmed through testing by adequately experienced pathologists or at laboratories. Testing should be performed with the approved *in vitro* diagnostic or medical device.

7.R.5 Dosage and administration

The proposed dosage and administration statement is "The usual adult dosage is 400 mg of capmatinib administered orally twice daily. The dosage should be reduced as appropriate according to the patient's condition." The following statement is included in the “Precautions for Dosage and Administration” section of the proposed package insert.

● Recommended capmatinib dosage modifications for adverse reactions

Based on Sections "6.R.1 Food effect," "7.R.2 Efficacy," and "7.R.3 Safety," and the discussions in the following subsections, PMDA concluded that the following statements should be presented in the “Precautions for Dosage and Administration” section. The proposed description of dosage and administration, i.e., "The usual adult dosage is 400 mg of capmatinib administered orally twice daily. The dosage should be reduced, as appropriate, according to the patient's condition." is appropriate.

● The efficacy and safety of capmatinib in combination with other anti-neoplastic drugs have not been established.

● Recommended capmatinib dosage modifications for adverse reactions

7.R.5.1 Dosage and administration of capmatinib

The applicant's explanation about the basis for the proposed dosing regimen of capmatinib for METex14 mutation-positive unresectable advanced or recurrent NSCLC:

The dosing regimen for Study A2201 was selected based on the following clinical study data etc., and the results from Cohorts 4 and 5b of Study A2201 demonstrated a certain level of efficacy and safety of capmatinib in patients with METex14 mutation-positive unresectable advanced or recurrent NSCLC. Thus, the proposed dosing regimen was selected based on Cohorts 4 and 5b of Study A2201.

- In the dose-escalation part of a foreign phase I study (Study X2102), following the oral administration of capmatinib (tablets) 400 mg BID under fasted conditions, no DLTs were observed, and capmatinib was also well tolerated [see Section 7.1.4.1].
- In a Japanese phase I study (Study X1101), following the oral administration of capmatinib (tablets) 200 or 400 mg BID under fasted conditions, a DLT was observed in 1 of 10 subjects in the 400 mg BID cohort, but the maximum tolerated dose (MTD) was not reached. The study demonstrated the tolerability and safety of capmatinib (tablets) 400 mg BID in Japanese patients [see Section 7.1.2.1].

In Cohorts 4 and 5b of Study A2201, a certain level of efficacy and safety of capmatinib were demonstrated when administered ≥1 hour before or ≥2 hours after a meal. However, given the following points etc., the dosage regimen of capmatinib should be defined without meal time specified.

- In a foreign phase I study (Study X2107), food increased the C_{max} and AUC of capmatinib (tablets) as compared with those after fasted doses, whereas the changes in exposure (AUC_{inf}) following the administration of capmatinib (tablets) 600 mg with food were within the range of capmatinib (tablets) exposure in a Japanese phase I study (Study X1101) that demonstrated the tolerable safety profile of capmatinib [see Sections 6.1.3.1 and 6.2.1.1].
- Based on the data from a Japanese phase I study (Study X1101), a global phase II study (Study A2201), and foreign phase I studies (Studies A2108 and X2102), the relationship between capmatinib (tablets) exposure and safety was explored. The results showed no relationship between capmatinib exposure and Grade ≥3 adverse events/serious adverse events, etc. [see Section 6.2.8.2].

At present, there are no clinical study data on the efficacy and safety of capmatinib in combination with other anti-neoplastic drugs. Thus, the use of capmatinib in combination with other anti-neoplastic drugs is not recommended.

PMDA's discussion:

The above explanation by the applicant is largely acceptable. However, given that there are no clinical study data on the efficacy and safety of capmatinib in combination with other anti-neoplastic drugs in patients with NSCLC, the “Precautions for Dosage and Administration” section should note that the efficacy and safety of capmatinib in combination with other anti-neoplastic drugs have not been established, and then the dosage

regimen of capmatinib should be defined as proposed, i.e., "The usual adult dosage is 400 mg of capmatinib administered orally twice daily. The dosage should be reduced as appropriate, according to the patient's condition."

7.R.5.2 Capmatinib dose modification

The applicant's explanation about capmatinib dose modification:

Study A2201 was conducted in Cohorts 4 and 5b according to the specific dose modification guidelines, which demonstrated a certain level of efficacy and safety of capmatinib in these cohorts. Thus, the “Precautions for Dosage and Administration” section of the proposed package insert presents dose modification guidelines based on those for Cohorts 4 and 5b of Study A2201.

PMDA's discussion:

PMDA accepted the above explanation by the applicant, and concluded that the following recommended dose modification should be presented in the “Precautions for Dosage and Administration” section.

- In the event of adverse reactions, interrupt or reduce the dose of capmatinib, or discontinue capmatinib therapy according to the tables below.

Table 43. Recommended dose reductions/discontinuation of therapy

Dose reduction levels	Dose
Usual dose	400 mg (twice daily)
First dose reduction	300 mg (twice daily)
Second dose reduction	200 mg (twice daily)
Discontinuation	Permanently discontinue capmatinib for patients who are unable to tolerate 200 mg twice daily.

Table 44. Recommended capmatinib dosage modifications for adverse reactions

Adverse reaction	Severity[*1]	Dosage modification
ILD	Grade ≥1	Permanently discontinue capmatinib.
Increased AST or ALT with increased total bilirubin[*2]	AST or ALT >3.0×ULN with total bilirubin >2.0×ULN	Permanently discontinue capmatinib.
Increased AST or ALT	Grade 3	Withhold capmatinib until recovery to Grade ≤1 or baseline. If recovered within 7 days, resume capmatinib at the same dose; otherwise resume capmatinib at 1 dose level lower.
	Grade 4	Permanently discontinue capmatinib.
Increased total bilirubin	Grade 2	Withhold capmatinib until recovery to Grade ≤1. If recovered within 7 days, resume capmatinib at the same dose; otherwise resume capmatinib at 1 dose level lower.
	Grade 3	Withhold capmatinib until recovery to Grade ≤1. If recovered within 7 days, resume capmatinib at 1 dose level lower; otherwise permanently discontinue capmatinib.
	Grade 4	Permanently discontinue capmatinib.
Other adverse reactions	Grade 2	If unmanageable and intolerable, withhold capmatinib until recovery to Grade ≤1, resume capmatinib at 1 dose level lower.
	Grade 3	Withhold capmatinib until recovery to Grade ≤2, resume capmatinib at 1 dose level lower.
	Grade 4	Permanently discontinue capmatinib.

*1 Grading according to NCI-CTCAE ver.4.03 *2 In the absence of cholestasis or hemolysis

7.R.6 Post-marketing investigations

The applicant's explanation about post-marketing investigations:
The applicant is planning to conduct post-marketing surveillance, covering all patients treated with capmatinib, to assess the safety etc. of capmatinib in the post-marketing setting.

The safety specification for the surveillance includes hepatotoxicity, ILD/pneumonitis, renal dysfunction, pancreatitis, and photosensitivity, because these events require particular attention during capmatinib therapy.

METex14 mutation-positive unresectable advanced or recurrent NSCLC is an extremely rare disease. Taking account of the feasibility of surveillance based on the number of patients in Japan, etc., a planned sample size of 20 to 30 patients was chosen.

The observation period is 1 year from the start of treatment with capmatinib, taking account of the time to the first onset of the above events included in the safety specification in Study A2201, etc.

PMDA's discussion:
Considering limited safety information from patients treated with capmatinib, including Japanese patients, etc., it is necessary to conduct post-marketing surveillance covering all patients treated with capmatinib over a specified period of time in order to collect safety information in a prompt and unbiased manner and to provide safety information to healthcare professionals in clinical practice as soon as available.

Based on the considerations in Section "7.R.3 Safety," the safety specification for the surveillance should include hepatic dysfunction, ILD, renal dysfunction, fluid retention, acute pancreatitis, and photosensitivity.

The planned sample size and observation period need to be reconsidered, taking account of the incidences of specific events included in the safety specification for the surveillance. If the surveillance is likely to take a long time period, an interim analysis should be performed when a certain amount of safety data are accumulated, without waiting for final results to be available. Based on the interim analysis results, the applicant should consider taking appropriate actions such as making changes in pharmacovigilance activities and providing information to healthcare professionals.

7.3 Adverse events etc. observed in clinical studies

Based on the clinical study data submitted for safety evaluation, deaths are described in Sections "7.1 Evaluation data" and 7.2 Reference data." The main adverse events other than deaths are described below.

7.3.1 Japanese phase I study (Study X1101)

Adverse events occurred in (a) 3 of 3 subjects (100%) in the capmatinib (capsules) 100 mg QD cohort, (b) 3 of 4 subjects (75.0%) in the capmatinib (capsules) 200 mg QD cohort, (c) 2 of 3 subjects (66.7%) in the capmatinib (capsules) 400 mg QD cohort, (d) 4 of 4 subjects (100%) in the capmatinib (capsules) 500 mg QD

cohort, (e) 4 of 4 subjects (100%) in the capmatinib (capsules) 600 mg QD cohort, (f) 4 of 4 subjects (100%) in the capmatinib (capsules) 800 mg QD cohort, (g) 4 of 4 subjects (100%) in the capmatinib (capsules) 400 mg BID cohort, (h) 3 of 3 subjects (100%) in the capmatinib (capsules) 600 mg BID cohort, (i) 3 of 3 subjects (100%) in the capmatinib (tablets) 200 mg BID cohort, and (j) 12 of 12 subjects (100%) in the capmatinib (tablets) 400 mg BID cohort. Those for which a causal relationship to capmatinib could not be ruled out occurred in (a) 2 of 3 subjects (66.7%) on capmatinib (capsules) 100 mg QD, (b) 2 of 4 subjects (50.0%) on capmatinib (capsules) 200 mg QD, (c) 2 of 3 subjects (66.7%) on capmatinib (capsules) 400 mg QD, (d) 3 of 4 subjects (75.0%) on capmatinib (capsules) 500 mg QD, 4 of 4 subjects (100%) on capmatinib (capsules) 600 mg QD, (f) 3 of 4 subjects (75.0%) on capmatinib (capsules) 800 mg QD, (g) 4 of 4 subjects (100%) on capmatinib (capsules) 400 mg BID, (h) 2 of 3 subjects (66.7%) on capmatinib (capsules) 600 mg BID, (i) 3 of 3 subjects (100%) on capmatinib (tablets) 200 mg BID, and (j) 12 of 12 subjects (100%) on capmatinib (tablets) 400 mg BID. Adverse events reported by ≥70% of subjects in any cohort were (b) vomiting (3 [75.0%]) in the capmatinib (capsules) 200 mg QD cohort, (d) diarrhoea (4 [100%]) in the capmatinib (capsules) 500 mg QD cohort; and blood creatinine increased (3 [75.0%]), (e) nausea; vomiting; blood creatinine increased; and decreased appetite (3 each [75.0%]) in the capmatinib (capsules) 600 mg QD cohort, and (g) blood creatinine increased (4 [100%]) in the capmatinib (capsules) 400 mg BID cohort.

Serious adverse events occurred in (b) 1 of 4 subjects (25.0%) on capmatinib (capsules) 200 mg QD, (d) 1 of 4 subjects (25.0%) on capmatinib (capsules) 500 mg QD, (e) 1 of 4 subjects (25.0%) on capmatinib (capsules) 600 mg QD, (f) 1 of 4 subjects (25.0%) on capmatinib (capsules) 800 mg QD, (g) 1 of 4 subjects (25.0%) on capmatinib (capsules) 400 mg BID, (i) 1 of 3 subjects (33.3%) on capmatinib (tablets) 200 mg BID, and (j) 1 of 12 subjects (8.3%) on capmatinib (tablets) 400 mg BID. These serious events were (b) decreased appetite (1 [25.0%]) in the capmatinib (capsules) 200 mg QD cohort, (d) pleural effusion; and performance status decreased (1 each [25.0%] [1 had both events]) in the capmatinib (capsules) 500 mg QD cohort, (e) lung infection (1 [25.0%]) in the capmatinib (capsules) 600 mg QD cohort, (f) cancer pain (1 [25.0%]) in the capmatinib (capsules) 800 mg QD cohort, (g) cardiac tamponade (1 [25.0%]) in the capmatinib (capsules) 400 mg BID cohort, (i) ulcerative colitis (1 [33.3%]) in the capmatinib (tablets) 200 mg BID cohort, and (j) tumour pain (1 [8.3%]) in the capmatinib (tablets) 400 mg BID cohort. A causal relationship to capmatinib could not be ruled out for (e) lung infection in 1 subject in the capmatinib (capsules) 600 mg QD cohort and (i) ulcerative colitis in 1 subject in the capmatinib (tablets) 200 mg BID cohort.

Adverse events leading to capmatinib discontinuation occurred in (f) 1 of 4 subjects (25.0%) on capmatinib (capsules) 800 mg QD, (h) 1 of 3 subjects (33.3%) on capmatinib (capsules) 600 mg BID, (i) 1 of 3 subjects (33.3%) on the capmatinib (tablets) 200 mg BID, and (j) 1 of 12 subjects (8.3%) on the capmatinib (tablets) 400 mg BID, which were (f) nausea (1 [25.0%]) in the capmatinib (capsules) 800 mg QD cohort, (h) suicidal ideation (1 [33.3%]) in the capmatinib (capsules) 600 mg BID cohort, (i) ulcerative colitis (1 [33.3%]) in the capmatinib (tablets) 200 mg BID cohort, and (j)depression (1 [8.3%]) in the capmatinib (tablets) 400 mg BID cohort. A causal relationship to capmatinib could not be ruled out for all those events.

7.3.2 Global phase II study (Study A2201)

Adverse events occurred in 328 of 334 subjects (98.2%), and those for which a causal relationship to capmatinib could not be ruled out occurred in 282 of 334 subjects (84.4%). Adverse events reported by ≥10% of subjects in all cohorts are shown in the table below.

Table 45. Adverse events reported by ≥10% of subjects (Study A2201)

SOC PT (MedDRA ver.22.0)	N (%) n = 334	
	All Grades	Grade ≥3
All adverse events	328 (98.2)	219 (65.6)
Gastrointestinal disorders		
Nausea	147 (44.0)	9 (2.7)
Vomiting	94 (28.1)	8 (2.4)
Diarrhoea	61 (18.3)	1 (0.3)
Constipation	60 (18.0)	3 (0.9)
General disorders and administration site conditions		
Peripheral oedema	166 (49.7)	28 (8.4)
Fatigue	72 (21.6)	16 (4.8)
Pyrexia	47 (14.1)	2 (0.6)
Asthenia	41 (12.3)	12 (3.6)
Non-cardiac chest pain	34 (10.2)	4 (1.2)
Investigations		
Blood creatinine increased	85 (25.4)	0
ALT increased	42 (12.6)	19 (5.7)
Weight decreased	34 (10.2)	2 (0.6)
Metabolism and nutrition disorders		
Decreased appetite	69 (20.7)	3 (0.9)
Musculoskeletal and connective tissue disorders		
Back pain	47 (14.1)	3 (0.9)
Respiratory, thoracic and mediastinal disorders		
Dyspnoea	81 (24.3)	23 (6.9)
Cough	54 (16.2)	2 (0.6)

Serious adverse events occurred in 169 of 334 subjects (50.6%). Those reported by ≥5 subjects were dyspnoea (23 [6.9%]); pneumonia (16 [4.8%]); pleural effusion (12 [3.6%]); general physical health deterioration (10 [3.0%]); vomiting (8 [2.4%]); nausea (7 [2.1%]); abdominal pain; and pulmonary embolism (6 each [1.8%]); and respiratory failure; cellulitis; pneumonitis; respiratory tract infection; and hyponatraemia (5 each [1.5%]), and a causal relationship to capmatinib could not be ruled out for vomiting; and nausea (5 each); pneumonitis (3); pleural effusion; and cellulitis (2 each); and abdominal pain; dyspnoea; and hyponatraemia (1 each).

Adverse events leading to capmatinib discontinuation occurred in 54 of 334 subjects (16.2%). Those reported by ≥4 subjects were pneumonitis; and peripheral oedema (6 each [1.8%]); and fatigue (5 [1.5%]), and a causal relationship to capmatinib could not be ruled out for peripheral oedema (6); and pneumonitis; and fatigue (5 each).

7.3.3 Foreign phase I study (Study A2106)

Adverse events occurred in 3 of 7 subjects with mild hepatic impairment (42.9%), 2 of 8 subjects with moderate hepatic impairment (25.0%), and 1 of 6 subjects with severe hepatic impairment (16.7%), and those for which a causal relationship to capmatinib could not be ruled out occurred in 2 of 8 subjects with moderate hepatic

impairment (25.0%) and 1 of 6 subjects with severe hepatic impairment (16.7%). Adverse events reported by ≥2 subjects in any group were nausea (2 [25.0%]) in the moderate hepatic impairment group.

There were no serious adverse events or adverse events leading to capmatinib discontinuation.

7.3.4 Foreign phase I study (Study A2108)

Adverse events occurred in all subjects, and those for which a causal relationship to capmatinib could not be ruled out occurred in (a) 6 of 8 subjects (75.0%) in the 300 mg BID cohort and (b) 22 of 27 subjects (81.5%) in the 400 mg BID cohort. Adverse events reported by ≥40% of subjects in either cohort were (a) fatigue (5 subjects [62.5%]) and peripheral oedema (4 [50.0%]) in the 300 mg BID cohort and (b) nausea; and fatigue (11 each [40.7%]) in the 400 mg BID cohort.

Serious adverse events occurred in (a) 3 of 8 subjects (37.5%) in the 300 mg BID cohort and (b) 10 of 27 subjects (37.0%) in the 400 mg BID cohort. Those reported by ≥2 subjects in either cohort were (b) abdominal pain; and dyspnoea (2 each [7.4%]) in the 400 mg BID cohort, and a causal relationship to capmatinib could not be ruled out for dyspnoea in 1 subject.

Adverse events leading to capmatinib discontinuation occurred in (a) 1 of 8 subjects (12.5%) in the 300 mg BID cohort and (b) 3 of 27 subjects (11.1%) in the 400 mg BID cohort. None of those events were reported by ≥2 subjects in either cohort.

7.3.5 Foreign phase I study (Study A2109)

Adverse events occurred in 39 of 77 subjects (50.6%), and those for which a causal relationship to capmatinib could not be ruled out occurred in 33 of 77 subjects (42.9%). Adverse events reported by ≥20% of subjects were headache (24 subjects [31.2%]).

There were no serious adverse events or adverse events leading to capmatinib discontinuation.

7.3.6 Foreign phase I study (Study X2102)

Adverse events occurred in all subjects in the dose-escalation part and 92 of 93 subjects (98.9%) in the dose-expansion part, and those for which a causal relationship to capmatinib could not be ruled out occurred in (a) 3 of 4 subjects (75.0%) in the capmatinib (capsules) 100 mg BID cohort, (b) 5 of 5 subjects (100%) in the capmatinib (capsules) 200 mg BID cohort, (c) 3 of 4 subjects (75.0%) in the capmatinib (capsules) 250 mg BID cohort, (d) 2 of 3 subjects (66.7%) in the capmatinib (capsules) 350 mg BID cohort, (e) 8 of 9 subjects (88.9%) in the capmatinib (capsules) 450 mg BID cohort, (f) 8 of 8 subjects (100%) in the capmatinib (capsules) 600 mg BID cohort, and (g) 4 of 5 subjects (80.0%) in the capmatinib (tablets) 400 mg BID cohort in the dose-escalation part, and (h) 76 of 93 subjects (81.7%) in the dose-expansion part. Adverse events reported by ≥60% of subjects in any cohort or part were (a) abdominal pain; and asthenia (3 each [75.0%]) in the capmatinib (capsules) 100 mg BID cohort, (c) decreased appetite; and cough (3 each [75.0%]) in the

capmatinib (capsules) 250 mg BID cohort, (d) peripheral oedema (3 [66.7%]) in the capmatinib (capsules) 350 mg BID cohort, and (g) nausea (3 [60.0%]) in the capmatinib (tablets) 400 mg BID cohort.

Serious adverse events occurred in (a) 3 of 4 subjects (75.0%) on capmatinib (capsules) 100 mg BID, (b) 3 of 5 subjects (60.0%)) on capmatinib (capsules) 200 mg BID, (c) 2 of 4 subjects (50.0%) on capmatinib (capsules) 250 mg BID, (d) 1 of 3 subjects (33.3%) on capmatinib (capsules) 350 mg BID, (e) 4 of 9 subjects (44.4%) on capmatinib (capsules) 450 mg BID, (f) 4 of 8 subjects (50.0%) on capmatinib (capsules) 600 mg BID, (g) 2 of 5 subjects (40.0%) on capmatinib (tablets) 400 mg BID, and (h) 45 of 93 subjects (48.4%) in the dose-expansion part. Serious events reported by ≥3 subjects in any cohort or part were (h) abdominal pain; and pneumonia (5 each [5.4%]), blood creatinine increased, general physical condition decreased, and nausea (4 each [4.3%]), confusional state, dehydration, pulmonary embolism, and vomiting (3 each [3.2%]) in the dose-expansion part. A causal relationship to capmatinib could not be ruled out for blood creatinine increased, nausea, vomiting in 2 subjects each and dehydration in 1 subject.

Adverse events leading to capmatinib discontinuation occurred in (e) 1 of 9 subjects (11.1%) in the capmatinib (capsules) 450 mg BID cohort and (h) 17 of 93 subjects (18.3%) in the dose-expansion part, and those reported by ≥3 subjects in any cohort or part were (h) nausea (4 [4.3%]); and peripheral oedema (3 [3.2%]) in the dose-expansion part. A causal relationship to capmatinib could not be ruled out for nausea (4) and peripheral oedema (2).

7.3.7 Foreign phase I study (Study X2106)

Adverse events occurred in 4 of 6 subjects (66.7%), and those for which a causal relationship to capmatinib could not be ruled out occurred in 1 of 6 subjects (16.7%). Adverse events reported by ≥2 subjects were headache (2 [33.3%]).

There were no serious adverse events or adverse events leading to capmatinib discontinuation.

7.3.8 Foreign phase I study (Study X2107)

Adverse events occurred in 13 of 24 subjects (54.2%), and those for which a causal relationship to capmatinib could not be ruled out occurred in 11 of 24 subjects (45.8%). Adverse events reported by ≥10% of subjects were headache (9 [37.5%]); and diarrhoea (3 [12.5%]).

There were no serious adverse events or adverse events leading to capmatinib discontinuation.

7.3.9 Foreign phase I study (Study A2101)

Adverse events occurred in 9 of 20 subjects (45.0%), and those for which a causal relationship to capmatinib could not be ruled out occurred in 7 of 20 subjects (35.0%). Adverse events reported by ≥20% of subjects were headache (7 [35.0%]).

There were no serious adverse events or adverse events leading to capmatinib discontinuation.

7.3.10 Foreign phase I study (Study A2102)

Adverse events occurred in 19 of 27 subjects (70.4%) in the inhibition cohort and 11 of 26 subjects (42.3%) in the induction cohort, and those for which a causal relationship to capmatinib could not be ruled out occurred in 13 of 27 subjects (48.1%) and 10 of 26 subjects (38.5%), respectively. No adverse events were reported by ≥20% of subjects in either cohort.

No serious adverse events were reported.

Adverse events leading to capmatinib discontinuation occurred in 3 of 27 subjects (11.1%) in the inhibition cohort and 1 of 26 subjects (3.8%) in the induction cohort, which were hypertension (2 [7.4%]) and amylase increased (1 [3.7%]) in the inhibition cohort and hypertension (1 [3.8%]) in the induction cohort. A causal relationship to capmatinib could not be ruled out for hypertension (1 each) in the inhibition and induction cohorts.

7.3.11 Foreign phase I study (Study A2103)

Adverse events occurred in all subjects, and those for which a causal relationship to capmatinib could not be ruled out occurred in 30 of 37 subjects (81.1%). Adverse events reported by ≥20% of subjects were peripheral oedema (15 [40.5%]), nausea (14 [37.8%]), diarrhoea, dyspnoea (10 each [27.0%]), abdominal pain, vomiting (9 each [24.3%]), dyspepsia, asthenia, general physical condition decreased, decreased appetite, and headache (8 each [21.6%]).

Serious adverse events occurred in 21 of 37 subjects (56.8%), and those reported by ≥2 subjects were general physical condition decreased (7 [18.9%]), and abdominal pain, ascites, constipation, pleural effusion, and respiratory tract infection (2 each [5.4%]). A causal relationship to capmatinib could not be ruled out for abdominal pain in 2 subjects.

Adverse events leading to capmatinib discontinuation occurred in 5 of 37 subjects (13.5%), and those reported by ≥2 subjects were general physical condition decreased (2 [5.4%]). A causal relationship to capmatinib was denied for both cases.

7.3.12 Foreign phase I study (Study A2105)

Adverse events occurred in all subjects, and those for which a causal relationship to capmatinib could not be ruled out occurred in 25 of 32 subjects (78.1%). Adverse events reported by ≥40% of subjects were nausea (18 [56.3%]), asthenia (14 [43.8%]), constipation, and vomiting (13 each [40.6%]).

Serious adverse events occurred in 17 of 32 subjects (53.1%), and those reported by ≥2 subjects were pulmonary embolism, vomiting (3 each [9.4%]), and dyspnoea (2 [6.3%]). A causal relationship to capmatinib could not be ruled out for vomiting in 3 subjects.

Adverse events leading to capmatinib discontinuation occurred in 3 of 32 subjects (9.4%). None of those events were reported by ≥2 subjects.

7.3.13 Foreign phase I study (Study X2101T)

Adverse events occurred in (a) 3 of 3 subjects (100%) in the 10 mg QD cohort, (b) 4 of 4 subjects (100%) in the 20 mg QD cohort, (c) 6 of 6 subjects (100%) in the 50 mg QD cohort, (d) 4 of 4 subjects (100%) in the 70 mg QD cohort, (e) 3 of 3 subjects (100%) in the 150 mg QD cohort, (f) 4 of 4 subjects (100%) in the 200 mg QD cohort, (g) 4 of 4 subjects (100%) in the 300 mg QD cohort, (h) 5 of 6 subjects (83.3%) in the 400 mg QD cohort, (i) 3 of 3 subjects (100%) in the 50 mg BID cohort, (j) 4 of 4 subjects (100%) in the 200 mg BID cohort, and (k) 4 of 4 subjects (100%) in the 300 mg BID cohort. Adverse events for which a causal relationship to capmatinib could not be ruled out occurred in (a) 1 of 3 subjects (33.3%) on 10 mg QD, (b) 3 of 4 subjects (75.0%) on 20 mg QD, (c) 5 of 6 subjects (83.3%) on 50 mg QD, (d) 4 of 4 subjects (100%) on 70 mg QD, (e) 3 of 3 subjects (100%) on 150 mg QD, (f) 3 of 4 subjects (75.0%) on 200 mg QD, (g) 4 of 4 subjects (100%) on 300 mg QD, (h) 5 of 6 subjects (83.3%) on 400 mg QD, (i) 2 of 3 subjects (66.7%) on 50 mg BID, (j) 4 of 4 subjects (100%) on 200 mg BID, and (k) 3 of 4 subjects (75.0%) on 300 mg BID. Adverse events reported by ≥70% of subjects in any cohort were (b) musculoskeletal pain (3 [75.0%]) in the 20 mg QD cohort, (d) fatigue (3 [75.0%]) in the 70 mg QD cohort, (j) nausea, peripheral oedema, taste abnormality, anxiety (3 each [75.0%]) in the 200 mg BID cohort, and (k) peripheral oedema (3 [75.0%]) in the 300 mg BID cohort.

Serious adverse events occurred in (a) 2 of 3 subjects (66.7%) on10 mg QD, (b) 1 of 4 subjects (25.0%) on 20 mg QD, (f) 1 of 4 subjects (25.0%) on 200 mg QD, (h) 3 of 6 subjects (50.0%) on 400 mg QD, (i) 1 of 3 subjects (33.3%) on 50 mg BID, and (j) 1 of 4 subjects (25.0%) on 200 mg BID. No serious adverse events were reported by ≥2 subjects in any cohort.

Adverse events leading to capmatinib discontinuation occurred in (b) 1 of 4 subjects (25.0%) on 20 mg QD, (c) 1 of 6 subjects (16.7%) on 50 mg QD, (f) 1 of 4 subjects (25.0%) on 200 mg QD, and (h) 1 of 6 subjects (16.7%) on 400 mg QD. These events were (b) clavicle fracture (1 [25.0%]) in the 20 mg QD cohort, (c) ALT increased (1 [16.7%]) in the 50 mg QD cohort, (f) ascites (1 [25.0%]) in the 200 mg QD cohort, and (h) hepatic encephalopathy (1 [16.7%]) in the 400 mg QD cohort. A causal relationship to capmatinib could not be ruled out for (c) ALT increased in 1 subject in the 50 mg QD cohort.

7.3.14 Foreign phase I study (Study X2103)

Adverse events occurred in 7 of 24 subjects (29.2%) following the administration of capmatinib (capsules) and 10 of 24 subjects (41.7%) following the administration of capmatinib (tablets). Adverse events for which a

causal relationship to capmatinib could not be ruled out occurred in 7 of 24 subjects (29.2%) and 8 of 24 subjects (33.3%), respectively. There were no adverse events reported by ≥40% of subjects.

There were no serious adverse events or adverse events leading to capmatinib discontinuation.

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 inspection and assessment are currently ongoing, and their results and PMDA's conclusion will be reported in the Review Report (2).

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

The inspection is currently ongoing, and its results and PMDA's conclusion will be reported in the Review Report (2).

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

On the basis of the data submitted, PMDA has concluded that capmatinib has a certain level of efficacy in the treatment of METex14 mutation-positive unresectable advanced or recurrent NSCLC, and that capmatinib has acceptable safety in view of its benefits. Capmatinib is a drug with a new active ingredient, which is expected to inhibit MET receptor tyrosine kinase. Capmatinib is clinically meaningful because it offers a new treatment option for patients with METex14 mutation-positive unresectable advanced or recurrent NSCLC. PMDA considers that the indication, dosage and administration, post-marketing investigations, etc. should be further discussed.

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

Review Report (2)

May 18, 2020

Product Submitted for Approval

Brand Name	Tabrecta Tablets 150 mg, Tabrecta Tablets 200 mg
Non-proprietary Name	Capmatinib Hydrochloride Hydrate
Applicant	Novartis Pharma K.K.
Date of Application	December 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 Cohorts 4 and 5b[59)] of a global phase II study in patients with METex14 mutation-positive unresectable advanced or recurrent NSCLC (Study A2201), the primary endpoint of the overall response rate per RECIST ver.1.1 as assessed by BIRC [95% CI] was 40.6% [28.9, 53.1] (28 of 69 subjects) and 67.9% [47.6, 84.1] (19 of 28 subjects), respectively.

PMDA's conclusion:

Based on the considerations in Section "7.R.2 Efficacy" in the Review Report (1), given that capmatinib is an inhibitor targeting METex14 mutations as oncogenic drivers, etc., the results of the above overall response rates etc. demonstrated a certain level of efficacy of capmatinib in these patients.

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

[59)] A cohort of patients with METex14 mutations who had received 1 or 2 prior lines of chemotherapy and a cohort of chemotherapy-naïve patients with METex14 mutations

1.2 Safety

PMDA's conclusion:

Based on the considerations in Section "7.R.3 Safety" in the Review Report (1), adverse events that require attention following the administration of capmatinib in patients with METex14 mutation-positive unresectable advanced or recurrent NSCLC are hepatic dysfunction, ILD, renal dysfunction, fluid retention (including hypoalbuminaemia), acute pancreatitis, and photosensitivity. Attention should be paid to the possible occurrence of these adverse events during treatment with capmatinib.

Although attention should be paid to the possible occurrence of the above adverse events during treatment with capmatinib, capmatinib is tolerable as long as physicians with adequate knowledge of and experience in cancer chemotherapy take appropriate measures, e.g. monitoring for and management of adverse events and interruption etc. of capmatinib.

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

1.3 Clinical positioning and indication

PMDA's conclusion:

Based on the considerations in Section "7.R.4 Clinical positioning and indication" in the Review Report (1), the following statements should be included in the “Precautions for Indication” section. The proposed indication should be modified to "*MET* exon 14 skipping mutation-positive unresectable advanced or recurrent non-small cell lung cancer."

Precautions for Indication

- Capmatinib should be used in patients with a *MET* exon 14 skipping mutation confirmed through testing by adequately experienced pathologists or at laboratories. Testing should be performed with the approved *in vitro* diagnostic or medical device.
- The efficacy and safety of capmatinib in a post-operative adjuvant setting have not been established.

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

Based on the above, PMDA instructed the applicant to handle the “INDICATION” and “Precautions for Indication” sections accordingly. The applicant agreed.

1.4 Dosage and administration

PMDA's conclusion:

Based on the considerations in Section "7.R.5 Dosage and administration" in the Review Report (1), the following statements should be included in the “Precautions for Dosage and Administration” section. The proposed dosage and administration statement of "The usual adult dosage is 400 mg of capmatinib administered

orally twice daily. The dosage should be reduced as appropriate, according to the patient's condition." is appropriate.

Precautions for Dosage and Administration

- The efficacy and safety of capmatinib in combination with other anti-neoplastic drugs have not been established.
- In the event of adverse reactions, interrupt or reduce the dose of capmatinib, or discontinue capmatinib therapy according to the tables below.

Table 46. Recommended dose reductions/discontinuation of therapy

Dose reduction levels	Dose
Usual dose	400 mg (twice daily)
First dose reduction	300 mg (twice daily)
Second dose reduction	200 mg (twice daily)
Discontinuation	Permanently discontinue capmatinib for patients who are unable to tolerate 200 mg twice daily.

Table 47. Recommended capmatinib dosage modifications for adverse reactions

Adverse reaction	Severity[*1]	Dosage modification
ILD	Grade ≥1	Permanently discontinue capmatinib.
Increased AST or ALT with increased total bilirubin[*2]	AST or ALT >3.0×ULN with total bilirubin >2.0×ULN	Permanently discontinue capmatinib.
Increased AST or ALT	Grade 3	Withhold capmatinib until recovery to Grade ≤1 or baseline. If recovered within 7 days, resume capmatinib at the same dose; otherwise resume capmatinib at 1 dose level lower.
	Grade 4	Permanently discontinue capmatinib.
Increased total bilirubin	Grade 2	Withhold capmatinib until recovery to Grade ≤1. If recovered within 7 days, resume capmatinib at the same dose; otherwise resume capmatinib at 1 dose level lower.
	Grade 3	Withhold capmatinib until recovery to Grade ≤1. If recovered within 7 days, resume capmatinib at 1 dose level lower; otherwise permanently discontinue capmatinib.
	Grade 4	Permanently discontinue capmatinib.
Other adverse reactions	Grade 2	If unmanageable and intolerable, withhold capmatinib until recovery to Grade ≤1, resume capmatinib at 1 dose level lower.
	Grade 3	Withhold capmatinib until recovery to Grade ≤2, resume capmatinib at 1 dose level lower.
	Grade 4	Permanently discontinue capmatinib.

*1 Grading according to NCI-CTCAE ver.4.03 *2 In the absence of cholestasis or hemolysis

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

Based on the above, PMDA instructed the applicant to handle the “DOSAGE and ADMINISTRATION” and “Precautions for Dosage and Administration” sections accordingly. The applicant agreed.

1.5 Risk management plan (draft)

The applicant is planning to conduct post-marketing surveillance, covering all patients treated with capmatinib, to assess the safety etc. of capmatinib in the post- marketing setting. The planned sample size is 20 to 30 patients, and the observation period is 1 year from the start of treatment with capmatinib.

PMDA's conclusion:

Based on the considerations in Section "7.R.6 Post-marketing investigations" in the Review Report (1), it is necessary to conduct post-marketing surveillance covering all patients treated with capmatinib over a specified period of time in order to collect safety information in a prompt and unbiased manner, and provide the obtained safety information to healthcare professionals immediately.

PMDA's conclusion on the surveillance plan:

- The safety specification should include hepatic dysfunction, ILD, renal dysfunction, fluid retention, acute pancreatitis, and photosensitivity.
- The planned sample size and observation period need to be reconsidered, taking account of the incidences of specific events included in the safety specification for the surveillance in clinical studies.
- If, as a result of reconsideration of the planned sample size and observation period, the surveillance is likely to require a long period of time, an interim analysis should be performed when certain safety information has been accumulated without waiting for final results to be available. Based on the analysis results, the applicant should consider taking appropriate actions such as making changes to pharmacovigilance activities and providing information to healthcare professionals.

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

Based on the above etc., PMDA instructed the applicant to reconsider the surveillance plan.

The applicant's response:

- The safety specification for the surveillance includes hepatic dysfunction, ILD, renal dysfunction, fluid retention, acute pancreatitis, and photosensitivity.
- Taking account of the incidences of specific events included in the safety specification for the surveillance in clinical studies, the planned sample size is 100 patients, and the observation period is 1 year from the start of treatment with capmatinib.
- If the surveillance is likely to require a longer time period time than planned, an interim analysis will be performed at that point, and based on the analysis results, the applicant will consider taking appropriate actions, e.g. making changes to pharmacovigilance activities and providing information to healthcare professionals.

PMDA accepted the applicant's response.

In view of the discussion above etc., PMDA has concluded that the risk management plan (draft) for capmatinib should include the safety specification presented in Table 48, and that the applicant should conduct additional pharmacovigilance activities and risk minimization activities presented in Tables 49 and 50.

Table 48. Safety and efficacy specifications in the risk management plan (draft)

Safety specification		
Important identified risks	Important potential risks	Important missing information
· Hepatic dysfunction · ILD · Renal dysfunction · Fluid retention	· Acute pancreatitis · Photosensitivity · Embryo-fetal toxicity	None
Efficacy specification		
None		

Table 49. Summary of additional pharmacovigilance activities, surveillance/studies for efficacy, and additional risk minimization activities included under the risk management plan (draft)

Additional pharmacovigilance activities	Surveillance/studies for efficacy	Additional risk minimization activities
● Early post-marketing phase vigilance ● Use-results survey (all-case surveillance) ● Post-marketing clinical study (an extension study of A2201)	None	● Disseminate data gathered during early post-marketing phase vigilance ● Develop and distribution of information materials for healthcare professionals. ● Develop and distribution of information materials for patients.

Table 50. Outline of use-results survey (draft)

Objective	To assess the safety etc. of capmatinib in clinical practice.
Survey method	All-case surveillance
Population	All patients treated with capmatinib
Observation period	1 year
Planned sample size	100 patients
Main survey items	Safety specification: hepatic dysfunction, ILD, renal dysfunction, fluid retention, acute pancreatitis, photosensitivity Other main survey items: patient characteristics (sex, age, disease stage, complications, prior treatment status, etc.), the use of capmatinib, concomitant medications, adverse events, etc.

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

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

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

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

The new drug application data (CTD 5.3.5.2-1) were subjected to an on-site GCP inspection, in accordance with the provisions of the Act on Securing Quality, Efficacy and Safety of Pharmaceuticals, Medical Devices, Regenerative and Cellular Therapy Products, Gene Therapy Products, and Cosmetics. On the basis of the inspection, PMDA concluded that since the clinical study as a whole was performed in compliance with GCP, there were no obstacles to conducting its review based on the application documents submitted. The inspection revealed the following discrepancies at some study sites, although which did not affect the overall assessment

of the study significantly. The discrepancies were notified to the heads of the relevant study sites and corrective actions were requested.

Findings requiring corrective action

Study sites

- Some study participants were enrolled in the study and received the study drug despite not meeting an inclusion criterion (serum lipase at or below the upper limit of normal).
- Consent was not obtained from some study participants based on the revised written information.

3. Overall Evaluation

As a result of the above review, PMDA has concluded that the product may be approved for the indication and dosage and administration shown below, with the following conditions, provided that necessary precautionary statements are presented in the package insert and information on the proper use of the product is appropriately disseminated after the market launch, and provided that the proper use of the product is ensured under the supervision of physicians with adequate knowledge of and experience in cancer chemotherapy at medical institutions where adequate emergency care is available. As the product was 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, and the drug product and its drug substance are both classified as powerful drugs.

Indication

MET exon 14 skipping mutation-positive unresectable advanced or recurrent non-small cell lung cancer

Dosage and Administration

The usual adult dosage is 400 mg of capmatinib administered orally twice daily. The dosage should be reduced as appropriate, according to the patient's condition.

Approval Conditions

1. The applicant is required to develop and appropriately implement a risk management plan.
2. Because of extremely limited number of patients participating in clinical studies in Japan, the applicant is required to conduct a post-marketing use-results survey covering all patients treated with the product, until data from a certain number of patients are collected, in order to understand the characteristics of patients treated with the product, promptly collect data on the safety and efficacy of the product, and take necessary measures to ensure proper use of the product.

Warnings

1. Capmatinib should be administered only to patients eligible for capmatinib therapy, under the supervision of physicians with adequate knowledge and experience in cancer chemotherapy at medical facilities providing adequate emergency care. Prior to the start of treatment, patients or their families should be fully informed of its efficacy and risks, and their consent should be obtained.

2. Because of reported of interstitial lung disease, including fatal cases, patients should be closely monitored for initial symptoms (shortness of breath, dyspnoea, cough, pyrexia, etc.) and undergo regular thoracic imaging. In case of abnormality, capmatinib should be discontinued, and the administration of corticosteroids or any other appropriate measures should be taken.

Contraindication

Patients with a history of hypersensitivity to any of the components of the product

Precautions for Indication

1. Capmatinib should be used in patients with a *MET* exon 14 skipping mutation confirmed through testing by adequately experienced pathologists or at laboratories. Testing should be performed with the approved *in vitro* diagnostic or medical device.
2. The efficacy and safety of capmatinib in a post-operative adjuvant setting have not been established.

Precautions for Dosage and Administration

1. The efficacy and safety of capmatinib in combination with other anti-neoplastic drugs have not been established.
2. In the event of adverse reactions, interrupt or reduce the dose of capmatinib, or discontinue capmatinib therapy according to the tables below.

Recommended dose reductions/discontinuation of therapy

Dose reduction levels	Dose
Usual dose	400 mg (twice daily)
First dose reduction	300 mg (twice daily)
Second dose reduction	200 mg (twice daily)
Discontinuation	Permanently discontinue capmatinib for patients who are unable to tolerate 200 mg twice daily.

Recommended capmatinib dosage modifications for adverse reactions

Adverse reaction	Severity[*1]	Dosage modification
ILD	Grade ≥1	Permanently discontinue capmatinib.
Increased AST or ALT with increased total bilirubin[*2]	AST or ALT >3.0×ULN with total bilirubin >2.0×ULN	Permanently discontinue capmatinib.
Increased AST or ALT	Grade 3	Withhold capmatinib until recovery to Grade ≤1 or baseline. If recovered within 7 days, resume capmatinib at the same dose; otherwise resume capmatinib at 1 dose level lower.
	Grade 4	Permanently discontinue capmatinib.
Increased total bilirubin	Grade 2	Withhold capmatinib until recovery to Grade ≤1. If recovered within 7 days, resume capmatinib at the same dose; otherwise resume capmatinib at 1 dose level lower.
	Grade 3	Withhold capmatinib until recovery to Grade ≤1. If recovered within 7 days, resume capmatinib at 1 dose level lower; otherwise permanently discontinue capmatinib.
	Grade 4	Permanently discontinue capmatinib.
Other adverse reactions	Grade 2	If unmanageable and intolerable, withhold capmatinib until recovery to Grade ≤1, resume capmatinib at 1 dose level lower.
	Grade 3	Withhold capmatinib until recovery to Grade ≤2, resume capmatinib at 1 dose level lower.
	Grade 4	Permanently discontinue capmatinib.

*1 Grading according to NCI-CTCAE ver.4.03 *2 In the absence of cholestasis or hemolysis

Appendix

List of Abbreviations

ABL1	abelson murine leukemia virus oncogene 1
ALK	anaplastic lymphoma kinase
ALT	alanine aminotransferase
ALP	alkaline phosphatase
AMP	adenosine monophosphate
AO	aldehyde oxidase
application	application for marketing approval
AST	aspartate aminotransferase
AT_1	angiotensin II type 1
ATP	adenosine triphosphate
BCRP	breast cancer resistance protein
BID	bis in die
BIRC	blinded independent review committee
BSEP	bile salt export pump
capmatinib	Capmatinib Hydrochloride Hydrate
CDDP	cisplatin
CDDP/GEM	the combination of CDDP and GEM
CDDP/PEM	the combination of CDDP and PEM
CDK11	cyclin-dependent kinase 11
CDx	companion diagnostics
CI	confidence interval
$C_{max,ss}$	maximum plasma concentration at steady state
CPP	critical process parameter
CQA	critical quality attribute
CR	complete response
CrCL	creatinine clearance
CYP	cytochrome P450
^{14}C-capmatinib	^{14}C-labeled capmatinib
DLT	dose-limiting toxicity
DMSO	dimethyl sulfoxide
DOC	docetaxel hydrate
efflux ratio	the ratio of apparent permeability coefficient in the secretory direction to the absorptive direction
EGFR	epidermal growth factor receptor
ELISA	enzyme-linked immunosorbent assay
ERK1/2	extracellular signal-regulated kinase 1 and 2
FAK	focal adhesion kinase
FMO	flavin-containing monooxygenase
GAB1	growth factor receptor bound protein 2-associated protein 1
GC	gas chromatography
GCN	gene copy number
GEM	gemcitabine hydrochloride
GGT	gamma-glutamyltransferase
HDL	high density lipoprotein
HER	human epidermal growth factor receptor
hERG	human *ether-a-go-go*-related gene
HLGT	high level group term
HTRF	homogeneous time-resolved fluorescence
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use

ICH Q3A guideline	Revision of the Guideline on Impurities in New Drug Substances (PMSB/ELD Notification No.1216001, dated December 16, 2002)
ICH Q3B guideline	Revision of the Guideline on Impurities in New Drug Products (PMSB/ELD Notification No. 0624001 dated June 24, 2003)
IHC	immunohistochemistry
ILD	interstitial lung disease
IR	infrared absorption spectrum
IRAK1	interleukin-1 receptor-associated kinase 1
LC	liquid chromatography
LC-MS/MS	liquid chromatography-tandem mass spectrometry
LDL	low density lipoprotein
MATE	multidrug and toxin extrusion
MedDRA	Medical Dictionary for Regulatory Activities
MET	mesenchymal-epithelial transition factor
METex14	*MET* exon 14 skipping
mRNA	messenger ribonucleic acid
MRP	multidrug resistance associated protein
MTD	maximum tolerated dose
NADPH	nicotinamide adenine dinucleotide phosphate hydrogen
NE	not evaluable
NIR	near infrared absorption spectrum
NMR	nuclear magnetic resonance spectrum
NOD/SCID mouse	non-obese diabetic/severe combined immunodeficiency mouse
NRG1	neuronal growth factor 1
Nrg1	neuregulin 1
NSCLC	non-small cell lung cancer
NSQ-NSCLC	non-squamous non-small cell lung cancer
NZW	New Zealand White
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
PBPK	physiologically based pharmacokinetic
PD	progressive disease
PD-1	programmed cell death-1
PDE	phosphodiesterase
PEM	pemetrexed sodium hydrate
PFS	Progression-free survival
P-gp	P-glycoprotein
PIP5K2C	phosphatidylinositol-5-phosphate 4-kinase, type II, gamma
PK	pharmacokinetics
platinum anticancer agent	carboplatin or CDDP
PMDA	Pharmaceuticals and Medical Devices Agency
PPK	population pharmacokinetics
PR	partial response
PS_{app}	apparent membrane permeability
PT	preferred term
PTP	press through packaging
QbD	quality by design
QD	quaque die

QT	QT interval
QTc	QT interval corrected
ΔQTcF	change from baseline in QT interval corrected using the Fridericia formula
RCC	renal cell carcinoma
RECIST	Response Evaluation Criteria in Solid Tumors
RP2D	recommended Phase 2 dose
RT-PCR	reverse transcription polymerase chain reaction
RTRT	real time release testing
SD	stable disease
SDH	sorbitol dehydrogenase
SMQ	standardized MedDRA queries
SOC	system organ class
STAT3/5	signal transducer and activator of transcription 3 and 5
Study A2101	Study CINC280A2101
Study A2102	Study CINC280A2102
Study A2103	Study CINC280A2103
Study A2105	Study CINC280A2105
Study A2106	Study CINC280A2106
Study A2108	Study CINC280A2108
Study A2109	Study CINC280A2109
Study A2201	Study CINC280A2201
Study X1101	Study CINC280X1101
Study X2101T	Study INCB 28060-101
Study X2102	Study CINC280X2102
Study X2103	Study CINC280X2103
Study X2106	Study CINC280X2106
Study X2107	Study CINC280X2107
Study 189	Study KEYNOTE-189
tepotinib	Tepotinib Hydrochloride Hydrate
TID	ter in die
ULN	upper limit of normal
VLDL	very low density lipoprotein
VMAT2	vesicular monoamine transporter 2
XO	xanthine oxidase
YSK4	yeast Sps1/Ste20-related kinase 4
Zeb2	zinc finger E-box binding homeobox transcriptional repressor
[redacted]	[redacted]
[redacted]	[redacted]