Report on the Deliberation Results

June 1, 2022
Pharmaceutical Evaluation Division, Pharmaceutical Safety and Environmental Health Bureau
Ministry of Health, Labour and Welfare

Brand Name	Jeselhy Tablets 40 mg
Non-proprietary Name	Pimitespib (JAN*)
Applicant	Taiho Pharmaceutical Co., Ltd.
Date of Application	September 14, 2021

Results of Deliberation

In its meeting held on May 30, 2022, 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 8 years. The drug product and its drug substance are classified as a powerful drug and a poisonous drug, respectively.

Approval Conditions

1. The applicant is required to develop and appropriately implement a risk management plan.
2. In view of the limited number of Japanese patients participated in the clinical studies, the applicant is required to conduct a drug use-results survey involving all Japanese patients treated with the product in the post-marketing settings until data of a certain number of patients are available, in order to understand the characteristics of patients using the product, and to promptly collect safety and efficacy data so that necessary measures are taken to ensure the proper use of the product.

**Japanese Accepted Name (modified INN)*

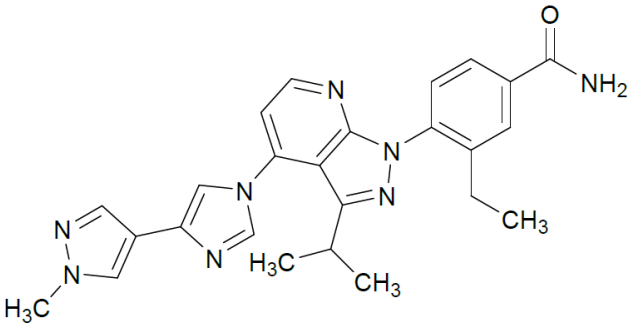
Review Report

May 16, 2022
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	Jeselhy Tablets 40 mg
Non-proprietary Name	Pimitespib
Applicant	Taiho Pharmaceutical Co., Ltd.
Date of Application	September 14, 2021
Dosage Form/Strength	Tablets, each containing 40 mg of pimitespib
Application Classification	Prescription drug, (1) Drug with a new active ingredient

Chemical Structure



Molecular formula: $C_{25}H_{26}N_8O$

Molecular weight: 454.53

Chemical name: 3-Ethyl-4-{4-[4-(1-methyl-1*H*-pyrazol-4-yl)-1*H*-imidazol-1-yl]-3-(propan-2-yl)-1*H*-pyrazolo[3,4-*b*]pyridin-1-yl}benzamide

Items Warranting Special Mention

None

Reviewing Office Office of New Drug V

Results of Review

On the basis of the data submitted, PMDA has concluded that the product has efficacy in the treatment of patients with gastrointestinal stromal tumor that has progressed after cancer chemotherapy, 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 approval conditions. Severe diarrhoea, eye disorders, and haemorrhage should be further investigated via post-marketing surveillance.

Indication

Gastrointestinal stromal tumor that has progressed after cancer chemotherapy

Dosage and Administration

The usual adult dosage is 160 mg of pimitespib administered orally once daily in the fasted state for 5 consecutive days. With a subsequent 2-day rest, this regimen is repeated. The dose may be reduced according to the patient's condition.

Approval Conditions

1. The applicant is required to develop and appropriately implement a risk management plan.
2. In view of the limited number of Japanese patients participated in the clinical studies, the applicant is required to conduct a drug use-results survey involving all Japanese patients treated with the product in the post-marketing settings until data of a certain number of patients are available, in order to understand the characteristics of patients using the product, and to promptly collect safety and efficacy data so that necessary measures are taken to ensure the proper use of the product.

Attachment

Review Report (1)

March 24, 2022

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	Jeselhy Tablets 40 mg
Non-proprietary Name	Pimitespib
Applicant	Taiho Pharmaceutical Co., Ltd.
Date of Application	September 14, 2021
Dosage Form/Strength	Tablets, each containing 40 mg of pimitespib
Proposed Indication	Gastrointestinal stromal tumor that has progressed after cancer chemotherapy

Proposed Dosage and Administration

The usual adult dosage is 160 mg of pimitespib administered orally once daily in the fasted state for 5 consecutive days. With a subsequent 2-day rest, this regimen is repeated in a 21-day cycle. The dose may be reduced according to the patient's condition.

Table of Contents

List of Abbreviations

See Appendix.

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

1.1 Outline of the proposed product

Heat shock protein 90 (HSP90) is a molecular chaperone that assists folding of the other proteins and thereby contributes to the formation and stabilization, etc. of their functional high-order structure (*Int J Mol Sci.* 2018;19:2560). Proteins folded into a functional high-order structure by HSP90 and stabilized (client proteins) have been found to contain many factors, such as receptor tyrosine kinases and signaling factors, involved in cell survival and proliferation. Elevated expression of HSP90 has been also observed in tumor cells (*Int J Mol Sci.* 2018;19:2560). HSP90 is therefore considered to contribute to tumor growth through the high-order structure formation and stabilization of these client proteins (*Clin Cancer Res.* 2012;18:64-76).

Pimitespib is a low molecular weight compound that inhibits HSP90 discovered by the applicant. Pimitespib is expected to suppress tumor growth by inhibiting the HSP90-mediated formation of a high-order structure of client proteins, which would enhance destabilization and degradation of high-order structure, leading to decreased expression of the proteins involved in tumor growth and apoptosis induction.

1.2 Development history etc.

The applicant initiated a global phase I study (Study 10058010 [Study 010]) in patients with advanced solid tumor in March 2014, and a Japanese phase III study (Study 10058030 [Study 030]) in October 2018 in patients with unresectable or metastatic gastrointestinal stromal tumor (GIST) which had progressed after treatment with imatinib mesilate (imatinib), sunitinib malate (sunitinib), and regorafenib hydrate (regorafenib).

As of February 2022, pimitespib has not been approved in any country or region.

An application for marketing approval (application) for pimitespib was submitted using data from Study 030 as pivotal data.

2. Quality and Outline of the Review Conducted by PMDA

2.1 Drug substance

2.1.1 Characterization

The drug substance occurs as a white crystalline powder. The general properties, including description, solubility, hygroscopicity, thermal analysis, acid dissociation constant, and partition coefficient, were determined. For crystal polymorphisms of the drug substance, 7 crystal forms including stable Form [redacted] ([redacted]) and Form [redacted] ([redacted]) were observed, but the commercial manufacturing process was shown to produce the drug substance only in Form [redacted], and no changes in crystal form were observed in stability studies [see Section 2.1.4].

The chemical structure of the drug substance was elucidated by elemental analysis, mass spectrometry, ultraviolet-visible spectroscopy (UV-VIS), infrared absorption spectroscopy (IR), nuclear magnetic resonance spectroscopy (^{1}H-NMR, ^{13}C-NMR), and single-crystal X-ray diffractometry.

2.1.2 Manufacturing process

The drug substance is synthesized using [redacted],[1] [redacted],[2] and [redacted][3] as starting materials.

Based on the investigations below, a quality control strategy has been established (Table 1).

- Identification of critical quality attributes (CQAs)
- Investigation of critical process parameters (CPPs) based on risk evaluation

Table 1. Outline of control strategy for drug substance

CQA	Control method
Identification	Manufacturing process and specifications
Related substances	Manufacturing process and specifications
Residual solvents	Manufacturing process and specifications
Elemental impurities	Manufacturing process
Content	Manufacturing process and specifications
Crystal form	Manufacturing process and specifications
Particle size distribution	Manufacturing process and specifications
Microbial limit	Manufacturing process

Critical steps include [redacted] of [redacted][4] and [redacted] and [redacted] of [redacted]. [redacted],[5] [redacted], and [redacted] are controlled as critical intermediates.

2.1.3 Control of drug substance

The proposed specifications for the drug substance consist of content, description, identification (UV-VIS, IR, and high performance liquid chromatography [HPLC]), purity (related substances [HPLC], residual solvents [gas chromatography (GC)]), water content, residue on ignition, assay (HPLC), crystal form, and particle size distribution.

2.1.4 Stability of drug substance

The main stability studies conducted on the drug substance are as shown in Table 2. The results demonstrated the stability of drug substance. The photostability testing showed the drug substance's stability to light.

Table 2. Stability studies of drug substance

Study	Primary batches	Temperature	Humidity	Storage form	Storage period
Long-term	3 pilot scale batches	25°C	60%RH	Double-layered low-density polyethylene bag + high-density polyethylene drum	12 months
Accelerated		40°C	75%RH		6 months

Based on the above, a retest period of 24 months was proposed for the drug substance when stored at room temperature in the double-layered low-density polyethylene bag, which is further placed in the high-density polyethylene drum, in accordance with Guidelines on Evaluation of Stability Data (ICH Q1E guidelines). Long-term testing will be continued up to [redacted] months.

1) [redacted]
2) [redacted]
3) [redacted]
4) [redacted]
5) [redacted]

2.2 Drug product

2.2.1 Description and composition of drug product and formulation development

The drug product is immediate-release film-coated tablets, each containing 40 mg of the drug substance. The drug product contains lactose monohydrate, corn starch, hydroxypropylcellulose, microcrystalline cellulose, magnesium stearate, hypromellose, macrogol 6000, and titanium oxide as excipients.

2.2.2 Manufacturing process

The drug product is manufactured through a process comprised of granulation/sizing, blending, lubrication, tableting, film-coating, and packaging/labeling. [redacted] and [redacted] have been defined as critical steps. Process control is specified in [redacted].

Based on the investigations below, a quality control strategy has been established (Table 3).

- Identification of CQAs
- Investigation of CPPs based on risk evaluation

Table 3. Outline of control strategy for drug product

CQA	Control method
Description	Specifications
Identification	Specifications
Related substances	Specifications
Uniformity of dosage units	Manufacturing process and specifications
Dissolution	Manufacturing process and specifications
Strength	Manufacturing process and specifications

2.2.3 Control of drug product

The proposed specifications for the drug product consist of strength, description, identification (HPLC and UV-VIS), purity (related substances [HPLC]), uniformity of dosage units (content uniformity [HPLC]), microbial limit, dissolution (HPLC), and assay (HPLC).

2.2.4 Stability of drug product

The main stability studies conducted on the drug product are as shown in Table 4 and have demonstrated that the drug product is stable. In addition, the photostability testing has showed that the drug product is stable to light.

Table 4. Stability studies of drug product

Study	Primary batches	Temperature	Humidity	Storage form	Storage period
Long-term	3 pilot scale batches	25°C	60%RH	Blister pack [redacted]	18 months
		[redacted]°C	[redacted]%RH		
Accelerated		40°C	75%RH		6 months

Based on the above, a shelf life of 30 months has been proposed for the drug product when stored at room temperature in a blister pack [redacted], in accordance with ICH Q1E guidelines. Long-term testing will be continued up to [redacted] months.

2.R Outline of the review conducted by PMDA

Based on the submitted data, PMDA has concluded that quality of the drug substance and drug product are appropriately controlled.

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

3.1 Primary pharmacodynamics

3.1.1 Binding affinity to HSP90 (CTD 4.3.12; *J Med Chem. 2021;64:2669-77)*

Binding affinity of pimitespib to human HSP90α NTD[6)] (recombinant protein) was investigated by isothermal titration calorimetry.[7)] The dissociation constant (K_D) value (n = 1) of pimitespib was determined as 0.17 μmol/L.

3.1.2 Inhibitory effect against binding of geldanamycin to HSP90 (CTD 4.2.1.1.1)

The inhibitory effect of pimitespib against binding of geldanamycin, a HSP90 inhibitor, to HSP90 species of (a) human HSP90α (recombinant protein) and (b) human HSP90β (recombinant protein) was investigated by a competitive binding technique using fluorescent-labeled geldanamycin. Concentrations resulting in 50% inhibition (IC_{50}) of pimitespib (mean ± standard deviation [SD], n = 3) were determined to be (a) 148 ± 28 and (b) 210 ± 26 nmol/L.

3.1.3 Effect on expression of HSP90 client proteins (CTD 4.2.1.1.2)

Using (a) human GIST-derived GIST-T1 cell line expressing mast/stem cell growth factor receptor (KIT) (del V560-Y578[8)]), (b) human colorectal carcinoma (CRC)-derived HT-29 cell line, (c) human acute myeloid leukemia-derived MV-4-11 cell line expressing FMS-like tyrosine kinase 3 internal tandem duplication (FLT3-ITD), (d) human non-small cell lung cancer (NSCLC)-derived NCI-H1975 cell line expressing epidermal growth factor receptor (EGFR) (L858R/T790M[9)]), and (e) human gastric cancer-derived NCI-N87 cell line, effects of pimitespib on the expression of HSP90 client proteins, namely, (a) KIT, (b) insulin-like growth factor 1 receptor (IGF1R), (c) FLT3-ITD, (d) EGFR (L858R/T790M) and mesenchymal-epithelial transition factor (MET), and (e) human epidermal growth factor receptor (HER) 2, HER3, and protein kinase B (AKT) were evaluated by Western blotting. Pimitespib was shown to decrease the expression of all these client proteins.

3.1.4 Inhibitory effect against growth of malignant tumor-derived cell lines

3.1.4.1 *In vitro* (CTD 4.2.1.1.3)

The inhibitory effect of pimitespib against the growth of various human malignant tumor-derived cell lines was investigated using adenosine triphosphate (ATP) as an indicator of viable cells. Table 5 shows the IC_{50} of pimitespib.

---

6) Recombinant protein representative of N-terminal domain of human HSP90α including ATP binding site (amino acid residue positions 1-236)
7) Caloric changes caused by the interactions of pimitespib with human HSP90α NTD were measured when pimitespib solution was added dropwise to a buffer solution containing human HSP90α NTD.
8) Valine at position 560 to tyrosine at position 578 deleted
9) Mutations in EGFR with leucine at position 858 and threonine at position 790 substituted by arginine and methionine, respectively

Table 5. Growth inhibition effect of pimitespib against various human malignant tumor-derived cell lines

Cell line	Origin	IC_{50} (μmol/L)
DU145	Prostate cancer	0.383 ± 0.0454
GIST-T1	GIST	0.311 ± 0.0780
Hs578T	Breast cancer	0.493 ± 0.143
HT-29	CRC	0.394 ± 0.0520
Kasumi-1	Acute myeloid leukaemia	0.197 ± 0.0289
MV-4-11		0.100 ± 0.0136
NCI-H146	Small cell lung cancer	0.323 ± 0.0225
NCI-H1975	NSCLC	0.485 ± 0.0571
NCI-N87	Gastric cancer	0.175 ± 0.00994
SK-OV-3	Ovarian cancer	2.31 ± 0.658

Mean ± SD, n = 3

3.1.4.2 *In vivo*

3.1.4.2.1 GIST-derived cell line (CTD 4.2.1.1.4 and 4.3.5; *Br J Cancer.* 2020;122:658-67)

Using nude mice subcutaneously implanted with GIST-T1 cell line (n = 6/group), the inhibitory effect of pimitespib against tumor growth was investigated. When the tumor volume reached 100 to 300 mm^3, the study was started (Day 0) with randomization. On Days 1 to 5, 8 to 12, and 15 to 19, pimitespib 7 or 14 mg/kg was orally administered QD, and tumor volumes were calculated. Pimitespib at both doses inhibited tumor growth as compared with the control (0.5% hydroxypropylmethylcellulose [HPMC] solution) on Day 22 in a statistically significant manner (Figure 1).

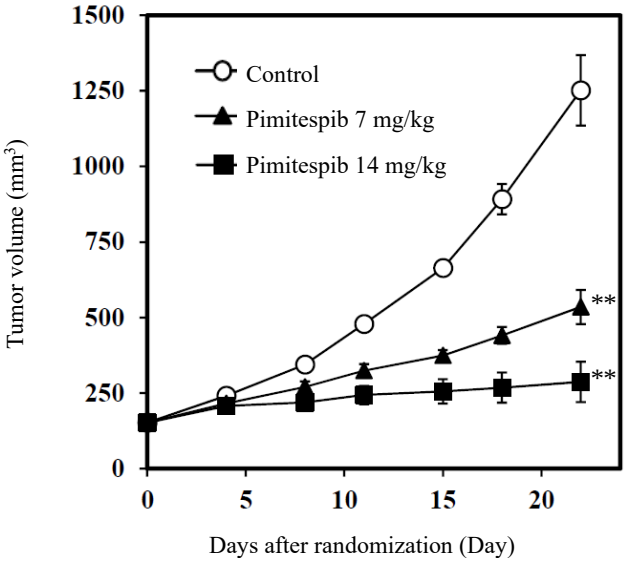


Figure 1. Inhibitory effect of pimitespib against tumor growth in nude mice subcutaneously implanted with GIST-T1 cell line

n = 6, Mean ± SD, ** $P < 0.0001$ vs. control (Dunnett's test for multiple comparison)

Using (a) nude mice subcutaneously implanted with human GIST-derived GIST-R8[10] (n = 6/group) or (b) severe combined immunodeficient (SCID) mice subcutaneously implanted with GIST-R9[11] cell line (n = 6/group), the inhibitory effect of pimitespib against tumor growth was investigated. When the tumor volume reached 150 mm^3, the study began (Day 0) with randomization. Pimitespib 14 mg/kg was orally administered QD on Days 1 to 5, 8 to 12, and 15 to 19, or imatinib 50 mg/kg was orally administered BID

[10] GIST-T1 cell line expressing KIT with D820Y (aspartic acid at position 820 substituted by tyrosine) mutation, which is reported to render the protein resistant to imatinib and sunitinib (*Oncotarget.* 2019;10:6286-7), in addition to del V560-Y578 mutation

[11] GIST-T1 cell line expressing KIT with D820V (aspartic acid at position 820 substituted by valine) mutation, which is reported to render the protein resistant to imatinib and sunitinib (*Oncotarget.* 2019;10:6286-7), in addition to del V560-Y578 mutation

on Days 1 to 21, and tumor volumes were calculated. Pimitespib inhibited tumor growth of both cell lines as compared with the control (0.5% HPMC solution) on Day 22 in a statistically significant manner ($P < 0.01$, Tukey's test), while imatinib did not statistically significantly inhibit tumor growth.

3.1.4.2.2 Non-GIST malignant tumor-derived cell line (CTD 4.2.1.1.5)

Using nude mice subcutaneously implanted with human gastric cancer-derived NCI-N87 cell line (n = 6/group), the inhibitory effect of pimitespib against tumor growth was investigated. When the tumor volume reached 100 to 300 mm^3, the study began (Day 0) with randomization. On Days 1 to 5, 8 to 12, and 15 to 19, pimitespib 3.5, 7, or 14 mg/kg was orally administered QD, and tumor volumes were calculated. Pimitespib at all doses inhibited tumor growth as compared with the control (0.5% HPMC solution) on Day 22 in a statistically significant manner ($P < 0.0001$, Dunnett's test for multiple comparison).

3.2 Safety pharmacology

3.2.1 Effects on central nervous system (CTD 4.2.1.3.1)

A single dose of pimitespib 4, 8, or 12 mg/kg was orally administered to rats (n = 5/group), and effects of pimitespib on clinical signs and behaviors were investigated by a functional observation battery. In the pimitespib 4 and 8 mg/kg groups, loose stool was observed.

3.2.2 Effects on cardiovascular system

3.2.2.1 Effect on hERG potassium current (CTD 4.2.1.3.2)

Using HEK 293 cell line transfected with human *ether-a-go-go* related gene (hERG), the effect of pimitespib 1, 10, and 30 μmol/L on hERG potassium current was investigated. Pimitespib 1, 10, and 30 μmol/L inhibited hERG potassium current by 2.2% ± 1.6%, 2.3% ± 3.1%, and 13.6% ± 2.3% (mean ± SD, n = 5), respectively, and pimitespib 30 μmol/L exhibited statistically significant inhibition as compared with the control (Tyrode solution[12)] containing 0.1% dimethyl sulfoxide [DMSO]) ($P < 0.01$, Dunnett's test for multiple comparison).

3.2.2.2 Effects on heart rate, blood pressure, and electrocardiogram (CTD 4.2.1.3.3)

A single dose of pimitespib 3, 6, or 12 mg/kg was orally administered to dogs (n = 4/group), and effects of pimitespib on heart rate, blood pressure (systolic blood pressure, diastolic blood pressure, and mean blood pressure), and electrocardiogram (PR, QRS, QT, and QT interval corrected [QTc]) were investigated. Pimitespib had no effects.

3.2.3 Effects on respiratory system (CTD 4.2.1.3.4)

A single dose of pimitespib 4, 8, or 12 mg/kg was orally administered to rats (n = 6/group), and effects of pimitespib on respiratory rate, tidal volume, and minute volume of ventilation were investigated. Pimitespib had no effects.

12) 137 mmol/L sodium chloride, 4 mmol/L potassium chloride, 1.8 mmol/L calcium chloride, 1 mmol/L magnesium chloride, 10 mmol/L glucose, and 10 mmol/L HEPES

3.R Outline of the review conducted by PMDA

On the basis of the data submitted and review of the following section, PMDA has concluded that the applicant's explanation about non-clinical pharmacology of pimitespib is acceptable.

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

The applicant's explanation about the action mechanism of pimitespib and the efficacy in treatment of GIST:

HSP90 is an ATP-dependent molecular chaperone that assists folding of client proteins and thereby contributes to the formation and stabilization of a high-order structure formation (*Int J Mol Sci.* 2018;19:2560). HSP90 client proteins include many factors involved in cell survival and proliferation such as receptor tyrosine kinases and signaling factors. Elevated expression of HSP90 in tumor cells is observed (*Int J Mol Sci.* 2018;19:2560). HSP90 is therefore considered to contribute to tumor growth through the formation and stabilization of a high-order structure of these client proteins (*Clin Cancer Res.* 2012;18:64-76). In addition, GIST growth is shown to involve activating mutations mainly in KIT or platelet-derived growth factor receptor α (PDGFRα) (mutation in *KIT* gene [exon 9 or 11], D842V[13)] mutation in *PDGFRA* gene, etc.) (*Lancet.* 2007;369:1731-41). These proteins are both HSP90 client proteins (*Nat Rev Cancer.* 2011;11:865-78).

Pimitespib is a low molecular weight chemical compound that inhibits interactions between HSP90 and a client protein by binding to the ATP binding site of HSP90 [see Sections 3.1.1 and 3.1.2] (*J Med Chem.* 2021;64:2669-77). Pimitespib inhibits the HSP90-mediated formation of a high-order structure of client proteins, causing the destabilization and decreased expression of the proteins [see Section 3.1.3] and apoptosis induction, through which tumor growth suppression is expected (*Br J Cancer.* 2020;122:658-67).

In addition to the above mechanism, pimitespib has an effect to inhibit tumor growth in *in viv*o models, including nude mice subcutaneously implanted with GIST-T1 cell line, and nude mice and SCID mice subcutaneously implanted with a cell line with mutation in KIT protein, which is reported to render its product protein resistant to imatinib and sunitinib (D820Y or D820V, respectively) [see Section 3.1.4.2.1]. Pimitespib is therefore expected to have efficacy in treatment of GIST, including GIST with resistance to imatinib and sunitinib.

PMDA accepted the applicant's explanation.

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

The pharmacokinetics (PK) of pimitespib was investigated in dogs, etc. Involvements of pimitespib in plasma-protein binding, drug-metabolizing enzymes, transporters, etc. were investigated using human- or animal-derived biological samples.

13) Mutation substituting aspartic acid at position 842 with valine

4.1 Absorption

4.1.1 Repeated-dose study

Pimitespib 3, 6, or 12 mg/kg was orally administered QD to male and female dogs for 28 days, and plasma pimitespib concentrations were determined (Table 6). Within a dose range investigated, exposure to pimitespib increased almost proportionally to the dose. There was no distinct increase in exposure to pimitespib associated with repeated doses. There were no clear sex-related differences in the PK parameters of pimitespib.

Table 6. PK parameters of pimitespib (male and female dogs, repeated oral administration for 28 days)

Day of measurement (Day)	Dose (mg/kg)	n	C_{max} (μg/mL)		t_{max}* (h)		AUC_{0-24} (μg•h/mL)	
			Male	Female	Male	Female	Male	Female
1	3	3	0.594 ± 0.161	0.486 ± 0.200	2.0 (2.0, 4.0)	2.0 (2.0, 2.0)	5.09 ± 0.363	3.93 ± 1.60
	6	3	0.786 ± 0.293	0.647 ± 0.324	2.0 (2.0, 4.0)	2.0 (1.0, 4.0)	7.09 ± 2.40	5.99 ± 2.91
	12	6	1.84 ± 0.982	2.00 ± 1.76	2.0 (1.0, 4.0)	4.0 (1.0, 4.0)	17.1 ± 10.1	22.7 ± 18.2
28	3	3	0.838 ± 0.311	0.669 ± 0.163	2.0 (1.0, 2.0)	2.0 (1.0, 4.0)	6.02 ± 1.37	5.10 ± 0.822
	6	3	0.832 ± 0.224	0.796 ± 0.370	2.0 (1.0, 4.0)	2.0 (1.0, 2.0)	7.22 ± 1.56	6.96 ± 2.95
	12	6	1.32 ± 0.507	1.30 ± 0.308	2.0 (1.0, 2.0)	2.0 (2.0, 2.0)	10.4 ± 3.97	11.6 ± 4.02

Mean ± SD, * Median (minimum, maximum)

4.1.2 *In vitro* membrane permeability

Membrane permeability of pimitespib was investigated using human colon cancer-derived Caco-2 cell line. The apparent permeability in apical to basal direction ($P_{app\ A\rightarrow B}$) of ^{14}C-labeled pimitespib (^{14}C-pimitespib) 6.1 μmol/L was 18.0 × 10^{-6} cm/s in the presence of a P-glycoprotein (P-gp) inhibitor (zosuquidar hydrochloride, 10 μmol/L) and breast cancer resistance protein (BCRP) inhibitor (Ko143, 10 μmol/L). The applicant explained that the membrane permeability of pimitespib is high in view of $P_{app\ A\rightarrow B}$ of highly membrane-permeable propranolol (0.02 μmol/L), which was 24.1 × 10^{-6} cm/s.

4.2 Distribution

4.2.1 Tissue distribution

To male pigmented rats and male albino rats, a single dose of ^{14}C-pimitespib 8 mg/kg was orally administered, and tissue distribution of the radioactivity was investigated by quantitative whole-body autoradiography. The radioactivity was shown to be extensively distributed in male pigmented and albino rats. In most of the tissues, the radioactivity concentration peaked by 4 hours post-dose. In pigmented rats, the maximum tissue concentrations in the liver, small intestine, uvea and retina, adrenal gland, and bladder (24.7, 14.5, 9.89, 9.41, and 9.24 μg Eq./g, respectively) were especially higher than that in blood (1.92 μg Eq./g). In albino rats, the maximum tissue concentrations in the liver, brown adipose tissue, and adrenal gland (11.0, 6.12, and 5.70 μg Eq./g, respectively) were especially higher than that in blood (2.17 μg Eq./g). Radioactivity concentrations in albino rats were below the lower limit of quantification in all the tissues at 48 hours post-dose, whereas in pigmented rats, radioactivity was detected in the uvea and retina (radioactivity concentration in the tissue was 0.317 μg Eq./g) at up to 168 hours post-dose.

The above results suggested that pimitespib and its metabolites might bind to melanin. The applicant, however, explained that a repeated-dose toxicity study in dogs presented neither abnormalities nor findings suggestive of toxicity in the ocular tissues [see Section 5.2], and the clinical studies raised no particular safety concerns over toxicity in the skin. Safety of pimitespib in eye is discussed in Section "7.R.3.3 Eye disorders."

4.2.2 Plasma protein binding

Pimitespib (0.5-10 μg/mL) was incubated with mouse, rat, dog, and human plasma specimens at 37°C for 10 minutes followed by ultrafiltration, and plasma protein binding of pimitespib was investigated. Plasma protein binding of pimitespib in mouse, rat, dog, and human plasma specimens were 95.7% to 96.1%, 85.5% to 86.5%, 82.6% to 86.0%, and 93.1% to 93.6%, respectively, which were almost similar within the concentration range investigated.

Pimitespib (0.5-10 μg/mL) was incubated with human serum albumin (45 mg/mL), human α1-acid glycoprotein (0.75 mg/mL), or human γ-globulin (10 mg/mL) at 37°C for 10 minutes followed by ultrafiltration, and binding of pimitespib to human serum albumin, human α1-acid glycoprotein, and human γ-globulin was investigated. Plasma protein binding of pimitespib after incubation with human serum albumin, human α1-acid glycoprotein, and human γ-globulin were 82.9% to 84.8%, 3.6% to 7.7%, and 4.5% to 6.5%, respectively. Accordingly, the applicant explained that pimitespib mainly binds to serum albumin in human plasma.

4.2.3 Distribution in blood cells

Pimitespib (0.5-10 μg/mL) was incubated with human blood at 37°C for 60 minutes, and the distribution of pimitespib in blood cells was investigated. The human blood/plasma ratio of pimitespib concentration was 0.525 to 0.630. Accordingly, the applicant explained that pimitespib is mainly distributed in plasma in humans.

4.2.4 Placental and fetal transfer

Placental and fetal transfer of pimitespib were not investigated. The applicant explained that pimitespib may possibly cross the placenta and be distributed in fetuses in view of teratogenicity and fetal deaths found in an embryo-fetal development study in rats [see Section 5.5].

4.3 Metabolism

4.3.1 *In vitro*

^{14}C-pimitespib (10 μmol/L) was incubated with microsomes or hepatocytes of rat, dog, and human liver at 37°C, and metabolites of pimitespib were investigated.[14)] After incubation, M2 (*N*-demethylated form) was mainly detected in dog and human liver microsomes, and M1 (oxidized form) and M2 were mainly detected in rat liver microsomes. M3 (amide-hydrolyzed form) was mainly detected in dog and human hepatocytes, and M1 and M3 were mainly detected in rat hepatocytes.

The applicant's explanation:

Based on the above results, carboxylesterase (CES) 1 is mainly involved in metabolism of pimitespib in humans.

- Pimitespib (10 μmol/L) was incubated with recombinant human cytochrome P450 (CYP) isoforms (CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, CYP3A4, and CYP3A5) as well as CES1 and CES2 in the presence of nicotinamide adenine dinucleotide phosphate hydrogen (NADPH) at 37°C for 2 hours, and metabolizing enzymes involved in the metabolism of pimitespib were

[14)] Pimitespib was incubated with liver microsomes in the presence of NADPH for 1 hour and with hepatocytes for 2 hours.

investigated. After incubation, M2 was detected in the presence of CYP3A4 and CYP3A5, and M3 was detected in the presence of CES1. In contrast, in the presence of the other metabolizing enzymes investigated, M2 and M3 were hardly detected.

- Pimitespib (1-100 μmol/L) was incubated with human hepatocytes at 37°C for 1 hour, and CL_{max} and CL_{int} were determined. CL_{max} based on the formation rate of M2 and CL_{int} based on the formation rate of M3 were determined as 0.0990 and 0.845 μL/min/10^6 cells, respectively.

4.3.2 *In vivo*

A single dose of ^{14}C-pimitespib (8 mg/kg) was orally administered to bile-duct cannulated male rats, and its metabolites in plasma, urine, feces, and bile were investigated. The following results were obtained:

- In plasma at 4 hours post-dose, unchanged pimitespib, M3, and M11 (desaturated metabolite) were mainly detected (accounting for 87.6%, 5.43%, and 1.80%, respectively, of the total radioactivity in plasma).
- In urine collected between 12 and 24 hours post-dose, unchanged pimitespib, M6 (oxidized form), M1, M3, and M4 (oxidized form of M5 [metabolite with a cleaved imidazole ring]) were mainly detected (accounting for 0.15%, 0.11%, 0.10%, 0.07%, and 0.04%, respectively, of the radioactivity administered).
- In feces collected until 24 hours post-dose, unchanged pimitespib, M6, and M1 were mainly detected (accounting for 16.1%, 4.39%, and 4.33%, respectively, of the radioactivity administered).
- In bile collected between 6 and 12 hours post-dose, unchanged pimitespib, M3, M1, M6, and M5 were mainly detected (accounting for 0.64%, 4.95%, 2.36%, 2.12%, and 1.92%, respectively, of the radioactivity administered).

4.4 Excretion

4.4.1 Excretion in urine, feces, bile, and expired air

The applicant's explanation:

Based on the following investigation results, pimitespib and its metabolites are mainly excreted in feces via bile:

- A single dose of ^{14}C-pimitespib (8 mg/kg) was orally administered to non-bile duct-cannulated male rats, and 2.8%, 94.1%, and 0.0% of the radioactivity administered were excreted in urine, feces, and expired air, respectively, until 120 hours post-dose.
- A single dose of ^{14}C-pimitespib (8 mg/kg) was orally administered to bile duct-cannulated male rats, and 5.3% and 64.7% of the radioactivity administered were excreted in urine and bile, respectively, until 48 hours post-dose.

4.4.2 Excretion in milk

The excretion of pimitespib in milk was not investigated. The applicant explained that pimitespib may possibly be excreted in milk in view of the membrane permeability [see Section 4.1.2] and physicochemical properties of pimitespib (molecular weight of 454.53 and log P value of ≥1).

4.5 Pharmacokinetic interactions

4.5.1 Enzyme inhibition

The applicant's explanation about pharmacokinetic interactions mediated by the inhibitory effect of pimitespib against metabolizing enzymes:

The clinical use of pimitespib is unlikely to cause pharmacokinetic interactions mediated by the inhibitory effect of pimitespib against CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, and CYP2D6 in light of the C_{max} (3.16 μg/mL[15)]) when administered according to the proposed dosage regimen, the plasma protein binding of pimitespib [see Section 4.2.2], and of the investigation outcomes below. In contrast, the inhibitory effect of pimitespib against CYP3A may mediate pharmacokinetic interactions. The pharmacokinetic interactions mediated by the inhibitory effect of pimitespib against CYP3A are discussed in Section "6.R.3 Pharmacokinetic interactions mediated by CYP3A, MATE1, and MATE2-K."

- Pimitespib (0.1-100 μmol/L) was incubated with human liver microsomes in the presence of each substrate of CYP isoforms (CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, and CYP3A)[16)] and NADPH, and the inhibitory effect of pimitespib against the metabolism of each substrate of the CYP isoforms was investigated. Pimitespib inhibited the metabolism of substrates of CYP2C8, CYP2C9, CYP2C19, and CYP3A with the IC_{50} of 34.2, 50.1, 66.3, and 61.2[17)] μmol/L, respectively. Pimitespib, in contrast, did not distinctly inhibit the metabolism of substrates of the other CYP isoforms investigated.
- Pimitespib (0.1-100 μmol/L) was pre-incubated with human liver microsomes in the presence of NADPH followed by incubation with each substrate[16)] of CYP isoforms (CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, and CYP3A), and time-dependent inhibitory effect of pimitespib against the metabolism of each substrate of the CYP isoforms was investigated. Pimitespib inhibited the metabolism of the CYP3A substrate in a time-dependent manner with the inhibitor concentration at 50% of maximum inhibition rate (K_I) and maximum inactivation rate constant (k_{inact}) of 33.8 μmol/L and 0.0308 min^{-1}, respectively.[18)] Pimitespib, in contrast, did not distinctly inhibit the metabolism of substrates of the other CYP isoforms investigated in a time-dependent manner.

4.5.2 Enzyme induction

The applicant's explanation about the pharmacokinetic interactions mediated by the induction of pimitespib of metabolizing enzymes:

The clinical use of pimitespib is unlikely to cause pharmacokinetic interactions mediated by its induction of CYP1A2, CYP2B6, and CYP3A in light of the C_{max} (3.16 μg/mL[15)]) when administered according to the proposed dosage regimen, the plasma protein binding of pimitespib [see Section 4.2.2], and investigation results below.

- Pimitespib (0.1-30 μmol/L) was incubated with primary human hepatocytes for 3 days, and messenger ribonucleic acid (mRNA) expression of CYP isoforms (CYP1A2, CYP2B6, and CYP3A4) was

---

15) Estimated by the population pharmacokinetics (PPK) analysis performed on PK data of pimitespib (2,434 measuring time points in 194 subjects) in a global phase I study (Study 010), Japanese phase I studies (Studies 10058040 [Study 040] and 10058050 [Study 050]), Japanese phase II study (Study 10058020 [Study 020]), and Japanese phase III study (Study 030).

16) Substrates of CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, and CYP2D6 used were phenacetin, bupropion, paclitaxel, diclofenac, S-mephenytoin, and dextromethorphan, respectively, and substrates of CYP3A used were testosterone and midazolam.

17) IC_{50} against the metabolism of midazolam used as a substrate of CYP3A. The IC_{50} against the metabolism of testosterone was >100 μmol/L.

18) K_I and k_{inact} against the metabolism of midazolam used as a substrate of CYP3A. The K_I and k_{inact} against the metabolism of testosterone were 185 μmol/L and 0.0609 min^{-1}, respectively.

investigated. Pimitespib did not distinctly induce mRNA expression of CYP1A2, CYP2B6, and CYP3A4.[19)]

4.5.3 Transporters

The applicant's explanation about the pharmacokinetic interactions mediated by transporters of pimitespib:

The investigation results below suggested that pimitespib is not a substrate of organic anion transporting polypeptide (OATP)1B1 or OATP1B3 but a substrate of P-gp and BCRP.

- Transport of ^{14}C-pimitespib (6.4 μmol/L) mediated by P-gp was investigated using porcine kidney LLC-PK1 cell line expressing human P-gp. The ratio of the efflux ratio (the ratio of permeability coefficient in the secretive direction to that in the absorptive direction) of pimitespib was 20.6 and 1.4, respectively, in the absence and presence of a P-gp inhibitor (zosuquidar hydrochloride, 10 μmol/L).
- Transport of ^{14}C-pimitespib (6.3 μmol/L) mediated by BCRP was investigated using canine kidney MDCKII cell line expressing human BCRP. The efflux ratio of pimitespib was 3.9 and 1.1, respectively, in the absence and presence of a BCRP inhibitor (Ko143, 10 μmol/L).
- Transport of ^{14}C-pimitespib (0.3-30 μmol/L) mediated by OATP1B1 and OATP1B3 was investigated using HEK293 cell line expressing human OATP1B1 or OATP1B3. The ratio of pimitespib intake in the cell line expressing OATP1B1 or OATP1B3 relative to that in the cell line not expressing OATP1B1 or OATP1B3 was <2 for either transporter.

The clinical use of pimitespib is unlikely to cause pharmacokinetic interactions mediated by its inhibitory effect against organic anion transporter (OAT)1, OAT3, organic cation transporter (OCT)2, and OATP1B3, in light of the C_{max} (3.16 μg/mL[15)]) when administered according to the proposed dosage regimen, the plasma protein binding of pimitespib [see Section 4.2.2], and investigation results below. The clinical use of pimitespib, however, may cause pharmacokinetic interactions mediated by its inhibitory effect against P-gp, BCRP, OATP1B1, multidrug and toxin extrusion (MATE)1, and MATE2-K. Nevertheless, concomitant use of pimitespib with a substrate of P-gp, BCRP, or OATP1B1 in clinical practice is considered unlikely to raise problems in view of the findings from the global phase I study (Study 010), Japanese phase II study (Study 020), or Japanese phase III study (Study 030), which raised no particular safety concerns about concomitant use of pimitespib with a substrate of these transporters. The pharmacokinetic interactions mediated by the inhibitory effect of pimitespib against MATE1 and MATE2 are discussed in Section "6.R.3 Pharmacokinetic interactions mediated by CYP3A, MATE1, and MATE2-K."

- The inhibitory effect of pimitespib (1-150 μmol/L) against the transport of substrates[20)] of P-gp and BCRP was investigated using Caco-2 cell line. Pimitespib inhibited the transport of substrates of P-gp and BCRP with the IC_{50} of 28.0 and 13.6 μmol/L, respectively.
- Using HEK293 cell line expressing human OAT1, OAT3, OCT2, OATP1B1, OATP1B3, MATE1, or MATE2-K, the inhibitory effect of pimitespib (0.3-100 μmol/L) against the transport of each

19) Of hepatocytes from 3 donors investigated, those from 2 donors after incubation with pimitespib at 2 to 30 or 4 to 30 μmol/L exhibited poor viability lower than 50% of that after incubation with the vehicle control (0.1% DMSO). Results in the concerned hepatocytes were excluded from the induction study.

20) Substrates of P-gp and BCRP used were ^{3}H-digoxin (37 MBq/mL) and ^{3}H-estrone sulfate (37 MBq/mL), respectively.

substrate[21)] of these transporters was investigated. Pimitespib inhibited the transport of substrates of OAT1, OAT3, OCT2, OATP1B1, OAT1B3, MATE1 and MATE2-K with the IC_{50} of 71.0, 6.14, 24.5, 8.46, 28.3, 3.39, and 0.359 μmol/L, respectively.

4.R Outline of the review conducted by PMDA

On the basis of the data submitted, PMDA has concluded that the applicant's explanation about non-clinical pharmacokinetics of pimitespib is acceptable except for discussion in the following section.

4.R.1 Pharmacokinetic interactions

Results from *in vitro* studies suggested that clinical use of pimitespib might cause pharmacokinetic interactions mediated by P-gp and BCRP [see Section 4.5.3].

The applicant's explanation about pharmacokinetic interactions mediated by the above transporters:
Concomitant use of pimitespib with a P-gp inhibitor is unlikely to pose problems in clinical settings, in view of the finding from the global phase I study (Study 010), Japanese phase II study (Study 020), or Japanese phase III study (Study 030), in which pimitespib was used concomitantly with a P-gp inhibitor and did not raise any particular safety concerns. In the clinical studies of pimitespib, however, none of the subjects concomitantly received any BCRP inhibitor, precluding a conclusion on whether concomitant use of pimitespib with a BCRP inhibitor would raise problems in clinical settings.

PMDA's view:
The above applicant's explanation is generally acceptable. However, information about pharmacokinetic interactions mediated by P-gp and BCRP is important for ensuring the proper use of pimitespib, and thus the applicant is required to provide currently available information to healthcare professionals appropriately via the package insert, and to continue collecting relevant information and appropriately provide healthcare professionals with valuable information once available.

5. Toxicity and Outline of the Review Conducted by PMDA

5.1 Single-dose toxicity

No single-dose toxicity studies of pimitespib have been conducted. Based on results of 2-week repeated oral dose toxicity studies in rats (CTD 4.2.3.2.1) and dogs (CTD 4.2.3.2.4), the 4-week repeated oral dose toxicity study in rats (CTD 4.2.3.2.2), micronucleus assay in rats (CTD 4.2.3.3.2.1), and study for effects on the central nervous system in rats (CTD 4.2.1.3.1), approximate lethal dose and acute toxicity of pimitespib were evaluated. Deaths occurred in rats at 12 mg/kg and in dogs at ≥15 mg/kg. The approximate lethal dose of pimitespib was determined as 12 mg/kg in rats and 15 mg/kg in dogs. A main acute symptom observed was transient loose stool in rats.

5.2 Repeated-dose toxicity

Repeated-dose toxicity studies in rats and dogs (4 and 13 weeks) were conducted (Table 7). The main toxicity findings in rats and dogs included tissue injuries in the liver, bile duct and gallbladder mucosa, renal tubule, and gastrointestinal mucosa,; inhibition against osteogenesis and bone marrow

[21)] Substrates of OAT1 and OAT3 used were ^{3}H-*p*-aminohippuric acid (1 μmol/L) and ^{3}H-estrone sulfate (0.05 μmol/L), respectively; a substrate of OATP1B1 and OATP1B3 used was ^{3}H-estradiol-17β-glucuronide (0.05 μmol/L); and a substrate of OCT2, MATE1, and MATE2-K used was ^{14}C-metformin (10 μmol/L).

hematopoietic cell growth; lymphocyte count decreased in the immune tissues; decreased erythroid parameters; and apoptosis in the dermal hair follicle, dermal erythema, and crust formation. The repeated dose toxicity studies in rats and dogs were conducted to determine the severely toxic dose in 10% of animals (STD_{10}) and highest non-severely toxic dose (HNSTD), in view of tolerability evaluation in humans. The no observed adverse effect level (NOAEL) has not been determined. According to the applicant, although the clinical studies revealed adverse events occurring at a certain percentage in association with these findings of pimitespib in the liver and bile duct, kidney, and hematopoietic and lymphoid systems observed in the toxicity studies, clinical use of pimitespib is unlikely to raise safety problems.

The main target organs of toxicity for pimitespib were the liver and bile duct, kidney, hematopoietic and lymphoid systems, and bone tissues. PMDA's conclusion on the effects of pimitespib on all target organs except for the bone tissues are discussed in Section "7.R.3 Safety" in view of clinical study results on safety of pimitespib.

Table 7. Repeated-dose toxicity

Test system	Route of administration	Dosing period	Dose (mg/kg/day)	Main findings	NOAEL (mg/kg/day)	Attached document CTD
Male and female rat (Sprague Dawley)	Oral	4 weeks + 4-week recovery	0,*[1] 4, 8, 12	<u>Dead animals*[2]</u> 12: 1 of 16 males, 8 of 16 females Hunchback position, decreased locomotor activity, bradypnea, hypothermia, colored/soiled fur, anemic state, haematuria, tip toe gait, piloerection, emaciation, lacrimation, abnormal stool (loose, mucinous, watery, or mucinous bloody stool), decreased feces High red blood cell count, haemoglobin, and haematocrit; low platelet count and reticulocyte count or ratio; high blood AST, ALT, ALP, GGT, and total bilirubin values; small thymus; petechial dark red area on the glandular stomach mucosa; thin duodenum and jejunum; watery and mucinous contents in the stomach and duodenum; mucous contents in the gastrointestinal tract; unclear Peyer's patch; large and dark red adrenal gland; low weight of spleen and thymus, increased apoptotic bodies in the thymic cortex; decreased bone marrow hematopoietic cells; atrophy of the thymus, splenic white pulp, mesenteric lymph node, and Peyer's patch, increased apoptotic bodies in the salivary gland acinus; atrophy of esophageal mucosa; localized ulcer in the anterior stomach; degeneration/necrosis and dilation of the glandular stomach fundus gland and increased apoptotic bodies in the pyloric gland; atrophy of the duodenum, jejunum, ileum, and mucosa and increased apoptotic bodies in the lacunar; inflammatory cell infiltration in the ileum mucosa; atrophy of the cecum, colon, and rectum mucosa; increased apoptotic bodies in the cecum lacunar; multifocal and single cell degeneration/necrosis of hepatocytes in the liver; epithelial hypertrophy in the liver and bile duct; localized atrophy of the tracheal epithelium; basophilic renal tubule in the kidney cortex and multifocal degeneration/necrosis of the renal tubular epithelium; vacuolar degeneration and hyaline droplet in proximal renal tubule in the kidney; atrophy of epithelium, increased apoptotic bodies, degeneration of mucosal epithelium in the vagina; congestion/haemorrhage single cell degeneration/necrosis in the adrenal gland cortex; decreased trabecula in the metaphyseal region; thickened epiphyseal growth plate; and increased apoptotic bodies in the dermal hair follicle, mammary alveolus <u>Survived animals</u> ≥8: High blood AST*[3] and ALT values; low spleen and thymus weights; high heart weight (male and female); low platelet count, low liver weight (male), loose stool, high blood ALP value (female) 12: Watery stool; low body weight and food consumption; increased apoptotic bodies in the thymic cortex; decreased	-	4.2.3.2.2

Test system	Route of administration	Dosing period	Dose (mg/kg/day)	Main findings	NOAEL (mg/kg/day)	Attached document CTD
				hematopoietic cells in the bone marrow; hypertrophy of bile duct epithelium in the liver; thickened epiphyseal growth plate (male and female); mucinous content in the ileum; atrophy of splenic white pulp (male); low platelet count; high blood GGT and total bilirubin values; small thymus and atrophy of the thymus; multifocal degeneration/necrosis of hepatocytes in the liver; increased apoptotic bodies in the vaginal epithelium; decreased trabecula and metaphyseal region (female) 8: Loose stool (male) Reversible		
Male and female rat (Sprague Dawley)	Oral	13 weeks (QD)	0,*[1] 2, 4, 8	≥2: Low platelet count (male and female) ≥4: Low spleen weight (male) 8: High blood AST, ALT, ALP, GGT, and total bilirubin values; small thymus; low thymus weight; high heart weight; atrophy of the thymus and increased apoptotic bodies in the thymic cortex; decreased splenic extramedullary hematopoiesis; hypertrophy of bile duct epithelium in the liver; sinusoidal congestion/hemorrhage in the adrenal gland cortex (male and female); gas retention in the ileum, cecum, and large intestine; decreased hematopoietic cells in the bone marrow; hepatocyte centrilobular vacuolation in the liver (male); bilateral white spots in the ovaries; high adrenal gland weight; decreased lymphocytes in the splenic white pulp and mesenteric lymph node, atrophy of the Peyer's patch follicular center; degeneration/necrosis of the adrenal gland cortex; ovary multifocal cysts, decreased corpus luteum, and interstitial cell hyperplasia (female)	-	4.2.3.2.3
Male and female dogs (beagle)	Oral	4 weeks (QD) + 4-week recovery	0,*[1] 3, 6, 12	≥6: Abnormal (loose, mucinous, and watery) stool (male and female) 12: Low body weight gain; low reticulocyte count; high platelet count; increased hematopoietic cells in the bone marrow; atrophy of the thymus (male and female); low red blood cell count and haemoglobin; raised gallbladder mucosa; retention of mucus in the gallbladder mucosa (male); bloody stool; low body weight and food consumption; low lymphocyte count; small Peyer's patch; dark red foci in the ileum and cecum mucosa; atrophy of the Peyer's patch; inflammatory cell infiltration in the duodenal papilla; degeneration/necrosis of foci in the duodenum and jejunum epithelium; brown pigmentation in the cecum proper lamina; increased apoptotic bodies in the gallbladder mucosa; inflammatory cell infiltration and haemorrhage in the jejunum and ileum proper lamina; and basophilic renal tubule in the kidney (female) 6: High reticulocyte count (male and female) Reversible	-	4.2.3.2.5
Male and female dogs (beagle)	Oral	13 weeks (QD)	0,*[1] 1, 3, 6	None	-	4.2.3.2.6
Male and female dogs (beagle)	Oral	13 weeks (QD)	0,*[1] 9, 12	<u>Dead animals*[2]</u> 12: 1 of 3 females Low body weight and food consumption; vomiting, bloody stool, watery stool, watery nasal discharge, prone position, decreased body temperature, decreased locomotor activity; low white blood cell count and platelet count; high red blood cell count, haemoglobin, haematocrit, and fibrinogen; low blood sodium and chloride values; high blood ALP, glucose, total cholesterol, triglyceride, total protein, globulin, urea nitrogen, creatinine, total bilirubin, and inorganic phosphorus; small thymus; dark red mesenteric lymph node; dark red duodenum, jejunum, ileum, and gallbladder mucosa; common bile duct dilation; low thymus weight; atrophy of the thymus; atrophy of the marginal spleen; decreased hematopoietic cells in the bone marrow; atrophy of the mesenteric lymph node and medullary sinusoidal blood absorption; atrophy of the Peyer's patch, macrophage infiltration, haemorrhage foci; increased single cell necrosis in the stomach fundus and pylorus mucosa; dilation of the duodenum lacunar, mucosal haemorrhage, increased single cell necrosis in the lacunar; increased single cell necrosis in the jejunum lacunar and ulcer foci in the mucosa; congestion in the ileum mucosa and ulcer, haemorrhage in the mucosa,	-	4.2.3.2.7

Test system	Route of administration	Dosing period	Dose (mg/kg/day)	Main findings	NOAEL (mg/kg/day)	Attached document CTD
				submucosal tissues, and muscle layer; congestion foci on mucosa in the large intestine and haemorrhage; edema of extrahepatic common bile duct binding tissue, haemorrhage, diffuse necrosis in the bile duct epithelium; edema of the gallbladder interstitium, haemorrhage in the mucosa and submucosal tissue, and multifocal necrosis in the mucosa; and haemorrhage in the duodenal bile duct interstitium and necrosis of mucosal epithelium <u>Survived animals</u> ≥9: Low red blood cell count; high MCV; atrophy of the thymus, increased hematopoietic cells in the bone marrow (male and female), high neutrophil count and platelet count; increased single cell necrosis in the stomach pylorus mucosa; increased single cell necrosis in the duodenum and ileum lacunar (male); high MCH; high blood ALP, GGT, total protein, and globulin values; low blood albumin and A/G ratio; increased single cell necrosis in the common bile duct epithelium in the duodenum part; increased single cell necrosis in the rectum lacunar (female) 12: High monocyte count; atrophy of the splenic white pulp; fibrous foci in the common bile duct in the duodenum and necrosis foci in the epithelium (male and female); high white blood cell count; atrophy of the Peyer's patch; increased single cell necrosis in the gallbladder mucosa; inflammatory cell infiltration in the common bile duct in the duodenum; increased single cell necrosis in the common bile duct epithelium in the duodenum; increased single cell necrosis in the cecum and colon lacunar; degeneration/necrosis in the testicular epithelium; decreased sperm count in the epididymis (male); low body weight and food consumption; auricular hair loss; erythema in the periocular/perioral and inguinal regions, crust formation on the head/auricle; red eyelid; low haemoglobin, haematocrit, and MCHC; high platelet count and fibrinogen; enhanced splenic extramedullary hematopoiesis; and increased single cell necrosis in the pylorus mucosa in the stomach (female)		

*[1] 5 mg/mL HPMC, *[2] The main toxicity findings related to pimitespib only, *[3] Excluding females at 8 mg/kg

5.3 Genotoxicity

Bacterial reverse mutation assay (Ames test), chromosomal aberration assay in mammalian cells, and micronucleus assay in rats were conducted (Table 8). Pimitespib was found to be clastogenic without metabolic activation in the chromosomal aberration assay in mammalian cells and induced micronuclei in the micronucleus assay in rats. The applicant explained that pimitespib was clastogenic.

Table 8. Genotoxicity

Type of study		Test system	Metabolic activation (treatment)	Concentrations or dose	Result	Attached document CTD
In vitro	Ames	*Salmonella typhimurium*: TA98, TA100, TA1535, TA1537 *Escherichia coli*: WP2*uvrA*	S9-/+	0,*[1] 39.1, 78.1, 156, 313, 625, 1,250, 2,500 μg/plate	Negative	4.2.3.3.1.1
	Chromosomal aberration	Chinese hamster lung cells (CHL/IU)	S9-/+ (6 hours)	0,*[1] 15.6, 31.3, 62.5 μg/mL	Negative	4.2.3.3.1.2
			S9- (24 hours)	0,*[1] 0.156, 0.313, 0.625 μg/mL	Positive Structural aberration	
In vivo	Micronucleus	Male rat (Sprague Dawley), 2 oral doses, bone marrow		0,*[2] 7.5, 15, 30 mg/kg	Positive 30 mg/kg	4.2.3.3.2.1

*[1] DMSO, *[2] 5 mg/mL HPMC

5.4 Carcinogenicity

Because pimitespib is an antineoplastic agent intended to treat patients with advanced cancer, no carcinogenicity study was conducted.

5.5 Reproductive and developmental toxicity

In the repeated-dose toxicity studies in rats and dogs, the effects on male and female reproductive organs were evaluated. In rats, seminiferous tubule degeneration in the testis (CTD 4.2.3.2.1), mucosal epithelium injury in the vagina, and atrophic changes in the ovaries such as multifocal cysts and decreased corpus luteum were observed. In dogs, sperm formation disorders such as degeneration and necrosis of germinal epithelium in the testis were observed [see Section 5.2].

An embryo-fetal development study was conducted in pregnant rats (Table 9). Main embryo-fetal toxicity findings were developmental inhibition, embryonic resorption, and visceral and skeletal deformities at a dose leading to the clinical exposure[22)] or lower. The NOAEL for embryo-fetal development was determined as 2 mg/kg. The increased incidence of ventricular septal defect, found at 2 mg/kg, fell within the historical data at the testing facility. The applicant therefore explained that it was not a toxicity finding.

Based on the above study results, the applicant explained that the following cautions would be raised: the use of pimitespib in patients in reproductive age warrants consideration of its effects on the gonads; women of childbearing potential and men with a female partner of childbearing potential should be advised to use appropriate contraception during treatment with pimitespib and a certain post-treatment period; and breast-feeding women should refrain breast-feeding during treatment with pimitespib because of its possible excretion into milk in humans [see Section 4.4.2].

[22)] Exposure in non-pregnant female rats after administration of pimitespib 4 mg/kg ($AUC_{0\text{-}24h}$ of unbound pimitespib) was 0.6 to 1.0 times the clinical exposure.

Table 9. Reproductive and developmental toxicity

Type of study	Test system	Route of administration	Dosing period	Dose (mg/kg/day)	Main findings	NOAEL (mg/kg/day)	Attached document CTD
Embryo-fetal development	Female rat (Sprague Dawley)	Oral	Gestation Days 7-17 (QD)	0,*1 1, 2, 4	Maternal animals 4: Genital hemorrhage, uterine edema, low body weight and food consumption Embryos and fetuses ≥2: Increased incidence of ventricular septal defect*2 4: Low mean number of live fetuses; high mean percentage of postimplantation loss; low fetal body weight; high number of fetuses with malformation; defective ridge of the ocular surface and small eye;*2 rima palpebrarum;*2 curved tail;*2 omphalocele;*2 anophthalmos and microphthalmia;*2 atrial septal defect;*2 ventricular wall dilation;*2 aortic valve malformation;*2 membranous and myogenic ventricular vascular muscle defect;*2 persistent atrioventricular canal;*2 interrupted aortic arch;*2 subclavian artery branch and retroesophageal aortic arch malposition;*2 pulmonary lobe morphological defect;*2; renal aplasia;*2 renal papillary dilation;*2 kidney malformation;*2 adrenal gland hypertrophy;*2 ametria;*2 umbilical artery transposition;*2 serpiginous ureter;*2 ureter dilation;*2 sternebra fusion*2 and malalignment;*2 rib defect;*2 bifid and complete supernumerary ribs;*2 rib and costal cartilage fusion;*2 short rib;*2 tibial cartilage split;*2 tibial vertebral arch and thoracic arch fusion;*2 thoracic bifida,*2 dumbbell ossification*2 and hemicentrum;*2 sternal defect*2 and supernumerary vertebra;*2 thoracic cartilage fusion and split;*2 lumbar hemicentrum;*2 lumbar cartilage split;*2 lumbar vertebrae defect;*2 lumbar hemivertebra;*2 rib cartilage split;*2 delayed ossification*3 (finger, middle finger, thoracic, rib, sacral, and coccygeal bones)	Maternal animals: 2 Embryo-fetus: 2	4.2.3.5.2.2

*1 5 mg/mL HPMC, *2 Malformation, *3 Mutation

5.6 Other toxicity studies

5.6.1 Photosafety

A neutral red-uptake phototoxicity test was conducted using mouse fibroblasts (Table 10). The applicant explained that pimitespib had no phototoxicity.

Table 10. Photosafety study

Test system	Test method	Main findings	Attached document CTD
Mouse fibroblasts (Balb/c 3T3)	0,*1 2.5, 5, 10, 20, 40, 60, 80, and 100 μg/mL UVA irradiation (5 J/cm^2)	PIF, -*2; MPE, 0.001 No phototoxicity	4.2.3.7.7.1

*1 DMSO, *2 Not calculated because of no cytotoxicity found

5.6.2 Safety evaluation of impurities

Impurity A is an impurity present in the drug substance at a level greater than the qualification threshold defined in Impurities in New Drug Substances (ICH Q3A Guidelines). The drug substance used in

13-week repeated oral dose toxicity studies in rats (CTD 4.2.3.2.3) and dogs (CTD 4.2.3.2.7) contained Impurity A[23] at 0.008 and 0.03 mg/kg per STD_{10} (rats) and HNSTD (dogs) of pimitespib, respectively, which are equivalent to or more than the amount of Impurity A present at the upper limit of the acceptance criteria in the clinical dose of pimitespib. The applicant therefore explains that the safety of Impurity A was adequately evaluated.

5.R Outline of the review conducted by PMDA

On the basis of the data submitted and review of the following section, PMDA has concluded that the applicant's explanation about toxicity of pimitespib is acceptable.

5.R.1 Effects on gastrointestinal system

The applicant's explanation about changes related to mucosal tissue injuries in the gastrointestinal system observed in rats and dogs after repeated doses of pimitespib:

In the repeated-dose toxicity studies in rats and dogs, atrophy of the gastrointestinal mucosa and fecal abnormalities were observed [see Section 5.2]. In the clinical studies of pimitespib, diarrhoea frequently occurred in the use of pimitespib as an adverse event related to gastrointestinal disorders [see Section 7.R.3.2]. Diarrhoea was also frequently reported from the clinical studies of the other HSP90 inhibitors (*Biochem Biophys Acta.* 2012;1823:742-55). Therefore, the applicant will raise caution via the package insert about gastrointestinal disorders in the use of pimitespib such as diarrhoea.

PMDA's view:

In view of the applicant's explanation and toxicity findings related to gastrointestinal injuries in the repeated-dose toxicity studies observed at a dose leading to exposure less than the clinical exposure, the applicant's intention to raise caution against gastrointestinal disorders such as diarrhoea is generally justifiable. The necessity of cautionary advice against gastrointestinal disorders in the use of pimitespib is discussed in Section 7.R.3.2 in view of the occurrence of relevant disorders in the clinical studies.

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

The applicant's explanation:

Embryo-fetal toxicity and teratogenicity observed in the embryo-fetal development study in rats [see Section 5.5]. In its view, the use of pimitespib is not recommended in pregnant women or women who may possibly be pregnant. Because of a poor prognosis of GIST, however, careful use of pimitespib may be allowable in pregnant women or women who may potentially be pregnant only when the expected therapeutic benefits [see Section 7.R.2] outweigh the possible risks associated with treatment and patients and their families have been adequately explained about potential risks of pimitespib in fetus. Such cautions will be given via the package insert.

PMDA accepted the applicant's explanation.

[23] The drug substance containing Impurity A at 0.65% was used.

5.R.3 Effects on bone

In the repeated-dose toxicity study in rats, thickened epiphyseal cartilage plate of the femur and decreased metaphyseal trabecula were observed at a dose producing exposure equivalent to the clinical exposure [see Section 5.2], which suggest that pimitespib may affect bone growth. However, in the current application, pimitespib is intended for adults, who have only closed epiphyseal growth plates. PMDA thus considers that pimitespib' effect on bone growth is unlikely to raise safety concerns. At the same time, in the use of pimitespib in patients in age brackets with immature secondary sexual characteristics whose epiphyseal growth plates remain open, the effects on the bones should be carefully evaluated.

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 pimitespib were presented as film-coated tablets (2, 10, 40, and 50 mg[24)]), which were used to investigate the PK of pimitespib (Table 11). Proposed commercial formulation is 40 mg film-coated tablets. The proposed commercial formulation and 40 mg film-coated tablets used in Study 030 were manufactured from the same formula but by different processes. Bioequivalence between these tablets was confirmed by dissolution test performed in accordance with the "Guideline for Bioequivalence Studies for Process Changes of Oral Solid Dosage Forms (in Japanese)" (Administrative Notice dated April 19, 2013).

Table 11. Oral formulations used in clinical studies

Formulation	Study ID
Film-coated tablets (2, 10, and 50 mg)	Global phase I study (Study 010), Japanese phase II study (Study 020*), and Japanese phase I study (Study 040*)
Film-coated tablets (40 mg)	Japanese phase III study (Study 030) and Japanese phase I studies (Studies 040 and 050)

* 10 and 50 mg tablets were used.

6.1.1 Assay

Pimitespib in human plasma and urine were determined by liquid chromatography-tandem mass spectrometry (LC-MS/MS), and the lower limit of quantification was 5[25)] and 10 ng/mL, respectively.

6.1.2 Japanese clinical studies

6.1.2.1 Japanese phase I study (CTD 5.3.1.1.1, Study 040 [ongoing since January 2019 (data cut-off on [redacted], 20[redacted])])

A 2-treatment, 2-period crossover study was conducted in 30 patients with advanced solid tumor (28 patients included in the PK analysis) to investigate effects of formulation and food on the PK of pimitespib. This study consisted of Cohort I for the effect of formulation and Cohort II for the effect of food. In Cohort I, a single dose of pimitespib 160 mg (3 × 50-mg tablets and 1 × 10-mg tablet, or 4 × 40-mg tablets) was orally administered in the fasted state[26)] with a ≥4-day washout period. In Cohort II, a

[24)] 2, 10, and 50 mg tablets were manufactured by the [redacted] method, while 40 mg tablets were manufactured by the [redacted] method. In addition, 2, 10, and 50 mg tablets and 40 mg tablets differed in the composition of excipients such as diluents.

[25)] Plasma specimens in the global phase I study (Study 010) and Japanese phase II study (Study 020) were analyzed by a method with the lower limit of quantification being 1 ng/mL, and plasma specimens in the Japanese phase III study (Study 030) and Japanese phase I studies (Studies 040 and 050) were analyzed by a method with the lower limit of quantification being 5 ng/mL.

[26)] Administered after ≥10-hour fasting, followed by ≥4-hour fasting

single dose of pimitespib 160 mg was orally administered in the fasted state or 30 minutes after a high-fat meal[27] with a ≥4-day washout period.

The geometric mean ratios [90% confidence interval (CI)] of C_{max} and AUC_{inf} of pimitespib after the administration of 4 × 40-mg tablets relative to those after administration of 3 × 50-mg tablets and 1 × 10-mg tablet were 0.81 [0.66, 0.99] and 0.81 [0.67, 0.98], respectively. The geometric mean ratios [90% CI] of C_{max} and AUC_{inf} of pimitespib taken after the high-fat meal relative to those under the fasted state were 1.92 [1.58, 2.34] and 1.64 [1.45, 1.85], respectively.

The applicant explanation about a potential reason for the greater exposure after administration in the fed state than that after administration in the fasted state:
The high-fat meal enhanced bile acid secretion, which increased the solubility of pimitespib in the gastrointestinal tract, leading to the increased absorption of pimitespib in the tract.

6.1.3 Effects of stomach pH on PK of pimitespib

The applicant's explanation:
While the solubility of pimitespib decreases with increasing pH, based on post-hoc estimate of AUC calculated by the population pharmacokinetics (PPK) analysis [see Section 6.2.4], gastric secretion inhibitors were expected to have a limited effect on AUC of pimitespib. Increased pH owing to a concomitant gastric secretion inhibitor is therefore unlikely to cause a clinically relevant effect on the PK of pimitespib.

6.2 Clinical pharmacology

The PK of pimitespib in patients with cancer was investigated with administration of pimitespib alone.

6.2.1 Global study

6.2.1.1 Global phase I study (CTD 5.3.3.2.1, Study 010 [March 2014 to [redacted] 20[redacted]])

An open-label, uncontrolled study was conducted in 61 patients with advanced solid tumor (56 patients included in the PK analysis)[28] to investigate the PK of pimitespib. Pimitespib was administered according to the following regimens, and pimitespib concentrations in plasma and urine were determined.

Step 1 (Dose Escalation Phase):	Pimitespib was orally administered at 4.8, 9.6, 19.2, 38.4, 76.8, 107.5, or 150.5 mg/m^2 in the fasted state QD daily.
Step 2 (Dose Escalation Phase):	Pimitespib was orally administered at 107.5, 150.5, 210.7, or 295.0 mg/m^2 in the fasted state once every other day.
Step 1 (Expansion Phase):	Pimitespib 160 mg was orally administered in the fasted state QD for 5 days followed by a 2-day rest, and this 7-day regimen was repeated.[29]
Step 2 (Expansion Phase):	Pimitespib 340 mg was orally administered in the fasted state every other day.

[27] A total of 572 to 715 kcal, of which approximately 50% is from fat.
[28] The number of non-Japanese subjects was 6 (5 in Step 1 [Expansion Phase] included in the PK analysis).
[29] For the investigation of the food effect on PK using a developmental formulation, the first 6 patients received a single oral dose of pimitespib in the fed state, and after a 2-day rest, received pimitespib according to the regimen in Step 1 (Expansion Phase).

Table 12 shows the PK parameters of pimitespib in Japanese patients. C_{max} and AUC_{last} of pimitespib mostly increased proportionally to the dose within a dose range investigated. After the repeated 7-day regimen consisting of fasted oral doses of pimitespib 160 mg QD for 5 days plus the subsequent 2-day rest, the accumulation ratio of pimitespib was 1.41.[30)] In urine collected for up to 24 hours after the first dose of pimitespib 150.5 mg/m^2 in 3 patients, unchanged pimitespib and M3 (amide-hydrolyzed form) were mainly detected.

Table 12. PK parameters of pimitespib (Japanese patients)

Part	Dose	Day of measurement	n	C_{max} (μg/mL)	t_{max}*1 (h)	AUC_{last} (μg•h/mL)	$t_{1/2}$ (h)	Fe*2 (%)
Step 1 Dose Escalation Phase	4.8 mg/m^2	1	1	0.165	1.00	1.27	9.28	7.6
		8	1	0.212	0.97	1.79	10.9	-
	9.6 mg/m^2	1	1	0.285	1.02	2.81	12.6	13.9
		8	1	0.429	1.97	4.33	14.7	-
	19.2 mg/m^2	1	1	0.370	1.98	4.02	20.3	7.9
		8	1	0.835	1.98	7.33	9.50	-
	38.4 mg/m^2	1	1	0.284	6.00	3.83	11.0	2.3
		8	1	0.694	2.00	8.78	10.2	-
	76.8 mg/m^2	1	3	1.79 ± 0.176	0.98 (0.95, 1.93)	18.0 ± 2.46	11.5 ± 3.16	4.6 ± 2.2
		8	3	1.85 ± 0.265	1.97 (0.95, 1.97)	24.9 ± 3 .14	10.4 ± 1.01	-
	107.5 mg/m^2	1	6	2.59 ± 1.89	1.48 (0.98, 8.07)	32.5 ± 23.1	13.2 ± 3.58*3	2.2 ± 1.1
		8	6	3.08 ± 0.515	1.95 (1.00, 4.00)	38.9 ± 14.1	12.8 ± 2.60*4	-
	150.5 mg/m^2	1	3	2.03 ± 1.67	1.97 (1.95, 2.95)	25.0 ± 15.2	14.3 ± 2.03	2.1 ± 0.9
		8	3	4.41 ± 2.45	2.02 (1.00, 3.97)	46.6 ± 11.5	11.0 ± 2.57	-
Step 2 Dose Escalation Phase	107.5 mg/m^2	1	3	1.47 ± 1.12	0.98 (0.95, 5.93)	26.8 ± 13.7	20.7 ± 12.5	-
		15	3	2.02 ± 1.44	2.00 (1.95, 7.87)	32.2 ± 24.2	11.6 ± 1.34	-
	150.5 mg/m^2	1	6	2.23 ± 0.957	1.50 (0.93, 12.08)	39.5 ± 14.3	15.9 ± 7.67	-
		15	4	3.52 ± 0.638	2.99 (0.98, 5.97)	49.3 ± 15.2	10.5 ± 1.95	-
	210.7 mg/m^2	1	6	3.10 ± 2.35	1.48 (0.95, 5.93)	43.3 ± 23.3	13.3 ± 4.30	-
		15	5	2.76 ± 1.70	1.98 (0.93, 2.00)	33.1 ± 19.5	9.91 ± 2.32	-
	295.0 mg/m^2	1	4	3.64 ± 2.22	1.97 (1.00, 2.95)	66.5 ± 29.3	11.9 ± 1.68	-
		15	3	3.97 ± 1.65	3.03 (1.95, 6.00)	61.1 ± 27.1	15.7 ± 10.1	-
Step 1 Expansion Phase	160 mg/body	1	6	1.96 ± 1.33	3.97 (0.97, 5.97)	23.5 ± 12.1	14.2 ± 3.45	-
		19	4	1.75 ± 0.607	2.97 (1.97, 3.97)	22.4 ± 7.93	8.56 ± 0.83*3	-
Step 2 Expansion Phase	340 mg/body	1	4	1.77 ± 1.32	2.02 (1.00, 3.00)	31.2 ± 14.7	10.4 ± 3.62	-
		15	4	2.61 ± 1.36	2.47 (1.93, 3.00)	40.0 ± 19.3	11.3 ± 2.99	-

Mean ± SD; -, Not measured; *1 Median (minimum, maximum); *2 Urine excretion rate of unchanged pimitespib until 24 hours after the first dose; *3 n = 3; *4 n = 5

6.2.2 Use of pimitespib in patients with renal impairment

No clinical study was conducted in patients with renal impairment to investigate effects of renal impairment on the PK of pimitespib.

The applicant's explanation:

The following outcomes indicate that dose adjustment of pimitespib is not necessary for patients with renal impairment.

- The results of the urinary excretion rate of unchanged pimitespib in the global phase I study (Study 010) suggested that renal excretion contributes only minimally to the elimination of pimitespib [see Section 6.2.1.1].

30) Ratio of AUC_{last} on Day 19 to that on Day 1

- In a pooled analysis of the global phase I study (Study 010), Japanese phase II study (Study 020), and Japanese phase III study (Study 030), the incidences of (a) Grade ≥3 adverse events, (b) adverse events resulting in death, (c) serious adverse events, (d) adverse events leading to treatment discontinuation, (e) adverse events leading to treatment interruption, and (f) adverse events leading to dose reduction in patients with normal renal function[31] (n = 45), patients with mild renal impairment (n = 62), and patients with moderate or severer renal impairment (n = 12) were (a) 35.6%, 56.5%, and 66.7%, (b) 2.2%, 4.8%, and 0%, (c) 20.0%, 37.1%, and 41.7%, (d) 6.7%, 0%, and 8.3%, (e) 66.7%, 71.0%, and 83.3%, and (f) 33.3%, 41.9%, and 50.0%, respectively. The incidences did not show any increasing trend associated with decreasing renal function.

6.2.3 Japanese phase I study for effects of pimitespib on QT/QTc interval (CTD 5.3.4.2.1, Study 050 [ongoing since [redacted] 20[redacted] (data cut-off on [redacted], 20[redacted])])

An open-label, uncontrolled study was conducted in 25 patients with advanced solid tumor (22 patients included in the PK analysis) to investigate effects of pimitespib on QT/QTc interval. In this study, the placebo was orally administered in the fasted state on Day 1, and pimitespib 160 mg was orally administered in the fasted state QD for 5 days, on Days 2 to 6.

The upper limit of 90% CI of a change in placebo-corrected, time-matched QT interval corrected using Fridericia formula (QTcF) from baseline (ΔΔQTcF) after oral administration of pimitespib 160 mg QD was 16.86 milliseconds.[32] Table 13 shows the PK parameters of pimitespib.

No Grade ≥3 QT interval prolonged occurred after the administration of pimitespib in the global phase I study (Study 010), Japanese phase I studies (Studies 040 and 050), Japanese phase II study (Study 020), and Japanese phase III study (Study 030). In view of all these findings, the applicant explained that it was unnecessary to raise caution about QT/QTc interval prolongation.

Table 13. PK parameters of pimitespib

Day of measurement	n	C_{max} (μg/mL)	t_{max}* (h)	AUC_{last} (μg•h/mL)	AUC_{inf} (μg•h/mL)	$t_{1/2}$ (h)
2	22	2.26 ± 0.76	3.87 (1.00, 8.00)	28.4 ± 7.35	38.6 ± 9.69	11.2 ± 3.48
6	22	2.60 ± 0.94	2.98 (1.00, 7.98)	35.3 ± 12.0	-	10.4 ± 2.32

Mean ± SD, * Median (minimum, maximum)

6.2.4 PPK analysis

The PPK analysis was performed using a non-liner mixed-effects model (software, Phoenix NLME version 8.1) based on PK data (2,434 measuring time points in 194 subjects) on pimitespib from the global phase I study (Study 010), Japanese phase I studies (Studies 040 and 050), Japanese phase II study (Study 020), and Japanese phase III study (Study 030). The PK of pimitespib was described by a 2-compartment model with the first order absorption process with lag-time.

[31] Renal function was classified according to the following criteria: Normal, CLcr ≥90 mL/min; mild impairment, CLcr ≥60 mL/min and <90 mL/min; moderate impairment, CLcr ≥30 mL/min and <60 mL/min; and severe impairment, CLcr ≥15 mL/min and <30 mL/min. All the clinical studies included patients with CLcr (mL/min) of ≥50.

[32] Value at 24 hours after administration of pimitespib on Day 6

In this analysis, possible covariates of pimitespib for (a) F1, (b) Ka, (c) CL, and (d) V2, respectively, were (a) and (b) body weight, body surface area, age, sex, fed or fasted state, formulation (2, 10, and 50 mg tablets or 40 mg tablets), dose, gastric secretion inhibitor,[33] race, Eastern Cooperative Oncology Group (ECOG) performance status (PS), carcinoma, gastrectomy, small intestinal resection, and P-gp inhibitor, (c) body weight, body surface area, age, sex, serum albumin, alkaline phosphatase (ALP), alanine aminotransferase (ALT), aspartate aminotransferase (AST), CLcr, total cholesterol, LDH, dose, race, ECOG PS, carcinoma, gastrectomy, small intestinal resection, and P-gp inhibitor, and (d) body weight, body surface area, age, sex, serum albumin, race, ECOG PS, carcinoma, gastrectomy, small intestinal resection, and P-gp inhibitor. As a result of assessment, fed or fasted state and gastric secretion inhibitor was identified as a significant covariate for F1, and formulation (2, 10, and 50 mg tablets or 40 mg tablets) for Ka.

The applicant's explanation based on the above results:

- Whether it is administered in the fed or fasted state may possibly have a clinically significant impact on the PK of pimitespib.
- The gastric secretion inhibitor and formulations had limited effects on the exposure to pimitespib, and thus these covariates are unlikely to affect the PK of pimitespib clinically significantly.

6.2.5 Relationships between exposure and efficacy or safety

Based on data from the Japanese phase II study (Study 020) and Japanese phase III study (Study 030), relationships between exposure to pimitespib and the efficacy and safety were investigated.

6.2.5.1 Relationship between exposure and efficacy

A relationship of exposure to pimitespib ($AUC_{96\text{-}120h}$, C_{max}, and C_{trough}) with progression free survival (PFS) and that with overall survival (OS) in patients with GIST were investigated. No clear relationships were observed between the exposure to pimitespib and either of these efficacy indicators.

6.2.5.2 Relationship between exposure and safety

Relationships of exposure to pimitespib ($AUC_{96\text{-}120h}$, C_{max}, and C_{trough}) with the incidences of adverse events (all adverse events, Grade ≥3 adverse events, serious adverse events, adverse events leading to treatment discontinuation, adverse events leading to treatment interruption, adverse events leading to dose reduction, gastrointestinal disorder, Grade ≥3 gastrointestinal disorder, eye disorder, Grade ≥2 eye disorder, bone marrow toxicity, Grade ≥3 bone marrow toxicity, hepatic dysfunction, Grade ≥3 hepatic dysfunction, renal dysfunction, Grade ≥3 renal dysfunction, rash, Grade ≥3 rash, etc.) were investigated. The incidences of adverse events leading to dose reduction, Grade ≥3 gastrointestinal disorder, eye disorder, bone marrow toxicity, hepatic dysfunction, and renal dysfunction tended to increase with increasing $AUC_{96\text{-}120h}$. In an investigation using C_{max} or C_{trough} as an exposure indicator also showed similar trends to that in the $AUC_{96\text{-}120h}$-based investigation.

[33] H_2 receptor antagonists, proton pump inhibitors, and antacids.

6.R Outline of the review conducted by PMDA

On the basis of the data submitted, PMDA has concluded that the applicant's explanation about the clinical pharmacology of pimitespib is acceptable except for discussion in the following subsection.

6.R.1 Food effect

The applicant's explanation about dose timing of pimitespib:

Results from Cohort II in the Japanese phase I study (Study 040) suggested that exposure to pimitespib administered in the fed state was greater than that administered in the fasted state [see Section 6.1.2.1]. The Japanese phase III study (Study 030) in which pimitespib was administered "≥1 hour before or ≥2 hours after meal" demonstrated clinical benefits of pimitespib. "Dosage and Administration" will clearly specify that pimitespib be administered in the fasted state, and the "Precautions Concerning Dosage and Administration" section in the package insert will advise that pimitespib not be administered from 1 hour before until 2 hours after meal [see Section 7.R.5.1].

PMDA accepted the applicant's explanation.

6.R.2 Use of pimitespib in patients with hepatic impairment

No clinical study was conducted in patients with hepatic impairment to investigate effects of hepatic impairment on the PK of pimitespib.

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

The following outcomes indicate that dose adjustment of pimitespib is not necessary in patients with mild hepatic impairment.

- In the PPK analysis, AST, ALT, ALP, and serum albumin at baseline were not identified as significant covariates for CL and V2 of pimitespib [see Section 6.2.4].
- For a pooled analysis of the global phase I study (Study 010), Japanese phase II study (Study 020), and Japanese phase III study (Study 030), in patients with normal hepatic function[34)] (n = 93) and patients with mild hepatic impairment (n = 26), the incidence of Grade ≥3 adverse events was 45.2% and 65.4%, adverse events resulting in death 4.3% and 0%, serious adverse events 29.0% and 38.5%, adverse events leading to treatment discontinuation 4.3% and 0%, adverse events leading to treatment interruption 66.7% and 84.6%, and adverse events leading to dose reduction 36.6% and 50.0%, respectively. There was no tendency toward consistent increase in incidences with decreasing hepatic function.

Pimitespib is eliminated mainly through hepatic metabolism [see Section 6.2.1.1]. Because no safety information of pimitespib is available from patients with moderate or severer hepatic impairment, the use of pimitespib in patients with moderate or severer hepatic impairment requires attention. Such advice will be given via the package insert.

34) Hepatic function was classified according to the following criteria: Normal, AST and total bilirubin below the upper limit of the normal range (ULN); mild impairment, AST exceed ULN or total bilirubin exceed ULN and ≤1.5 × ULN; moderate impairment, total bilirubin >1.5 × ULN and ≤3 × ULN; and severe impairment, total bilirubin >3 × ULN.

PMDA's view:

The above applicant's explanation is generally acceptable. However, pimitespib is mainly eliminated through hepatic metabolism, and safety information of pimitespib in patients with hepatic impairment including mild cases is limited. Therefore, the use of pimitespib in patients with hepatic impairment, irrespective of severity, warrants attention. Accordingly, the package insert should caution that (a) the use of pimitespib, which is mainly metabolized in the liver, in patients with hepatic impairment may lead to greater exposure to pimitespib than that in patients with normal hepatic function, and that (b) no clinical studies were conducted in patients with hepatic impairment. Information about the PK of pimitespib in patients with hepatic impairment is critical for the proper use of pimitespib and should thus be further collected. New finding should be communicated appropriately to healthcare professionals once available.

6.R.3 Pharmacokinetic interactions mediated by CYP3A, MATE1, and MATE2-K

The applicant's explanation about the pharmacokinetic interactions of pimitespib mediated by CYP3A, MATE1, and MATE2-K:

Pimitespib inhibited CYP3A, MATE1, and MATE2-K *in vitro* [see Sections 4.5.1 and 4.5.3]. Effects of pimitespib on the PK of midazolam (substrate of CYP3A) and metformin (substrate of MATE1 and MATE2-K) were investigated using a PBPK model. Simcyp version 20.1 was used for the PBPK model analysis. The 1st order absorption model was selected as the absorption model, and the Full PBPK model was selected as the distribution model. K_I and k_{inact} of pimitespib against CYP3A were determined as 33.8 μmol/L and 1.848 h^{-1}, respectively, and the inhibition constant (K_i) of pimitespib against MATE1 and MATE2-K were determined as 3.39 and 0.359 μmol/L, respectively, based on results of *in vitro* studies [see Sections 4.5.1 and 4.5.3]. In addition, the appropriateness of the PBPK model of pimitespib was examined based on results of Studies 010 and 020, and the appropriateness of the PBPK model of midazolam and metformin was examined based on publications (*Clin Pharmacol.* 2010;88:499-505, *Clin Pharmacokinet.* 2020;59:1627-39).

Using the above PBPK models, exposure to midazolam and metformin after a single dose of midazolam 5 mg or metformin 390 mg was estimated in patients with cancer receiving pimitespib 160 mg QD. The geometric mean ratios [90% CI] of C_{max} and $AUC_{0\text{-}72h}$ of midazolam and metformin after the administration of either substrate concomitantly with pimitespib relative to those the after administration of either substrate alone were 2.09 [2.00, 2.19] and 3.16 [2.92, 3.43] and 1.60 [1.56, 1.63] and 2.12 [2.05, 2.20], respectively (Table 14 [i]). Table 14 (ii) shows results of a sensitivity analysis using a conservative setting for K_I and k_{inact} of pimitespib against CYP3A as well as K_i of pimitespib against MATE2-K. These findings indicate that concomitant pimitespib may increase exposure to substrates of CYP3A, MATE1, and MATE2-K. Thus the use of pimitespib in combination with substrates of CYP3A, MATE1, and MATE2-K requires attention, and caution will be raised.

Table 14. Changes in effect of pimitespib on PK of each substrate when K_I and k_{inact} of pimitespib against CYP3A as well as K_i of pimitespib against MATE2-K were varied

		(i)*2	(ii)*3		
Midazolam (substrate of CYP3A)	K_I (μmol/L)	33.8*1	21.0	3.38	3.38
	k_{inact} (h^{-1})	1.85*1			18.5
	Geometric mean ratio of $AUC_{0\text{-}72h}$*4	3.16	3.95	12.0	26.3
	kinact (h^{-1})	1.85*1	9.81	18.5	18.5
	K_I (μmol/L)	33.8*1			3.38
	Geometric mean ratio of $AUC_{0\text{-}72h}$*4	3.16	8.91	12.8	26.3
Metformin (substrate of MATE1 and MATE2-K)	K_i (μmol/L)*5	0.359*1	0.223	0.036	0.012
	Geometric mean ratio of $AUC_{0\text{-}72h}$*4	2.12	2.52	3.03	3.14

*1 Established based on results of *in vitro* studies [see Sections 4.5.1 and 4.5.3]
*2 K_I, k_{inact}, and K_i were established based on results of *in vitro* studies
*3 K_I, k_{inact}, and K_i were established conservatively.
*4 Administration of each substrate concomitantly with pimitespib/administration of each substrate alone
*5 K_i of pimitespib against MATE1 was 3.39 μmol/L.

In the global phase I study (Study 010), Japanese phase II study (Study 020), and Japanese phase III study (Study 030), 11 subjects received pimitespib concomitantly with a substrate of CYP3A, and 2 of them experienced adverse events related to the concomitant drug, but both were Grade ≤2. In 2 subjects receiving pimitespib concomitantly with a substrate of MATE1 and MATE2-K, no adverse events related to the concomitant drug were observed.

PMDA's view:
The applicant's explanation about the use of pimitespib in combination with substrates of CYP3A, MATE1, and MATE2-K is generally acceptable. However, no clinical studies have been conducted to evaluate quantitatively the effects of pimitespib on the PK of substrates of CYP3A, MATE1, and MATE2-K. Furthermore, the earlier-mentioned sensitivity analysis using the PBPK model indicates to what extent concomitant pimitespib will increase its exposure to substrates of CYP3A, MATE1, and MATE2-K remains unclear at present. The applicant should therefore consider conducting a clinical study to evaluate the effects of pimitespib on the PK of substrates of CYP3A, MATE1, and MATE2-K, and take appropriate measures including updating healthcare professionals with new findings related to pharmacokinetic interactions of pimitespib mediated by CYP3A, MATE1, and MATE2-K.

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

The applicant submitted efficacy and safety evaluation data in the form of results from a total of 5 studies including 2 Japanese phase I studies, 1 Japanese phase II study, 1 Japanese phase III study, and 1 global phase I study presented in Table 15. The applicant also submitted results from a foreign phase I study presented in Table 15 as reference data.

Table 15. List of clinical studies for efficacy and safety

Data category	Region	Study ID	Phase	Study population	Number of enrollments	Dosage regimen	Major endpoints
Evaluation	Japan	Study 040	I	Patients with advanced solid tumor	30 (a) 13 (b) 17	(a) Cohort I (for comparison of formulations) PK evaluation period: A single dose of pimitespib 160 mg (4 × 40-mg tablets or 3× 50-mg tablets and 1 × 10-mg tablet) is orally administered in the fasted state. Continuous treatment period: Pimitespib 160 mg is orally administered in the fasted state QD for 5 days followed by a 2-day rest, and this 7-day regimen is repeated. (b) Cohort II (for food effect) PK evaluation period: A single dose of pimitespib 160 mg is orally administered in the fasted state or after a meal. Continuous treatment period: Pimitespib 160 mg is orally administered in the fasted state QD for 5 days followed by a 2-day rest, and this 7-day regimen is repeated.	PK
		Study 050	I	Patients with advanced solid tumor	25	Cardiovascular safety evaluation period: A single dose of the placebo is orally administered in the fasted state on Day 1, then pimitespib 160 mg is orally administered in the fasted state QD on Days 2 to 6. Continuous treatment period: Pimitespib 160 mg is orally administered in the fasted state QD for 5 days followed by a 2-day rest, and this 7-day regimen is repeated.	PK
		Study 020	II	Patients with unresectable or metastatic advanced GIST progressing after treatment with imatinib, sunitinib, and regorafenib	41	Pimitespib 160 mg is orally administered in the fasted state QD for 5 days followed by a 2-day rest, and this 7-day regimen is repeated.	Efficacy Safety
		Study 030	III	Patients with unresectable or metastatic advanced GIST progressing after treatment with imatinib, sunitinib, and regorafenib	86 (a) 58 (b) 28	(a) Pimitespib 160 mg or (b) the placebo is orally administered in the fasted state QD for 5 days followed by a 2-day rest, and this 7-day regimen is repeated.	Efficacy Safety
	Global	Study 010	I	Patients with advanced solid tumor	61 (a) 16 (b) 19 (c) 20 (d) 6	(a) Step 1 (Dose Escalation Phase): Pimitespib 4.8 to 150.5 mg/m^2 is orally administered in the fasted state QD daily. (b) Step 1 (Expansion Phase): Pimitespib 160 mg is orally administered in the fasted state QD for 5 days followed by a 2-day rest, and this 7-day regimen is repeated. (c) Step 2 (Dose Escalation Phase): Pimitespib 107.5 to 295.0 mg/m^2 is orally administered in the fasted state every other day. (d) Step 2 (Expansion Phase): Pimitespib 340 mg is orally administered in the fasted state every other day.	Safety Tolerability PK
Reference	Foreign		I	(a) Patients with inoperable or recurrent HER2-positive breast cancer (b) Patients with unresectable advanced or recurrent *EGFR* mutation-positive NSCLC progressing after treatment with osimertinib (c) Patients with unresectable advanced or recurrent *ALK* fusion gene-positive NSCLC progressing after the first-line treatment with alectinib or treatment with ≥2 ALK inhibitors	32 (a) 12 (b) 18 (c) 2	Pimitespib 160 mg is orally administered in the fasted state QD for 5 days followed by a 2-day rest, and this 7-day regimen is repeated.	Efficacy Safety Tolerability

Each clinical study is summarized below.

The main adverse events other than death observed in each clinical study are described in Section "7.3 Adverse events, etc. observed in clinical studies" and results of clinical PK studies in Sections "6.1 Summary of biopharmaceutic studies and associated analytical methods" and "6.2 Clinical pharmacology."

7.1 Evaluation data

7.1.1 Clinical pharmacology

The applicant submitted results of 2 clinical pharmacology studies in patients with advanced solid tumors, as described below, [see Section 6.2]. No deaths occurred during the study drug treatment or within 10 days after the end of the treatment in the evaluation phases for PK and cardiovascular safety in these studies. After these periods, 1 patient in Study 050 died of depressed level of consciousness, for which a causal relationship to pimitespib was ruled out.

7.1.1.1 Japanese phase I study (CTD 5.3.1.1.1 and 5.3.1.2.1, Study 040 [ongoing since January 2019 (data cut-off on [redacted])])

7.1.1.2 Japanese phase I study (CTD 5.3.4.2.1, Study 050 [ongoing since [redacted] (data cut-off on [redacted])])

7.1.2 Japanese clinical studies

7.1.2.1 Japanese phase II study (CTD 5.3.5.2.1, Study 020 [ongoing since May 2016 (efficacy data cut-off on June 9, 2017, safety data cut-off on [redacted])])

An open-label, uncontrolled study was conducted to evaluate the efficacy and safety of pimitespib in patients with unresectable or metastatic advanced GIST progressing after treatment with imatinib, sunitinib, and regorafenib[35] (target sample size, 40 subjects) at 5 study centers in Japan.

Pimitespib 160 mg was orally administered in the fasted state QD for 5 days followed by a 2-day rest, and this 7-day regimen was repeated until disease progression or criteria for treatment discontinuation were met.

Of 41 patients enrolled in the study, 40 patients were included in the efficacy and safety analysis populations excluding 1 patient who did not receive pimitespib.

The primary endpoint of the study was PFS assessed by the independent review committee (IRC) as per Response Evaluation Criteria in Solid Tumors (RECIST) ver.1.1. The primary analysis was performed when an imaging examination at Week 6 of treatment was completed in the last enrolled patient.

The median PFS [95% CI] (months), the primary endpoint, was 4.4 [2.8, 6.0], and Kaplan-Meier curve is as presented in Figure 2 (data cut-off on June 9, 2017).

[35] Patients in whom progression as per RECIST, or clinical progression or intolerance to treatment with imatinib, sunitinib, and regorafenib was identified were included.

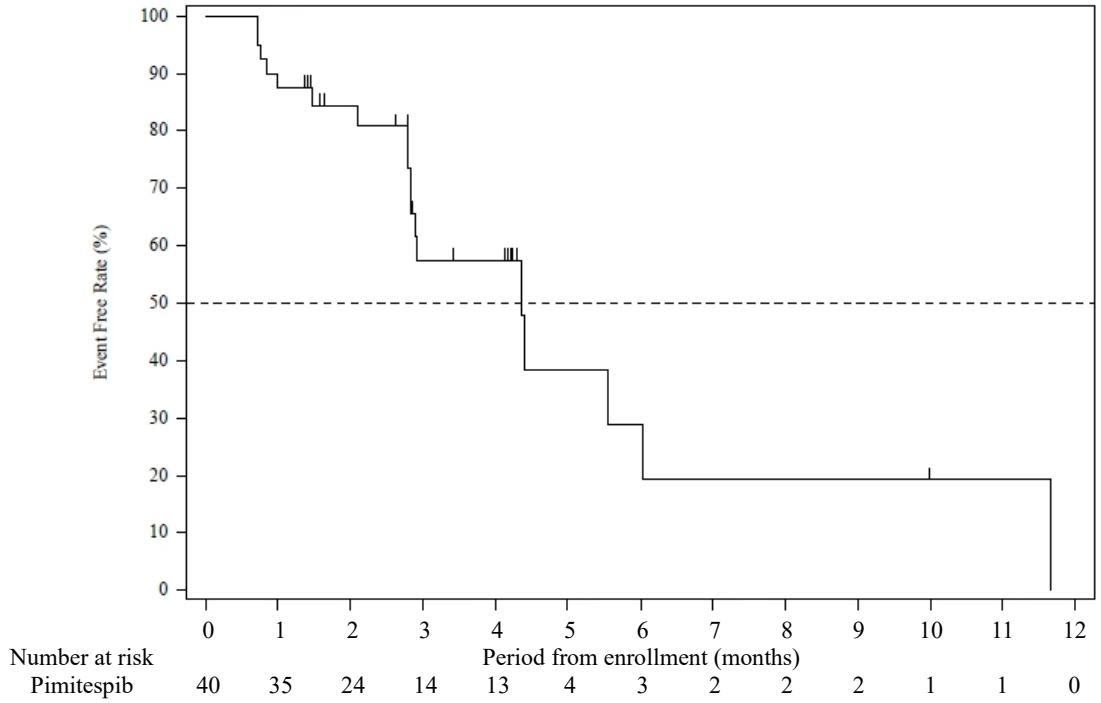


Figure 2. Kaplan-Meier curve of PFS at primary analysis
(Study 020, efficacy analysis population, IRC-assessed, data cut-off on June 9, 2017)

Death occurred in 4 of 40 patients (10.0%) during treatment with pimitespib or within 35 days after the end of the treatment. Causes of deaths, except for disease progression in 2 patients, were hepatic encephalopathy and unknown cause in 1 patient each, and a causal relationship to pimitespib was ruled out for both events.

7.1.2.2 Japanese phase III study (CTD 5.3.5.1.1, Study 030 [ongoing since October 2018 (data cut-off on June 23, 2020)])

A randomized, double-blind study was conducted to compare the efficacy and safety of pimitespib with those of the placebo in patients with unresectable or metastatic advanced GIST progressing after treatment with imatinib, sunitinib, and regorafenib[36] (target sample size, 81 subjects) at 6 study centers in Japan.

Pimitespib 160 mg or the placebo was orally administered in the fasted state QD for 5 days followed by a 2-day rest, and this 7-day regimen was repeated until disease progression or criteria for treatment discontinuation were met.

All 86 patients enrolled and randomized in the study (58 in the pimitespib group, 28 in the placebo group)[37] received the study drug and were included in the efficacy and safety analysis populations. Patients in the placebo group satisfying the criteria, such as progressive disease (PD) confirmed by assessment of the blinded independent central review (BICR) as per modified RECIST ver.1.1,[38] were

[36] Patients in whom progression as per RECIST, or clinical progression or intolerance to treatment with imatinib, sunitinib, and regorafenib was identified
[37] Patients were randomized to receive pimitespib or the placebo in the ratio of 2:1.
[38] The criteria included the following modifications from the original RECIST ver.1.1 made by reference to the criteria used in a global phase III study of regorafenib in patients with GIST, which were more specific to the characteristic of GIST (*Lancet.* 2013;381:295-302)
(a) Lymph nodes were chosen as non-target lesions.

allowed to switched to pimitespib. A total of 17 of 28 patients in the placebo group switched to pimitespib.

The primary endpoint in the study was PFS assessed by BICR as per the modified RECIST ver.1.1.[38)] The primary analysis was performed when 70 PFS events were observed in the pimitespib and placebo groups[39).]

Table 16 shows results of the primary analysis on PFS, the primary endpoint (data cut-off on June 23, 2020) and Figure 3 shows Kaplan-Meier curve, demonstrating the superiority of pimitespib to the placebo.

Table 16. Results of the primary analysis on PFS
(Study 030, efficacy analysis population, BICR-assessed, data cut-off on June 23, 2020)

	Pimitespib	Placebo
n	58	28
Number of events (%)	46 (79.3)	27 (96.4)
Median [95% CI] (months)	2.8 [1.6, 2.9]	1.4 [0.9, 1.8]
Hazard ratio [95% CI]*1	0.51 [0.30, 0.87]	
P value*2	0.006	

*1 Stratified Cox proportional hazards model using the number of prior treatments (3 or ≥4) and age (<65 years or ≥65 years) as stratification factors

*2 Stratified log-rank test (using similar stratification factors as that in the Cox proportional hazards model) with the significance level (one-sided) of 0.025

(b) A new tumor nodule within a pre-existing tumor mass was assessed as a new lesion when the following criteria were met; (i) the lesion was ≥2 cm in size and enhanced by contrast in dynamic computed tomography (CT), and (ii) the lesion was identified in ≥2 consecutive tumor imaging examinations separated by a ≥21 day interval.

39) According to the procedures defined in the first version of the protocol (dated [redacted], 20[redacted]), a blinded review was performed before data fixing to examine sufficiency of the stratification factor specified at baseline (number of prior treatments, 3 or ≥4). Of possible factors examined (sex [male or female], age [<65 years or ≥65 years], ECOG PS [0 or 1], the primary lesion [small intestine, stomach, or others], hepatic metastasis [with or without], and peritoneal metastasis [withs or without]), age (<65 years or ≥65 years) which provided the largest hazard ratio for PFS was added as a stratification factor (Version [redacted] of the protocol, dated [redacted], 20[redacted]).

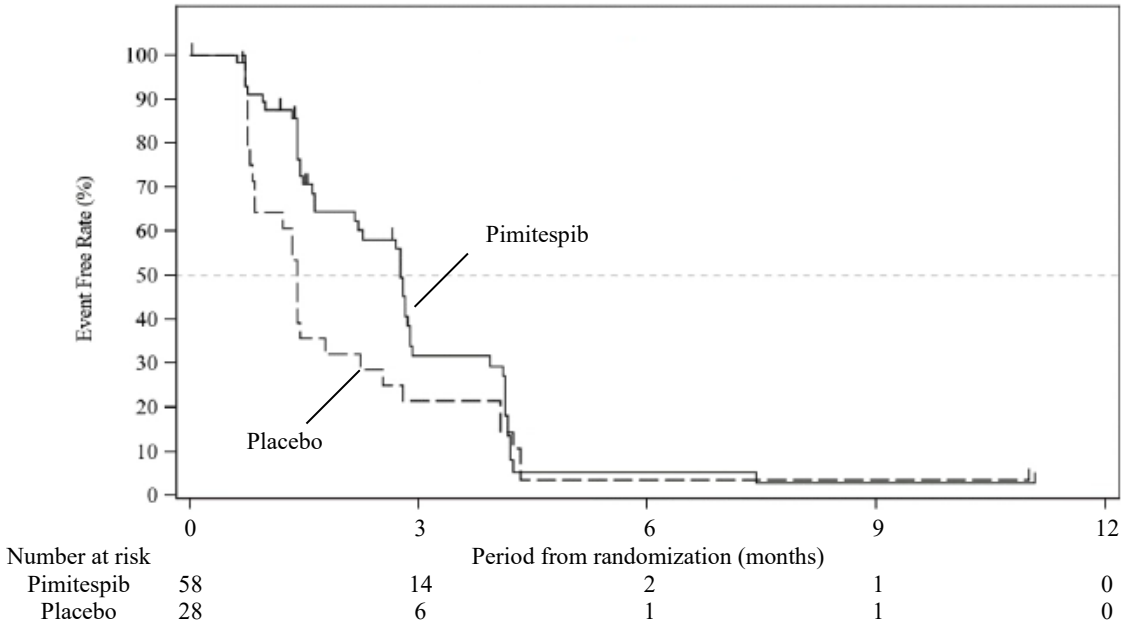


Figure 3. Kaplan-Meier curve of PFS at primary analysis
(Study 030, efficacy analysis population, BICR-assessed, data cut-off on June 23, 2020)

Death occurred in 4 of 58 patients (6.9%) in the pimitespib group and in 1 of 28 patients (3.6%) in the placebo group during treatment with the study drug or within 35 days after end of the treatment. All deaths were caused by disease progression.

7.1.3 Global study

7.1.3.1 Global phase I study (CTD 5.3.3.2.1, Study 010 [Dose Escalation Phase, Expansion Phase], March 2014 to [redacted])

An open-label, uncontrolled study was conducted in patients with advanced solid tumors (maximum target sample size, 150 subjects) to investigate the safety, tolerability, PK, etc. of pimitespib at 5 study centers in 2 countries including Japan.

The regimens used in the study were as follows:

(a) Dose Escalation Phase of Step 1: Pimitespib 4.8, 9.6, 19.2, 38.4, 76.8, 107.5, or 150.5 mg/m^2 was orally administered in the fasted state QD daily.
(b) Expansion Phase of Step 1: Pimitespib 160 mg[40)] was orally administered in the fasted state QD for 5 days followed by a 2-day rest, and this 7-day regimen ("160 mg on QD 5-day on/2-day off treatment") was repeated.
(c) Dose Escalation Phase of Step 2: Pimitespib 107.5, 150.5, 210.7, or 295.0 mg/m^2 was orally administered in the fasted state every other day.
(d) Expansion Phase of Step 2: Pimitespib 340 mg[40)] was orally administered in the fasted state every other day.

[40)] The Dose Escalation Phases of Step 1 and Step 2 identified no correlation between the oral clearance and body surface area. This fixed doses of 160 mg and 340 mg were selected for Expansion Phases of Step 1 and Step 2 by the following process according to the FDA Guidance (Guidance for Industry: Estimating the Maximum Safe Starting Dose in Initial Clinical Trials for Therapeutics in Adult Healthy Volunteers. U.S. Department of Health and Human Services, Food and Drug Administration. July 2005): 107.5 mg/m^2 and 210.7 mg/m^2, determined as MTDs of pimitespib in the continuous and alternate-day regimens, were multiplied by 1.62 m^2, which is equivalent to the body surface area of an adult weighing 60 kg, and rounded in view of dosing convenience.

The treatment was continued until disease progression or criteria for treatment discontinuation were met.

All 61 patients with advanced solid tumors enrolled in the study[41] (16 in the Dose Escalation Phase of Step 1, 19 in the Expansion Phase of Step 1, 20 in the Dose Escalation Phase of Step 2, 6 in the Expansion Phase of Step 2) received pimitespib and were included in the safety analysis population (of these, 55 were Japanese [16, 13, 20, 6]).

In the Dose Escalation Phase of Step 1 and Step 2, dose limiting toxicity (DLT) was evaluated until 21 days after the first dose of pimitespib. In the Dose Escalation Phase of Step 1, DLT was observed in 1 of 6 patients at 107.5 mg/m^2 (Grade 2 decreased appetite) and 3 of 3 patients at 150.5 mg/m^2 (Grade 3 night blindness, Grade 3 ALT increased/AST increased/γ-glutamyltransferase [GGT] increased, and Grade 3 visual impairment in 1 patient each). The maximum tolerated dose (MTD) of pimitespib in the continuous regimen was thus determined as 107.5 mg/m^2 QD.[42] In the Dose Escalation Phase of Step 2, DLT was observed in 2 of 5 patients at 295.0 mg/m^2 (Grade 3 platelet count decreased and Grade 3 febrile neutropenia/Grade 4 pneumonia/Grade 4 respiratory failure/Grade 4 septic shock in 1 patient each). The MTD of pimitespib in the alternate-day regimen was determined as 210.7 mg/m^2.[43]

In the Expansion Phase of Step 1 (160 mg QD 5-day on/2-day off regimen), the incidence of Grade ≥3 adverse events was higher in patients on the 160 mg QD 5-day on/2-day off regimen than that at MTD (107.5 mg/m^2 QD continuous regimen) in the Dose Escalation Phase of Step 1,[44] but incidences of adverse events leading to treatment discontinuation (1 of 19 patients [5.3%] on the 160 mg QD 5-day on/2-day off regimen, 3 of 6 patients [50.0%] on the 107.5 mg/m^2 QD continuous regimen) and eye disorder (6 of 19 patients [31.6%], 5 of 6 patients [83.3%]) were lower in patients on the 160 mg QD 5-day on/2-day off regimen. Based on the above, the 160 mg QD 5-day on/2-day off regimen was considered tolerable.

No death occurred in the Dose Escalation Phase of Step 1, while 1 of 19 patients (5.3%) in the Expansion Phase of Step 1, 1 of 20 patients (5.0%) in the Dose Escalation Phase of Step 2, and 1 of 6 patients (16.7%) in the Expansion Phase of Step 2 died during treatment with pimitespib or within 28 days after the end of treatment. All deaths were caused by disease progression.

7.2 Reference data

41) The types of cancers of study participants included lung cancer in 23 patients, GIST in 7 patients, pancreatic cancer in 5 patients, biliary cancer in 4 patients, stomach and gastroesophageal junction cancer in 2 patients, breast cancer in 2 patients, and other cancers in 18 patients

42) For the Expansion Phase of Step 1, a 7-day regimen comprising treatment with pimitespib for 5 days and subsequent rest for 2 days was selected based on the following findings at the MTD of pimitespib (107.5 mg/m^2 QD) in the Dose Escalation Phase of Step 1: (i) The relative dose intensity was low (52.38%); (ii) adverse events leading to treatment discontinuation occurred in 3 of 6 patients; and (iii) eye disorders occurred in 5 of 6 patients but resolved during a rest period, and pimitespib was considered to be eliminated from the retina in 2 days of a rest period based on the PK of pimitespib.

43) In the Expansion Phase of Step 2, tolerability was evaluated by comparing findings at MTD (210.7 mg/m^2 alternate-day) in the Dose Escalation Phase of Step 2. The incidences of adverse events did not differ between the 340 mg and 210.7 mg/m^2 alternate-day regimens, and the incidence of adverse events such as eye disorders was lower at 340 mg (0 of 6 patients [0%]) than at 210.7 mg/m^2 (1 of 6 patients [16.7%]). The 340 mg alternate-day regimen was thus considered tolerable.

44) In the Expansion Phase of Step 1 (160 mg QD 5-day on/2-day off regimen) and at MTD (107.5 mg/m^2 QD) in the Dose Escalation Phase of Step 1, all-grade adverse events occurred in 19 of 19 patients (100%) and 6 of 6 patients (100%), respectively, Grade 2 adverse events occurred in 7 of 19 patients (36.8%) and 4 of 6 patients (66.7%), respectively, and Grade ≥3 adverse events occurred in 10 of 19 patients (52.6%) and 2 of 6 patients (33.3%).

7.2.1 Foreign study

7.2.1.1 Foreign phase I study (CTD 5.3.3.2.2, Study 010 [Indication Extension Phase], July 2017 to May 2019)

An open-label, uncontrolled study was conducted to evaluate the safety of pimitespib in (a) patients with inoperable or recurrent HER2-positive breast cancer, (b) patients with unresectable advanced or recurrent *EGFR* mutation-positive NSCLC progressing after treatment with osimertinib mesilate (osimertinib),[45)] or (c) patients with unresectable advanced or recurrent *anaplastic lymphoma kinase* (*ALK)* fusion gene-positive NSCLC progressing after the first-line treatment with alectinib hydrochloride (alectinib) or treatment with ≥2 ALK inhibitors[45)] (maximum target sample size, 100 subjects) at 11 study centers overseas.

Pimitespib 160 mg was orally administered in the fasted state QD for 5 days followed by a 2-day rest, and this 7-day regimen was repeated until disease progression or criteria for treatment discontinuation were met.

Of 32 patients enrolled in the study, 31 patients were included in the safety analysis population excluding 1 patient who did not receive pimitespib ([a] 12, [b] 17, [c] 2).

Death occurred in 3 of 31 patients (9.7%) during treatment with pimitespib or within 30 days after end of the treatment. The causes of deaths were respiratory failure, dyspnea, and post procedural complication in 1 patient each, and a causal relationship to pimitespib was ruled out for all events.

7.R Outline of the review conducted by PMDA

7.R.1 Data for review

PMDA determined that, among the evaluation data submitted, the pivotal study for the evaluation of efficacy and safety of pimitespib was the Japanese phase III study (Study 030) in patients with unresectable or metastatic advanced GIST progressing after treatment with imatinib, sunitinib, and regorafenib, and decided to evaluate the submitted data focusing on this study.

7.R.2 Efficacy

Based on the following review, PMDA concluded that pimitespib had been demonstrated to have the efficacy in patients with unresectable or metastatic advanced GIST progressing after treatment with imatinib, sunitinib, and regorafenib.

7.R.2.1 Control group

The applicant's explanation about the reason for using the placebo as the control in Study 030:
When Study 030 was planned, no standard treatment was recommended for patients with unresectable or metastatic advanced GIST progressing after treatment with imatinib, sunitinib, and regorafenib in the National Comprehensive Cancer Network Clinical Practice Guidelines in Oncology, Soft Tissue Sarcoma (NCCN guidelines for soft tissue sarcoma) (v.2.2018), and thus the placebo was planned to be used as the control.

[45)] Patients in whom progression as per RECIST, or clinical progression or intolerance to prior treatment was identified were included.

PMDA accepted the applicant's explanation.

7.R.2.2 Efficacy endpoints

The applicant's explanation about the appropriateness of PFS as the primary endpoint in Study 030 selected as per modified RECIST ver.1.1:

(a) The metastasis of GIST into lymph nodes is reported to be extremely rare (*Ann Surg.* 1993:217:72-7), and the judgment on the diagnosis can be biased by assessors owning to its difficulty. (b) It had been pointed out that the original RECIST does not adequately serve to assess disease progression associated with a progressive nodal lesion newly emerging within a pre-existing tumor mass in the patients with unresectable or metastatic advanced GIST (*Radiology.* 2005;235:892-8). For these reasons, cytoreductive effect was decided to be assessed on non-lymph node lesions and according to the modified RECIST ver.1.1, which defines criteria for the assessment of newly emerging tumor nodes within a pre-existing tumor mass. In the patient population of Study 030, prolonged PFS leads to prolonged duration to disease progression or recurrence, and is expected to delay the onset of clinical symptoms associated with disease progression, which is clinically meaningful and justifies the primary endpoint of PFS.

PMDA's view:

In Study 030, patients were treated with an expectation of prolonged survival, and thus the primary endpoint of Study 030 should have been OS. Nevertheless, the applicant's explanation about the reason for using modified RECIST ver.1.1 in the assessment of PFS and the clinical significance of the prolonged PFS in the patient population is understandable. The efficacy of pimitespib may be evaluated based on PFS as per modified RECIST ver.1.1, specified as the primary endpoint, while OS results in Study 030 are also checked.

7.R.2.3 Efficacy evaluation results

In Study 030, results on the primary endpoint, i.e., PFS assessed by BICR as per the modified RECIST ver.1.1, demonstrated superiority of pimitespib to the placebo [see Section 7.1.2.2]. Table 17 shows analysis results on OS, the secondary endpoint, at the time of the primary analysis on PFS (data cut-off on June 23, 2020). Figure 4 shows the Kaplan-Meier curve.

Table 17. Analysis results on OS (Study 030, efficacy analysis population, data cut-off on June 23, 2020)

	Pimitespib		Placebo
n	58		28
Number of events (%)	23 (39.7)		15 (53.6)
Median [95% CI] (months)	13.8 [9.2, -]		9.6 [5.5, -]
Hazard ratio [95% CI]*[1]		0.63 [0.32, 1.21]	
P value*[2]		0.081	

-, Not estimable; *[1] Non-stratified Cox proportional hazards model; *[2] Log-rank test

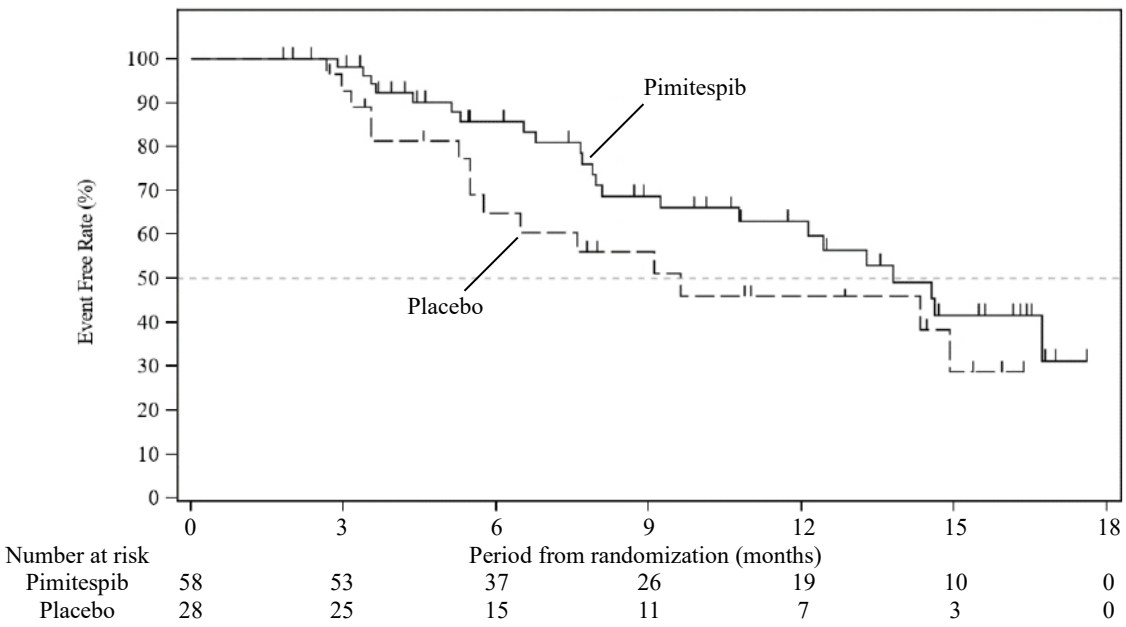


Figure 4. Kaplan-Meier curve of OS
(Study 030, efficacy analysis population, data cut-off on June 23, 2020)

The applicant's explanation about the efficacy of pimitespib in patients with unresectable or metastatic advanced GIST progressing after treatment with imatinib, sunitinib, and regorafenib:

In view of the following clinical study data, conventional treatments extremely rarely contribute to PFS prolongation in patients with unresectable or metastatic advanced GIST progressing after treatment with imatinib, sunitinib, and regorafenib. The prolonged PFS achieved in Study 030 is therefore considered clinically meaningful.

- In a foreign phase III study in patients with unresectable or metastatic advanced GIST progressing after treatment with imatinib and sunitinib conducted to compare the efficacy and safety of re-administered imatinib with those of the placebo, the median PFS [95% CI] (months) was 1.8 [1.7, 3.6] and 0.9 [0.9, 1.7], respectively (*Lancet Oncol.* 2013;14:1175-82).
- In a foreign phase III study in patients with unresectable or metastatic advanced GIST progressing after treatment with imatinib, sunitinib, and regorafenib to compare the efficacy and safety of ripretinib (unapproved in Japan) with those of the best supportive care (BSC), the median PFS [95% CI] (months) of BSC was 1.0 [0.9, 1.7] (*Lancet Oncol.* 2020;21:923-34).

Sensitivity analyses were performed using the following adjustment factors to investigate a potential impact on the PFS and OS results of the distribution imbalance in prognostic factors between the dose groups. None of the sensitivity analyses presented any clearly different trend from that of the primary analysis results.

- Factors with a greater hazard ratio for PFS (number of prior treatments [3 or ≥4], age [<65 or ≥65], hepatic metastasis [with or without], and peritoneal metastasis [with or without]) than that of the stratification factor (number of prior treatments [3 or ≥4]) specified at baseline
- Factors showing a distribution imbalance in between pimitespib and placebo (prior adjuvant therapy [with or without] and other prior treatments [with or without])
- Factors with a potential impact on the prognosis of GIST (primary organ [small intestine or the other organs] and tumor size [below or above median])

The applicant's explanation about the efficacy of pimitespib used as the fourth-line treatment in patients with unresectable or metastatic GIST:

Approximately 80%, 10%, and 2% of GIST cases have been found to have activating mutations in *KIT* gene (exons 9 and 11), *PDGFRA* gene (D842V, etc.), and *B-Raf proto-oncogene, serine/threonine kinase (BRAF)* gene, respectively, which contribute to tumor growth (*Lancet.* 2007;369:1731-41, etc.). KIT, PDGFRα, and BRAF are client proteins of HSP90 (*Nat Rev Cancer.* 2011;11:865-78). The *KIT* gene mutation (in exons 13, 14, 17, and 18) has been found to be a resistance mutation to imatinib, while the *KIT* gene mutation (in exons 17 and 18) to be a resistance mutation to sunitinib (*Expert Opin Pharmacother.* 2014;15:1979-89). Pimitespib is expected to inhibit the formation of the HSP90-mediated high-order structure of client proteins, enhancing the destabilization and degradation of them. This mechanism leads to decreased expression of the proteins involved in tumor growth and enhances apoptosis induction, and thereby suppresses tumor growth. Pimitespib is thus shown to have cytoreductive effects on tumors derived from human GIST cell line with resistant mutations to imatinib and sunitinib [see Section 3.R.1].

With the above-mentioned tumor biological background, in Study 30, the efficacy of pimitespib was analyzed by gene mutation, targeting activating mutations in *KIT* gene, *PDGFRA* gene, and *BRAF* gene frequently detected in GIST, as well as resistant mutations to imatinib, sunitinib, or regorafenib (*J Clin Oncol.* 2008;26:5360-7, *Clin Cancer Res.* 2012;18:4458-64, etc.). Hazard ratios [95% CI] of pimitespib to the placebo for PFS in the patient population with any of the activating mutations were 0.60 [0.31, 1.16] for blood specimens (31 patients in the pimitespib group, 15 patients in the placebo group) and 0.17 [0.04, 0.65] for tumor tissue specimens[46] (13 patients in the pimitespib group, 5 patients in the placebo group). Hazard ratios [95% CI] in the patient population with any of the resistant mutations were 0.52 [0.26, 1.07] for blood specimens (24 patients in the pimitespib group, 14 patients in the placebo group) and <0.01 [<0.01, -] for tumor tissue specimens (3 patients in the pimitespib group, 1 patient in the placebo group). Pimitespib showed a prolonging trend of PFS in both patient populations. Based on the action mechanism of pimitespib, the non-clinical study data, and the results of this investigation, albeit exploratory, pimitespib has promising efficacy in patients with unresectable or metastatic GIST, including those with resistant mutations to imatinib, sunitinib, or regorafenib. In populations of the patients found to be free from the gene mutations analyzed (mutations in *KIT* gene [in exons 9, 11, 13, 14, 17, and 18], *PDGFRA* gene [in exon 18 and D842V[47]], and *BRAF* gene), the hazard ratio [95% CI] of pimitespib to the placebo for PFS was 0.94 [0.39, 2.28] with blood specimens (18 patients in the pimitespib group, 9 patients in the placebo group) and 1.40 [0.38, 5.14] with tumor tissue specimens[48] (11 patients in the pimitespib group, 4 patients in the placebo group). It is, however, difficult to draw a definitive conclusion on the efficacy of pimitespib based on the investigation in the limited number of patients. These results do not rule out the efficacy of pimitespib in patients free from the activating or resistant mutations analyzed in this study.

---

46) Because the tumor tissue specimens were not analyzed for *BRAF* gene, the analysis targeted the population of patients who were found to have the activating mutation of either *KIT* gene or *PDGFRA* gene.
47) Mutation substituting aspartic acid at position 842 with valine
48) Because the tumor tissue specimens were not analyzed for *BRAF* gene, the analysis targeted the population of patients who were found not to have a mutation of *KIT* gene or *PDGFRA* gene.

In view of the investigation results and the above-mentioned PFS and OS results in the overall population in Study 030, pimitespib is shown to have the efficacy in patients with unresectable or metastatic advanced GIST progressing after treatment with imatinib, sunitinib, and regorafenib.

PMDA's view:
The efficacy of pimitespib was demonstrated in the patient population of Study 030 for the following reasons.

- In Study 030, results of PFS demonstrated the superiority of pimitespib to the placebo. The standard treatment has not been established for patients with unresectable or metastatic advanced GIST progressing after treatment with imatinib, sunitinib, and regorafenib. In view of this, the applicant's explanation about clinical significance of the prolonged PFS achieved in Study 030 is understandable to a certain extent.
- In Study 030, OS as the secondary endpoint, was tended to be prolonged by pimitespib as compared with the placebo.
- The investigation in the limited number of patients allow for limited discussion, but in view of the action mechanism of pimitespib, non-clinical study data, as well as results of the investigation in the populations of patients with and without gene mutations, the applicant's explanation about pimitespib's promising efficacy in patients with GIST carrying resistant mutations to imatinib, sunitinib, or regorafenib is understandable.

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

PMDA's view:
The following review has revealed that adverse events including diarrhoea, eye disorder, haemorrhage, and renal disorder warrant vigilance in treatment with pimitespib. Attention should be paid to these possible adverse events in the use of pimitespib.

Although the above-mentioned adverse events require attention during treatment, pimitespib will be tolerable when appropriate measures, such as monitoring and controlling of adverse events and interruption or dose reduction of pimitespib, are taken by physicians with adequate knowledge and experience of cancer chemotherapy.

7.R.3.1 Safety profile of pimitespib

The applicant's explanation about the safety profile of pimitespib based on the safety data obtained from Studies 030 and 020:
Table 18 shows the outline of the safety profiles in Studies 030 and 020. For Study 030, adverse events in the placebo group include only events observed during the placebo treatment. Adverse events observed in patients in the placebo group who switched to pimitespib due to disease progression were separately collected as such.

Table 18. Outline of safety profile (Studies 030 and 020)

	Number of patients (%)			
	Study 030			Study 020
	Pimitespib n = 58	Placebo n = 28	Pimitespib (Switch) n = 17	Pimitespib n = 40
All adverse events	56 (96.6)	22 (78.6)	15 (88.2)	40 (100)
Grade ≥3 adverse events	25 (43.1)	8 (28.6)	8 (47.1)	24 (60.0)
Adverse events resulting in death	1 (1.7)	0	0	2 (5.0)
Serious adverse events	16 (27.6)	5 (17.9)	5 (29.4)	14 (35.0)
Adverse events leading to treatment discontinuation	4 (6.9)	2 (7.1)	0	0
Adverse events leading to treatment interruption	39 (67.2)	9 (32.1)	8 (47.1)	34 (85.0)
Adverse events leading to dose reduction	21 (36.2)	1 (3.6)	6 (35.3)	20 (50.0)

In Study 030, all-grade adverse events occurring at a ≥10% higher incidence in the pimitespib group than in the placebo group were diarrhoea (43 patients [74.1%] in the pimitespib group, 5 patients [17.9%] in the placebo group), decreased appetite (21 patients [36.2%], 4 patients [14.3%]), malaise (18 patients [31.0%], 5 patients [17.9%]), blood creatinine increased (15 patients [25.9%], 3 patients [10.7%]), renal dysfunction (10 patients [17.2%], 0 patients), tumour pain (8 patients [13.8%], 1 patient [3.6%]), and night blindness (8 patients [13.8%], 0 patients). Grade ≥3 adverse events occurring at a ≥3% higher incidence in the pimitespib group than in the placebo group were diarrhoea (8 patients [13.8%], 0 patients), decreased appetite (4 patients [6.9%], 0 patients), tumour haemorrhage (3 patients [5.2%], 0 patients), malaise (2 patients [3.4%], 0 patients), and renal dysfunction (2 patients [3.4%], 0 patients). Serious adverse events occurring at a ≥3% higher incidence in the pimitespib group than in the placebo group were decreased appetite (3 patients [5.2%], 0 patients) and tumour haemorrhage (3 patients [5.2%], 0 patients). Adverse events leading to treatment interruption occurring at a ≥3% higher incidence in the pimitespib group than in the placebo group were diarrhoea (15 patients [25.9%], 0 patients), blood creatinine increased (5 patients [8.6%], 0 patients), anaemia (4 patients [6.9%], 1 patient [3.6%]), nausea (4 patients [6.9%], 0 patients), malaise (4 patients [6.9%], 0 patients), pyrexia (3 patients [5.2%], 0 patients), AST increased (3 patients [5.2%], 0 patients), gastrointestinal haemorrhage (2 patients [3.4%], 0 patients), influenza like illness (2 patients [3.4%], 0 patients), pneumonia (2 patients [3.4%], 0 patients), ALT increased (2 patients [3.4%], 0 patients), blood ALP increased (2 patients [3.4%], 0 patients), and hyperglycaemia (2 patients [3.4%], 0 patients). Adverse events leading to dose reduction occurring at a ≥3% higher incidence in the pimitespib group than in the placebo group were diarrhoea (7 patients [12.1%], 0 patients), decreased appetite (3 patients [5.2%], 0 patients), renal dysfunction (3 patients [5.2%], 0 patients), and malaise (2 patients [3.4%], 0 patients). There were neither adverse events resulting in death nor those leading to treatment discontinuation occurring at a ≥3% higher incidence in the pimitespib group than in the placebo group.

In Study 030, all-grade adverse events with an incidence of ≥10% in patients switching to pimitespib were diarrhoea in 11 patients (64.7%), nausea and decreased appetite in 6 patients (35.3%) each, malaise and blood creatinine increased in 5 patients (29.4%) each, anaemia and dysgeusia in 3 patients (17.6%) each, blood bilirubin increased and tumour pain in 2 patients (11.8%) each. Grade ≥3 adverse events reported in ≥2 patients switching to pimitespib were diarrhoea (4 patients, 23.5%) and anaemia (2 patients, 11.8%). The adverse event leading to treatment interruption reported in ≥2 patients switching to pimitespib was diarrhoea (5 patients, 29.4%). Adverse events leading to dose reduction reported in ≥2 patients switching to pimitespib were diarrhoea and nausea (2 patients, 11.8% each). There were no

adverse events resulting in death, serious adverse events or adverse events leading to treatment discontinuation reported in ≥2 patients switching to pimitespib.

In Study 020, all-grade adverse events with an incidence of ≥10% were diarrhoea in 34 patients (85.0%), decreased appetite in 20 patients (50.0%), nausea in 19 patients (47.5%), blood creatinine increased in 18 patients (45.0%), blood ALP increased in 13 patients (32.5%), ALT increased in 12 patients (30.0%), AST increased in 11 patients (27.5%), anaemia in 9 patients (22.5%), malaise, pyrexia, GGT increased, and tumour pain in 6 patients (15.0%) each, abdominal pain, vomiting, cystitis, neutrophil count decreased, platelet count decreased, dehydration, proteins urine, dysphonia, and rash in 5 patients (12.5%) each, and night blindness, vision blurred, constipation, fatigue, nasopharyngitis, and blood albumin decreased in 4 patients (10.0%) each. Grade ≥3 adverse events with an incidence of ≥5% were diarrhoea in 9 patients (22.5%), anaemia and decreased appetite in 6 patients (15.0%) each, and nausea, blood albumin decreased, lymphocyte count decreased, neutrophil count decreased, platelet count decreased, blood ALP increased, and tumour pain in 2 patients (5.0%) each. Serious adverse events with an incidence of ≥5% were decreased appetite in 4 patients (10.0%), and diarrhoea and tumour pain in 2 patients (5.0%) each. Adverse events leading to treatment interruption with an incidence of ≥5% were diarrhoea in 18 patients (45.0%), decreased appetite in 7 patients (17.5%), nausea and blood creatinine increased in 6 patients (15.0%) each, ALT increased in 4 patients (10.0%), anaemia, malaise, and AST increased in 3 patients (7.5%) each, and fatigue, pyrexia, cystitis, neutrophil count decreased, platelet count decreased, blood ALP increased, and dehydration in 2 patients (5.0%) each. Adverse events leading to dose reduction with an incidence of ≥5% were diarrhoea in 12 patients (30.0%), decreased appetite in 7 patients (17.5%), nausea in 6 patients (15.0%), malaise in 4 patients (10.0%), and blood creatinine increased in patients 2 (5.0%). There were neither adverse events resulting in death nor those leading to treatment discontinuation with an incidence of ≥5%.

PMDA's view:
Observed adverse events with a high incidence, Grade ≥3 adverse events, and serious adverse events in the pimitespib group in Study 030 and in Study 020 are likely to occur in the use of pimitespib and thus require careful attention in view of their association with pimitespib. Many of these events, however, were controllable by the interruption or dose reduction of pimitespib. With this taken into account, pimitespib will be tolerable when appropriate measures, such as adverse event monitoring and control and dose interruption or reduction of pimitespib, are taken by physicians with adequate knowledge and experience of cancer chemotherapy. Given extremely limited safety information of pimitespib in patients with GIST, the applicant should therefore continue collecting relevant information in post-marketing settings and promptly update healthcare professionals with new findings.

In the following sections, PMDA reviewed results on the safety in Studies 030 and 020 with the focus on adverse events with a higher incidence in the pimitespib group than in the placebo group in Study 030 and those with a high incidence in the clinical studies of the other HSP90 inhibitors.

7.R.3.2 Diarrhoea

The applicant's explanation about diarrhoea associated with pimitespib:
Adverse events classified into "Diarrhoea," a preferred term (PT) in the Medical Dictionary for Regulatory Activities (MedDRA), were tabulated as adverse events of diarrhoea.

Table 19 shows incidences of diarrhoea in Studies 030 and 020.

Table 19. Incidences of diarrhoea (Studies 030 and 020)

PT*	Number of patients (%)							
	Study 030						Study 020	
	Pimitespib n = 58		Placebo n = 28		Pimitespib (Switch) n = 17		Pimitespib n = 40	
	All Grades	Grade ≥3	All Grades	Grade ≥3	All Grades	Grade ≥3	All Grades	Grade ≥3
Diarrhoea	43 (74.1)	8 (13.8)	5 (17.9)	0	11 (64.7)	4 (23.5)	34 (85.0)	9 (22.5)
Diarrhoea	43 (74.1)	8 (13.8)	5 (17.9)	0	11 (64.7)	4 (23.5)	34 (85.0)	9 (22.5)

* MedDRA ver.23.0 in Study 030 and MedDRA ver.22.0 in Study 020

In Study 030, serious diarrhoea occurred in 1 of 58 patients (1.7%) in the pimitespib group but did not occur in the placebo group or in patients switching to pimitespib. A causal relationship to pimitespib could not be ruled out for the event in 1 patient in the pimitespib group. Diarrhoea leading to treatment interruption occurred in 15 of 58 patients (25.9%) in the pimitespib group and 5 of 17 patients switching to pimitespib (29.4%) but did not occur in the placebo group. Diarrhoea leading to dose reduction occurred in 7 of 58 patients (12.1%) in the pimitespib group and 2 of 17 patients switching to pimitespib (11.8%) but did not occur in the placebo group. No diarrhoea resulting in death or leading to treatment discontinuation occurred.

In Study 020, serious diarrhoea occurred in 2 of 40 patients (5.0%), and a causal relationship to pimitespib could not be ruled out in both patients. Diarrhoea leading to treatment interruption occurred in 18 of 40 patients (45.0%). Diarrhoea leading to dose reduction occurred in 12 of 40 patients (30.0%). No diarrhoea resulting in death or leading to treatment discontinuation occurred.

The median time to the first onset of diarrhoea (minimum, maximum) was 3 days (2, 89) in the pimitespib group, 31 days (12, 55) in the placebo group, and 2 days (2, 13) in patients switching to pimitespib in Study 030, and 3 days (2, 109) in Study 020.

Table 20 shows details of the patients with serious diarrhoea associated with pimitespib (causally related to pimitespib) in the clinical studies of pimitespib including studies other than the above-mentioned.

Table 20. List of patients with serious diarrhoea (causally related to pimitespib)

Study ID	Sex	Age	Dose*1 (mg)	PT*2	Grade	Time to onset (Day)	Duration (days)	Measure on pimitespib	Outcome
Study 030	Female	8[redacted]	160	Diarrhoea	3	18	9	Dose reduction, interruption	Recovered
Study 020	Male	3[redacted]	160	Diarrhoea	3	2	12	Dose reduction, interruption	Recovered
	Male	7[redacted]	160	Diarrhoea	3	2	52	Dose reduction, interruption	Not recovered
Study 050	Male	7[redacted]	160	Diarrhoea	2	2	7	None	Recovered

*1 Pimitespib is orally administered in the fasted state QD for 5 days followed by a 2-day rest, and this 7-day regimen is repeated.
*2 MedDRA ver.23.0 in Study 030, MedDRA ver.22.0 in Study 020, and MedDRA ver.23.0 in Study 050

PMDA's view:

Data of clinical studies submitted show a certain incidence of diarrhoea including that of Grade ≥3 in patients receiving pimitespib and the occurrence serious diarrhoea for which a causal relationship to pimitespib could be ruled out, indicating that the use of pimitespib warrants attention to diarrhoea. The occurrence of diarrhoea and measures taken in the clinical studies should be communicated appropriately to healthcare professionals via the package insert.

7.R.3.3 Eye disorders

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

Adverse events classified into MedDRA system organ class (SOC) of "Eye disorders" were tabulated as adverse events of eye disorders.

Table 21 shows incidences of eye disorders in Studies 030 and 020.

Table 21. Incidences of eye disorders (Studies 030 and 020)

PT*1	Number of patients (%)							
	Study 030						Study 020	
	Pimitespib n = 58		Placebo n = 28		Pimitespib (Switch) n = 17		Pimitespib n = 40	
	All Grades	Grade ≥3	All Grades	Grade ≥3	All Grades	Grade ≥3	All Grades	Grade ≥3
Eye disorders*2	17 (29.3)	0	0	0	1 (5.9)	0	9 (22.5)	0
Night blindness	8 (13.8)	0	0	0	1 (5.9)	0	4 (10.0)	0
Vision blurred	4 (6.9)	0	0	0	0	0	4 (10.0)	0
Visual impairment	4 (6.9)	0	0	0	0	0	1 (2.5)	0
Eye disorder	3 (5.2)	0	0	0	0	0	0	0
Conjunctival haemorrhage	1 (1.7)	0	0	0	0	0	0	0
Conjunctivitis allergic	1 (1.7)	0	0	0	0	0	0	0
Retinal vein occlusion	1 (1.7)	0	0	0	0	0	0	0
Retinopathy	1 (1.7)	0	0	0	0	0	0	0
Visual acuity reduced	1 (1.7)	0	0	0	0	0	0	0
Colour blindness acquired	0	0	0	0	1 (5.9)	0	0	0
Punctate keratitis	0	0	0	0	0	0	1 (2.5)	0

*1 MedDRA ver.23.0 in Study 030 and MedDRA ver.22.0 in Study 020
*2 All events to be tabulated

In Study 030, an eye disorder leading to treatment discontinuation occurred in 1 of 58 patients (1.7%, retinal vein occlusion in 1 patient) in the pimitespib group but did not occur in the placebo group or in patients switching to pimitespib. Eye disorders leading to treatment interruption occurred in 4 of 58 patients (6.9%; retinal vein occlusion, retinopathy, vision blurred, and visual impairment in 1 patient each) in the pimitespib group but did not occur in the placebo group or in patients switching to pimitespib.

Eye disorders leading to dose reduction occurred in 3 of 58 patients (5.2%; retinopathy, vision blurred, and visual impairment in 1 patient each) in the pimitespib group but did not occur in the placebo group or in patients switching to pimitespib. No eye disorder resulting in death or serious eye disorder occurred.

In Study 020, an eye disorder leading to treatment interruption occurred in 1 of 40 patients (2.5%; vision blurred in 1 patient). No eye disorder resulting in death or serious eye disorder, or eye disorder leading to treatment discontinuation or dose reduction occurred.

The median time to the first onset of eye disorder (minimum, maximum) was 18 days (5, 127) in the pimitespib group and 95 days (95, 95) in patients switching to pimitespib in Study 030, and 36 days (10, 336) in Study 020.

Table 22 shows details of the patient with a serious eye disorder associated with pimitespib (causally related to pimitespib) in clinical studies of pimitespib including those other than the above.

Table 22. List of patients with serious eye disorder (causally related to pimitespib)

Study ID	Sex	Age	Dose (mg)	PT*2	Grade	Time to onset (Day)	Duration (Day)	Measure on pimitespib	Outcome
Study 010	Female	6[redacted]	252*1	Visual impairment	3	4	341	Interruption, dose reduction	Recovering

*1 Pimitespib is orally administered in the fasted state QD without rest.
*2 MedDRA ver.20.1 in Study 010

PMDA asked the applicant to explain the mechanism of how eye disorders develop in patients receiving pimitespib and risk factors.

The applicant's response:
An HSP90 inhibitor induced apoptosis in the retinal external granular layer in non-clinical studies (*Toxicol Appl Pharmacol.* 2013;273:401-9, etc.). Eye disorders frequently occurred in the clinical studies of other HSP90 inhibitors (*Ann Oncol.* 2012;23 Suppl 9: ix152-74, etc.). Pimitespib has been reported to be less distributed in the retina than other HSP90 inhibitors (*Mol Cancer Ther.* 2015;14:14-22), and no abnormalities such as retinal disorders were observed in the repeated-dose toxicity studies [see Section 5.2]. Nevertheless, the occurrence of pimitespib in the clinical studies suggests the need for attention to eye disorders during treatment with pimitespib. In the clinical studies of pimitespib, eye disorders mostly resolved or were resolving after treatment interruption or dose reduction. Eye disorders in patients receiving pimitespib are considered reversible, but no predictive factors for pimitespib-associated eye disorders have been identified.

PMDA's view:
Data of clinical studies submitted show that eye disorders occurred in patients receiving pimitespib at certain percentages, and a causal relationship to pimitespib could not be ruled out for some serious eye disorders. In this view, treatment with pimitespib warrant attention to eye disorders. The occurrence of eye disorders and measures taken in the clinical studies should be communicated appropriately to healthcare professionals via the package insert to raise cautions.

7.R.3.4 Haemorrhage

The applicant's explanation about haemorrhage in patients receiving pimitespib:

Adverse events classified into the Standardised MedDRA Queries (SMQ) of "Haemorrhages (Narrow)," were tabulated as adverse events of haemorrhage.

Table 23 shows incidences of haemorrhage in Studies 030 and 020.

Table 23. Incidences of haemorrhage (Studies 030 and 020)

PT*1	Number of patients (%)							
	Study 030						Study 020	
	Pimitespib n = 58		Placebo n = 28		Pimitespib (Switch) n = 17		Pimitespib n = 40	
	All Grades	Grade ≥3	All Grades	Grade ≥3	All Grades	Grade ≥3	All Grades	Grade ≥3
Haemorrhages*2	12 (20.7)	7 (12.1)	1 (3.6)	1 (3.6)	4 (23.5)	1 (5.9)	6 (15.0)	2 (5.0)
Tumour haemorrhage	3 (5.2)	3 (5.2)	0	0	0	0	1 (2.5)	1 (2.5)
Gastrointestinal haemorrhage	2 (3.4)	2 (3.4)	1 (3.6)	1 (3.6)	0	0	0	0
Conjunctival haemorrhage	1 (1.7)	0	0	0	0	0	0	0
Duodenal ulcer haemorrhage	1 (1.7)	1 (1.7)	0	0	0	0	0	0
Haematoma	1 (1.7)	0	0	0	0	0	0	0
Blood urine present	1 (1.7)	0	0	0	0	0	0	0
Oesophageal varices haemorrhage	1 (1.7)	1 (1.7)	0	0	0	0	0	0
Anal haemorrhage	1 (1.7)	0	0	0	0	0	1 (2.5)	0
Contusion	1 (1.7)	0	0	0	0	0	0	0
Haemorrhoidal haemorrhage	1 (1.7)	0	0	0	1 (5.9)	0	0	0
Haematochezia	0	0	0	0	1 (5.9)	0	0	0
Haemorrhage subcutaneous	0	0	0	0	1 (5.9)	0	0	0
Haemorrhage	0	0	0	0	1 (5.9)	0	1 (2.5)	0
Intra-abdominal haemorrhage	0	0	0	0	1 (5.9)	1 (5.9)	0	0
Haematuria	0	0	0	0	0	0	2 (5.0)	1 (2.5)
Petechiae	0	0	0	0	0	0	1 (2.5)	0
Lower gastrointestinal haemorrhage	0	0	0	0	0	0	1 (2.5)	0

*1 MedDRA ver.23.0 in Study 030 and MedDRA ver.22.0 in Study 020
*2 All events to be tabulated

In Study 030, haemorrhage resulted in death in 1 of 58 patients (1.7%; tumour haemorrhage in 1 patient) in the pimitespib group but did not occur in the placebo group or in patients switching to pimitespib. A causal relationship to pimitespib was ruled out for the event in 1 patient in the pimitespib group. Serious haemorrhage occurred in 7 of 58 patients (12.1%; tumour haemorrhage in 3 patients, gastrointestinal haemorrhage in 2 patients, and duodenal ulcer haemorrhage and oesophageal varices haemorrhage in 1 patient each) in the pimitespib group, 1 of 28 patients (3.6%; gastrointestinal haemorrhage in 1 patient) in the placebo group, and 1 of 17 patients switching to pimitespib (5.9%; intra-abdominal haemorrhage in 1 patient). A causal relationship to pimitespib could not be ruled out for the events in 1 patient (duodenal ulcer haemorrhage) in the pimitespib group and 1 patient switching to pimitespib (intra-abdominal haemorrhage). Haemorrhage leading to treatment interruption occurred in 5 of 58 patients (8.6%; gastrointestinal haemorrhage in 2 patients and duodenal ulcer haemorrhage, oesophageal varices haemorrhage, and tumour haemorrhage in 1 patient each) in the pimitespib group and 1 of 17 patients switching to pimitespib (5.9%; haematochezia in 1 patient) but did not occur in the placebo group. Haemorrhage leading to dose reduction occurred in 1 of 58 patients (1.7%; duodenal ulcer haemorrhage in 1 patient) in the pimitespib group but did not occur in the placebo group or in patients switching to pimitespib. No haemorrhage leading to treatment discontinuation occurred.

In Study 020, serious haemorrhage occurred in 1 of 40 patients (2.5%; tumour haemorrhage in 1 patient), and a causal relationship to pimitespib was ruled out for the event. Haemorrhage leading to treatment interruption occurred in 2 of 40 patients (5.0%; haematuria and tumour haemorrhage in 1 patient each). Haemorrhage leading to dose reduction occurred in 1 of 40 patients (2.5%; haematuria in 1 patient). No haemorrhage resulting in death or leading to treatment discontinuation occurred.

The median time to the first onset of haemorrhage (minimum, maximum) was 39.5 days (8, 414) in the pimitespib group, 43 days (43, 43) in the placebo group, and 30.5 days (4, 99) in patients switching to pimitespib in Study 030, and 53 days (6, 72) in Study 020.

Table 24 shows details of the patients with serious haemorrhage while receiving pimitespib in the clinical studies including those other than the above-mentioned.

Table 24. List of patients with serious haemorrhage

Study ID	Sex	Age	Dose (mg)	PT*3	Grade	Time to onset (Day)	Duration (Day)	Measure on pimitespib	Causal relationship	Outcome
Study 030	Male	6[redacted]	160*1	Gastrointestinal haemorrhage	3	414	18	Interruption	Unrelated	Recovered
	Male	6[redacted]	160*1	Gastrointestinal haemorrhage	3	187	32	Interruption	Unrelated	Recovered
	Male	6[redacted]	160*1	Duodenal ulcer haemorrhage	3	27	57	Dose reduction, interruption	Related	Recovered
	Male	6[redacted]	160*1	Tumour haemorrhage	3	86	-	Interruption	Unrelated	Not recovered
	Female	8[redacted]	160*1	Tumour haemorrhage	5	206	-	Treatment discontinuation	Unrelated	Death
	Female	7[redacted]	160*1	Oesophageal varices haemorrhage	3	8	12	Interruption	Unrelated	Recovered
			160*1	Oesophageal varices haemorrhage	3	38	12	Interruption	Unrelated	Recovered
	Female	6[redacted]	160*1	Tumour haemorrhage	3	40	23	None	Unrelated	Recovered
	Male	5[redacted]	160*1	Intra-abdominal haemorrhage	3	131	16	None	Related	Recovered
Study 010	Male	4[redacted]	226*2	Gastrointestinal haemorrhage	3	12	2	Treatment discontinuation	Unrelated	Not recovered
	Male	6[redacted]	340*2	Upper gastrointestinal haemorrhage	3	17	2	Treatment discontinuation	Unrelated	Recovered

-, Unknown
*1 Pimitespib is orally administered in the fasted state QD for 5 days followed by a 2-day rest, and this 7-day regimen is repeated.
*2 Pimitespib is orally administered in the fasted state every other day.
*3 MedDRA ver.23.0 in Study 030 and MedDRA ver.20.1 in Study 010

PMDA asked the applicant to explain the mechanism of how pimitespib-associated haemorrhage develops and its risk factors.

The applicant's explanation:
Non-clinical studies suggested an association of haemorrhage with platelet count decreased and histological damage such as mucosal injuries. In the clinical studies, however, Grade ≥3 haemorrhage tended to occur more frequently in patients with age ≥65 years, PS 1, mild or moderate renal impairment,

mild hepatic impairment, and the primary lesion of the stomach.[49)] Patient predisposing factors such as primary disease may contribute to the development of haemorrhage. In addition, most of the haemorrhage events observed in the clinical studies were gastrointestinal haemorrhage. In these views, these events were possibly associated with their primary diseases, and a relationship to pimitespib is considered unknown.

PMDA's view:
According to the clinical study data submitted, there were serious haemorrhage for which a causal relationship to pimitespib could not be ruled, but they could be attributable to non-pimitespib-associated factors (patient predisposing factors such as primary disease). Special cautionary advice needs not be given against haemorrhage at the current stage on the premise that the occurrence of haemorrhage in the clinical studies is communicated through the package insert, relevant information is collected further in the post-marketing settings, and healthcare professionals are provided with updated safety information.

7.R.3.5 Renal disorders

The applicant's explanation about renal disorders associated with pimitespib:
Adverse events classified into MedDRA SMQs of "Acute renal failure (Broad)" and "Tubulointerstitial diseases (Narrow)," and the PT of "Beta 2 microglobulin urine increased" were tabulated as adverse events of renal disorders.

Table 25 shows incidences of renal disorders in Studies 030 and 020.

Table 25. Incidences of renal disorders (Studies 030 and 020)

PT*1	Number of patients (%)							
	Study 030						Study 020	
	Pimitespib n = 58		Placebo n = 28		Pimitespib (Switch) n = 17		Pimitespib n = 40	
	All Grades	Grade ≥3	All Grades	Grade ≥3	All Grades	Grade ≥3	All Grades	Grade ≥3
Renal disorders*2	28 (48.3)	2 (3.4)	4 (14.3)	0	6 (35.3)	0	22 (55.0)	0
Blood creatinine increased	15 (25.9)	0	3 (10.7)	0	5 (29.4)	0	18 (45.0)	0
Renal dysfunction	10 (17.2)	2 (3.4)	0	0	1 (5.9)	0	2 (5.0)	0
Proteinuria	4 (6.9)	0	1 (3.6)	0	1 (5.9)	0	5 (12.5)	0
Creatinine renal clearance decreased	0	0	0	0	0	0	1 (2.5)	0
Protein urine present	0	0	0	0	0	0	1 (2.5)	0

*1 MedDRA ver.23.0 in Study 030 and MedDRA ver.22.0 in Study 020
*2 All events to be tabulated

In Study 030, renal disorders leading to treatment interruption occurred in 7 of 58 patients (12.1%, blood creatinine increased in 5 patients, and renal dysfunction and proteinuria in 1 patient each) in the pimitespib group and in 1 of 17 patients switching to pimitespib (5.9%, blood creatinine increased in 1 patient) but did not occur in the placebo group. Renal disorders leading to dose reduction occurred in 4 of 58 patients (6.9%; renal dysfunction in 3 patients and blood creatinine increased in 1 patient) in the

[49)] A pooled analysis of Studies 010, 020, and 030 revealed that Grade ≥3 haemorrhage occurred in 5 of 75 patients aged <65 years (6.7%) and 5 of 44 patients aged ≥65 years (11.4%), 7 of 97 patients with PS 0 (7.2%) and 3 of 22 patients with PS 1 (13.6%), 1 of 45 patients with normal renal function (2.2%), 7 of 62 patients with mild renal impairment (11.3%), and 2 of 12 patients with moderate renal impairment (16.7%), 6 of 93 patients with normal hepatic function (6.5%) and 4 of 26 patients with mild hepatic impairment (15.4%), 4 of 65 patients with the primary lesion of the small intestine (6.2%), 5 of 39 patients with the primary lesion of the stomach (12.8%), and 1 of 11 patients with the primary lesion of the other tissues and organs (9.1%).

pimitespib group and 1 of 17 patients switching to pimitespib (5.9%; blood creatinine increased in 1 patient) but did not occur in the placebo group. No renal disorders resulting in death, serious renal disorders, or renal disorders leading to treatment discontinuation occurred.

In Study 020, renal disorders leading to treatment interruption occurred in 7 of 40 patients (17.5%, blood creatinine increased in 6 patients, and creatinine renal clearance decreased and renal dysfunction in 1 patient each [some patients experienced multiple events]). Renal disorders leading to dose reduction occurred in 2 of 40 patients (5.0%; blood creatinine increased in 2 patients). No renal disorders resulting in death, serious renal disorders, or renal disorders leading to treatment discontinuation occurred.

The median time to the first onset of renal disorders (minimum, maximum) was 5 days (4, 43) in the pimitespib group, 16.5 days (13, 229) in the placebo group, 5 days (4, 5) in patients switching to pimitespib in Study 030, and 5 days (5, 84) in Study 020.

Table 26 shows details of the patients with serious renal disorder associated with pimitespib (causally related to pimitespib) in clinical studies of pimitespib including those other than the above-mentioned.

Table 26. List of patients with serious renal disorders (causally related to pimitespib)

Study ID	Sex	Age	Dose*1 (mg)	PT*2	Grade	Time to onset (Day)	Duration (Day)	Measure on pimitespib	Outcome
Study 050	Male	7[redacted]	160	Acute kidney injury	2	2	5	None	Recovered

*1 Pimitespib is orally administered in the fasted state QD for 5 days followed by a 2-day rest, and this 7-day regimen is repeated.
*2 MedDRA ver.23.0 in Study 050

PMDA asked the applicant to explain the mechanism of how renal disorders develop in patients receiving pimitespib and their risk factors.

The applicant's explanation:
The findings from the non-clinical studies suggested the possibility that pimitespib may inhibit MATE1 and MATE2-K, which are involved in renal tubular secretion of creatinine [see Section 4.5.3]. Thus, pimitespib may increase blood creatinine; and most of the renal disorder events observed in the clinical studies were considered secondary to increased blood creatinine, diarrhoea, or anorexia attributable to the inhibitory effect of pimitespib against MATE1 and MATE2-K. In the clinical studies of pimitespib, the incidences of renal disorders tended to high in men aged ≥65 years, indicating that aging-associated decrease in physiological function may contribute to the development of renal disorders.

PMDA's view:
The data of clinical studies submitted show a serious renal disorder (acute kidney injury in 1 patient) for which a causal relationship to pimitespib could not be ruled out. The event was considered acute kidney injury secondary to diarrhoea. Many of renal disorders observed were Grade ≤2. In these views, renal disorder events are mostly controllable by the interruption or dose reduction of pimitespib and symptomatic treatment. In view of the high incidences of renal disorders in the clinical studies, however, the use of pimitespib warrant attention to renal disorders secondary to diarrhoea. The package insert should advise regular monitoring for symptoms such as dehydration during treatment with pimitespib.

7.R.3.6 Others

(a) Gastrointestinal ulcer and perforation

The applicant's explanation about gastrointestinal ulcer and perforation associated with pimitespib:
Adverse events classified into the MedDRA high level group term (HLGT) of "Gastrointestinal ulceration and perforation" were tabulated as adverse events of gastrointestinal ulcer and perforation.

Table 27 shows incidences of gastrointestinal ulcer and perforation in Studies 030 and 020.

Table 27. Incidences of gastrointestinal ulcer and perforation (Studies 030 and 020)

PT*1	Number of patients (%)							
	Study 030						Study 020	
	Pimitespib n = 58		Placebo n = 28		Pimitespib (Switch) n = 17		Pimitespib n = 40	
	All Grades	Grade ≥3	All Grades	Grade ≥3	All Grades	Grade ≥3	All Grades	Grade ≥3
Gastrointestinal ulcer and perforation*2	2 (3.4)	2 (3.4)	0	0	0	0	1 (2.5)	0
Duodenal ulcer haemorrhage	1 (1.7)	1 (1.7)	0	0	0	0	0	0
Small intestinal perforation	1 (1.7)	1 (1.7)	0	0	0	0	0	0
Anal erosion	0	0	0	0	0	0	1 (2.5)	0

*1 MedDRA ver.23.0 in Study 030 and MedDRA ver.22.0 in Study 020
*2 All events to be tabulated

In Study 030, serious gastrointestinal ulcer and perforation occurred in 2 of 58 patients (3.4%; duodenal ulcer haemorrhage and small intestinal perforation in 1 patient each) in the pimitespib group but did not occur in the placebo group or in patients switching to pimitespib. A causal relationship to pimitespib could not be ruled out for duodenal ulcer haemorrhage in 1 patient in the pimitespib group. Gastrointestinal ulcer and perforation leading to treatment interruption occurred in 2 of 58 patients (3.4%; duodenal ulcer haemorrhage and small intestinal perforation in 1 patient each) in the pimitespib group but did not occur in the placebo group or in patients switching to pimitespib. Gastrointestinal ulcer and perforation leading to dose reduction occurred in 1 of 58 patients (1.7%; duodenal ulcer haemorrhage in 1 patient) in the pimitespib group but did not occur in the placebo group or in patients switching to pimitespib. No gastrointestinal ulcer and perforation resulting in death or leading to treatment discontinuation occurred.

In Study 020, no gastrointestinal ulcer and perforation resulting in death, serious gastrointestinal ulcer and perforation, or gastrointestinal ulcer and perforation leading to treatment discontinuation, interruption or dose reduction occurred.

The median time to the first onset of gastrointestinal ulcer and perforation (minimum, maximum) was 270.5 days (27, 514) in the pimitespib group in Study 030 and 53 days (53, 53) in Study 020.

Table 28 shows details of the patients with serious gastrointestinal ulcer and perforation associated with pimitespib (causally related to pimitespib) in the clinical studies of pimitespib including those other than the above-mentioned.

Table 28. List of patients with serious gastrointestinal ulcer and perforation (causally related to pimitespib)

Study ID	Sex	Age	Dose*1 (mg)	PT*2	Grade	Time to onset (Day)	Duration (Day)	Measure on pimitespib	Outcome
Study 030	Male	6[redacted]	160	Duodenal ulcer haemorrhage	3	27	57	Dose reduction, interruption	Recovered

*1 Pimitespib is orally administered in the fasted state QD for 5 days followed by a 2-day rest, and this 7-day regimen is repeated.
*2 MedDRA ver.23.0 in Study 030

PMDA asked the applicant to explain the mechanism of how gastrointestinal ulcer and perforation develop in patients receiving pimitespib.

The applicant's explanation:
A relationship to pimitespib is considered unknown because of no gastrointestinal ulcer or perforation-related findings from the non-clinical studies. Although gastrointestinal ulcer and perforation occurred in patients receiving pimitespib in the clinical studies, tumour peptic ulcer was reported as a complication of GIST (*J Clin Gastroenterol Treat*. 2019;5:071), indicating a possible involvement of patients' primary diseases or any other predisposing factors.

(b) Myelosuppression
The applicant's explanation about myelosuppression associated with pimitespib:
Adverse events classified into MedDRA SMQs of "Haematopoietic erythropenia (Broad)," "Haematopoietic leucopenia (Broad)," and "Haematopoietic thrombocytopenia (Broad)" were tabulated as adverse events of myelosuppression.

Table 29 shows incidences of myelosuppression in Studies 030 and 020.

Table 29. Incidences of myelosuppression (Studies 030 and 020)

PT*1	Number of patients (%)							
	Study 030						Study 020	
	Pimitespib n = 58		Placebo n = 28		Pimitespib (Switch) n = 17		Pimitespib n = 40	
	All Grades	Grade ≥3	All Grades	Grade ≥3	All Grades	Grade ≥3	All Grades	Grade ≥3
Myelosuppression*2	8 (13.8)	5 (8.6)	4 (14.3)	4 (14.3)	4 (23.5)	3 (17.6)	18 (45.0)	10 (25.0)
Anaemia	6 (10.3)	4 (6.9)	3 (10.7)	3 (10.7)	3 (17.6)	2 (11.8)	9 (22.5)	6 (15.0)
Lymphocyte count decreased	1 (1.7)	1 (1.7)	0	0	1 (5.9)	1 (5.9)	2 (5.0)	2 (5.0)
Platelet count decreased	1 (1.7)	0	0	0	1 (5.9)	0	5 (12.5)	2 (5.0)
Aplasia pure red cell	0	0	1 (3.6)	1 (3.6)	0	0	0	0
Neutrophil count decreased	0	0	0	0	0	0	5 (12.5)	2 (5.0)
White blood cell count decreased	0	0	0	0	0	0	2 (5.0)	1 (2.5)
Febrile neutropenia	0	0	0	0	0	0	1 (2.5)	1 (2.5)

*1 MedDRA ver.23.0 in Study 030 and MedDRA ver.22.0 in Study 020
*2 All events to be tabulated

In Study 030, serious myelosuppression did not occur in the pimitespib group but occurred in 1 of 28 patients (3.6%; aplasia pure red cell in 1 patient) in the placebo group and 1 of 17 patients switching to pimitespib (5.9%; anaemia in 1 patient). A causal relationship to pimitespib could not be ruled out for the event in 1 patient switching to pimitespib (anaemia in 1 patient). Myelosuppression leading to treatment interruption occurred in 4 of 58 patients (6.9%; anaemia in 4 patients) in the pimitespib group and 2 of 28

patients (7.1%; anaemia and aplasia pure red cell in 1 each) in the placebo group but did not occur in patients switching to pimitespib. Myelosuppression leading to dose reduction occurred in 1 of 58 patients (1.7%; anaemia in 1 patient) in the pimitespib group but did not occur in the placebo group or in patients switching to pimitespib. No myelosuppression resulting in death or leading to treatment discontinuation occurred.

In Study 020, serious myelosuppression occurred in 1 of 40 patients (2.5%; febrile neutropenia in 1 patient), and a causal relationship to pimitespib could not be ruled out for the event. Myelosuppression leading to treatment interruption occurred in 7 of 40 patients (17.5%; anaemia in 3 patients, neutrophil count decreased and platelet count decreased in 2 patients each, and febrile neutropenia and white blood cell count decreased in 1 patient each). Myelosuppression leading to dose reduction occurred in 1 of 40 patients (2.5%; anaemia in 1 patient). No myelosuppression resulting in death or leading to treatment discontinuation occurred.

The median time to the first onset of myelosuppression (minimum, maximum) was 73 days (15, 217) in the pimitespib group, 29.5 days (5, 110) in the placebo group, and 18 days (12, 29) in patients switching to pimitespib in Study 030, and 18.5 days (5, 694) in Study 020.

Table 30 shows details of the patients with serious myelosuppression associated with pimitespib (causally related to pimitespib) in the clinical studies of pimitespib including those other than the above-mentioned.

Table 30. List of patients with serious myelosuppression (causally related to pimitespib)

Study ID	Sex	Age	Dose (mg)	PT*3	Grade	Time to onset (Day)	Duration (Day)	Measure on pimitespib	Outcome
Study 030	Male	5[redacted]	160*1	Anaemia	3	77	-	Interruption	Not recovered
Study 020	Male	5[redacted]	160*1	Febrile neutropenia	3	78	8	Interruption	Recovered
Study 010	Male	7[redacted]	486*2	Neutrophil count decreased	4	14	3	None	Recovered
				Platelet count decreased	3	14	8	None	Recovered

-, Unknown
*1 Pimitespib is orally administered in the fasted state QD for 5 days followed by a 2-day rest, and this 7-day regimen is repeated.
*2 Pimitespib is orally administered in the fasted state every other day.
*3 MedDRA ver.23.0 in Study 030, MedDRA ver.22.0 in Study 020, and MedDRA ver.20.1 in Study 010

(c) Hepatic dysfunction

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

Adverse events classified into MedDRA SMQs of "Liver related investigations, signs and symptoms (Narrow and Broad)," "Cholestasis and jaundice of hepatic origin (Narrow and Broad)," "Hepatitis, non-infectious (Narrow and Broad)," "Hepatic failure, fibrosis and cirrhosis and other liver damage-related conditions (Narrow and Broad)," and "Liver-related coagulation and bleeding disturbances (Narrow)" were tabulated as adverse events of hepatic dysfunction.

Table 31 shows incidences of hepatic dysfunction in Studies 030 and 020.

Table 31. Incidences of hepatic dysfunction (Studies 030 and 020)

PT*1	Number of patients (%)							
	Study 030						Study 020	
	Pimitespib n = 58		Placebo n = 28		Pimitespib (Switch) n = 17		Pimitespib n = 40	
	All Grades	Grade ≥3	All Grades	Grade ≥3	All Grades	Grade ≥3	All Grades	Grade ≥3
Hepatic dysfunction*2	12 (20.7)	6 (10.3)	7 (25.0)	1 (3.6)	3 (17.6)	0	20 (50.0)	6 (15.0)
AST increased	5 (8.6)	1 (1.7)	1 (3.6)	0	1 (5.9)	0	11 (27.5)	0
ALT increased	4 (6.9)	1 (1.7)	1 (3.6)	0	1 (5.9)	0	12 (30.0)	1 (2.5)
Liver disorder	2 (3.4)	1 (1.7)	1 (3.6)	0	0	0	2 (5.0)	1 (2.5)
Blood bilirubin increased	2 (3.4)	0	1 (3.6)	0	2 (11.8)	0	3 (7.5)	0
Blood ALP increased	2 (3.4)	0	0	0	0	0	13 (32.5)	2 (5.0)
GGT increased	1 (1.7)	1 (1.7)	1 (3.6)	1 (3.6)	0	0	6 (15.0)	0
Hepatic function abnormal	1 (1.7)	1 (1.7)	1 (3.6)	0	1 (5.9)	0	2 (5.0)	1 (2.5)
Oesophageal varices haemorrhage	1 (1.7)	1 (1.7)	0	0	0	0	0	0
Hepatic enzyme increased	1 (1.7)	0	0	0	0	0	0	0
Hyperammonaemia	1 (1.7)	0	0	0	0	0	0	0
Ascites	1 (1.7)	0	0	0	0	0	0	0
Hypoalbuminaemia	0	0	4 (14.3)	1 (3.6)	1 (5.9)	0	0	0
Hepatic encephalopathy	0	0	1 (3.6)	0	0	0	1 (2.5)	1 (2.5)
International normalised ratio increased	0	0	0	0	0	0	1 (2.5)	0
Jaundice cholestatic	0	0	0	0	0	0	1 (2.5)	0

*1 MedDRA ver.23.0 in Study 030 and MedDRA ver.22.0 in Study 020
*2 All events to be tabulated

In Study 030, serious hepatic dysfunction occurred in 3 of 58 patients (5.2%; hepatic function abnormal, liver disorder, and oesophageal varices haemorrhage in 1 patient each) in the pimitespib group but did not occur in the placebo group or in patients switching to pimitespib. A causal relationship to pimitespib could not be ruled out for the events in 2 patients (hepatic function abnormal and liver disorder in 1 patient each) in the pimitespib group. Hepatic dysfunction leading to treatment discontinuation occurred in 1 of 58 patients (1.7%; liver disorder in 1 patient) in the pimitespib group and 1 of 28 patients (3.6%; hepatic encephalopathy in 1) in the placebo group but did not occur in patients switching to pimitespib. Hepatic dysfunction leading to treatment interruption occurred in 8 of 58 patients (13.8%; AST increased in 3 patients, ALT increased and blood ALP increased in 2 patients each, and blood bilirubin increased, GGT increased, hepatic function abnormal, liver disorder, oesophageal varices haemorrhage, and hepatic enzyme increased in 1 patient each [some patients experienced multiple events]) in the pimitespib group, 2 of 28 patients (7.1%; GGT increased and hepatic encephalopathy in 1 patient each) in the placebo group, and 2 of 17 patients switching to pimitespib (11.8%; ALT increased, AST increased, and blood bilirubin increased in 1 patient each [some patients experienced multiple events]). Hepatic dysfunction leading to dose reduction occurred in 3 of 58 patients (5.2%; blood bilirubin increased, hepatic function abnormal, and liver disorder in 1 patient each) in the pimitespib group, 1 of 28 patients (3.6%; ALT increased/AST increased in 1 patient) in the placebo group, and 1 of 17 patients switching to pimitespib (5.9%; ALT increased/AST increased in 1 patient). No hepatic dysfunction resulting in death occurred.

In Study 020, hepatic dysfunction resulted in death in 1 of 40 patients (2.5%; hepatic encephalopathy in 1 patient), and a causal relationship to pimitespib was ruled out for the event. Serious hepatic dysfunction occurred in 1 of 40 patients (2.5%; hepatic encephalopathy in 1 patient), and a causal relationship to pimitespib was ruled out for the event. Hepatic dysfunction leading to treatment interruption occurred in 7 of 40 patients (17.5%; ALT increased in 4 patients, AST increased in 3 patients, blood ALP increased in 2 patients, and blood bilirubin increased, hepatic function abnormal, and liver disorder in 1 patient each

[some patients experienced multiple events]). Hepatic dysfunction leading to dose reduction occurred in 3 of 40 patients (7.5%; ALT increased, international normalised ratio increased, and blood ALP increased in 1 patient each). No hepatic dysfunction leading to treatment discontinuation occurred.

The median time to the first onset of hepatic dysfunction (minimum, maximum) was 35.5 days (5, 274) in the pimitespib group, 33 days (5, 117) in the placebo group, and 5 days (4, 83) in patients switching to pimitespib in Study 030, and 11.5 days (3, 106) in Study 020.

Table 32 shows details of the patients with serious hepatic dysfunction associated with pimitespib (causally related to pimitespib) in the clinical studies of pimitespib including those other than the above-mentioned.

Table 32. List of patients with serious hepatic dysfunction (causally related to pimitespib)

Study ID	Sex	Age	Dose (mg)	PT*3	Grade	Time to onset (Day)	Duration (Day)	Measure on pimitespib	Outcome
Study 030	Male	7[redacted]	160*1	Hepatic function abnormal	3	5	Unknown	Dose reduction, interruption	Recovering
	Female	6[redacted]	160*1	Liver disorder	3	5	Unknown	Dose reduction, interruption, discontinuation	Recovering
Study 010	Male	5[redacted]	280*2	AST increased	3	22	24	Dose reduction, interruption	Recovered
				ALT increased	3	22	98	Dose reduction, interruption	Recovered
				GGT increased	3	22	101	Dose reduction, interruption	Recovered

*1 Pimitespib is orally administered in the fasted state QD for 5 days followed by a 2-day rest, and this 7-day regimen is repeated.
*2 Pimitespib is orally administered in the fasted state QD without rest.
*3 MedDRA ver.23.0 in Study 030 and MedDRA ver.20.1 in Study 010

(d) Gastrointestinal disorders (except diarrhoea and gastrointestinal ulcer and perforation)

The applicant's explanation about gastrointestinal disorders (except diarrhoea and gastrointestinal ulcer and perforation) associated with pimitespib:

Adverse events classified into the MedDRA SOC of "Gastrointestinal disorders," excluding those classified into the PT of "Diarrhoea" and the HLGT of "Gastrointestinal ulceration and perforation," were tabulated as adverse events of gastrointestinal disorders.

Table 33 shows incidences of gastrointestinal disorders reported by ≥2 patients in any group in Studies 030 and 020.

Table 33. Incidences of gastrointestinal disorders reported by ≥2 patients in any group (Studies 030 and 020)

PT*1	Number of patients (%)							
	Study 030						Study 020	
	Pimitespib n = 58		Placebo n = 28		Pimitespib (Switch) n = 17		Pimitespib n = 40	
	All Grades	Grade ≥3	All Grades	Grade ≥3	All Grades	Grade ≥3	All Grades	Grade ≥3
Gastrointestinal disorders*2	32 (55.2)	3 (5.2)	14 (50.0)	3 (10.7)	11 (64.7)	2 (11.8)	28 (70.0)	2 (5.0)
Nausea	16 (27.6)	0	5 (17.9)	0	6 (35.3)	0	19 (47.5)	2 (5.0)
Abdominal pain upper	3 (5.2)	0	2 (7.1)	0	1 (5.9)	1 (5.9)	2 (5.0)	0
Vomiting	3 (5.2)	0	2 (7.1)	0	1 (5.9)	0	5 (12.5)	0
Abdominal distension	2 (3.4)	0	3 (10.7)	1 (3.6)	0	0	0	0
Dyspepsia	2 (3.4)	0	0	0	1 (5.9)	0	0	0
Gastrointestinal haemorrhage	2 (3.4)	2 (3.4)	1 (3.6)	1 (3.6)	0	0	0	0
Stomatitis	2 (3.4)	0	0	0	0	0	3 (7.5)	0
Abdominal pain	1 (1.7)	0	3 (10.7)	1 (3.6)	0	0	5 (12.5)	0
Constipation	1 (1.7)	0	3 (10.7)	0	0	0	4 (10.0)	0
Dry mouth	1 (1.7)	0	0	0	0	0	2 (5.0)	0

*1 MedDRA ver.23.0 in Study 030 and MedDRA ver.22.0 in Study 020
*2 All events to be tabulated

In Study 030, serious gastrointestinal disorders occurred in 5 of 58 patients (8.6%, gastrointestinal haemorrhage in 2 patients, and abdominal distension, enterocolitis, and oesophageal varices haemorrhage in 1 patient each) in the pimitespib group, 3 of 28 patients (10.7%; abdominal distension, abdominal pain, and gastrointestinal haemorrhage in 1 patient each) in the placebo group, and 2 of 17 patients switching to pimitespib (11.8%; abdominal pain upper and intra-abdominal haemorrhage in 1 patient each). A causal relationship to pimitespib could not be ruled out for enterocolitis in 1 patient in the pimitespib group and intra-abdominal haemorrhage 1 patient switching to pimitespib. Gastrointestinal disorders leading to treatment interruption occurred in 10 of 58 patients (17.2%; nausea in 4 patients, gastrointestinal haemorrhage in 2 patients, and dyspepsia, enterocolitis, oesophageal varices haemorrhage, and vomiting in 1 patient each) in the pimitespib group, 1 of 28 patients (3.6%; abdominal pain in 1 patient) in the placebo group, and 1 of 17 patients switching to pimitespib (5.9%; haematochezia in 1 patient). Gastrointestinal disorders leading to dose reduction did not occur in the pimitespib group or placebo group but occurred in 2 of 17 patients switching to pimitespib (11.8%; nausea in 2 patients). No gastrointestinal disorder resulting in death or leading to treatment discontinuation occurred.

In Study 020, gastrointestinal disorders leading to treatment interruption occurred in 7 of 40 patients (17.5%; nausea in 6 patients, and abdominal discomfort and vomiting in 1 patient each [some patients experienced multiple events]). Gastrointestinal disorders leading to dose reduction occurred in 6 of 40 patients (15.0%; nausea in 6 patients). No gastrointestinal disorders resulting in death or serious gastrointestinal disorder, or gastrointestinal disorder leading to treatment discontinuation occurred.

The median time to the first onset of gastrointestinal disorder (minimum, maximum) was 9.5 days (2, 229) in the pimitespib group, 15.5 days (5, 201) in the placebo group, and 3 days (2, 99) in patients switching to pimitespib in Study 030, and 3 days (2, 67) in Study 020.

Table 34 shows details of the patients with serious gastrointestinal disorders associated with pimitespib (causally related to pimitespib) in clinical studies of pimitespib including those other than the above.

Table 34. List of patients with serious gastrointestinal disorder (causally related to pimitespib)

Study ID	Sex	Age	Dose*1 (mg)	PT*2	Grade	Time to onset (Day)	Duration (Day)	Measure on pimitespib	Outcome
Study 030	Male	6[redacted]	160	Enterocolitis	2	62	21	Interruption	Recovered
	Male	5[redacted]	160	Intra-abdominal haemorrhage	3	131	16	None	Recovered

*1 Pimitespib is orally administered in the fasted state QD for 5 days followed by a 2-day rest, and this 7-day regimen is repeated.
*2 MedDRA ver.23.0 in Study 030

PMDA's view:

The review of clinical study data submitted for the above (a) to (d) revealed the occurrence of serious events for which a causal relationship to pimitespib could not be ruled out, but in view of the following observation, special cautionary advice needs not be given against these events on the premise that the occurrence of these events in the clinical studies is communicated through the package insert, relevant information is further collected in the post-marketing settings, and healthcare professionals are provided with updated safety information.

- A limited number of patients experienced (a) gastrointestinal ulcer and perforation including serious events.
- The incidence of (b) myelosuppression did not tend to be clearly higher in the pimitespib group than in the placebo group.
- (c) Most cases of hepatic dysfunction were abnormal clinical laboratory values.
- Many of (d) gastrointestinal disorders (except diarrhoea and gastrointestinal ulcer and perforation) were at Grade ≤2.

7.R.4 Clinical positioning and indication

The proposed indication of pimitespib was "gastrointestinal stromal tumor that has progressed after cancer chemotherapy." The "Precautions Concerning Indication" section was proposed to present the following notes:

- Pimitespib should be used for patients who have been treated with imatinib, sunitinib, and regorafenib.
- The efficacy and safety of pimitespib have not been established for use in postoperative adjuvant chemotherapy.

As a result of the discussion in Sections "7.R.2 Efficacy," "7.R.3 Safety," and the following subsections, PMDA has concluded that the indication of pimitespib should be "gastrointestinal stromal tumor that has progressed after cancer chemotherapy," as proposed, with the following notes included in the "Precautions Concerning Indication" section to raise caution:

- Pimitespib should be used for patients who have been treated with imatinib, sunitinib, and regorafenib.
- The efficacy and safety of pimitespib have not been established for use in postoperative adjuvant therapy.

7.R.4.1 Clinical positioning and indication of pimitespib

Japanese and foreign clinical practice guidelines or representative textbooks on clinical oncology do not have descriptions about the use of pimitespib in patients with GIST.

The applicant's explanation about the clinical positioning and indication of pimitespib:
Study 030 in patients with unresectable or metastatic advanced GIST progressing after treatment with imatinib, sunitinib, and regorafenib demonstrated the clinical benefits of pimitespib [see Sections 7.R.2.2 and 7.R.2.3]. Pimitespib is therefore expected to be recognized as the first-line drug for this patient population. However, pimitespib is not recommended for patients with GIST who have not received imatinib, sunitinib, or regorafenib because of the lack of efficacy and safety data from the clinical studies. The use of pimitespib as postoperative adjuvant therapy is not recommended either because of the lack of efficacy and safety data from the clinical studies.

Based on the above, the proposed indication of pimitespib was specified as "gastrointestinal stromal tumor that has progressed after cancer chemotherapy" with the following cautionary notes included in the "Precautions Concerning Indication" section to raise caution:

- Pimitespib should be used for patients who have been treated with imatinib, sunitinib, and regorafenib.
- The efficacy and safety of pimitespib have not been established for use in postoperative adjuvant chemotherapy.

Accepting the above applicant's explanation, PMDA has concluded that the indication of pimitespib should be "gastrointestinal stromal tumor that has progressed after cancer chemotherapy," as proposed, with modified descriptions in the "Precautions Concerning Indication" section as follows.

- Pimitespib should be used for patients who have been treated with imatinib, sunitinib, and regorafenib.
- The efficacy and safety of pimitespib have not been established for use in postoperative adjuvant therapy.

7.R.5 Dosage and administration

The proposed dosage and administration of pimitespib was "the usual adult dosage is 160 mg of pimitespib administered orally once daily in the fasted state for 5 consecutive days. With a subsequent 2-day rest, this regimen is repeated in a 21-day cycle. The dose may be reduced according to the patient's condition." The following notes in the "Precautions Concerning Dosage and Administration" section were proposed:

- The efficacy and safety of pimitespib have not been established for use in combination with other antineoplastic agents.
- C_{max} and AUC of pimitespib increase when administered after meal. In order to avoid food effect, pimitespib should not be taken from 1 hour before until 2 hours after meal.
- Criteria for treatment interruption and dose reduction to manage adverse drug reactions

As a result of the discussion in Sections "6.R.1 Food effect," "7.R.2 Efficacy," "7.R.3 Safety," and the following subsection, PMDA has concluded that the dosage and administration of pimitespib should be "the usual adult dosage is 160 mg of pimitespib administered orally once daily in the fasted state for 5 consecutive days. With a subsequent 2-day rest, this regimen is repeated. The dose may be reduced according to the patient's condition" with the following cautionary notes presented in the "Precautions Concerning Dosage and Administration" section:

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

- C_{max} and AUC of pimitespib increase when administrated after meal. In order to avoid food effect, pimitespib should be taken from 1 hour before until 2 hours after meal.
- Criteria for treatment interruption and dose reduction to manage adverse drug reactions

7.R.5.1 Dosage and administration of pimitespib

The applicant's explanation about dosage and administration of pimitespib:

Study 030 was conducted using the dosage regimen specified based on study results summarized below, and it demonstrated the clinical benefits of pimitespib in patients with unresectable or metastatic advanced GIST progressing after treatment with imatinib, sunitinib, and regorafenib [see Sections 7.R.2 and 7.R.3]. Based on the dosage regimen in Study 030, the proposed dosage and administration of pimitespib was specified as "the usual adult dosage is 160 mg of pimitespib administered orally once daily in the fasted state for 5 consecutive days. With a subsequent 2-day rest, this regimen is repeated in a 21-day cycle. The dose may be reduced according to the patient's condition."

- Study 030 Expansion Phase of Step 1 employed the repetitive regimen with oral pimitespib 160 mg administered in the fasted state QD for 5 days followed by a 2-day rest, which was specified based on the results of Dose Escalation Phase of Step 1 in the global phase I study (Study 010) in patients with advanced solid tumors. The tolerability of the regimen was demonstrated. Furthermore, the Japanese phase II study (Study 020) in patients with GIST using the same regimen confirmed pimitespib's acceptable safety profile.

At present, clinical study results on the efficacy and safety of pimitespib concomitantly used with the other antineoplastic agents are not available, and thus concomitant use of pimitespib with the other antineoplastic agents is not recommended.

In addition, the Japanese phase I study (Study 040) investigating food effect on the PK of pimitespib suggested that pimitespib administered in the fed state would lead to greater exposure than that administered in the fasted state [see Section 6.1.2.1]. The Japanese phase III study (Study 030) in which pimitespib was administered "≥1 hour before or ≥2 hours after a meal" demonstrated the clinical benefits of pimitespib. The administration of pimitespib should be avoided from 1 hour before until 2 hours after meal.

Based on the above, the "Precautions Concerning Dosage and Administration" section will present the following cautionary notes:

- The efficacy and safety of pimitespib have not been established for use in combination with the other antineoplastic agents.
- C_{max} and AUC of pimitespib increase when administered after meal. In order to avoid food effect, pimitespib should not be taken from 1 hour before until 2 hours after meal.

PMDA's view:

The applicant's explanation is acceptable. The dosage and administration of pimitespib should be defined as "the usual adult dosage is 160 mg of pimitespib administered orally once daily in the fasted state for 5 consecutive days. With a subsequent 2-day rest, this regimen is repeated. The dose may be reduced

according to the patient's condition," with the following cautionary notes presented in the "Precautions Concerning Dosage and Administration" section.

- The efficacy and safety of pimitespib have not been established for use in combination with other antineoplastic agents.
- C_{max} and AUC of pimitespib increase when administered after meal. In order to avoid food effect, pimitespib should not be taken 1 hour before until 2 hours after meal.

7.R.5.2 Dose adjustment of pimitespib

The applicant's explanation about criteria for dose adjustment of pimitespib:

In Study 030, specific criteria for dose adjustment of pimitespib were presented, and clinical benefits of pimitespib was demonstrated when administered in accordance with the criteria. The proposed "Precautions Concerning Dosage and Administration" section therefore included the modified criteria for dose adjustment with the following changes made in the criteria in Study 030:

- In terms of diarrhoea, in Study 030, the dose adjustment criteria recommended treatment interruption after a Grade 3 event. However, diarrhoea frequently occurred in the clinical studies, with some cases requiring hospitalized management. For early treatment of diarrhoea, unmanageable and intolerable[50] Grade 2 events should be subjected to treatment interruption. In Study 030 criteria, after Grade 3 diarrhoea, pimitespib was once interrupted and resumed at a 1-level lower dose upon recovery to Grade ≤2 or at the same dose upon recovery to Grade ≤1. The modified criteria require resumption in a more cautious manner, i.e., pimitespib may be resumed at a 1-level reduced dose or the same dose after recovery to Grade ≤1.
- In Study 030, dose adjustment criteria for the management of bilirubin total, neutrophil count decreased, platelet count decreased, anaemia, and QT interval prolonged were specified. However, in the clinical studies, the incidences of these events were low. Furthermore, among those with GIST receiving pimitespib in the clinical studies, most patients resuming pimitespib after any of these Grade ≥2 events did not experience worsening of the events.[51] Given these, dose adjustment criteria will not be defined for these respective events.
- The following dose adjustment criteria for the management of other events (except diarrhoea and eye disorders) were provided in Study 030: Pimitespib should be resumed at a 1-level lower dose upon recovery to Grade 2 or at the same dose upon recovery to Grade ≤1. In consideration that pimitespib is expected to be used by physicians with adequate knowledge and experience in cancer chemotherapy, pimitespib may be resumed at the same dose upon recovery not only to Grade ≤1 but also to Grade 2 depending on the conditions of individual patients. Accordingly, the criteria will define that pimitespib be resumed at a 1-level lower dose or the same dose upon recovery to Grade 2 or ≤1.

PMDA's view:

The applicant's explanation is generally acceptable. The criteria for dose adjustment for other events (except diarrhoea and eye disorders) were defined in Study 030 as: Pimitespib should be resumed at a

[50] Unmanageable and intolerable Grade 2 diarrhoea may include (a) Grade 2 diarrhoea that is not abated by symptomatic treatment with antidiarrheal agents and thus is difficult to manage; (b) Grade 2 diarrhoea accompanied by adverse drug reactions secondary to diarrhoea such as dehydration; and (c) Grade 2 diarrhoea accompanied by other adverse drug reactions such as anorexia and malaise with a poor performance status.

[51] Of 119 patients with GIST who received pimitespib and were included in the pooled analysis of Studies 010, 020, and 030, pimitespib was administered to 2 patients with Grade ≥2 neutrophil count decreased (Grades 2 and 3 in 1 patient each), 8 patients with anaemia (Grade 2 in all), and 1 patient with QT interval prolonged (Grade 2) after onset of these events. These events did not worsen. In 1 patient, Grade 2 thrombocytopenia occurred but pimitespib was continued. The event worsened to Grade 3 before resolving after treatment interruption.

1-level lower dose upon recovery to Grade 2 or at the same dose upon recovery to Grade ≤1. In this view, it remains unknown whether resuming pimitespib at the same dose after recovery to Grade 2 is appropriate. In the "Precautions Concerning Dosage and Administration" section, the criteria for treatment interruption and dose reduction with pimitespib for adverse drug reaction management should be defined as follows.

- If any adverse drug reaction occurs, pimitespib should be interrupted or reduced in dose based on the following criteria according to symptoms and their severity.

Dose reduction

Reduced level	Dose
Usual dose	160 mg/day
1-level lower dose	120 mg/day
2-level lower dose	80 mg/day
3-level lower dose	40 mg/day

Criteria for interruption and dose reduction following adverse drug reactions

Adverse drug reaction	Severity*	Action
Diarrhoea	Grade 2	If unmanageable and intolerable, interrupt pimitespib until recovery to Grade ≤1. After recovery, pimitespib may be resumed at the same dose.
	Grade ≥3	Interrupt pimitespib until recovery to Grade ≤1. After recovery, pimitespib may be resumed at the 1-level lower dose or same dose.
Eye disorders	Grade ≥2	Interrupt pimitespib until recovery to Grade ≤1. After recovery, pimitespib may be resumed at the 1-level lower dose or same dose.
Adverse drug reactions other than the above	Grade ≥3	Interrupt pimitespib until recovery to Grade 2 or ≤1. Pimitespib may be resumed at a 1-level lower dose after recovery to Grade 2 or at the same dose after recovery to Grade ≤1.

* Graded according to NCI-Common Terminology Criteria for Adverse Events (CTCAE) ver.4.03.

7.R.6 Post-marketing investigations

The applicant's explanation about post-marketing investigation:

In order to investigate the safety of pimitespib in post marketing clinical use, the applicant planned to conduct post-marketing surveillance in all patients treated with pimitespib.

The safety specification of the surveillance includes the use of pimitespib in patients with hepatic impairment and patients with renal impairment, in view of the limited safety information in these population, in addition to diarrhoea and eye disorders, which warrant special attention during treatment based on the occurrence in the clinical studies (Studies 020 and 030),

The planned sample size and observation period for the surveillance are 100 patients and 15 weeks, respectively, in view of the occurrence of events in the clinical studies that are included in the above safety specification.

PMDA's view:

Because of the extremely limited safety information of pimitespib used in Japanese or non-Japanese patients, the post-marketing surveillance should be conducted for a certain period after market launch covering all patients treated with pimitespib, to collect the safety data promptly in an unbiased manner. Obtained safety information should be promptly provided to healthcare professionals.

The safety specification of the surveillance should include severe diarrhoea, eye disorders, and haemorrhage in view of the review in Section "7.R.3 Safety," and information including safety data of pimitespib used in patients with hepatic impairment and patients with renal impairment should be collected.

The planned sample size and observation period for the surveillance should be reconsidered in light of the above-mentioned events that are to be specified in the safety specification, with their occurrence in the clinical studies taken into account.

7.3 Adverse events, etc. observed in clinical studies

Deaths reported in the safety evaluation data were detailed in Sections "7.1 Evaluation data" and "7.2 Reference data." The following subsection summarize major adverse events other than deaths.

7.3.1 Japanese phase I study (Study 040)

In Cohort I, adverse events occurred in 5 of 13 patients (38.5%) receiving pimitespib (Formulation A) and 6 of 13 patients (46.2%) receiving pimitespib (Formulation B), and adverse events for which a causal relationship to pimitespib could not be ruled out occurred in 2 of 13 patients (15.4%) in Formulation A and 3 of 13 patients (23.1%) in Formulation B. Adverse events reported in ≥2 patients were diarrhoea (2 patients, 15.4%) in Formulation A and insomnia (2 patients, 15.4%) in Formulation B.

Neither serious adverse events nor adverse events leading to discontinuation of pimitespib occurred.

In Cohort II, adverse events occurred in 7 of 17 patients (41.2%) receiving pimitespib in the fasted state and 5 of 17 patients (29.4%) receiving pimitespib in the fed state, and adverse events for which a causal relationship to pimitespib could not be ruled out occurred in 3 of 17 patients (17.6%) and 4 of 17 patients (23.5%), respectively. Adverse events reported in ≥2 patients were diarrhoea (3 patients, 17.6%) and diarrhoea (5 patients, 29.4%), respectively.

Neither serious adverse events nor adverse events leading to discontinuation of pimitespib occurred.

7.3.2 Japanese phase I study (Study 050)

Adverse events occurred in 24 of 25 patients (96.0%), and a causal relationship to pimitespib could not be ruled out for events in 21 of 25 patients (84.0%). Adverse events reported in ≥2 patients were diarrhoea (18 patients, 72.0%), blood creatinine increased (10 patients, 40.0%), nausea and vomiting (5 patients, 20.0% each), decreased appetite (3 patients, 12.0%), and platelet count decreased and dehydration (2 patients, 8.0% each).

Serious adverse events occurred in 4 of 25 patients (16.0%). The observed serious adverse events were dehydration in 2 patients (8.0%), and diarrhoea, decreased appetite, depressed level of consciousness, and acute kidney injury in 1 patient (4.0%) each, and a causal relationship to pimitespib could not be ruled out for dehydration in 2 patients, and diarrhoea, decreased appetite, and acute kidney injury in 1 patient each.

Adverse events leading to discontinuation of pimitespib occurred in 2 of 25 patients (8.0%). These events were diarrhoea, dehydration, and decreased appetite in 1 patient (4.0%) each, and a causal relationship to pimitespib could not be ruled out for all events.

7.3.3 Japanese phase II study (Study 020)

Adverse events occurred in 40 of 40 patients (100%), and a causal relationship to pimitespib could not be ruled out for events in 40 of 40 patients (100%). Adverse events with an incidence of ≥15% were diarrhoea in 34 patients (85.0%), decreased appetite in 20 patients (50.0%), nausea in 19 patients (47.5%), blood creatinine increased in 18 patients (45.0%), blood ALP increased in 13 patients (32.5%), ALT increased in 12 patients (30.0%), AST increased in 11 patients (27.5%), anaemia in 9 patients (22.5%), and malaise, pyrexia, GGT increased, and tumour pain in 6 patients (15.0%) each.

Serious adverse events occurred in 14 of 40 patients (35.0%). Serious adverse events reported in ≥2 patients were decreased appetite (4 patients, 10.0%), and diarrhoea and tumour pain (2 patients, 5.0% each), and a causal relationship to pimitespib could not be ruled out for decreased appetite in 3 patients and diarrhoea in 2 patients.

No adverse events leading to discontinuation of pimitespib occurred.

7.3.4 Japanese phase III study (Study 030)

Adverse events occurred in 56 of 58 patients (96.6%) in the pimitespib group, 22 of 28 patients (78.6%) in the placebo group, and 15 of 17 patients switching to pimitespib (88.2%), and adverse events for which a causal relationship to the study drug could not be ruled out occurred in 54 of 58 patients (93.1%) in the pimitespib group, 11 of 28 patients (39.3%) in the placebo group and 15 of 17 patients switching to pimitespib (88.2%). Table 35 shows adverse events with an incidence of ≥15% in any group.

Table 35. Adverse events with an incidence of ≥15%

SOC PT (MedDRA ver.23.0)	Number of patients (%)					
	Pimitespib n = 58		Placebo n = 28		Pimitespib (Switch) n = 17	
	All Grades	Grade ≥3	All Grades	Grade ≥3	All Grades	Grade ≥3
All adverse events	56 (96.6)	25 (43.1)	22 (78.6)	8 (28.6)	15 (88.2)	8 (47.1)
Blood and lymphatic system disorders						
Anaemia	6 (10.3)	4 (6.9)	3 (10.7)	3 (10.7)	3 (17.6)	2 (11.8)
Gastrointestinal disorders						
Diarrhoea	43 (74.1)	8 (13.8)	5 (17.9)	0	11 (64.7)	4 (23.5)
Nausea	16 (27.6)	0	5 (17.9)	0	6 (35.3)	0
General disorders and administration site conditions						
Malaise	18 (31.0)	2 (3.4)	5 (17.9)	0	5 (29.4)	0
Investigations						
Blood creatinine increased	15 (25.9)	0	3 (10.7)	0	5 (29.4)	0
Metabolism and nutrition disorders						
Decreased appetite	21 (36.2)	4 (6.9)	4 (14.3)	0	6 (35.3)	0
Nervous system disorders						
Dysgeusia	3 (5.2)	0	0	0	3 (17.6)	0
Renal and urinary disorders						
Renal dysfunction	10 (17.2)	2 (3.4)	0	0	1 (5.9)	0

Serious adverse events occurred in 16 of 58 patients (27.6%) in the pimitespib group, 5 of 28 patients (17.9%) in the placebo group, and 5 of 17 patients switching to pimitespib (29.4%). Serious adverse events reported in ≥2 patients were decreased appetite and tumour haemorrhage (3 patients, 5.2% each) and gastrointestinal haemorrhage (2 patients, 3.4%) in the pimitespib group, and a causal relationship to the study drug could not be ruled out for decreased appetite in 1 patient.

Adverse events leading to discontinuation of the study drug occurred in 4 of 58 patients (6.9%) in the pimitespib group, 2 of 28 patients (7.1%) in the placebo group, and 0 of 17 patients switching to pimitespib. The observed events were retinal vein occlusion, malaise, liver disorder, and drug eruption in 1 patient each (1.7%) in the pimitespib group and peritonitis and hepatic encephalopathy in 1 patient (3.6%) each in the placebo group. A causal relationship to the study drug could not be ruled out for retinal vein occlusion, liver disorder, and drug eruption in 1 patient each in the pimitespib group.

7.3.5 Global phase I study (Study 010, Dose Escalation Phase and Expansion Phase)

In Dose Escalation Phase of Step 1, adverse events occurred in 1 of 1 patient (100%) in the pimitespib 4.8 mg/m^2 QD group, 0 of 1 patient in the pimitespib 9.6 mg/m^2 QD group, 1 of 1 patient (100%) in the pimitespib 19.2 mg/m^2 QD group, 1 of 1 patient (100%) in the pimitespib 38.4 mg/m^2 QD group, 3 of 3 patients (100%) in the pimitespib 76.8 mg/m^2 QD group, 6 of 6 patients (100%) in the pimitespib 107.5 mg/m^2 QD group, and 3 of 3 patients (100%) in the pimitespib 150.5 mg/m^2 QD group. Adverse events for which a causal relationship to pimitespib could not be ruled out occurred in 1 of 1 patient (100%) in the 4.8 mg/m^2 QD group, 0 of 1 patient in the 9.6 mg/m^2 QD group, 1 of 1 patient (100%) in the 19.2 mg/m^2 QD group, 1 of 1 patient (100%) in the 38.4 mg/m^2 QD group, 3 of 3 patients (100%) in the 76.8 mg/m^2 QD group, 6 of 6 patients (100%) in the 107.5 mg/m^2 QD group, and 3 of 3 patients (100%) in the 150.5 mg/m^2 QD group. Adverse events reported in ≥2 patients in each group were blood creatinine increased (3 patients, 100%), diarrhoea, ALT increased, AST increased, haemoglobinuria, and blood ALP increased (2 patients, 66.7% each) in the 76.8 mg/m^2 QD group, diarrhoea and decreased appetite (6 patients, 100% each), night blindness and blood creatinine increased (5 patients, 83.3% each),

nausea and weight decreased (4 patients, 66.7% each), fatigue, AST increased, electrocardiogram QT prolonged, and rash (3 patients, 50.0% each), vision blurred, stomatitis, vomiting, cystitis, ALT increased, platelet count decreased, blood phosphorus increased, blood ALP increased, and acneiform dermatitis (2 patients, 33.3% each) in the 107.5 mg/m^2 QD group, and diarrhoea and blood creatinine increased (3 patients, 100% each), and nausea, fatigue, AST increased, and decreased appetite (2 patients, 66.7% each) in the 150.5 mg/m^2 QD group.

Serious adverse events occurred in 0 of 1 patient in the 4.8, 9.6, 19.2, or 38.4 mg/m^2 group, 2 of 3 patients (66.7%) in the 76.8 mg/m^2 QD group, 1 of 6 patients (16.7%) in the 107.5 mg/m^2 QD group, and 2 of 3 patients (66.7%) in the 150.5 mg/m^2 QD group. The observed serious adverse events were pulmonary embolism and interstitial lung disease (ILD) in 1 patient (33.3%) each in the 76.8 mg/m^2 QD group, pulmonary oedema in 1 patient (16.7%) in the 107.5 mg/m^2 QD group, and ALT increased, AST increased, GGT increased, and visual impairment in 1 patient (33.3%) each in the 150.5 mg/m^2 QD group. A causal relationship to pimitespib could not be ruled out for pulmonary embolism and ILD in 1 patient each in the 76.8 mg/m^2 QD group and ALT increased, AST increased, GGT increased, and visual impairment in 1 patient each in the 150.5 mg/m^2 QD group.

Adverse events leading to discontinuation of pimitespib occurred in 0 of 1 patient in the 4.8, 9.6, 19.2, or 38.4 mg/m^2 group, 1 of 3 patients (33.3%) in the 76.8 mg/m^2 QD group, 3 of 6 patients (50.0%) in the 107.5 mg/m^2 QD group, and 1 of 3 patients (33.3%) in the 150.5 mg/m^2 QD group. The observed events were ILD in 1 patient (33.3%) in the 76.8 mg/m^2 QD group, cystitis, macular oedema, and decreased appetite in 1 patient (16.7%) each in the 107.5 mg/m^2 QD group, and night blindness in 1 patient (33.3%) in the 150.5 mg/m^2 QD group. A causal relationship to pimitespib could not be ruled out for all events.

In Expansion Phase of Step 1, adverse events occurred in 19 of 19 patients (100%), and adverse events for which a causal relationship to pimitespib could not be ruled out occurred in 18 of 19 patients (94.7%). Adverse events reported in ≥3 patients were diarrhoea (15 patients, 78.9%), nausea (in 12 patients, 63.2%), fatigue and decreased appetite in 9 patients (47.4%) each, blood creatinine increased in 8 patients (42.1%), blood ALP increased in 6 patients (31.6%), night blindness and dysgeusia in 5 patients (26.3%) each, constipation, vomiting, pyrexia, ALT increased, AST increased, and insomnia in 4 patients (21.1%) each, and anaemia, abdominal pain, blood potassium decreased, white blood cell count decreased, blood phosphorus increased, and acneiform dermatitis in 3 patients (15.8%) each.

Serious adverse events occurred in 7 of 19 patients (36.8%). The observed events were bile duct stenosis in 2 patients (10.5%), and anaemia, rectal stenosis, fatigue, disease progression, cholangitis, jaundice cholestatic, dizziness, urinary tract obstruction, and dyspnea in 1 patient (5.3%) each, and a causal relationship to pimitespib was ruled out for all events.

Adverse events leading to discontinuation of pimitespib occurred in 1 of 19 patients (5.3%). The observed event was dyspnoea in 1 patient (5.3%), and a causal relationship to pimitespib was ruled out for the event.

In Dose Escalation Phase of Step 2, adverse events occurred in 3 of 3 patients (100%) in the pimitespib 107.5 mg/m^2 every other day group, 6 of 6 patients (100%) in the pimitespib 150.5 mg/m^2 every other day group, 6 of 6 patients (100%) in the pimitespib 210.7 mg/m^2 every other day group, and 5 of 5 patients (100%) in the pimitespib 295.0 mg/m^2 every other day group. Adverse events for which a causal relationship to pimitespib could not be ruled out occurred in 3 of 3 patients (100%) in the 107.5 mg/m^2 every other day group, 6 of 6 patients (100%) in the 150.5 mg/m^2 every other day group, 6 of 6 patients (100%) in the 210.7 mg/m^2 every other day group, and 5 of 5 patients (100%) in the 295.0 mg/m^2 every other day group. Adverse events reported in ≥3 patients were diarrhoea (3 patients, 100%) in the 107.5 mg/m^2 every other day group, diarrhoea (5 patients, 83.3%), ALT increased, and decreased appetite (3 patients, 50.0% each) in the 150.5 mg/m^2 every other day group, diarrhoea (6 patients, 100%), blood creatinine increased (4 patients, 66.7%), nausea, fatigue, ALT increased, AST increased, and decreased appetite (3 patients, 50.0% each) in the 210.7 mg/m^2 every other day group, diarrhoea and blood creatinine increased (5 patients, 100% each), stomatitis, platelet count decreased and decreased appetite (4 patients, 80.0% each), and eye disorder, constipation, nausea, pyrexia, and rash (3 patients, 60.0% each) in the 295.0 mg/m^2 every other day group.

Serious adverse events occurred in 0 of 3 patients in the 107.5 mg/m^2 every other day group, 2 of 6 patients (33.3%) in the 150.5 mg/m^2 every other day group, 0 of 6 patients in the 210.7 mg/m^2 every other day group, 1 of 5 patients (20.0%) in the 295.0 mg/m^2 every other day group. The observed serious adverse events were gastrointestinal haemorrhage, disease progression and decreased appetite in 1 patient (16.7%) each in the 150.5 mg/m^2 every other day group, septic shock, respiratory failure, pneumonia, neutrophil count decreased, and platelet count decreased in 1 patient (20.0%) each in the 295.0 mg/m^2 every other day group. A causal relationship to pimitespib could not be ruled out for septic shock, respiratory failure, pneumonia, neutrophil count decreased, and platelet count decreased in 1 patient each.

Adverse events leading to discontinuation of pimitespib occurred in 0 of 3 patients in the 107.5 mg/m^2 every other day group, 1 of 3 patients (33.3%) in the 150.5 mg/m^2 every other day group, 0 of 6 patients in the 210.7 mg/m^2 every other day group, and 2 of 5 patients (40.0%) in the 295.0 mg/m^2 every other day group. The observed events were gastrointestinal haemorrhage in 1 patient (33.3%) in the 150.5 mg/m^2 every other day group and anaemia, septic shock, respiratory failure, and pneumonia in 1 patient (20.0%) each in the 295.0 mg/m^2 every other day group. A causal relationship to pimitespib could not be ruled out for anaemia, septic shock, respiratory failure, and pneumonia in 1 patient each.

In Expansion Phase of Step 2, adverse events occurred in 6 of 6 patients, and adverse events for which a causal relationship to pimitespib could not be ruled out occurred in 6 of 6 patients. Adverse events reported in ≥2 patients were diarrhoea (6 patients, 100%), decreased appetite (4 patients, 66.7%), blood creatinine increased (3 patients, 50.0%), and nausea, stomatitis, vomiting, pyrexia, ALT increased, AST increased, blood ALP increased, dry skin, and rash maculo-papular (2 patients, 33.3% each).

Serious adverse events occurred in 4 of 6 patients (66.7%). The observed serious adverse events were upper gastrointestinal haemorrhage, disease progression, cholangitis, jaundice cholestatic, enterocolitis infectious, dehydration, and malignant neoplasm progression in 1 patient (16.7%) each. A causal

relationship to pimitespib could not be ruled out for enterocolitis infectious and dehydration in 1 patient each.

No adverse events leading to discontinuation of pimitespib occurred.

7.3.6 Foreign phase I study (Study 010, Indication Extension Phase)

Adverse events occurred in all patients, and adverse events for which a causal relationship to pimitespib could not be ruled out occurred in 28 of 31 patients (90.3%). Adverse events with an incidence of ≥15% were diarrhoea in 25 patients (80.6%), nausea in 21 patients (67.7%), fatigue in 18 patients (58.1%), vomiting in 15 patients (48.4%), urinary tract infection and decreased appetite in 11 patients (35.5%) each, abdominal pain in 10 patients (32.3%), anaemia and constipation in 7 patients (22.6%) each, blood creatinine increased and acute kidney injury in 6 patients (19.4%) each, dry mouth, weight decreased, back pain, muscle spasms, headache, dyspnoea, cough, and rash in 5 patients (16.1%) each.

Serious adverse events occurred in 16 of 31 patients (51.6%). Serious adverse events reported in ≥2 patients were diarrhoea (3 patients, 9.7%) and abdominal pain, urinary tract infection, acute kidney injury, and dyspnea (2 patients, 6.5% each). A causal relationship to pimitespib could not be ruled out for diarrhoea in 3 patients, acute kidney injury in 2 patients, and abdominal pain and urinary tract infection in 1 patient each.

Adverse events leading to discontinuation of pimitespib occurred in 8 of 31 patients (25.8%). An adverse event leading to discontinuation of pimitespib reported in ≥2 patients was diarrhoea (3 patients, 9.7%), and a causal relationship to pimitespib could not be ruled out for all events.

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 assessment is currently ongoing, and the results and the conclusion of PMDA will be reported in the Review Report (2).

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

The assessment is currently ongoing, and the results and the conclusion of PMDA 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 pimitespib has efficacy in the treatment of unresectable or metastatic GIST that has progressed after cancer chemotherapy, and that pimitespib has acceptable safety in view of its benefits. Pimitespib is a drug with a new active ingredient expected to inhibit the formation of an HSP90-mediated high-order structure of client proteins so that the destabilization and degradation of these proteins are promoted, causing decreased expression of proteins involved in tumor growth and apoptosis induction, thereby suppressing tumor growth. Pimitespib is thus expected to be a treatment option for unresectable or metastatic GIST that has progressed after cancer

chemotherapy, which is of clinical significance. The efficacy, safety, and post-marketing investigations should be further reviewed.

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

Review Report (2)

May 13, 2022

Product Submitted for Approval

Brand Name	Jeselhy Tablets 40 mg
Non-proprietary Name	Pimitespib
Applicant	Taiho Pharmaceutical Co., Ltd.
Date of Application	September 14, 2021

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

As a result of the discussion in Section "7.R.2 Efficacy" of the Review Report (1), PMDA concluded that pimitespib is shown to have efficacy in patients with unresectable or metastatic advanced GIST who progressed after treatment with imatinib, sunitinib, and regorafenib by the Japanese phase III study (Study 030) in the concerned patients, which demonstrated superiority of pimitespib to the placebo in terms of PFS, the primary endpoint.

The above conclusion of PMDA was supported by the expert advisors at the Expert Discussion.

1.2 Safety

As a result of the discussion in Section "7.R.3 Safety" of the Review Report (1), PMDA concluded that adverse events requiring special attention during use of pimitespib in patients with unresectable or metastatic advanced GIST who progressed after treatment with imatinib, sunitinib, and regorafenib are diarrhoea, eye disorders, haemorrhage, and renal disorders.

PMDA has also concluded that although the above-mentioned adverse events warrant attention during treatment with pimitespib, pimitespib is tolerable as long as physicians with adequate knowledge and experience in cancer chemotherapy take appropriate measures, such as monitoring and controlling of adverse events, and interruption and dose reduction of pimitespib.

The above conclusion of PMDA was supported by the expert advisors at the Expert Discussion. The following comment was raised from the expert advisors.

- Haemorrhage distinctly tended to occur more frequently in the pimitespib group than in the placebo group in Study 030. Because of the limited safety information, at present, it is difficult to determine that patient predispositions such as primary disease contribute to the development, and thus haemorrhage should be listed as an adverse event requiring special attention in the package insert to raise caution among healthcare professionals.

In view of the following points in addition to the above comment at the Expert Discussion, PMDA has concluded that haemorrhage should be listed in the "Clinically Significant Adverse Reactions" section in the package insert to raise caution among healthcare professionals:

- In Study 030, serious haemorrhage for which a causal relationship to the study drug could not be ruled out occurred only in 1 patient in the pimitespib group, but serious haemorrhage irrespective of the causal relationship status occurred in 7 patients (12.1%) in the pimitespib group and in 1 (3.6%) in the placebo group, showing a higher trend of the incidence in the pimitespib group.
- In Study 030, all-grade haemorrhage occurred in 1 patient (3.6%) in the placebo group and 4 patients switching to pimitespib (23.5%), indicating that a certain number of patients experienced haemorrhage after the treatment was switched to pimitespib.

1.3 Clinical positioning and indication

As a result of the discussion in Section "7.R.4 Clinical positioning and indication" of the Review Report (1), PMDA concluded that the indication of pimitespib should be defined as "gastrointestinal stromal tumor that has progressed after cancer chemotherapy," as proposed, with the following notes in the "Precautions Concerning Indication" section to raise caution.

Precautions Concerning Indication

- Pimitespib should be used for patients who have been treated with imatinib, sunitinib, and regorafenib.
- The efficacy and safety of pimitespib have not been established for use in postoperative adjuvant therapy.

The above conclusion of PMDA was supported by the expert advisors at the Expert Discussion.

PMDA instructed the applicant to provide the cautionary notes on the "Indication" and "Precautions Concerning Indication" sections as above, and the applicant agreed.

1.4 Dosage and administration

As a result of the discussion in Section "7.R.5 Dosage and administration" of the Review Report (1), PMDA concluded that, with the cautionary advice provided in the "Precautions Concerning Dosage and Administration" section, the Dosage and Administration of pimitespib should be specified as "The usual adult dosage is 160 mg of pimitespib administered orally once daily in the fasted state for 5 consecutive days. With a subsequent 2-day rest, this regimen is repeated. The dose may be reduced according to the patient's condition."

Precautions Concerning Dosage and Administration

- The efficacy and safety of pimitespib have not been established for use in combination with other antineoplastic agents.
- C_{max} and AUC of pimitespib increase when administered after meal. In order to avoid food effect, pimitespib should not be taken from1 hour before until 2 hours after meal.
- If any adverse drug reaction occurs, pimitespib should be interrupted or reduced in dose based on the following criteria according to symptoms and their severity.

Dose reduction

Reduced level	Dose
Usual dose	160 mg/day
1-level lower dose	120 mg/day
2-level lower dose	80 mg/day
3-level lower dose	40 mg/day

Criteria for interruption and dose reduction following adverse drug reactions

Adverse drug reaction	Severity*	Action
Diarrhoea	Grade 2	If unmanageable and intolerable, interrupt pimitespib until recovery to Grade ≤1. After recovery, pimitespib may be resumed at the same dose.
	Grade ≥3	Interrupt pimitespib until recovery to Grade ≤1. After recovery, pimitespib may be resumed at the 1-level lower dose or same dose.
Eye disorders	Grade ≥2	Interrupt pimitespib until recovery to Grade ≤1. After recovery, pimitespib may be resumed at the 1-level lower dose or same dose.
Adverse drug reactions other than the above	Grade ≥3	Interrupt pimitespib until recovery to Grade 2 or ≤1. Pimitespib may be resumed at a 1-level lower dose after recovery to Grade 2 or at the same dose after recovery to Grade ≤1.

* Graded according to NCI-CTCAE ver.4.03.

The above conclusion of PMDA was supported by the expert advisors at the Expert Discussion.

PMDA instructed the applicant to describe the "Dosage and Administration" and "Precautions Concerning Dosage and Administration" sections as above, and the applicant agreed.

1.5 Risk management plan (draft)

In order to investigate the safety of pimitespib pin its post-marketing clinical use, the applicant plans to conduct post-marketing surveillance in all patients treated with pimitespib. The safety specification includes diarrhoea, eye disorders, and its use in patients with hepatic impairment and patients with renal impairment. The planned sample size is 100 patients, and the observation period is 15 weeks.

As a result of the discussion in Section "7.R.6 Post-marketing investigations" of the Review Report (1), PMDA concluded that the post-marketing surveillance should be conducted in all patients treated with pimitespib for a certain period after its launch to collect the safety information promptly and in an unbiased manner, and obtained safety information should be promptly provided to healthcare professionals.

PMDA further concluded on the surveillance plan as follows:

- The safety specification of the surveillance should be severe diarrhoea, eye disorders, and haemorrhage, and information including the safety of pimitespib used in patients with hepatic impairment and patients with renal impairment should be collected.

- The planned sample size and observation period for the surveillance should be re-examined in light of the events to be included in the safety specification, with their occurrence in the clinical studies taken into account.

The above conclusion of PMDA was supported by the expert advisors at the Expert Discussion.

Based on the above review, PMDA instructed the applicant to discuss the surveillance plan again.

The applicant's response:
- The safety specification of this surveillance will include severe diarrhoea, eye disorders, and haemorrhage, and the surveillance will be designed to collect information including safety of pimitespib used in patients with hepatic impairment and patients with renal impairment.
- The planned sample size and observation period for the surveillance will be 100 patients and 15 weeks, respectively, in light of the events to be included in the safety specification, with their occurrence in the clinical studies taken into account.

PMDA accepted the applicant's response.

Accordingly, PMDA has concluded that the risk management plan (draft) for pimitespib should include the safety specification presented in Table 36, and that the applicant should conduct additional pharmacovigilance activities and risk minimization activities presented in Tables 37 and 38.

Table 36. Safety and efficacy specifications in the risk management plan (draft)

Safety specification		
Important identified risks	Important potential risks	Important missing information
• Severe diarrhoea • Eye disorders • Haemorrhage	• Embryo-fetal toxicity	None
Efficacy specification		
Not applicable		

Table 37. Summary of additional pharmacovigilance activities, efficacy survey and studies, and additional risk minimization activities included under the risk management plan (draft)

Additional pharmacovigilance activities	Efficacy survey and studies	Additional risk minimization activities
• Early post-marketing phase vigilance • Use-results survey (all-case surveillance)	Not applicable	• Information provision based on the early post-marketing phase vigilance • Preparation and distribution of materials for healthcare professionals

Table 38. Outline of use-results survey (draft)

Objective	To investigate the safety in clinical use
Survey method	All-case surveillance
Population	All patients treated with pimitespib
Observation period	15 weeks
Planned sample size	100 patients
Main survey items	Safety specification: Severe diarrhoea, eye disorders, and haemorrhage Other main survey items: Patient characteristics (age, sex, medical history, complications, prior treatment, etc.), use status of pimitespib, concomitant drugs, 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 Products Including Pharmaceuticals and Medical Devices. On the basis of the inspection and assessment, PMDA concluded that there were no obstacles to conducting its review based on the application documents submitted.

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

The new drug application data (CTD 5.3.5.1.1) were subjected to an on-site GCP inspection, in accordance with the provisions of the Act on Securing Quality, Efficacy and Safety of Products Including Pharmaceuticals and Medical Devices. On the basis of the inspection, PMDA concluded that there were no obstacles to conducting its review based on the application documents submitted.

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 approval conditions, provided that the package insert includes appropriate cautionary advice; information about proper use is delivered appropriately in post-marketing settings; and pimitespib is properly used by physicians with adequate knowledge and experience in cancer chemotherapy at a medical institution capable of emergency response. The product is a drug with a new active ingredient, and the re-examination period is 8 years. The product is not classified as a biological product or a specified biological product. The drug product and its drug substance are classified as a powerful drug and a poisonous drug, respectively.

Indication

Gastrointestinal stromal tumor that has progressed after cancer chemotherapy

Dosage and Administration

The usual adult dosage is 160 mg of pimitespib administered orally once daily in the fasted state for 5 consecutive days. With a subsequent 2-day rest, this regimen is repeated. The dose may be reduced according to the patient's condition.

Approval Conditions

1. The applicant is required to develop and appropriately implement a risk management plan.
2. In view of the limited number of Japanese patients participated in the clinical studies, the applicant is required to conduct a drug use-results survey involving all Japanese patients treated with the product in the post-marketing settings until data of a certain number of patients are available, in order to understand the characteristics of patients using the product, and to promptly collect safety and efficacy data so that necessary measures are taken to ensure the proper use of the product.

Warnings

The product should be administered only to patients found eligible for treatment with the product by a physician with adequate knowledge and experience in cancer chemotherapy at a medical institution capable of emergency response. Prior to treatment, the benefits and risks of the treatment should be thoroughly explained to the patient or their family member, and consent should be obtained.

Contraindication

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

Precautions Concerning Indication

1. Pimitespib should be used for patients who have been treated with imatinib, sunitinib, and regorafenib.
2. The efficacy and safety of pimitespib have not been established for use in postoperative adjuvant therapy.

Precautions Concerning Dosage and Administration

1. The efficacy and safety of pimitespib have not been established for use in combination with other antineoplastic agents.
2. C_{max} and AUC of pimitespib increase when administered after meal. In order to avoid food effect, pimitespib should not be taken from 1 hour before until 2 hours after meal.
3. If any adverse drug reaction occurs, pimitespib should be interrupted or reduced in dose based on the following criteria according to symptoms and their severity.

Dose reduction

Reduced level	Dose
Usual dose	160 mg/day
1-level lower dose	120 mg/day
2-level lower dose	80 mg/day
3-level lower dose	40 mg/day

Criteria for interruption and dose reduction following adverse drug reactions

Adverse drug reaction	Severity*	Action
Diarrhoea	Grade 2	If unmanageable and intolerable, interrupt pimitespib until recovery to Grade ≤1. After recovery, pimitespib may be resumed at the same dose.
	Grade ≥3	Interrupt pimitespib until recovery to Grade ≤1. After recovery, pimitespib may be resumed at the 1-level lower dose or same dose.
Eye disorders	Grade ≥2	Interrupt pimitespib until recovery to Grade ≤1. After recovery, pimitespib may be resumed at the 1-level lower dose or same dose.
Adverse drug reactions other than the above	Grade ≥3	Interrupt pimitespib until recovery to Grade 2 or ≤1. Pimitespib may be resumed at a 1-level lower dose after recover to Grade 2 or at the same dose after recovery to Grade ≤1.

* Graded according to NCI-CTCAE ver.4.03.

Appendix

List of Abbreviations

A/G	albumin/globulin
AKT	protein kinase B
Alectinib	Alectinib hydrochloride
ALK	anaplastic lymphoma kinase
ALP	alkaline phosphatase
ALT	alanine aminotransferase
Application	Application for marketing approval
AST	aspartate aminotransferase
ATP	adenosine triphosphate
BCRP	breast cancer resistance protein
BICR	blinded independent central review
BRAF	B-Raf proto-oncogene, serine/threonine kinase
BSC	best supportive care
CES	carboxylesterase
CI	confidence interval
CLcr	creatinine clearance
CL_{int}	intrinsic clearance
CL_{max}	maximum clearance
CPP	critical process parameter
CQA	critical quality attribute
CRC	colorectal carcinoma
CT	computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
CYP	cytochrome P450
^{14}C-pimitespib	14C-labeled pimitespib
DLT	dose limiting toxicity
DMSO	dimethyl sulfoxide
DNA	deoxyribonucleic acid
ECOG	Eastern Cooperative Oncology Group
efflux ratio	The ratio of secretion permeability coefficient in the secretive direction to that in the absorptive direction
EGFR	epidermal growth factor receptor
FLT3	FMS-like tyrosine kinase 3
GC	gas chromatography
GGT	γ-glutamyltransferase
GIST	gastrointestinal stromal tumor
HER2	human epidermal growth factor receptor 2
hERG	human *ether-a-go-go* related gene
HLGT	high level group term
HNSTD	highest non-severely toxic dose
HPLC	high performance liquid chromatography
HPMC	hydroxypropylmethylcellulose
HSP90	heat shock protein 90
IC_{50}	concentration that results in 50% inhibition
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
ICH Q1E guidelines	“Guidelines on Evaluation of Stability Data” (PFSB/ELD Notification No. 0603004 dated June 3, 2003)
ICH Q3A guidelines	“Impurities in New Drug Substances” (PFSB/ELD Notification No. 1204001 dated December 4, 2006)
IGF1R	insulin-like growth factor 1 receptor

ILD	interstitial lung disease
Imatinib	Imatinib mesilate
IR	infrared absorption spectroscopy
IRC	independent review committee
ITD	internal tandem duplication
K_d	dissociation constant
K_I	inhibitor concentration at 50% of maximum inhibition rate
K_i	inhibition constant
k_{inact}	maximum inactivation rate constant
KIT	mast/stem cell growth factor receptor
LC-MS/MS	liquid chromatography-tandem mass spectrometry
MATE	multidrug and toxin extrusion
MCH	mean corpuscular hemoglobin
MCHC	mean corpuscular hemoglobin concentration
MCV	mean corpuscular volume
MedDRA	Medical Dictionary for Regulatory Activities
MET	mesenchymal-epithelial transition factor
MPE	mean photo effect
mRNA	messenger ribonucleic acid
MTD	maximum tolerated dose
NADPH	nicotinamide adenine dinucleotide phosphate hydrogen
NCCN guidelines for soft tissue sarcoma	National Comprehensive Cancer Network Clinical Practice Guidelines in Oncology, Soft Tissue Sarcoma
NMR	nuclear magnetic resonance spectroscopy
NSCLC	non-small cell lung cancer
OAT	organic anion transporter
OATP	organic anion transporting polypeptide
OCT	organic cation transporter
OS	overall survival
Osimertinib	Osimertinib mesilate
$P_{app\ A \rightarrow B}$	apparent permeability in apical to basal direction
PD	progressive disease
PDGFRα	platelet-derived growth factor receptor α
PFS	progression free survival
P-gp	P-glycoprotein
PIF	photo-irritancy factor
Pimitespib	Pimitespib
PK	pharmacokinetics
PMDA	Pharmaceuticals and Medical Devices Agency
PPK	population pharmacokinetics
PS	performance status
PT	preferred term
PTP	press through packaging
QD	quaque die
QTc	QT interval corrected
QTcF	QT interval corrected using Fridericia formula
RECIST	Response Evaluation Criteria in Solid Tumors
Regorafenib	Regorafenib hydrate
SCID mice	severe combined immunodeficient mouse
SMQ	standardized MedDRA queries
SOC	system organ class
STD_{10}	severely toxic dose in 10% of animals
Study 010	Study 10058010

Study 020	Study 10058020
Study 030	Study 10058030
Study 040	Study 10058040
Study 050	Study 10058050
Sunitinib	Sunitinib malate
UV	ultraviolet
UV-VIS	ultraviolet-visible spectroscopy
160 mg QD on 5-day on/2-day off treatment	7-day regimen in which pimitespib 160 mg is orally administered in the fasted state QD for 5 days followed by a 2-day rest
ΔΔQTcF	Change in placebo-corrected, time-matched QT interval corrected using Fridericia formula from baseline