Report on the Deliberation Results

June 3, 2019

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

Brand Name	Vanflyta Tablets 17.7 mg Vanflyta Tablets 26.5 mg
Non-proprietary Name	Quizartinib Hydrochloride (JAN*)
Applicant	Daiichi Sankyo Company, Limited
Date of Application	October 17, 2018

Results of Deliberation

In its meeting held on May 30, 2019, the Second Committee on New Drugs concluded that the product may be approved and that this result should be presented to the Pharmaceutical Affairs Department of the Pharmaceutical Affairs and Food Sanitation Council.

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

Approval Conditions

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

2. Because only a limited number of Japanese patients participated in the clinical studies, the applicant is required to conduct a post-marketing drug use-results survey involving all Japanese patients treated with the product until data from a certain number of patients are compiled, to identify 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)*

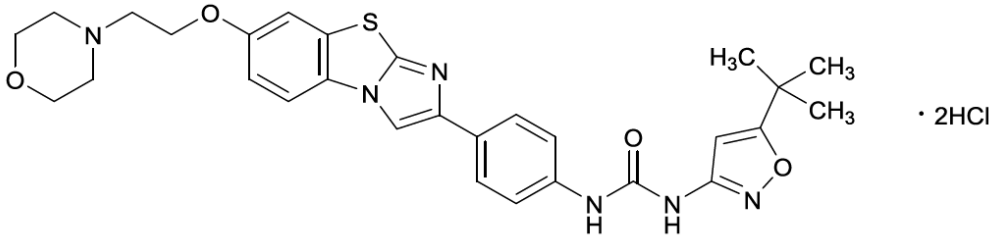
Review Report

May 22, 2019
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	Vanflyta Tablets 17.7 mg Vanflyta Tablets 26.5 mg
Non-proprietary Name	Quizartinib Hydrochloride
Applicant	Daiichi Sankyo Company, Limited
Date of Application	October 17, 2018
Dosage Form/Strength	Tablets, each containing 20 mg or 30 mg of Quizartinib Hydrochloride (17.7 mg or 26.5 mg of quizartinib).
Application Classification	Prescription drug, (1) Drug(s) with a new active ingredient

Chemical Structure



Molecular formula: $C_{29}H_{32}N_6O_4S \bullet 2HCl$

Molecular weight: 633.59

Chemical name: 1-(5-*tert*-Butyl-1,2-oxazol-3-yl)-3-(4-{7-[2-(morpholin-4-yl)ethoxy]imidazo[2,1-*b*][1,3]benzothiazol-2-yl}phenyl)urea dihydrochloride

Items Warranting Special Mention

Orphan drug (Orphan Drug Designation No. 417 of 2018 [*30 yaku*]; PSEHB/PED Notification No. 0906-1 dated September 6, 2018, by the Pharmaceutical Evaluation Division, Pharmaceutical Safety and Environmental Health Bureau, Ministry of Health, Labour and Welfare)

Reviewing Office Office of New Drug V

Results of Review

On the basis of the data submitted, PMDA has concluded that the product has efficacy in the treatment of patients with relapsed or refractory FMS-like tyrosine kinase 3-internal tandem duplication (FLT3-ITD) mutation-positive acute myeloid leukemia, and that the product has acceptable safety in view of its benefits.

As a result of its review, PMDA has concluded that the product may be approved for the indication and dosage and administration shown below, with the following conditions. The occurrence of QT interval prolonged, myocardial infarction, acute kidney injury, and interstitial lung disease need to be further investigated via post-marketing surveillance.

Indication

Relapsed or refractory FLT3-ITD mutation-positive acute myeloid leukemia

Dosage and Administration

The usual adult dosage is 26.5 mg of quizartinib orally administered once daily for 2 weeks followed by 53 mg orally administered once daily. The dose may be decreased according to the patient's condition.

Approval Conditions

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

2. Because only a limited number of Japanese patients participated in the clinical studies, the applicant is required to conduct a post-marketing drug use-results survey involving all Japanese patients treated with the product until data from a certain number of patients are compiled, to identify 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 20, 2019

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	Vanflyta Tablets 17.7 mg Vanflyta Tablets 26.5 mg
Non-proprietary Name	Quizartinib Hydrochloride
Applicant	Daiichi Sankyo Company, Limited
Date of Application	October 17, 2018
Dosage Form/Strength	Tablets, each containing 20 mg or 30 mg of Quizartinib Hydrochloride (17.7 mg or 26.5 mg of quizartinib).
Proposed Indication	Relapsed or refractory FLT3-ITD mutation-positive acute myeloid leukemia

Proposed Dosage and Administration

The usual adult dosage is 26.5 mg of quizartinib orally administered once daily for the first 2 weeks, which is then increased to 53 mg orally administered once daily. The dose may be decreased according to the patient's condition.

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List of Abbreviations

See Appendix.

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

1.1 Outline of the proposed product

FMS-like tyrosine kinase 3 (FLT3) is a receptor tyrosine kinase mainly expressed on the cell membrane of hematopoietic progenitor cells and acute myeloid leukemia (AML) cells. FLT3 is thought to be involved in the differentiation and proliferation, etc. of hematopoietic progenitor cells (*Blood.* 2002;100:1532-42, etc.). In AML, consistent activation of FLT3-mediated signal transduction, which was caused by activating mutation of the *FLT3* gene, was reported (*Leukemia.* 1998;12:1333-7, etc.).

Quizartinib Hydrochloride (hereinafter referred to as quizartinib), found by Ambit Biosciences Corporation (US) (currently Daiichi Sankyo Company, Limited), is a low molecular weight compound that inhibits tyrosine kinases such as FLT3. Quizartinib is expected to inhibit FLT3-mediated signal transduction, thereby suppressing the proliferation of *FLT3* gene mutation-positive AML cells.

1.2 Development history etc.

Outside Japan, Ambit Biosciences Corporation (US) began a phase I study (Study CP0001) in patients with relapsed or refractory AML in [redacted] 20[redacted]. A phase II study (Study 2689-CL-2004 [Study 2004]) and phase III study (Study AC220-007 [Study 007]) began in patients with relapsed or refractory FLT3-internal tandem duplication (ITD) mutation-positive AML in [redacted] 20[redacted] and [redacted] 20[redacted], respectively.

In the US and EU, the application was submitted in September and October, respectively, in 2018, with the pivotal study results from Study 007. The applications are currently under review.

As of February 2019, quizartinib has not been approved in any country or region.

In Japan, a phase I study (Study AC220-A-J101 [Study J101]) in patients with relapsed or refractory AML and a phase II study (Study AC220-A-J201 [Study J201]) in patients with relapsed or refractory FLT3-ITD mutation-positive AML were initiated in [redacted] 20[redacted] and [redacted] 20[redacted], respectively, by the applicant.

The approval application for quizartinib was filed with data from Studies 007 and J201 as the pivotal study results.

Quizartinib was designated as an orphan drug in September 2018 with the intended indication of "*FLT3* gene mutation-positive acute myeloid leukaemia" (Orphan Drug Designation No. 417 of 2018 [*30 yaku*]).

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

2.1 Drug substance

2.1.1 Characterization

The drug substance is a white to light gray or yellowish light gray solid. The general properties including description, solubility, hygroscopicity, melting point, thermal analysis, dissociation constant, and distribution coefficient were determined. Although the drug substance is in a total of 10 crystal forms,

including [redacted], only in Form B was confirmed to be generated in commercial production and to remain unchanged in the stability study.

The chemical structure of the drug substance was elucidated by ultraviolet spectrum, infrared absorption spectrum (IR), nuclear magnetic resonance spectrum (NMR) (^{1}H- and ^{13}C-NMR), mass spectrum, and X-ray crystallography.

2.1.2 Manufacturing process

The drug substance is synthesized from starting materials of [redacted], [redacted], and [redacted].

The critical step identified is the [redacted] process of [redacted], and the process control items and process control values have been established in the process for [redacted] up to synthesis of the drug substance. [redacted], a product in the [redacted] process, is controlled as [redacted] intermediate.

2.1.3 Control of drug substance

The proposed specifications for the drug substance include content, description, identification (IR), purity (related substances [liquid chromatography (LC)] and residual solvents [gas chromatography]), water content, residue on ignition, chlorine, and assay (LC).

2.1.4 Stability of drug substance

Main stability studies of the drug substance are shown in Table 1. The photostability study showed that the drug substance is photostable.

Table 1. Stability studies of drug substance

Study	Primary batch	Temperature	Humidity	Storage package	Storage period
Long-term	Commercial production 4 batches	25 ± 2°C	60 ± 5%RH	Polyethylene sleeve/polyethylene bag/aluminum-laminated bag	48 months
Accelerated		40 ± 2°C	75 ± 5%RH		6 months

Based on the above, a retest period of 60 months has been proposed for the drug substance when stored in the polyethylene sleeve/polyethylene bag/aluminum-laminated bag at room temperature, in accordance with the ICH Q1E guideline. Furthermore, the long-term testing will be continued up to 60 months.

2.2 Drug product

2.2.1 Description and composition of drug product and formulation development

The drug product is immediate-release film-coated tablets, each containing 20 or 30 mg of the drug substance (17.7 or 26.5 mg of quizartinib). The drug product contains hydroxypropyl-β-cyclodextrin (HPβCD), microcrystalline cellulose, magnesium stearate, and [redacted][1)] as excipients.

[1)] Some excipients contained in [redacted] in 17.7-mg tablets are different from those in 26.5-mg tablets.

2.2.2 Manufacturing process

The drug product is manufactured through the process consisting of [redacted], mixing, tableting, film-coating, and packaging and labeling.

The quality control strategy has been constructed based on the following investigations by a quality-by-design (QbD) approach (Table 2):

- Identification of critical quality attributes (CQAs)
- Identification of material attributes potentially affecting the CQA of the product and investigation of acceptable ranges for process parameters based on the quality risk assessment

Table 2. Summary of control strategy of drug product

CQA	Control method
[redacted]	[redacted]

Critical steps identified are [redacted], and processes, and the process control items and process control values were specified in the [redacted], and processes. [redacted] is controlled as a critical intermediate.

2.2.3 Control of drug product

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

2.2.4 Stability of drug product

Stability studies of the drug product are as shown in Table 3. The photostability study has shown that the drug product is photostable.

Table 3. Stability studies of drug product

Study	Primary batch	Temperature	Humidity	Storage package	Storage period
Long-term	Commercial production 3 batches	25 ± 2°C	60 ± 5%RH	Blister pack (polychlorotrifluoroethylene/ polyvinyl chloride and aluminum)	36 months*
Accelerated		40 ± 2°C	75 ± 5%RH		6 months

* [redacted] was performed with samples taken out at [redacted] months after start of the study.

Based on the above, a shelf life of 36 months was proposed for the drug product when packaged in a blister pack (polychlorotrifluoroethylene/polyvinyl chloride and aluminum) and stored at room temperature.

2.R Outline of the review conducted by PMDA

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

2.R.1 Novel excipients

The drug product contains HPβCD, a novel excipient in an amount exceeding that in the previous use for oral formulations.

Based on the following review, PMDA has concluded that HPβCD may be used in the drug product.

2.R.1.1 Specifications and stability

HPβCD conforms to [redacted] or [redacted] Pharmacopeia. PMDA concluded that there were no problems with the specification and stability.

2.R.1.2 Safety

Based on the submitted data, PMDA concluded that there were no problems with the safety of HPβCD at the amount used in this product.

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

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

3.1 Primary pharmacodynamics

3.1.1 Binding to various kinases (CTD 4.2.1.1-1 and 4.2.1.1-2)

(a) Binding of quizartinib to 441 types of kinases (recombinant proteins) and (b) binding of AC886 (a metabolite of quizartinib, [see Section 4.3]) to 391 types of kinases (recombinant proteins) were investigated by a competitive binding assay. Kinases presenting a dissociation constant (K_D) value of quizartinib <100 nmol/L are shown in Table 4.

Table 4. Binding of quizartinib and AC886 to various kinases

Kinase	K_D value (nmol/L)				Kinase	K_D value (nmol/L)			
	n	Quizartinib	n	AC886		n	Quizartinib	n	AC886
CSF1R	22	9.6 ± 5.1	6	8.6 ± 0.73	$KIT^{A829P*6}$	2	3.1, 4.0	-	
DDR1	2	75, 87	2	450, 570	$KIT^{L576P*7}$	2	6.2, 6.5	2	0.81, 1.1
FLT1	4	44 ± 2.6	2	91, 96	$KIT^{V559D*8}$	4	5.2 ± 0.94	2	1.0, 1.0
FLT3	26	1.3 ± 0.70	4	0.54 ± 0.18	$KIT^{V559D/T670I*9}$	4	5.9 ± 1.1	2	1.8, 1.9
$FLT3^{D835H*1}$	14	3.9 ± 1.2	2	1.2, 2.6	$KIT^{V559D/V654A*10}$	4	42 ± 1.4	2	7.8, 13
$FLT3^{D835Y*2}$	4	8.3 ± 2.0	2	5.3, 5.7	PDGFRα	4	14 ± 0.96	2	3.0, 4.1
FLT3-ITD	4	9.4 ± 0.70	2	5.7, 5.8	PDGFRβ	4	8.4 ± 0.94	2	1.5, 2.0
$FLT3^{K663Q*3}$	2	2.1, 2.4	2	0.66, 0.73	RET	8	7.1 ± 2.1	4	14 ± 1.9
$FLT3^{N841I*4}$	4	4.4 ± 0.65	2	0.69, 0.85	$RET^{M918T*11}$	2	2.8, 3.3	2	18, 20
$FLT3^{R834Q*5}$	2	3.7, 6.5	-		$RET^{V804L*12}$	2	13, 14	2	49, 52
FLT4	4	49 ± 8.9	2	38, 100	$RET^{V804M*13}$	2	8.9, 9.3	2	19, 20
KIT	14	4.9 ± 1.9	4	0.97 ± 0.22					

Mean ± standard deviation (SD); Individual values at n = 2; -, Not investigated. *[1] Aspartic acid at position 835 is replaced by histidine, *[2] Aspartic acid at position 835 is replaced by tyrosine, *[3] Lysine at position 663 is replaced by glutamine, *[4] Asparagine at position 841 is replaced by isoleucine, *[5] Arginine at position 834 is replaced by glutamine, *[6] Alanine at position 829 is replaced by proline, *[7] Leucine at position 576 is replaced by proline, *[8] Valine at position 559 is replaced by aspartic acid, *[9] Valine at position 559 is replaced by aspartic acid and threonine at position 670 is replaced by isoleucine, *[10] Valine at position 559 is replaced by aspartic acid and valine at position 654 is replaced by alanine, *[11] Methionine at position 918 is replaced by threonine, *[12] Valine at position 804 is replaced by leucine, *[13] Valine at position 804 is replaced by methionine.

3.1.2 Inhibitory effect against FLT3 phosphorylation

3.1.2.1 *In vitro* (CTD 4.2.1.1-3)

The inhibitory effect of quizartinib against FLT3 phosphorylation was investigated using human AML-derived FLT3-ITD mutation-positive MV4-11 cell line by Western blotting. Quizartinib inhibited FLT3 phosphorylation.

3.1.2.2 *In vivo* (CTD 4.2.1.1-5)

When the tumor volume reached 150 to 350 mm^3, a single dose of quizartinib 10 mg/kg[2)] was orally administered to severe combined immunodeficient (SCID) mice subcutaneously implanted with MV4-11 cell line (4 mice/group), and the inhibitory effect of quizartinib against FLT3 phosphorylation in tumor tissue was investigated by electrochemiluminescence (ECL). Table 5 shows the FLT3 phosphorylation rate[3)] at 0.25, 1, 2, 6, 16, 24, 48, and 96 hours after the administration of quizartinib.

Table 5. FLT3 phosphorylation rate after the administration of quizartinib

Time (hours)	Phosphorylation rate (%)	Time (hours)	Phosphorylation rate (%)
0.25	96 ± 16	16	16 ± 1
1	6 ± 1	24	28 ± 3
2	4 ± 0	48	57 ± 6
6	7 ± 0	96	61 ± 12

Mean ± standard error (SE), n = 4

3.1.3 Growth inhibitory effect against malignant tumor-derived cell lines

3.1.3.1 *In vitro* (CTD 4.2.1.1-4)

The growth inhibitory effect of quizartinib against MV4-11 cell line and human acute lymphocytic leukaemia-derived RS4;11 cell line expressing wild-type FLT3 was investigated using living cell-derived activity as indicator. Against MV4-11 cell line and RS4;11 cell line, IC_{50} (mean ± standard deviation [SD]) of quizartinib were 0.3 ± 0.09 nmol/L (n = 24) and 990 ± 550 nmol/L (n = 26).

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2) Amount of quizartinib hydrochloride

3) Phosphorylation rate = ([ratio of phosphorylated FLT3 with respect to FLT3 at each time point]/[ratio of phosphorylated FLT3 with respect to FLT3 at 0.25 hours after the administration of vehicle (5% HPβCD solution)]) × 100

3.1.3.2 *In vivo* (CTD 4.2.1.1-6 and 4.2.1.1-7)

The tumor growth inhibitory effect of quizartinib was investigated using nude mice subcutaneously implanted with MV4-11 cell line (10 mice/group). When the tumor volume reached 150 to 200 mm^3, the study was started (Day 0). In the study, quizartinib was orally administered QD at 1, 3, or 10 mg/kg[2)] for 28 days, starting on Day 0, and the tumor volume was calculated. All the quizartinib groups presented a statistically significant tumor growth inhibitory effect compared with the control (22% HPβCD solution) group (Figure 1).

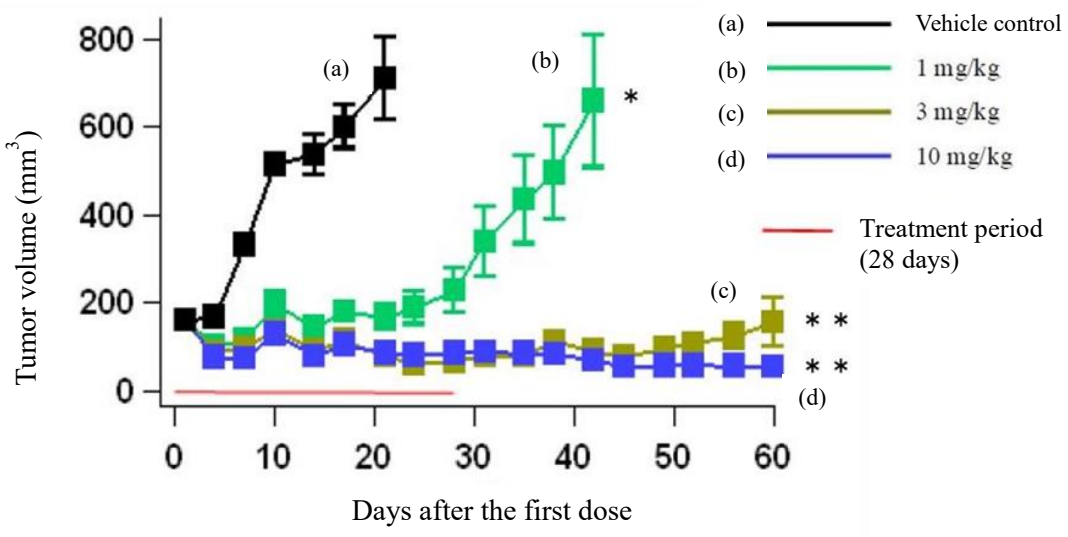

Figure 1. Tumor growth inhibitory effect of quizartinib in nude mice subcutaneously implanted with MV4-11 cell lines

n = 10; Mean ± SE; * $P < 0.05$ for control group (log-rank test), ** $P < 0.001$ for control group (log-rank test)

3.2 Secondary pharmacodynamics

3.2.1 Effects on various receptors, enzymes, transporters, and ion channels (CTD 4.2.1.2-1)

The inhibitory effect of quizartinib 10 μmol/L against 118 types of receptors, enzymes, transporters, and ion channels was investigated using radiolabeled ligands. Table 6 shows IC_{50} values of quizartinib against the receptors, etc. that were inhibited by ≥50%.

Table 6. Inhibitory effect of quizartinib against various receptors, etc.

Receptor, etc.	IC_{50} value (μmol/L)
Prostanoid receptor (EP_4)	5.55 [3.12, 9.89]
Sigma receptor (σ1)	7.16*
Sigma receptor (σ2)	5.04*
Lipoxygenase (15-LO)	5.12 [3.51, 7.45]
Peptidase (renin)	10.3 [6.88, 15.4]
Sodium channel (site2)	2.71 [2.14, 3.44]

Mean (95% confidence interval [CI]); n = 2; * 95% CI could not be calculated.

The applicant explanation about the above results:
The inhibitory effect of quizartinib against these receptors, etc. is unlikely to raise safety issues during the clinical use of quizartinib in light of C_{max} of unbound quizartinib in plasma, which was 0.0086 μmol/L at the recommended clinical dose (53 mg) of quizartinib.[4)]

3.3 Safety pharmacology

Effects of quizartinib on the central nervous system and respiratory system were investigated in 13-week repeated-dose toxicity studies in rats, dogs, and monkeys. The result revealed no effects [see Section 5.2].

3.3.1 Effects on cardiovascular system

3.3.1.1 Effects on human *ether-a-go-go* related gene (hERG) potassium current (CTD 4.2.1.3-5)

Effects of quizartinib and AC886 at 0.1, 0.3, 1.0, and 3.0 μmol/L on human *ether-a-go-go* related gene (hERG) potassium current were investigated using human embryonic kidney-derived HEK293 cell lines introduced with hERG. Table 7 shows the inhibitory rates against hERG potassium current, and all the IC_{50} values are >3.0 μmol/L. In addition, quizartinib 3.0 μmol/L and AC886 3.0 μmol/L showed a statistically significant inhibition of the current as compared with the control (HEPES buffered physiological saline[5)] containing 0.3% dimethyl sulfoxide [DMSO]) ($P < 0.05$, Dunnett's multiple comparison test).

Table 7. Inhibitory rate of quizartinib and AC886 against hERG potassium current

Concentration of quizartinib or AC886 (μmol/L)	Inhibitory rate (%)			
	n	Quizartinib	n	AC886
0.1	3	1.8 ± 1.6	3	–0.4 ± 0.8
0.3	3	3.8 ± 0.5	3	3.3 ± 0.1
1.0	3	4.3 ± 0.9	3	3.9 ± 1.6
3.0	6	16.4 ± 2.1	3	12.0 ± 2.0

Mean ± SE

3.3.1.2 Effects on myocardial ion channel (CTD 4.2.1.3-6, 4.2.1.3-7, 4.2.1.3-8, and 4.2.1.3-9)

Effects of quizartinib 0.1, 0.3, 1.0, and 2.9 μmol/L on potassium channel and those of AC886 0.1, 0.3, 0.9, and 2.9 μmol/L were investigated using human KvLQT1/mink-expressing HEK293 cell lines. Table 8 shows the inhibitory rates against potassium channel. The IC_{50} value of quizartinib was <0.3 μmol/L, while the IC_{50} value of AC886 could not be calculated. Quizartinib at all the concentrations and AC886 at 0.3, 0.9, and 2.9 μmol/L showed a statistically significant inhibition of the channel as compared with the control (HEPES buffered physiological saline[5)] containing 0.3% DMSO) ($P < 0.05$, Dunnett's multiple comparison test).

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4) C_{max} of unbound quizartinib in plasma was calculated in light of the following data: In Study J201 in Japanese patients with relapsed or refractory FLT3-ITD mutation-positive AML, the arithmetic mean C_{max} at quizartinib 53 mg was 480 ng/mL; the molar mass of quizartinib is 560.7 g/mol; and the plasma protein binding rate of quizartinib in humans is ≥99% [see Section 4.2.2].

5) 137 mmol/L sodium chloride, 4.0 mmol/L potassium chloride, 1.8 mmol/L calcium chloride, 1.0 mmol/L magnesium chloride, 10 mmol/L HEPES, and 10 mmol/L glucose

Table 8. Inhibitory rate of quizartinib and AC886 against potassium channel

Concentration of quizartinib or AC886 (μmol/L)	Inhibitory rate (%)			
	n	Quizartinib	n	AC886
0.1	5	28.9 ± 7.5	4	11.0 ± 3.3
0.3	3	55.2 ± 4.2	4	20.6 ± 4.0
1.0 or 0.9	7	56.5 ± 2.5	5	21.2 ± 2.7
2.9	5	67.5 ± 3.3	5	26.9 ± 2.7

Mean ± SE

Effects of quizartinib and AC886 0.1, 0.3, 1.0, and 3.0 μmol/L on sodium channel were investigated using human Nav1.5-expressing HEK293 cell lines. The IC_{50} values of quizartinib and AC886 were both >3.0 μmol/L.

Effects of quizartinib 0.1, 0.3, 1, and 3.0 μmol/L on late sodium current and those of AC886 0.1, 0.2, 0.8, and 2.5 μmol/L were investigated using human Nav1.5-expressing HEK293 cell lines. The IC_{50} values of quizartinib and AC886 were >3.0 μmol/L and >2.5 μmol/L, respectively.

Effects of quizartinib 0.1, 0.3, 1, and 2.3 μmol/L on L-type calcium channel and those of AC886 0.1, 0.2, 1.0, and 3.0 μmol/L were investigated using human Cav1.2-expressing Chinese hamster ovary (CHO) cell lines. The IC_{50} values of quizartinib and AC886 were >2.3 μmol/L and >3.0 μmol/L, respectively.

3.3.1.3 Effects on blood pressure, heart rate, and electrocardiogram (CTD 4.2.1.3-10)

A single dose of quizartinib 3, 10, 30, 100, and 200 mg/kg was orally administered to 4 cynomolgus monkeys at intervals of 3 days and in this sequential order to investigate the effects on blood pressure (systolic blood pressure, diastolic blood pressure, mean arterial pressure, and pulse pressure), heart rate, and electrocardiogram (PR interval, QRS interval, QT interval, and QTc interval). QTc interval prolonged at ≥10 mg/kg of quizartinib, and blood pressure increased transiently at ≥100 mg/kg.

The applicant explained that prolonged QT interval was also observed in the clinical studies [see Section 7.R.3.6] and accordingly, appropriate advice would be provided on QT interval prolongation to healthcare professionals via the package insert.

3.R Outline of the review conducted by PMDA

Based on the submitted data, PMDA concluded that the applicant's explanation about non-clinical pharmacology findings of quizartinib is acceptable, while showing a different view in the following subsection.

3.R.1 Mechanism of action of quizartinib and its efficacy

The applicant's explanation about the action mechanism and efficacy of quizartinib:

FLT3 is a Class III receptor tyrosine kinase mainly expressed on the cell membrane of hematopoietic progenitor cells and AML cells. FLT is thought to be involved in the differentiation and proliferation of hematopoietic progenitor cells (*Blood.* 2002;100:1532-42, etc.).

FLT3 gene mutation is a type of gene mutations observed in AML, and major mutations are FLT3-ITD mutation (approximately 25%) involving the juxtamembrane domain of the receptor and FLT3-tyrosine

kinase domain (TKD) mutation (approximately 7%) involving the kinase domain (*Blood.* 2002;100:1532-42, etc.). The FLT3-ITD mutation leads to a conformational change at the juxtamembrane domain of FLT3, allowing ligand-independent dimerization or activation of FLT3, which is considered to contribute to the proliferation of AML cells (*Blood.* 2002;100:1532-42, etc.).

Quizartinib is a low molecular weight compound that inhibits tyrosine kinases such as FLT3. Mainly the compound binds to FLT3 with the ITD mutation [see Section 3.1.1] and thereby inhibits the phosphorylation of downstream signaling molecules (signal transducer and activator of transcription 5 [STAT5], extracellular signal-regulated kinase [ERK], etc.) (*Blood.* 2017;130:48-58, etc.), consequently exerting its tumor growth inhibitory effect.

Based on its mechanism of action and inhibitory effect on tumor growth in nude mice subcutaneously implanted with FLT3-ITD mutation-positive AML cell lines [see Section 3.1.3], quizartinib is expected to have an effect in treating FLT3-ITD mutation-positive AML. Furthermore, in light of the following observations, the inhibitory effect of quizartinib against kinases such as mast/stem cell growth factor receptor (KIT) and platelet derived growth factor receptor (PDGFR) may contribute to the efficacy of quizartinib against AML:

- Some patients with AML had *KIT* gene mutation and expression of *PDGFR* fusion gene (*Blood.* 2010;116:2429-37).

- Quizartinib inhibited the proliferation of human AML cell line with *KIT* gene mutation (Kasumi-1 cell line) and human leukemia cell line with *PDGFR* fusion gene (EOL-1 cell line) (*Mol Cancer.* 2013;12:19).

The applicant's explanation about differences in pharmacological properties between quizartinib and gilteritinib fumarate (gilteritinib), the other FLT3 inhibitor approved in Japan:
Both quizartinib and gilteritinib inhibit FLT3 phosphorylation. The following are the differences between quizartinib and gilteritinib reported:

- The FLT3-TKD mutation affects the conformation of kinase domain of FLT3. While the FLT3-TKD mutation does not affect gilteritinib's binding to FLT3, it decreases quizartinib's binding to FLT3 (*Cancer Discov.* 2015;5:668-79).

- Quizartinib inhibited phosphorylation of FLT3 with the ITD mutation only, but the inhibitory effect against phosphorylation of FLT3 with both ITD and TKD mutations was weak (*Nature.* 2012;485:260-3). Gilteritinib, on the other hand, inhibited the phosphorylation of FLT3 with ITD mutation only (*Blood.* 2017;129:257-60) and the phosphorylation of FLT3 having both ITD and TKD mutations (see "Review Report on Xospata Tablets 40 mg dated August 2, 2018").

PMDA's view:
The applicant's explanation is generally acceptable. However, the level of contribution of kinases other than FLT3 (KIT, PDGFR, etc.) to FLT3-ITD mutation-positive AML cell proliferation and the association of the inhibitory effect of quizartinib against phosphorylation of kinases other than FLT3 with tumor growth inhibitory effect against FLT3-ITD mutation-positive AML remain unclear. This fact

and the findings on the pharmacological properties of quizartinib, including differences from gilteritinib, can be useful information in selecting eligible patients for the clinical use of quizartinib. The applicant should continue the investigation and provide new findings, once available, to healthcare professionals appropriately.

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

In this section, unless otherwise specified, doses of quizartinib and quizartinib or AC886 concentration is expressed as free base. The pharmacokinetics (PK) of quizartinib in animals was investigated in rats, dogs, etc. Plasma protein binding, drug-metabolizing enzyme, and transporters of quizartinib were investigated in human or animal biological samples.

4.1 Absorption

4.1.1 Single-dose administration

A single dose of quizartinib was administered intravenously at 1 mg/kg or orally at 1, 3, and 10 mg/kg to male and female dogs, and plasma quizartinib concentrations were determined (Table 9). Exposure to quizartinib increased roughly dose-proportionally within the oral dose range investigated. Exposure to quizartinib was higher in females than in males. The applicant explained that the concerned result was considered attributable to sex differences in metabolism that contributed to the elimination of quizartinib. The bioavailability (BA) of quizartinib following oral dose of 1 mg/kg was 28%.

Table 9. PK parameters of quizartinib
(single intravenous or single oral administration in male and female dogs)

Route of administration	Dose (mg/kg)	Sex	n	C_{max} (ng/mL)	t_{max} (h)	AUC_{inf} (ng·h/mL)	$t_{1/2}$ (h)	CL (mL/min/kg)	V_z (L/kg)
Intravenous	1	Male	3	2,580 ± 2,600	-	2,620 ± 600	6.0 ± 0.6	6.6 ± 1.3	3.4 ± 0.58
	1	Female	3	1,920 ± 1,030	-	3,840 ± 320	8.7 ± 2.5	4.4 ± 0.35	3.4 ± 0.79
Oral	1	Male	3	129 ± 25	1.2 ± 0.76	746 ± 75	-	-	-
	3	Male	3	942 ± 112	1.0 ± 0	5,110 ± 300	-	-	-
	10	Male	2	1,640, 1,470	2, 1	11,800, 7,350	-	-	-
	10	Female	3	2,210 ± 660	1.2 ± 0.76	20,500 ± 10,200	-	-	-

Mean ± SD (individual values for n = 2); -, Not calculated

4.1.2 Repeated-dose administration

Quizartinib was orally administered QD to male and female rats at 1 and 10 mg/kg for 4 weeks, and plasma concentrations of quizartinib and its metabolite, AC886 (hydroxide form, [see Section 4.3.2]), were determined (Table 10). Exposures to quizartinib and AC886 were higher in females than in males. Exposures to quizartinib and AC886 on Day 28 were higher than those on Day 1.

Table 10. PK parameters of quizartinib and AC886*
(4-week repeated oral administration in male and female rats)

Day of measurement (Day)	Dose (mg/kg)	Analyte	C_{max} (ng/mL)		t_{max} (h)		AUC_{last} (ng·h/mL)	
			Male	Female	Male	Female	Male	Female
1	1	Quizartinib	66.1	69.3	4.00	6.00	925	954
		AC886	50.3	70.3	4.00	2.00	647	885
	10	Quizartinib	1,330	1,885	4.00	4.00	15,727	23,380
		AC886	659	708	4.00	4.00	8,601	9,704
28	1	Quizartinib	141	136	6.00	1.00	2,184	1,780
		AC886	73.7	126	4.00	2.00	1,193	1,629
	10	Quizartinib	2,008	2,858	6.00	4.00	32,705	46,694
		AC886	733	940	6.00	4.00	12,156	15,947

* Calculated from mean plasma concentrations at measurement timepoints (n = 3)

4.1.3 *In vitro* membrane permeability

Membrane permeability of quizartinib was investigated using human colon cancer-derived Caco-2 cell line. The apparent permeability in apical to basolateral direction ($P_{app\ A\rightarrow B}$) of quizartinib 10 μmol/L was 0.981×10^{-6} cm/second. The applicant explained that quizartinib was considered to have a medium membrane permeability based on the fact that $P_{app\ A\rightarrow B}$ of poorly membrane permeable ^{14}C-mannitol (9.09 μmol/L) and highly membrane permeable ^{3}H-propranolol (26.9 nmol/L) were 0.682×10^{-6} and 23.8×10^{-6} cm/second, respectively.

4.2 Distribution

4.2.1 Tissue distribution

A single dose of ^{14}C-labeled quizartinib hydrochloride (^{14}C-quizartinib) 6 mg/kg was orally administered to male pigmented rats, and tissue distribution of the radioactivity was investigated by quantitative whole-body autoradiography. The radioactivity was widely distributed in the tissues, and the radioactivity concentration peaked by 2 hours post-dose in most of the tissues including blood. The ratio of AUC_{all} of tissue radioactivity to that of blood radioactivity was remarkably high in the uvea, meninx, small intestine, Harderian gland, large intestine, liver, adrenal gland, pigmented skin, cecum, and renal cortex (544, 119, 48, 28, 20, 19, 15, 15, 13, and 11, respectively). In most of the tissues, the radioactivity concentration decreased to the lower limit of quantitation (0.053 μg Eq./g) or lower at up to 336 hours post-dose except the uvea, in which the radioactivity concentration at 336 hours post-dose was still 23 μg Eq./g, showing the slowest elimination rate. The applicant therefore explained that the above findings suggested the binding of quizartinib or its metabolite to melanin.

4.2.2 Plasma protein binding

Quizartinib or AC886 (50-2,500 ng/mL for both) was incubated with plasma specimens from mice, rats, dogs, monkeys, or humans at 37°C for 10 minutes, and plasma protein binding of quizartinib or AC886 was investigated by ultracentrifugation. The plasma protein binding rates of quizartinib and AC886 were ≥99% and were generally constant across the concentrations in any animal species.

Quizartinib (5 μmol/L) was incubated with human serum albumin (ALB) (300 μmol/L) at 37°C, and binding of quizartinib to human serum ALB was investigated by an equilibrium dialysis method.[6)] The

[6)] Although the binding to human α1-acid glycoprotein was investigated, quizartinib concentrations were not measured, resulting in a failure of calculation of the binding rate.

binding rate of quizartinib to human serum ALB was 99.8%. The applicant explained that the above finding suggested the binding of quizartinib mainly to serum ALB in human plasma.

4.2.3 Distribution in blood cells

Quizartinib or AC886 (10, 200, 1,600, and 4,000 ng/mL for both) was incubated with human blood at 37°C for 80 minutes, and the distributions of quizartinib and AC886 in blood cells were investigated. The blood/plasma concentration ratios of (a) quizartinib and (b) AC886 at 10, 200, 1,600, and 4,000 ng/mL were (a) 1.48, 1.31, 1.10, and 0.97; and (b) 3.40, 2.79, 1.62, and 1.30; respectively. The applicant explained that the results suggested the distribution of quizartinib and AC886 into erythrocytes.

4.2.4 Placental and fetal transfer

Placental and fetal transfer of quizartinib was not investigated. The applicant explained that quizartinib may possibly cross the placenta by passive diffusion and be distributed in fetuses in light of its physicochemical properties (molecular mass, 560.7; logP value, 2.33).

4.3 Metabolism

4.3.1 *In vitro*

Quizartinib (1 μmol/L) was incubated with liver microsome of mice, rats, dogs, monkeys, or humans at 37°C for 60 minute in the presence of nicotinamide adenine dinucleotide phosphate hydrogen (NADPH), and the intrinsic clearance (CL_{int}) and metabolites of quizartinib were investigated. The CL_{int} calculated from the elimination rate of quizartinib was <23 μL/min/mg in mice, rats, and humans, and 42 and 73 μL/min/mg, respectively, in dogs and monkeys. AC886 was detected in rats, dogs, monkeys, and humans, and M2 (*N*-deethyl form) was detected in all animal species.

Cytochrome P450 (CYP) isoforms involved in the metabolism of quizartinib and AC886 in humans were investigated as described below. The applicant explained that quizartinib and AC886 are substrates of CYP3A, and CYP3A plays a main role in metabolism from quizartinib to AC886.

- Quizartinib or AC886 (1 μmol/L for both) was incubated with microsomes prepared from insect cells expressing human CYP isoforms (CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, CYP3A4, and CYP3A5) at 37°C for 60 minutes[7)] in the presence of NADPH. Quizartinib and AC886 were mainly metabolized by CYP3A4 and CYP3A5, and quizartinib was metabolized to AC886 only in the presence of CYP3A4 and CYP3A5. Quizartinib and AC886 were hardly metabolized by the other CYP isoforms.

- Quizartinib or AC886 (1 μmol/L for both) was incubated with human liver microsomes in the presence of inhibitors (furafylline, montelukast, sulfaphenazole, benzylnirvanol, quinidine, and ketoconazole, respectively) against CYP isoforms (CYP1A2, CYP2C8, CYP2C9, CYP2C19, CYP2D6, and CYP3A) and NADPH at 37°C for 60 minutes.[8)] The metabolism of quizartinib and AC886 was inhibited by 95.0% and 85.0%, respectively, in the present of ketoconazole, and metabolism from quizartinib to AC886 was inhibited by 89.6%.

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7) In the investigation for CYP isoforms involved in metabolism from quizartinib to AC886, the incubation time was 5 minutes.
8) In the investigation for CYP isoforms involved in metabolism from quizartinib to AC886, the incubation time was 15 minutes.

4.3.2 *In vivo*

A single dose of ^{14}C-quizartinib 30 mg/kg was orally administered to intact male and female rats, and metabolites in plasma, urine, and feces were investigated. In plasma at 24 hours post-dose, unchanged quizartinib (accounting for 59.0% and 75.7%, respectively, of the radioactivity in plasma from males and females) and AC886 (31.6% and 21.0%) were mainly detected. In urine until 72 hours post-dose, AC886 (accounting for 0.58% and 0.64%, respectively, of the administered radioactivity in males and females) was mainly detected, while in feces, unchanged quizartinib (25.3% and 19.0%) was mainly detected.

A single dose of quizartinib 30 mg/kg was orally administered to bile duct-cannulated male rats, and metabolites in bile were investigated. In bile until 48 hours post-dose, unchanged quizartinib (accounting for 6.04% of the dose) and AC886 (3.81%) were mainly detected.

4.4 Excretion

4.4.1 Excretion in urine, feces, and bile

A single dose of ^{14}C-quizartinib 30 mg/kg was orally administered to intact male and female rats, and urinary and fecal excretion rates of the radioactivity (percentage of the administered radioactivity) were investigated. The urinary and fecal excretion rates of the radioactivity until 168 hours post-dose were 1.53% and 90.0%, respectively, in males and 1.68% and 93.0%, respectively, in females. The applicant explained that quizartinib and its metabolite is mainly excreted in feces through bile based on the above results and detected unchanged quizartinib and quizartinib metabolite in bile from bile duct-cannulated male rats treated with quizartinib [see Section 4.3.2].

4.4.2 Excretion in milk

The excretion of quizartinib in milk was not investigated. The applicant explained that quizartinib may possibly be excreted in milk in light of its physicochemical properties (acid dissociation constant [pKa] value, 4.75; logD value at pH 7.2, 2.31; and human plasma protein binding [see Section 4.2.2]).

4.5 Pharmacokinetic interactions

4.5.1 Enzyme inhibition

The applicant's explanation:

The clinical use of quizartinib is unlikely to cause pharmacokinetic interactions mediated by the inhibitory effect of quizartinib or AC886 against CYP isoforms in light of the following observations and the C_{max} values of quizartinib and AC886 (0.69 and 0.48 μmol/L[9)], respectively) at a steady state reached by multiple oral doses of quizartinib 53 mg.

- Quizartinib or AC886 (0.31-40 μmol/L[10)] for both) was incubated with human liver microsomes in the presence of substrates (phenacetin, bupropion, paclitaxel, diclofenac, *S*-mephenytoin, dextromethorphan, and testosterone, respectively) of CYP isoforms (CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, and CYP3A) and NADPH, and inhibitory effects of quizartinib and AC886 against the CYP isoforms were investigated. Quizartinib did not clearly inhibit the

9) C_{max} on Day 1 of Cycle 2, which followed treatment with oral quizartinib 30 mg QD from Days 1 to 15 and 60 mg from Day 16 onward in Cycle 1 in Study J201 in Japanese patients with relapsed or refractory FLT3-ITD mutation-positive AML

10) Amount of quizartinib hydrochloride

metabolism of substrates of CYP isoforms. In addition, AC886 inhibited the metabolism of CYP2C19 substrate with the inhibition constant (K_i) value of 10.4 μmol/L. AC886 did not clearly inhibit the metabolism of substrates of the other CYP isoforms.

- Quizartinib or AC886 (1 μmol/L[10)] for both) was incubated with human liver microsomes in the presence of NADPH, followed by incubation with substrates (phenacetin, bupropion, paclitaxel, diclofenac, *S*-mephenytoin, and bufuralol, respectively) of CYP isoforms (CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, and CYP2D6), and time-dependent inhibitory effects of quizartinib and AC886 against CYP isoforms were investigated. As with the above, time-dependent inhibitory effects of quizartinib and AC886 (10 and 1 μmol/L[10)], respectively) against CYP3A substrates (midazolam and ^{14}C-testosterone) were investigated. Neither quizartinib nor AC886 clearly inhibited the metabolism of substrates of CYP isoforms in a time-dependent manner.

4.5.2 Enzyme induction

Human hepatocytes were treated with quizartinib (1-10 μmol/L[10)]) for 3 days, and the messenger ribonucleic acid (mRNA) expression level of CYP isoforms (CYP1A2, CYP2B6, and CYP3A) induced by quizartinib were determined. Quizartinib did not clearly induce mRNA expression of any level of these CYP isoforms. The applicant explained that the clinical use of quizartinib is unlikely to cause pharmacokinetic interactions mediated by CYP isoform induction.

4.5.3 Transporters

Transport of ^{14}C-quizartinib (3 μmol/L) was investigated using Madin-Darby canine kidney strain-II (MDCKII) cell lines expressing human P-glycoprotein (P-gp). The efflux ratio (ratio of secretion permeability rate to absorption permeability rate) of ^{14}C-quizartinib in cell lines expressing P-gp was 3.6 times higher than that in cell lines not expressing P-gp. In addition, the efflux ratios in cell lines expressing P-gp in the presence a P-gp inhibitor (verapamil 200 μmol/L or ketoconazole 50.0 μmol/L) or in the absence of P-gp inhibitor were 1.5, 2.5, and 5.8, respectively. The applicant explained that the above results showed that quizartinib is a substrate of P-gp.

The clinical use of quizartinib may cause a pharmacokinetic interaction mediated by the inhibitory effect of quizartinib against P-gp in light of (a) the observations below; (b) C_{max} of and AC886 (0.69 and 0.48 μmol/L[9)], respectively) at a steady state reached following multiple oral doses of quizartinib 53 mg; (c) the estimated quizartinib concentration (378 μmol/L) in the gastrointestinal tract following the dose of quizartinib 53 mg.

- Using MDCKII cell line expressing human P-gp, inhibitory effects of quizartinib and AC886 (1-100 μmol/L[11)] for both) against transport of digoxin (1 μmol/L) were investigated. Quizartinib and AC886 inhibited the transport of the P-gp substrate with the IC_{50} values of 9.55 and >30 μmol/L, respectively.

- Using MDCKII cell line expressing human breast cancer resistance protein (BCRP), inhibitory effects of quizartinib and AC886 (10 μmol/L for both) against transport of prazosin (100 nmol/L)

[11)] Because of insoluble matters found in the samples containing quizartinib 100 μmol/L or AC886 50 or 100 μmol/L, data on the quizartinib concentrations up to 50 μmol/L and the AC886 concentrations up to 30 μmol/L were used in the calculation of the IC_{50} values.

were investigated. Quizartinib did not clearly inhibit the transport of the BCRP substrate, while AC886 inhibited the transport of the BCRP substrate by 29.1%.

- Using membrane vesicles prepared from Sf9 insect cell line expressing human bile salt export pump (BSEP), inhibitory effects of quizartinib (0.032-10 μmol/L) and AC886 (10 μmol/L) against transport of taurocholate (1 μmol/L) were investigated. Quizartinib inhibited transport of the BSEP substrate with the IC_{50} value of 4.92 μmol/L. AC886 did not clearly inhibit transport of the BSEP substrate.

- Using MDCKII cell line expressing human organic anion transporting polypeptide (OATP) 1B1, OATP1B3, organic anion transporter (OAT) 1, OAT3, organic cation transporter (OCT) 1, OCT2, or multidrug and MATE1, inhibitory effects of quizartinib and AC886 (10 μmol/L for both) against transport of these transporters' substrates[12)] were investigated. Quizartinib did not clearly inhibit transport of any transporter substrate. AC886 did not clearly inhibit transport of the OATP1B1, OATP1B3, OAT1, OAT3, and OCT1 substrates and inhibited transport of OCT2 and MATE1 substrates by 15.7% and 46.5%, respectively.

- Using MDCKII cell line expressing human MATE2-K, inhibitory effects of quizartinib (10 μmol/L) and AC886 (0.032-10 μmol/L) against transport of metformin (10 μmol/L) were investigated. Quizartinib and AC886 10 μmol/L inhibited the transport of the MATE2-K substrate by 35.7% and 42.2%, respectively.

4.R Outline of the review conducted by PMDA

Based on the submitted data and review in the following section, PMDA accepted the applicant's explanation about non-clinical pharmacokinetic findings of quizartinib.

4.R.1 Tissue distribution

Because quizartinib or its metabolite was suggested to bind to melanin [see Section 4.2.1], PMDA asked the applicant to explain the safety of quizartinib in melanin-containing tissues.

The applicant's response:

In light of the following observations, safety problems attributable to the distribution of quizartinib or its metabolite into the melanin-containing tissues are unlikely to occur during the clinical use of quizartinib.

(a) In the 13-week repeated oral dose toxicity studies in rats, dogs, and monkeys, no toxicity was observed in the skin or eyes, melanin-containing tissues [see Section 5.2].
(b) The pooled analysis including foreign phase I studies (Study CP0001 and Study 2689-CL-0011 [Study 0011], foreign phase II studies (Study AC220-002 [Study 002] and Study 2004), and foreign phase III study (Study 007) showed that incidence of skin and subcutaneous tissue disorders and

12) Substrates used for (a) OATP1B1 and OATP1B3, (b) OAT1 and OAT3, (c) OCT1, and (d) OCT2 and MATE1 were (a) estradiol-17β-glucuronide (2 μmol/L) and cholecystokinin-8 (2 μmol/L), (b) *p*-aminohippurate (2 μmol/L for OAT1 substrate, 10 μmol/L for OAT3 substrate), (c) 1-methyl-4-phenylpyridinium (2 μmol/L), and (d) metformin (10 μmol/L).

eye disorders was 52.6% (388 of 737 of subjects) and 16.4% (121 of 737 of subjects), respectively, but most events were non-serious and Grade ≤2, raising no particular clinical concerns.

PMDA accepted the applicant's explanation.

4.R.2 Pharmacokinetic interactions

Results from *in vitro* studies suggested that quizartinib was P-gp substrate and inhibited P-gp [see Section 4.5.3]. Study data on whether quizartinib acts as a substrate of transporters other than P-gp were not submitted with this application.

The applicant's explanation about the pharmacokinetic interactions of quizartinib with a (a) P-gp inhibitor, (b) P-gp substrate, and (c) BCRP inhibitor:

(a) Because no particular safety concerns were raised during the concomitant use of quizartinib with a P-gp inhibitor in the Japanese phase II study (Study J201) or foreign phase III study (Study 007), such combination is unlikely to raise problems in the clinical use of quizartinib.

(b) No particular safety concerns were raised during the concomitant use of quizartinib with a P-gp substrate in the Japanese phase II study (Study J201) or foreign phase III study (Study 007). However, healthcare professionals should be advised to use caution in the concomitant use of quizartinib with a P-gp substrate, given the extremely limited number of subjects treated concomitantly with the P-gp substrate.

(c) Transport of quizartinib (3 and 30 μmol/L) and AC886 (3 and 15 μmol/L) mediated by BCRP was investigated using porcine kidney LLC-PK1 cell line expressing human BCRP. The efflux ratio of quizartinib 3 and 30 μmol/L in cell line expressing BCRP was 1.27 and 1.11 times higher, respectively, than that in cell line not expressing BCRP. The efflux ratio of AC886 3 and 15 μmol/L in cell line expressing BCRP was 0.88 and 0.83, respectively, in the presence of a BCRP inhibitor (Ko143 at 1 μmol/L), and 3.14 and 1.29, respectively, in the absence of the BCRP inhibitor. These results show that quizartinib is not a substrate of BCRP, but AC886 is. However, no particular safety concerns were raised during the concomitant use of quizartinib with a BCRP inhibitor in the foreign phase III study (Study 007), and such combination is unlikely to raise problems in the clinical use of quizartinib.

PMDA's view:

The applicant's explanation about the pharmacokinetic interaction of quizartinib with a P-gp inhibitor or BCRP inhibitor is generally acceptable. Given that no clinically serious concerns potentially attributable to the interaction between quizartinib and a P-gp inhibitor or BCRP inhibitor were raised in the Japanese phase II study (Study J201) or foreign phase III study (Study 007), the need of cautionary advice on the concomitant use with a P-gp substrate is low at present. However, information on the pharmacokinetic interactions of quizartinib mediated by transporters is important for the proper use of quizartinib. Therefore, the applicant should continue collecting relevant data and, once available, useful information should be disseminated to healthcare professionals appropriately.

5. Toxicity and Outline of the Review Conducted by PMDA

In this section, unless otherwise specified, doses of quizartinib are expressed as free base.

5.1 Single-dose toxicity

Acute toxicity of quizartinib was evaluated based on results from a single-dose toxicity study in rats and single ascending dose studies in dogs and monkeys (Table 11).

Table 11. Single-dose toxicity

Test system	Route of administration	Dose (mg/kg)	Major findings	Approximate lethal dose (mg/kg)	Attached document CTD
Male and female rats (Sprague Dawley)	Oral	100, 150, 200, 250, 300[a)]	Death: 150 (1 of 3 females), 200 (1 of 3 females), 250 (2 of 3 females), 300 (2 of 3 females) ≥150: Decreased locomotor activity, soft stool or dark stool, hematuria, half closed eyelid, pale skin, dark/pale kidney	Male: >300 Female: 150	4.2.3.1-1
Male and female dogs (beagle)	Oral	10, 20, 40, 80, 100, 150, 200[b)]	≥40: Decreased weight	>200	4.2.3.1-2
Male and female monkeys (cynomolgus)	Oral	30, 100, 200, 300, 400[a)]	≥100: Decreased food consumption, decreased weight ≥200: Soft stool or liquid stool 400: Decreases in lymphocyte count and monocyte count, decreased reticulocyte count	>400	Reference 4.2.3.1-3

a) 22% HPβCD solution; b) 10% HPβCD solution was used in dosing solutions for 10 to 100 mg/kg as vehicle, and 22% HPβCD solution was used in dosing solutions for 150 and 200 mg/kg as vehicle.

5.2 Repeated-dose toxicity

Repeated-dose toxicity studies (1 and 3 months) were conducted in rats, dogs, and monkeys[13)] (Table 12). Quizartinib caused toxicity in the blood, bone marrow, and lymphoid tissue (rats, dogs, and monkeys), liver (dogs and monkeys), kidneys (rats and dogs), and male and female genital organs (rats and monkeys). In 3 months repeated-dose toxicity studies in rats, dogs, and monkeys, $AUC_{0\text{-}24h}$ of quizartinib at the no observed adverse effect levels (NOAELs) of 3, 5, and 3 mg/kg/day were 12,100, 3,930, and 727 ng·h/mL, respectively, which were 1.31, 0.43, and 0.08 fold, respectively, the clinical exposure (9,240 ng·h/mL[14)]).

13) In dogs, a metabolite (morpholine-ring oxidized form) that was not detected in the other animals (including humans) was detected, and remarkable hepatotoxicity (birefringent crystal deposition) was observed only in dogs and thus considered potentially related to the concerned metabolite. A repeated-dose toxicity study was conducted in monkeys as well.

14) AUC_{tau} (arithmetic mean) on Day 1 of Cycle 2 following treatment with oral quizartinib26.5 mg QD from Days 1 to 15 and 53 mg from Day 16 onward in Cycle 1 in Study J201 in Japanese patients with relapsed or refractory FLT3-ITD mutation-positive AML

Table 12. Repeated-dose toxicity

Test system	Route of administration	Treatment period	Dose (mg/kg/day)	Major findings	NOAEL (mg/kg/day)	Attached document CTD
Male and female rats (Sprague Dawley)	Oral	4 weeks (QD) + 4 weeks withdrawal	0,[a] 5, 15, 60/30[b]	Death or moribund euthanasia[h]: 0 (2 of 10 males),[i] 15 (2 of 20 males),[i] 60/30 (20 of 20 males or females)[j] ≥5: Increases in white blood cell count, lymphocyte count, MCV, and MCH; decreases in red blood cell count, hemoglobin, hematocrit, neutrophil count, monocyte count, and eosinophil count; increases in serum ALT, AST, and ALP; decreased weight of ovary, spleen, and testis; and decreased bone marrow cell density ≥15: Increased reticulocyte count; microcytosis; macrocytosis; anisocytosis; polychromasia; decreased thymus weight; thymus atrophy; and renal tubular epithelium vacuolation, basophilic change, and granular casts Reversibility: Reversible[k]	<5	4.2.3.2-1
Male and female rats (Sprague Dawley)	Oral	13 weeks (QD) + 30 days withdrawal	0,[c] 1, 3, 10	Death: 10 (1 of 15 females)[l] ≥1[m]: Decreased thymus weight; increased pigmentation and decreased weight of spleen; and thymus lymphoid tissue atrophy/necrosis ≥3[m]: Decreases in white blood cell count, red blood cell count, hemoglobin, hematocrit, platelet count, and reticulocyte count; increases in MCV, MCH, red cell distribution width, and mean platelet volume; increases in serum glucose, ALT, AST, and ALP; decreased hematopoietic cell density; decreased weight of uterus and spleen; decreased bone marrow hematopoietic cell density; ovarian cyst; and abnormal and increased epithelial mucification in the vagina ≥10: Eosinopenia; increases in serum urea and creatinine; renal tubular epithelium basophilic change, crystallization, vacuolation, dilatation, and mononuclear cell infiltration; splenic extramedullary hematopoiesis and pigmentation; decreased testis weight; seminiferous epithelium degeneration and atrophy; sperm cell undescended; and epididymis semen decreased/aspermia or ductus epididymis cell residue accumulation Reversibility: Reversible except for increased epithelial mucification in the vagina	3	4.2.3.2-2
Male and female dogs (beagle)	Oral	4 weeks (QD)	0,[a] 10/5,[d] 50/25,[d] 150/40[d]	Moribund euthanasia: 150/40 (1 of 3 males); decreased locomotor activity; decubitus position; emaciation; yellowish whole body; and decreases in body weight and food consumption ≥10/5: Emaciation,[n] and decreased reticulocyte count[m] ≥50/25: No-feces; decreased body weight; decreases in red blood cell count, hemoglobin, hematocrit, white blood cell count, neutrophil count, lymphocyte count, and monocyte count; increases in serum ALT, AST, ALP, and total bilirubin; small thymus; pale liver; decreased thymus weight; liver crystal deposition and periportal hepatocyte vacuolation; thymus and spleen atrophy; decreased femur and sternum bone marrow cell density; renal tubular epithelium basophilic change; and adrenocortical hypertrophy 150/40: Decreased locomotor activity; yellowish whole body; hunchback position; feeling cold in contact; excessive salvation; large platelet or platelet aggregate; macrocytosis; and anisocytosis	10/5	4.2.3.2-3

Test system	Route of administration	Treatment period	Dose (mg/kg/day)	Major findings	NOAEL (mg/kg/day)	Attached document CTD
Male and female dogs (beagle)	Oral	13 weeks (QD) + 30 days withdrawal	0,[a)] 1, 5, 15	≥1[m)]: Decreased thymus weight; and renal tubular epithelium basophilic change ≥5[m)]: Pale skin; decreased body weight; decreased reticulocyte count; liver pigmentation; sinusoidal parietal cell activation; bile duct hyperplasia; and renal tubular single cell necrosis 15: Pale skin; decreases in red blood cell count, hemoglobin, hematocrit, neutrophil count, lymphocyte count, monocyte count, eosinophil count, basophil count, and large unstained cell count; increases in serum AST, ALT, ALP, total bilirubin, conjugated bilirubin, and triglyceride; increased liver weight; renal tubular epithelium pigmentation; and hepatocyte single cell necrosis, vacuolation, hepatic fibrosis, inflammation, and extramedullary hematopoiesis Reversibility: Reversible	5	4.2.3.2-4
Male and female monkeys (cynomolgus)	Oral	4 weeks (QD) + 4 weeks withdrawal	0,[c)] 10, 30, 100/60[f)]	Death or moribund euthanasia: 100/60 (2 of 5 males and 1 of 5 females); decreased locomotor activity; half closed eyelid; hunchback position; dehydration; emaciation; and decreases in body weight and food consumption[o)] ≥10 [m)]: Decreases in lymphocyte count, monocyte count, basophil count, red blood cell count, hemoglobin, and hematocrit; increased serum ALT; decreased serum ALP, phosphorus, and cholesterol; decreased weight of spleen and thymus; decreased bone marrow hematopoietic cell density; emperipolesis; and atrophy/necrosis of spleen, thymus, and various lymphoid tissue ≥30: Hunchback position; dehydration; emaciation; decreased body weight; decreased reticulocyte count; and decreases in serum total protein, ALB, globulin, and calcium 100/60: Decreased locomotor activity; half closed eyelid; increased neutrophil count; increases in serum creatinine, urea, and AST; increased liver weight; acute renal tubular degeneration; glandular stomach mucosal erosion/ulceration; and small intestinal villi atrophy Reversibility: Reversible	10	4.2.3.2-6

Test system	Route of administration	Treatment period	Dose (mg/kg/day)	Major findings	NOAEL (mg/kg/day)	Attached document CTD
Male and female monkeys (cynomolgus)	Oral	13 weeks (QD) + 4 weeks withdrawal	0,[c] 3, 10/6,[g] 30/12[g]	Death or moribund euthanasia: 10/6 (2 of 6 females), 30/12 (1 of 6 males and 2 of 6 females), deterioration of clinical condition; anaemia; and decreased bone marrow cell density ≥3[m]: Increases in neutrophil count, MCV, red cell distribution width, and platelet count; increases in serum AST, ALT, total bilirubin, urea, creatinine, glucose, and triglyceride; decreases in lymphocyte count, eosinophil count, red blood cell count, hemoglobin, hematocrit, and reticulocyte count; decreases in serum total protein, ALB, globulin, phosphorus, sodium, potassium, and chloride; decreased weight of testis, spleen, uterus, and ovary; atrophy of thymus, spleen, and various lymphoid tissues; and decreased bone marrow hematopoietic cell density ≥10/6: Decreased locomotor activity; hunchback position; dehydration; half closed eyelid; impaired coordination; soft feces and liquid stool; vomiting; prominent backbone; decreases in body weight and food consumption; decreased thymus weight; increased weight of adrenal gland and liver; esophageal and lingual epithelial degeneration/atrophy; hepatocellular cytoplasm rarefaction, single cell necrosis and vacuolation; centrilobular hepatocyte necrosis; chronic inflammation in cecum and colon; decreased testis germ cell; uterus, vagina, and ovary atrophy; epicardial fat atrophy; and adrenal cortex hyperplasia Reversibility: Reversible	3	4.2.3.2-7

a) 22% HPβCD solution; b) Serious toxicity associated with quizartinib [see j)] was observed, and the dose was decreased to 30 mg/kg/day on Days 5 to 7; c) 5% HPβCD solution; d) Serious toxicity associated with quizartinib (including moribund euthanasia) was observed by Day 9, and the doses of 10, 50, and 150 mg/kg/day were decreased to 5, 25, and 40 mg/kg/day, respectively; e) With use of 22% HPβCD solution, deterioration of clinical condition (fecal changes [soft feces or liquid stool], vomiting, and decreased food consumption) was observed in all the dose groups including the control group, and thus 22% HPβCD solution was changed to 5% HPβCD solution on Day 12; f) Serious toxicity associated with quizartinib and vehicle (including death or moribund euthanasia) was observed, and the treatment was withheld from Day 16 for 5 days, and the dose was reduced to 60 mg/kg/day; g) Serious toxicity associated with quizartinib (including death or moribund euthanasia) was observed, the doses of 10 and 30 mg/kg/day were reduced to 6 and 12 mg/kg/day, respectively; h) Including the toxicokinetic group; i) A definite cause of death has not been identified; j) The death was considered attributable to complex effects of the following toxic changes in multiple organs in association with quizartinib: deterioration of clinical condition, increased urinary crystal, renal tubular necrosis, decreased bone marrow cell density, atrophy of thymus and various lymphoid tissue, liver single cell necrosis, adrenal gland hypertrophy, testis germ cell degeneration, ductus epididymis cell residue, myocardial vacuolation, gastric single cell necrosis, and small intestine and large intestine mucosa atrophy; k) Abnormal changes in the haematology and clinical chemistry, organ weights, and macroscopic pathology resolved. Histopathology was not performed; l) Bleeding (clot) was observed in skeletal muscle of the ventral chest, and the death was considered attributable to bleeding associated with the blood collection procedure; m) Although considered related to quizartinib, the change was not judged as toxicity in light of its pharmacological nature, the incidence, seriousness of the change, and the presence of related changes; n) Emaciation observed in clinical condition was assessed as toxicologically insignificant due to no clear impact on body weight; o) The death was considered attributable to complex effects of quizartinib or vehicle.

5.3 Genotoxicity

In vitro studies conducted were bacterial reverse mutation test, gene mutation assay in mammalian cells, and chromosomal aberration assay in mammalian cells. *In vivo* studies conducted were micronucleus assays in rodents (single dose and 28-day repeated doses) (Table 13). The bacterial reverse mutation test showed positive results. The other *in vitro* studies and an *in vivo* micronucleus assay in rodents (single dose study) showed negative results, but increased frequency of immature erythrocytes with micronucleus was observed in the 15 mg/kg/day group in the micronucleus assay in rodents (28-day repeated-dose study). The change fell within the historical data, but a clear judgement in terms of whether it is positive or negative was not made taking into account that the change was potentially caused by the direct effect of quizartinib or by the secondary effect of bone marrow suppression by

quizartinib or compensated change (increased reticulocyte count). The applicant, however, explained that quizartinib had genotoxicity based on the suggested ability of quizartinib to induce reverse mutation.

Table 13. Genotoxicity

Type of study		Test system	Metabolic activation (treatment)	Concentration (μg/plate or μg/mL) or dose (mg/kg/day)	Result	Attached document CTD
In vitro	Bacterial reverse mutation test (Ames)	*Salmonella typhimurium*: TA98, TA100, TA1535, TA1537, *Escherichia coli*: WP2*uvrA*	S9–/+	0,[a] 1.58, 5.0, 15.8, 50, 158, 500, 1,581, 5,000	TA98 and TA100: Positive	4.2.3.3.1-1
	Gene mutation assay in mammalian cells	Mouse lymphoma L5178Y TK+/-(clone 3.7.2) cells	S9–- (3 hours)	0,[a] 1.84, 5.83, 18.4, 23.0, 28.8	Negative	4.2.3.3.1-2
			S9+ (3 hours)	0,[a] 3.32, 6.63, 8.29, 10.4, 13.0, 16.2, 20.2		
			S9– (24 hours)	0,[a] 0.00894, 0.0179, 0.0358, 0.0506, 0.101[b,] 0.143[b]		
	Chromosomal aberration assay in mammalian cells	Human peripheral lymphocytes	S9– (4 hours)	0,[a] 40, 80, 160, 320	Negative	4.2.3.3.1-3
			S9+ (4 hours)	0,[a] 160, 320, 640,[c] 1,280[b][c]		
			S9– (21 hours)	0,[a] 5, 10, 20		
In vivo	Micronucleus assay in rodents	Male and female rats (Sprague Dawley) Bone marrow		0,[d] 15, 50, 100 (orally, single)	Negative	4.2.3.3.2-1
		Male and female rats (Sprague Dawley) Bone marrow		0,[a] 5, 15, 60/30[e] (orally, 28 days)	Whether positive or negative not judged	4.2.3.3.2-2

a) 22% HPβCD solution; b) Cell growth inhibition was observed; c) Precipitates were observed in the culture medium; d) 5% HPβCD solution; and e) Not evaluated because all the animals died.

5.4 Carcinogenicity

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

5.5 Reproductive and developmental toxicity

Because quizartinib is an antineoplastic agent intended to treat patients with advanced cancer, (a) fertility and early embryonic development to implantation and (b) pre- and postnatal development, including maternal function, were not conducted.

The applicant's explanation:

In terms of effects on fertility and early embryonic development to implantation, the following observations suggests that quizartinib may affect male and female fertility:

- Quizartinib can induce reverse mutation [see Section 5.3].

- In the repeated-dose toxicity studies in rats and monkeys, toxicological changes were observed in the male and female genital organs (seminiferous tubule degeneration and undescended sperm cells, and ovarian cyst and increased epithelial mucification in the vagina in rats; decreased germ cells and atrophy of uterus/ovary/vagina in monkeys) [see Section 5.2].

- In mice treated with quizartinib, survival and motility of sperms, which express FLT3, were decreased (*Theriogenology.* 2019;126:145-52).

- Exposure in non-FLT3 expressing genital organs was equivalent to (1.31 fold in rats) or less than (0.08 fold in monkeys) the clinical exposure (9,240 ng·h/mL[14)]).

In an embryo-fetal development study in rats (Table 14), fetal toxicity (delayed ossification, fetal low weight) and teratogenicity (systemic subcutaneous edema)[15)] were observed. $AUC_{0\text{-}24h}$ of quizartinib at the NOAEL (2 mg/kg/day) for embryo-fetal development in rats was 4,390 ng·h/mL, which was 0.48 fold the clinical exposure (9,240 ng·h/mL[14)]).

Table 14. Reproductive and developmental toxicity

Type of study	Test system	Route of administration	Treatment period	Dose (mg/kg/day)	Major findings	NOAEL (mg/kg/day)	Attached document CTD
Embryo-fetal development	Female rats (Sprague Dawley)	Oral	Gestation Days 6 to 17 (QD)	0,[a)] 0.6, 2, 6	Maternal animals: 6: Reduced body weight gain and decreased food consumption[b)] Fetuses: 6: Lower body weight; and increased malformations (systemic subcutaneous edema, edema in the hind-limb tip, edema in the ventral cervical region) and skeletal variations (incomplete ossification of frontal bone, absent/incomplete/ partially bifurcated/ bifurcated ossification of thoracic vertebra)	Maternal animals (general toxicity and fertility): 6 Embryo-fetal development: 2	4.2.3.5.2-2

a) 5% HPβCD solution; b) The change was attributable to quizartinib but was non-serious with no impact on reproductive function of maternal animals, and thus it was not considered a change caused by toxicity of quizartinib.

5.6 Local tolerance

Although quizartinib is intended to be orally administered in clinical use, an eye mucosa and skin local tolerance test was performed in rabbits (Table 15). Quizartinib was found mildly irritative to the eye mucosa and skin in rabbits.

15) In the dose finding study in which quizartinib was administered at 1 to 20 mg/kg/day (CTD 4.2.3.5.2-1), post-implantation deaths associated with increased late embryonic resorption increased in maternal animals, and changes such as edema, short upper jaw and lower jaw (micrognathia), and brachyury were observed in fetuses.

Table 15. Local tolerance

Test system	Site of application	Test method	Major findings	Attached document CTD
Female Rabbit (NZW)	Eye	Quizartinib 0.0354 g was applied into the right eye (the left eye left untreated as the control), and the eyes were assessed at 1, 24, 48, and 72 hours post-dose.	Conjunctivitis occurred at 1 hour post-dose and resolved by 72 hours post-dose. Mildly irritative.	4.2.3.7.7-2
Male Rabbit (NZW)	Skin	Quizartinib 0.57 g was applied onto the skin, and the site was kept in the half-occlusive dressing for 4 hours. The site was assessed at 1, 24, 48, and 72 hours after application.	Erythema occurred at 1 hour post-dose and resolved by 72 hours post-dose. Mildly irritative.	4.2.3.7.7-3

5.7 Other toxicity studies

5.7.1 Juvenile animal toxicity study

A juvenile animal toxicity study was conducted in rats aged 10 days, and changes observed were similar to those in adult rats (Table 16). $AUC_{0\text{-}t}$ of quizartinib at the NOAEL (0.3 mg/kg/day) in the juvenile animal toxicity study was 587 ng·h/mL, which was 0.06 fold the clinical exposure (9,240 ng·h/mL[14)]).

Table 16. Juvenile animal toxicity study

Test system	Route of administration	Treatment period	Dose (mg/kg/day)	Major changes	NOAEL (mg/kg/day)	Attached document CTD
Male and female rats (Sprague Dawley)	Oral	9 weeks (from 10 to 70 days after birth) + 6 weeks withdrawal	0,[a)] 0.3, 3, 10	Death or moribund euthanasia: 0 (1 of 50 males),[b)] 0.3 (2 of 50 males),[b)] 2 (1 of 50 males,[b)] 1 of 50 females),[b)] 46 (25 of 50 males, 21 of 50 females)[c)] ≥0.3 [b)]: Decreased neutrophil count; increased MCV and MCH; and decreased weight of testis and epididymis 3: Decreases in lymphocyte count, white blood cell count, red blood cell count, reticulocyte count, and NK cell count; decreases in total T-cell, helper T-cell, cytotoxic T-cell, and B-lymphocyte counts; increases in serum urea nitrogen and creatinine; small testis and epididymis; degeneration/atrophy, dilatation, multinucleated giant cells in the testis seminiferous tubule; decreased sperm in the ductus epididymis; and decreased bone marrow cell density	0.3	4.2.3.5.4-2

a) 5% HPβCD solution; b) No additional changes related to quizartinib were observed until the day before the death or moribund euthanasia, and changes suggesting an administration error were observed, thus, these changes was not judged as attributable to quizartinib; c) The death or moribundity was judged as a change caused by bone marrow toxicity related to quizartinib.

5.7.2 Antigenicity

An antigenicity study was conducted in guinea pigs. Quizartinib did not induce contact sensitization (Table 17).

Table 17. Antigenicity

Test system	Site of application	Test method	Major changes	Attached document CTD
Male and female albino guinea pigs (Hartley)	Skin	Quizartinib (0.3 g/site)[a)] was applied once weekly for 3 weeks, and after 2-week withdrawal, quizartinib was re-applied (challenged) and followed by reaction assessment.	No changes No contact sensitization induced	4.2.3.7.1-1

a) In 0.3 mL of purified water, 0.3 g of quizartinib was dissolved (100% concentration).

5.7.3 Toxicity of impurities

A repeated-dose toxicity study was conducted in rats using quizartinib and quizartinib spiked with impurities (Impurity A, Impurity B, Impurity C, Impurity D, and Impurity E) (Table 18). Changes observed in the impurity-spiked group (5 + [redacted] and 5 + [redacted] mg/kg/day) were similar to those in the non-spiked group (5 + 0 mg/kg/day), and no relevant histopathological changes were observed. Accordingly, these changes were judged to be not caused by toxicity of the impurities, and the impurities were confirmed to be safe.

Table 18. Repeated-dose toxicity

Test system	Route of administration	Treatment period	Dose[a)] (mg/kg/day)	Major findings	Attached document CTD
Male and female rats (Sprague Dawley)	Oral	4 weeks (QD)	0 + 0, 5 + [redacted],[b)] 5 + [redacted],[b)] 5 + 0	≥5 + [redacted]: Increased MCV 5 + [redacted]: Decreases in red blood cell count, hemoglobin, and hematocrit; increases in serum AST and ALP; and decreased spleen weight	4.2.3.7.6-1

a) Dose of quizartinib + dose of impurities (amount each of Impurity A, Impurity B, Impurity C, Impurity D, and Impurity E); b) 5% HPβCD solution

5.7.4 Photosafety

An *in vitro* phototoxicity study was conducted using mouse fibroblast cell line, and quizartinib was judged to have no phototoxicity (Table 19).

Table 19. Photosafety

Type of study	Test system	Test method	Major findings	Attached document CTD
Phototoxicity	Mouse fibroblast cell line, Balb/c 3T3	0.18-10.05 mg/L (with UV-A irradiation) 0.18-10.05 mg/L (without UV-A irradiation)	No phototoxicity	4.2.3.7.7-1

5.R Outline of the review conducted by PMDA

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

5.R.1 Use of quizartinib in pregnant women or women who may possibly be pregnant

PMDA asked the applicant to explain use of quizartinib in pregnant women or women who may possibly be pregnant.

The applicant's explanation:

Given the following toxicological findings indicating a possible impact of quizartinib on fetus in pregnant women or women who may possibly be pregnant, the use of quizartinib in this population is

not recommended: (a) The bacterial reverse mutation test showed that quizartinib induces reverse mutations [see Section 5.3] (b) The reproductive and developmental toxicity study in rats showed fetal toxicity and teratogenicity of quizartinib [see Section 5.5]. However, because of an extremely poor prognosis of FLT3-ITD mutation-positive AML, limited therapeutic options for the disease, and difficulty to postpone or cancel the treatment to avoid a pregnancy period. The use of quizartinib in pregnant women or women who may possibly be pregnant can be allowed only when the expected therapeutic benefits outweigh the possible risks associated with the treatment, and the physician and patient should fully understand its potential risks on the fetuses. Caution will be given against this matter in the package insert.

PMDA accepted the applicant's explanation.

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

In this section, doses of quizartinib are expressed as amounts of its hydrochloride, and strengths of the tablets are expressed as free base.

6.1 Summary of biopharmaceutic studies and associated analytical methods

Oral formulations of quizartinib are available in solution and tablets. The PK of quizartinib was investigated using these formulations (Table 20). In addition, the bioequivalence between the 17.7 and 26.5 mg tablets, to-be-marketed formulations, was confirmed by the dissolution test performed in accordance with the "Guideline for Bioequivalence Studies for Different Strengths of Oral Solid Dosage Forms" (PMSB/ELD Notification No. 64 dated February 14, 2000, partially revised by PFSB/ELD Notification No. 0229-10 dated February 29, 2012).

Table 20. Formulations used in clinical studies

Formulation	Study
Oral solutions*[1]	Foreign phase I studies (Studies CP0001, 006, 008, 012, 014, 0005, and 0011) and foreign phase II studies (Studies 002 and 2004)
Tablets (17.7 and 26.5 mg)	Japanese phase I study (Study J101), Japanese phase Ib study (Study J102*[2]), Japanese phase II study (Study J201), foreign phase I studies (Studies 014,*[3, 4] 015,*[3, 4] 016,*[4] 018,*[4] 019,*[4] and 0011), foreign phase II study (Study 2004*[4]), and foreign phase III study (Study 007)

*[1] In the clinical studies other than Study CP0001, the solution was prepared from a powder of quizartinib compound with HPβCD; *[2] The 17.7 mg tablets were used; *[3] Film-coated tablets different from the to-be-marketed formulation were used; *[4] The 26.5 mg tablets were used.

6.1.1 Analytical methods

In Studies J201, 002, 2004, and 007, "FLT3-ITD Mutation Assay" (Navigate BioPharma Services) was used to examine FLT3-ITD mutation. In addition, a partial change application for "LeukoStrat CDx *FLT3* Mutation Assay" was submitted by LabPMM GK on November 15, 2018 to use it as an *in vitro* diagnostic intended for assisting the eligibility assessment of quizartinib.

6.1.2 Assay

The amounts of quizartinib and AC886 (hydroxide form) in human plasma were determined by liquid chromatography-tandem mass spectrometry (LC-MS/MS), and the lower limit of quantitation was 2.00 ng/mL[16)] for both compounds.

6.1.3 Foreign clinical studies

6.1.3.1 Foreign phase I study (CTD 5.3.1.1-2, Study AC220-019 [Study 019], ■ to ■ 20■)

An open-label, randomized study was conducted in 66 healthy adults (63 subjects included in the PK analysis) to investigate food effect on the PK of quizartinib.

A single dose of quizartinib 30 mg was orally administered in the fasted state (administered after a ≥10-hour fasting, followed by a ≥4-hour fasting) or after a high-fat meal (a total of approximately 800-1,000 kcal, including approximately 500-600 kcal of fat).

The least squares geometric mean ratios [90% confidence interval (CI)] of C_{max} and AUC_{inf} of quizartinib after the consumption of high-fat meal to those of quizartinib administered in the fasted state were 0.92 [0.82, 1.02] and 1.08 [0.92, 1.28], respectively.

Based on the above, the applicant explained that quizartinib may be administered irrespective of meal timing.

6.1.3.2 Foreign phase I study (CTD 5.3.3.4-2, Study AC220-018 [Study 018], ■ to ■, 20■)

An open-label, randomized study was conducted in 64 healthy adults (62 subjects included in the PK analysis) to investigate an effect of lansoprazole (proton pump inhibitor) on the PK of quizartinib.

In the quizartinib alone group, a single dose of quizartinib 30 mg was orally administered. In the lansoprazole co-administered group, lansoprazole 60 mg was orally administered QD from Days 1 to 5, and a single dose of quizartinib 30 mg was orally administered on Day 5.

The least squares geometric mean ratios [90% CI] of C_{max} and AUC_{inf} of quizartinib following the concomitant use with lansoprazole to that following the administration of quizartinib alone were 0.86 [0.78, 0.95] and 0.95 [0.80, 1.13] respectively.

The applicant explained that the results indicate the unlikeliness of a pharmacokinetic interaction between quizartinib and a concomitant drug affecting gastric pH such as proton pump inhibitors.

6.2 Clinical pharmacology

The PK of quizartinib in healthy adults and patients with cancer was investigated in quizartinib alone or quizartinib co-administered with ketoconazole or fluconazole.

16) The concentrations in plasma samples from Studies 016, 018, 019, J101, and J201 were measured with a method which lower limit of quantitation was 0.500 ng/mL.

6.2.1 Japanese clinical studies

6.2.1.1 Japanese phase I study (CTD 5.3.3.2-1, Study J101 [ongoing since [redacted] 20[redacted] (data cutoff [redacted], 20[redacted])])

An open-label, uncontrolled study was conducted in 17 patients with relapsed or refractory AML (16 patients included in the PK analysis) to investigate the PK of quizartinib.

Quizartinib 20 to 60 mg was orally administered QD to determine plasma concentrations of quizartinib and AC886.

Table 21 shows the PK parameters of quizartinib and AC886. C_{max} and AUC_{tau} of quizartinib and AC886 on Day 1 were higher at quizartinib 30 mg than at 20 mg, where as they were similar between 30 mg and 60 mg. C_{max} and AUC_{tau} of quizartinib and AC886 on Day 15 increased with the dose within the dose range investigated. The applicant explained that the non-linear changes in C_{max} and AUC_{tau} of quizartinib and AC886 on Day 1 were attributable to large inter-individual variability in C_{max} and AUC_{tau}. The accumulation indices[17] of quizartinib and AC886 in subjects receiving quizartinib 30 mg were 1.88 and 5.77, respectively. The applicant explained that the steady state was reached by 15 days after the start of treatment because the plasma trough concentrations of quizartinib and AC886 almost remained unchanged on Day 15 onward.

Table 21. PK parameters of quizartinib and AC886

Dose (mg)	Day of administration (Day)	Analyte	n	C_{max} (ng/mL)	t_{max}* (h)	AUC_{tau} (ng·h/mL)	CL/F (L/h)
20	1	Quizartinib	9	42.8 (70.9)	2.15 (1.95, 6.05)	550 (99.3)	-
		AC886	9	24.6 (58.5)	18.08 (3.95, 23.88)	451 (55.3)	-
	15	Quizartinib	8	81.5 (65.3)	4.03 (2.08, 6.12)	1,280 (63.1)	13.8 (63.1)
		AC886	8	132 (41.4)	6.05 (0.57, 6.12)	2,650 (41.3)	-
30	1	Quizartinib	3	73.4 (65.5)	2.00 (2.00, 6.02)	1,070 (54.9)	-
		AC886	3	28.9 (95.8)	5.97 (5.97, 6.02)	547 (92.8)	-
	15	Quizartinib	3	148 (37.7)	4.00 (2.07, 4.03)	2,010 (66.2)	13.2 (66.2)
		AC886	3	160 (67.3)	6.03 (4.00, 6.15)	3,160 (62.6)	-
60	1	Quizartinib	4	62.6 (49.6)	4.04 (4.00, 6.03)	1,060 (49.2)	-
		AC886	4	30.1 (116.4)	14.89 (5.92, 23.78)	534 (119.0)	-
	15	Quizartinib	3	283 (20.4)	6.08 (3.97, 6.12)	5,080 (29.3)	10.4 (29.3)
		AC886	3	231 (23.4)	6.12 (6.03, 23.70)	4,930 (19.9)	-

Geometric mean (coefficient of variation, %); * Median (range); -, Not calculated

6.2.2 Foreign clinical studies

6.2.2.1 Foreign phase I study (CTD 5.3.3.1-1, Study AC220-006 [Study 006], [redacted] to [redacted] 20[redacted])

An open-label, uncontrolled study was conducted in 6 healthy adults (all included in the PK analysis) to investigate mass balance.

A single dose of ^{14}C-quizartinib 60 mg was orally administered to determine radioactivity concentrations in blood, plasma, urine, and feces.

Unchanged quizartinib and AC886 were mainly detected in the plasma up to 48 hours post-dose. The urinary and fecal excretion rates of the radioactivity (percentage of the administered radioactivity) up to

[17] The ratio of AUC_{tau} on Day 15 to that on Day 1

336 hours post-dose were 1.64% and 76.3%, respectively. The unchanged quizartinib and M37 (oxidative dealkylated form) were mainly detected in feces within 336 hours post-dose (percentage of the administered radioactivity, 4.00% and 3.46%, respectively).

6.2.2.2 Foreign phase II study (CTD 5.3.5.2-2, Study 2004, [redacted] 20[redacted] to [redacted] 20[redacted])

An open-label, uncontrolled study was conducted in 76 patients with relapsed or refractory FLT3-ITD mutation-positive AML (72 patients included in the PK analysis) to investigate the PK of quizartinib.

Quizartinib 30 or 60 mg was orally administered QD to determine plasma concentrations of quizartinib and AC886.

Table 22 shows the PK parameters of quizartinib and AC886. The accumulation indices[17)] of quizartinib and AC886 in subjects receiving quizartinib 30 mg were 3.73 and 5.09, respectively.

Table 22. PK parameters of quizartinib and AC886

Dose (mg)	Day of administration (Day)	Analyte	n	C_{max} (ng/mL)	t_{max}*1 (h)	AUC_{tau} (ng·h/mL)	CL/F (L/h)
30	1	Quizartinib	36	62.8 (48.3)	2.05 (1.00, 6.33)	932 (36.7)*2	-
		AC886	36	17.5 (129.9)	5.88 (1.00, 25.1)	366 (96.5)*2	-
	15	Quizartinib	35	186 (66.0)	2.00 (0.983, 4.00)	3,370 (72.5)*3	7.88 (72.5)*3
		AC886	35	91.5 (58.4)	4.00 (1.00, 23.9)	1,867 (58.6)*3	-
60	1	Quizartinib	36	112 (75.5)	2.33 (1.00, 6.13)	1,455 (79.0)*3	-
		AC886	36	32.9 (89.1)	21.7 (2.00, 24.5)	525 (83.8)*3	-
	15	Quizartinib	31	487 (80.8)	2.00 (0.833, 6.00)	8,276 (95.7)*4	6.42 (95.7)*4
		AC886	31	192 (63.4)	4.20 (1.00, 23.0)	4,232 (67.8)*4	-

Geometric mean (coefficient of variation, %); *1 Median (range); *2 n = 28; *3 n = 30; *4 n = 25; -, Not calculated

6.2.3 Drug-drug interaction

6.2.3.1 Interactions with ketoconazole or fluconazole (CTD 5.3.3.4-1, Study AC220-015 [Study 015], [redacted] to [redacted], 20[redacted])

An open-label, randomized study was conducted in 93 healthy adults (86 subjects included in the PK analysis) to investigate effects of ketoconazole (strong CYP3A inhibitor) and fluconazole (moderate CYP3A inhibitor) on the PK of quizartinib and AC886.

In the ketoconazole group, ketoconazole was orally administered at 200 mg BID from Days 1 to 28, and a single dose of quizartinib 30 mg was orally administered on Day 8. In the fluconazole group, fluconazole 200 mg was orally administered BID from Days 1 to 28, and a single dose of quizartinib 30 mg was orally administered on Day 8. In the placebo group, placebo was orally administered BID from Days 1 to 28, and a single dose of quizartinib 30 mg was orally administered on Day 8.

The geometric least squares mean ratios [90% CI] of C_{max} and AUC_{inf} of (a) quizartinib and (b) AC886 after the concomitant use of quizartinib with ketoconazole to those after the dose of quizartinib alone were (a) 1.17 [1.05, 1.30] and 1.94 [1.69, 2.23], respectively, and (b) 0.40 [0.31, 0.51] and 0.85 [0.68, 1.05], respectively. In addition, the geometric least squares mean ratios [90% CI] of C_{max} and AUC_{inf} of (a) quizartinib and (b) AC886 after the concomitant use of quizartinib with fluconazole to those after

the dose quizartinib alone were (a) 1.11 [1.00, 1.24] and 1.20 [1.04, 1.38], respectively, and (b) 1.02 [0.80, 1.31] and 1.14 [0.94, 1.40], respectively.

The applicant's explanation about concomitant use of quizartinib with a CYP3A inhibitor, based on the above results:
In consideration of the ratios of AUC_{inf} of quizartinib after the concomitant use of quizartinib with ketoconazole to that after the dose of quizartinib alone, the dose of quizartinib should be reduced to about half when a strong CYP3A inhibitor is concomitantly administered. On the other hand, the extent of increase in AUC_{inf} of quizartinib after the concomitant use with fluconazole fell within a range of the coefficient of variation (35.9%) of AUC_{inf} of quizartinib after the dose of quizartinib alone. Given these observations, cautionary advice is not required on the concomitant use of quizartinib with a moderate or weaker CYP3A inhibitor.

The applicant's explanation and PMDA's view on the guidelines for dose adjustment of quizartinib to be used with a strong CYP3A inhibitor are provided in Section 7.R.5.2.

6.2.4 Foreign phase I study for effect of hepatic impairment on the PK of quizartinib (CTD 5.3.3.3-1, Study AC220-016 [Study 016], [redacted] 20[redacted] to [redacted] 20[redacted])

An open-label, uncontrolled study was conducted in 8 patients with mild (Child-Pugh Class A) hepatic impairment and 8 patients with moderate (Child-Pugh Class B) hepatic impairment (a total of 16 patients, 8 each included in the PK analysis) and 14 healthy adults (matched healthy control subjects [MHC]) (14 subjects included in the PK analysis[18)]) with matching age, sex, and body weight to patients with mild or moderate hepatic impairment to investigate effects of hepatic impairment on the PK of quizartinib and AC886.

A single dose of quizartinib 30 mg was orally administered to determine plasma concentrations of quizartinib and AC886.

Table 23 shows the PK parameters of quizartinib and AC886. The least squares geometric mean ratios [90% CI] of C_{max} and AUC_{inf} of (a) quizartinib, (b) AC886, and (c) the sum of quizartinib and AC886 in the mild hepatic impairment group to those in the mild hepatic impairment MHC group were (a) 1.13 [0.83, 1.52] and 1.30 [0.81, 2.06], respectively, (b) 1.20 [0.68, 2.11] and 1.20 [0.79, 1.82], respectively, and (c) 1.13 [0.89, 1.44] and 1.17 [0.86, 1.59], respectively. The least squares geometric mean ratios [90% CI] of C_{max} and AUC_{inf} of (a) quizartinib, (b) AC886, and (c) the sum of quizartinib and AC886 in the moderate hepatic impairment group to those in the moderate hepatic impairment MHC group were (a) 1.09 [0.81, 1.48] and 1.15 [0.73, 1.80], respectively, (b) 0.68 [0.39, 1.19] and 0.65 [0.43, 0.96], respectively, and (c)1.01 [0.79, 1.29] and 0.96 [0.72, 1.30], respectively.

The applicant's explanation about the use of quizartinib in patients with hepatic impairment, based on the above results:

18) Of 14 subjects, 2 subjects had subject characteristics accepted as the control of either mild or moderate hepatic impairment group, and thus these subjects were included in groups of MHC with mild and moderate hepatic impairment.

Mild or moderate hepatic impairment is not considered to clearly affect the PK of quizartinib and the sum of quizartinib and AC886, and the dose adjustment of quizartinib is not required for patients with mild or moderate hepatic impairment. For patients with severe hepatic impairment, on the other hand, quizartinib has not been used, of which healthcare professionals should be informed.

Table 23. PK parameters of quizartinib and AC886 by severity of hepatic impairment

Group	Analyte	n	C_{max} (ng/mL)	t_{max}*1 (h)	AUC_{inf} (ng·h/mL)	$t_{1/2}$ (h)
Mild hepatic impairment MHC	Quizartinib	8	97.1 (37.3)	3.50 (2.00, 4.00)	7,304 (54.5)	85.8 (25.2)
	AC886	8	19.7 (66.2)	6.50 (4.00, 48.0)	2,716 (37.6)	114 (26.4)
Mild hepatic impairment	Quizartinib	8	109 (30.6)	3.00 (2.00, 4.00)	9,462 (25.9)*2	115 (28.0)*2
	AC886	8	23.7 (59.9)	4.50 (3.00, 48.0)	3,256 (21.2)*3	108 (32.1)*3
Moderate hepatic impairment MHC	Quizartinib	8	90.2 (37.9)	3.00 (2.00, 5.00)	6,132 (42.7)	86.2 (26.8)
	AC886	8	23.7 (73.7)	5.00 (5.00, 36.0)	3,052 (49.3)	82.9 (25.7)
Moderate hepatic impairment	Quizartinib	8	98.7 (40.3)	2.00 (1.00, 4.00)	7,043 (90.2)	107 (46.1)
	AC886	8	16.1 (95.3)	5.00 (4.00, 8.00)	1,972 (70.6)*2	102 (30.4)*2

Geometric mean (coefficient of variation, %); *1 Median (range); *2 n = 7; *3 n = 6; -, Not calculated

6.2.5 Use of quizartinib in patients with renal impairment

No clinical studies were conducted to investigate effects of renal impairment on the PK of quizartinib and AC886 in patients with renal impairment.

The applicant explained that no dose adjustment of quizartinib is required for patients with renal impairment in light of the following observations:

- Results from a foreign phase I study (Study 006) indicate little contribution of renal excretion of quizartinib to its elimination [see Section 6.2.2.1].

- In a foreign phase III study (Study 007), incidences of (a) Grade ≥3 adverse events and (b) serious adverse events in patients grouped by the degree of renal function,[19] i.e., normal renal function (n = 153), mild renal impairment (n = 62), and moderate and severe renal impairment (n = 25[20]), were (a) 87.6%, 87.1%, and 88.0%, respectively, and (b) 67.3%, 77.4%, and 64.0%, respectively, showing no clear relationship between severity of renal impairment and incidences of adverse events.

6.2.6 Relationship of exposure with changes in QT/QTc interval

Based on results from a foreign phase III study (Study 007), the association of plasma concentrations of quizartinib and AC886 with change in QTcF from baseline (ΔQTcF) was investigated using a sigmoid E_{max} model. The ΔQTcF tended to be prolonged with increasing plasma concentrations of quizartinib and AC886. The upper limit of 90% CI of ΔQTcF at C_{max} (geometric mean, 401 ng/mL) of quizartinib at a steady state in the multiple oral QD doses of quizartinib 60 mg was estimated to be 23.6 milliseconds.

Prolonged QT interval was also observed in the clinical studies [see Section 7.R.3.6]. The applicant explained that caution would be appropriately given to healthcare professionals against QT interval prolongation via the package insert.

[19] Renal function was classified as follows: Normal, CrCL ≥90 mL/min; mild, CrCL ≥60 mL/min and <90 mL/min; moderate, CrCL ≥30 mL/min and <60 mL/min; severe, CrCL <30 mL/min

[20] Only 3 patients had severe renal impairment, they were pooled with 22 patients with moderate renal impairment for the analysis.

The applicant's explanation and PMDA's view on the dose adjustment of quizartinib based on the QT interval corrected with the Fridericia approach (QTcF) value are presented in Section 7.R.5.1.

6.2.7 Population pharmacokinetic (PPK) analysis

A population pharmacokinetic (PPK) analysis was performed using the non-liner mixed-effects model (software, NONMEM Version 7.3.0), based on the PK data of quizartinib and AC886 (11,488 measuring time points for quizartinib and 10,679 measuring time points for AC886 in 638 patients) from Japanese clinical studies (Studies J101 and J201) and foreign clinical studies (Studies 0011, AC220-014 [014], 015, 016, 018, 2004, and 007). The PK of quizartinib was described by a 3-compartment model with the zero and first order absorption processes as well as the first order elimination process, and that of AC886 was described by a 2-compartment model.

For the analysis, a PPK model[21)] previously constructed based on results from the foreign clinical studies was used as the base model, and possible covariate for CL, CL_m, V_c, V_{cm}, V_p, and Q1 was ethnic group (Japanese and non-Japanese). For any parameter, ethnic group (Japanese and non-Japanese) was not selected as a significant covariate.

6.2.8 Exposure-response relationship for efficacy or safety

6.2.8.1 Exposure-response for efficacy

Based on the data from a foreign phase III study (Study 007), the quizartinib group was divided into 4 groups[22)] by quartiles of exposure to quizartinib[23)] (AUC[24)]), and the overall survival (OS) in each exposure group was estimated using the Kaplan-Meier plots. In the lowest exposure group, the OS tended to be shorter than those in the other 3 exposure groups.

6.2.8.2 Exposure-response for safety

Based on the data from a foreign phase I study (Study 0011), a foreign phase II study (Study 2004), and a foreign phase III study (Study 007), the association of the exposure[22)] (C_{max}, AUC[25)], and trough concentrations) to quizartinib and AC886 with anaemia, febrile neutropenia, thrombocytopenia, infection, haemorrhage, hepatic dysfunction, Grade ≥3 adverse events, or serious adverse events was investigated. There was no clear relationship between either quizartinib or AC886 with the occurrence of these events.

6.2.9 Difference in PK of quizartinib between Japanese and non-Japanese patients

The applicant's explanation:

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21) The model was constructed by a PPK analysis (software, NONMEM Version 7.3.0) performed on the PK data of quizartinib and AC886 (10,396 measuring time points for quizartinib and 9,629 measuring time points for AC886 in 585 subjects) from foreign clinical studies (Studies 0011, 014, 015, 016, 018, 2004, and 007). Covariates for (a) CL, (b) CL_m, (c) V_c, (d) V_{cm}, (e) V_p, and (f) F1 included in the analysis were (a) disease and concomitant use of a strong CYP3A inhibitor, (b) body surface area, race (black and non- black), and concomitant use of a strong CYP3A inhibitor, (c) albumin, disease, and body surface area, (d) concomitant use of a strong CYP3A inhibitor and disease, (e) disease as well as (f) concomitant use of a strong CYP3A inhibitor.

22) AUC (ng·h/mL) in each group ranged from ≥564 to ≤3,160, from >3,160 to ≤5,750.5, from >5,750.5 to ≤8,577, and from >8,577 to ≤31,841.

23) Estimated by the PPK analysis [see Section 6.2.7]

24) Mean daily AUC calculated by dividing the AUC for a period to death or censoring by the number of days of treatment with quizartinib

25) Mean daily AUC calculated by dividing the AUC for a period from the first dose of quizartinib or time point 30 days before the onset of an adverse event to the first onset of the event by the number of days of treatment with quizartinib

In the Japanese phase II study (Study J201) and foreign phase II study (Study 2004), no clear differences were observed in C_{max} and AUC_{tau} of quizartinib following multiple oral 30 mg QD doses (Table 24). Thus, there was no clear difference in the PK of quizartinib between Japanese and non-Japanese patients.

Table 24. PK parameters of quizartinib*[1]

	Day of administration (Day)	n	C_{max} (ng/mL)	AUC_{tau} (ng·h/mL)
Japanese patients	1	34	59.4 (98.8)	907 (94.8)
	15	33	168 (81.1)	2,980 (100)
Non-Japanese patients	1	26	69.9 (29.8)	963 (35.5)*[2]
	15	26	196 (63.8)	3,640 (73.4)*[3]

Geometric mean (coefficient of variation, %); *[1] Calculated excluding patients using a concomitant strong CYP3A inhibitor; *[2] n = 20; *[3] n = 21

6.R Outline of the review conducted by PMDA

Based on the submitted data and review in the following subsection, PMDA concluded that the applicant's explanation about clinical pharmacology findings of quizartinib is acceptable.

6.R.1 Pharmacokinetic interactions mediated by induction of CYP3A

The applicant's explanation about the concomitant use of quizartinib with a CYP3A inducer:
In a foreign phase I study (Study AC220-012 [Study 012]), effect of rifampicin (CYP3A inducer) on the PK of quizartinib and AC886 was investigated. However, because of inaccuracy in measurements of plasma concentrations of quizartinib and AC886,[26)] a physiologically based pharmacokinetic (PBPK) model was used to investigate the effect of rifampicin on the PK of quizartinib and AC886.

The PBPK model analysis was performed using Simcyp version 17. An advanced dissolution absorption and metabolism (ADAM) model was selected to describe the absorption of quizartinib, and a minimal PBPK model was selected to describe the distribution of quizartinib and AC886. The relative contribution of CYP3A to metabolism of (a) quizartinib and (b) AC886 used in the analysis were (a) 60% and (b) 85%, respectively, which were estimated from the results from *in vitro* studies [see Section 4.3.1] and the retrograde model. Physiological parameters and rifampicin-related compound parameters used in the analysis were default values in Simcyp. The following observations support the appropriateness of the PBPK model used for the estimation of CYP3A-mediated pharmacokinetic interactions of quizartinib and AC886:

- In terms of exposure (geometric mean of C_{max} and AUC_{inf}) to (a) quizartinib and (b) AC886 after a single oral dose of quizartinib 30 mg, observed values ([a] 105 ng/mL and 8,665 ng·h/mL, respectively, [b] 21.2 ng/mL and 2,848 ng·h/mL, respectively) obtained from a foreign phase I study (Study 018) were almost comparable to the simulated values ([a] 108 ng/mL and 9,409 ng·h/mL, respectively, [b] 19.3 ng/mL and 2,649 ng·h/mL, respectively) obtained from the above PBPK model, and the predicted plasma concentration-time profiles of quizartinib and AC886 were also consistent with the observed data.

- The geometric mean ratios of C_{max} and AUC[27)] of (a) quizartinib and (b) AC886 after the dose of quizartinib with concomitant ketoconazole to those after the dose of quizartinib alone, observed

[26)] The applicant explained that the failure was attributable to storage of blood samples on ice employed in Study 012
[27)] For comparison of AUC of quizartinib and AC886, AUC_{inf} and $AUC_{0\text{-}504h}$, respectively, were used.

values ([a] 1.17 and 1.94, respectively, [b] 0.40 and 0.71, respectively) obtained from a foreign phase I study (Study 015) were almost comparable to the simulated values ([a] 1.05 and 1.88, respectively, [b] 0.24 and 0.57, respectively) obtained from the above PBPK model.

- The geometric mean ratios of C_{max} and AUC_{inf} of midazolam (CYP3A substrate) after a dose of midazolam in combination with rifampicin to those after the dose of midazolam alone, observed values (0.17 and 0.12, respectively; *Clin Pharmacol Ther.* 2006;79:350-61) were almost comparable to simulated values (0.16 and 0.11, respectively) obtained from the above PBPK model.

The above PBPK model was used to estimate exposures to quizartinib and AC886 after a single oral dose of quizartinib 60 mg alone and a single oral dose of quizartinib 60 mg on Day 8 during treatment with oral rifampicin 600 mg QD from Day 1 to Day 20. The geometric mean ratios of C_{max} and AUC_{inf} of (a) quizartinib and (b) AC886 after the concomitant use of quizartinib with rifampicin to those after the dose of quizartinib alone were (a) 0.85 and 0.28, respectively, and (b) 1.39 and 0.34, respectively. The estimated geometric mean ratios of C_{max} and AUC_{inf} of quizartinib were comparable to reference values obtained from Study 012 (0.84 and 0.32, respectively). Given these results, caution should be exercised against the concomitant use of quizartinib with a CYP3A inducer, and such advice will be given via the package insert.

PMDA's view:
The applicant's explanation is acceptable. However, information on the pharmacokinetic interactions of quizartinib mediated by CYP3A induction is important for justifying the caution against the use of quizartinib with a CYP3A inducer based on the simulated values from the PBPK model. The applicant should continue collecting relevant information and provide new findings, once available, to healthcare professionals appropriately.

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

The efficacy and safety evaluation data submitted were the results from a total of 12 clinical studies comprising 1 Japanese phase I study, 1 Japanese phase II study, 7 foreign phase I studies, 2 foreign phase II studies, and 1 foreign phase III study, as listed in Table 25. The reference data submitted included the results from a total of 5 clinical studies comprising 1 Japanese phase Ib study and 4 foreign phase I studies, as listed in Table 25. In this section, doses of quizartinib are expressed as amounts of its hydrochloride.

Table 25. 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	J101	I	Patients with relapsed or refractory AML	17	Dose-escalation cohort: Oral quizartinib 20, 30, or 60 mg QD Dose-expansion cohort: Oral quizartinib 20 mg QD	Safety PK
		J201	II	Patients with relapsed or refractory FLT3-ITD mutation-positive AML	37	Starting dose of oral quizartinib 30 mg QD and oral quizartinib 60 mg from Day 16 or 29	Efficacy Safety
	Foreign	CP 0001	I	Patients with relapsed or refractory AML	76	Oral quizartinib solution 12, 18, 27, 40, 60, 90, 135, 200, 300, or 450 mg QD from Days 1 to 14, followed by 14-day washout or oral quizartinib solution 200 or 300 mg QD in each 28-day cycle	Safety PK
		0011	I	Patients with AML previously undergoing allogeneic HSCT	13	Oral quizartinib 40 or 60 mg QD from Days 30 to 60 after allogeneic HSCT	Safety
		014	I	Healthy adults	80	A single oral dose of quizartinib solution 60 mg, quizartinib tablet 60 mg, 30 mg, or 90 mg	PK
		015	I	Healthy adults	93 (a) 31 (b) 31 (c) 31	(a) A single oral dose of quizartinib 30 mg on Day 8 during treatment with ketoconazole (b) A single oral dose of quizartinib 30 mg on Day 8 during treatment with fluconazole (c) A single oral dose of quizartinib 30 mg	PK
		016	I	Healthy adults or patients with hepatic impairment	30	A single oral dose of quizartinib 30 mg in the fasted state	PK
		018	I	Healthy adults	64 (a) 31 (b) 33	(a) A single oral dose of quizartinib 30 mg in the fasted state (b) A single oral dose of quizartinib 30 mg in the fasted state during treatment with lansoprazole	PK
		019	I	Healthy adults	66 (a) 34 (b) 32	(a) A single oral dose of quizartinib 30 mg in the fasted state (b) A single oral administration of quizartinib at 30 mg after a meal	PK
		002	II	Patients with relapsed or refractory AML	333	Oral quizartinib solution 90, 135, or 200 mg QD	Efficacy Safety
		2004	II	Patients with relapsed or refractory FLT3-ITD mutation-positive AML	76	Oral quizartinib 30 or 60 mg QD	Efficacy Safety
		007	III	Patients with relapsed or refractory FLT3-ITD mutation-positive AML	367 (a) 245 (b) 122	(a) Quizartinib group: Starting dose of oral quizartinib 30 mg QD and oral quizartinib 60 mg from Day 16 or 29 (b) Control group: MEC,*1 FLAG-IDA*2 or low-dose Ara-C*3 selected by the investigator	Efficacy Safety
Reference	Japan	J102	Ib	Patients with treatment-naive AML	7	Oral quizartinib 20 or 40 mg QD from Days 8 to 21 during the standard chemotherapy in each 28-day treatment cycle	Safety PK
	Foreign	0005	I	Patients with treatment-naive AML	19	Oral quizartinib 60 mg QD from Days 4 to 10, 40 or 60 mg QD from Days 4 to 17 during the concomitant standard chemotherapy, or administered daily at 60 mg QD.	Safety
		006	I	Healthy adult men	6	A single oral dose of quizartinib solution 60 mg in the fasted state	PK
		008	I	Healthy adults	58 (a) 8 (b) 50	(a) A single oral dose of quizartinib solution 20 mg in the fasted or fed state (b) A single oral dose of quizartinib solution 60 mg in the fasted or fed state	PK
		012	I	Healthy adults	83 (a) 30 (b) 27 (c) 26	(a) A single oral dose of quizartinib solution 60 mg on Day 8 during concomitant use with ketoconazole (b) A single oral dose of quizartinib solution 60 mg on Day 8 during concomitant use with rifampicin (c) A single oral dose of quizartinib solution 60 mg on Day 8	PK

*[1] Mitoxantrone hydrochloride (mitoxantrone) at 8 mg/m^2, etoposide at 100 mg/m^2, and cytarabine (Ara-C) at 1,000 mg/m^2 were intravenously administered from Days 1 to 5; *[2] Granulocyte-colony stimulating factor (G-CSF) preparation was subcutaneously (5 μg/kg) or intravenously (300 μg/m^2) administered from Days 1 to 5, fludarabine phosphate (fludarabine) at 30 mg/m^2 and Ara-C at 2,000 mg/m^2 were intravenously administered from Days 2 to 6, and idarubicin hydrochloride (IDA) at 10 mg/m^2 was intravenously administered from Days 2 to 4; *[3] Ara-C was subcutaneously administered at 20 mg BID from Days 1 to 10.

Each study is summarized below. The main adverse events observed in each clinical study, excluding deaths, are described in Section "7.3 Adverse events observed in clinical studies," and clinical studies for PK are described in Sections "6.1 Summary of biopharmaceutic studies and associated analytical methods" and "6.2 Clinical pharmacology."

7.1 Evaluation data

In all of Japanese phase I study (Study J101), foreign phase I study (Study CP0001), Japanese phase II study (Study J201), foreign phase II studies (Studies 002 and 2004), and foreign phase III study (Study 007) summarized below, the determination of complete remission (CR), complete remission with incomplete platelet recovery (CRp), complete remission with incomplete hematologic recovery (CRi), or composite complete remission (CRc) were initially performed in accordance with the following definitions, which were partially modified from the definitions published by the International Working Group (IWG) (*J Clin Oncol.* 2003;21:4642-9):

- CR: All of the following criteria are met:
  - Bone marrow blasts of <5% without Auer rods
  - No extramedullary leukemia, and peripheral blasts of ≤1%
  - Absolute neutrophil count of ≥1,000 /μL, platelet count of ≥100,000 /μL, and independence of red blood cell transfusions for 4 weeks and platelet transfusion for 1 week

- CRp: All of the criteria for CR except for platelet count of <100,000 /μL are met.

- CRi: All of the criteria for CR except for absolute neutrophil count of <1,000 /μL are met, irrespective of platelet count recovery as well as the transfusion status of red blood cells and platelets

- CRc: CR, CRp, or CRi is met.

In Studies J201 and 007, however, the statistical analysis plan was revised after data-cut off, and CRib was additionally defined under CRi (the former CRi was re-defined as CRia), and the definition of the CRc rate was changed to the percentage of patients who achieved CR, CRp, or CRi (CRia and CRib).

- CRib: Dependent on transfusion of red blood cells or platelets, but all the other criteria for CR or CRp are met.

7.1.1 Clinical pharmacology studies

The applicant submitted the results of the following 5 clinical pharmacology studies in healthy adults and patients with hepatic impairment [see Sections 6.1 and 6.2]. No deaths occurred during these studies.

7.1.1.1 Foreign phase I study (CTD 5.3.1.1-1, Study 014, ■ 20■ to ■ 20■)
7.1.1.2 Foreign phase I study (CTD 5.3.3.4-1, Study 015, ■ 20■ to ■ 20■)
7.1.1.3 Foreign phase I study (CTD 5.3.3.3-1, Study 016, ■ 20■ to ■ 20■)
7.1.1.4 Foreign phase I study (CTD 5.3.3.4-2, Study 018, ■ 20■ to ■ 20■)
7.1.1.5 Foreign phase I study (CTD 5.3.1.1-2, Study 019, ■ 20■ to ■ 20■)

7.1.2 Japanese clinical studies

7.1.2.1 Japanese phase I study (CTD 5.3.3.2-1, Study J101, ■ 20■ to ■ 20■)

An open-label, uncontrolled clinical study was conducted in patients with relapsed or refractory AML (target sample size, 15-21 patients) to investigate the safety and PK of quizartinib in 8 study centers in Japan.

In the dose-escalation cohort, quizartinib was orally administered at 20, 30, or 60 mg QD. Patients continued receiving treatment until the discontinuation criteria met. In the dose-expansion cohort, quizartinib was orally administered at 20 mg QD. Patients continued receiving treatment until the discontinuation criteria met.

Of 17 patients enrolled in the study (12 in the dose-escalation cohort, 5 in the dose-expansion cohort[28)]), 16 patients (9 in the 20 mg group, 3 in the 30 mg group, 4 in the 60 mg group) were included in the safety analysis, except for 1 patient who did not receive quizartinib. Of those included in the safety analysis, 9 patients in the dose-escalation cohort were included in dose limiting toxicity (DLT) assessment.

During a period of 28 days after the first dose, defined as the DLT assessment period, no DLT was observed.

Death occurred during treatment or within 28 days after the completion of treatment with quizartinib in 3 of 16 patients (1 of 9 in the 20 mg group, 1 of 3 in the 30 mg group, 1 of 4 in the 60 mg group). The cause of death except for disease progression in 2 patients (1 each in the 20 and 60 mg groups) was haemorrhage intracranial (1 in the 30 mg group), for which a causal relationship to quizartinib was ruled out.

7.1.2.2 Japanese phase II study (CTD 5.3.5.2-1, Study J201, ■ 20■ to ■ 20■)

An open-label, uncontrolled clinical study was conducted in patients with relapsed or refractory FLT3-ITD mutation-positive AML (target sample size, 41 patients) to investigate the efficacy and safety of quizartinib in 34 study centers in Japan.

[28)] In the dose-escalation cohort, ≥3 patients were included in each dose cohort, and the recommended dose was determined by a modified continual reassessment method based on the Bayesian logistic regression model. In addition, in the case where the number of patients enrolled in the 20 mg group did not reach 9 until determination of maximum tolerated dose (MTD) or recommended dose, patients were included in the dose-expansion cohort until the total number of patients who received quizartinib 20 mg QD reached ≥9. In the 20 mg QD group, a total of 10 patients were included in either dose-escalation cohort or dose-expansion cohort, and of these, 9 patients received quizartinib.

Oral administration of quizartinib was started at 30 mg QD. Patients with QTcF value measured on Day 15 of ≤450 milliseconds received oral doses of 60 mg QD from Day 16 onward.[29] Among the patients for whom the dose was not increased from Day 16 onward, those who met specific criteria on Day 29 and later were allowed to receive oral quizartinib 60 mg QD. Patients continued to receive quizartinib until the discontinuation criteria met.

All of 37 patients enrolled in the study received quizartinib and were included in the safety analysis. Of the 37 patients, 32 patients were included in the efficacy analysis except for 5 patients who were centrally assessed as FLT3-ITD mutation-negative. In addition, of the 32 patients included in the efficacy analysis, 26 patients were identified as evaluable for the primary endpoint and thus were included in the primary endpoint analysis.[30]

The primary endpoint in the study was initially the CRc rate (the percentage of patients who achieved CR, CRp, or CRi) partially modified from the IWG definitions. The definition of the CRc rate, however, was changed to the percentage of patients who achieved CR, CRp, or CRi (CRia and CRib) because the statistical analysis plan was revised on [redacted], 20[redacted] after the data cutoff ([redacted], 20[redacted]) and the data monitoring committee (DMC) ([redacted], 20[redacted]), and CRib was additionally defined under CRi (the former CRi was re-defined as CRia) [see Section 7.1]. The protocol was not revised after this change.

Table 26 shows investigator-assessed CRc rates, the primary endpoint. Among those included in the analysis for the primary endpoint, 14 patients[31] of the first 25 patients achieved CRc, meeting the prespecified criteria for early termination for efficacy based on a 2-step design,[32] and thus the DMC recommended termination.

Table 26. Results of CRc (investigator-assessed, data cutoff on [redacted], 20[redacted])

	Number of patients (%) (n = 26)
CR	0
CRp	1 (3.8)
CRi	13 (50.0)*[1]
CRc	14
(CRc [CR + CRp + CRi] rate [90% CI*[2]] [%])	(53.8 [36.2, 70.8])

*[1] Including 3 patients who were assessed as responder (CRib), although not defined in the protocol.
*[2] Clopper-Pearson method

The investigator-assessed CRc rate [95% CI] (%) in patients with relapsed[33] FLT3-ITD mutation-positive AML was 44.4% [21.5, 69.2] (8 of 18 of patients),[31] and that in patients with refractory[34] FLT3-ITD mutation-positive AML was 75.0% [34.9, 96.8] (6 of 8 of patients).

29) Patients treated with a strong CYP3A inhibitor at baseline were assigned to orally receive quizartinib 20 mg QD, and of these, those who had the QTcF value on Day 15 of ≤450 milliseconds received 30 mg OD orally from Day 16 onward.
30) Any of (a) the response was rated as CR, CRp, or CRi; (b) discontinued from study; or (c) evaluation completed on Day 85 was met.
31) Including 3 patients who were assessed to be responder (CRib), although not defined in the protocol.
32) Based on the 2-step design with a threshold CRc rate of 23.5%, an expected CRc rate of 42%, a one-sided significance level of 5%, and a power of 80%, the first step assessment included 25 subjects. In the case where of the 25 subjects, 4 to 10 patients achieved CRc, the study was to be transferred to the second step; and in the case where of the 25 subjects, 11 patients or more achieved CRc, the study was to be early terminated for efficacy. The threshold CRc rate was specified based on the CR rate of salvage chemotherapy in patients with relapsed or refractory AML (*Leuk Res.* 2010;34:752-6, etc.).
33) Relapse was defined as development within 6 months after achieving CR, CRp, or CRi with an initial remission induction therapy. Whether the patient underwent consolidation therapy, maintenance therapy, or HSCT was not taken into account.
34) Refractory was defined as the disease in which (a) 1 cycle of chemotherapy reduced myeloblasts by <50%, failing to achieve CR, CRp, or CRi; or (b) 2 cycles of chemotherapy did not achieve CR, CRp, or CRi.

Death occurred in 1 of 37 patients during quizartinib treatment or within 30 days after the completion of treatment, and the cause of death was disease progression.

7.1.3 Foreign clinical studies

7.1.3.1 Foreign phase I study (CTD 5.3.3.2-2, Study CP0001, ■ 20■ to ■ 20■)

An open-label, uncontrolled study was conducted in patients with relapsed or refractory AML (target sample size, approximately 20-40 patients) to investigate the safety and PK of quizartinib in 6 study centers in 2 countries.

In 28-day treatment cycles, quizartinib solution was orally administered at 12, 18, 27, 40, 60, 90, 135, 200, 300, or 450 mg QD from Days 1 to 14 followed by a 14-day washout or quizartinib solution at 200 or 300 mg QD.

All of 76 patients enrolled in the study (3 in the 12 mg intermittent dose group, 8 in the 18 mg intermittent dose group, 6 in the 27 mg intermittent dose group, 5 in the 40 mg intermittent dose group, 5 in the 60 mg intermittent dose group, 3 in the 90 mg intermittent dose group, 5 in the 135 mg intermittent dose group, 6 in the 200 mg intermittent dose group, 4 in the 300 mg intermittent dose group, 6 in the 450 mg intermittent dose group, 17 in the 200 mg daily dose group, 8 in the 300 mg daily dose group) received quizartinib and were included in the safety analysis and in the DLT assessment.[35)]

During the DLT assessment period, DLT occurred in 4 patients, which included 1 of 5 patients in the 135 mg intermittent dose group (Grade 3 pyrexia), 1 of 17 patients in the 200 mg daily dose group (Grade 3 QT interval prolonged), and 2 of 8 patients in the 300 mg daily dose group (Grade 3 QT interval prolonged in 2 patients). The maximum tolerated dose (MTD) was determined to be 200 mg QD oral dose.

Death occurred during treatment with quizartinib or the follow-up period (until the end of the study) in 74 of 76 patients (3 of 3 in the 12 mg intermittent dose group, 8 of 8 in the 18 mg intermittent dose group, 6 of 6 in the 27 mg intermittent dose group, 5 of 5 in the 40 mg intermittent dose group, 5 of 5 in the 60 mg intermittent dose group, 3 of 3 in the 90 mg intermittent dose group, 5 of 5 in the 135 mg intermittent dose group, 5 of 6 in the 200 mg intermittent dose group, 4 of 4 in the 300 mg intermittent dose group, 6 of 6 in the 450 mg intermittent dose group, 16 of 17 in the 200 mg daily dose group, 8 of 8 in the 300 mg daily dose group). The causes of deaths other than disease progression in 66 patients (2 in the 12 mg intermittent dose group, 6 in the 18 mg intermittent dose group, 6 in the 27 mg intermittent dose group, 4 in the 40 mg intermittent dose group, 5 in the 60 mg intermittent dose group, 3 in the 90 mg intermittent dose group, 4 in the 135 mg intermittent dose group, 5 in the 200 mg intermittent dose group, 3 in the 300 mg intermittent dose group, 5 in the 450 mg intermittent dose group, 15 in the 200 mg daily dose group, 8 in the 300 mg daily dose group) were unknown in 2 patients (1 each in the 18 mg intermittent dose group and 450 mg intermittent dose group); and gastrointestinal fungal infection

35) MTD was determined according to a 3 + 3 design. After determination of MTD, a total of 8 patients including ≥4 patients with *FLT3* gene mutation-positive AML were added to the MTD dose group. Of patients who received quizartinib in the intermittent dose groups, those who did not discontinue quizartinib within 14 days due to other than adverse events or safety were assessed for the DLT. Of patients who received quizartinib daily, those who did not discontinue quizartinib within 1 cycle due to other than DLT were assessed for DLT.

(12 mg intermittent dose group), cardiac failure congestive (18 mg intermittent dose group), sinusitis fungal (40 mg intermittent dose group), cerebrovascular accident (135 mg intermittent dose group), haemorrhage (300 mg intermittent dose group), and Creutzfeldt-Jakob disease (200 mg daily dose group) in 1 patient each. A causal relationship to quizartinib was ruled out for all of the causes other than unknown causes in 2 patients.

7.1.3.2 Foreign phase I study (CTD 5.3.4.2-1, Study 0011, ■ 20■ to ■ 20■)

An open-label, uncontrolled study was conducted in patients with AML in morphologic remission (blasts of <5%) after allogeneic hematopoietic stem cell transplantation (HSCT) (target sample size, 4-30 patients) to investigate the safety of quizartinib used as maintenance therapy in 5 study centers in 1 country.

The treatment with oral quizartinib 40 or 60 mg QD was started between 30 and 60 days after allogeneic HSCT and continued for up to 672 days.

All of the 13 patients enrolled in this study (7 in the 40 mg group, 6 in the 60 mg group) received quizartinib and were included in the safety analysis and DLT assessment.

During the DLT assessment period, i.e., a period of 56 days after the first dose of quizartinib, DLTs occurred in 2 patients (1 of 7 in the 40 mg group [Grade 3 gastric haemorrhage], 1 of 6 in the 60 mg group [Grade 3 anaemia]).

Death occurred during the treatment with quizartinib or until the end of the study in 3 of 13 patients (1 of 7 in the 40 mg group, 2 of 6 in the 60 mg group). The causes of deaths except for disease progression in 1 patient (40 mg group) were peritoneal haemorrhage and unknown in 1 patient each (60 mg group). A causal relationship to quizartinib was not ruled out for the unknown cause in 1 patient.

7.1.3.3 Foreign phase II study (CTD 5.3.5.2-3, Study 002, ■ 20■ to ■ 20■)

An open-label, uncontrolled study was conducted in patients with relapsed or refractory AML (target sample size, approximately 300 patients) to investigate the efficacy and safety of quizartinib in 102 study centers in 9 countries.

Quizartinib solution was orally administered at 90 or 135 mg[36] QD. Patients continued to receive treatment until the discontinuation criteria met.

All of 333 patients enrolled in this study (157 [112 patients with FLT3-ITD mutation-positive AML, 44 patients with FLT3-ITD mutation-negative AML, 1 patient with AML unknown for FLT3-ITD mutation] in Cohort 1,[37] 176 [136 patients with FLT3-ITD mutation-positive AML, 40 patients with FLT3-ITD

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[36] In Study 002, initially quizartinib solution was planned to be orally administered at 200 mg QD. However, of 17 patients who were included in the study and received quizartinib at the beginning, 6 patients (35.3%) presented with QT interval prolonged with the QTcF value of >500 milliseconds. The protocol was revised accordingly with the modified regimen for oral quizartinib 135 mg QD for men and 60 mg QD for women.

[37] Patients aged ≥60 years with AML who relapsed within 1 year after the initial remission induction therapy or who did not sufficiently respond to the initial remission induction therapy were included.

mutation-negative AML] in Cohort 2[38]) received quizartinib and were included in the safety analysis. A total of 287 patients (133 [98 patients with FLT3-ITD mutation-positive AML, 35 patients with FLT3-ITD mutation-negative AML] in Cohort 1, 154 [121 patients with FLT3-ITD mutation-positive AML, 33 patients with FLT3-ITD mutation-negative AML] in Cohort 2) were included in the efficacy analysis, while those who discontinued quizartinib for any other reasons than adverse events including disease progression were excluded.

The centrally-assessed CRc rate [95% CI] (%),[39] the primary endpoint, was 56.3% [46.6, 65.6] (63 of 112) in patients with FLT3-ITD mutation-positive AML in Cohort 1, 45.6% [37.0, 54.3] (62 of 136) in patients with FLT3-ITD mutation-positive AML in Cohort 2, 36.4% [22.4, 52.2] (16 of 44) in patients with FLT3-ITD mutation-negative AML in Cohort 1, and 30% [16.6, 46.5] (12 of 40) in patients with FLT3-ITD mutation-negative AML in Cohort 2.

Death occurred during quizartinib treatment or within 30 days after the completion of treatment in 120 of 333 patients (64 in cohort 1, 56 in cohort 2). The causes of deaths except for disease progression in 57 patients (30 in Cohort 1, 27 in Cohort 2) were sepsis in 8 patients (2 in Cohort 1, 6 in Cohort 2); pneumonia in 6 patients (5 in Cohort 1, 1 in Cohort 2); septic shock (2 in Cohort 1, 1 in Cohort 2), haemorrhage intracranial (Cohort 1) and pneumonia fungal (Cohort 2) in 3 patients each; subdural haematoma, cerebral haemorrhage, cardiac failure (2 each in Cohort 1), bacterial sepsis (1 each in Cohorts 1 and 2), and cardiac arrest (2 in Cohort 2) bronchopulmonary aspergillosis, sepsis syndrome, bacteraemia, hepatic failure, acute hepatic failure, myocardial infarction, systemic inflammatory response syndrome, renal failure acute, febrile infection, coma, unknown, haemorrhagic stroke, respiratory distress/sepsis, cellulitis/general physical health deterioration, pneumonia/AML (1 each in Cohort 1), multi-organ failure, intraventricular haemorrhage, pulmonary alveolar haemorrhage, haemorrhage, ileitis, febrile bone marrow aplasia, respiratory failure, lung infection, neutropenia, meningitis bacterial, respiratory tract infection fungal, disseminated intravascular coagulation/haemorrhage intracranial/respiratory failure, pyrexia/pancytopenia, AML/general physical health deterioration, and AML/infection (1 each in Cohort 2). A causal relationship to quizartinib could not be ruled out for pneumonia in 2 patients (Cohort 1), cerebral haemorrhage, septic shock, sepsis syndrome, acute hepatic failure, febrile infection, respiratory distress/sepsis, cellulitis/general physical health deterioration (1 each in Cohort 1), neutropenia, pneumonia fungal, haemorrhage, sepsis, cardiac arrest, lung infection, and pyrexia/pancytopenia (1 each in Cohort 2).

7.1.3.4 Foreign phase II study (CTD 5.3.5.2-2, Study 2004, ■ 20■ to ■ 20■)

An open-label, uncontrolled study was conducted in patients with relapsed or refractory FLT3-ITD mutation-positive AML (target sample size, approximately 70 patients) to investigate the efficacy and safety of quizartinib in 31 study centers in 4 countries.

[38]) Patients aged ≥18 years with relapsed or refractory AML after 1 cycle of salvage chemotherapy or hematopoietic stem cell transplantation were included.
[39]) Including patients who met the definition of CRib, although not defined in the protocol.

Quizartinib was orally administered at 30 or 60 mg QD. For patients who did not adequately respond, the dose of quizartinib was increased from 30 mg to 60 mg or from 60 mg to 90 mg. Patients continued to receive treatment until the discontinuation criteria met.

A total of 76 patients enrolled in the study (38 in the 30 mg group, 38 in the 60 mg group) were included in the intent-to-treat (ITT) population and in the efficacy analysis. Of the ITT population, 74 patients were included in the safety analysis, except for 2 patients who did not receive quizartinib (the 60 mg group).

The centrally-assessed CRc rate [90% CI] (%),[39] the primary endpoint, was 47.4% [33.3, 61.8] (18 of 38 of patients) in the 30 mg group and 47.4% [33.3, 61.8] (18 of 38 of patients) in the 60 mg group.

Death occurred during treatment with quizartinib or within 30 days after the completion of treatment in 22 of 74 patients (9 in the 30 mg group, 13 in the 60 mg group). The causes of deaths other than disease progression in 11 patients (5 in the 30 mg group, 6 in the 60 mg group) were leukocytosis, pericardial effusion/pleural effusion, lung infection, septic shock (the 30 mg group), Clostridium difficile sepsis, pneumonia, sinusitis, neoplasm malignant, pneumonitis, venoocclusive disease/multi-organ failure, and renal failure acute/disseminated intravascular coagulation/multi-organ failure/respiratory failure/sepsis (the 60 mg group) in 1 patient each. A causal relationship to quizartinib could not be ruled out for pericardial effusion/pleural effusion in 1 patient (the 30 mg group).

7.1.3.5 Foreign phase III study (CTD 5.3.5.1-1, Study 007, [redacted] 20[redacted] to February 2018)

An open-label, randomized study was conducted in patients with relapsed or refractory FLT3-ITD mutation-positive AML (target sample size, 363 patients) to compare the efficacy and safety of quizartinib with those of investigator-selected chemotherapy in 94 study centers in 18 countries or regions.

In the quizartinib group, oral QD administration was started at 30 mg. Patients who had QTcF of ≤450 milliseconds on Day 15 were treated with the oral dose of 60 mg QD from Day 16 onward.[29] Of the patients for whom the dose was not increased on Day 16, those who met specific criteria on Day 29 and later were allowed to receive oral quizartinib 60 mg QD. In the control group, either one of 3 chemotherapies, namely, (a) combination therapy of mitoxantrone hydrochloride (mitoxantrone), etoposide, and cytarabine (Ara-C) (MEC), (b) combination therapy of fludarabine, idarubicin, Ara-C, and granulocyte-colony stimulating factor (G-CSF) preparation (FLAG-IDA), or (c) low-dose Ara-C, was selected by the investigator and implemented in 28-day treatment cycles. The regimens of chemotherapies are as follows:

(a) MEC: Mitoxantrone 8 mg/m^2, etoposide 100 mg/m^2, and Ara-C 1,000 mg/m^2 were intravenously administered from Days 1 to 5.
(b) FLAG-IDA: G-CSF preparation was subcutaneously (5 μg/kg) or intravenously (300 μg/m^2) administered from Days 1 to 5, fludarabine 30 mg/m^2 and Ara-C 2,000 mg/m^2 were intravenously administered from Days 2 to 6, and IDA 10 mg/m^2 was intravenously administered from Days 2 to 4.
(c) Low-dose Ara-C: Ara-C was subcutaneously administered at 20 mg BID from Days 1 to 10.

A total of 367 patients who were enrolled and randomized in the study (245 in the quizartinib group, 122 in the control group) were included in the ITT population and in the efficacy analysis. Of the ITT population, 335 patients (241 in the quizartinib group, 94 in the control group) were included in the safety analysis, except for 32 patients who did not receive quizartinib (4 in the quizartinib group, 28 in the control group).

The primary endpoint of the study was OS. To evaluate the efficacy, 1 interim analysis and final analysis (to be performed when the number of events in the ITT population reaches 140 and 280, respectively) were planned. To adjust the type I error rate associated with the interim analysis, the significance level in the interim and final analyses was calculated according to the O'Brien-Fleming type alpha spending function based on the Lan-DeMets method.

Table 27 and Figure 2 show the final analysis results on OS, the primary endpoint, (data cutoff on February 22, 2018) and Kaplan-Meier curve, respectively, demonstrating the superiority of quizartinib to the control.

Table 27. Results from final analysis on OS (ITT population, data cutoff on February 22, 2018)

	Quizartinib	Control
Number of patients	245	122
Number of deaths (%)	190 (77.6)	86 (70.5)
Median (95% CI) (months)	6.2 [5.3, 7.2]	4.7 [4.0, 5.5]
Hazard ratio*[1] (95% CI)	0.76 [0.58, 0.98]	
P value (one-sided)*[2]	0.018	

*[1] Calculated using a Cox proportional hazards model stratified by response to the previous treatment (relapsed within 6 months after HSCT, relapsed within 6 months without HSCT, or refractory) and type of chemotherapy selected by the investigator in advance (low-intensive or consolidation chemotherapy); *2 Stratified log-rank test (using the same stratification factors as those in the Cox proportional hazards model) with a one-sided significance level of 0.0231.

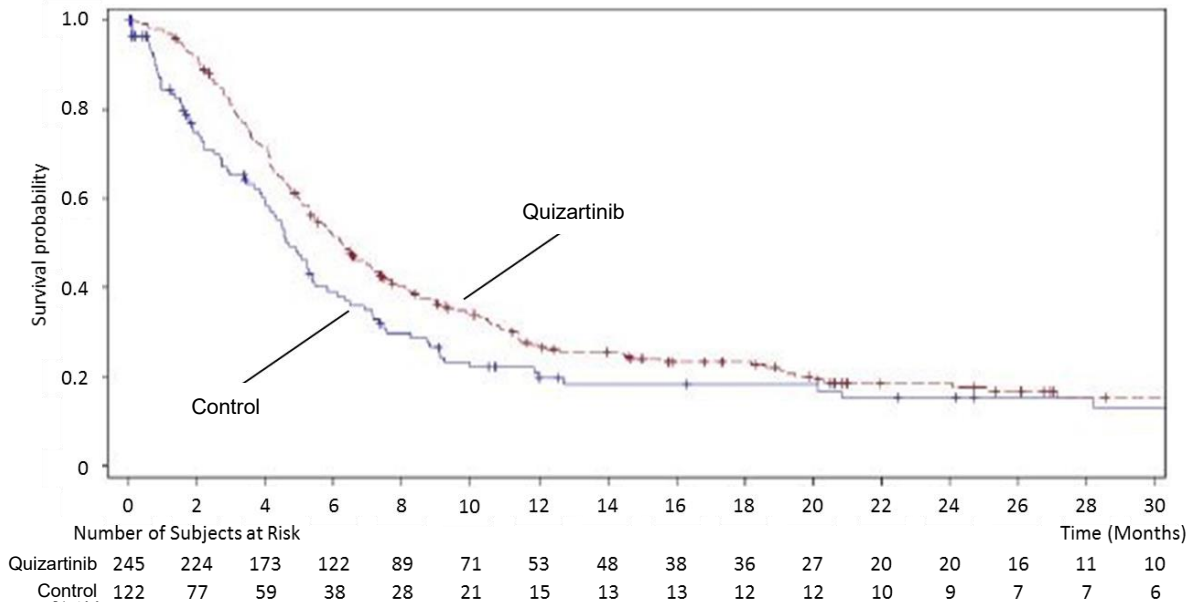

Figure 2. Kaplan-Meier curve based on results from final analysis on OS (ITT population, data cutoff on February 22, 2018)

The median OS in patients with relapsed[33)] FLT3-ITD mutation-positive AML (165 in the quizartinib group, 81 in the control group) was 5.8 months in the quizartinib group and 4.5 months in the control group (hazard ratio [95% CI], 0.75 [0.56, 1.02]), and the median OS in patients with refractory[34)] FLT3-ITD mutation-positive AML (80 in the quizartinib group, 41 in the control group) was 7.9 months in the quizartinib group and 5.4 months in the control group (hazard ratio [95% CI], 0.79 [0.49, 1.26]).

Death occurred during quizartinib treatment or within 30 days after the completion of treatment in 80 of 241 patients (33.2%) in the quizartinib group and 16 of 94 patients (17.0%) in the control group. The causes of deaths other than disease progression in 56 patients (49 in the quizartinib group, 7 in the control group) were pneumonia in 5 patients; haemorrhage intracranial in 4 patients; cerebral haemorrhage, sepsis, and septic shock in 2 patients each; and bronchopulmonary aspergillosis, cardiac failure, disseminated intravascular coagulation, intestinal graft versus host disease (GVHD), leukocytosis, lung infection, multi-organ failure, myocardial infarction, neutropenic sepsis, performance status decreased, pneumococcal sepsis, pulmonary embolism, renal failure acute, respiratory distress, respiratory failure, and thrombocytopenia in 1 patient each in the quizartinib group; and pneumonia, haemorrhage intracranial, septic shock, neutropenic sepsis, acute myocardial infarction, lung disorder, necrotising fasciitis, pneumonia aspiration, and subdural haemorrhage in 1 patient each in the control group. A causal relationship to the study drug could not be ruled out for cerebral haemorrhage, sepsis, bronchopulmonary aspergillosis, myocardial infarction, neutropenic sepsis, performance status decreased, and thrombocytopenia in 1 patient each in the quizartinib group and septic shock, necrotising fasciitis, and pneumonia aspiration in 1 patient each in the control group.

7.2 Reference data

7.2.1 Clinical pharmacology studies

The applicant submitted the results of the following 3 clinical pharmacology studies in healthy adults [see Section 6.2]. No deaths occurred during a study period of any of these studies.

7.2.1.1 Foreign phase I study (CTD 5.3.3.1-1, Study 006, [redacted] 20[redacted] to [redacted] 20[redacted])

7.2.1.2 Foreign phase I study (CTD 5.3.1.1-3, Study AC220-008 [Study 008], [redacted] 20[redacted] to [redacted] 20[redacted])

7.2.1.3 Foreign phase I study (CTD 5.3.3.4-3, Study 012, [redacted] 20[redacted] to [redacted] 20[redacted])

7.2.2 Japanese clinical studies

7.2.2.1 Japanese phase Ib study (CTD 5.3.5.4-1, Study AC220-A-J102 [Study J102], [redacted] 20[redacted] to [redacted] 20[redacted]

An open-label, uncontrolled study was conducted in patients with treatment-naive AML (target sample size, 6-18 patients) to investigate the safety and PK of quizartinib administered concomitantly with remission induction therapy or consolidation therapy in 9 study centers in Japan.

All of the 7 patients enrolled in this study received quizartinib and concomitant drugs and were included in the safety analysis.

No deaths occurred during or within 28 days after the completion of the study drug treatment.

7.2.3 Foreign clinical studies

7.2.3.1 Foreign phase I study (CTD 5.3.5.4-2, Study 2689-CL-0005 [Study 0005], [redacted] 20[redacted] to [redacted] 20[redacted])

An open-label, uncontrolled study was conducted in patients with treatment-naive AML (target sample size, 6-18 patients in Part 1, 14-34 patients in Part 2) to investigate the safety and PK of quizartinib administered concomitantly with remission induction therapy in 5 study centers in 1 country.

All of the 19 patients enrolled in the study received the study drug and were included in the safety analysis.

One patient died during study drug treatment or within 30 days after the completion of treatment. A cause of the death was cardiac arrest, and a causal relationship to quizartinib was ruled out.

7.R Outline of the review conducted by PMDA

7.R.1 Data for review

PMDA determined that, among the evaluation data submitted, the foreign phase III study (Study 007) in patients with relapsed or refractory FLT3-ITD mutation-positive AML is the pivotal study for the evaluation of efficacy and safety of quizartinib.

In addition, PMDA decided to evaluate the efficacy and safety of quizartinib in Japanese patients mainly based on data from the Japanese phase II study (Study J201) in patients with relapsed or refractory FLT3-ITD mutation-positive AML.

7.R.2 Efficacy

Based on the following review, PMDA concluded that quizartinib has efficacy in patients with relapsed or refractory FLT3-ITD mutation-positive AML.

7.R.2.1 Control group

The applicant's explanation about the rationale for use of the control group in Study 007:
When Study 007 was being planned (20[redacted]), the National Comprehensive Cancer Network Clinical Practice Guidelines in Oncology, Acute Myeloid Leukemia (NCCN guideline) (v.2.2012) recommended therapies such as MEC, FLAG-IDA, or low-dose Ara-C for patients with relapsed or refractory AML irrespective of FLT3-ITD mutation. Thus, an investigator-selected chemotherapy (MEC, FLAG-IDA, or low-dose Ara-C) was used in the control group in Study 007.

PMDA accepted the applicant's explanation.

7.R.2.2 Efficacy endpoint and evaluation results

OS was the primary endpoint of Study 007, and the results on OS demonstrated the superiority of quizartinib to the control [see Section 7.1.3.5].

PMDA's view:
Treatment in patients with relapsed or refractory FLT3-ITD mutation-positive AML is intended for survival prolongation, and the primary endpoint of OS in Study 007 is appropriate.

In addition, the results from Study 007 demonstrate the benefit of quizartinib in patients with relapsed or refractory FLT3-ITD mutation-positive AML.

7.R.2.3 Efficacy of quizartinib in Japanese patients

The applicant's explanation about the efficacy of quizartinib in Japanese patients:
The primary endpoint of Study J201, i.e., the CRc rate including CRib, met the prespecified criteria for early termination for efficacy[32] [see Section 7.1.2.2]. In Study 007, the CRc rate including CRib (%) [95% CI] was 48.2% [41.8, 54.6] (118 of 245) of patients in the quizartinib group and 27.0% [19.4, 35.8] (33 of 122) of patients in the control group.

Based on the above results, quizartinib is expected to have efficacy in Japanese patients with relapsed or refractory FLT3-ITD mutation-positive AML.

PMDA asked the applicant to justify the efficacy evaluation of quizartinib in Study J201, in which CRib was regarded as CRc despite not being defined in the protocol.

The applicant's explanation:
In Study 007, CRib [see Section 7.1] was regarded as a clinical response to quizartinib, but it was not clearly mentioned in the definition of CRc. Thus, the statistical analysis plan was revised to add the definition of CRib to that of CRc (the former CRi was re-defined as CRia) ([redacted], 20[redacted]). Similarly, in Study J201, the statistical analysis plan was revised on [redacted], 20[redacted] after data cutoff ([redacted], 20[redacted]) and DMC ([redacted], 20[redacted]). In Study J201, however, patients who met the definition of CRib as of data cutoff had already been assessed as CRi responders by the investigator, and the revision of protocol was considered unnecessary. Accordingly, the above revision of the statistical analysis plan associated with the definition of CRc was intended to clarify the definition of CRc, and it is possible to evaluate the efficacy in Japanese patients in accordance with the revised statistical analysis plan.

On the assumption that 3 patients assessed as CRib in Study J201 were regarded as non-CRc, the CRc rate [95% CI] (%) would be 42.3% [25.8, 60.2] (11 of 26 of patients) in the analysis set for the primary endpoint or 44.0% [27.0, 62.1] (11 of 25 of patients) in the analysis set for the early termination for efficacy. Even if CRib was not regarded as CRc, the criteria for early termination for efficacy based on the 2-step design[32] would be met.

PMDA's view:
In Study J201, the protocol-based definition of CRc did not clearly indicate the inclusion of CRib, which led to a subjective evaluation of efficacy by the assessors. The applicant should have taken appropriate measures (a) to be fully compliant with the protocol and (b) to conduct an objective evaluation by a third party, namely, central assessment, to minimize the evaluation bias. Furthermore, in Study J201 the post

hoc change in the definition of the primary endpoint was also inappropriate because of a likely overestimation of efficacy.

However, a certain level of CRc was observed even without CRib in Study J201 and that (a) no clear differences are observed in the diagnosis and treatment system for AML or the PK of quizartinib between Japanese and non-Japanese patients [see Section 6.2.9] and (b) OS, the primary endpoint, demonstrated the superiority of quizartinib to the control in Study 007. Given these, quizartinib is considered to have promising efficacy in Japanese patients with relapsed or refractory FLT3-ITD mutation-positive AML.

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

Based on the following review, PMDA concluded that adverse events requiring particular attention in treatment with quizartinib are infection, haemorrhage, myelosuppression, cardiac disorder (QT interval prolonged and myocardial infarction), renal dysfunction, and interstitial lung disease (ILD). Caution should be exercised against these adverse events in the use of quizartinib.

Although these adverse events are attention calling in the use of quizartinib, quizartinib is tolerated in patients appropriately followed up by physicians with adequate knowledge and experience in treating hematopoietic malignancies, through monitoring and controlling of these adverse events. Clinical experience with quizartinib in Japanese patients, however, is extremely limited, and post-marketing safety information should be further collected [see Section 7.R.7].

7.R.3.1 Safety profile of quizartinib

The applicant's explanation about the safety profile of quizartinib, based on the safety data obtained from Study 007:

Table 28 shows the outline of safety in Study 007.

Table 28. Outline of safety profile (Study 007)

	Number of patients (%)	
	Quizartinib	Control
	241	94
All adverse events	238 (98.8)	93 (98.9)
Grade ≥3 adverse events	211 (87.6)	74 (78.7)
Adverse events resulting in death	36 (14.9)	11 (11.7)
Serious adverse events	168 (69.7)	37 (39.4)
Adverse events leading to treatment discontinuation	44 (18.3)	1 (1.1)
Adverse events leading to interruption	84 (34.9)	1 (1.1)
Adverse events leading to dose reduction	52 (21.6)	1 (1.1)

Table 29 shows adverse events with an incidence of ≥20% in any group in Study 007.

Table 29. Adverse events with an incidence of ≥20% in any group (Study 007)

SOC PT (MedDRA/J ver. 16.1)	Number of patients (%)			
	Quizartinib 241		Control 94	
	All Grades	Grades ≥3	All Grades	Grades ≥3
All adverse events	238 (98.8)	211 (87.6)	93 (98.9)	74 (78.7)
Blood and lymphatic system disorders				
Anaemia	88 (36.5)	72 (29.9)	29 (30.9)	27 (28.7)
Febrile neutropenia	81 (33.6)	74 (30.7)	26 (27.7)	20 (21.3)
Thrombocytopenia	63 (26.1)	58 (24.1)	20 (21.3)	20 (21.3)
Neutropenia	50 (20.7)	48 (19.9)	11 (11.7)	10 (10.6)
Gastrointestinal disorders				
Nausea	116 (48.1)	6 (2.5)	39 (41.5)	1 (1.1)
Vomiting	80 (33.2)	8 (3.3)	20 (21.3)	1 (1.1)
Diarrhoea	70 (29.0)	4 (1.7)	34 (36.2)	3 (3.2)
Constipation	47 (19.5)	0	22 (23.4)	0
General disorders and administration site conditions				
Pyrexia	92 (38.2)	6 (2.5)	42 (44.7)	4 (4.3)
Fatigue	67 (27.8)	12 (5.0)	18 (19.1)	1 (1.1)
Oedema peripheral	51 (21.2)	3 (1.2)	22 (23.4)	0
Investigations				
Electrocardiogram QT prolonged	64 (26.6)	10 (4.1)	2 (2.1)	0
Metabolism and nutrition disorders				
Hypokalaemia	77 (32.0)	28 (11.6)	25 (26.6)	8 (8.5)
Decreased appetite	49 (20.3)	6 (2.5)	10 (10.6)	1 (1.1)
Respiratory, thoracic and mediastinal disorders				
Cough	56 (23.2)	1 (0.4)	13 (13.8)	0
Dyspnoea	49 (20.3)	12 (5.0)	8 (8.5)	5 (5.3)
Nervous system disorders				
Headache	52 (21.6)	1 (0.4)	16 (17.0)	0

Adverse events with a ≥10% higher incidence in the quizartinib group than in the control group in Study 007 were electrocardiogram QT prolonged (64 patients [26.6%], 2 patients [2.1%]), vomiting (80 [33.2%], 20 [21.3%]), and dyspnoea (49 [20.3%], 8 [8.5%]). Grade ≥3 adverse events with a ≥5% higher incidence in the quizartinib group than in the control group were febrile neutropenia (74 [30.7%], 20 [21.3%]) and neutropenia (48 [19.9%], 10 [10.6%]). Adverse events resulting in death with a higher incidence in the quizartinib group than in the control group which occurred in >1 patient were pneumonia (7 [2.9%], 1 [1.1%]), lung infection (2 [0.8%], 0), sepsis (2 [0.8%], 0), cerebral haemorrhage (2 [0.8%], 0), GVHD (2 [0.8%], 0), and haemorrhage intracranial (4 [1.7%], 1 [1.1%]). Serious adverse events with a ≥2% higher incidence in the quizartinib group than in the control group were febrile neutropenia (50 [20.7%], 9 [9.6%]), pneumonia (22 [9.1%], 3 [3.2%]), cellulitis (6 [2.5%], 0), sepsis (16 [6.6%], 4 [4.3%]), urinary tract infection (6 [2.5%], 0), anaemia (6 [2.5%], 0), upper respiratory tract infection (5 [2.1%], 0), nausea (5 [2.1%], 0), vomiting (5 [2.1%], 0), syncope (5 [2.1%], 0), electrocardiogram QT prolonged (5 [2.1%], 0), and renal failure acute (6 [2.5%], 0). There was no adverse event leading to study drug discontinuation with a ≥5% higher incidence in the quizartinib group than in the control group. An adverse event leading to the interruption of the study drug with a ≥5% higher incidence in the quizartinib group than in the control group was febrile neutropenia (15 [6.2%], 0). An adverse event leading to the dose reduction of study drug with a ≥5% higher incidence in the quizartinib group than in the control group was electrocardiogram QT prolonged (23 [9.5%], 0).

PMDA's view:

Adverse events with a higher incidence in the quizartinib group than in the control group, adverse events resulting in death, those leading to serious adverse events or treatment discontinuation reported in the quizartinib group in Study 007 may occur in patients receiving quizartinib and thus require attention.

Information on the incidence of these events should be appropriately provided to healthcare professionals via the package insert.

7.R.3.2 Difference in safety between Japanese and non-Japanese patients

The applicant's explanation about difference in safety between Japanese and non-Japanese patients:
Table 30 shows the outline of safety in Study J201 in Japanese patients and in the quizartinib group in Study 007 in non-Japanese patients.

Table 30. Outline of difference in safety between Japanese and non-Japanese patients (Studies J201 and 007 [quizartinib group])

	Number of patients (%)	
	Study J201 37	Study 007 (quizartinib) 241
All adverse events	37 (100)	238 (98.8)
Grade ≥3 adverse events	34 (91.9)	211 (87.6)
Adverse events resulting in death	1 (2.7)	36 (14.9)
Serious adverse events	17 (45.9)	168 (69.7)
Adverse events leading to treatment discontinuation	2 (5.4)	44 (18.3)
Adverse events leading to interruption	4 (10.8)	84 (34.9)
Adverse events leading to dose reduction	7 (18.9)	52 (21.6)

An adverse event with a ≥10% higher incidence in Japanese patients than in non-Japanese patients was platelet count decreased (14 Japanese [37.8%], 33 non-Japanese [13.7%]). The Grade ≥3 adverse event with a ≥10% higher incidence in Japanese patients than in non-Japanese patients was platelet count decreased (11 Japanese [29.7%], 29 non-Japanese [12.0%]). There was no adverse events resulting in death, serious adverse events, and adverse events leading to the discontinuation, interruption, or dose reduction of quizartinib with a ≥5% higher incidence in Japanese patients than in non-Japanese patients.

PMDA's view:
Because of the limited number of Japanese patients included in the clinical studies, it is difficult to draw a clear conclusion on the difference in safety profiles between Japanese and non-Japanese patients. However, caution should be exercised against the adverse events observed more frequently in Japanese patients than in non-Japanese patients, and the occurrence of these events should be appropriately communicated to healthcare professionals via the package insert. Given limited information about the safety of quizartinib in Japanese patients, the applicant should continue collecting post-marketing information and, once available, new findings should be provided to healthcare professionals appropriately.

The following subsections summarize safety review by PMDA mainly based on the safety results from Studies 007 and J201 with the focus on the adverse events resulting in death, Grade ≥3 adverse events and serious adverse events with a higher incidence in the quizartinib group than in the control group in Study 007, and adverse events with a higher incidence in Japanese than in non-Japanese.

7.R.3.3 Infection

The applicant's explanation about the occurrence of infection associated with quizartinib:

Adverse events related to infection were tabulated based on preferred terms (PTs) classified under Medical Dictionary for Regulatory Activities (MedDRA) system organ class (SOC) of "Infections and infestations." Table 31 shows the incidences of infection in Studies 007 and J201.

Table 31. Incidences of infection reported by ≥5% of patients in either study (Studies 007 and J201)

MedDRA PT*	Number of patients (%)					
	Study 007				Study J201	
	Quizartinib 241		Control 94		37	
	All Grades	Grades ≥3	All Grades	Grades ≥3	All Grades	Grades ≥3
Infection	167 (69.3)	108 (44.8)	61 (64.9)	32 (34.0)	15 (40.5)	11 (29.7)
Pneumonia	31 (12.9)	22 (9.1)	9 (9.6)	7 (7.4)	3 (8.1)	2 (5.4)
Sepsis	22 (9.1)	21 (8.7)	5 (5.3)	4 (4.3)	2 (5.4)	2 (5.4)
Urinary tract infection	22 (9.1)	10 (4.1)	0	0	0	0
Upper respiratory tract infection	21 (8.7)	5 (2.1)	1 (1.1)	0	1 (2.7)	1 (2.7)
Cellulitis	16 (6.6)	8 (3.3)	1 (1.1)	0	3 (8.1)	2 (5.4)
Oral herpes	12 (5.0)	0	4 (4.3)	0	0	0
Device related infection	11 (4.6)	8 (3.3)	7 (7.4)	5 (5.3)	2 (5.4)	1 (2.7)
Bacteraemia	5 (2.1)	5 (2.1)	6 (6.4)	3 (3.2)	3 (8.1)	2 (5.4)
Enterococcal infection	1 (0.4)	0	5 (5.3)	1 (1.1)	0	0
Acarodermatitis	1 (0.4)	1 (0.4)	0	0	3 (8.1)	0

* Medical Dictionary for Regulatory Activities Japanese version (MedDRA/J) ver. 16.1 for Study 007 and MedDRA/J ver. 20.1 for Study J201.

In Study 007, infection resulted in death of 16 patients in the quizartinib group (6.6%, pneumonia in 7; lung infection, sepsis, and septic shock in 2 each; bronchopulmonary aspergillosis, neutropenic sepsis, and pneumococcal sepsis in 1 each) and 5 patients in the control group (5.3%, pneumonia, septic shock, neutropenic sepsis, necrotising fasciitis, and pneumonia fungal in 1 each). A causal relationship to the study drug could not be ruled out for sepsis, bronchopulmonary aspergillosis, and neutropenic sepsis in 1 patient each in the quizartinib group, and septic shock, necrotising fasciitis, and pneumonia aspiration in 1 patient each in the control group. Serious infection occurred in 101 patients in the quizartinib group (41.9%, events reported by ≥3 patients were pneumonia in 22; sepsis in 16; neutropenic sepsis in 7; cellulitis and urinary tract infection in 6 each; septic shock and upper respiratory tract infection in 5 each; bacteraemia and Staphylococcal infection in 4 each; and device related infection, Enterobacter infection, gastroenteritis, lung infection, and pneumonia fungal in 3 each [some patients had >1 event]) and in 21 patients in the control group (22.3%, events reported by ≥3 patients were sepsis in 4; and pneumonia and Escherichia sepsis in 3 each [some patients had >1 event]). A causal relationship to the study drug could not be ruled out for sepsis in 6 patients, neutropenic sepsis in 4 patients, cellulitis and pneumonia fungal in 2 patients each, and upper respiratory tract infection, device related infection, Enterobacter infection and urinary tract infection in 1 patient each in the quizartinib group, and Escherichia sepsis in 2 patients, and sepsis and pneumonia in 1 patient each in the control group. In the quizartinib group, infection leading to the discontinuation of study drug occurred in 15 patients (6.2%); infection leading to the interruption of study drug occurred in 26 patients (10.8%); and infection leading to dose reduction of the study drug occurred in 7 patients (2.9%). In the control group, there was no infection leading to study discontinuation or interruption or dose reduction.

In Study J201, no infection resulting in death occurred. Serious infection occurred in 7 patients (18.9%, events reported by ≥2 patients were bacteraemia and sepsis in 2 each). A causal relationship to quizartinib could not be ruled out for bacteraemia in 2 patients and sepsis in 1 patient. There was no

infection leading to the discontinuation of quizartinib. Infection leading to dose reduction occurred in 2 patients (5.4%), and infection leading to the interruption of quizartinib occurred in 1 patient (2.9%).

PMDA's view:
Caution should be exercised against infection during quizartinib treatment because Grade ≥3 infection frequently occurred in patients receiving quizartinib and serious infection occurred in >1 patient in Studies 007 and J201 including fatal cases for which a causal relationship to quizartinib could not be ruled out. Thus, the occurrence of infection in the clinical studies should be appropriately communicated to healthcare professionals via the package insert.

7.R.3.4 Hemorrhage

The applicant's explanation about the occurrence of hemorrhage associated with quizartinib:
Adverse events related to hemorrhage were tabulated based on PTs classified MedDRA standard MedDRA queries (SMQ) of "Haemorrhage terms (excl laboratory terms) (narrow)." Table 32 shows the incidences of hemorrhage in Studies 007 and J201.

Table 32. Incidences of hemorrhage reported by ≥2% of patients in any study (Studies 007 and J201)

MedDRA PT*	Number of patients (%)					
	Study 007				Study J201	
	Quizartinib 241		Control 94		37	
	All Grades	Grades ≥3	All Grades	Grades ≥3	All Grades	Grades ≥3
Haemorrhage	119 (49.4)	24 (10.0)	36 (38.3)	8 (8.5)	7 (18.9)	2 (5.4)
Epistaxis	28 (11.6)	4 (1.7)	8 (8.5)	1 (1.1)	0	0
Petechiae	27 (11.2)	2 (0.8)	6 (6.4)	0	0	0
Gingival bleeding	16 (6.6)	1 (0.4)	3 (3.2)	1 (1.1)	0	0
Contusion	15 (6.2)	2 (0.8)	2 (2.1)	0	1 (2.7)	0
Haematuria	12 (5.0)	1 (0.4)	2 (2.1)	0	1 (2.7)	0
Haematoma	10 (4.1)	2 (0.8)	4 (4.3)	2 (2.1)	1 (2.7)	1 (2.7)
Mouth haemorrhage	10 (4.1)	0	2 (2.1)	0	0	0
Vaginal haemorrhage	6 (2.5)	1 (0.4)	2 (2.1)	0	0	0
Haemorrhage intracranial	5 (2.1)	5 (2.1)	2 (2.1)	2 (2.1)	0	0
Haemoptysis	5 (2.1)	1 (0.4)	2 (2.1)	0	1 (2.7)	1 (2.7)
Ecchymosis	5 (2.1)	0	0	0	0	0
Disseminated intravascular coagulation	3 (1.2)	2 (0.8)	1 (1.1)	0	2 (5.4)	0
Purpura	3 (1.2)	0	1 (1.1)	0	1 (2.7)	0
Gastric haemorrhage	1 (0.4)	1 (0.4)	0	0	1 (2.7)	0
Shock haemorrhagic	0	0	0	0	1 (2.7)	1 (2.7)

* MedDRA/J ver. 16.1 for Study 007 and MedDRA/J ver. 20.1 for Study J201.

In Study 007, hemorrhage resulted in death in 7 patients in the quizartinib group (2.9%, haemorrhage intracranial in 4, cerebral haemorrhage in 2, disseminated intravascular coagulation in 1) and in 2 patients in the control group (2.1%, haemorrhage intracranial and subdural haematoma in 1 each). A causal relationship to the study drug was ruled out for any event. Serious hemorrhage occurred in 19 patients in the quizartinib group (7.9%, haemorrhage intracranial in 5; cerebral haemorrhage and hematuria in 2 each; and disseminated intravascular coagulation, gastric haemorrhage, gastrointestinal haemorrhage, haematemesis, haemoptysis, melaena, petechiae, post procedural haemorrhage, subdural haematoma, upper gastrointestinal haemorrhage, and vaginal haemorrhage in 1 each [some patients had >1 event]), and in 3 patients in the control group (3.2%, haemorrhage intracranial in 2 and subdural haematoma in 1). A causal relationship to the study drug could not be ruled out for cerebral haemorrhage,

gastrointestinal haemorrhage, petechiae, subdural haemorrhage, and vaginal haemorrhage in 1 patient each in the quizartinib group. Hemorrhage leading to study drug discontinuation occurred in 8 patients (3.3%) in the quizartinib group and 1 patient (1.1%) in the control group. Hemorrhage leading to study drug interruption occurred in 2 patients (0.8%) in the quizartinib group. No hemorrhage leading to interruption occurred in the control group, and no hemorrhage leading to dose reduction occurred in either quizartinib group or control group.

In Study J201, no hemorrhage resulted in death. Serious hemorrhage occurred in 3 patients (8.1%, disseminated intravascular coagulation, haematoma, haemoptysis, and shock haemorrhagic in 1 each [some patients had >1 event]). A causal relationship to quizartinib was ruled out for any event. There was no haemorrhage leading to study drug discontinuation or interruption, or dose reduction.

PMDA's view:
Serious hemorrhage for which a causal relationship to quizartinib could not be ruled out occurred in >1 patient in Studies 007 and J201, and caution should be exercised against hemorrhage in patients receiving quizartinib. Thus, the occurrence of hemorrhage in the clinical studies should be appropriately communicated to healthcare professionals. In addition, healthcare professionals should also be advised via the package insert to monitor patients on quizartinib by regular hematology testing so that appropriate measures, such as treatment interruption or dose reduction, are taken in case of abnormality.

7.R.3.5 Myelosuppression

The applicant's explanation about the occurrence of myelosuppression associated with quizartinib:
Adverse events related to myelosuppression were tabulated based on MedDRA PTs of "anaemia," "haematocrit decreased," "haemoglobin decreased," "red blood cell count decreased," "thrombocytopenia," "platelet count decreased," "white blood cell count decreased," "leukopenia," "neutropenia," "neutrophil count decreased," "lymphocyte count decreased," "lymphopenia," "pancytopenia," and "febrile neutropenia." Table 33 shows the incidences of myelosuppression in Studies 007 and J201.

Table 33. Incidences of myelosuppression reported by ≥10% of patients in either study (Studies 007 and J201)

MedDRA PT*	Number of patients (%)					
	Study 007				Study J201	
	Quizartinib 241		Control 94		37	
	All Grades	Grades ≥3	All Grades	Grades ≥3	All Grades	Grades ≥3
Myelosuppression	177 (73.4)	165 (68.5)	53 (56.4)	47 (50.0)	30 (81.1)	29 (78.4)
Anaemia	88 (36.5)	72 (29.9)	29 (30.9)	27 (28.7)	10 (27.0)	9 (24.3)
Febrile neutropenia	81 (33.6)	74 (30.7)	26 (27.7)	20 (21.3)	16 (43.2)	14 (37.8)
Thrombocytopenia	63 (26.1)	58 (24.1)	20 (21.3)	20 (21.3)	4 (10.8)	4 (10.8)
Neutropenia	50 (20.7)	48 (19.9)	11 (11.7)	10 (10.6)	3 (8.1)	3 (8.1)
White blood cell count decreased	35 (14.5)	29 (12.0)	14 (14.9)	13 (13.8)	8 (21.6)	8 (21.6)
Platelet count decreased	33 (13.7)	29 (12.0)	12 (12.8)	12 (12.8)	14 (37.8)	11 (29.7)
Neutrophil count decreased	32 (13.3)	29 (12.0)	14 (14.9)	14 (14.9)	8 (21.6)	8 (21.6)

* MedDRA/J ver. 16.1 for Study 007 and MedDRA/J ver. 20.1 for Study J201.

In Study 007, myelosuppression resulted in death in 1 patient (0.4%, thrombocytopenia in 1) in the quizartinib group, and a causal relationship to quizartinib could not be ruled out for the event. Serious

myelosuppression occurred in 63 patients in the quizartinib group (26.1%, events reported by ≥2 patients were febrile neutropenia in 50; anaemia in 6; neutropenia in 4; pancytopenia and thrombocytopenia in 3 each; neutrophil count decreased in 2 [some patients had >1 event]), and in 9 patients in the control group (9.6%, febrile neutropenia in 9). A causal relationship to the study drug could not be ruled out for febrile neutropenia in 18 patients; anaemia and thrombocytopenia in 3 patients each; pancytopenia in 2 patients; and neutropenia in 1 patient in the quizartinib group and febrile neutropenia in 5 patients in the control group. Myelosuppression leading to treatment discontinuation occurred in 5 patients (2.1%) in the quizartinib group; myelosuppression leading to treatment interruption occurred in 32 patients (13.3%) in the quizartinib group; and myelosuppression leading to dose reduction occurred in 17 patients (7.1%) in the quizartinib group. In the control group, there was no myelosuppression resulting in death, leading to treatment discontinuation or interruption or dose reduction.

In Study J201, there was no myelosuppression resulting in death. Serious myelosuppression occurred in 7 patients (18.9%; febrile neutropenia in 6; anaemia, neutropenia, and platelet count decreased in 1 patient each [some patients had >1 event]). A causal relationship to quizartinib could not be ruled out for febrile neutropenia in 4 patients, anaemia, neutropenia, and platelet count decreased in 1 patient each. There was no myelosuppression leading to treatment discontinuation or interruption. Myelosuppression led to dose reduction in 1 patient (2.7%).

PMDA's view:
Caution should be exercised against myelosuppression during treatment with quizartinib, given that Grade ≥3 myelosuppression frequently occurred in patients receiving quizartinib in Studies 007 and J201 and serious myelosuppression occurred in >1 patient, including fatal cases for which a causal relationship to quizartinib could not be ruled out. Thus, the occurrence of myelosuppression in the clinical studies should be appropriately communicated to healthcare professionals. Healthcare professionals should also be advised via the package insert to monitor patients on quizartinib by regular hematology testing, so that appropriate measures, such as treatment interruption or dose reduction, in case of abnormality.

7.R.3.6 Cardiac disorders

The applicant's explanation about the occurrence of cardiac disorders associated with quizartinib:
Adverse events related to cardiac disorders were tabulated based on PTs classified under MedDRA SMQs of "Torsade de pointes/QT prolongation (broad)," "Arrhythmia related investigations, signs and symptoms (broad)," "cardiac failure (narrow)," and "myocardial infarction (broad)," and PTs of "cardiac hypertrophy," "diastolic dysfunction," "left ventricular dysfunction," "cardiomyopathy," "cardiotoxicity," "cytotoxicity," "cardiomyopathy," and "ejection fraction decreased." Table 34 shows the incidences of cardiac disorder in Studies 007 and J201.

Table 34. Incidences of cardiac disorders (Studies 007 and J201)

MedDRA PT*	Number of patients (%)					
	Study 007				Study J201	
	Quizartinib 241		Control 94		37	
	All Grades	Grades ≥3	All Grades	Grades ≥3	All Grades	Grades ≥3
Cardiac disorders	89 (36.9)	22 (9.1)	14 (14.9)	5 (5.3)	14 (37.8)	0
Electrocardiogram QT prolonged	64 (26.6)	10 (4.1)	2 (2.1)	0	13 (35.1)	0
Syncope	12 (5.0)	9 (3.7)	2 (2.1)	1 (1.1)	0	0
Tachycardia	11 (4.6)	1 (0.4)	4 (4.3)	0	0	0
Palpitations	7 (2.9)	0	1 (1.1)	0	0	0
Cardiac failure	2 (0.8)	1 (0.4)	1 (1.1)	1 (1.1)	0	0
Ejection fraction decreased	2 (0.8)	1 (0.4)	0	0	1 (2.7)	0
Troponin I increased	2 (0.8)	0	0	0	0	0
Cardiomyopathy	1 (0.4)	1 (0.4)	1 (1.1)	1 (1.1)	0	0
Myocardial infarction	1 (0.4)	1 (0.4)	0	0	0	0
Ventricular tachycardia	1 (0.4)	0	2 (2.1)	1 (1.1)	0	0
Blood CK increased	1 (0.4)	0	0	0	1 (2.7)	0
Pulmonary oedema	1 (0.4)	0	0	0	0	0
Bradycardia	0	0	3 (3.2)	0	0	0
Acute myocardial infarction	0	0	1 (1.1)	1 (1.1)	0	0
Cardiac arrest	0	0	1 (1.1)	1 (1.1)	0	0

* MedDRA/J) ver. 16.1 for Study 007 and MedDRA/J ver. 20.1 for Study J201.

In Study 007, cardiac disorders resulted in death in 2 patients (0.8%; cardiac failure and myocardial infarction in 1 each) in the quizartinib group and in 1 patient (1.1%; acute myocardial infarction in 1) in the control group. A causal relationship to the study drug could not be ruled out for myocardial infarction 1 in the quizartinib group. Serious cardiac disorder occurred in 12 patients in the quizartinib group (5.0%; electrocardiogram QT prolonged and syncope in 5 each; and cardiac failure and myocardial infarction in 1 each) and in 2 patients in the control group (2.1%; myocardial infarction and cardiomyopathy in 1 each). A causal relationship to the study drug could not be ruled out for electrocardiogram QT prolonged in 5 patients, syncope in 2 patients, and myocardial infarction in 1 patient in the quizartinib group and cardiomyopathy in 1 patient in the control group. Cardiac disorders leading to the study drug discontinuation occurred in 2 patients (0.8%) in the quizartinib group; cardiac disorders leading to the study drug interruption occurred in 12 patients (5.0%) in the quizartinib group; and cardiac disorders leading to the dose reduction of study drug occurred in 24 patients (10.0%) in the quizartinib group. In the control group, there was no cardiac disorder leading to the discontinuation, interruption, or dose reduction of the study drug.

In Study J201, no cardiac disorder resulting in death or serious cardiac disorder occurred. A cardiac disorder led to the dose reduction of quizartinib in 1 patient (2.7%), and there was no cardiac disorder leading to the discontinuation or interruption of quizartinib.

The applicant's additional explanation about the need for caution about QT interval prolongation associated with quizartinib:
In Studies 007 and J201, 12-lead electrocardiography was regularly performed. Patients with screening QTcF of >450 milliseconds, those with long QT syndrome, and those with hypokalemia and hypomagnesemia were excluded, and caution was given against the use of quizartinib with a concomitant QT or QTc interval prolonging drug. Table 35 shows maximum values and changes in QTcF in patients in whom QTcF values were measured in Studies 007 and J201.

Table 35. Maximum values and changes in QTcF in patients receiving quizartinib (Studies 007 and J201)

	Number of patients (%)	
	Study 007	Study J201
	241	37
Maximum		
≤450 milliseconds	125 (51.9)	22 (59.5)
>450 and ≤480 milliseconds	76 (31.5)	14 (37.8)
>480 and ≤500 milliseconds	30 (12.4)	1 (2.7)
>500 milliseconds	8 (3.3)	0
Missing	2 (0.8)	0
Change from baseline (maximum)		
<0 milliseconds	1 (0.4)	1 (2.7)
≥0 and ≤30 milliseconds	81 (33.6)	21 (56.8)
>30 and ≤60 milliseconds	121 (50.2)	14 (37.8)
>60 milliseconds	30 (12.4)	1 (2.7)
Missing	8 (3.3)	0

As described above, serious electrocardiogram QT prolonged for which a causal relationship to quizartinib could not be ruled out occurred in the clinical studies; and QTcF of >500 milliseconds were observed in Study 007. The applicant therefore plans to give caution about QT interval prolongation in the package insert.

PMDA's view:
Serious myocardial infarction observed in Studies 007 and J201 included fatal cases for which a causal relationship to quizartinib could not be ruled out. Nevertheless, only a small number of patients experienced these events, precluding to draw a definite conclusion on the relationship between quizartinib and myocardial infarction based on the currently available data. Given that a patient experienced serious myocardial infarction for which a causal relationship to quizartinib could not be ruled out, caution should be used against cardiac disorders including myocardial infarction. The occurrence of cardiac disorders in the clinical studies should be appropriately communicated to healthcare professionals via the package insert.

Because >1 patient experienced serious QT interval prolongation for which a causal relationship to quizartinib could not be ruled out, caution should be used against the event. Thus, electrocardiography and an electrolyte test (potassium, magnesium, etc.) should be performed before starting the treatment and regularly during the treatment with quizartinib so that abnormalities, if any, are managed by treatment interruption, dose reduction, or electrolyte correction, etc. Such advice should be given appropriately to healthcare professionals via the package insert.

7.R.3.7 Renal dysfunction

The applicant's explanation about the occurrence of renal dysfunction associated with quizartinib:
Adverse events related to renal dysfunction were tabulated based on PTs classified under MedDRA SMQ of "Acute renal failure (broad)." Table 36 shows the incidences of renal dysfunction in Studies 007 and J201.

Table 36. Incidences of renal dysfunction reported by ≥5% of patients in either study (Studies 007 and J201)

MedDRA PT*	Number of patients (%)					
	Study 007				Study J201	
	Quizartinib 241		Control 94		37	
	All Grades	Grades ≥3	All Grades	Grades ≥3	All Grades	Grades ≥3
Renal dysfunction	35 (14.5)	6 (2.5)	6 (6.4)	1 (1.1)	1 (2.7)	0
Blood creatinine increased	16 (6.6)	1 (0.4)	2 (2.1)	0	1 (2.7)	0
Renal failure acute	14 (5.8)	5 (2.1)	3 (3.2)	1 (1.1)	0	0

* MedDRA/J ver. 16.1 for Study 007 and MedDRA/J ver. 20.1 for Study J201.

In Study 007, renal dysfunction resulting in death occurred in 1 patient (0.4%, renal failure acute in 1 patient) in the quizartinib group, and a causal relationship to the study drug was ruled out for the event. Serious renal dysfunction occurred in 7 patients (2.9%; renal failure acute in 6 patients and renal failure in 1 patient) in the quizartinib group, and a causal relationship to the study drug could not be ruled out for renal failure acute in 2 patients and renal failure in 1 patient. Renal dysfunction leading to study drug discontinuation occurred in 2 patients (0.8%) in the quizartinib group, and renal dysfunction leading to the interruption of the study drug occurred in 1 patient (0.4%) in the quizartinib group. In the control group, there was no renal dysfunction resulting in death, serious renal dysfunction, or renal dysfunction leading to study drug discontinuation or interruption. There was no renal dysfunction leading to dose reduction of the study drug occurred in either quizartinib group or control group.

In Study J201, there was no renal dysfunction resulting in death, serious renal dysfunction, or renal dysfunction leading to the discontinuation, interruption, or dose reduction of quizartinib.

PMDA's view:
The limited number of patients experienced serious renal dysfunction for which a causal relationship to quizartinib could not be ruled out in Studies 007 and J201, and it precludes a definite conclusion on the relationship of quizartinib with renal dysfunction based on the currently available data. Given that a causal relationship to quizartinib could not be ruled out for renal dysfunctions such as serious acute renal failure in >1 patient in both Japanese and foreign clinical studies, caution should be used against renal dysfunction during quizartinib treatment. The occurrence of renal dysfunction in the clinical studies should be appropriately communicated to healthcare professionals via the package insert.

7.R.3.8 ILD

The applicant's explanation about the occurrence of ILD associated with quizartinib:
Adverse events related to ILD were tabulated based on PTs classified under MedDRA SMQ of "Interstitial lung disease (narrow)." Table 37 shows the incidences of ILD in Studies 007 and J201.

Table 37. Incidences of ILD (Studies 007 and J201)

MedDRA PT*	Number of patients (%)					
	Study 007				Study J201	
	Quizartinib 241		Control 94		37	
	All Grades	Grades ≥3	All Grades	Grades ≥3	All Grades	Grades ≥3
ILD	2 (0.8)	2 (0.8)	2 (2.1)	1 (1.1)	1 (2.7)	0
Pneumonitis	2 (0.8)	2 (0.8)	1 (1.1)	0	1 (2.7)	0
ILD	0	0	1 (1.1)	1 (1.1)	0	0

* MedDRA/J ver. 16.1 for Study 007 and MedDRA/J ver. 20.1 for Study J201.

In Study 007, no ILD resulting in death occurred in either quizartinib group or control group. Serious ILD occurred in 2 patients (0.8%; pneumonitis in 2 patients) in the quizartinib group. A causal relationship to the study drug could not be ruled out for pneumonitis in 1 patient.[40)] There was no ILD leading to the discontinuation, interruption, or dose reduction of study drug.

In Study J201, no ILD resulting in death occurred. A serious ILD occurred in 1 patient[41)] (2.7%; pneumonitis in 1 patient), and a causal relationship to quizartinib could not be ruled out for the event. There was no ILD leading to the discontinuation, interruption, or dose reduction of quizartinib.

In the clinical studies other than Studies 007 and J201 (including the studies that did not follow dosage regimen in Studies 007 and J201), serious ILD occurred in 3 patients (2 patients in Study 002 [pneumonitis and bronchiolitis in 1 each] and 1 patient in Study 2004 [pneumonitis in 1 patient]). A causal relationship to quizartinib could not be ruled out for pneumonitis in 1 patient[42)] in Study 002.

PMDA's view:
The limited number of patients experienced ILD for which a causal relationship to quizartinib could not be ruled out in Japanese and foreign clinical studies, and it precludes a definite conclusion on the relationship of quizartinib with ILD based on the currently available data. Given that a causal relationship to quizartinib could not be ruled out for serious ILD in >1 patient in both Japanese and foreign clinical studies, caution should be used against ILD during treatment with quizartinib. The occurrence of ILD in the clinical studies should be appropriately communicated to healthcare professionals via the package insert.

40) A 2[redacted]-year old Caucasian man, who was a post-HSCT patient. He experienced extramedullary relapse at Day 375 of quizartinib treatment and received Ara-C and methotrexate intrathecally as well as radiation therapy to treat extramedullary leukemia in the spine. At Day 404, the diagnostic imaging confirmed Grade 3 pneumonitis. Treatment with a steroid, antibacterial agent, antifungal agent, and G-CSF preparation improved respiratory condition at Day 410. No discontinuation, interruption, or dose reduction of quizartinib was implemented.

41) A 5[redacted]-year old Japanese woman with Grade 2 pneumonitis confirmed by diagnostic imaging at Day 32 of quizartinib treatment. She received an antibacterial agent, antifungal agent, and immunoglobulin. On Day 41, the dose of prednisolone, started before the first dose of the study drug, was increased to 30 mg/day. On Day 98, the imaging examination showed improving pneumonitis at Day 98.

42) A 7[redacted]-year old Caucasian woman. The patient experienced febrile neutropenia and pneumonia at Day 8 of quizartinib treatment and was treated with an antibacterial agent and antifungal agent, but disease progression was observed at Day 31. She died of disease progression at Day 51. The events of febrile neutropenia and pneumonia were ongoing at the time of death.

7.R.4 Clinical positioning and indication

The proposed indication of quizartinib is "Relapsed or refractory FLT3-ITD mutation-positive acute myeloid leukemia." The "Precautions Concerning Indication" section presents the following advice:

- FLT3-ITD mutation-positive should be confirmed with an approved *in vitro* diagnostic at a testing center with adequate experience. Quizartinib should be administered only to patients confirmed to be mutation-positive.

Based on the review in Sections "7.R.2 Efficacy" and "7.R.3 Safety" as well as the discussion in following subsection, PMDA concluded that the indication of quizartinib should be "Relapsed or refractory FLT3-ITD mutation-positive acute myeloid leukemia" as proposed, with the following cautionary advice presented in the "Precautions Concerning Indication" section:

- Quizartinib should be administered only to patients who are FLT3-ITD mutation-positive confirmed by a pathologist or at a testing center with adequate experience. The test should be performed with an approved *in vitro* diagnostic.

7.R.4.1 Clinical positioning of quizartinib

Japanese or foreign clinical practice guidelines[43)] or internationally recognized textbooks[44)] on clinical oncology and hematology do not have descriptions about the use of quizartinib for patients with relapsed or refractory FLT3-ITD mutation-positive AML.

PMDA asked the applicant to explain the clinical positioning of quizartinib.

The applicant's explanation:

In Japan, patients with relapsed or refractory AML are treated with MEC, FLAG-IDA, or low-dose Ara-C regardless of FLT3-ITD mutation (Clinical Practice Guidelines for Tumors of Hematopoietic and Lymphoid Tissues 2018 [edited by the Japanese Society of Hematology]). However, there is no established standard treatment and treatment options are extremely limited. *FLT3* gene mutation is a poor prognostic factor of AML, and *FLT3* gene mutation-positive AML are highly likely to relapse, potentially resulting in extremely poor prognosis (*Leuk Res.* 2004:28;1069-74, etc.).

In Japan, gilteritinib was approved for the indication of "Relapsed or refractory *FLT3* gene mutation-positive acute myeloid leukemia" in September 2018. Because of no clinical study data comparing the efficacy and safety between quizartinib and gilteritinib at present, there was no known decisive factor in the choice between quizartinib and gilteritinib.

In this situation, Study 007 demonstrated the clinical benefit of quizartinib in patients with relapsed or refractory FLT3-ITD mutation-positive AML [see Sections 7.R.2 and 7.R.3], and thus quizartinib can be one of treatment options for this patient population.

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43) NCCN guideline (v.3.2018), Clinical Practice Guidelines for Tumors of Hematopoietic and Lymphoid Tissues 2018 (Japanese Society of Hematology ed.) and European LeukemiaNet (ELN) guidelines (*Blood.* 2017;129:424-47)

44) *Textbook of Hematology*. second ed. Nankodo; 2015 and *Best Pract Res Clin Haematol*. 2013;26:253-9

PMDA's view:
Because Study 007 demonstrated the clinical benefit of quizartinib [see Sections 7.R.2 and 7.R.3], quizartinib can be recognized as one of the treatment standards for patients with relapsed or refractory FLT3-ITD mutation-positive AML.

7.R.4.2 Patients eligible for quizartinib and its indication

The applicant's explanation about patients eligible for quizartinib and its indication:
Quizartinib is intended for the use in patients with relapsed or refractory FLT3-ITD mutation-positive AML, which was the target population of Study 007. The indication of quizartinib was thus proposed as "Relapsed or refractory FLT3-ITD mutation-positive acute myeloid leukemia." Because quizartinib should be administered to patients who are confirmed to have FLT3-ITD mutation, the "Precautions Concerning Indication" section will give the following caution:

- FLT3-ITD mutation-positive should be confirmed with an approved *in vitro* diagnostic at a testing center with adequate experience. Quizartinib should be administered only to patients confirmed to be mutation-positive.

PMDA's view:
PMDA generally accepted the applicant's explanation. The "Precautions Concerning Indication" section, however, should be modified as follows:

- Quizartinib should be administered only to patients who are FLT3-ITD mutation-positive confirmed by a pathologist or at a testing center with adequate experience. The test should be performed with an approved *in vitro* diagnostic.

7.R.5 Dosage and administration

The proposed dosage and administration is as presented below, with the following itemized precautions. In this section, doses of quizartinib in dosage regimens in clinical studies are expressed as amounts of its hydrochloride, while they are expressed as free base in the "Dosage and Administration" and "Precautions Concerning Dosage and Administration" sections of the package insert.

Dosage and Administration
The usual adult dosage is 26.5 mg of quizartinib orally administered once daily for the first 2 weeks and then increased to 53 mg orally administered once daily. The dose may be decreased according to the patient's condition.

Precautions Concerning Dosage and Administration

- Criteria for dose increase after the first 2 weeks of treatment
- Dose adjustment for concomitant use with a strong CYP3A inhibitor
- Dose adjustment criteria following an adverse drug reaction associated with quizartinib
- Time of day for the administration of quizartinib
- Continued treatment with quizartinib
- Administration after a missed dose or vomiting
- Use of quizartinib before hematopoietic stem cell transplant

Based on the review in Sections “7.R.2 Efficacy” and “7.R.3 Safety” and the following discussion in this sections, PMDA concluded that the "Dosage and Administration" and “Precautions Concerning Dosage and Administration” sections of quizartinib should be modified as shown below.

Dosage and Administration

The usual adult dosage is 26.5 mg of quizartinib orally administered once daily for 2 weeks followed by 53 mg orally administered once daily. The dose may be decreased according to the patient’s condition.

Precautions Concerning Dosage and Administration

- The efficacy and safety of concomitant use of quizartinib with the other antineoplastic agents have not been established.
- Electrocardiography should be performed prior to the treatment with quizartinib, and the treatment should not be started when QTcF is >450 milliseconds. The dose of quizartinib should not be increased for patients with prolonged QTcF of >450 milliseconds after the first 2 weeks of treatment.
- It is desirable to avoid the concomitant use of quizartinib with a strong CYP3A inhibitor. However, when such use is inevitable, the dose of quizartinib should be reduced by 1 level in accordance with the dose reduction criteria. Once the completion of dosing of the concomitant strong CYP3A inhibitor, the dose of quizartinib should be increased to the previous level.
- In case of an adverse drug reaction during treatment with quizartinib, the treatment should be interrupted or discontinued, or the dose should be reduced according to the following criteria.

Dose reduction of quizartinib

Dose level	Dose
Usual dose	53 mg
1-level lower dose	26.5 mg
2-level lower dose	17.7 mg

Criteria for dose interruption, dose reduction, or discontinuation of quizartinib

Adverse drug reaction	Severity of adverse drug reaction	Action
QT interval prolongation	>500 milliseconds	• Interrupt quizartinib. After recovery of QTcF to ≤450 milliseconds, quizartinib may be resumed at the 1-level lower dose. Patients previously treated with the 17.7-mg dose may resume at 17.7 mg after recovery. • If QTcF shows no recovery to ≤450 milliseconds even after a 2-week interruption, discontinue quizartinib.
	QT interval prolongation associated with a symptom/sign of life-threatening arrhythmia	Discontinue quizartinib.
Non-hematological adverse drug reaction (excluding QT interval prolongation)	Grade ≥3	• Interrupt quizartinib. After improvement to Grade ≤1, quizartinib may be resumed at the 1-level lower dose. • If a Grade ≥2 adverse drug reaction persists for >2 weeks, discontinue quizartinib.
Myelosuppression	Platelet count <100,000/mm^3 and neutrophil count <1,000/mm^3	• Continue quizartinib at the 1-level lower dose or interrupt quizartinib. After recovery, quizartinib may be resumed at the dose before the adverse drug reaction. • If an adverse drug reaction persists for >2 weeks, discontinue quizartinib.

Graded based on National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE).

7.R.5.1 Dosage and administration of quizartinib and cutoff value on QTcF to increase the dose

The applicant’s explanation about the dosage regimen of quizartinib:

Based on a foreign phase I study in patients with relapsed or refractory AML (Study CP0001), the MTD of quizartinib (solution) was determined as 200 mg QD, and this dosage regimen was used in a foreign phase II study (Study 002). In Study 002, of 17 patients who started quizartinib (solution) at 200 mg QD, 6 patients (35.3%) experienced QTcF prolongation to >500 milliseconds. In a foreign phase II study in patients with relapsed or refractory FLT3-ITD mutation-positive AML (Study 2004), quizartinib was thus started at 30 or 60 mg QD, and for patients who did not respond adequately to the starting dose, the dose could be increased from 30 mg QD to 60 mg QD or from 60 mg QD to 90 mg QD, depending on to the starting dose. Study 2004 showed higher efficacy in the 60 mg group than in the 30 mg group, but no clear differences were observed in safety between these groups. Accordingly, the recommended dose of quizartinib was determined to be 60 mg.

In Study 007, in light of the above results and from the viewpoint of risk reduction of QT interval prolongation at the beginning of treatment, quizartinib was started at 30 mg QD, and the dose was increased to 60 mg QD for patients with QTcF remaining ≤450 milliseconds after the first 2 weeks of treatment. Quizartinib treatment was not started if the screening electrocardiography showed QTcF of >450 milliseconds.

Study 007 conducted in accordance with the above design demonstrated clinical benefit of quizartinib [see Sections 7.R.2 and 7.R.3], and the proposed dosage and administration of quizartinib were specified based on the dosage regimen in the study. The reference QTcF value used for the selection of the second dose of quizartinib after the first 2 weeks of treatment was changed from the value specified in Study 007 (450 milliseconds) to 470 milliseconds in light of the following observations:

- A relationship between QT interval prolongation caused by quizartinib and safety was investigated based on results from Study 007. The investigation revealed that the change in the reference QTcF value from 450 to 470 milliseconds was assumed to increase the number of patients eligible for dose increase to 60 mg QD after the first 2 weeks of treatment by 23.6%, while the number of patients who discontinue quizartinib due to QTcF of >500 milliseconds following the dose increase to 60 mg would be increased only by 0.36%. In Study 007, 7 patients received the 60 mg QD although QTcF after the first 2 weeks of treatment was >450 milliseconds and ≤470 milliseconds,[45)] and of these, 3 patients achieved CRi, but 2 patients experienced QTcF prolongation (Grades 2 and 3 in 1 each).

- An investigation on the relationship of plasma concentrations of quizartinib with QTc based on results from Study 007 revealed that the upper limit of 90% CI of ΔQTcF at steady state following quizartinib 60 mg QD was estimated to be 23.6 milliseconds [see Section 6.2.6]. Therefore, a risk of QTcF >500 milliseconds is unlikely to be increased by the reference QTcF value of 470 milliseconds as compared with that of 450 milliseconds.

PMDA's view:
The applicant's explanation is generally acceptable. For the following reasons, however, the reference QTcF value in the "Precautions Concerning Dosage and Administration" section should be 450 milliseconds as per Study 007:

45) In Study 007, the dose was allowed to be increased based on the QTcF value measured at a study center. In these 7 patients, however, the QTcF values re-measured at the central assessment were >450 milliseconds and ≤470 milliseconds.

- The clinical use of quizartinib based on the reference QTcF value of 470 milliseconds is extremely limited.

- In Study 007, of 7 patients with the QTcF value of >450 milliseconds and ≤470 milliseconds who received an increased dose of quizartinib, 1 patient experienced Grade ≥3 QT interval prolongation.

- Study 007 conducted with the reference QTcF value of 450 milliseconds demonstrated clinical benefit of quizartinib.

Based on the above, the "Dosage and Administration" and “Precautions Concerning Dosage and Administration” sections should be modified as below. Precautions about time period for oral administration, continuation of treatment, and missed dose and vomiting are common advice in the use of drugs, and the criteria for the discontinuation or resumption of quizartinib associated with HSCT are also commonly provided as general precautions for HSCT. These precautions, therefore, do not have to be presented in the section.

Dosage and Administration
The usual adult dosage is 26.5 mg of quizartinib orally administered once daily for 2 weeks followed by 53 mg orally administered once daily. The dose may be decreased according to the patient’s condition.

Precautions Concerning Dosage and Administration
- Electrocardiography should be performed prior to the treatment with quizartinib, and the treatment should not be started when QTcF is >450 milliseconds. The dose of quizartinib should not be increased for patients with prolonged QTcF of >450 milliseconds after the first 2 weeks of treatment.

7.R.5.2 Dosage regimens for concomitant use with a strong CYP3A inhibitor

Because the concomitant use of quizartinib with ketoconazole (strong CYP3A inhibitor) increased plasma concentration of quizartinib, the dose of quizartinib should be reduced to about half when a strong CYP3A inhibitor is used in combination [see Section 6.2.3.1]. In Studies 007 and J201, the dosage regimen for concomitant use of quizartinib with a strong CYP3A inhibitor was specified as follows:
- When treatment with quizartinib begins with a concomitant strong CYP3A inhibitor, quizartinib should be started at 20 mg QD, and the dose may be increased to 30 mg QD for patients with QTcF of ≤450 milliseconds after the first 2 weeks of treatment.

- When a strong CYP3A inhibitor is used concomitantly during the treatment with quizartinib, the dose of quizartinib should be reduced from 60 mg to 30 mg or from 30 mg to 20 mg.

Based on the result of Study 007 that demonstrated the clinical benefit of quizartinib administered according to the above regimen [see Sections 7.R.2 and 7.R.3] and the review in Section “7.R.5.1 Dosage and administration of quizartinib and cutoff value on QTcF to increase the dose,” the following cautionary advice is presented in the “Precautions Concerning Dosage and Administration” section:
- When the concomitant use of quizartinib with a strong CYP3A inhibitor is inevitable, the dose of quizartinib should be reduced in accordance with the dose adjustment table below. Once the

completion of dosing of the strong CYP3A inhibitor, the dose of quizartinib should be increased to the previous level.

Dose adjustment table for concomitant use with a strong CYP3A inhibitor

A concomitant strong CYP3A inhibitor is used at the beginning of treatment with quizartinib	• Start quizartinib at 17.7 mg QD. • QTcF after the first 2 weeks of treatment, ≤470 milliseconds: Increase quizartinib to 26.5 mg. • QTcF after the first 2 weeks of treatment, >470 and ≤500 milliseconds: Do not increase quizartinib.
A concomitant strong CYP3A inhibitor is used during treatment with quizartinib	Reduce quizartinib from 53 mg to 26.5 mg or from 26.5 mg to 17.7 mg according to the dose before the start of the strong CYP3A inhibitor.

PMDA asked the applicant to explain the effect of a concomitant strong CYP3A inhibitor on the efficacy and safety of quizartinib.

The applicant's explanation:
In Study 007, the median OS [95% CI] in patients (n = 46[46)]) for whom the dose of quizartinib was reduced due to a concomitant a strong CYP3A inhibitor was 6.6 [4.2, 9.4] months, while the median OS [95% CI] in patients (n = 199) who did not receive a CYP3A inhibitor in the quizartinib group was 6.2 [5.3, 7.3] months. The safety profiles of patients who received a concomitant strong CYP3A inhibitor (concomitant strong CYP3A inhibitor group) and in patients who did not (non-concomitant group) are as follows: (a) All Grade adverse events occurred in 97.8% (45 of 46) of patients and 99.0% (193 of 195) of patients, respectively; (b) Grade ≥3 adverse events in 84.8% (39 of 46) of patients and 88.2% (172 of 195) of patients, respectively; (c) adverse events resulting in death in 13.0% (6 of 46) of patients and 15.4% (30 of 195) of patients, respectively; and (d) serious adverse events in 82.6% (38 of 46) of patients and 66.7% (130 of 195) of patients, respectively. QTcF of >500 milliseconds was observed in 0% and 4.1% (8 of 195) of patients, respectively.

$AUC_{0\text{-}24h}$ and C_{max} of quizartinib in the concomitant strong CYP3A inhibitor group and the non-concomitant group were calculated based on results from Study 007 using a PPK model.[47)] No clear differences were observed in calculated parameter values between the groups.

As described above, no clear differences were observed in efficacy or safety between patients who receive quizartinib with a strong CYP3A inhibitor and those who did not.

PMDA's view:
The applicant's explanation is generally acceptable. However, the description of the advice in the "Precautions Concerning Dosage and Administration" section should be modified as below.

46) Including patients who started quizartinib with a concomitant strong CYP3A inhibitor and patients in whom the dose of quizartinib was reduced owing to start of the concomitant use during the treatment.
47) PK profile comparison was performed between patients receiving quizartinib 60 mg alone and those receiving quizartinib 30 mg with a concomitant strong CYP3A inhibitor and between patients receiving quizartinib 30 mg alone and those receiving quizartinib 20 mg with a concomitant strong CYP3A inhibitor.

Precautions Concerning Dosage and Administration

- It is desirable to avoid the concomitant use of quizartinib with a strong CYP3A inhibitor. However, when such use is inevitable, the dose of quizartinib should be reduced by 1 level in accordance with the dose reduction criteria. Once the completion of dosing of the concomitant strong CYP3A inhibitor, the dose of quizartinib should be increased to the previous level.

7.R.5.3 Dose adjustment of quizartinib

The applicant's explanation about dose adjustment of quizartinib following an adverse drug reaction:
Studies 007 and J201 were conducted according to the criteria for interruption, dose reduction, and discontinuation and demonstrated the clinical benefit of quizartinib, thus, the "Precautions Concerning Dosage and Administration" section specified the criteria for interruption, dose reduction, and discontinuation as per Studies 007 and J201. The reference QTcF value, used as a criterion for treatment resumption after QT interval prolongation, was changed from the value used in both studies (450 milliseconds) to 470 milliseconds based on the review on the reference QTcF value for dose selection of quizartinib [see Section 7.R.5.1].

PMDA's view:
The applicant's explanation is generally acceptable. For the criterion for treatment resumption following QT interval prolongation, however, the appropriated reference QTcF value should be 450 milliseconds as per Studies 007 and J201, based on results of the review on the reference QTcF value for dose selection of quizartinib [see Section 7.R.5.1].

7.R.5.4 Concomitant use with the other antineoplastic agents

PMDA asked the applicant to explain the concomitant use of quizartinib with the other antineoplastic agents.

The applicant's response:
The concomitant use of quizartinib with the other antineoplastic agents is not recommended at present, given no clinical study data demonstrating its clinical benefit.

PMDA's view:
The applicant's explanation is acceptable. The "Precautions Concerning Dosage and Administration" section, however, should provide a cautionary note that the efficacy and safety in the use of quizartinib with other antineoplastic agents have not been established.

7.R.6 Development for pediatric use

PMDA asked the applicant to explain the development of quizartinib for pediatric patients with FLT3-ITD mutation-positive AML.

The applicant's explanation:
Outside Japan, a phase I study on quizartinib used with other antineoplastic agents was conducted in pediatric patients aged ≥1 month to <21 years with relapsed or refractory AML or acute lymphoblastic

leukemia (ALL) (completed in the US), and the following 3 clinical studies are being conducted or planned:

- A phase I/II study on quizartinib used with other antineoplastic agents in pediatric patients aged ≥1 month to <18 years with relapsed or refractory FLT3-ITD mutation-positive AML (ongoing in Europe)

- A phase II study on quizartinib used with other antineoplastic agents in pediatric patients aged ≥1 month to <18 years with treatment-naive FLT3-ITD mutation-positive AML (to be conducted in Europe)

- An exposure-response model analysis study using data from adult and pediatric patients with treatment-naive FLT3-ITD mutation-positive AML (planned in Europe)

For the development of quizartinib for pediatric use in Japan, [redacted], is being planned.

PMDA's view:
The applicant should take appropriate actions for the development of dosage regimens for pediatric Japanese patients, in response to a request for the development.

7.R.7 Post-marketing investigations

The applicant's explanation about the post-marketing surveillance plan:
Post-marketing surveillance is planned to investigate the safety of quizartinib in all patients treated with quizartinib in the post-marketing setting.

The safety specification of the planned surveillance includes QT interval prolongation, an event requiring special attention during the treatment with quizartinib.

The planned sample size for the surveillance is 150 patients in light of the occurrence of QT interval prolongation in Study 007.

The planned observation period is 1 year because QT interval prolonged with a QTcF of >500 milliseconds was observed at Day 331 of quizartinib treatment in Study 007.

PMDA's view:
Because of limited safety information of quizartinib in Japanese patients, the applicant should conduct post-marketing surveillance in all patients treated with quizartinib for a certain period, and safety data should be collected promptly in a biased manner to provide available safety information to healthcare professionals immediately.

Based on the review in Section "7.R.3 Safety," the safety specification of the surveillance should include cardiac disorders such as myocardial infarction, renal dysfunctions such as renal failure acute, and ILD,

which are the adverse events requiring special attention during the treatment with quizartinib except for those observed constantly (infection, haemorrhage, and myelosuppression).

The planned sample size and observation period of the surveillance should be reviewed in light of the occurrence of the above events selected as the safety specification of the surveillance.

7.3 Adverse events observed in clinical studies

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

7.3.1 Foreign phase I study (Study 014)

Adverse events occurred in 12 of 26 subjects (46.2%) receiving quizartinib solution 60 mg, 9 of 26 subjects (34.6%) receiving quizartinib tablet 60 mg, 5 of 14 subjects (35.7%) receiving quizartinib tablet 30 mg, and 6 of 14 subjects (42.9%) receiving quizartinib tablet 90 mg. Adverse events for which a causal relationship to quizartinib could not be ruled out occurred in 4 of 26 subjects (15.4%) in the solution 60 mg group, 2 of 26 subjects (7.7%) in the tablet 60 mg group, 2 of 14 subjects (14.3%) in the tablet 30 mg group, and 4 of 14 subjects (28.6%) in the tablet 90 mg group. Adverse events with an incidence of ≥10% were headache in 3 subjects (11.5%) in the solution 60 mg group, and headache, abdominal discomfort, and folliculitis in 2 subjects (14.3%) each in the tablet 90 mg group (0 in the tablet 60 mg and tablet 30 mg groups).

A serious adverse event occurred in 1 of 14 subjects (7.1%) in the tablet 90 mg group (0 in the solution 60 mg, tablet 60 mg, and tablet 30 mg groups). The observed serious adverse event was abscess limb in 1 subject, and a causal relationship to quizartinib was ruled out for this event.

An adverse event leading to the discontinuation of quizartinib occurred in 1 of 14 subjects (7.1%) tablet 90 mg group (0 in the solution 60 mg, tablet 60 mg, and tablet 30 mg groups). The observed adverse event leading to the discontinuation of quizartinib was abscess limb in 1 subject, and a causal relationship to quizartinib was ruled out for this event.

7.3.2 Foreign phase I study (Study 019)

Adverse events occurred in 9 of 34 subjects (26.5%) in the fasted group and 5 of 30 subjects (16.7%) in the fed group. Adverse events for which a causal relationship to quizartinib could not be ruled out occurred in 4 of 34 subjects (11.8%) in the fasted group and 2 of 30 subjects (6.7%) in the fed group.

No adverse events with an incidence of ≥10%, serious adverse events, or adverse events leading to the discontinuation of quizartinib occurred in either group.

7.3.3 Japanese phase I study (Study J101)

Adverse events occurred in 15 of 16 patients (93.8%), and adverse events for which a causal relationship to quizartinib could not be ruled out occurred in 14 of 16 patients (87.5%). Adverse events with an incidence of ≥20% were electrocardiogram QT prolonged in 7 patients (43.8%); nausea and pyrexia in 6 patients (37.5%) each; febrile neutropenia, stomatitis, and vomiting in 5 patients (31.3%) each; oedema

in 4 patients (25.0%); anaemia, decreased appetite, hypophosphataemia, headache, and diarrhoea in 3 patients (18.8%) each.

Serious adverse events occurred in 6 of 16 patients (37.5%). A serious adverse event reported by ≥ 2 patients was disease progression in 2 patients, and a causal relationship to quizartinib was ruled out for both cases.

Adverse events leading to the discontinuation of quizartinib occurred in 3 of 16 patients (12.5%). These events were bronchopulmonary aspergillosis, haemorrhage intracranial, and respiratory failure in 1 patient (6.3%) each. A causal relationship to quizartinib could not be ruled out for bronchopulmonary aspergillosis.

7.3.4 Foreign phase I study (Study CP0001)

Adverse events occurred in 73 of 76 patients (96.1%), and a causal relationship to quizartinib could not be ruled out for the events occurred in 39 of 76 patients (51.3%). Adverse events with an incidence of ≥20% were nausea in 32 patients (42.1%), pyrexia in 27 patients (35.5%), fatigue in 26 patients (34.2%), disease progression and diarrhoea in 24 patients (31.6%) each, anaemia in 23 patients (30.3%), oedema peripheral and vomiting in 22 patients (28.9%) each, febrile neutropenia in 18 patients (23.7%), petechiae in 17 patients (22.4%), and hypokalaemia in 16 patients (21.1%).

Serious adverse events occurred in 47 of 76 patients (61.8%). Serious adverse events reported by ≥3 patients were disease progression in 24 patients (31.6%), febrile neutropenia in 7 patients (9.2%), and pneumonia and electrocardiogram QT prolonged in 3 patients (3.9%) each. A causal relationship to quizartinib could not be ruled out for electrocardiogram QT prolonged in 3 patients.

Adverse events leading to the discontinuation of quizartinib occurred in 21 of 76 patients (27.6%). Adverse events leading to discontinuation reported by ≥3 patients were disease progression in 10 patients (13.2%) and electrocardiogram QT prolonged in 3 patients (3.9%). A causal relationship to quizartinib could not be ruled out for electrocardiogram QT prolonged in 3 patients.

7.3.5 Foreign phase I study (Study 016)

Adverse events occurred in 4 of 8 subjects (50.0%) in the mild hepatic impairment group, 2 of 8 subjects (25.0%) in the moderate hepatic impairment group, 0 of 8 subjects (0%) in the mild MHC group, and 1 of 8 subjects (12.5%) in the moderate MHC group. Adverse events for which a causal relationship to quizartinib could not be ruled out occurred in 4 of 8 subjects (50%) in the mild hepatic impairment group and 1 of 8 subjects (12.5%) in the moderate hepatic impairment group (0 in the moderate MHC group). Adverse events with an incidence of ≥10% were constipation, diarrhoea, gastrooesophageal reflux disease, dysgeusia, and headache in 1 subject (12.5%) each in the mild hepatic impairment group; cough and thrombophlebitis in 1 subject (12.5%) each in the moderate hepatic impairment group; and chest pain 1 subject (12.5%) in the moderate MHC group.

No serious adverse events or adverse events leading to the discontinuation of quizartinib occurred in any group.

7.3.6 Foreign phase I study (Study 015)

Adverse events occurred in 5 of 31 subjects (16.1%) in the quizartinib + ketoconazole group, 11 of 31 subjects (35.5%) in the quizartinib + fluconazole group, and 10 of 31 subjects (32.3%) in the quizartinib + placebo group. A causal relationship to the study drug could not be ruled out for events in 1 of 31 subjects (3.2%) in the quizartinib + ketoconazole group, 1 of 31 subjects (3.2%) in the quizartinib + fluconazole group, and 3 of 31 subjects (9.7%) in the quizartinib + placebo group. Adverse events with an incidence of ≥10% were diarrhoea in 4 subjects (12.9%) in the quizartinib + fluconazole group (0 in the quizartinib + ketoconazole and quizartinib + placebo groups).

Adverse events leading to the discontinuation of the study drug occurred in 2 of 31 subjects (6.5%) in the quizartinib + fluconazole group (0 in the quizartinib + ketoconazole and quizartinib + placebo groups). Observed adverse events leading to the discontinuation of study drug were vaginitis bacterial and animal bite in 1 subject each, and a causal relationship to the study drug was ruled out for either event.

No serious adverse events occurred in any group.

7.3.7 Foreign phase I study (Study 018)

Adverse events occurred in 9 of 30 subjects (30.0%) receiving quizartinib alone and 11 of 33 subjects (33.3%) receiving quizartinib + lansoprazole. Adverse events for which a causal relationship to the study drug could not be ruled out occurred in 2 of 30 subjects (6.7%) in the quizartinib alone group and 1 of 33 subjects (3.0%) in the quizartinib + lansoprazole group. Adverse events with an incidence of ≥10% were headache in 3 subjects (10.0%) in the quizartinib alone group (0 in the quizartinib + lansoprazole group).

No serious adverse events or adverse events leading to the discontinuation of the study drug occurred in either group.

7.3.8 Foreign phase I study (Study 0011)

Adverse events occurred in 7 of 7 patients (100%) in the 40 mg group and 6 of 6 patients (100%) in the 60 mg group, and adverse events for which a causal relationship to quizartinib could not be ruled out occurred in 5 of 7 patients (71.4%) in the 40 mg group and 6 of 6 patients (100%) in the 60 mg group. Adverse events with an incidence of ≥50% were diarrhoea in 6 patients (85.7%), vomiting in 5 patients (71.4%), and neutropenia in 4 patients (57.1%) in the 40 mg group; fatigue in 5 patients (83.3%), nausea in 4 patients (66.7%), diarrhoea, vomiting, GVHD in skin, contusion, and headache in 3 patients (50.0%) each in the 60 mg group.

Serious adverse events occurred in 4 of 7 patients (57.1%) in the 40 mg group and 5 of 6 patients (83.3%) in the 60 mg group. A serious adverse event reported by ≥2 patients was pneumonia in 2 patients (33.3%) in the 60 mg group. A causal relationship to quizartinib could not be ruled out for pneumonia in 1 patient (0 in the 40 mg group).

Adverse events leading to the discontinuation of quizartinib occurred in 1 of 7 patients (14.3%) in the 40 mg group and 3 of 6 patients (50.0%) in the 60 mg group. Adverse events leading to the discontinuation of quizartinib were neutropenia in 1 patient in the 40 mg group; corneal epithelium defect, Epstein-Barr virus associated lymphoproliferative disorder, and GVHD/pneumonia/peritoneal haemorrhage in 1 patient each in the 60 mg group. A causal relationship to quizartinib could not be ruled out for neutropenia in the 40 mg group and corneal epithelium defect in the 60 mg group.

7.3.9 Foreign phase III study (Study 007)

Adverse events occurred in 238 of 241 patients (98.8%) in the quizartinib group and 93 of 94 patients (98.9%) in the control group. A causal relationship to the study drug could not be ruled out for events in 205 of 241 patients (85.1%) in the quizartinib group and 66 of 94 patients (70.2%) in the control group. Table 29 shows adverse events with an incidence of ≥20% in either group.

Serious adverse events occurred in 168 of 241 patients (69.7%) in the quizartinib group and 37 of 94 patients (39.4%) in the control group. Serious adverse events reported by ≥2 patients were febrile neutropenia in 50 patients (20.7%), pneumonia in 22 patients (9.1%); sepsis in 16 patients (6.6%); pyrexia in 8 patients (3.3%); neutropenic sepsis in 7 patients (2.9%); cellulitis, urinary tract infection, anaemia, and renal failure acute in 6 patients (2.5%) each; septic shock, upper respiratory tract infection, nausea, vomiting, haemorrhage intracranial, syncope, and electrocardiogram QT prolonged in 5 patients (2.1%) each; neutropenia, GVHD in intestine, bacteraemia, and Staphylococcal infection in 4 patients (1.7%) each; pancytopenia, thrombocytopenia, GVHD in skin, device related infection, Enterobacter infection, gastroenteritis, lung infection, and pneumonia fungal in 3 patients (1.2%) each; leukocytosis, atrial fibrillation, pericarditis, diarrhoea, Clostridium difficile infection, Escherichia sepsis, infection, Klebsiella sepsis, neutropenic infection, skin infection, Staphylococcal bacteraemia, neutrophil count decreased, cerebral haemorrhage, hematuria, dyspnoea, pneumonitis, respiratory failure, acute febrile neutrophilic dermatosis, and rash generalized in 2 patients (0.8%) each in the quizartinib group; febrile neutropenia in 9 patients (9.6%); sepsis in 4 patients (4.3%); pneumonia and Escherichia sepsis in 3 patients (3.2%) each; and pyrexia, neutropenic sepsis, pneumonia fungal, and haemorrhage intracranial in 2 patients (2.1%) each in the control group. A causal relationship to the study drug could not be ruled out for febrile neutropenia in 18 patients; sepsis in 6 patients; nausea and electrocardiogram QT prolonged in 5 patients each; vomiting and neutropenic sepsis in 4 patients each; anaemia and thrombocytopenia in 3 patients each; pancytopenia, diarrhoea, pneumonia fungal, acute febrile neutrophilic dermatosis, rash generalised, cellulitis, syncope, and renal failure acute in 2 patients each; neutropenia, pericarditis, GVHD in intestine, device related infection, infection, Klebsiella sepsis, neutrophil count decreased, cerebral haemorrhage, pneumonitis, respiratory failure, pyrexia, upper respiratory tract infection, and urinary tract infection in 1 patient each in the quizartinib group; febrile neutropenia in 5 patients; pyrexia and Escherichia sepsis in 2 patients each; sepsis and pneumonia in 1 patient each in the control group.

Adverse events leading to the discontinuation of the study drug occurred in 44 of 241 patients (18.3%) in the quizartinib group and 1 of 94 patients (1.1%) in the control group. Adverse events leading to the discontinuation of the study drug reported by ≥2 patients were pneumonia in 6 patients (2.5%); GVHD in intestine and haemorrhage intracranial in 3 patients (1.2%) each; blood bilirubin increased,

electrocardiogram QT prolonged, febrile neutropenia, leukocytosis, pyrexia, renal failure acute, and sepsis in 2 patients (0.8%) each in the quizartinib group. A causal relationship to the study drug could not be ruled out for electrocardiogram QT prolonged in 2 patients, and GVHD in intestine, blood bilirubin increased, febrile neutropenia, pyrexia, and sepsis in 1 patient each.

7.3.10 Japanese phase II study (Study J201)

Adverse events occurred in 37 of 37 patients (100%), and adverse events for which a causal relationship to quizartinib could not be ruled out occurred in 35 of 37 patients (94.6%). Table 38 shows adverse events with an incidence of ≥10%.

Table 38. Adverse events with an incidence of ≥10%

SOC PT (MedDRA/J ver. 20.1)	Number of patients (%) 37	
	All Grades	Grades ≥3
All adverse events	37 (100)	34 (91.9)
Blood and lymphatic system disorders		
Febrile neutropenia	16 (43.2)	14 (37.8)
Anaemia	10 (27.0)	9 (24.3)
Thrombocytopenia	4 (10.8)	4 (10.8)
Metabolism and nutrition disorders		
Decreased appetite	5 (13.5)	1 (2.7)
Hypokalaemia	4 (10.8)	3 (8.1)
Nervous system disorders		
Headache	4 (10.8)	0
Gastrointestinal disorders		
Nausea	11 (29.7)	0
Vomiting	6 (16.2)	1 (2.7)
Diarrhoea	4 (10.8)	0
Skin and subcutaneous tissue disorders		
Rash	4 (10.8)	1 (2.7)
Musculoskeletal and connective tissue disorders		
Back pain	4 (10.8)	0
General disorders and administration site conditions		
Pyrexia	5 (13.5)	0
Investigations		
Platelet count decreased	14 (37.8)	11 (29.7)
Electrocardiogram QT prolonged	13 (35.1)	12 (32.4)
Neutrophil count decreased	8 (21.6)	8 (21.6)
White blood cell count decreased	8 (21.6)	8 (21.6)
ALT increased	4 (10.8)	2 (5.4)

Serious adverse events occurred in 17 of 37 patients (45.9%). Serious adverse events reported by ≥2 patients were febrile neutropenia in 6 patients (16.2%), and bacteraemia and sepsis in 2 patients (5.4%) each. A causal relationship to quizartinib could not be ruled out for febrile neutropenia in 4 patients, bacteraemia in 2 patients, and sepsis in 1 patient.

Adverse events leading to the discontinuation of quizartinib occurred in 2 of 37 patients (5.4%). These events were disease progression and lipase increased in 1 patient (2.7%) each. A causal relationship to quizartinib could not be ruled out for lipase increased in 1 patient.

7.3.11 Foreign phase II study (Study 2004)

Adverse events occurred in 37 of 38 patients (97.4%) in the 30 mg group and 36 of 36 patients (100%) in the 60 mg group, and adverse events for which a causal relationship to quizartinib could not be ruled out occurred in 30 of 38 patients (78.9%) in the 30 mg group and 29 of 36 patients (80.6%) in the 60 mg

group. Adverse events with an incidence of ≥20% were anaemia in 18 patients (47.4%); fatigue in 13 patients (34.2%); febrile neutropenia in 12 patients (31.6%); vomiting and pyrexia in 11 patients (28.9%) each; thrombocytopenia, nausea, and diarrhoea in 10 patients (26.3%) each; hypokalaemia and cough in 9 patients (23.7%) each; and oedema peripheral and dyspnoea in 8 patients (21.1%) each in the 30 mg group; nausea in 17 patients (47.2%); pyrexia in 14 patients (38.9%); febrile neutropenia, vomiting, and diarrhoea in 13 patients (36.1%) each; abdominal pain in 11 patients (30.6%); anaemia, headache, and cough in 9 patients (25.0%) each; fatigue and pneumonia in 8 patients (22.2%) each in the 60 mg group.

Serious adverse events occurred in 25 of 38 patients (65.8%) in the 30 mg group and 23 of 36 patients (63.9%) in the 60 mg group. Serious adverse events reported by ≥4 patients were febrile neutropenia in 7 patients (18.4%) and AML in 5 patients (13.2%) in the 30 mg group; AML in 7 patients (19.4%), febrile neutropenia and pneumonia in 6 patients (16.7%) each, and pyrexia in 5 patients (13.9%) in the 60 mg group. A causal relationship to quizartinib could not be ruled out for febrile neutropenia in 3 patients in the 30 mg group and febrile neutropenia in 2 patients in the 60 mg group.

Adverse events leading to the discontinuation of quizartinib occurred in 9 of 38 patients (23.7%) in the 30 mg group and 8 of 36 patients (22.2%) in the 60 mg group. Adverse events leading to the discontinuation reported by ≥2 patients were leukocytosis in 2 patients (5.3%) in the 30 mg group and renal failure acute in 2 patients (5.6%) in the 60 mg group, and a causal relationship to quizartinib was ruled out for these events.

7.3.12 Foreign phase II study (Study 002)

Adverse events occurred in 157 of 157 patients (100%) in Cohort 1 and 176 of 176 patients (100%) in Cohort 2. Adverse events for which a causal relationship to quizartinib could not be ruled out occurred in 146 of 157 patients (93.0%) in Cohort 1 and 159 of 176 patients (90.3%) in Cohort 2. Adverse events with an incidence of ≥30% were nausea in 86 patients (54.8%), febrile neutropenia and diarrhoea in 66 patients (42.0%) each, fatigue in 63 patients (40.1%), vomiting in 58 patients (36.9%), and pyrexia in 49 patients (31.2%) in Cohort 1; nausea in 92 patients (52.3%), febrile neutropenia and vomiting in 73 patients (41.5%) each, diarrhoea in 70 patients (39.8%), electrocardiogram QT prolonged in 57 patients (32.4%), and pyrexia in 54 patients (30.7%) in Cohort 2.

Serious adverse events occurred in 134 of 157 patients (85.4%) in Cohort 1 and 136 of 176 patients (77.3%) in Cohort 2. Serious adverse events reported by ≥5 patients were febrile neutropenia in 60 patients (38.2%), AML in 37 patients (23.6%), pneumonia in 24 patients (15.3%), electrocardiogram QT prolonged in 17 patients (10.8%), sepsis in 12 patients (7.6%), pyrexia in 10 patients (6.4%), atrial fibrillation in 8 patients (5.1%), anaemia in 7 patients (4.5%), urinary tract infection and bacteraemia in 6 patients (3.8%) each, and cellulitis and dehydration in 5 patients (3.2%) each in Cohort 1; febrile neutropenia in 66 patients (37.5%), AML in 36 patients (20.5%), pneumonia and electrocardiogram QT prolonged in 16 patients (9.1%) each, sepsis in 13 patients (7.4%), pyrexia in 8 patients (4.5%), pneumonia fungal and gastrointestinal haemorrhage in 7 patients (4.0%) each, urinary tract infection, lung infection, anaemia, and thrombocytopenia in 6 patients (3.4%) each, and nausea in 5 patients (2.8%) in Cohort 2. A causal relationship to quizartinib could not be ruled out for febrile neutropenia in 34 patients, electrocardiogram QT prolonged in 17 patients, pneumonia in 7 patients, atrial fibrillation in 6

patients, sepsis, anaemia, and pyrexia in 5 patients each, and urinary tract infection, cellulitis, and dehydration in 1 patient each in Cohort 1; febrile neutropenia in 42 patients, electrocardiogram QT prolonged in 15 patients, pneumonia in 7 patients, anaemia in 6 patients, thrombocytopenia and nausea in 5 patients each, gastrointestinal haemorrhage in 4 patients, sepsis and urinary tract infection in 3 patients each, and pneumonia fungal and lung infection in 2 patients each in Cohort 2.

Adverse events leading to the discontinuation of quizartinib occurred in 59 of 157 patients (37.6%) in Cohort 1 and 46 of 176 patients (26.1%) in Cohort 2. Adverse events leading to the discontinuation reported by ≥3 patients were AML in 22 patients (14.0%), febrile neutropenia, pneumonia, and gastrointestinal haemorrhage in 4 patients (2.5%) each, and electrocardiogram QT prolonged in 3 patients (1.9%) in Cohort 1; AML in 20 patients (11.4%), febrile neutropenia in 5 patients (2.8%), and electrocardiogram QT prolonged in 3 patients (1.7%) in Cohort 2. A causal relationship to quizartinib could not be ruled out for febrile neutropenia in 4 patients, electrocardiogram QT prolonged in 3 patients, and pneumonia and gastrointestinal haemorrhage in 1 patient in Cohort 1; febrile neutropenia in 4 patients and electrocardiogram QT prolonged in 3 patients in Cohort 2.

7.3.13 Japanese phase I study (Study J102)

Adverse events occurred in 4 of 4 patients (100%) in the 20 mg group and 3 of 3 patients (100%) in the 40 mg group. Adverse events for which a causal relationship to quizartinib could not be ruled out occurred in 4 of 4 patients (100%) in the 20 mg group and 3 of 3 patients (100%) in the 40 mg group. Adverse events reported by ≥2 patients were febrile neutropenia in 4 patients (100%), decreased appetite, dysgeusia, diarrhoea, nausea, abdominal pain upper, stomatitis, alopecia, and gamma-glutamyltransferase (GGT) increased in 3 patients (75.0%) each, anaemia, hypokalaemia, and alanine aminotransferase (ALT) increased in 2 patients (50.0%) each in the 20 mg group; febrile neutropenia and electrocardiogram QT prolonged in 3 patients (100%) each, diarrhoea, nausea, constipation, alopecia, rash, and arthralgia in 2 patients (66.7%) each in the 40 mg group.

Serious adverse events occurred in 2 of 3 patients (66.7%) in the 40 mg group (0 in the 20 mg group). Observed serious adverse events were pneumonia and Staphylococcal bacteraemia in 1 patient (33.3%) each, and a causal relationship to quizartinib could not be ruled out for either event.

No adverse events leading to the discontinuation of quizartinib occurred in any group.

7.3.14 Foreign phase I study (Study 0005)

Adverse events occurred in 6 of 6 patients (100%) in the 60 mg 7-day group, 7 of 7 patients (100%) in the 60 mg 14-day group, and 6 of 6 patients (100%) in the 40 mg 14-day group. A causal relationship to the study drug could not be ruled out for events in 6 of 6 patients (100%) in the 60 mg 7-day dose group, 4 of 7 patients (57.1%) in the 60 mg 14-day group, and 5 of 6 patients (83.3%) in the 40 mg 14-day group. Adverse events with an incidence of ≥50% were neutropenia and nausea in 5 patients (83.3%) each, thrombocytopenia, vomiting, hypokalaemia, hypophosphataemia, and hypertension in 4 patients (66.7%) each, and febrile neutropenia, anaemia, diarrhoea, constipation, pyrexia, hypomagnesaemia, and hypocalcaemia in 3 patients (50.0%) each in the 60 mg 7-day group; nausea in 6 patients (85.7%), constipation and hypomagnesaemia in 5 patients (71.4%) each, and diarrhoea, hypokalaemia, and drug

eruption in 4 patients (57.1%) each in the 60 mg 14-day group; diarrhoea in 5 patients (83.3%), nausea in 4 patients (66.7%), and febrile neutropenia, constipation, haemorrhoids, rash, and hypotension in 3 patients (50.0%) each in the 40 mg 14-day group.

Serious adverse events occurred in 4 of 6 patients (66.7%) in the 60 mg 7-day group, 4 of 7 patients (57.1%) in the 60 mg 14-day group, and 4 of 6 patients (66.7%) in the 40 mg 14-day group. A serious adverse event reported by ≥2 patients was febrile neutropenia in 2 patients (33.3%) in the 40 mg 14-day group (0 in the 60 mg 7-day and 60 mg 14-day groups), and a causal relationship to the study drug was ruled out for all events.

Adverse events leading to the discontinuation of the study drug occurred in 1 of 7 patients (14.3%) in the 60 mg 14-day group and 1 of 6 patients (16.7%) in the 40 mg 14-day group (0 in the 60 mg 7-day group). These events were palmar-plantar erythrodysaesthesia syndrome in 1 patient (14.3%) in the 60 mg 14-day group and nausea/pericarditis in 1 patient (16.7%) in the 40 mg 14-day group, and a causal relationship to the study drug could not be ruled out for either event.

7.3.15 Foreign phase I study (Study 006)

Adverse events occurred in 2 of 6 subjects (33.3%), and adverse event for which a causal relationship to quizartinib could not be ruled out occurred in 1 of 6 subjects (16.7%). Adverse events with an incidence of ≥10% were diarrhoea and dry skin in 1 subject (16.7%) each.

Neither serious adverse events nor adverse events leading to the discontinuation of quizartinib occurred.

7.3.16 Foreign phase I study (Study 008)

Adverse events occurred in 20 of 58 subjects (34.5%). A causal relationship to quizartinib could not be ruled out for events occurred in 5 of 58 subjects (8.6%).

No adverse events with an incidence of ≥10%, serious adverse events, or adverse events leading to the discontinuation of quizartinib occurred.

7.3.17 Foreign phase I study (Study 012)

Adverse events occurred in 18 of 30 subjects (60.0%) in the quizartinib + ketoconazole group, 10 of 27 subjects (37.0%) in the quizartinib + rifampicin group, and 7 of 26 subjects (26.9%) in the quizartinib + placebo group. Adverse events for which a causal relationship to the study drug could not be ruled out occurred in 13 of 30 subjects (13.3%) in the quizartinib + ketoconazole group, 4 of 27 subjects (14.8%) in the quizartinib + rifampicin group, and 3 of 26 subjects (11.5%) in the quizartinib + placebo group. Adverse events with an incidence of ≥10% were nausea in 7 subjects (23.3%) and headache in 5 subjects (16.7%) in the quizartinib + ketoconazole group, and headache in 3 subjects (11.1%) in the quizartinib + rifampicin group (0 in the quizartinib + placebo group).

Adverse events leading to the discontinuation of the study drug occurred in 1 of 30 subjects (3.3%) in the quizartinib + ketoconazole group and 1 of 27 subjects (3.7%) in the quizartinib + rifampicin group (0 in the quizartinib + placebo group). These events were drug eruption in 1 subject in the quizartinib +

ketoconazole group and neutropenia in 1 subject in the quizartinib + rifampicin group, and a causal relationship to the study drug could not be ruled out for either event.

No serious adverse events occurred in any group.

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 PMDA's conclusion will be reported in the Review Report (2).

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

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

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

On the basis of the data submitted, PMDA has concluded that quizartinib has efficacy in the treatment of relapsed or refractory FLT3-ITD mutation-positive AML, and that quizartinib has acceptable safety in view of its benefits. Quizartinib is a new active ingredient with an inhibitory effect against tyrosine kinases such as FLT3, and is expected to suppress tumor growth by inhibiting FLT3-mediated signal transduction. Quizartinib is therefore considered to have a clinical significance as an option in standard care for relapsed or refractory FLT3-ITD mutation-positive AML. The efficacy, indication, and dosage and administration of quizartinib should be further reviewed.

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

Review Report (2)

May 20, 2019

Product Submitted for Approval

Brand Name	Vanflyta Tablets 17.7 mg Vanflyta Tablets 26.5 mg
Non-proprietary Name	Quizartinib Hydrochloride
Applicant	Daiichi Sankyo Company, Limited
Date of Application	October 17, 2018

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 review on Section "7.R.2 Efficacy" of the Review Report (1), PMDA has concluded that the efficacy of quizartinib has been demonstrated in patients with relapsed or refractory FLT3-ITD mutation-positive AML, based on the demonstrated superiority of quizartinib to the control in the primary endpoint, OS, in this patient population participated in the foreign phase III study (Study 007).

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

1.2 Safety

As a result of the review on Section "7.R.3 Safety" of the Review Report (1), PMDA has concluded that treatment with quizartinib requires special attention to adverse events, namely, infection, hemorrhage, myelosuppression, cardiac disorder (QT interval prolongation and myocardial infarction), renal dysfunction, and ILD.

In addition, although caution should be used against the above adverse events during the treatment, PMDA has concluded that quizartinib is tolerated in patients appropriately followed up by physicians with adequate knowledge and experience in treating hematopoietic malignancies, thorough monitoring and controlling the adverse events.

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

After the Expert Discussion, the applicant reported that cardiac disorder-related adverse events with fatal outcome in >1 patient in an ongoing clinical study. PMDA asked the applicant to explain the occurrence of event.

The applicant's explanation:
A global, double-blind, randomized phase III study (Study AC220-A-U302 [Study 302]) is ongoing in patients with treatment-naive FLT3-ITD mutation-positive AML to compare the efficacy and safety between quizartinib and placebo, which are used as an add-on therapy to the standard chemotherapy.[48)] In the study, cardiac disorder-related adverse events resulting in death were cardiac arrest in 3 patients, sudden death in 1 patient, and serious ventricular fibrillation/cardiac arrest in 1 patient. All 5 patients (all non-Japanese) received quizartinib.[49)] A causal relationship to quizartinib could not be ruled out for ventricular fibrillation/cardiac arrest in 1 patient[50)] and cardiac arrest in 1 patient.[51)]

Based on the above, the package insert will inform of the occurrence of ventricular fibrillation, cardiac arrest, and sudden death in the clinical study in patients with treatment-naive FLT3-ITD mutation-positive AML.

PMDA's view:
Study 302 revealed the cases of cardiac arrest resulting in death for which a causal relationship to quizartinib could not be ruled out and serious ventricular fibrillation/cardiac arrest, but the number of patients experiencing such events was limited. In addition, in light of the following observation, it is difficult to draw a definite conclusion on the onset of ventricular fibrillation or cardiac arrest in patients receiving quizartinib.

- In Study 302, quizartinib was administered concomitantly with the standard chemotherapy,[48)] and some patients received QT interval prolonging drugs. Any drug other than quizartinib could have contributed to the events.

Nevertheless, the concerned events may be associated with prolonged QT interval, which requires special attention during treatment with quizartinib. The applicant should inform of the occurrence of

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48) The remission induction therapy consisted of intravenous Ara-C 100 mg/m^2 from Days 1 to 7 and intravenous IDA 12 mg/m^2 or daunorubicin hydrochloride (daunorubicin) 60 mg/m^2 from Days 1 to 3. The consolidation therapy consisted of intravenous Ara-C 1.5 or 3.0 g/m^2 every 12 hours on Days 1, 3, and 5. Patients underwent the treatment in 28 day-cycles including 1 to 2 cycles of the remission induction therapy and up to 4 cycles of the consolidation therapy.

49) As a result of consultation with Food and Drug Administration (FDA) based on the safety data from Study 302, the blindness of 5 patients was broken with the blindness of the study retained.

50) 6[redacted]-year old [redacted] woman intravenously received Ara-C from Days 1 to 7 and IDA from Days 1 to 3 in Cycle 1 and then orally received quizartinib 20 mg QD for 5 days from Days 8. On Day 12, she experienced cardiac arrest accompanied by ventricular fibrillation. Cardiopulmonary resuscitation was performed for 1 minute, and ventricular fibrillation was found but spontaneous circulation was restored by defibrillation. Grade 4 hypokalaemia (2.4 mmol/L) was observed, and potassium supplementation was performed. The QTcF value was 489 milliseconds 30 minutes after the onset and 587 milliseconds 5 hours later, but no of arrhythmia occurred. Quizartinib was discontinued. Posaconazole (not approved in Japan), a strong CYP3A inhibitor with QT interval prolongation action, was administered from Days 5 to 12.

51) 5[redacted]-year old Caucasian woman intravenously received Ara-C from Days 1 to 7 and daunorubicin from Days 1 to 3 in Cycle 1, and orally received quizartinib 40 mg QD for 15 days from Day 11. In Cycle 2, she started quizartinib 40 mg QD on Day 8 after the remission induction therapy in Cycle 1. QT interval prolonged occurred, and quizartinib was interrupted on Day 9. QT interval was centrally assessed as normal, and quizartinib was resumed at a reduced dose of 30 mg QD on Day 10. Cardiac arrest attributable to ventricular fibrillation occurred and resulted in death on Day 16. Cardiac arrest was accompanied by Grade 3 hypokalemia. A causal relationship to quizartinib was ruled out by the investigator, but the applicant concluded that the causal relationship to quizartinib could not be ruled out.

cardiac disorder-related adverse events with fatal outcome in Study 302 via the package insert, etc., and continue to collect information in the post-marketing setting. New findings should be communicated to healthcare professionals appropriately.

1.3 Clinical positioning and indication

As a result of the review on Section "7.R.4 Clinical positioning and indication" of the Review Report (1), PMDA concluded that the indication of quizartinib should be defined as "Relapsed or refractory FLT3-ITD mutation-positive acute myeloid leukemia," as proposed, with the following cautionary advice in the "Precautions Concerning Indication" section.

Precautions Concerning Indication

- Quizartinib should be administered only to patients who are FLT3-ITD mutation-positive confirmed by a pathologist or at a testing center with adequate experience. The test should be performed with an approved *in vitro* diagnostic.

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

Accordingly, PMDA instructed the applicant to specify the indication and "Precautions Concerning Indication" section as described above. The applicant responded to accept the instruction.

1.4 Dosage and administration

As a result of the review on Section "7.R.5 Dosage and administration" of the Review Report (1), PMDA concluded that the "Dosage and Administration" section and the "Precautions Concerning Dosage and Administration" section should be modified as shown below.

Dosage and Administration

The usual adult dosage is 26.5 mg of quizartinib orally administered once daily for 2 weeks followed by 53 mg orally administered once daily. The dose may be decreased according to the patient's condition.

Precautions Concerning Dosage and Administration

- The efficacy and safety of concomitant use of quizartinib with the other antineoplastic agents have not been established.

- Electrocardiography should be performed prior to the treatment with quizartinib, and the treatment should not be started when QTcF is >450 milliseconds. The dose of quizartinib should not be increased for patients with prolonged QTcF of >450 milliseconds after the first 2 weeks of treatment.

- It is desirable to avoid the concomitant use of quizartinib with a strong CYP3A inhibitor. However, when such use is inevitable, the dose of quizartinib should be reduced by 1 level in accordance with the dose reduction criteria. Once the completion of dosing of the concomitant strong CYP3A inhibitor, the dose of quizartinib should be increased to the previous level.

- If adverse drug reaction occurs during treatment with quizartinib, treatment should be interrupted or discontinued, or the dose of quizartinib should be reduced according to the following criteria.

Dose reduction of quizartinib

Dose level	Dose
Usual dose	53 mg
1-level lower dose	26.5 mg
2-level lower dose	17.7 mg

Criteria for dose interruption, dose reduction, or discontinuation of quizartinib

Adverse drug reaction	Severity of adverse drug reaction	Action
QT interval prolongation	>500 milliseconds	• Interrupt quizartinib. After recovery of QTcF to ≤450 milliseconds, quizartinib may be resumed at the 1-level lower dose. Patients previously treated with the 17.7-mg dose may resume at 17.7 mg after recovery. • If QTcF shows no recovery to ≤450 milliseconds even after a 2-week interruption, discontinue quizartinib.
	QT interval prolongation associated with a symptom/sign of life-threatening arrhythmia	Discontinue quizartinib.
Non-hematological adverse drug reaction (excluding QT interval prolongation)	Grade ≥3	• Interrupt quizartinib. After improvement to Grade ≤1, quizartinib may be resumed at the 1-step lower dose. • If a Grade ≥2 adverse drug reaction persists for >2 weeks, discontinue quizartinib.
Myelosuppression	Platelet count <100,000/mm^3 and neutrophil count <1,000/mm^3	• Continue quizartinib at the 1-level lower dose or interrupt quizartinib. After recovery, quizartinib may be resumed at the dose before the adverse drug reaction. • If an adverse drug reaction persists for 2 weeks, discontinue quizartinib.

Graded based on NCI-CTCAE.

At the Expert Discussion, the expert advisors supported the above PMDA's conclusion and also raised the following comments.

- A statement in the "Precautions Concerning Dosage and Administration" section, "It is desirable to avoid the concomitant use of quizartinib with a strong CYP3A inhibitor," may mislead healthcare professionals. Rewording is advisable.

PMDA's view:

Given that (a) Study 007 demonstrated the clinical benefit of quizartinib administered with a concomitant strong CYP3A inhibitor according to the dose adjustment criteria for the combination regimen, and that (b) in patients receiving quizartinib, a strong CYP3A inhibitor such as voriconazole is assumed to be used often concomitantly, the caution against concomitant use with a strong CYP3A inhibitor should be described as below, without mentioning that the concomitant use of quizartinib with such drug should preferably avoided.

- For concomitant use with a strong CYP3A inhibitor, the dose of quizartinib should be reduced by 1 level in accordance with the dose reduction criteria. Once the completion of dosing of the concomitant strong CYP3A inhibitor, the dose of quizartinib should be increased to the previous level.

In addition, cardiac disorder-related adverse events with fatal outcome occurred in >1 patient in an ongoing clinical study after the Expert Discussion [see Section 1.2], the applicant explained that the

dose adjustment criteria of quizartinib following QT interval prolongation would have the following additional criterion in accordance with the criteria in Study 007.

Criteria for dose interruption, dose reduction, or discontinuation of quizartinib

Adverse drug reaction	Severity	Action
QT interval prolongation	>480 and ≤500 milliseconds	Continue quizartinib at the 1-level lower dose. After recovery of QTcF to ≤450 milliseconds, the dose may be increased to the previous level. For patients previously treated with the 17.7-mg dose, interrupt the treatment for up to 2 weeks until recovery of QTcF to ≤450 milliseconds.

PMDA's view:

The applicant's explanation is generally acceptable. However, the dose adjustment criteria of quizartinib should be modified as below.

Criteria for dose interruption, dose reduction, or discontinuation of quizartinib

Adverse drug reaction	Severity	Action
QT interval prolongation	>480 and ≤500 milliseconds	• 53 or 26.5 mg-dose: Reduce quizartinib by 1 level. After improvement of QTcF to ≤450 milliseconds, quizartinib may be increased to the dose before the adverse drug reaction. • 17.7 mg-dose: Interrupt quizartinib. If no improvement of QTcF to ≤450 milliseconds even after a 2-week interruption, discontinue quizartinib.
	>500 milliseconds	• Interrupt quizartinib. After recovery of QTcF to ≤450 milliseconds, quizartinib may be resumed at the 1-step lower dose. Patients previously treated with the 17.7-mg dose may resume at 17.7 mg after recovery. • If QTcF shows no recovery to ≤450 milliseconds even after a 2-week interruption, discontinue quizartinib.
	QT interval prolongation associated with a life-threatening arrhythmia symptom/sign	Discontinue quizartinib.
Non-hematological adverse drug reaction (excluding QT interval prolongation)	Grade ≥3	• Interrupt quizartinib. After improvement to Grade ≤1, quizartinib may be resumed at the 1-level lower dose. • If a Grade ≥2 adverse reaction persists for >2 weeks, discontinue quizartinib.
Myelosuppression	Platelet count <100,000/mm^3 and neutrophil count <1,000/mm^3	• Continue quizartinib at the 1-level lower dose or interrupt quizartinib. After recovery, quizartinib may be resumed at the dose before the adverse drug reaction. • If an adverse reaction persists for >2 weeks, discontinue quizartinib.

Graded based on NCI-CTCAE.

Accordingly, PMDA instructed the applicant to specify the "Dosage and Administration" section and "Precautions Concerning Dosage and Administration" section as described above. The applicant agreed.

1.5 Risk management plan (draft)

The applicant plans to conduct post-marketing surveillance in all patients treated with quizartinib to investigate the safety of quizartinib in post-marketing clinical use. The target sample size is 150 patients and the observation period is planned to be 1 year.

As a result of the review on Section "7.R.7 Post-marketing investigations" of the Review Report (1), PMDA concluded that the applicant should conduct post-marketing surveillance in all patients on quizartinib treatment for a certain time period, to collect safety information promptly in an unbiased manner and provide obtained safety information to healthcare professionals as soon as available.

PMDA's conclusion on the surveillance plan:

- The safety specification of the surveillance should include cardiac disorders such as myocardial infarction, renal dysfunction such as acute renal failure, and ILD.

- The planned sample size and observation period should be reviewed in light of clinical study data on the events selected as the safety specification of the surveillance.

The above conclusion of PMDA was supported at the Expert Discussion. The following comments were raised from the expert advisors:

- (a) QT interval prolongation is characteristic of quizartinib and (b) limited safety information is available from Japanese patients treated with quizartinib. Information about QT interval prolongation should also be collected through the surveillance appropriately.

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

The applicant's reply:

- The safety specification will include QT interval prolongation, myocardial infarction, acute kidney injury, and ILD.

- The planned sample size and observation period will be specified as 210 patients and 6 months, respectively, in light of the occurrence in the clinical studies of the events included in the safety specification.

PMDA accepted the applicant's explanation.

In view of the discussion above, PMDA has concluded that the risk management plan (draft) for quizartinib should include the safety specification presented in Table 39, and that additional pharmacovigilance activities, surveillances and studies for the efficacy, and risk minimization activities should be conducted as per Tables 40 and 41.

Table 39. Safety and efficacy specifications in the risk management plan (draft)

Safety specification		
Important identified risks	Important potential risks	Important missing information
• QT interval prolongation • Infection • Hemorrhage • Myelosuppression • Drug interactions with CYP3A inhibitors	• Myocardial infarction • Acute kidney injury • ILD • Embryo-fetal toxicity	None
Efficacy specification		
None		

Table 40. Summary of additional pharmacovigilance activities, surveillances and studies for efficacy, and risk minimization activities included under the risk management plan (draft)

Additional pharmacovigilance activities	Surveillances and studies for efficacy	Additional risk minimization activities
• Early post-marketing phase vigilance • General use-results survey (all-case surveillance)	None	• Provision of information from early post-marketing phase vigilance • Preparation and distribution of materials for healthcare professionals

Table 41. Outline of post-marketing surveillance (draft)

Objective	To investigate the safety of quizartinib in post-marketing clinical use
Survey method	All-case surveillance
Population	All patients who have received quizartinib
Observation period	6 months
Planned sample size	210 patients
Main survey items	Safety specification: QT interval prolongation, myocardial infarction, acute kidney injury, and ILD Other main survey items: Patient characteristics (sex, age, complications, prior treatment, etc.), use status of quizartinib, concomitant medications, adverse events, etc.

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

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

The new drug application data were subjected to a document-based compliance inspection and a data integrity assessment in accordance with the provisions of the Act on Securing Quality, Efficacy and Safety of Pharmaceuticals, Medical Devices, Regenerative and Cellular Therapy Products, Gene Therapy Products, and Cosmetics. The inspection and assessment revealed the sponsor's failure in the as-per-protocol analysis of "CRi," which is important for the assessment of the efficacy primary endpoint in Study 5.3.5.2-1, consequently requiring re-analysis. Despite this, PMDA concluded that there were no obstacles to conducting its review based on the application documents submitted.

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

The new drug application data (CTD 5.3.5.2-1) were subjected to an on-site GCP inspection, in accordance with the provisions of the Act on Securing Quality, Efficacy and Safety of Pharmaceuticals, Medical Devices, Regenerative and Cellular Therapy Products, Gene Therapy Products, and Cosmetics. On the basis of the inspection and assessment, 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 the dosage and administrations modified as below, with the following conditions. However, the approval presupposes necessary caution given through the package insert, appropriate information provision on the proper use of the product in the post-marketing setting, and strict adherence to the proper use of the product under the supervision of physicians with adequate knowledge and experience in treating hematopoietic malignancies at medical institutions capable of emergency care. Because the product is designated as an orphan drug, the re-examination period is 10 years. The product is not classified as a biological product or a specified biological product, and the drug product and its drug substance are both classified as powerful drugs.

Indication

Relapsed or refractory FLT3-ITD mutation-positive acute myeloid leukemia

Dosage and Administration

The usual adult dosage is 26.5 mg of quizartinib orally administered once daily for 2 weeks followed by 53 mg orally administered once daily. The dose may be decreased according to the patient's condition.

Approval conditions

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

2. Because only a limited number of Japanese patients participated in the clinical studies, the applicant is required to conduct a post-marketing drug use-results survey involving all Japanese patients treated with the product until data from a certain number of patients are compiled, to identify 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 determined eligible for the treatment by a physician with adequate knowledge and experience in treating hematopoietic malignancies at medical institutions capable of emergency care. 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

Quizartinib should be administered only to patients who are FLT3-ITD mutation-positive confirmed by a pathologist or at a testing center with adequate experience. The test should be performed with an approved *in vitro* diagnostic.

Precautions Concerning Dosage and Administration

1. The efficacy and safety of quizartinib used in combination with other antineoplastic agents have not been established.

2. Electrocardiography should be performed prior to the treatment with quizartinib, and the treatment should not be started when QTcF is >450 milliseconds. The dose of quizartinib should not be increased for patients with prolonged QTcF of >450 milliseconds during the first 2 weeks of treatment.

3. For concomitant use with a strong CYP3A inhibitor, the dose of quizartinib should be reduced by 1 level in accordance with the dose reduction criteria. Once the completion of dosing of the strong CYP3A inhibitor, the dose of quizartinib should be increased to the previous level.

4. In case of an adverse drug reaction during treatment with quizartinib, the treatment should be interrupted or discontinued, or the dose of quizartinib should be reduced according to the following criteria.

Dose reduction of quizartinib

Dose level	Dose
Usual dose	53 mg
1-level lower dose	26.5 mg
2-level lower dose	17.7 mg

Criteria for dose interruption, dose reduction, or discontinuation of quizartinib

Adverse drug reaction	Severity	Action
QT interval prolongation	>480 and ≤500 milliseconds	• 53 or 26.5 mg-dose: Reduce quizartinib by 1 level. After improvement of QTcF to ≤450 milliseconds, quizartinib may be increased to the dose before the adverse drug reaction. • 17.7 mg-dose: Interrupt quizartinib. If no improvement of QTcF to ≤450 milliseconds even after a 2-week interruption, discontinue quizartinib.
	>500 milliseconds	• Interrupt quizartinib. After recovery of QTcF to ≤450 milliseconds, quizartinib may be resumed at the 1-level lower dose. Patients previously treated with the 17.7-mg dose may resume at 7.7 mg after recovery. • If QTcF shows no recovery to ≤450 milliseconds even after a 2-week interruption, discontinue quizartinib.
	QT interval prolonged associated with a life-threatening arrhythmia symptom/sign	Discontinue quizartinib.
Non-hematological adverse drug reaction (excluding QT interval prolongation)	Grade ≥3	• Interrupt quizartinib. After improvement to Grade ≤1, quizartinib may be resumed at the 1-level lower dose. • If a Grade ≥2 adverse drug reaction persists for >2 weeks, discontinue quizartinib.
Myelosuppression	Platelet count <100,000/mm^3 and neutrophil count <1,000/mm^3	• Continue quizartinib at the 1-level lower dose or interrupt quizartinib. After recovery, quizartinib may be resumed at the same dose before the adverse drug reaction. • If an adverse drug reaction persists for >2 weeks, discontinue quizartinib.

Graded based on NCI-CTCAE.

Appendix

List of Abbreviations

ALB	albumin
ALL	acute lymphoblastic leukemia
ALP	alkaline phosphatase
ALT	alanine aminotransferase
AML	acute myeloid leukemia
Application	application for marketing approval
Ara-C	cytarabine
AST	aspartate aminotransferase
BA	bioavailability
BCRP	breast cancer resistance protein
BID	Bis in die
BSA	bovine serum albumin
BSEP	bile salt export pump
CHO cell line	chinese hamster ovary cell line
CI	confidence interval
CK	creatine phosphokinase
CL_{int}	intrinsic clearance
CL_m	apparent clearance of AC886
CQA	critical quality attribute
CR	complete remission
CRc	composite complete remission
CrCL	creatinine clearance
CRi	complete remission with incomplete hematologic recovery
CRp	complete remission with incomplete platelet recovery
CSF1R	colony stimulating factor 1 receptor
CYP	cytochrome P450
^{14}C-quizartinib	^{14}C-labeled quizartinib hydrochloride
daunorubicin	daunorubicin hydrochloride
DDR1	discoidin domain receptor 1
DLT	dose limiting toxicity
DMC	data monitoring committee
DMSO	dimethyl sulfoxide
ECL	electrochemiluminescence
efflux ratio	ratio of secretion permeability rate to absorption permeability rate
ELN	European LeukemiaNet
ERK	extracellular signal-regulated kinase
F1	relative bioavailability
FDA	Food and Drug Administration
FLAG-IDA	Combination therapy of fludarabine, idarubicin, Ara-C, and G-CSF preparation
FLT3	FMS-like tyrosine kinase 3
fludarabine	fludarabine phosphate
G-CSF	granulocyte-colony stimulating factor
GGT	gamma-glutamyltransferase
gilteritinib	gilteritinib fumarate
GVHD	graft versus host disease
hERG	human *ether-a-go-go*-related gene
HPβCD	hydroxypropyl-β-cyclodextrin
HSCT	allogeneic hematopoietic stem cell transplantation
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use

ICH Q1E guideline	"Guideline on Evaluation of Stability Data" (PFSB/ELD Notification No. 0603004 dated June 3, 2003)
IDA	idarubicin hydrochloride
ILD	interstitial lung disease
IR	infrared absorption spectrum
ITD	internal tandem duplication
ITT	intent-to-treat
K_D	dissociation constant
K_i	inhibition constant
KIT	mast/stem cell growth factor receptor
LC	liquid chromatography
LC-MS/MS	liquid chromatography-tandem mass spectrometry
LDH	lactate dehydrogenase
MCH	mean corpuscular hemoglobin
MCV	mean corpuscular volume
MDCKII	Madin-Darby canine kidney strain-II
MEC	Combination therapy of mitoxantrone, etoposide, and Ara-C
MedDRA/J	Medical Dictionary for Regulatory Activities Japanese version
MHC	matched healthy control subjects
mitoxantrone	mitoxantrone hydrochloride
mRNA	messenger ribonucleic acid
MTD	maximum tolerated dose
NADPH	nicotinamide adenine dinucleotide phosphate hydrogen
NCCN guideline	National Comprehensive Cancer Network Clinical Practice Guidelines in Oncology, Acute Myeloid Leukemia
NCI-CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
NE	not estimable
NMR	nuclear magnetic resonance spectrum
NZW	New Zealand White
OAT	organic anion transporter
OATP	organic anion transporting polypeptide
OCT	organic cation transporter
OS	overall survival
$P_{app\ A \rightarrow B}$	apparent permeability in apical to basolateral direction
PBPK	physiologically based pharmacokinetic
PDGFR	platelet derived growth factor receptor
P-gp	P-glycoprotein
PK	pharmacokinetics
pKa	acid dissociation constant
PMDA	Pharmaceuticals and Medical Devices Agency
PPK	population pharmacokinetics
PS	performance status
PT	preferred term
Q1	apparent inter-compartmental clearance of Quizartinib
QbD	quality by design
QD	quaque die
QTcF	QT interval corrected with Fridericia approach
quizartinib	quizartinib hydrochloride
RET	rearranged during transfection
SCID mouse	severe combined immunodeficient mouse
SMQ	standard MedDRA queries
SOC	system organ class
STAT5	signal transducer and activator of transcription 5
Study 0005	Study 2689-CL-0005

Study 0011	Study 2689-CL-0011
Study 002	Study AC220-002
Study 006	Study AC220-006
Study 007	Study AC220-007
Study 008	Study AC220-008
Study 012	Study AC220-012
Study 014	Study AC220-014
Study 015	Study AC220-015
Study 016	Study AC220-016
Study 018	Study AC220-018
Study 019	Study AC220-019
Study 2004	Study 2689-CL-2004
Study 302	Study AC220-A-U302
Study J101	Study AC220-A-J101
Study J102	Study AC220-A-J102
Study J201	Study AC220-A-J201
TKD	tyrosine kinase domain
V_c	apparent volume of distribution of central compartment of Quizartinib
V_{cm}	apparent volume of distribution of central compartment of AC886
V_p	apparent peripheral volume of distribution of Quizartinib
V_{pm}	apparent volume of distribution of peripheral compartment of AC886
ΔQTcF	Change in QTcF from baseline