Report on the Deliberation Results

September 4, 2018
Pharmaceutical Evaluation Division, Pharmaceutical Safety and Environmental Health Bureau
Ministry of Health, Labour and Welfare

Brand Name	Xospata Tablets 40 mg
Non-proprietary Name	Gilteritinib Fumarate (JAN*)
Applicant	Astellas Pharma Inc.
Date of Application	March 23, 2018

Results of Deliberation

In its meeting held on August 29, 2018, 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, and the re-examination period is 10 years. The drug product and its drug substance are both classified as powerful drugs.

Conditions of Approval

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

**Japanese Accepted Name (modified INN)*

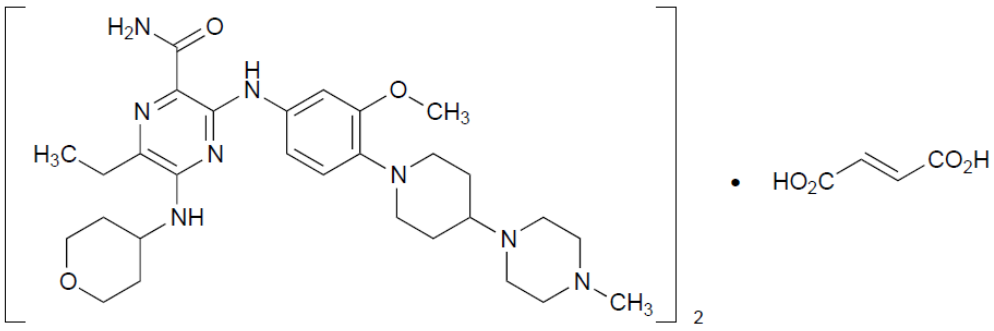
Review Report

August 2, 2018
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	Xospata Tablets 40 mg
Non-proprietary Name	Gilteritinib Fumarate
Applicant	Astellas Pharma Inc.
Date of Application	March 23, 2018
Dosage Form/Strength	Tablet: Each tablet contains 44.2 mg of Gilteritinib Fumarate (40 mg of Gilteritinib).
Application Classification	Prescription drug, (1) Drug with a new active ingredient

Chemical Structure



Molecular formula: $(C_{29}H_{44}N_8O_3)_2 \cdot C_4H_4O_4$
Molecular weight: 1221.50
Chemical name:
6-Ethyl-3-{3-methoxy-4-[4-(4-methylpiperazin-1-yl)piperidin-1-yl]anilino}-5-[(oxan-4-yl) amino]pyrazine-2-carboxamide hemifumarate

Items Warranting Special Mention

SAKIGAKE designation drug (SAKIGAKE Drug Designation No. 5 of 2015 [*27 yaku*]; PSEHB/ELD Notification No. 1027-1 dated October 27, 2015, by the Evaluation and Licensing Division, Pharmaceutical Safety and Environmental Health Bureau, Ministry of Health, Labour and Welfare).

Orphan drug (Orphan Drug Designation No. 412 of 2018 [*30 yaku*]; PSEHB/PED Notification No. 0320-1 dated March 20, 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 a certain level of efficacy in the treatment of *FLT3* mutation-positive relapsed or refractory acute myeloid leukemia, and that the product has acceptable safety in view of its benefits (see Attachment).

As a result of its review, PMDA has concluded that the product may be approved for the indication and dosage and administration shown below, with the following conditions. The following events should be further investigated via post-marketing surveillance: myelosuppression, infection, hemorrhage, prolonged QT interval, cardiac failure, pericarditis, pericardial effusion, hepatic dysfunction, renal disorders, gastrointestinal perforation, interstitial lung disease, hypersensitivity, and posterior reversible encephalopathy syndrome.

Indication

FLT3 mutation-positive relapsed or refractory acute myeloid leukemia

Dosage and Administration

The usual adult dosage is 120 mg of gilteritinib administered orally once daily. The dosage may be adjusted according to the patient's condition, but should not exceed 200 mg once daily.

Conditions of Approval

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

Attachment

Review Report (1)

June 29, 2018

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.

Product Submitted for Approval

Brand Name	Xospata Tablets 40 mg
Non-proprietary Name	Gilteritinib Fumarate
Applicant	Astellas Pharma Inc.
Date of Application	March 23, 2018
Dosage Form/Strength	Tablet: Each tablet contains 44.2 mg of Gilteritinib Fumarate (40 mg of Gilteritinib).
Proposed Indication	*FLT3* mutation-positive relapsed or refractory acute myeloid leukemia

Proposed Dosage and Administration

The usual adult dosage is 120 mg of gilteritinib administered orally once daily. According to the patient's condition, the dose may be increased up to 200 mg once daily, or reduced from 120 mg to 80 mg or from 200 mg to 120 mg.

Table of Contents

List of Abbreviations

See Appendix.

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

1.1 Overview of product submitted for approval

FMS-like tyrosine kinase 3 (FLT3) is a receptor tyrosine kinase expressed on the surface of hematopoietic progenitor cells and acute myeloid leukemia (AML) cells and is considered to be involved in the differentiation, proliferation, etc. of hematopoietic progenitor cells (*Immunity*. 1995; 3: 147-61). *FLT3*-activating mutations lead to constitutive activation of FLT3 receptor signaling, etc. (*Blood*. 1992; 80: 2584-93, etc.)

Gilteritinib Fumarate (hereinafter referred to as "gilteritinib") is a small molecule with inhibitory activity against tyrosine kinases including FLT3, discovered by the applicant and Kotobuki Pharmaceutical Co., Ltd. It is considered to suppress the growth of *FLT3*-mutated tumors by inhibiting FLT3 receptor signaling.

1.2 History of development etc.

The applicant initiated a foreign phase I/II study in patients with relapsed or refractory AML (Study 0101) in October 2013. Then, the applicant initiated a global phase III study in patients with *FLT3* mutation-positive relapsed or refractory AML (Study 0301) in October 2015.

In the US, a new drug application for gilteritinib was filed based mainly on the results from Study 0301 in March 2018, and is currently under review.

As of May 2018, gilteritinib has not been approved in any country or region.

In Japan, the applicant initiated a phase I study in patients with relapsed or refractory AML (Study 0102) in June 2014. Study 0301 initiated enrollment in May 2016.

The applicant has submitted a marketing application for gilteritinib in Japan based mainly on the results from Study 0301.

Gilteritinib received a SAKIGAKE designation (SAKIGAKE Drug Designation No. 5 of 2015 [*27 yaku*]) with the intended indication of "FLT3 mutation-positive first relapsed or refractory acute myeloid leukemia" in October 2015 and an orphan drug designation (Orphan Drug Designation No. 412 of 2018 [*30 yaku*]) with the intended indication of "*FLT3* mutation-positive acute myeloid leukemia" in March 2018.

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 light yellow to yellow powder or crystals, and its general properties, including description, acid dissociation constant, partition coefficient, solubility, hygroscopicity, melting point, and thermal analysis, have been determined. Four crystalline forms of the drug substance (hemifumarate salt, [redacted], and 2 types of [redacted]) occur, but hemifumarate salt only is

formed at production scale, and stability studies demonstrated that no changes occurred in the hemifumarate salt.

The chemical structure of the drug substance has been elucidated by elemental analysis, infrared spectrophotometry (IR), nuclear magnetic resonance spectrometry (NMR) (^{1}H-NMR, ^{13}C-NMR), mass spectrometry, and ultraviolet-visible spectrophotometry.

2.1.2 Manufacturing process

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

[redacted] synthesis and [redacted] of gilteritinib fumarate have been defined as critical steps, and process control items and values have been established for these critical steps.

2.1.3 Control of drug substance

The proposed specifications for the drug substance consist of content, description, identification (ultraviolet-visible spectrophotometry, IR, thin layer chromatography), purity ([redacted] [inductively coupled plasma-optical emission spectroscopy], related substances [HPLC], residual solvents [[redacted], [redacted], [redacted], [redacted] (gas chromatography [GC])]), water content, residue on ignition, and assay (HPLC).

2.1.4 Stability of drug substance

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

Table 1. Stability studies on drug substance

Study	Primary batches	Temperature	Humidity	Storage package	Storage period
Long-term	3 pilot-scale batches	25°C	60%RH	double low-density polyethylene bags + polyethylene tube + steel drum	24 months
Accelerated		40°C	75%RH		6 months

Based on the above, in accordance with the ICH Q1E guideline, a re-test period of 36 months has been proposed for the drug substance when packaged in double low-density polyethylene bags within a polyethylene tube and stored in a steel drum at room temperature, protected from light. The long-term testing will be continued for at least [redacted] months (up to [redacted] months).

2.2 Drug product

2.2.1 Description and composition of drug product and formulation development

The drug product is an immediate-release film-coated tablet containing 44.2 mg of gilteritinib fumarate (40 mg of gilteritinib) and the following excipients: D-mannitol, hydroxypropyl cellulose, low-substituted

hydroxypropyl cellulose, magnesium stearate, hypromellose, Macrogol [redacted], titanium dioxide, talc, and yellow ferric oxide.

2.2.2 Manufacturing process

The drug product is manufactured through a process comprised of milling, granulation, blending, tableting, blending of film coating components, film coating, filling, and packaging/labeling.

Quality by design (QbD) approaches were used, and a quality control strategy was established based on the following studies etc. (Table 2)

- Identification of critical quality attributes (CQAs)
- Quality risk assessments and risk assessment of the manufacturing process using Failure Mode Effects Analysis

Table 2. Overview of drug product control strategy

CQA	Method of control
Dissolution	Manufacturing process, specification
Assay	Manufacturing process, specification
Uniformity of dosage units	Manufacturing process, specification
Related substances	Manufacturing process, specification
[redacted] and [redacted]	Manufacturing process

[redacted] has been defined as a critical step, and process control items and values have been established for the critical step.

2.2.3 Control of drug product

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

Real time release testing (RTRT), performed as in-process testing, has been proposed for [redacted] and [redacted] to make release decisions of the drug product (see below for details).

- Using [redacted] sampled at [redacted] step, [redacted] of gilteritinib is calculated by near-infrared spectrophotometry. Batch release decisions are made according to [redacted] based on [redacted].

If RTRT cannot be used for batch release, the specification tests will be performed in accordance with the pre-defined acceptance criteria and procedures to make batch release decisions.

2.2.4 Stability of drug product

Stability studies on the drug product are shown in Table 3. The photostability data show that the drug product is photostable.

Table 3. Stability studies on drug product

Study	Primary batches	Temperature	Humidity	Storage package	Storage period
Long-term	3 pilot-scale batches	25°C	60%RH	Blister pack (polyvinyl chloride/aluminum)	24 months
Accelerated		40°C	75%RH		6 months

Based on the above, in accordance with the ICH Q1E guideline, a shelf life of 36 months has been proposed for the drug product when packaged in a blister pack (polyvinyl chloride/aluminum) and stored at room temperature. The long-term testing will be continued for at least [redacted] months.

2.R Outline of the review conducted by PMDA

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

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

In this section, the doses and concentrations of gilteritinib are expressed as free base.

3.1 Primary pharmacodynamics

3.1.1 Inhibitory activity against different kinases (CTD 4.2.1.1-1, 4.2.1.1-2, 4.2.1.1-3, 4.2.1.1-5, 4.2.1.1-7, 4.2.1.1-8)

The ability of gilteritinib 5 nmol/L to inhibit phosphorylation of different kinases (recombinant proteins) was tested by detecting phosphorylated substrates using a mobility shift assay. Gilteritinib inhibited the phosphorylation of the following kinases by ≥50%, as shown in Table 4.

Table 4. Inhibitory activity of gilteritinib against different kinases

Kinase	Inhibition of phosphorylation (%)	Kinase	Inhibition of phosphorylation (%)
FLT3	96.4	TRKA	74.9
NPM1-ALK fusion protein	99.5	ROS	71.7
LTK	97.5	RET	65.5
ALK	97.6	MER	55.7
AXL	85.5		

n = 1

Table 5 shows the IC_{50} values of gilteritinib for the inhibition of the phosphorylation of different kinases (FLT3, KIT, AXL, leukocyte tyrosine kinase [LTK], echinoderm microtubule-associated protein-like 4-anaplastic lymphoma kinase [EML4-ALK] fusion protein).

Table 5. Inhibitory activity of gilteritinib against different kinases

Kinase	IC_{50} (nmol/L)
FLT3	0.291 [0.262, 0.324]
KIT	229 [189, 277]
AXL	0.726 [0.514, 1.02]
LTK	0.350 [0.287, 0.427]
EML4-ALK fusion protein variant 1*	1.2 [0.68, 2.0]

Geometric mean [95% CI], n = 3,
* Exon 13 of *EML4* fused to exon 20 of *ALK*

Using mouse pro-B Ba/F3 cell lines expressing FLT3 mutants (FLT3-internal tandem duplication [ITD], FLT3-D835Y,[1)] or FLT3-ITD-D835Y) and human AML MV4-11 cell line expressing FLT3-ITD, the effects of gilteritinib 0.1, 1, and 10 nmol/L on the phosphorylation of different kinases (proteins associated with FLT3 receptor signaling) were assessed by Western blotting. Table 6 shows phosphorylated FLT3, STAT5, AKT, and ERK levels after treatment with gilteritinib, expressed as a percentage of those after treatment with vehicle control (0.1% dimethylsulfoxide [DMSO]).

Table 6. Effects of gilteritinib on phosphorylation of different kinases

Cell line	FLT3 mutant	Gilteritinib (nmol/L)	Phosphorylation of different kinases (%)			
			FLT3	STAT5	AKT	ERK
Ba/F3	FLT3-ITD	0.1	78	99	81	93
		1	34	55	64	62
		10	3	5	5	10
	FLT3-D835Y	0.1	74	80	100	115
		1	45	43	62	55
		10	1	3	14	13
	FLT3-ITD-D835Y	0.1	75	107	51	57
		1	42	86	27	40
		10	4	19	9	19
MV4-11	FLT3-ITD	0.1	57	114	65	54
		1	8	23	48	22
		10	1	0	9	1

n = 1

3.1.2 Induction of cell cycle arrest and apoptosis (CTD 4.2.1.1-9, 4.2.1.1-10)

Using the MV4-11 cell line, induction of (1) cell cycle arrest was determined by propidium iodide staining, and (2) apoptosis induction by gilteritinib was determined by flow cytometric analysis of Annexin V and 7-amino actinomycin D (7-AAD) staining. Results showed that gilteritinib increased (1) the percentage of cells in the G_1 phase of the cell cycle and (2) the percentage of Annexin V-positive cells and 7-AAD-negative cells.

3.1.3 Anti-proliferative activity against cancerous cell lines

3.1.3.1 *In vitro* (CTD 4.2.1.1-4, 4.2.1.1-6)

The anti-proliferative activity of gilteritinib against Ba/F3 and MV4-11 cell lines expressing FLT3 mutants (FLT3-ITD, FLT3-D835Y, or FLT3-ITD-D835Y) was evaluated based on the amount of adenosine triphosphate (ATP) from viable cells. The IC_{50} values of gilteritinib are shown in Table 7.

Table 7. Anti-proliferative activity of gilteritinib against Ba/F3 and MV4-11 cell lines expressing FLT3 mutants

Cell line	FLT3 mutant	IC_{50} (nmol/L)
Ba/F3	FLT3-ITD	1.8 [1.0, 3.0]
	FLT3-D835Y	1.6 [1.1, 2.4]
	FLT3-ITD-D835Y	2.1 [1.4, 3.0]
MV4-11	FLT3-ITD	0.92 [0.23, 3.6]

Geometric mean [95% CI], n = 3

[1)] A mutation of aspartic acid at position 835 of FLT3 substituted with tyrosine

3.1.3.2 *In vivo* (CTD 4.2.1.1-11, 4.2.1.1-13)

The anti-tumor activity of gilteritinib was evaluated in nude mice (6/group) subcutaneously xenografted with the MV4-11 cell line. The day when tumor volume reached 100 to 400 mm^3 was designated as Study Day 0, and animals began treatment on Study Day 0. Gilteritinib 1, 3, 6, or 10 mg/kg was administered orally once daily for 28 days, and tumor volumes were calculated. On Study Day 28, statistically significant inhibition of tumor growth was observed at all dose levels of gilteritinib compared to vehicle control (0.5% methylcellulose solution) (Figure 1).

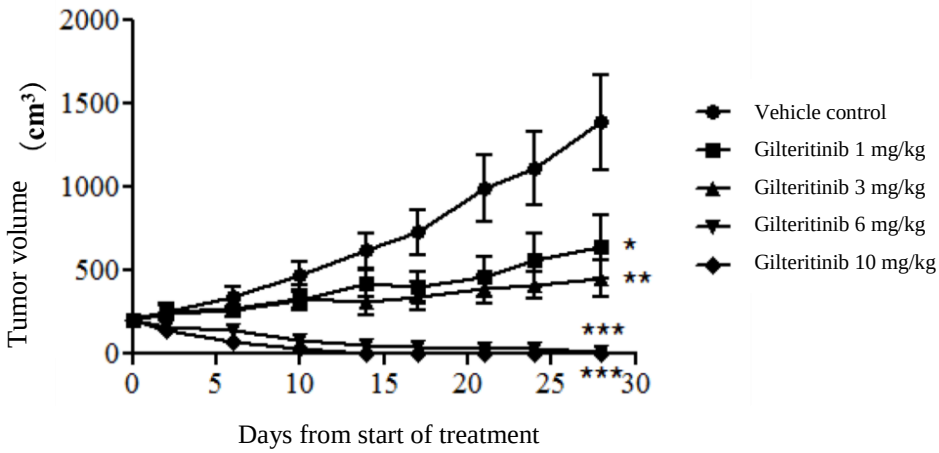


Figure 1. Anti-tumor activity of gilteritinib in nude mice subcutaneously xenografted with MV4-11 cell line
n = 6, Mean ± standard error (SE), * $P < 0.05$ vs. control group,
** $P < 0.01$ vs. control group, *** $P < 0.001$ vs. control group (Dunnett's test)

The anti-tumor activity of gilteritinib was evaluated in non-obese diabetic/severe combined immunodeficient (NOD/SCID) mice (10/group) injected with luciferase-expressing MV4-11 cell line into the bone marrow. The day of transplantation was designated as Study Day 0, and animals began treatment on Study Day 15. Gilteritinib 30 mg/kg was administered orally once daily for 56 days, and whole-body bioluminescence was determined to assess whole-body tumor burden on Study Day 42. The gilteritinib group showed statistically significant inhibition of tumor growth, compared to the control group (0.5% methylcellulose solution) ($P <$ 0.001, Student's t-test).

3.2 Secondary pharmacodynamics

3.2.1 Effect on ALK (CTD 4.2.1.2-1, 4.2.1.2-2, 4.2.1.2-3)

Using the NCI-H2228 cell line, inhibition of ALK phosphorylation by gilteritinib 0.1, 1, and 10 nmol/L was assessed by Western blotting. Phosphorylated ALK levels after treatment with gilteritinib were 69% (0.1 nmol/L), 18% (1 nmol/L), and 2% (10 nmol/L) of those in untreated control cells.

Table 8 shows the results of anti-proliferative activity of gilteritinib against the mouse fibroblast 3T3 cell line expressing EML4-ALK fusion protein and the human NSCLC NCI-H2228 cell line expressing EML4-ALK fusion protein.

Table 8. Anti-proliferative activity of gilteritinib against different cell lines expressing EML4-ALK

Cell line	EML4-ALK fusion protein	IC_{50} (nmol/L)
3T3	Variant 1	0.42 [0.19, 0.93]
	Variant 2*[1]	0.50 [0.16, 1.5]
	Variant 3*[2]	0.95 [0.35, 2.6]
NCI-H2228	Variant 3*[2]	0.74 [0.53, 1.0]

Geometric mean [95% CI], n = 3,
*[1] Exon 20 of *EML4* fused to exon 20 of *ALK*,
*[2] Exon 6 of *EML4* fused to exon 20 of *ALK*

3.2.2 Effects on receptors, ion channels, etc. (CTD 4.2.1.2-4, 4.2.1.2-5)

Gilteritinib 10 μmol/L was assessed for inhibitory activity against 46 receptors, 5 ion channels, 3 transporters, and 3 enzymes, using radioligands, etc. Gilteritinib caused ≥50% inhibition of specific radioligand binding to the adenosine A_1 receptor, the 5-HT_1 receptor, the 5-HT_{2B} receptor, and the sigma receptor, with IC_{50} [95% confidence interval (CI)] (geometric mean, n = 3) of 4.57 [3.84, 5.44], 4.90 [2.43, 9.91], 0.190 [0.134, 0.269], and 0.615 [0.493, 0.766] μmol/L,[2)] respectively.

Gilteritinib was evaluated for inhibitory effects against human 5-HT_{2B} receptors expressed on the Chinese hamster ovary (CHO)-K1 cell line, based on intracellular calcium concentrations. The IC_{50} value of gilteritinib [95% CI] (geometric mean, n = 3) was 5.82 [2.08, 16.3] μmol/L. No agonist activity was observed up to 10 μmol/L of gilteritinib.

The applicant's explanation about the above results:
Given the following points etc., gilteritinib-induced inhibition of the sigma receptor or the 5-HT_{2B} receptor is unlikely to cause safety issues in the clinical use of gilteritinib.

- Neuropsychiatric disorders and motor coordination disorders may occur as sigma receptor-mediated effects (*CNS Drugs*. 2004; 18: 269-84, *Neuroscience*. 2010; 167: 247-55). However, no findings suggestive of these disorders were observed in safety pharmacology studies etc., and no events such as drug-realted motor coordination disorders were reported in a clinical study (Study 0301).
- Abnormal cardiac development observed in an embryo-fetal development study in rats [see Section 5.5] was probably caused by impaired proliferative capacity of cardiomyocytes due to inhibition of the 5-HT_{2B} receptor, etc. (*Proc Natl Acad Sci USA*. 2000; 97: 9508-13, *Circulation*. 2001; 103: 2973-9). In humans, however, adverse events associated with inhibition of this receptor are unlikely to occur, because human cardiomyocytes stop proliferating by 4 months after birth (*Birth Def Res Part B Dev Reprod Toxicol*. 2003; 68: 309-20).

3.3 Safety pharmacology

3.3.1 Effects on central nervous system (CTD 4.2.1.3-1, 4.2.1.3-2, 4.2.1.3-4)

Rats (6/group) received a single oral dose of gilteritinib 10, 30, or 100 mg/kg, and the effects of gilteritinib on clinical signs and behavior were assessed up to 24 hours post-dose by modified Irwin's test. There were

2) The C_{max} of plasma protein unbound gilteritinib following oral administration of gilteritinib 120 mg QD was calculated to be 66.67 ng/mL (approximately 0.121 μmol/L), based on the plasma protein binding of gilteritinib [see Section 4.2.2] and Study 0102 in Japanese patients with AML.

essentially no effects of gilteritinib on clinical signs and behavior. In the 30 mg/kg group, the number of urinating animals decreased, but then returned to a normal level by 72 post-dose. In the 100 mg/kg group, the number of urinating and defecating animals decreased, but then returned to a normal level by 42 hours post-dose.

Single oral doses of gilteritinib 1, 3, 10, 30, and 100 mg/kg were administered sequentially to dogs (4/group) at an interval of 7 days, to assess the effects of gilteritinib on clinical signs, behavior, and body temperature. Retching was observed at 3 mg/kg. Vomiting, positive fecal occult blood, etc. were observed at 10, 30, and 100 mg/kg.

3.3.2 Effects on cardiovascular system

3.3.2.1 Effects on human *ether-a-go-go*-related gene (hERG) potassium current (CTD 4.2.1.3-3)

The effects of gilteritinib 1, 3, 10, and 30 μmol/L on the hERG potassium current were assessed using the human embryonic kidney HEK293 cell line transfected with hERG. Gilteritinib inhibited the hERG potassium current by 1.0 ± 4.3% (gilteritinib dose, 1 μmol/L), 18.1 ± 8.0% (3 μmol/L), 32.8 ± 6.3% (10 μmol/L), and 70.7 ± 5.4% (30 μmol/L) (mean ± standard deviation [SD], n = 5), with IC_{50} of 16 μmol/L. Statistically significant inhibition occurred in the gilteritinib 3, 10, and 30 μmol/L groups compared to the control (0.1% DMSO) group ($P < 0.01$, Dunnett's test).

3.3.2.2 Effects on myocardial ion channels (CTD 4.2.1.3-5)

The effects of gilteritinib 0.1, 1, and 10 μmol/L on different myocardial ion channels were assessed using the HEK293 cell lines expressing human Nav1.5 or Kv7.1/minK (n = 5 each) and the CHO cell lines expressing human Cav1.2, Kv4.3, or Kir2.1 (n = 5 each). Statistically significant inhibition of Kv7.1/minK was observed at 10 μmol/L gilteritinib compared to the control (0.1% DMSO) ($P < 0.01$, Dunnett's test). Gilteritinib at ≥1 μmol/L increased the currents via Cav1.2 in 2 of the 5 preparations. Gilteritinib at 1 μmol/L increased the currents via Kv7.1/minK in 1 of the 5 preparations.

3.3.2.3 Effects on blood pressure, heart rate, ECG, etc. (CTD 4.2.1.3-4)

Single oral doses of gilteritinib 1, 3, 10, 30, and 100 mg/kg were administered sequentially to dogs (4/group) at an interval of 7 days, to assess the effects of gilteritinib on blood pressure, heart rate, ECG, and blood electrolyte concentrations. There were no effects of gilteritinib.

3.3.3 Effects on respiratory system (CTD 4.2.1.3-4)

Single oral doses of gilteritinib 1, 3, 10, 30, and 100 mg/kg were administered sequentially to dogs (n = 4) at an interval of 7 days, to assess the effects of gilteritinib on respiratory rate and blood gases. There were no effects of gilteritinib.

3.R Outline of the review conducted by PMDA

Based on the submitted data and the following considerations, PMDA concluded that the efficacy of gilteritinib in the treatment of *FLT3* mutation-positive AML is expected.

3.R.1 Mechanism of action of gilteritinib

The applicant's explanation about the mechanism of action of gilteritinib and other matters:

FLT3, a member of the class III receptor tyrosine kinase family, is expressed on the surface of hematopoietic progenitor cells and AML cells, and is considered to be involved in the differentiation, proliferation, etc. of hematopoietic progenitor cells (*Blood.* 1992; 80:2584-93).

The *FLT3* mutation is one of genetic mutations associated with AML, and mainly includes FLT3-ITD mutations in the juxtamembrane domain (28%-34%) and FLT3-D835 mutations in the kinase domain (11%-14%) (*Curr Opin Hematol*. 2009; 16: 98-104). These mutations are considered to transform cells by causing constitutive activation of FLT3 receptor signaling (*Blood*. 2001; 97: 2434-9). Furthermore, these mutations are associated with a poor prognosis in AML patients (*Hematologica*. 2003; 88:19-24, etc.).

Gilteritinib is a small molecule that inhibits tyrosine kinases including FLT3. It suppresses tumor growth by binding to FLT3, inhibiting FLT3 receptor signaling, and inducing apoptosis of *FLT3* mutation-positive tumor cells, etc. [see Sections 3.1.1, 3.1.2, and 3.1.3]. The following findings suggest that inhibition of AXL by gilteritinib may contribute to the efficacy of gilteritinib in the treatment of AML.

- Higher expression of AXL was observed in some AML patients (*Blood.* 2013; 122: 2443-52, etc.).
- AXL inhibition suppressed FLT3 activation in *FLT3* mutation-positive AML cell line (MV4-11 cell line) (*Blood.* 2013; 121: 2064-73).
- Gilteritinib 5 nmol/L inhibited the phosphorylation of AXL by 85.5% [see Section 3.1.1].

PMDA's discussion:

PMDA largely accepted the applicant's explanation. The following issues, however, are not fully understood at present: (a) the degree of contribution of AXL to the growth of *FLT3* mutation-positive AML, etc.; (b) the relationship between inhibition of AXL phosphorylation by gilteritinib and inhibition of *FLT3* mutation-positive AML tumor growth. As these issues may be important in the clinical use of gilteritinib in terms of predicting efficacy and selecting appropriate patients, the applicant should continue to investigate them and appropriately inform healthcare professionals about new findings as they become available.

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

In this section, the doses and concentrations of gilteritinib are expressed as free base. Non-clinical PK of gilteritinib were studied in rats and dogs. Studies on the plasma protein binding of gilteritinib, drug metabolizing enzymes, transporters, etc. were conducted using human or animal biomaterials.

4.1 Absorption

4.1.1 Single-dose studies

Male rats received a single intravenous dose of 1 mg/kg of gilteritinib or a single oral dose of 1, 3, or 10 mg/kg of gilteritinib under fasting conditions, and plasma gilteritinib concentrations were determined (Table 9). The C_{max} and AUC_{inf} of gilteritinib increased more than dose-proportionally over the dose range tested. The applicant explained that this finding is likely due to the saturation of first-pass effects. The bioavailability (BA) of oral gilteritinib 1 mg/kg was 26.8%.

Table 9. PK parameters of gilteritinib (male rats, single IV or oral administration)

Route of administration	Dose (mg/kg)	C_{max} (ng/mL)	t_{max} (h)	AUC_{inf} (ng·h/mL)	$t_{1/2}$ (h)	CL_{tot} (L/h/kg)	V_{ss} (L/kg)
IV	1	—	—	257	6.93	3.89	25.7
Oral	1	5.36	6.00	69.0*	—	—	—
	3	23.29	6.00	276	6.64	—	—
	10	125.47	4.00	1760	6.41	—	—

PK parameters were calculated based on the mean plasma gilteritinib concentration at each time point (n = 3).
* AUC_{48h}, —: Not calculated

4.1.2 Repeated-dose studies

Male and female dogs received gilteritinib 1, 2.5, or 5 mg/kg QD orally under non-fasting conditions for 13 weeks, and plasma gilteritinib concentrations were determined (Table 10). There were no evident gender-related differences in the PK parameters of gilteritinib. The C_{max} and AUC_{24h} of gilteritinib increased more than dose-proportionally over the dose range tested. The applicant explained that this finding is likely due to the saturation of first-pass effects, etc. The C_{max} and AUC_{24h} of gilteritinib on Day 7 were higher than those on Day 1, and the C_{max} and AUC_{24h} of gilteritinib essentially reached a steady state by Day 7.

Table 10. PK parameters of gilteritinib (male and female dogs, 13-week oral administration)

Sampling day (Day)	Dose (mg/kg)	Sex	n	C_{max} (ng/mL)	t_{max} (h)	AUC_{24h} (ng·h/mL)
1	1	M	4	15.48 ± 5.05	5.0 ± 1.2	215.54 ± 67.52
		F	4	13.85 ± 2.91	5.5 ± 1.9	226.61 ± 40.73
	2.5	M	7	43.31 ± 3.37	5.7 ± 0.8	619.25 ± 54.87
		F	7	35.05 ± 12.11	6.0 ± 2.3	573.91 ± 189.96
	5	M	7	97.60 ± 22.79	6.9 ± 1.1	1606.44 ± 386.19
		F	7	84.98 ± 14.33	6.9 ± 1.6	1426.55 ± 188.92
7	1	M	4	24.85 ± 8.30	5.5 ± 1.9	385.94 ± 124.07
		F	4	25.16 ± 2.60	7.0 ± 1.2	417.40 ± 38.73
	2.5	M	7	90.23 ± 15.03	6.0 ± 0	1427.77 ± 205.64
		F	7	71.20 ± 13.93	6.0 ± 2.0	1211.37 ± 284.88
	5	M	7	290.42 ± 121.26	6.6 ± 1.0	5573.19 ± 2597.87
		F	7	179.43 ± 51.56	6.0 ± 2.0	3336.22 ± 1018.23
14	1	M	4	20.57 ± 4.98	7.0 ± 2.6	360.37 ± 97.03
		F	4	23.57 ± 4.68	6.0 ± 1.6	391.63 ± 53.26
	2.5	M	7	85.05 ± 8.40	6.3 ± 0.8	1449.28 ± 143.19
		F	7	80.18 ± 23.49	7.1 ± 2.0	1426.29 ± 466.58
	5	M	7	308.47 ± 84.81	6.9 ± 1.1	5783.35 ± 1786.05
		F	7	251.61 ± 40.55	7.7 ± 1.4	4798.73 ± 764.95
56	1	M	4	24.83 ± 8.48	5.0 ± 2.6	398.50 ± 138.04
		F	4	29.42 ± 4.03	4.5 ± 1.0	454.79 ± 69.48
	2.5	M	7	88.19 ± 14.54	6.6 ± 1.0	1483.58 ± 269.58
		F	7	86.15 ± 31.72	5.1 ± 1.6	1467.42 ± 475.08
	5	M	6	320.16 ± 84.32	7.3 ± 1.6	6315.16 ± 1745.30
		F	7	237.69 ± 60.02	5.7 ± 2.1	4617.89 ± 1136.62
91	1	M	4	24.24 ± 7.41	5.0 ± 1.2	388.83 ± 129.52
		F	4	23.95 ± 4.49	5.5 ± 1.0	400.44 ± 50.95
	2.5	M	7	79.45 ± 21.74	6.3 ± 0.8	1355.33 ± 340.68
		F	7	81.75 ± 24.34	6.6 ± 1.5	1392.26 ± 481.79
	5	M	5	329.27 ± 120.63	5.2 ± 2.3	6470.34 ± 2559.33
		F	7	305.43 ± 63.16	6.9 ± 2.3	6001.47 ± 1500.22

Mean ± SD

4.1.3 *In vitro* cell permeability

The cell permeability of gilteritinib was evaluated in the human colon carcinoma Caco-2 cell line. The apparent apical-to-basolateral permeability coefficients ($P_{app\ A\rightarrow B}$) of ^{14}C-gilteritinib 30, 100, and 300 µmol/L were 1.20 × 10^{-6}, 0.708 × 10^{-6}, and 0.448 × 10^{-6} cm/sec, respectively. The applicant explained that gilteritinib is moderately permeable, given that the $P_{app\ A\rightarrow B}$ values of poorly permeable ^{14}C-mannitol (10 µmol/L) and highly permeable ^{3}H-propranolol (100 µmol/L) were 0.271 × 10^{-6} and 7.16 × 10^{-6} cm/sec, respectively.

4.2 Distribution

4.2.1 Tissue distribution

Male albino and pigmented rats received a single oral dose of ^{14}C-gilteritinib 1 mg/kg, and the tissue distribution of radioactivity was studied. Tissue radioactivity levels were determined at 4 to 72 hours post-dose in albino rats and at 4 hours to 270 days post-dose in pigmented rats. In albino rats, extensive tissue distribution of radioactivity was observed, and radioactivity concentrations peaked at 4 hours post-dose in most tissues including blood. The tissue to plasma radioactivity concentration ratio at 4 hours post-dose was particularly high in the small intestine, liver, spleen, kidneys, adrenal glands, and lung (1510, 401, 227, 216, 211, and 150, respectively). The tissue radioactivity concentration at 72 hours post-dose was <10% of the maximum level in

most tissues. The maximum concentration of radioactivity in the eyeballs of pigmented rats was approximately 30 times higher than that in albino rats, and the radioactivity concentration in the eyeballs at 270 days post-dose was 36.4% of the maximum level. In pigmented rats, radioactivity was distributed into the melanin-rich tissues (ciliary body, retina, choroid) in the eyeballs at 4 hours post-dose, and gilteritinib only was detected in the eyeballs at 3 days post-dose. The applicant explained that the above results indicated that gilteritinib binds to melanin.

Male albino rats received ^{14}C-gilteritinib 1 mg/kg QD orally for 4 weeks, and the tissue distribution of radioactivity was studied. Except for the stomach and small intestine, the tissue radioactivity concentrations after repeated dosing were higher than those on Day 1, and reached a steady state by Day 21. At 336 hours after the last dose, radioactivity was detected in all tissues, but not in blood or plasma.

4.2.2 Plasma protein binding and distribution in blood cells

The plasma from mouse, rat, rabbit, dog, monkey, and human was incubated with ^{14}C-gilteritinib (0.1-10 μg/mL) at 37°C for 16 hours, and the plasma protein binding of radioactivity was determined using an equilibrium dialysis method. The plasma protein binding of gilteritinib was 75.4% to 89.6% (mouse), 77.7% to 79.2% (rat), 75.5% to 78.7% (rabbit), 78.0% to 80.7% (dog), 81.3% to 82.4% (monkey), and 90.2% to 90.5% (human).

^{14}C-gilteritinib (0.1 μg/mL) was incubated with the following proteins at 37°C for 16 hours: human serum albumin (HSA) (40 mg/mL), α1-acid glycoprotein (AGP) (1 mg/mL), low-density lipoprotein (LDL) (3 mg/mL), high-density lipoprotein (HDL) (3 mg/mL), or γ-globulin (10 mg/mL). The binding of gilteritinib to the proteins was determined using an equilibrium dialysis method. The binding of gilteritinib to HSA, AGP, LDL, HDL, and γ- globulin was 68.8%, 33.4%, 28.9%, 41.1%, and 23.5%, respectively. The applicant explained that the above results indicated that gilteritinib binds primarily to HSA in human plasma.

Male rats and male dogs received a single oral dose of ^{14}C-gilteritinib 1 mg/kg, and radioactivity distribution in blood cells was determined. The blood to plasma radioactivity concentration ratios were 3.09 to 3.42 at 4 to 8 hours post-dose in rats and 2.1 to 2.7 at 1 to 48 hours post-dose in dogs, showing higher radioactivity levels in blood than in plasma.

4.2.3 Placental transfer to fetus

Pregnant rats received a single oral dose of ^{14}C-gilteritinib 1 mg/kg, and placental transfer of radioactivity to the fetus was determined. At 4 hours post-dose, the placental to maternal plasma radioactivity concentration ratio was 35.9, and the fetal to maternal plasma radioactivity concentration ratio was 1.06. The applicant explained that the above results indicated that gilteritinib and its metabolites cross the placenta into the fetus.

4.3 Metabolism

4.3.1 *In vitro*

Mouse, rat, rabbit, dog, monkey, and human liver microsomes or hepatocytes were incubated with ^{14}C-gilteritinib (10 μmol/L) in the presence or absence of NADPH at 37°C for 2 or 6 hours, and the metabolites of gilteritinib were identified. No human-specific metabolites were detected in either the liver microsomes or the hepatocytes. In human hepatocytes, metabolites formed via *N*-demethylation, oxidization, or hydrolysis of the glutathione conjugate were detected as primary metabolites. The applicant explained that the above results indicated that the major metabolic pathways of gilteritinib in human hepatocytes are *N*-demethylation, oxidation, and glutathione conjugation.

Microsomes prepared from insect cells expressing human CYP isoforms (CYP1A2, CYP1B1, CYP2A6, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, CYP2E1, CYP3A4, CYP3A5) were incubated with ^{14}C-gilteritinib (10 μmol/L) in the presence or absence of NADPH at 37°C for 2 hours, and CYP isoforms involved in the metabolism of gilteritinib were identified. In the presence of CYP3A4, 48.3% of gilteritinib remained. In the presence of other CYP isoforms, 99.4% to 103.4% of gilteritinib remained. The applicant explained that the above results showed that gilteritinib is metabolized primarily via CYP3A4 in humans.

4.3.2 *In vivo*

Male rats received a single oral dose of ^{14}C-gilteritinib 1 mg/kg, and its metabolites in plasma, urine, feces, and bile were identified. In the plasma collected at 4 hours post-dose from male rats, the unchanged drug and M1 (formed via oxidization) were mainly detected, accounting for 78.9% and 2.7%, respectively, of the total radioactivity in plasma. In the urine and feces collected up to 48 hours post-dose from male rats, the unchanged drug was mainly detected, representing 0.5% (urine) and 54.8% (feces) of the administered radioactivity. In the bile collected up to 48 hours post-dose, M5 (formed via glutathione conjugation of the oxane) and the unchanged drug were mainly detected, representing 7.3% and 5.7%, respectively, of the administered radioactivity.

Male dogs received a single oral dose of ^{14}C-gilteritinib 1 mg/kg, and its metabolites in plasma, urine, and feces were identified. In the plasma collected at 24 hours post-dose from male dogs, the unchanged drug was mainly detected, accounting for 68.4% of the total radioactivity in plasma. In the urine and feces collected up to 144 hours post-dose, the unchanged drug was mainly detected, representing 4.7% (urine) and 25.8% (feces) of the administered radioactivity.

4.4 Excretion

4.4.1 Urinary, fecal, and biliary excretion

Intact male rats and male dogs, and bile duct-cannulated male rats received a single oral dose of ^{14}C-gilteritinib 1 mg/kg, and the recoveries of radioactivity in urine, feces, and bile (the percentage of the administered radioactivity) were determined. In intact male rats, 1.4% and 89.9% of the administered radioactivity were recovered in urine and feces, respectively, over 168 hours. In male dogs, 9.5% and 88.1% of the administered radioactivity were recovered in urine and feces, respectively, over 504 hours. In bile duct-cannulated male rats,

8.6% and 29.3% of the administered radioactivity were recovered in urine and bile, respectively, over 48 hours. The applicant explained that the above results indicated that gilteritinib and its metabolites are excreted predominantly in feces via bile.

4.4.2 Enterohepatic circulation

Bile was collected from donor male rats that had received a single oral dose of ^{14}C-gilteritinib 1 mg/kg. The bile was then intraduodenally administered to bile duct-cannulated recipient male rats, and the recoveries of radioactivity in urine and bile were determined. Over 48 hours, 1.6% and 5.7% of radioactivity were recovered in urine and bile, respectively. The applicant explained that the above results indicated enterohepatic circulation of gilteritinib and its metabolites.

4.4.3 Excretion into milk

Lactating female rats received a single oral dose of ^{14}C-gilteritinib 1 mg/kg, and lacteal secretion of radioactivity was evaluated. The maximum milk concentration of radioactivity, observed at 4 hours post-dose, was 20.2 times higher than the plasma radioactivity concentration. The applicant explained that the above results indicated that gilteritinib and its metabolites are excreted in milk.

4.5 Pharmacokinetic interactions

4.5.1 Enzyme inhibition

Human liver microsomes were incubated with substrates for CYP isoforms (CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, CYP3A)[3] in the presence of gilteritinib (1-100 μmol/L) and NADPH, and the potential of gilteritinib to inhibit CYP isoforms was assessed. The IC_{50} values of gilteritinib for the inhibition of the metabolism of CYP2C19 and CYP3A substrates were both ≥61.7 μmol/L, indicating that gilteritinib is an inhibitor of these enzymes. On the other hand, gilteritinib did not cause evident inhibition of the metabolism of the substrates for other CYP isoforms tested. Gilteritinib did not cause time-dependent inhibition of any of the CYP isoforms tested. The applicant explained that given the above study results and the C_{max} after oral administration of gilteritinib 120 mg QD [1.23 μmol/L,[4] see Section 6.2.1.1], gilteritinib is unlikely to cause pharmacokinetic interactions via inhibition of CYP isoforms in clinical use.

4.5.2 Enzyme induction

Human hepatocytes were treated with gilteritinib (1-100 μmol/L) for 2 or 3 days, and the potential of gilteritinib to induce the mRNA expression or activities of CYP isoforms (CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP3A) was assessed. Gilteritinib caused no evident increases in CYP1A2 and CYP2C19 mRNA expression or CYP1A2 activity. While gilteritinib increased the mRNA levels of CYP2B6, CYP2C8, CYP2C9, and CYP3A4 and the activities of CYP2B6, CYP2C8, CYP2C9, CYP2C19, and CYP3A, the increases in the mRNA levels and activities of the CYP isoforms were not concentration-dependent or consistent among human

[3] The following substrates were used: phenacetin (CYP1A2), bupropion (CYP2B6), paclitaxel (CYP2C8), diclofenac (CYP2C9), S-mephenytoin (CYP2C19), dextromethorphan (CYP2D6), midazolam (CYP3A), and testosterone (CYP3A).
[4] Expressed as median.

hepatocyte donors. The applicant explained that the above results indicated that gilteritinib is unlikely to cause pharmacokinetic interactions via induction of CYP isoforms in clinical use.

4.5.3 Transporters

The applicant's explanation about transporter-mediated pharmacokinetic interactions with gilteritinib:

The results of the following studies showed that gilteritinib is a substrate of P-glycoprotein (P-gp), but not a substrate of breast cancer resistance protein (BCRP), organic anion transporting polypeptide 1B1 (OATP1B1), OATP1B3, or organic cation transporter 1 (OCT1).

- P-gp- or BCRP-mediated transport of ^{14}C-gilteritinib (5 μmol/L) was investigated using the pig kidney LLC-PK1 cell lines expressing human P-gp or BCRP. The ratio of the efflux ratio of ^{14}C-gilteritinib in the P-gp-expressing cell line to the efflux ratio in the parental cell line, was 2.6 in the absence of a P-gp inhibitor, 0.9 in the presence of verapamil 30 μmol/L (a P-gp inhibitor), and 0.8 in the presence of ketoconazole 10 μmol/L (a P-gp inhibitor). The ratio of the efflux ratio of ^{14}C-gilteritinib in the BCRP-expressing cell line to the efflux ratio in the parental cell line was 1.4.
- Transporter-mediated transport of ^{14}C-gilteritinib (5 μmol/L) was investigated using the HEK293 cell lines expressing human OATP1B1, OATP1B3, or OCT1. The ratio of the uptake of ^{14}C-gilteritinib in the OATP1B1-, OATP1B3-, or OCT1-expressing cell line to the uptake in the parental cell line was 0.782 to 0.899, 0.803 to 0.904, and 0.885 to 1.06, respectively.

Given the results of the following studies and the C_{max} of gilteritinib after oral administration of gilteritinib 120 mg QD [1.23 μmol/L,[4)] see Section 6.2.1.1], gilteritinib has the potential to cause pharmacokinetic interactions via inhibition of BCRP, multidrug and toxin extrusion 1 (MATE1), and OCT1 in clinical use. Moreover, taking account of the estimated gilteritinib concentration in the gastrointestinal tract after administration of gilteritinib 120 mg (868 μmol/L), gilteritinib has the potential to cause pharmacokinetic interactions via inhibition of P-gp in the gastrointestinal tract, in clinical use.

- The potential of gilteritinib (1-100 μmol/L)[5)] to inhibit P-gp-mediated transport of ^{3}H-digoxin (1 μmol/L) was assessed using LLC-PK1 cells expressing human P-gp. The IC_{50} value of gilteritinib for the inhibition of P-gp-mediated transport was >30 μmol/L. Gilteritinib 30 μmol/L inhibited P-gp-mediated transport by 33%.
- The potential of gilteritinib (0.1-10 μmol/L) to inhibit BCRP-mediated uptake of ^{3}H-methotrexate (100 μmol/L) in the membrane vesicles was assessed using the membrane vesicles from the Sf9 insect cell line expressing human BCRP. The IC_{50} value of gilteritinib for the inhibition of BCRP-mediated uptake was 1.41 μmol/L, indicating that gilteritinib is an inhibitor of BCRP.
- The potential of gilteritinib (0.003-3 μmol/L or 0.3-50 μmol/L, respectively) to inhibit MATE1- or MATE2-K-mediated transport of their substrate[6)] was assessed using HEK293 cells expressing human MATE1 or MATE2-K. The IC_{50} values of gilteritinib for MATE1- or MATE2-K-mediated transport were 0.0543 and 47.7 μmol/L, respectively, indicating that gilteritinib is an inhibitor of these transporters.

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5) As a cytotoxic effect was suggested at 50 and 100 μmol/L of gilteritinib, these concentrations were not used for calculation of the IC_{50} value.

6) ^{14}C-metformin 20 μmol/L was used as a substrate for MATE1 and ^{14}C-metformin 5 μmol/L for MATE2-K.

- The potential of gilteritinib (0.3-50 μmol/L) to inhibit OATP1B1-, OATP1B3-, or OCT1-mediated transport of their substrates[7)] was assessed using HEK293 cells expressing human OATP1B1, OATP1B3, or OCT1. The IC_{50} values of gilteritinib for OATP1B1- and OCT1-mediated transport were 29.4 and 2.92 μmol/L, respectively, indicating that gilteritinib is an inhibitor of these transporters. On the other hand, gilteritinib did not cause evident inhibition of OATP1B3-mediated transport.
- The potential of gilteritinib (0.3-50 μmol/L) to inhibit OAT1-, OAT3-, or OCT2-mediated transport of their substrates[8)] was assessed using HEK293 cells expressing human OAT1, OAT3, or OCT2. Gilteritinib caused no evident inhibition of OAT1- or OAT3-mediated transport. On the other hand, the IC_{50} value of gilteritinib for OCT2-mediated transport was 34.9 μmol/L, indicating that gilteritinib is an inhibitor of this transporter.

4.R Outline of the review conducted by PMDA

Based on the submitted data and the following considerations, PMDA concluded that the applicant's discussion on the absorption, distribution, metabolism, excretion, and pharmacokinetic interactions of gilteritinib is acceptable.

4.R.1 Tissue distribution

A study in rats suggested that gilteritinib bound to melanin [see Section 4.2.1]. PMDA asked the applicant to explain the safety of gilteritinib in melanin-containing tissues.

The applicant's response:

The results of a tissue distribution study in pigmented rats indicated that gilteritinib may accumulate in melanin-containing tissues after repeated dosing at the proposed dosage. However, the following findings suggest that the distribution of gilteritinib in melanin-containing tissues is unlikely to cause safety issues in clinical use.

- The following findings were obtained from 4- and 13-week repeated oral dose toxicity studies in dogs.
  - Ocular toxicity findings were observed, but resolved after the end of dosing. These findings were considered reversible.
  - Toxicity findings such as erosion and ulcer were noted in melanin-containing epithelia (skin), and similar toxicity findings were observed also in non-melanin containing epithelia (oral mucosa and lacrimal gland). The incidence of toxicities in the epithelia did not clearly differ according to the presence or absence of melanin.
- In a global phase III study (Study 0301), the incidence of Grade ≥3 eye disorders was 1.8% (3 of 168 subjects) and the incidence of Grade ≥3 skin and subcutaneous tissue disorders was 6.5% (11 of 168 subjects). A causal relationship to gilteritinib was ruled out for most of the events. In the study, subjects underwent periodic ophthalmologic examination, which revealed no clinically relevant ophthalmologic findings.

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7) ^{3}H-estradiol 17β-D-glucuronide was used as a substrate for OATP1B1 and OATP1B3 (0.05 μmol/L for both OATP1B1 and OATP1B3) and ^{14}C-metformin (10 μmol/L) for OCT1.

8) ^{3}H-*p*-aminohippuric acid (1 μmol/L) was used as a substrate for OAT1, ^{3}H-estrone-3-sulfate (0.01 μmol/L) for OAT3, and ^{14}C-metformin (5 μmol/L) for OCT2.

PMDA's discussion:
PMDA accepted the applicant's explanation. PMDA's conclusions on eye disorders associated with gilteritinib are described in Section 5.R.1 (based on the ocular toxicity findings observed in toxicity studies) and Section 7.R.4 (based on the incidence of eye disorders in clinical studies).

4.R.2 Pharmacokinetic interactions

The applicant's explanation:
In vitro studies suggested that gilteritinib inhibits P-gp, BCRP, and OCT1 [see Section 4.5.3], but a global phase III study (Study 0301) raised no particular safety concerns about coadministration with P-gp, BCRP, or OCT1 substrates, etc. This means that coadministration of gilteritinib with these drugs is unlikely to cause a problem in clinical use. Pharmacokinetic interaction studies have suggested that gilteritinib was a P-gp substrate and an inhibitor of MATE1 [see Section 4.5.3] (see Section "6.2.3 Drug interaction studies.").

PMDA's discussion:
PMDA largely accepted the applicant's explanation. However, as the information on gilteritinib pharmacokinetic interactions via inhibition of P-gp, BCRP, and OCT1 is important for the proper use of gilteritinib, the applicant should continue to collect relevant information and appropriately provide any beneficial information to healthcare professionals in clinical practice.

5. Toxicity and Outline of the Review Conducted by PMDA

In this section, the doses and concentrations of gilteritinib are expressed as free base. The applicant submitted results from toxicity studies of gilteritinib: single-dose toxicity, repeated-dose toxicity, genotoxicity, reproductive and developmental toxicity, and other toxicity studies (an *in vitro* phototoxicity study, toxicity studies on impurity).

In *in vivo* studies, 0.5% methylcellulose aqueous solution was used as vehicle.

5.1 Single-dose toxicity

A single oral dose toxicity study was conducted in rats. The acute toxicity of gilteritinib was assessed based on the findings after the first dose in a 4-week repeated oral dose toxicity study in dogs (Table 11).

Table 11. Single-dose toxicity studies

Test system	Route of administration	Dose (mg/kg)	Principal findings	Approximate lethal dose (mg/kg)	Attached document CTD
Male and female Sprague-Dawley rats	Oral	100, 300	Deaths or moribund sacrifices: 300 (9 of 10 animals), sparse fur, hypothermia, cecal lymphoid follicles/thymic lymphocyte necrosis, thymic hemorrhage, erosion in the forestomach, gastrointestinal hemorrhage, inflammatory cell infiltration/mucosal epithelial vacuolation in the duodenum, anterior chamber hemorrhage ≥100: no feces, reduced feces, black stools, positive fecal occult blood, decreased body weight, decreased food consumption 300: decreased spontaneous locomotor activity, pallor	300	4.2.3.1-1
Male dogs (Beagle)	Oral	0, 1, 2.5, 5, 10, 100, 1000	Acute toxicity was assessed in a 4-week repeated oral dose toxicity study. Deaths or moribund sacrifices: 1000 (6 of 7 animals),[a)] vomiting, diarrhea, red stools, decreased spontaneous locomotor activity, decreased/no response, lateral position, prone position, gasping respiration, pale oral mucosa, gastrointestinal hemorrhage, lymphocyte necrosis in the thymus/submandibular lymph nodes/mesenteric lymph nodes/Peyer's patches	1000	4.2.3.2-5

a) After 2 days of dosing, subsequent dosing was discontinued.

5.2 Repeated-dose toxicity

Repeated oral dose toxicity studies in rats (13 weeks) and dogs (4 and 13 weeks) were conducted (Tables 12-14). In both rats and dogs, the primary target organs/tissues of toxicity identified were the lymphoid organs/tissues, bone marrow, lung, gastrointestinal tract, liver, kidney, eye, and epithelial tissue (dogs only). The following are pharmacokinetic parameters at the lowest observed adverse effect level (LOAEL) (2.5 mg/kg/day) and at the no observed adverse effect level (NOAEL) (1 mg/kg/day) in the 13-week repeated oral dose toxicity studies in rats and dogs:

C_{max} at LOAEL in rats: 32.48 to 32.99 ng/mL (0.05 times the human exposure[9)])

C_{max} at NOAEL in dogs: 23.95 to 24.24 ng/mL (0.04 times the human exposure)

AUC_{24h} at LOAEL in rats: 422.54 to 440.32 ng·h/mL (0.03 times the human exposure)

AUC_{24h} at NOAEL in dogs: 388.83 to 400.44 ng·h/mL (0.03 times the human exposure)

9) In Study 0102 in Japanese patients with AML, the C_{max} and AUC_{24h} (n = 2, individual values) following repeated administration of gilteritinib 120 mg/day were 668.89 and 691.57 ng/mL (C_{max}) and 13,151.21 and 13,775.49 ng·h/mL (AUC_{24h}).

Table 12. The 13-week repeated-dose toxicity study in rats

Test system	Route of administration	Duration of dosing	Dose (mg/kg/day)	Principal findings	NOAEL (mg/kg/day)	Attached document CTD
Male and female Sprague-Dawley rats	Oral	13 weeks (once daily) + 4-week recovery period	0, 2.5, 5, 10, 20	Deaths: 20 (1 of 10 females in the main study, 1 of 9 males in the satellite group[a]), hypothermia, pallor, slow respiration, lacrimation, red urine, white foci in the kidney, red left auricle, inflammation of the left atrial myocardium/endocardium, bacterial thrombi in the left ventricle, lymphocyte necrosis in submandibular lymph nodes, pulmonary congestion/edema/hemorrhage, microvacuolation of the duodenal mucosal epithelium, bacterial colonies in the cecum/kidney, Kupffer cell hypertrophy/vacuolation of the intermediate zone in the liver, tubular necrosis/neutrophil infiltration/pyogenic inflammation in the kidney, adrenal congestion/hypertrophy of adrenal zona fasciculata cells ≥2.5: decreased body weight, decreased body weight gain, decreased leukocyte count/lymphocyte count, decreased γ-globulin fraction, decreased spleen weight ≥5: decreased food consumption, increased red blood cell count, decreased MCV/MCH, increased β-globulin fraction, decreased albumin to globulin ratio, decreased pituitary weight, sinusoidal dilatation in the spleen, lymphocyte necrosis in Peyer's patches, micro-granulomas in mesenteric lymph nodes ≥10: increased AST/ALT, decreased albumin fraction, decreased urinary excretion of Na/K/Cl, increased lung weight, decreased thymic weight, thymic atrophy, accumulation of foam cells in the lung (phospholipidosis),[b] microvacuolation of the ileal/cecal mucosal epithelium 20: decreased spontaneous locomotor activity, reduced feces, anterior capsule opacification, increased neutrophil count, decreases in eosinophil count/basophil count/large unstained cell count, decreases in blood triglycerides/Cl/albumin, increased α-globulin fraction, decreased urine pH, positive urine occult blood, increased incidence of positive urine glucose, decreased incidence of positive urine ketone bodies, increased urine volume, white foci in the lung, increased kidney weight, decreased sternal marrow/femoral marrow cellularity, thymic lymphocyte necrosis, atrophy of the splenic white pulp, micro-granulomas in the spleen/submandibular lymph nodes, lymphoid follicle atrophy in mesenteric lymph nodes, vasodilation in the pancreatic islets, renal tubular basophilic alterations/hyaline droplet/hyalin cast/edematous change in the papilla/increased mesangial matrix/medullary tubular vacuolation (phospholipidosis),[b] inflammatory cell infiltration in the choroid/ciliary body/iris/conjunctiva in the eye These findings were reversible.	<2.5	4.2.3.2-3

a) The cause of death was determined to be bacterial infection due to deterioration of general condition.
b) Electron microscopy revealed lamellar bodies in alveolar macrophages and the collecting ducts of the kidney. These findings were reversible etc., and were therefore not considered to pose a serious concern for humans.

Table 13. The 4-week repeated dose toxicity study in dogs

Test system	Route of administration	Duration of dosing	Dose (mg/kg/day)	Principal findings	NOAEL (mg/kg/day)	Attached document CTD
Male and female beagle dogs[a)]	Oral	4 weeks (once daily)[b)] + 4-week recovery period[c)]	0, 1, 10, 100, 1000 + 0, 1, 2.5, 5[d)]	Deaths or moribund sacrifices[e)]: 10 (1 of 4 males in the main study), 100 (7 of 7 males in the main study), 1000 (6 of 7 males in the main study), decreased food consumption, soft stools, decreased spontaneous locomotor activity, decreased/no response, prone position, lateral position, gasping respiration, pale oral mucosa/oral mucosal ulcer, increased red blood cell parameters, decreases in platelet count/lymphocyte count/eosinophil count, increases in leukocyte count/basophil count/large unstained cell count, increased activated partial thromboplastin time (APTT), increases in ALT/γ-GTP/triglycerides/glucose/creatinine/urea nitrogen, decreases in Na/K/Cl/total protein, decreased sternal marrow/femoral marrow cellularity, lymphocyte necrosis in the thymus/Peyer's patches, congestion in the thymus/submandibular lymph nodes/mesenteric lymph nodes, accumulation of foam cells/neutrophil infiltration/congestion/hemorrhage/edema in the lung, gastrointestinal hemorrhage, mucosal hemorrhage in the gallbladder, adrenal congestion, degeneration and necrosis of germ cells/multinucleated giant cell formation in the testis, single cell necrosis of the epithelia of the epididymal head, neutrophil infiltration in the ciliary body/cornea, hemorrhage/ulcer in the iris/cornea, oral mucosal ulcer ≥2.5: decreased body weight, positive fecal occult blood, increased platelet count, increases in AST/ALP/globulin/α_2-globulin fraction/γ-globulin fraction, decreases in total bilirubin/albumin/albumin to globulin ratio/albumin fraction/inorganic phosphate/Ca, thymic atrophy, lymphocyte necrosis in mesenteric lymph nodes 5: diarrhea, red stools, vomiting, abnormal color of the ocular fundus, focal hyperreflective changes between the outer limiting membrane and retinal pigment epithelium, positive urine occult blood, erythrocytes in urine sediment, increased urine protein, increased neutrophil count, increases in β-globulin fraction/phospholipids/total cholesterol, decreased thymic weight, lymphocyte necrosis in submandibular lymph nodes, increased foam cells in Peyer's patches, hypertrophy of/increases in goblet cells in the ileum/colon/rectum, hypertrophy of the duodenal mucosal epithelium These findings were reversible. (The reversibility of increases in phospholipids and cholesterol and erythrocytes in urine sediment was not evaluated.)	1	4.2.3.2-5

a) Only males were used in the original dose groups.
b) All animals in the original 10 to 1000 mg/kg groups were necropsied by Day 12, except for 1 animal that received gilteritinib at 1000 mg/kg/day for 2 days and then underwent a 4-week recovery period.
c) A recovery period was scheduled for animals in the 2.5 and 5 mg/kg/day groups only.
d) Additional dose groups were included because serious toxicities occurred in the early phase of dosing and the duration of dosing was less than 4 weeks at ≥10 mg/kg.
e) The cause of death was determined to be deterioration of general condition due to gastrointestinal hemorrhage.

Table 14. The 13-week repeated-dose toxicity study in dogs

Test system	Route of administration	Duration of dosing	Dose (mg/kg/day)	Principal findings	NOAEL (mg/kg/day)	Attached document CTD
Male and female beagle dogs	Oral	13 weeks (once daily) + 4-week recovery period[a)]	0, 1, 2.5, 5	Death or moribund sacrifice[b)]: 5 (2 of 4 males in the main study), gingival ulcer, pale oral mucosa, nasal bleeding, increased body temperature, tachypnea, decreased spontaneous locomotor activity, lateral position, salivation, decreased/no response, increased basophil count, decreased platelet count/eosinophil count, increases in triglycerides/urea nitrogen/α1-globulin fraction/α2-globulin fraction, decreased potassium, red foamy fluid retention in the trachea/bronchus, consolidation of the lung, pleural effusion, red foci in the gallbladder mucosa/serosa, footpad induration, decreased nucleated cell count in the bone marrow, increased lung/kidney weights, decreased spleen weight, cellular debris in the bronchus, decreased lymphocytes in the splenic white pulp/mesenteric lymph nodes, decreased sternal marrow/femoral marrow cellularity, oral mucosal acanthosis, distal renal tubular dilatation, focal hemorrhage in the gallbladder serosa, acanthosis/crusts on the footpads ≥2.5: erosion in footpads, positive fecal occult blood, increased neutrophil count/platelet count, increased APTT, increases in AST/ALP/globulin/total protein/β-globulin fraction/γ-globulin fraction, decreases in albumin/albumin to globulin ratio/albumin fraction, red foci/white foci/edema/interstitial fibrosis/inflammatory cell infiltration/alveolar epithelial hypertrophy and hyperplasia/alveolar fibrin-like material deposition/focal hemorrhage in the lung, inflammation of the alveolus/gingiva 5: oral mucosal/skin erosion, swelling of the cheek/neck, decreased body weight, decreased food consumption, abnormal color of the ocular fundus, focal hyperreflective changes between the outer limiting membrane and retinal pigment epithelium/in the outer nuclear layer, focal thinning of the outer nuclear layer, positive urine occult blood, increased incidences of positive erythrocytes in urine sediment/positive urine glucose/positive urine ketone bodies, increases in urine protein/urinary excretion of Na, decreased red blood cell parameters, increases in reticulocyte ratio/leukocyte count/monocyte count/large unstained cell count, decreased lymphocyte count, decreases in inorganic phosphate/total bilirubin/glucose/Ca, increased liver/kidney weights, red foci in the renal medulla, recessed area in the oral mucosa, thymic atrophy, decreased lymphocytes in Peyer's patches, lymphocyte necrosis in submandibular lymph nodes, congestion in the spleen, hepatocellular vacuolation/hepatocellular atrophy/hemosiderin deposition in Kupffer cells/perivascular mononuclear cell infiltration in the liver, mucosal hypertrophy/increased mucus secretion in the gallbladder, decreased zymogen granules in the pancreas, renal medullary and pelvic inflammatory cell infiltration/regenerated tubule/focal congestion in the medulla/vacuolation of the renal tubule in the corticomedullary junction, vacuolation of bladder transitional epithelial cells, vacuolation in the rod-cone layer/the outer nuclear layer of the retina, atrophy of the lacrimal gland, ulcer/inflammation/acanthosis/crusts of the skin, ulcer/inflammation in the oral mucosa/footpads These findings were reversible. (The reversibility of positive urine glucose, increased large unstained cell count, and decreases in lymphocyte count and blood glucose was not evaluated.)	1	4.2.3.2-6

a) A recovery period was scheduled for animals in the 2.5 and 5 mg/kg/day groups only.
b) The cause of death was determined to be lung disorder and deterioration of general condition.

5.3 Genotoxicity

The applicant performed an *in vitro* bacterial reverse mutation assay, an *in vitro* chromosomal aberration assay using cultured mammalian cells, and an *in vivo* rodent micronucleus assay (Table 15). The rodent micronucleus assay was positive, and gilteritinib was considered to be clastogenic. In the rodent micronucleus assay, AUC_{24h} at the highest dose without micronucleus induction (20 mg/kg/day) was 4250.55-4409.43 ng·h/mL, which was 0.3 times the human exposure.[9)]

Table 15. Genotoxicity studies

Type of study		Test system	Metabolic activation (Treatment)	Concentration (μg/plate or μg/mL) or dose (mg/kg/day)	Test result	Attached document CTD
In vitro	Bacterial reverse mutation assay	*Salmonella typhimurium*: TA98, TA100, TA1535, TA1537	S9−/+	0, 156, 313, 625, 1250, 2500, 5000	Negative	4.2.3.3.1-3
		Escherichia coli: WP2*uvrA*	S9−/+			
	Chromosomal aberration assay using cultured mammalian cells	Chinese hamster lung (CHL) cells	S9− (6, 24 hours)	6 hours: 0, 0.371, 0.667, 1.20, 2.16 24 hours: 0, 0.0988, 0.222, 0.333, 0.5	Negative	4.2.3.3.1-5
			S9+ (6 hours)	0, 0.667, 1.20, 2.16, 3.89		
In vivo	Rodent micronucleus assay	Male and female mice (CD1) bone marrow		0, 20, 65, 200 (2 days/oral)	Positive for ≥65	4.2.3.3.2-2

5.4 Carcinogenicity

The applicant did not conduct carcinogenicity studies because gilteritinib is an anti-neoplastic drug intended to treat patients with advanced cancer.

5.5 Reproductive and developmental toxicity

The applicant did not conduct a study of fertility and early embryonic development to implantation for gilteritinib because the drug is an anti-neoplastic agent intended to treat patients with advanced cancer.

With respect to the effects of gilteritinib on fertility and early embryonic development to implantation, the applicant explained that gilteritinib is unlikely to affect fertility for the following reasons.

- There were no gilteritinib-related effects on the male and female reproductive organs in 13-week repeated oral dose toxicity studies in rats and dogs.
- In a 4-week repeated oral dose toxicity study in dogs, animals receiving ≥10 mg/kg/day showed the degeneration and necrosis of germ cells and multinucleated giant cell formation in the testis, and single cell necrosis of the epithelia of the epididymal head. These changes were considered secondary to the deterioration of general condition, because death, moribundity, etc. also occurred in animals receiving ≥10 mg/kg/day.

An embryo-fetal development study was conducted in rats (Table 16). Increased post-implantation loss, teratogenicity, etc. were observed. The C_{max} and AUC_{24h} at the NOAEL for maternal and embryo-fetal toxicity (10 mg/kg/day) were 119 ng/mL and 1610 ng·h/mL, respectively, which were 0.2 and 0.1 times the human exposure,[9] respectively.

Table 16. Reproductive and developmental toxicity study

Type of study	Test system	Route of administration	Duration of dosing	Dose (mg/kg/day)	Principal findings	NOAEL (mg/kg/day)	Attached document CTD
Embryo-fetal development	Female Sprague-Dawley rats	Oral	Gestation days 7-17 (once daily)	0, 0.3, 3, 10, 30	Dams: 30: decreased body weight/food consumption Embryo/fetus: 30: increased post-implantation loss, decreases in fetal weight/placental weight, decreased numbers of ossification sites (sternebrae/sacral and caudal vertebrae), anasarca, local edema, exencephaly, cleft lip, cleft palate, short tail, umbilical hernia, microphthalmia, enlarged atrial chamber, enlarged ventricular chamber, membranous ventricular septal defect, hypoplastic right ventricle, absent kidney, fused kidney, abnormal revolution kidney, malpositioned kidney, misshapen kidney, small kidney, malpositioned adrenal gland, malpositioned ovary, sternoschisis, absent rib, fused rib, fused cervical arch, misaligned cervical vertebra, absent thoracic vertebra, visceral/skeletal variations	Dams: 10 Embryo /fetus: 10	4.2.3.5.2-2

5.6 Other toxicity studies

5.6.1 Photosafety

An *in vitro* phototoxicity study using a mouse fibroblast cell line was conducted (Table 17). Gilteritinib was not phototoxic.

Table 17. Photosafety study

Type of study	Test system	Test method	Principal findings	Attached document CTD
In vitro phototoxicity study	Mouse fibroblast cell line Balb/c 3T3	0, 9.49, 13.3, 18.6, 26.0, 36.4, 51.0, 71.4, 100 µg/mL UV-A irradiation	Not phototoxic (photo irritation factor, 1.018)	4.2.3.7.7-1

5.6.2 Toxicity studies on impurity

The drug substance contains Related Substance A (an impurity) and its acceptance criteria exceed the qualification threshold specified in "Revision of the Guideline on Impurities in New Drug Substances (PMSB/ELD Notification No.1216001, dated December 16, 2002)." The applicant conducted a 4-week repeated oral dose toxicity study in rats, a bacterial reverse mutation assay, and a chromosomal aberration assay using cultured mammalian cells for Related Substance A. These studies demonstrated the safety of Related Substance A in the drug substance (Tables 18 and 19).

Table 18. General toxicity study on impurity

Test system	Route of administration	Duration of dosing	Dose (mg/kg/day)	Principal findings	NOAEL (mg/kg/day)	Attached document CTD
Male and female Sprague-Dawley rats	Oral	4 weeks	0, [redacted], [redacted], [redacted]	No toxic signs	[redacted]	4.2.3.7.6-1

Table 19. Genotoxicity studies on impurity

Type of study		Test system	Metabolic activation (Treatment)	Concentration (μg/plate or μg/mL)	Test result	Attached document CTD
In vitro	Bacterial reverse mutation assay	*Salmonella typhimurium*: TA98, TA100, TA1535, TA1537	S9−	TA100, TA1535, TA1537: 0, 39.1, 78.1, 156, 313, 625, 1250, 2500 TA98: 0, 78.1, 156, 313, 625, 1250, 2500, 5000	Negative	4.2.3.7.6-2
			S9+	0, 19.5, 39.1, 78.1, 156, 313, 625		
		Escherichia coli: WP2*uvrA*	S9−	0, 78.1, 156, 313, 625, 1250, 2500, 5000		
			S9+	0, 19.5, 39.1, 78.1, 156, 313, 625		
	Chromosomal aberration assay using cultured mammalian cells	CHL cells	S9− (6, 24 hours)	6 hours: 0, 2.5, 3, 3.5, 4 24 hours: 0, 2, 2.5, 3, 3.5	Negative	4.2.3.7.6-3
			S9+ (6 hours)	0, 2.5, 3, 3.5, 4		

5.R Outline of the review conducted by PMDA

Based on the submitted data and the following considerations, PMDA concluded that there is no problem with the clinical use of gilteritinib from a non-clinical toxicological perspective.

5.R.1 Effects on eye

Ocular findings were observed in repeated oral dose toxicity studies in dogs [see Section 5.2]. PMDA asked the applicant to discuss whether these findings are relevant to humans using gilteritinib in clinical practice.

The applicant's response:

The following study results suggest that the ocular effects observed in the repeated-dose toxicity studies in dogs are probably irrelevant to humans using gilteritinib.

- In a 13-week repeated oral dose toxicity study in dogs, abnormal color of the ocular fundus and hyperreflective changes between the outer limiting membrane and retinal pigment epithelium were observed at Week 4, and the number of animals with these findings increased thereafter. Hyperreflective changes in the outer nuclear layer, focal thinning of the outer nuclear layer, and histopathological findings in the retina were also noted at Week 13 (these findings were not observed following 4 weeks of dosing). However, there was no clear trend towards worsening of the observed findings with prolonged duration of dosing, and these findings were reversible following the end of dosing. Visual reaction test and walk test revealed no abnormalities.
- The dog to human exposure ratios (C_{max} and AUC) at the dose level causing ocular findings in the repeated oral dose toxicity studies in dogs were both <1, but no clinically relevant ophthalmic findings associated with gilteritinib were reported in clinical studies [see Section 7.R.4].

PMDA's discussion:

PMDA largely accepted the applicant's explanation. However, taking account of the following points, it is difficult to draw a definitive conclusion on the effects of gilteritinib on the eye at present. Thus, healthcare professionals in clinical practice should appropriately be informed of the findings from the repeated oral dose toxicity studies in dogs, via package insert etc.

- The dog to human exposure ratios at the dose level causing ocular toxicity were <1.
- The incidence of ocular toxicity increased with increasing duration of dosing.
- The 13-week repeated oral dose toxicity study revealed new histopathological findings in the retina that had not been observed after 4 weeks of dosing, and no toxicity data are available from animals treated for >13 weeks. This means that prolonged treatment with gilteritinib may result in more serious effects on the retina.

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

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

The applicant's response:

Gilteritinib was genotoxic in a mouse micronucleus assay [see Section 5.3] and an embryo-fetal development study in rats demonstrated embryo-fetal toxicity [see Section 5.5]. This suggests that gilteritinib taken by pregnant women or women who may be pregnant, may affect their fetuses. The use of gilteritinib is thus not recommended to pregnant women or women who may be pregnant. However, because *FLT3* mutation-positive AML has a very poor prognosis with limited treatment options, pregnant women or women who may be pregnant should be allowed to use gilteritinib only when its therapeutic benefits are expected to outweigh its risks, as long as the women and their physicians fully understand the potential fetal risks associated with gilteritinib. The package insert will include precautionary statements about the potential fetal risks associated with gilteritinib.

PMDA's discussion:

PMDA largely accepted the applicant's explanation. However, prior to the use of gilteritinib in pregnant women or women who may be pregnant, the patient or their family should appropriately be informed of the genotoxicity and reproductive and developmental toxicity of gilteritinib.

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

6.1 Summary of biopharmaceutic studies and associated analytical methods

The oral formulations of gilteritinib, the clinical trial formulations (10-, 40-, and 100-mg tablets) and the proposed commercial formulation (40-mg tablets) are available. The PK etc. of gilteritinib were studied using these formulations (Table 20).

Table 20. Formulations used in clinical studies

Formulation	Study ID
Clinical trial formulations (10, 40, and 100 mg)	Japanese phase I study (Study 0102[*]), Japanese phase Ib/II study (Study 5101[*]), foreign phase I studies (Studies 0110[*], 0105[*], 0106[*], and 0108[*]), foreign phase I/II study (Study 0101[*])
Proposed commercial formulation (40 mg)	Foreign phase I studies (Studies 0110 and 0113), global phase III study (Study 0301)

*1: The 10- and 100-mg tablets were used. *2: The 40-mg tablets were used. *3: The 10-mg tablets were used. *4: The 10-, 40-, and 100-mg tablets were used.

6.1.1 Analytical method

Invivoscribe Technologies, Inc.'s "LeukoStrat CDx *FLT3* Mutation Assay" was used for *FLT3* mutation testing in Study 0301. LabPMM G.K. submitted a marketing application for an *in vitro* diagnostic, "LeukoStrat CDx *FLT3* Mutation Assay," as an aid in identifying AML patients eligible for treatment with gilteritinib, as of April 27, 2018.

6.1.2 Assay

Gilteritinib in human (a) plasma and (b) urine was quantified by liquid chromatography/tandem mass spectrometry (LC-MS/MS), and the lower limits of quantification were (a) 0.1,[10] 0.5,[11] and 10[12] ng/mL, and (b) 0.5 ng/mL.

6.1.3 Food effect study (CTD 5.3.1.1-1, Study 0113 [January 2017 to March 2017])

An open-label, randomized study was conducted in 32 healthy adults (32 subjects included in PK analysis) to assess the effect of food on the PK of gilteritinib. Gilteritinib 40 mg was orally administered under fasting conditions[13] or 30 minutes after a high-fat meal (approximately 800-1000 total calories with 500-600 fat calories), and plasma gilteritinib concentrations were determined. The median t_{max} of gilteritinib was 6.00 hours after administration under fasting conditions and 7.98 hours after administration with a high-fat meal. The geometric least-squares mean ratios (fed vs. fasted) of the C_{max} and AUC_{inf} of gilteritinib were 0.740 [90% CI: 0.622, 0.881] and 0.938 [90% CI: 0.812, 1.084], respectively.

The applicant's explanation about the effect of food on the PK of gilteritinib, based on the above results:
There is a possibility that a high-fat meal decreased the gastric emptying rate, resulting in delayed t_{max} and decreased C_{max}. However, since there was no clear relationship between the C_{max} of gilteritinib and efficacy/safety [see Section 6.2.7], a decrease in the C_{max} following administration of gilteritinib with food is unlikely to pose a problem in clinical use, and gilteritinib can be taken without regard to meals.

6.1.4 Effect of gastric pH on PK of gilteritinib

The applicant's explanation:
The PK of gilteritinib is unlikely to be affected by an increase in gastric pH associated with low gastric acid levels, the use of proton pump inhibitors, and other conditions, for the following reasons:

- Although the solubility of gilteritinib decreased with increasing pH, the solubility of gilteritinib was ≥82 mg/mL over the pH range of 1 to 5. Even if gilteritinib is administered at the maximum proposed dose of 200 mg, gilteritinib should dissolve from the tablets within the stomach.
- In a global phase III study (Study 0301) etc., the efficacy and safety of gilteritinib did not tend to differ clearly between patients receiving and not receiving concomitant drugs affecting gastric pH.

10) Samples from Studies 0106, 0108, 0110, and 0113 were analyzed.
11) Samples from Studies 0101, 0102, and 5101 were analyzed.
12) Samples from Studies 0101, 0105, and 0301 were analyzed.
13) Subjects fasted for ≥10 hours (overnight) before administration and for ≥4 hours after administration.

6.2 Clinical pharmacology

The PK of gilteritinib alone or in combination with itraconazole, fluconazole, or rifampicin were studied in healthy adults and patients with cancer. The effects of gilteritinib on the PK of midazolam or cephalexin were assessed.

6.2.1 Japanese clinical studies

6.2.1.1 Japanese phase I study (CTD 5.3.5.2-2, Study 0102 [June 2014 to June 27, 2016])

An open-label, uncontrolled study was conducted in 24 patients with relapsed or refractory AML (24 subjects included in PK analysis) to assess the safety, PK, etc. of gilteritinib. Subjects received a single oral dose of gilteritinib 20, 40, 80, 120, 200, or 300 mg, followed by a 2-day observation period (the single-dose phase). The subjects then received oral gilteritinib QD at the same dose that they were taking during the single-dose phase, in 28-day cycles (the repeated-dose phase). Plasma and urine gilteritinib concentrations were determined.

The PK parameters of gilteritinib are shown in Table 21. The accumulation indices[14)] after repeated dosing of 80 to 200 mg of gilteritinib were 5.97 to 8.10. According to the applicant, the plasma trough concentrations after Day 15 were almost constant, suggesting that gilteritinib concentration generally reaches a steady state by Day 15.

Across all dose levels, ≤3.64% of administered dose was excreted unchanged in urine after a single dose, and ≤13.11% on Day 28 of the repeated-dose phase.

14) The ratio of AUC_{tau} after repeated dosing to AUC_{24h} after single dosing

Table 21. PK parameters of gilteritinib

Dose (mg)	n	Sampling day	C_{max} (ng/mL)	t_{max}*1 (h)	AUC_{24h} (ng·h/mL)	$t_{1/2}$*2 (h)	CL/F (L/h)
20	1	Cycle 1 Day −2	15.32	2.08	241.65	—	—
	1	Cycle 1 Day 28	70.53	6.15	1345.53	84.04	14.86
40	4	Cycle 1 Day −2	29.81 ± 13.56	4.01 (3.88, 4.08)	435.59 ± 167.16	—	—
	3	Cycle 1 Day 28	122.96 ± 66.06	3.92 (2.05, 3.95)	2411.97 ± 1181.65	88.93 ± 11.65	21.35 ± 14.58
80	4	Cycle 1 Day −2	67.07 ± 26.02	4.03 (2.00, 9.93)	1047.54 ± 574.97	—	—
	3	Cycle 1 Day 28	205.9 ± 36.78	6.08 (1.93, 6.12)	4142.27 ± 738.07	90.65 ± 68.18	19.78 ± 3.92
120	4	Cycle 1 Day −2	216.38 ± 167.00	3.03 (1.93, 6.17)	3340.23 ± 2353.76	—	—
	2	Cycle 1 Day 28	668.89, 691.57	4.03, 6.08	13,151.21, 13,775.49	71.79, 176.40	8.71, 9.12
200	9	Cycle 1 Day −2	221.22 ± 97.05	5.92 (3.85, 10.00)	3595.61 ± 1463.99	—	—
	5	Cycle 1 Day 28	1016.28 ± 295.23	6.00 (3.98, 10.00)	21,573.86 ± 6230.86	126.23 ± 61.54	9.78 ± 2.25
300	2	Cycle 1 Day −2	170.40, 414.58	3.88, 9.98	2810.75, 7924.49	—	—

Mean ± SD (Individual values are listed for n = 1 or 2), *1: Median (Range), *2: Estimated using the accumulation index.
—: Not calculated

6.2.2 Foreign clinical studies

6.2.2.1 Foreign phase I study (CTD 5.3.3.2-1, Study 0105 [March 2016 to June 19, 2017)

An open-label, uncontrolled study was conducted in 6 patients with advanced solid tumors (5 subjects included in PK analysis) to determine the mass balance etc. of gilteritinib. Subjects received oral gilteritinib 120 mg QD on Days 1 to 14 and on Days 16 to 47, with a single oral dose of ^{14}C-gilteritinib 120 or 240 mg on Day 15. Radioactivity concentrations in blood, plasma, urine, and feces, etc. were determined.

The PK parameters of gilteritinib and radioactivity on Day 15 are shown in Table 22. The applicant explained that the blood to plasma radioactivity AUC_{tau} ratios after administration of 120 and 240 mg of gilteritinib were 0.8514 and 1.361, respectively, indicating limited distribution of gilteritinib into blood cells. The following are primary metabolites in plasma: M10 (piperazine 4-demethylated form), M16 (4-hydroxy piperidine form), and M17 (4-oxo-2,3-dehydro piperidine form); the AUC_{24h} values of these metabolites were all <10% of the AUC_{24h} of the unchanged drug.

The recoveries of radioactivity in urine and feces (% of the administered radioactivity) were 16.4% and 64.5%, respectively, over 768 hours.

Table 22. PK parameters of gilteritinib and radioactivity

Analyte	Sample	Dose (mg)	n	C_{max} (ng Eq./mL[*1])	t_{max} (h)	AUC_{tau} (ng Eq.·h/mL[*2])	CL/F (L/h)	$t_{1/2}$ (h)
Gilteritinib	Plasma	120	2	383, 1060	1.98, 3.00	7257, 19,668	6.15, 16.54	－
		240	2	563, 603	3.02, 4.02	9967[*3]	24.1[*3]	－
Radioactivity	Plasma	120	2	144, 534	3.00, 3.00	2777, 8643	1.937[*3]	123.2[*3]
		240	2	205, 324	2.02, 4.02	3976, 5585	7.00, 8.48	77.7, 137
	Blood	120	2	165, 447	3.00, 3.00	2369, 7344	2.379[*3]	117.3[*3]
		240	2	291, 329	3.02, 7.98	6103, 6478	6.520[*3]	88.40[*3]

Individual values are shown.
*1 ng/mL for gilteritinib, *2 ng·h/mL for gilteritinib, *3 n = 1
－: Not calculated

6.2.2.2 Foreign phase I/II study (CTD 5.3.5.2-1, Study 0101, dose-escalation cohort [ongoing since October 2013 (data cutoff date of August 4, 2017)])

An open-label, uncontrolled study was conducted in 25 patients with relapsed or refractory AML (23 subjects included in PK analysis) to assess the safety, PK, etc. of gilteritinib. Subjects received a single oral dose of gilteritinib 20, 40, 80, 120, 200, 300, or 450 mg, followed by a 2-day observation period (the single-dose phase). The subjects then received oral gilteritinib QD at the same dose that they were taking during the single-dose phase, in 28-day cycles. Plasma gilteritinib concentrations following a single dose and on Day 15 of the 28-day cycle were determined.

The PK parameters of gilteritinib are shown in Table 23.

The applicant's explanation:
Based on the obtained PK data, an analysis using a power model was performed. The exposure (C_{max} and AUC_{24h}) following a single dose or repeated doses of gilteritinib increased in an almost dose-proportional manner over the dose range tested.

The accumulation indices[14)] after repeated dosing of 80 to 200 mg of gilteritinib were 5.987 to 9.041.

Table 23. PK parameters of gilteritinib

Dose (mg)	Sampling day	n	C_{max} (ng/mL)	t_{max}*1 (h)	AUC_{24h} (ng·h/mL)	$t_{1/2}$*2 (h)
20	Cycle 1 Day −2	5	28.13 ± 21.49	2.00 (0.500, 4.03)	302.1 ± 207.0	−
	Cycle 1 Day 15	4	64.64 ± 48.77	4.01 (4.00, 6.00)	1299 ± 1,006*4	62.14 ± 17.88*4
40	Cycle 1 Day −2	3	24.98 ± 14.58	5.98 (3.97, 24.0)	360.0 ± 223.5	−
	Cycle 1 Day 15	3	107.6 ± 31.92	3.87 (0.500, 6.00)	2458, 2505*3	60.5, 243*3
80	Cycle 1 Day −2	3	75.29 ± 25.22	4.00 (4.00, 4.08)	1216 ± 472.6	−
	Cycle 1 Day 15	3	376.4 ± 150.5	4.33 (4.00, 4.42)	6958 ± 3273	86.11 ± 24.08
120	Cycle 1 Day −2	3	136.7 ± 94.37	2.08 (2.00, 3.83)	2480 ± 1972	−
	Cycle 1 Day 15	3	374.2 ± 190.1	2.17 (1.95, 5.75)	6943 ± 3221	45.85 ± 18.83
200	Cycle 1 Day −2	3	168.2 ± 45.34	5.23 (4.00, 5.97)	3022 ± 843.6	−
	Cycle 1 Day 15	2	886, 2038	6.00, 6.07	16,288, 46,568	98.4, 185
300	Cycle 1 Day −2	3	204.3 ± 136.4	6.07 (4.08, 24.1)	4163 ± 3178	−
	Cycle 1 Day 15	3	1525 ± 664.6	6.05 (4.08, 6.07)	31,005 ± 10,068	142.2 ± 55.04
450	Cycle 1 Day −2	3	207.6 ± 51.81	5.78 (4.08, 5.92)	3168, 3480*3	−
	Cycle 1 Day 15	1	1528	5.93	34,768	−

Mean ± SD (Individual values are listed for n = 1 or 2), *1: Median (Range), *2: Estimated using the accumulation index. *3: n = 2, *4: n = 3, −: Not calculated

6.2.3 Drug interaction studies

6.2.3.1 Drug interaction study with itraconazole, fluconazole, or rifampicin (CTD 5.3.3.4-1, Study 0108 [April 2015 to September 2015])

An open-label, randomized study was conducted in 81 healthy adults (81 subjects included in PK analysis) to assess the effects of itraconazole (a combined P-gp and strong CYP3A inhibitor), fluconazole (a moderate CYP3A inhibitor), or rifampicin (a combined P-gp and CYP3A inducer) on the PK of gilteritinib. In Cohort 1, gilteritinib was administered orally as a single 10 mg dose alone. In Cohort 2, gilteritinib was administered orally as a single 10 mg dose on Day 6 in combination with 200 mg itraconazole administered orally BID on Day 1 and QD on Days 2 to 28. In Cohort 3, gilteritinib was administered orally as a single 10 mg dose on Day 6 in combination with once daily 400 mg oral fluconazole on Day 1 and 200 mg oral fluconazole on Days 2 to 28. In Cohort 4, oral rifampicin 600 mg QD was administered on Days 1 to 21, and gilteritinib was administered orally as a single 20 mg dose on Day 8.

The geometric least-squares mean ratios of the C_{max} and AUC_{inf} of gilteritinib for gilteritinib + (a) itraconazole, (b) fluconazole, or (c) rifampicin vs. gilteritinib alone [90% CI][15] were (a) 1.1980 [1.0009, 1.4339] and 2.2139 [1.8826, 2.6036], respectively, (b) 1.1573 [0.9669, 1.3852] and 1.4346 [1.2199, 1.6871], respectively, and (c) 0.7344 [0.6136, 0.8791] and 0.2847 [0.2421, 0.3348], respectively.

[15] Dose-normalized PK parameters were calculated for coadministration with rifampicin.

Based on the above results, the applicant explained coadministration of gilteritinib with a combined P-gp and strong CYP3A inhibitor, a moderate CYP3A inhibitor, or a combined P-gp and CYP3A inducer.

The applicant's explanation:
Since coadministration of a combined P-gp and strong CYP3A inhibitor resulted in increased gilteritinib exposure, and coadministration of a combined P-gp and CYP3A inducer resulted in decreased gilteritinib exposure, caution should be exercised when coadministering gilteritinib with these drugs, and the relevant precautionary statements will be included in the package insert. On the other hand, there is no need to caution against coadministration of gilteritinib with mild or moderate CYP3A inhibitors, because a foreign phase I/II study (Study 0101) showed no clear differences in the incidence of adverse events between subjects treated with gilteritinib with or without a moderate CYP3A inhibitor, etc.

6.2.3.2 Drug interaction study with midazolam or cephalexin (CTD 5.3.5.2-1, Study 0101, dose-expansion cohort [ongoing since October 2013 (data cutoff date of August 4, 2017)])

(a) Drug interaction study with midazolam
An open-label, uncontrolled study was conducted in 16 patients with relapsed or refractory AML (16 subjects included in PK analysis) to assess the effects of gilteritinib on the PK of midazolam (a CYP3A substrate). Gilteritinib was administered in 28-day cycles. Oral gilteritinib 300 mg QD was administered on Days 1 to 28 of Cycle 1, and oral midazolam 2 mg was administered on Day -1 and Day 15 of Cycle 1.

The geometric least-squares mean ratios of the C_{max} and AUC_{24h} of midazolam for midazolam + gilteritinib vs. midazolam alone [90% CI] were 1.1164 [0.6954, 1.7925] and 1.0946 [0.4982, 2.4048], respectively. The applicant explained that the above results indicated that coadministration of gilteritinib with CYP3A substrates is unlikely to lead to pharmacokinetic interactions.

(b) Drug interaction study with cephalexin
An open-label, uncontrolled study was conducted in 20 patients with relapsed or refractory AML (20 subjects included in PK analysis) to assess the effects of gilteritinib on the PK of cephalexin (a MATE1 substrate). Gilteritinib was administered in 28-day cycles. Oral gilteritinib 200 mg QD was administered on Days 1 to 28 of Cycle 1, and oral cephalexin 500 mg was administered on Day -1 and Day 15 of Cycle 1.

The geometric least-squares mean ratios of the C_{max} and AUC_{inf} of cephalexin for cephalexin + gilteritinib vs. cephalexin alone [90% CI] were 0.9146 [0.7460, 1.1212] and 0.9396 [0.7529, 1.1726], respectively. The applicant explained that the above results indicated that coadministration of gilteritinib with MATE1 substrates is unlikely to lead to pharmacokinetic interactions.

6.2.4 Foreign phase I study to assess the effect of hepatic impairment on PK of gilteritinib (CTD 5.3.3.3-1, Study 0106 [October 2015 to March 2016])

An open-label, uncontrolled study was conducted in 24 subjects (8 healthy adults, 8 subjects with mild hepatic impairment [Child-Pugh class A], 8 subjects with moderate hepatic impairment [Child-Pugh class B]) (8 subjects each included in PK analysis) to assess the effect of hepatic impairment on the PK of gilteritinib, etc. A single oral dose of gilteritinib 10 mg was administered, and plasma gilteritinib concentrations were determined.

The PK parameters of gilteritinib are shown in Table 24. The geometric mean ratios of the C_{max} and AUC_{inf} of plasma protein unbound gilteritinib for (a) subjects with mild hepatic impairment vs. healthy adults and (b) subjects with moderate hepatic impairment vs. healthy adults [90%CI] were (a) 1.1949 [0.9125, 1.5646] and 0.8842 [0.6592, 1.1861], respectively, and (b) 1.1772 [0.8990, 1.5415] and 0.8848 [0.6597, 1.1869], respectively. The plasma protein unbound fractions of gilteritinib were 0.0572 in healthy adults, 0.0640 in subjects with mild hepatic impairment, and 0.0865 in subjects with moderate hepatic impairment; the applicant explained that the plasma protein unbound fraction of gilteritinib tended to increase with increasing severity of hepatic impairment.

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

There were no clear differences in the exposure of plasma protein unbound gilteritinib between healthy adults and subjects with mild or moderate hepatic impairment. Therefore, no dose adjustment of gilteritinib is required in patients with mild or moderate hepatic impairment. As there is no clinical experience with gilteritinib in patients with severe hepatic impairment, etc., gilteritinib should be administered with care to such patients.

Table 24. PK parameters of gilteritinib by severity of hepatic impairment

Severity of hepatic impairment	n	Analyte	C_{max} (ng/mL)	AUC_{inf} (ng·h/mL)	$t_{1/2}$ (h)	CL/F (L/h)	V_z/F (L)
Normal	8	Total	7.48 ± 2.23	542 ± 167	116 ± 12.3	19.9 ± 5.51	3340 ± 977
		Unbound	0.429 ± 0.138	31.0 ± 10.8	―	349 ± 90.4	58,500 ± 15,500
Mild	8	Total	8.10 ± 2.67	425 ± 108	126 ± 19.2	25.3 ± 8.19	4520 ± 1310
		Unbound	0.518 ± 0.177	27.2 ± 7.49	―	398 ± 132	70,900 ± 20,500
Moderate	8	Total	6.40 ± 2.47	351 ± 152	112 ± 31.9	34.5 ± 16.9	5090 ± 1680
		Unbound	0.520 ± 0.198	29.8 ± 17.6	―	423 ± 185	61,500 ± 16,500

Mean ± SD
Bound: plasma protein-bound gilteritinib
Unbound: plasma protein unbound gilteritinib
―: Not calculated

6.2.5 Relationship between exposure and change in QT/QTc interval

The relationship between plasma gilteritinib concentration and ΔQTcF was analyzed using an E_{max} model, based on the data from a Japanese phase I study (Study 0102), a global phase III study (Study 0301), and a foreign phase I/II study (Study 0101).

ΔQTcF tended to increase with increasing plasma gilteritinib concentration. At the steady state C_{max} (median, 886.5 ng/mL) following oral administration of gilteritinib 200 mg QD in the Japanese phase I study (Study 0102), the upper limit of the one-sided 95% confidence interval for ΔQTcF was estimated at 11.41 ms.

The applicant explained that given the above results, the possibility that gilteritinib 200 mg causes QT/QTc interval prolongation cannot be ruled out.

6.2.6 PPK analysis

PPK analysis was performed by non-linear mixed effects modeling (software, NONMEM Version 7.3.0), based on gilteritinib PK data from a Japanese phase I study (Study 0102), a global phase III study (Study 0301), foreign phase I studies (Studies 0106, 0108, 0110, and 0113), and a foreign phase I/II study (Study 0101) (7529 PK samples from 618 subjects). The PK of gilteritinib were described by a 2-compartment model with first-order absorption and elimination.

The following were tested as potential covariates on the CL, central volume of distribution (Vc), inter-compartmental clearance (Q), peripheral volume of distribution (Vp), apparent absorption rate (k_a), and relative bioavailability (F_1) of gilteritinib:

Body weight, age, ALT, AST, ALP, creatine phosphokinase (CK), body surface area (BSA), lean body mass (LBM), body mass index (BMI), total bilirubin, serum creatinine, albumin, sex, race, formulation (clinical trial formulation or proposed commercial formulation), food intake, disease (AML patient or healthy adult), concomitant use of a strong CYP3A inhibitor, concomitant use of a moderate CYP3A inhibitor, concomitant use of a CYP3A inducer, concomitant use of a P-gp inhibitor, hepatic function,[16)] and Eastern Cooperative Oncology Group performance status (ECOG PS).

The following were identified as significant covariates for (a) CL, (b) Vc, (c) Q, (d) Vp, (e) k_a, and (f) F_1

(a) Age, body weight, albumin, ALT, serum creatinine, concomitant use of a strong CYP3A inhibitor, concomitant use of a moderate CYP3A inhibitor, concomitant use of a CYP3A inducer, and concomitant use of a P-gp inhibitor
(b) Body weight, disease, and ECOG PS
(c) Total bilirubin, disease, and concomitant use of a CYP3A inducer
(d) Albumin and body weight
(e) Food intake, disease, and hepatic function
(f) Formulation

The applicant's explanation:

As all of these covariates had limited influence on gilteritinib exposure (AUC_{ss}), these covariates are unlikely to have clinically relevant effects on the PK of gilteritinib. However, given the results of Study 0108, caution

[16)] Classified as per the National Cancer Institute organ dysfunction working group (NCI-ODWG) criteria.

should be exercised when coadministering gilteritinib with (i) a combined P-gp and strong CYP3A inhibitor, e.g. itraconazole, or (ii) a combined P-gp and CYP3A inducer, e.g. rifampicin.

6.2.7 Relationship between gilteritinib exposure and efficacy or safety

6.2.7.1 Exposure-efficacy relationship

Based on the data from a global phase III study (Study 0301), the applicant assessed the potential relationship between gilteritinib exposure (C_{max})[17)] and complete remission (CR) or complete remission with partial hematologic recovery (CRh). The C_{max} values of gilteritinib in patients who achieved or did not achieve a CR or CRh were 799 ± 258 and 797 ± 245 ng/mL, respectively, showing no clear differences between these patients.

6.2.7.2 Exposure-safety relationship

Based on the data from a Japanese phase I study (Study 0102), a global phase III study (Study 0301), and a foreign phase I/II study (Study 0101), the applicant assessed the potential relationship between gilteritinib exposure (C_{max})[17)] and the occurrence of adverse events for which a causal relationship to gilteritinib could not be ruled out. The C_{max} values of gilteritinib in patients with or without these events were 985 ± 509 and 835 ± 507 ng/mL, respectively, showing no clear differences between these patients.

6.2.8 Differences in PK of gilteritinib between Japanese and non-Japanese populations

The applicant's explanation:

Gilteritinib exposures (C_{max} and AUC_{24h}) after single or repeated dosing in a Japanese phase I study (Study 0102) were compared with those in a foreign phase I/II study (Study 0101). Gilteritinib exposures were largely similar in both studies. Thus, there should be no clear differences in the PK of gilteritinib between Japanese and non-Japanese populations.

[17)] Estimated from PPK analysis [see Section 6.2.6].

6.R Outline of the review conducted by PMDA

Based on the submitted data and the following considerations, PMDA concluded that the applicant's discussion on the clinical pharmacology etc. of gilteritinib is acceptable.

6.R.1 Use of gilteritinib in patients with renal impairment

The applicant explained that no dose adjustment of gilteritinib is required in patients with renal impairment, for the following reasons.

- The results of a foreign phase I study (Study 0105) etc. indicated that renal excretion contributes little to the clearance of gilteritinib [see Section 6.2.2.1].
- In a global phase III study (Study 0301), there were no clear differences in (a) the incidence of overall adverse events or (b) adverse events for which a causal relationship to gilteritinib could not be ruled out, between patients with normal renal function and patients with mild or moderate renal impairment (see below for details):

  (a) The incidences of overall adverse events, regardless of causality to gilteritinib
  (1) 100% in patients with normal renal function (n = 97)
  (2) 97.9% in patients with mild renal impairment (n = 48)
  (3) 100% in patients with moderate renal impairment (n = 23)

  (b) The incidences of adverse events for which a causal relationship to gilteritinib could not be ruled out
  (1) 84.5% in patients with normal renal function (n = 97)
  (2) 81.3% in patients with mild renal impairment (n = 48)
  (3) 78.3% in patients with moderate renal impairment (n = 23).

PMDA accepted the applicant's explanation.

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

The applicant submitted efficacy and safety evaluation data, in the form of the results from 8 studies presented in Table 25: 1 Japanese phase I study, 5 foreign phase I studies, 1 foreign phase I/II study, and 1 global phase III study. The applicant also submitted the results from 1 Japanese phase Ib/II study as reference data.

Table 25. Listing of efficacy and safety clinical studies

Data category	Country	Study ID	Phase	Study population	No. of patients enrolled	Dosing regimen	Main endpoints
Evaluation data	Japan	0102	I	Patients with relapsed or refractory AML	27	Gilteritinib 20, 40, 80, 120, 200, or 300 mg QD orally	Safety PK
	Global	0301	III	Patients with *FLT3* mutation-positive relapsed or refractory AML	255	Gilteritinib group: gilteritinib 120 mg QD orally Control group: low dose Ara-C, azacytidine, MEC, or FLAG-IDA selected by the investigator	Efficacy Safety
	Foreign	0101	I/II	Patients with relapsed or refractory AML	265	Dose-escalation cohort: gilteritinib 20, 40, 80, 120, 200, 300, or 450 mg QD orally Dose-expansion cohort: gilteritinib 20, 40, 80, 120, 200, or 300 mg QD orally	Efficacy Safety PK
		0105	I	Patients with advanced solid tumors	6	Gilteritinib 120 mg QD orally on Days 1-14 and Days 16-47 with a single oral dose of ^{14}C-gilteritinib 120 mg on Day 15	PK
		0106	I	Healthy adults and patients with hepatic impairment	24	A single oral dose of gilteritinib 10 mg	PK
		0108	I	Healthy adults	81 (a) 21 (b) 20 (c) 20 (d) 20	(a) A single oral dose of gilteritinib 10 mg (b) A single oral dose of gilteritinib 10 mg on Day 6, in combination with itraconazole (c) A single oral dose of gilteritinib 10 mg on Day 6, in combination with fluconazole (d) A single oral dose of gilteritinib 20 mg on Day 8, in combination with rifampicin	PK
		0110	I	Healthy adults	42	A single oral dose of gilteritinib 40 mg	PK
		0113	I	Healthy adults	32	A single oral dose of gilteritinib 40 mg	PK
Reference data	Japan	5101	Ib/II	Patients with *EGFR* mutation-positive advanced/recurrent NSCLC	10	Gilteritinib 40, 80, 120, 200, or 320 mg QD orally, in combination with erlotinib	Efficacy Safety

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

7.1 Evaluation data

In a Japanese phase I study (Study 0102), a global phase III study (Study 0301), and a foreign phase I/II study (Study 0101), CR, CRh, complete remission with incomplete platelet recovery (CRp), complete remission with incomplete hematologic recovery (CRi), and composite complete remission (CRc) were defined by modified Cheson criteria (*J Clin Oncol*. 2003; 21: 4642-9), as shown below. In Studies 0301 and 0101, subjects were allowed to receive hematopoietic stem cell transplantation (HSCT) during the study period, and to undergo efficacy assessment without regard to the timing of HSCT; subjects who met the following criteria after HSCT were also counted as responders.

● Definition of CR (patients must meet all of the following criteria).

- Bone marrow blast <5% blasts, bone marrow exhibits normal differentiation.
- An absolute neutrophil count $\geq 1\times10^9$/L and a platelet count $\geq 100\times10^9$/L; and independent of red blood

cell and platelet transfusion.[18)]

- No evidence of extramedullary leukemia. Absence of Auer rods, and ≤2% blasts in the peripheral blood.

● Definition of CRh:

Patients must have an absolute neutrophil count of $\geq 0.5\times10^9$/L and platelet count of $\geq 50\times10^9$/L, and meet all the other CR criteria.

● Definition of CRp:

Patients must have a platelet count of $<100\times10^9$/L and meet all the other CR criteria.

● Definition of CRi:

Patients must have an absolute neutrophil count of $<1\times10^9$/, with or without complete platelet recovery, and meet all the other CR criteria. They are either dependent on, or independent of, red blood cell and/or platelet transfusions.

● Definition of CRc:

Patients must achieve CR, CRp, or CRi.

7.1.1 Clinical pharmacology studies

The applicant submitted data from the following 5 clinical pharmacology studies in healthy adults, subjects with hepatic impairment, or patients with advanced solid tumors [see Section 6.2]. Death during the gilteritinib treatment period or within 30 days after the last dose of gilteritinib occurred in 1 of 6 subjects (chondrosarcoma) in Study 0105, and its causal relationship to gilteritinib was ruled out.

7.1.1.1 Foreign phase I study (CTD 5.3.3.2-1, Study 0105 [March 2016 to June 2017])

7.1.1.2 Foreign phase I study (CTD 5.3.3.3-1, Study 0106 [October 2015 to March 2016])

7.1.1.3 Foreign phase I study (CTD 5.3.3.4-1, Study 0108 [April 2015 to September 2015])

7.1.1.4 Foreign phase I study (CTD 5.3.1.2-1, Study 0110 [July 2015 to October 2015])

7.1.1.5 Foreign phase I study (CTD 5.3.1.1-1, Study 0113 [January 2017 to March 2017])

7.1.2 Japanese clinical studies

7.1.2.1 Japanese phase I study (CTD 5.3.5.2-2, Study 0102 [June 2014 to June 2016])

An open-label, uncontrolled study was conducted at 5 sites in Japan to assess the safety, PK, etc. of gilteritinib in patients with relapsed or refractory AML (target sample size, up to 36 subjects).

Subjects received a single oral dose of gilteritinib 20, 40, 80, 120, 200, or 300 mg, followed by a 2-day observation period (the single-dose phase). The subjects then received oral gilteritinib QD at the same dose that they were taking during the single-dose phase, in 28-day cycles, until a discontinuation criterion was met.

[18)] This condition was defined as "1 week without red blood cell and/or platelet transfusion" in Studies 0101 and 0301 and "4 weeks without red blood cell transfusion" in Study 0102.

Of 27 subjects enrolled in the study, 24 (1 in the 20 mg group, 4 each in the 40 mg, 80 mg, and 120 mg groups, 9 in the 200 mg group, 2 in the 300 mg group) received gilteritinib and were included in safety analysis and dose limiting toxicity (DLT) assessment.

The DLT assessment period was defined as the single-dose phase and Cycle 1 (a total of 30 days). During the DLT assessment period, DLTs occurred in 3 subjects (1 of 4 subjects in the 120 mg group [Grade 3 TLS (1 subject)], 2 of 2 subjects in the 300 mg group [Grade 3 blood LDH increased and Grade 3 syncope; and Grade 3 amylase increased and Grade 3 blood CK increased, 1 subject each]). The maximum tolerated dose (MTD) was determined to be 200 mg QD.

Safety results:
One death occurred during the gilteritinib treatment period or within 28 days after the last dose of gilteritinib (1 subject with subdural haematoma in the 80 mg group), and its causal relationship to gilteritinib could not be ruled out.

7.1.3 Global studies

7.1.3.1 Global phase III study (CTD 5.3.5.1-1, Study 0301 [ongoing since October 2015 (data cutoff date of August 4, 2017)])

An open-label, randomized study was conducted at 83 sites in 14 countries including Japan to compare the efficacy and safety of gilteritinib and salvage chemotherapy selected by the investigator in patients with *FLT3* mutation-positive[19] relapsed or refractory AML (target sample size, 369 subjects).

Subjects in the gilteritinib group received gilteritinib 120 mg QD orally. Treatment was continued until a discontinuation criterion was met. Subjects in the control group received chemotherapy selected by the investigator in 28-day cycles. Chemotherapy options included (1) low-dose cytarabine (Ara-C), (2) azacytidine, (3) the combination of mitoxantrone, etoposide, and cytarabine (MEC), and (4) the combination of fludarabine, cytarabine, and filgrastim (genetical recombination) with idarubicin (FLAG-IDA). These chemotherapy dosing regimens are shown below.

(1) Low-dose Ara-C: Ara-C 20 mg BID was administered by subcutaneous or intravenous injection on Days 1 to 10 until a discontinuation criterion was met.
(2) Azacytidine: Azacytidine 75 mg/m^2 QD was administered by subcutaneous or intravenous injection on Days 1 to 7 until a discontinuation criterion was met.
(3) MEC: Mitoxantrone 8 mg/m^2, etoposide 100 mg/m^2, and Ara-C 1000 mg/m^2 were administered by intravenous injection on Days 1 to 5.
(4) FLAG-IDA: Filgrastim (genetical recombination) 300 μg/m^2 was administered by subcutaneous or intravenous injection on Days 1 to 5, fludarabine 30 mg/m^2 and Ara-C 2000 mg/m^2 were administered by intravenous injection on Days 2 to 6, and IDA 10 mg/m^2 was administered by intravenous injection on Days 2 to 4.

[19] Patients were eligible for the study if they had any of the following *FLT3* mutants: *FLT3*-ITD, *FLT3*-TKD/D835, and *FLT3*-TKD/I836.

Patients enrolled and randomized were included in the intent-to-treat (ITT) set, which was used for efficacy analyses. At the time of the first interim analysis, 255 patients (169 in the gilteritinib group, 86 in the control group) had been randomized. Of the 255 patients, 142 in the gilteritinib group were included in the response analysis set (RAS), because in these patients at least 112 days had passed since the first dose of gilteritinib.[20] RAS was used for efficacy analyses for the first interim analysis. Patients in the ITT set who received study drug were included in the safety analysis set. The first interim analysis was not intended to analyze the efficacy and safety in control patients; therefore, the safety analysis set at the first interim analysis included 168 of the 169 patients in the gilteritinib group. (The remaining 1 patient never received gilteritinib and was therefore excluded.)

In the original protocol, the primary endpoint was overall survival (OS) (ITT set was used for efficacy analyses), and an interim analysis for efficacy evaluation was planned to be performed when approximately 50% of 258 OS events occurred; the Lan-DeMets α spending function that approximates an O'Brien-Fleming approach was to be used to control the type I error rate in the interim analysis. The protocol, however, was amended during the study as of [redacted], 20[redacted] to conduct earlier assessment of efficacy. The following are details of amendments:

- ✓ The CR+CRh rate was added as a co-primary endpoint.
- ✓ The first interim analysis for the CR+CRh rate in the gilteritinib group only was planned to be performed earlier than the initially planned interim analysis of OS.
- ✓ Hypothesis testing is not conducted for the CR+CRh rate in the gilteritinib group to be calculated at the first interim analysis. The CR+CRh rate and its 95% confidence interval, calculated by descriptive statistics, are submitted to the Independent Data Monitoring Committee (IDMC). The IDMC then notifies the sponsor of whether the lower limit of the 95% confidence interval for the CR+CRh rate exceeds the prespecified threshold of 12%.[21]
- ✓ In order to adjust for multiplicity of the two co-primary endpoints, the one-sided significance level of 0.025 was allocated as 0.0245 to OS and 0.0005 to the CR+CRh rate.

At the first interim analysis (data cutoff date of August 4, 2017), the results of the co-primary efficacy endpoint of the CR+CRh rate in the gilteritinib group in the overall population and the Japanese subgroup, based on central testing, are shown in Table 26.

[20] Among subjects included in efficacy analyses, 1 subject who was identified as *FLT3*-negative based on central testing after randomization did not receive gilteritinib.

[21] The threshold was selected based on the CR rate with salvage chemotherapy in a clinical study in patients with relapsed or refractory AML (*J Clin Oncol.* 2014; 32: 1919-26).

Table 26. Results of CR and CRh (Central testing, RAS, data cutoff date of August 4, 2017)

Best overall response	n (%)	
	Overall population	Japanese subgroup
	Gilteritinib N = 142	Gilteritinib N = 18
CR	27 (19.0)	4 (22.2)
CRh	13 (9.2)	1 (5.6)
CR+CRh (CR+CRh rate [95% CI]* (%))	40 (28.2 [20.9, 36.3])	5 (27.8 [9.7, 53.5])

* Exact confidence interval based on binomial distribution

The CR+CRh rate [95% CI] in patients with *FLT3* mutation-positive relapsed[22] AML, based on central testing, was 32.1% [22.4%, 43.2%] (27 of 84 patients), and the CR+CRh rate [95% CI] in patients with *FLT3* mutation-positive refractory[23] AML, based on central testing, was 22.4% [12.5%, 35.3%] (13 of 58 subjects). All of the Japanese patients had relapsed AML, and no Japanese patients with refractory AML were enrolled in the study.

The results of the testing for OS in the ITT set at the second interim analysis (data cutoff date of [redacted], 20[redacted]) did not meet the prespecified criteria for termination for efficacy or futility; the IDMC therefore recommended continuation of the study. In order to maintain the integrity of the study, the observed CR+CRh rate in the control group at the first interim analysis and the results of the testing for OS at the second interim analysis were not submitted with the present application.

Safety results:

In total, 43 of 168 subjects (25.6%) died during the gilteritinib treatment period or within 30 days after the last dose of gilteritinib. The causes of deaths other than disease progression (17 subjects) were septic shock (4 subjects); cerebral haemorrhage; and disease progression and cardiac arrest (2 subjects each); sepsis; cardiac arrest; pericardial effusion; cardiac failure congestive; large intestine perforation; bronchopulmonary aspergillosis; cellulitis; lung infection; bacterial colitis; infection; lower respiratory tract infection bacterial; sinusitis fungal; acute respiratory distress syndrome; pneumonia aspiration; pericardial effusion, pleural effusion, and respiratory tract infection fungal; large intestine perforation, respiratory failure, and sepsis; general physical condition decreased, dyspnoea, and hypotension; and metabolic acidosis and septic shock (1 subject each). A causal relationship to gilteritinib could not be ruled out for large intestine perforation (2 subjects), cardiac failure congestive (1 subject), cellulitis (1 subject), and cerebral haemorrhage (1 subject).

7.1.4 Foreign clinical studies

7.1.4.1 Foreign phase I/II study (CTD 5.3.5.2-1, Study 0101 [ongoing since October 2013 (data cutoff date of August 4, 2017)])

An open-label, uncontrolled study was conducted at 27 sites in 3 countries to assess the safety, PK, etc. of gilteritinib in patients with relapsed or refractory AML (target sample size, up to 270 subjects).

22) Patients who relapsed after achieving a CR, CRp or CRi with first-line treatment.

23) Patients who did not achieve a CR, CRp, or CRi with first-line treatment. Patients eligible for standard therapy were required to have received at least 1 cycle of an anthracycline-containing induction regimen. Patients not eligible for standard therapy were required to have received at least 1 complete course of induction therapy.

Subjects in the dose-escalation cohort received a single oral dose of gilteritinib 20, 40, 80, 120, 200, 300, or 450 mg, followed by a 2-day observation period (the single-dose phase). The subjects then received oral gilteritinib QD at the same dose that they were taking during the single-dose phase, in 28-day cycles. Subjects in the dose-expansion cohort received oral gilteritinib QD at the recommended doses[24] determined from the dose-escalation cohort, in 28-day cycles.

Among 265 subjects enrolled in the study (25 in the dose-escalation cohort, 240 in the dose-expansion cohort),[25] 252 subjects (17 in the 20 mg group, 16 in the 40 mg group, 24 in the 80 mg group, 69 in the 120 mg group, 103 in the 200 mg group, 20 in the 300 mg group, 3 in the 450 mg group) received gilteritinib and were included in the safety analysis set, and 221 subjects from the safety analysis set were included in DLT assessment.[26]

During the DLT assessment period,[27] DLTs occurred in 31 subjects: 1 of 12 subjects in the 20 mg group (Grade 5 haemorrhage intracranial), 1 of 14 subjects in the 40 mg group (Grade 3 toxic shock syndrome), 2 of 21 subjects in the 80 mg group (Grade 5 septic shock; and Grade 3 conjunctival oedema, 1 subject each), 7 of 65 subjects in the 120 mg group (Grade 3 lower gastrointestinal haemorrhage and Grade 3 haematochezia; Grade 5 ventricular fibrillation; Grade 3 hyperbilirubinaemia; Grade 3 hypoxia and Grade 3 pleural effusion; Grade 3 liver function test abnormal; Grade 4 renal tubular necrosis; and Grade 3 blood LDH increased, 1 subject each), 15 of 90 subjects in the 200 mg group (Grade 3 transaminases increased [2 subjects]; Grade 3 electrocardiogram QT prolonged, Grade 4 hypoxia, and Grade 3 acute promyelocytic leukaemia differentiation syndrome; Grade 3 blood CK increased; Grade 3 GGT increased; Grade 3 abdominal pain and Grade 3 pelvic pain; Grade 3 acidosis, Grade 3 hypotension, and Grade 4 hypoxia; Grade 3 dizziness and Grade 3 myalgia; Grade 3 haematochezia; Grade 3 hypotension; Grade 3 intestinal perforation; Grade 3 ALT increased; Grade 2 decreased appetite, Grade 2 dysgeusia, and Grade 2 fatigue; Grade 4 posterior reversible encephalopathy syndrome (PRES); and Grade 2 nausea, 1 subject each), 3 of 16 subjects in the 300 mg group (Grade 5 pulmonary embolism; Grade 3 hypertension, Grade 3 AST increased, Grade 3 disseminated intravascular coagulation, and Grade 3 gastrointestinal haemorrhage; Grade 4 blood CK increased and Grade 3 rhabdomyolysis, 1 subject each), and 2 of 3 subjects in the 450 mg group (Grade 3 diarrhoea; and Grade 3 AST increased, 1 subject each). The MTD was determined to be 300 mg QD.

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24) (1) A dose level(s) that induced a CRc in 1 subject in the dose-escalation cohort; or
(2) A dose level(s) that did not induce a CRc in any subjects but resulted in a ≥90% decrease in FLT3 phosphorylation in ≥3 subjects in the dose-escalation cohort.

25) A dose level(s) that have induced a CRc in 1 subject in the dose-escalation cohort proceed to the dose-expansion cohort. The dose-expansion cohort of each dose level enrolls at least 3 patients and, if DLT has occurred in 0 of 3 patients or 1 of 6 patients in the dose-escalation cohort, enrolls additional 17 patients. An expanded dose level must enroll ≥10 patients with FLT3 mutation-positive AML in the dose-escalation and dose-expansion cohorts combined. An expanded dose level at ≥120 mg must enroll ≥42 patients with FLT3 mutation-positive AML in the dose-escalation and dose-expansion cohorts combined.

26) Patients were assessed for DLT if they remained on treatment for ≥80% period of Cycle 1 or experienced DLT in Cycle 1.

27) DLT assessment period was defined as the 30-day period consisting of the single-dose phase and Cycle 1 for the dose-escalation cohort, and the 28-day period of Cycle 1 for the dose-expansion cohort.

Safety results:

In total, 105 of 252 subjects died during the gilteritinib treatment period or within 30 days after the last dose of gilteritinib (5 of 17 subjects in the 20 mg group, 6 of 16 subjects in the 40 mg group, 11 of 24 subjects in the 80 mg group, 24 of 69 subjects in the 120 mg group, 50 of 103 subjects in the 200 mg group, 8 of 20 subjects in the 300 mg group, 1 of 3 subjects in the 450 mg group). The causes of deaths other than disease progression (44 subjects: 3 in the 20 mg group, 5 in the 40 mg group, 5 in the 80 mg group, 10 in the 120 mg group, 16 in the 200 mg group, 5 in the 300 mg group) were sepsis (6 subjects: 1 in the 120 mg group, 5 in the 200 mg group), respiratory failure (6 subjects: 1 each in the 80 mg, 120 mg, and 300 mg groups, 3 in the 200 mg group), multiple organ dysfunction syndrome (6 subjects: 1 each in the 40 mg and 120 mg groups, 4 in the 200 mg group), pneumonia (4 subjects: 2 each in the 120 mg and 200 mg groups), haemorrhage intracranial (4 subjects: 2 in the 20 mg group, 1 each in the 120 mg and 200 mg groups), septic shock (3 subjects: 1 in the 80 mg group, 2 in the 200 mg group), death (3 subjects: 2 in the 120 mg group, 1 in the 200 mg group), bronchopulmonary aspergillosis (2 subjects: 1 each in the 120 mg and 200 mg groups), staphylococcal sepsis (2 in the 200 mg group), renal failure (2 subjects: 1 each in the 200 mg and 300 mg groups), respiratory failure and sepsis (2 in the 200 mg group), bacteraemia (1 in the 80 mg group), staphylococcal bacteraemia (1 in the 80 mg group), haemoptysis (1 in the 80 mg group), diabetic ketoacidosis and septic shock (1 in the 80 mg group), neutropenia (1 in the 120 mg group), ventricular fibrillation (1 in the 120 mg group), neutropenic colitis (1 in the 120 mg group), bacterial infection (1 in the 120 mg group), hepatic infection (1 in the 120 mg group), anaemia (1 in the 200 mg group), myocardial infarction (1 in the 200 mg group), ventricular tachycardia (1 in the 200 mg group), sudden death (1 in the 200 mg group), lung infection (1 in the 200 mg group), cerebral ischaemia (1 in the 200 mg group), hypoxia (1 in the 200 mg group), febrile neutropenia and sepsis (1 in the 200 mg group), AML and loss of consciousness (1 in the 200 mg group), acute respiratory failure, cellulitis, colitis, and septic shock (1 in the 200 mg group), pulmonary embolism (1 in the 300 mg group), and cardiac arrest (1 in the 450 mg group). A causal relationship to gilteritinib could not be ruled out for haemorrhage intracranial (1 subject in the 20 mg group), septic shock (1 subject in the 80 mg group), haemoptysis (1 subject in the 80 mg group), ventricular fibrillation (1 subject in the 120 mg group), neutropenia (1 subject in the 120 mg group), and pulmonary embolism (1 subject in the 300 mg group).

7.2 Reference data

7.2.1 Japanese clinical studies

7.2.1.1 Japanese phase Ib/II study (CTD 5.3.5.4-1, Study 5101 [September 2015 to September 2016])

An open-label, uncontrolled study was conducted at 4 sites in Japan to evaluate the safety and PK of gilteritinib in combination with erlotinib in patients with epidermal growth factor receptor (*EGFR*) mutation-positive advanced/recurrent NSCLC who had acquired resistance to epidermal growth factor receptor-tyrosine kinase inhibitor (EGFR-TKI) (target sample size,[28)] 30 subjects in phase Ib part, 60 subjects in phase II part).

All of 10 subjects enrolled in the study (7 in the 80 mg group, 3 in the 120 mg group) received gilteritinib and were included in the safety analysis set.

[28)] Multiple cases of Grade 3 or higher ALT increased and AST increased were reported during the phase Ib part, and this part was cancelled in accordance with the Dose Escalation Committee's recommendation. Thus, phase II part was not conducted.

Safety results:
No deaths occurred during the gilteritinib treatment period or within 30 days after the last dose of gilteritinib.

7.R Outline of the review conducted by PMDA

7.R.1 Review strategy

PMDA review strategy:
Among the evaluation data submitted, the pivotal clinical study to evaluate the efficacy and safety of gilteritinib is a global phase III study in patients with *FLT3* mutation-positive relapsed or refractory AML (Study 0301). PMDA decided to focus its review on this study.

7.R.2 Clinical positioning

There is no mention of gilteritinib for the treatment of patients with *FLT3* mutation-positive relapsed or refractory AML in the Japanese and foreign clinical practice guidelines[29] or the major international textbooks of clinical oncology and hematology.[30]

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

The applicant's response:
In Japan, combination chemotherapy with cytarabine, etc. are used in patients with relapsed or refractory AML, regardless of *FLT3* mutation (Clinical Practice Guidelines for Tumors of Hematopoietic and Lymphoid Tissues 2013 [Japanese Society of Hematology ed.]). However, no standard of care has been established, and treatment options are very limited. The presence of *FLT3* mutation is recognized as a poor prognostic factor for AML, and patients with *FLT3* mutation-positive AML have a high relapse rate and a very poor prognosis (*Leuk Res*. 2004; 28: 1069-74, etc.).

Under these circumstances, Study 0301 demonstrated the clinical benefit of gilteritinib in patients with *FLT3* mutation-positive relapsed or refractory AML [see Sections 7.R.3 and 7.R.4], etc. Thus, gilteritinib can become standard treatment for these patients.

PMDA's discussion:
The results of the co-primary endpoint of OS for Study 0301, etc. are not available at present. However, for the following reasons, the results of the first interim analysis of Study 0301 [see Sections 7.R.3 and 7.R.4] are clinically meaningful, and gilteritinib is positioned as a treatment option for Japanese patients with *FLT3* mutation-positive relapsed or refractory AML. The clinical positioning of gilteritinib will be further defined, based on the future results of the final analysis of OS in the ongoing Study 0301, etc.

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[29] National Comprehensive Cancer Network Clinical Practice Guidelines in Oncology, Acute Myeloid Leukemia (NCCN guidelines) (v.1.2018), European LeukemiaNet (ELN) guidelines (*Blood.* 2017;129:424-47), and Clinical Practice Guidelines for Tumors of Hematopoietic and Lymphoid Tissues 2013 (Japanese Society of Hematology ed.)

[30] Wintrobe's Clinical Hematology, Thirteenth Edition (Lippincott Williams & Wilkins, 2014, USA), Williams Hematology, Ninth Edition (The McGraw-Hill Company, Inc, 2016, USA)

- *FLT3* mutation-positive AML is a rare disease with a very poor prognosis (*Blood*. 2008; 111: 2776-84, etc.).
- At present, no standard of care has been established for patients with *FLT3* mutation-positive relapsed or refractory AML, and treatment options are very limited.

7.R.3 Efficacy

Based on the following considerations, PMDA has concluded that gilteritinib was shown to have a certain level of efficacy in patients with *FLT3* mutation-positive relapsed or refractory AML.

7.R.3.1 Efficacy endpoint and analysis plan

The applicant's explanation about the primary endpoint and the efficacy analysis plan for Study 0301:

Patients with *FLT3* mutation-positive relapsed or refractory AML receive treatment, hoping that it will prolong their survival. OS was therefore selected for the primary endpoint at the time of initiation of Study 0301. Then, the protocol of Study 0301 was amended to include both OS and the CR+CRh rate as primary endpoints, for the following reasons [see Section 7.1.3].

- Achievement of a CR or CRh in this study population is clinically meaningful, for the following reasons:
  - Patients with relapsed or refractory AML eligible for HSCT undergo HSCT, hoping that it will prolong their OS. HSCT yields better outcomes in patients in remission than in patients not in remission (*Cancer*. 2017;123:2025-34, etc.).
  - Patients with relapsed or refractory AML not eligible for HSCT receive treatment, hoping that disease progression will be slowed by induction of remission, etc.
- The change from 1 to 2 primary endpoints would not cause statistical issues in terms of the type I error rate, for the following reasons:
  - The change from 1 to 2 primary endpoints is made before the initially planned efficacy analyses are performed.
  - No multiplicity concerns should arise, because (1) the nominal one-sided significance level is allocated as 0.0005 to the CR+CRh rate and as 0.0245 to OS after the change of the primary endpoints, and (2) a between-group comparison of the CR+CRh rate based on hypothesis testing is not performed.

PMDA's discussion:

As to the primary endpoint for Study 0301, the efficacy of gilteritinib should have been evaluated based on the results of OS, because patients with *FLT3* mutation-positive relapsed or refractory AML receive treatment, hoping that it will prolong their survival. At present, however, there is no standard of care that can prolong OS in these patients. Therefore, the applicant's explanation is understandable to a certain extent, and the certain aspects of efficacy of gilteritinib can be evaluated based on the observed CR+CRh rate.

In Study 0301, if the efficacy of gilteritinib is explained based on the results of the CR+CRh rate (one co-primary endpoint) in the gilteritinib group, the explanation affects the interpretation of the results of OS (the other co-primary endpoint). Therefore the analysis plan should have been as follows: Hypothesis testing is conducted also for the CR+CRh rate, and then multiplicity adjustment for the two co-primary endpoints is performed.

7.R.3.2 Results of efficacy evaluation

In Study 0301, the co-primary endpoint of the CR+CRh rate [95% CI] in the gilteritinib group, based on central testing, at the first interim analysis, was 28.2% [20.9%, 36.3%], and the lower limit of the 95% confidence interval exceeded the threshold of 12%. (This threshold was selected based on the CR rate with salvage chemotherapy in a clinical study in patients with relapsed or refractory AML.) (*J Clin Oncol*. 2014; 32: 1919-26) [see Section 7.1.3]. The secondary endpoints of the median durations of CR and CRh [95%CI] in Study 0301 were 421 [134, not estimable (NE)] and 122 [31, 252] days, respectively.[31)]

In Study 0301, patients who were considered by the investigator to be eligible for HSCT were allowed to undergo HSCT[32)] without withdrawing from the study and, if they met the specified criteria,[33)] to resume treatment with gilteritinib after HSCT. PMDA asked the applicant to explain the rate of CR+CRh prior to HSCT.

The applicant's response:

In Study 0301, 8 patients achieved first CR or CRh after HSCT. After excluding these patients, the CR+CRh rate [95% CI] was 22.5% [16.0%, 30.3%] (32 of 142 patients) (18 patients with a CR, 14 patients with a CRh). Gilteritinib therapy resulted in a certain level of CR+CRh rate prior to HSCT also.

The applicant's explanation about the efficacy of gilteritinib in Japanese patients:

The efficacy in Japanese population has not been fully evaluated because of the limited number of Japanese patients enrolled in Study 0301. However, as there were no clear differences in the CR+CRh rate between the overall population and the Japanese subgroup [see Section 7.1.3.1], gilteritinib is expected to be effective also in Japanese patients.

PMDA's discussion:

PMDA has concluded that gilteritinib was shown to have a certain level of efficacy of in patients with *FLT3* mutation-positive relapsed or refractory AML, for the following reasons.

- In Study 0301, gilteritinib therapy resulted in a certain level of CR+CRh rate.
- In Study 0301, there were no clear differences in the CR+CRh rate between the overall population and the Japanese subgroup, although the efficacy in Japanese population has not been fully evaluated because of the limited number of Japanese patients enrolled in the study.

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31) At the first interim analysis, 19 of 40 patients remained in CR or CRh.

32) Patients were required to discontinue gilteritinib before receiving a conditioning regimen for HSCT.

33) Patients were allowed to resume gilteritinib if they met all of the following criteria: (1) a lapse of 30-90 days post-HSCT, (2) evidence of successful engraftment as demonstrated by an absolute neutrophil count $\geq 0.5\times10^9$/L and a platelet count $\geq 20\times10^9$/L without transfusions, (3) no Grade ≥2 acute graft versus host disease (GVHD), and (4) achievement of CRc.

The applicant should take necessary actions promptly and appropriately. For example, it should communicate the following data from Study 0301, as they become available, to healthcare professionals: (a) results of the final OS analysis and (b) the CR+CRh rate in the control group.

7.R.4 Safety [for adverse events, see Section "7.3 Adverse events etc. observed in clinical studies"]

PMDA's conclusion:

Based on the following considerations, adverse events that require particular attention following administration of gilteritinib are myelosuppression, infection, hemorrhage, cardiac disorders, hepatic dysfunction, renal disorders, gastrointestinal perforation, interstitial lung disease (ILD), hypersensitivity, and PRES. Attention should be paid to the possible occurrence of these adverse events during treatment with gilteritinib.

Although attention should be paid to the possible occurrence of the above adverse events during treatment with gilteritinib, gilteritinib is tolerable as long as physicians with adequate knowledge of and experience in the treatment of hematological malignancies take appropriate measures, e.g. monitoring for and management of adverse events. However, as there is very limited clinical experience with gilteritinib in Japanese patients, it is necessary to collect further safety information after the market launch [see Section 7.R.6].

7.R.4.1 Safety profile of gilteritinib and differences in safety between Japanese and non-Japanese populations

The applicant's explanation about the safety profile of gilteritinib and differences in safety between Japanese and non-Japanese populations, based on safety information from Study 0301:

(a) Safety profile of gilteritinib

Safety data from Study 0301 are summarized in Table 27.

Table 27. Summary of safety data (Study 0301)

	n (%)		
	Overall population	Japanese	Non-Japanese
	N = 168	N = 24	N = 144
All adverse events	167 (99.4)	24 (100)	143 (99.3)
Grade 3 or higher adverse events	156 (92.9)	22 (91.7)	134 (93.1)
Adverse events leading to death	43 (25.6)	1 (4.2)	42 (29.2)
Serious adverse events	125 (74.4)	13 (54.2)	112 (77.8)
Adverse events leading to treatment discontinuation	34 (20.2)	2 (8.3)	32 (22.2)
Adverse events leading to dose interruption	66 (39.3)	12 (50.0)	54 (37.5)
Adverse events leading to dose reduction	15 (8.9)	2 (8.3)	13 (9.0)

Adverse events of any grade reported by ≥20% of subjects in Study 0301 are shown in Table 28.

Table 28. Adverse events reported by ≥20% of subjects (Study 0301)

MedDRA PT (MedDRA/J ver.19.1)	n (%) Gilteritinib N = 168	
	All Grades	Grade 3 or higher
Any adverse event	167 (99.4)	156 (92.9)
Febrile neutropenia	82 (48.8)	82 (48.8)
Anaemia	69 (41.1)	58 (34.5)
ALT increased	64 (38.1)	22 (13.1)
AST increased	59 (35.1)	25 (14.9)
Pyrexia	58 (34.5)	5 (3.0)
Nausea	54 (32.1)	3 (1.8)
Diarrhoea	53 (31.5)	3 (1.8)
Fatigue	49 (29.2)	3 (1.8)
Constipation	49 (29.2)	2 (1.2)
Cough	48 (28.6)	1 (0.6)
Hypokalaemia	45 (26.8)	20 (11.9)
Headache	42 (25.0)	3 (1.8)
Platelet count decreased	40 (23.8)	37 (22.0)
Blood ALP increased	40 (23.8)	5 (3.0)
Dyspnoea	39 (23.2)	7 (4.2)
Vomiting	38 (22.6)	1 (0.6)
Thrombocytopenia	37 (22.0)	31 (18.5)
Oedema peripheral	35 (20.8)	1 (0.6)

Serious adverse events reported by ≥1.5% of subjects were febrile neutropenia (53 subjects [31.5%]); disease progression (29 subjects [17.3%]); pyrexia (18 subjects [10.7%]); pneumonia (15 subjects [8.9%]); lung infection (10 subjects [6.0%]); sepsis; and ALT increased (8 subjects each [4.8%]); bacteraemia; septic shock; and acute kidney injury (7 subjects each [4.2%]); anaemia; diarrhoea; and AST increased (6 subjects each [3.6%]); hypotension (5 subjects [3.0%]); staphylococcal bacteraemia; fall; syncope; dyspnoea; and respiratory failure (4 subjects each [2.4%]); pancytopenia; thrombocytopenia; cardiac arrest; cardiac failure; pericarditis; fatigue; bronchitis; cellulitis; device related infection; headache; and acute respiratory distress syndrome (3 subjects each [1.8%]). A causal relationship to gilteritinib could not be ruled out for febrile neutropenia (16 subjects); pneumonia; ALT increased; and AST increased (6 subjects each); anaemia (4 subjects); thrombocytopenia; and pericarditis (3 subjects each); acute kidney injury; cardiac failure; device related infection; and headache (2 subjects each); pyrexia; sepsis; pancytopenia; hypotension; bronchitis; cellulitis; and syncope (1 subject each). Adverse events leading to treatment discontinuation reported by ≥5% of subjects were disease progression (10 subjects [6.0%]). Adverse events leading to dose interruption reported by ≥5% of subjects were febrile neutropenia (14 subjects [8.3%]), ALT increased (13 subjects [7.7%]), and AST increased (12 subjects [7.1%]). There were no adverse events leading to dose reduction reported by ≥5% of subjects.

Laboratory abnormalities,[34)] regardless of whether they were reported as adverse events, in Study 0301, are shown in Table 29.

[34)] Clinical chemistry findings are listed in this section.

Table 29. Laboratory abnormalities reported by ≥10% of subjects (Study 0301)

NCI-CTCAE ver.4.03 CTCAE Terms (MedDRA/J ver.19.1)	n (%)	
	Gilteritinib N = 168	
	All Grades	Grade 3 or higher
Laboratory abnormalities	167 (99.4)	71 (42.3)
Creatinine increased	154 (91.7)	5 (3.0)
Hyperglycaemia	152 (90.5)	18 (10.7)
Hypertriglyceridaemia	132 (78.6)	8 (4.8)
AST increased	128 (76.2)	15 (8.9)
ALT increased	125 (74.4)	18 (10.7)
ALP increased	100 (59.5)	1 (0.6)
Hypocalcaemia	92 (54.8)	9 (5.4)
Hypoalbuminaemia	82 (48.8)	5 (3.0)
CK increased	74 (44.0)	7 (4.2)
Hypophosphataemia	72 (42.9)	18 (10.7)
Hyponatraemia	59 (35.1)	20 (11.9)
Hypokalaemia	54 (32.1)	12 (7.1)
Hypermagnesaemia	32 (19.0)	5 (3.0)
Blood bilirubin increased	30 (17.9)	4 (2.4)
Hypomagnesaemia	28 (16.7)	0

(b) Differences in safety between Japanese and non-Japanese populations

Safety data in Japanese and non-Japanese patients in Study 0301 are shown in Table 27.

Adverse events reported at a ≥15% higher incidence in the Japanese subgroup than in the non-Japanese subgroup were blood LDH increased (8 subjects [33.3%] in the Japanese subgroup, 6 subjects [4.2%] in the non-Japanese subgroup), blood CK increased (6 subjects [25.0%], 10 subjects [6.9%]), and malaise (5 subjects [20.8%], 4 subjects [2.8%]). Grade 3 or higher adverse events reported at a ≥10% higher incidence in the Japanese subgroup than in the non-Japanese subgroup were white blood cell count decreased (6 subjects [25.0%], 16 subjects [11.1%]) and blood LDH increased (3 subjects [12.5%], 2 subjects [1.4%]). Adverse events leading to dose interruption reported at a ≥5% higher incidence in the Japanese subgroup than in the non-Japanese subgroup were ALT increased (4 subjects [16.7%], 9 subjects [6.3%]), neutropenia (2 subjects [8.3%], 0 subjects), hepatic function abnormal (2 subjects [8.3%], 0 subjects), blood LDH increased (2 subjects [8.3%], 0 subjects), and AST increased (3 subjects [12.5%], 9 subjects [6.3%]). There were no serious adverse events or adverse events leading to treatment discontinuation or dose reduction reported at a ≥5% higher incidence in the Japanese subgroup than in the non-Japanese subgroup.

PMDA's discussion:

During treatment with gilteritinib, attention should be paid to the possible occurrence of the following adverse events: (a) adverse events leading to death, serious adverse events, and adverse events leading to treatment discontinuation observed in Study 0301; and (b) adverse events reported at a high incidence in Study 0301. Healthcare professionals in clinical practice should appropriately be informed of the incidence of these events in clinical studies, via package insert etc. Data regarding laboratory abnormalities can be used as reference safety information by physicians when administering gilteritinib to patients. The data should therefore be appropriately provided to healthcare professionals, through information materials etc.

It is difficult to draw a definitive conclusion on the differences in the safety of gilteritinib between Japanese and non-Japanese populations, due to the limited number of Japanese patients. Attention should be paid to adverse events reported at a higher incidence in Japanese patients than in non-Japanese patients. Thus, healthcare professionals in clinical practice should appropriately be informed of the incidence of these events in clinical studies, via information materials etc. It is necessary to collect post-marketing information and appropriately provide any new finding to healthcare professionals in clinical practice.

PMDA conducted a safety review, focusing on adverse events leading to death, serious adverse events, and adverse events reported at a higher incidence in the Japanese subgroup than in the non-Japanese subgroup, based on the safety results from Study 0301. The review results are presented in the following sections.

7.R.4.2 Myelosuppression

The applicant's explanation about the occurrence of myelosuppression associated with gilteritinib:
As myelosuppression-related adverse events, preferred terms (PTs) in the MedDRA SMQs "haematopoietic cytopenias affecting more than one type of blood cell (narrow)," "haematopoietic leucopenia (narrow)," "haematopoietic erythropenia (narrow)," and "haematopoietic thrombocytopenia (narrow)" and MedDRA PT "anaemia" were counted.

The incidence of myelosuppression in Studies 0301, 0102, and 0101 is shown in Table 30.

Table 30. Myelosuppression reported by ≥5% of subjects in any study (Studies 0301, 0102, and 0101)

MedDRA PT (MedDRA/J ver.19.1)	n (%)					
	Study 0301 N = 168		Study 0102 N = 24		Study 0101 N = 252	
	All Grades	Grade 3 or higher	All Grades	Grade 3 or higher	All Grades	Grade 3 or higher
Myelosuppression	130 (77.4)	123 (73.2)	9 (37.5)	7 (29.2)	174 (69.0)	164 (65.1)
Febrile neutropenia	82 (48.8)	82 (48.8)	5 (20.8)	3 (12.5)	100 (39.7)	100 (39.7)
Anaemia	69 (41.1)	58 (34.5)	2 (8.3)	2 (8.3)	88 (34.9)	64 (25.4)
Platelet count decreased	40 (23.8)	37 (22.0)	4 (16.7)	4 (16.7)	42 (16.7)	38 (15.1)
Thrombocytopenia	37 (22.0)	31 (18.5)	0	0	39 (15.5)	33 (13.1)
Neutrophil count decreased	28 (16.7)	28 (16.7)	0	0	27 (10.7)	22 (8.7)
White blood cell count decreased	22 (13.1)	22 (13.1)	0	0	17 (6.7)	15 (6.0)
Neutropenia	16 (9.5)	16 (9.5)	0	0	22 (8.7)	21 (8.3)

In Study 0301, no fatal myelosuppression was reported. Serious myelosuppression occurred in 64 subjects (38.1%) (febrile neutropenia [53 subjects]; anaemia [6 subjects]; pancytopenia; and thrombocytopenia [3 subjects each]; neutropenic sepsis; neutrophil count decreased; and platelet count decreased [2 subjects each]; neutropenia; and white blood cell count decreased [1 subject each] [some subjects were counted more than once because more than one event occurred]). A causal relationship to gilteritinib could not be ruled out for febrile neutropenia (16 subjects); anaemia (4 subjects); thrombocytopenia (3 subjects); neutrophil count decreased (2 subjects); pancytopenia; platelet count decreased; neutropenia; and white blood cell count decreased (1 subject each). Myelosuppression leading to treatment discontinuation occurred in 3 subjects

(1.8%), myelosuppression leading to dose interruption occurred in 21 subjects (12.5%), and myelosuppression leading to dose reduction occurred in 2 subjects (1.2%).

In Study 0102, no fatal myelosuppression was reported. Serious myelosuppression occurred in 1 subject (4.2%) (febrile neutropenia), and its causal relationship to gilteritinib could not be ruled out. There was no myelosuppression leading to treatment discontinuation or dose interruption/reduction.

In Study 0101, fatal myelosuppression occurred in 3 subjects (1.2%) (febrile neutropenia; anaemia; and neutropenia [1 subject each]), and a causal relationship to gilteritinib could not be ruled out for neutropenia. Serious myelosuppression occurred in 89 subjects[35)] (35.3%) (febrile neutropenia [80 subjects]; anaemia [6 subjects]; neutropenia [3 subjects]; pancytopenia; platelet count decreased; and thrombocytopenia [2 subjects each] [some subjects were counted more than once because more than one event occurred]), and a causal relationship to gilteritinib could not be ruled out for febrile neutropenia (5 subjects); neutropenia (2 subjects); anaemia; pancytopenia; and thrombocytopenia (1 subject each). Myelosuppression leading to treatment discontinuation occurred in 6 subjects (2.4%), myelosuppression leading to dose interruption occurred in 22 subjects (8.7%), and myelosuppression leading to dose reduction occurred in 3 subjects (1.2%).

PMDA's discussion:
Attention should be paid to the possible occurrence of myelosuppression during treatment with gilteritinib because, in Japanese and foreign clinical studies, there were many cases of Grade 3 or higher myelosuppression associated with gilteritinib and multiple cases of fatal or serious myelosuppression for which a causal relationship to gilteritinib could not be ruled out. Thus, healthcare professionals in clinical practice should be informed of the incidence of myelosuppression in clinical studies. The package insert etc. should appropriately advise physicians to perform periodic hematologic monitoring during therapy so that action such as dose interruption/reduction, can be taken if any abnormality is detected.

[35)] In Study 0101, 7 of 84 subjects with serious myelosuppression had received gilteritinib at higher doses than the proposed dose: 300 mg (6 subjects) and 450 mg (1 subject) (anaemia).

7.R.4.3 Infection

The applicant's explanation about the occurrence of infections associated with gilteritinib:
As infection-related adverse events, PTs in the MedDRA SOC "infections and infestations" were counted.

The incidence of infections in Studies 0301, 0102, and 0101 is shown in Table 31.

Table 31. Infections reported by ≥5% of subjects in any study (Studies 0301, 0102, and 0101)

MedDRA PT (MedDRA/J ver.19.1)	n (%)					
	Study 0301 N = 168		Study 0102 N = 24		Study 0101 N = 252	
	All Grades	Grade 3 or higher	All Grades	Grade 3 or higher	All Grades	Grade 3 or higher
Infection	126 (75.0)	77 (45.8)	10 (41.7)	6 (25.0)	170 (67.5)	125 (49.6)
Pneumonia	27 (16.1)	15 (8.9)	5 (20.8)	3 (12.5)	42 (16.7)	36 (14.3)
Lung infection	16 (9.5)	14 (8.3)	2 (8.3)	1 (4.2)	16 (6.3)	11 (4.4)
Cellulitis	12 (7.1)	5 (3.0)	1 (4.2)	0	14 (5.6)	9 (3.6)
Bacteraemia	11 (6.5)	9 (5.4)	0	0	21 (8.3)	18 (7.1)
Sepsis	10 (6.0)	10 (6.0)	2 (8.3)	1 (4.2)	39 (15.5)	38 (15.1)
Sinusitis	10 (6.0)	5 (3.0)	0	0	8 (3.2)	5 (2.0)
Upper respiratory tract infection	9 (5.4)	1 (0.6)	1 (4.2)	0	18 (7.1)	4 (1.6)
Urinary tract infection	8 (4.8)	3 (1.8)	0	0	23 (9.1)	12 (4.8)
Pneumonia fungal	3 (1.8)	2 (1.2)	0	0	15 (6.0)	12 (4.8)

In Study 0301, fatal infections occurred in 15 subjects (8.9%) (septic shock [5 subjects]; sepsis [2 subjects]; bacterial colitis; bronchopulmonary aspergillosis; cellulitis; infection; lower respiratory tract infection bacterial; lung infection; respiratory tract infection fungal; and sinusitis fungal [1 subject each]), and a causal relationship to gilteritinib could not be ruled out for cellulitis. Serious infections occurred in 66 subjects (39.3%) (Events reported by ≥3 subjects were pneumonia [15 subjects]; lung infection [10 subjects]; sepsis [8 subjects]; bacteraemia; and septic shock [7 subjects each]; staphylococcal bacteraemia [4 subjects]; bronchitis; cellulitis; and device related infection [3 subjects each] [some subjects were counted more than once because more than one event occurred]), and a causal relationship to gilteritinib could not be ruled out for pneumonia (6 subjects); device related infection (2 subjects); sepsis; bronchitis; and cellulitis (1 subject each). Infections leading to treatment discontinuation occurred in 8 subjects (4.8%), infections leading to dose interruption occurred in 14 subjects (8.3%), and infections leading to dose reduction occurred in 2 subjects (1.2%).

In Study 0102, no fatal infections were reported. Serious infections occurred in 3 subjects (12.5%) (pneumonia [2 subjects]; bronchopulmonary aspergillosis; device related infection; and sepsis [1 subject each] [some subjects were counted more than once because more than one event occurred]), and a causal relationship to gilteritinib could not be ruled out for pneumonia; and device related infection (1 subject each). Infections leading to treatment discontinuation occurred in 2 subjects (8.3%), infection leading to dose interruption occurred in 1 subject (4.2%), and infection leading to dose reduction occurred in 1 subject (4.2%).

In Study 0101, fatal infections occurred in 27 subjects (10.7%) (sepsis [9 subjects]; septic shock [5 subjects]; pneumonia [4 subjects]; bronchopulmonary aspergillosis; and staphylococcal sepsis [2 subjects each]; bacteraemia; bacterial infection; cellulitis; hepatic infection; lung infection; and staphylococcal bacteraemia [1

subject each] [some subjects were counted more than once because more than one event occurred]), and a causal relationship to gilteritinib could not be ruled out for septic shock (1 subject). Serious infections occurred in 120 subjects[36] (47.6%) (Events reported by ≥3 subjects were sepsis [39 subjects]; pneumonia [33 subjects]; bacteraemia [14 subjects]; pneumonia fungal [11 subjects]; lung infection [9 subjects]; cellulitis; and urinary tract infection [8 subjects each]; clostridium difficile colitis; and septic shock [7 subjects each]; bronchopulmonary aspergillosis; clostridium difficile infection; skin infection; streptococcal bacteraemia; and upper respiratory tract infection [4 subjects each]; enterococcal bacteraemia; Klebsiella bacteraemia; and sinusitis [3 subjects each] [some subjects were counted more than once because more than one event occurred]), and a causal relationship to gilteritinib could not be ruled out for sepsis; and streptococcal bacteraemia (2 subjects each); bacteraemia; clostridium difficile colitis; and septic shock (1 subject each). Infections leading to treatment discontinuation occurred in 29 subjects (11.5%), infections leading to dose interruption occurred in 32 subjects (12.7%), and no infections leading to dose reduction occurred.

PMDA's discussion:
In Japanese and foreign clinical studies, there were many cases of Grade 3 or higher infections associated with gilteritinib and multiple cases of fatal or serious infections for which a causal relationship to gilteritinib could not be ruled out. Attention should therefore be paid to the possible occurrence of infections during the use of gilteritinib. Thus, healthcare professionals in clinical practice should appropriately be informed of the incidence of infections in clinical studies, via package insert etc.

7.R.4.4 Haemorrhage

The applicant's explanation about the occurrence of haemorrhage associated with gilteritinib:
As haemorrhage-related adverse events, PTs in the MedDRA SMQs "gastrointestinal haemorrhage (broad)" and "haemorrhage terms (excl laboratory terms) (narrow)" were counted.

The incidence of haemorrhage in Studies 0301, 0102, and 0101 is shown in Table 32.

[36] In Study 0101, 9 of 120 subjects with serious infections had received gilteritinib at a higher dose (300 mg) than the proposed dose.

Table 32. Haemorrhage reported by ≥5% of subjects in any study (Studies 0301, 0102, and 0101)

MedDRA PT (MedDRA/J ver.19.1)	n (%)					
	Study 0301 N = 168		Study 0102 N = 24		Study 0101 N = 252	
	All Grades	Grade 3 or higher	All Grades	Grade 3 or higher	All Grades	Grade 3 or higher
Haemorrhage	87 (51.8)	16 (9.5)	12 (50.0)	4 (16.7)	132 (52.4)	33 (13.1)
Epistaxis	26 (15.5)	1 (0.6)	2 (8.3)	0	52 (20.6)	3 (1.2)
Retinal haemorrhage	12 (7.1)	0	1 (4.2)	0	4 (1.6)	0
Haematuria	11 (6.5)	1 (0.6)	0	0	10 (4.0)	0
Petechiae	9 (5.4)	2 (1.2)	1 (4.2)	0	19 (7.5)	0
Mouth haemorrhage	9 (5.4)	0	0	0	13 (5.2)	0
Haematoma	7 (4.2)	1 (0.6)	2 (8.3)	0	14 (5.6)	2 (0.8)
Disseminated intravascular coagulation	6 (3.6)	2 (1.2)	4 (16.7)	3 (12.5)	4 (1.6)	4 (1.6)
Contusion	6 (3.6)	0	1 (4.2)	0	19 (7.5)	0
Ecchymosis	2 (1.2)	0	0	0	16 (6.3)	0
Subdural haematoma	1 (0.6)	1 (0.6)	2 (8.3)	1 (4.2)	7 (2.8)	6 (2.4)

In Study 0301, fatal haemorrhage occurred in 2 subjects (1.2%) (cerebral haemorrhage [2 subjects]), and a causal relationship to gilteritinib could not be ruled for 1 case of cerebral haemorrhage. Serious haemorrhage occurred in 12 subjects (7.1%) (cerebral haemorrhage; disseminated intravascular coagulation; haematoma; and mouth haemorrhage [2 subjects each]; haemorrhage; petechiae; subdural haematoma; vaginal haemorrhage; haematochezia; haemorrhage intracranial; lower gastrointestinal haemorrhage; pericardial haemorrhage; subarachnoid haemorrhage; and tongue haematoma [1 subject each] [some subjects were counted more than once because more than one event occurred]), and a causal relationship to gilteritinib could not be ruled out for cerebral haemorrhage; mouth haemorrhage; haemorrhage; petechiae; subdural haematoma; and vaginal haemorrhage (1 subject each). Haemorrhage leading to treatment discontinuation occurred in 2 subjects (1.2%), haemorrhage leading to dose interruption occurred in 3 subjects (1.8%), and haemorrhage leading to dose reduction occurred in 1 subject (0.6%).

In Study 0102, fatal haemorrhage occurred in 1 subject (4.2%) (subdural haematoma), and its causal relationship to gilteritinib could not be ruled out. Serious haemorrhage occurred in 2 subjects (8.3%) (subdural haematoma [2 subjects]), and their causal relationship to gilteritinib could not be ruled out. Haemorrhage leading to treatment discontinuation occurred in 1 subject (4.2%), haemorrhage leading to dose interruption occurred in 1 subject (4.2%), and no haemorrhage leading to dose reduction occurred.

In Study 0101, fatal haemorrhage occurred in 5 subjects (2.0%) (haemorrhage intracranial [4 subjects]; haemoptysis [1 subject in the 80 mg group]), and a causal relationship to gilteritinib could not be ruled out for haemorrhage intracranial; and haemoptysis (1 subject each). Serious haemorrhage occurred in 31 subjects[37)] (12.3%) (gastrointestinal haemorrhage; and subdural haematoma [6 subjects each]; haemorrhage intracranial [4 subjects]; haematoma [3 subjects]; disseminated intravascular coagulation; epistaxis; and lower gastrointestinal haemorrhage [2 subjects each]; gastric haemorrhage; haematemesis; haematochezia; haemoptysis; haemorrhage; post procedural haemorrhage; pulmonary haemorrhage; rectal haemorrhage; and

[37)] In Study 0101, 3 of 31 subjects with serious haemorrhage had received gilteritinib at a higher dose (300 mg) than the proposed dose.

upper gastrointestinal haemorrhage [1 subject each] [some subjects were counted more than once because more than one event occurred]), and a causal relationship to gilteritinib could not be ruled out for gastrointestinal haemorrhage (3 subjects); lower gastrointestinal haemorrhage (2 subjects); subdural haematoma; haemorrhage intracranial; disseminated intravascular coagulation; gastric haemorrhage; haematochezia; haematoma; and haemoptysis (1 subject each). Haemorrhage leading to treatment discontinuation occurred in 8 subjects (3.2%), haemorrhage leading to dose interruption occurred in 12 subjects (4.8%), and no haemorrhage leading to dose reduction occurred.

PMDA's discussion:
In Japanese and foreign clinical studies, there were multiple cases of fatal or serious haemorrhage for which a causal relationship to gilteritinib could not be ruled out. Attention should therefore be paid to the possible occurrence of haemorrhage during the use of gilteritinib. Thus, healthcare professionals in clinical practice should be informed of the incidence of haemorrhage in clinical studies. The package insert etc. should appropriately advise physicians to perform periodic hematologic monitoring during therapy so that action such as dose interruption/reduction, can be taken if any abnormality is detected.

7.R.4.5 Cardiac disorders

The applicant's explanation about the occurrence of cardiac disorders associated with gilteritinib:
As cardiac disorder-related adverse events, PTs in the MedDRA SMQs "cardiac failure (narrow)" and "torsade de pointes/QT prolongation (broad)," PTs in the MedDRA HLT "noninfectious pericarditis," and MedDRA PT "pericardial effusion" were counted.

The incidence of cardiac disorders in Studies 0301, 0102, and 0101 is shown in Table 33.

Table 33. Incidence of cardiac disorders (Studies 0301, 0102, and 0101)

MedDRA PT (MedDRA/J ver.19.1)	n (%)					
	Study 0301 N = 168		Study 0102 N = 24		Study 0101 N = 252	
	All Grades	Grade 3 or higher	All Grades	Grade 3 or higher	All Grades	Grade 3 or higher
Cardiac disorder	40 (23.8)	19 (11.3)	4 (16.7)	3 (12.5)	59 (23.4)	39 (15.5)
Electrocardiogram QT prolonged	10 (6.0)	1 (0.6)	2 (8.3)	1 (4.2)	21 (8.3)	9 (3.6)
Pulmonary oedema	9 (5.4)	1 (0.6)	0	0	4 (1.6)	1 (0.4)
Syncope	6 (3.6)	6 (3.6)	2 (8.3)	2 (8.3)	15 (6.0)	13 (5.2)
Pericardial effusion	6 (3.6)	2 (1.2)	0	0	8 (3.2)	2 (0.8)
Pericarditis	5 (3.0)	0	0	0	3 (1.2)	1 (0.4)
Cardiac failure	4 (2.4)	4 (2.4)	0	0	1 (0.4)	0
Cardiac arrest	3 (1.8)	3 (1.8)	0	0	2 (0.8)	2 (0.8)
Cardiac failure congestive	2 (1.2)	2 (1.2)	0	0	4 (1.6)	4 (1.6)
Ejection fraction decreased	2 (1.2)	2 (1.2)	0	0	6 (2.4)	5 (2.0)
Ventricular tachycardia	2 (1.2)	0	0	0	1 (0.4)	1 (0.4)
Acute pulmonary oedema	1 (0.6)	1 (0.6)	0	0	0	0
Hepatic congestion	1 (0.6)	1 (0.6)	0	0	0	0
Chronic left ventricular failure	1 (0.6)	0	0	0	0	0
Loss of consciousness	0	0	0	0	2 (0.8)	1 (0.4)
Ventricular fibrillation	0	0	0	0	1 (0.4)	1 (0.4)
Sudden death	0	0	0	0	1 (0.4)	1 (0.4)
Ventricular arrhythmia	0	0	0	0	1 (0.4)	0

In Study 0301, fatal cardiac disorders occurred in 6 subjects (3.6%) (cardiac arrest [3 subjects]; pericardial effusion [2 subjects]; cardiac failure congestive [1 subject]), and a causal relationship to gilteritinib could not be ruled out for cardiac failure congestive. Serious cardiac disorders occurred in 17 subjects (10.1%) (syncope [4 subjects]; cardiac arrest; cardiac failure; and pericarditis [3 subjects each]; cardiac failure congestive; and pericardial effusion [2 subjects each]; electrocardiogram QT prolonged [1 subject] [some subjects were counted more than once because more than one event occurred]), and a causal relationship to gilteritinib could not be ruled out for pericarditis (3 subjects); cardiac failure (2 subjects); cardiac failure congestive; electrocardiogram QT prolonged; and syncope (1 subject each). Cardiac disorders leading to treatment discontinuation occurred in 3 subjects (1.8%), cardiac disorders leading to dose interruption occurred in 5 subjects (3.0%), and cardiac disorders leading to dose reduction occurred in 4 subjects (2.4%).

In Study 0102, there were no fatal or serious cardiac disorders or cardiac disorders leading to treatment discontinuation or dose interruption/reduction.

In Study 0101, fatal cardiac disorders occurred in 5 subjects[38)] (2.0%) (ventricular fibrillation; loss of consciousness; sudden death; ventricular tachycardia; and cardiac arrest [1 subject each]), and a causal relationship to gilteritinib could not be ruled out for ventricular fibrillation. Serious cardiac disorders occurred

38) In Study 0101, 1 of 5 subjects with fatal cardiac disorders had received gilteritinib at a higher dose (450 mg) than the proposed dose.

in 23 subjects[39] (9.1%) (syncope [6 subjects]; cardiac failure congestive; and ejection fraction decreased [3 subjects each]; cardiac arrest; and pericardial effusion [2 subjects each]; cardiac failure; electrocardiogram QT prolonged; loss of consciousness; pericarditis; sudden death; ventricular fibrillation; and ventricular tachycardia [1 subject each]), and a causal relationship to gilteritinib could not be ruled out for syncope; cardiac failure congestive; electrocardiogram QT prolonged; pericardial effusion; pericarditis; and ventricular fibrillation (1 subject each). Cardiac disorders leading to treatment discontinuation occurred in 5 subjects (2.0%), cardiac disorders leading to dose interruption occurred in 10 subjects (4.0%), and cardiac disorder leading to dose reduction occurred in 1 subject (0.4%).

The applicant's explanation about the need for a precautionary statement regarding prolonged QT interval following administration of gilteritinib:
In Study 0301, 12-lead ECGs were performed periodically. Patients were excluded from enrollment if they had a QTcF >450 ms, long QT syndrome, or hypokalaemia and hypomagnesaemia at screening. The investigators were advised to exercise caution when administrating gilteritinib in combination with drugs that prolong QT or QTc interval.

QTcF changes in patients with QTcF data in Study 0301 are shown in Table 34.

Table 34. QTcF changes in patients with QTcF data (Study 0301)

	n (%)
	N = 167
Maximum QTcF	
≤450 ms	119 (71.3)
>450 ms and ≤480 ms	41 (24.6)
>480 ms and ≤500 ms	6 (3.6)
>500 ms	1 (0.6)
Increase from baseline (maximum value)	
<0 ms	19 (11.4)
≥0 ms and ≤30 ms	107 (64.1)
>30 ms and ≤60 ms	33 (19.8)
>60 ms	8 (4.8)

As shown above, some patients had serious electrocardiogram QT prolonged for which a causal relationship to gilteritinib could not be ruled out in clinical studies, and a patient had a QTcF value of >500 ms in Study 0301. Thus, a precautionary statement regarding prolonged QT interval will be included in the package insert etc.

PMDA's discussion:
In Studies 0301 and 0101, there were multiple cases of fatal or serious cardiac disorders for which a causal relationship to gilteritinib could not be ruled out. Attention should therefore be paid to the possible occurrence of cardiac disorders, such as prolonged QT interval, cardiac failure, pericarditis, and pericardial effusion, during

[39] In Study 0101, 1 of 23 subjects with serious cardiac disorders had received gilteritinib at a higher dose (450 mg) than the proposed dose.

treatment with gilteritinib. Thus, healthcare professionals in clinical practice should appropriately be informed of the incidence of these events in clinical studies, via package insert etc.

As to prolonged QT interval following administration of gilteritinib, the package insert etc. should appropriately advise physicians to perform ECG and electrolyte test (potassium, magnesium, etc.) at baseline and periodically during therapy so that action such as dose interruption/reduction and correction of electrolytes, can be taken if any abnormality is detected.

7.R.4.6 Hepatic dysfunction

The applicant's explanation about the occurrence of hepatic dysfunction associated with gilteritinib:
As hepatic dysfunction-related adverse events, PTs in the MedDRA SMQ "liver related investigations, signs and symptoms (narrow)" were counted.

The incidence of hepatic dysfunction in Studies 0301, 0102, and 0101 is shown in Table 35.

Table 35. Hepatic dysfunction reported by ≥3% of subjects in any study (Studies 0301, 0102, and 0101)

MedDRA PT (MedDRA/J ver.19.1)	n (%)					
	Study 0301 N = 168		Study 0102 N = 24		Study 0101 N = 252	
	All Grades	Grade 3 or higher	All Grades	Grade 3 or higher	All Grades	Grade 3 or higher
Hepatic dysfunction	80 (47.6)	38 (22.6)	14 (58.3)	0	104 (41.3)	37 (14.7)
ALT increased	64 (38.1)	22 (13.1)	2 (8.3)	0	52 (20.6)	14 (5.6)
AST increased	59 (35.1)	25 (14.9)	2 (8.3)	0	68 (27.0)	17 (6.7)
Blood bilirubin increased	14 (8.3)	8 (4.8)	1 (4.2)	0	24 (9.5)	8 (3.2)
GGT increased	6 (3.6)	4 (2.4)	0	0	1 (0.4)	1 (0.4)
Hyperbilirubinaemia	5 (3.0)	2 (1.2)	0	0	13 (5.2)	5 (2.0)
Transaminases increased	4 (2.4)	1 (0.6)	0	0	16 (6.3)	7 (2.8)
Hepatic function abnormal	3 (1.8)	1 (0.6)	9 (37.5)	0	0	0
Ammonia increased	0	0	1 (4.2)	0	0	0
Liver function test abnormal	0	0	1 (4.2)	0	0	0

In Study 0301, no fatal hepatic dysfunction was reported. Serious hepatic dysfunction occurred in 10 subjects (6.0%) (ALT increased [8 subjects]; AST increased [6 subjects]; blood bilirubin increased [2 subjects]; GGT increased; hepatic function abnormal; and transaminases increased [1 subject each] [some subjects were counted more than once because more than one event occurred]), and a causal relationship to gilteritinib could not be ruled out for ALT increased; and AST increased (6 subjects each); blood bilirubin increased; GGT increased; hepatic function abnormal; and transaminases increased (1 subject each). Hepatic dysfunction leading to treatment discontinuation occurred in 2 subjects (1.2%), hepatic dysfunction leading to dose interruption occurred in 21 subjects (12.5%), and hepatic dysfunction leading to dose reduction occurred in 3 subjects (1.8%).

In Study 0102, there was no fatal or serious hepatic dysfunction or hepatic dysfunction leading to treatment discontinuation or dose interruption/reduction.

In Study 0101, no fatal hepatic dysfunction was reported. Serious hepatic dysfunction occurred in 13 subjects[40] (5.2%) (AST increased; and blood bilirubin increased [4 subjects each]; hyperbilirubinaemia [3 subjects]; ALT increased; and transaminases increased [2 subjects each] [some subjects were counted more than once because more than one event occurred]), and a causal relationship to gilteritinib could not be ruled out for AST increased (4 subjects); blood bilirubin increased (3 subjects); ALT increased; and transaminases increased (2 subjects each); and hyperbilirubinaemia (1 subject). Hepatic dysfunction leading to treatment discontinuation occurred in 3 subjects (1.2%), hepatic dysfunction leading to dose interruption occurred in 16 subjects (6.3%), and hepatic dysfunction leading to dose reduction occurred in 2 subjects (0.8%).

PMDA's discussion:
In Japanese and foreign clinical studies, there were many cases of Grade 3 or higher hepatic dysfunction associated with gilteritinib and multiple cases of serious hepatic dysfunction for which a causal relationship to gilteritinib could not be ruled out. Attention should therefore be paid to the possible occurrence of hepatic dysfunction during treatment with gilteritinib. Thus, healthcare professionals in clinical practice should be informed of the incidence of hepatic dysfunction in clinical studies. The package insert etc. should appropriately advise physicians to perform periodic blood tests during therapy so that action such as dose interruption/reduction, can be taken if any abnormality is detected.

7.R.4.7 Renal disorders

The applicant's explanation about the occurrence of renal disorders associated with gilteritinib:
As renal disorder-related adverse events, PTs in the MedDRA SMQ "acute renal failure (broad)" were counted.

The incidence of renal disorders in Studies 0301, 0102, and 0101 is shown in Table 36.

Table 36. Incidence of renal disorders (Studies 0301, 0102, and 0101)

MedDRA PT (MedDRA/J ver.19.1)	n (%)					
	Study 0301 N = 168		Study 0102 N = 24		Study 0101 N = 252	
	All Grades	Grade 3 or higher	All Grades	Grade 3 or higher	All Grades	Grade 3 or higher
Renal disorder	41 (24.4)	7 (4.2)	6 (25.0)	0	69 (27.4)	19 (7.5)
Blood creatinine increased	21 (12.5)	3 (1.8)	1 (4.2)	0	43 (17.1)	5 (2.0)
Acute kidney injury	13 (7.7)	6 (3.6)	0	0	27 (10.7)	10 (4.0)
Proteinuria	8 (4.8)	0	0	0	1 (0.4)	0
Azotaemia	3 (1.8)	0	0	0	0	0
Oliguria	2 (1.2)	1 (0.6)	0	0	0	0
Renal failure	2 (1.2)	0	0	0	7 (2.8)	4 (1.6)
Blood urea increased	1 (0.6)	0	0	0	3 (1.2)	1 (0.4)
Renal impairment	0	0	5 (20.8)	0	2 (0.8)	0
Glomerular filtration rate decreased	0	0	0	0	3 (1.2)	0
Renal tubular necrosis	0	0	0	0	2 (0.8)	2 (0.8)
Urine output decreased	0	0	0	0	1 (0.4)	0

[40] In Study 0101, 2 of 13 subjects with serious hepatic dysfunction had received gilteritinib at higher doses than the proposed dose: 300 mg and 450 mg (1 subject each).

In Study 0301, no fatal renal disorders were reported. Serious renal disorders occurred in 7 subjects (4.2%) (acute kidney injury [7 subjects]; blood creatinine increased [1 subject] [some subjects were counted more than once because more than one event occurred]), and a causal relationship to gilteritinib could not be ruled out for acute kidney injury (2 subjects) and blood creatinine increased (1 subject). Renal disorders leading to treatment discontinuation occurred in 2 subjects (1.2%), renal disorder leading to dose interruption occurred in 1 subject (0.6%), and no renal disorder leading to dose reduction occurred.

In Study 0102, there were no fatal or serious renal disorders or renal disorders leading to treatment discontinuation or dose interruption/reduction.

In Study 0101, fatal renal disorders occurred in 2 subjects[41)] (0.8%) (renal failure [2 subjects]), and their causal relationship to gilteritinib was ruled out. Serious renal disorders occurred in 34 subjects[42)] (13.5%) (acute kidney injury [27 subjects]; blood creatinine increased; and renal failure [3 subjects each]; renal tubular necrosis [2 subjects] [some subjects were counted more than once because more than one event occurred]), and a causal relationship to gilteritinib could not be ruled out for acute kidney injury (5 subjects); blood creatinine increased; and renal tubular necrosis (1 subject each) (some subjects were counted more than once because more than one event occurred). Renal disorder leading to treatment discontinuation occurred in 1 subject (0.4%), renal disorders leading to dose interruption occurred in 6 subjects (2.4%), and renal disorder leading to dose reduction occurred in 1 subject (0.4%).

PMDA's discussion:
In Studies 0301 and 0101, there were multiple cases of serious renal disorders for which a causal relationship to gilteritinib could not be ruled out. Attention should therefore be paid to the possible occurrence of renal disorders during treatment with gilteritinib. Thus, healthcare professionals in clinical practice should be informed of the incidence of renal disorders in clinical studies. The package insert etc. should appropriately advise physicians to perform periodic blood tests during therapy so that action such as dose interruption/reduction, can be taken if any abnormality is detected.

7.R.4.8 Gastrointestinal perforation

The applicant's explanation about the occurrence of gastrointestinal perforation associated with gilteritinib:
As gastrointestinal perforation-related adverse events, PTs in the MedDRA SMQ "gastrointestinal perforation (narrow)" were counted.

In Study 0301, gastrointestinal perforation of any grade occurred in 4 subjects (2.4%) (large intestine perforation [2 subjects]; perirectal abscess; and anal abscess [1 subject each]), and all those events were of Grade 3 or higher severity. Fatal gastrointestinal perforation occurred in 2 subjects (1.2%) (large intestine perforation [2 subjects]), and their causal relationship to gilteritinib could not be ruled out. Serious

41) In Study 0101, 1 of 2 subjects with fatal renal disorders had received gilteritinib at a higher dose (300 mg) than the proposed dose.
42) In Study 0101, 2 of 34 subjects with serious renal disorders had received gilteritinib at a higher dose (300 mg) than the proposed dose.

gastrointestinal perforation occurred in 3 subjects (1.8%) (large intestine perforation [2 subjects]; perirectal abscess [1 subject]), and a causal relationship to gilteritinib could not be ruled out for large intestine perforation (2 subjects). Gastrointestinal perforation leading to treatment discontinuation occurred in 1 subject (0.6%), gastrointestinal perforation leading to dose interruption occurred in 1 subject (0.6%), and no gastrointestinal perforation leading to dose reduction occurred.

In Study 0102, no gastrointestinal perforation was reported.

In Study 0101, gastrointestinal perforation of any grade occurred in 3 subjects (1.2%) (intestinal perforation; perirectal abscess; duodenal perforation; and anal fistula [1 subject each] [some subjects were counted more than once because more than one event occurred]), and Grade 3 or higher gastrointestinal perforation occurred in 3 subjects (1.2%) (intestinal perforation; duodenal perforation; and anal fistula [1 subject each]). Serious gastrointestinal perforation occurred in 1 subject (0.4%) (intestinal perforation [1 subject]), and its causal relationship to gilteritinib could not be ruled out. Gastrointestinal perforation leading to dose interruption occurred in 1 subject (0.4%), and no gastrointestinal perforation leading to death, treatment discontinuation, or dose reduction was reported.

PMDA's discussion:
In Studies 0301 and 0101, there were multiple cases of fatal or serious gastrointestinal perforation for which a causal relationship to gilteritinib could not be ruled out. Attention should therefore be paid to the possible occurrence of gastrointestinal perforation during treatment with gilteritinib. Thus, healthcare professionals in clinical practice should appropriately be informed of the incidence of gastrointestinal perforation in clinical studies, via package insert etc.

7.R.4.9 ILD

The applicant's explanation about the occurrence of ILD associated with gilteritinib:
As ILD-related adverse events, PTs in the MedDRA SMQ "interstitial lung disease (broad)" were counted.

The incidence of ILD in Studies 0301 and 0101 is shown in Table 37. No ILD was reported in Study 0102.

Table 37. Incidence of ILD (Studies 0301 and 0101)

MedDRA PT (MedDRA/J ver.19.1)	n (%)			
	Study 0301 N = 168		Study 0101 N = 252	
	All Grades	Grade 3 or higher	All Grades	Grade 3 or higher
ILD	11 (6.5)	6 (3.6)	9 (3.6)	3 (1.2)
Acute respiratory distress syndrome	4 (2.4)	4 (2.4)	1 (0.4)	1 (0.4)
Organising pneumonia	4 (2.4)	1 (0.6)	0	0
ILD	1 (0.6)	1 (0.6)	0	0
Bronchiolitis	1 (0.6)	0	1 (0.4)	0
Lung infiltration	1 (0.6)	0	3 (1.2)	1 (0.4)
Pulmonary fibrosis	1 (0.6)	0	0	0
Pulmonary haemosiderosis	1 (0.6)	0	0	0
Pneumonitis	0	0	3 (1.2)	1 (0.4)
Obliterative bronchiolitis	0	0	1 (0.4)	0

In Study 0301, fatal ILD occurred in 1 subject (0.6%) (acute respiratory distress syndrome), and its causal relationship to gilteritinib was ruled out. Serious ILD occurred in 5 subjects (3.0%) (acute respiratory distress syndrome [3 subjects]; ILD; and organising pneumonia [1 subject each]), and a causal relationship to gilteritinib could not be ruled out for ILD. ILD leading to treatment discontinuation occurred in 2 subjects (1.2%), ILD leading to dose interruption occurred in 1 subject (0.6%), and no ILD leading to dose reduction occurred.

In Study 0101, no fatal ILD was reported. Serious ILD occurred in 3 subjects (1.2%) (acute respiratory distress syndrome; pneumonitis; and lung infiltration [1 subject each]), and a causal relationship to gilteritinib could not be ruled out for pneumonitis. ILD leading to dose interruption occurred in 1 subject (0.4%), and no ILD leading to treatment discontinuation or dose reduction was reported.

PMDA's discussion:
In Studies 0301 and 0101, there were multiple cases of serious ILD for which a causal relationship to gilteritinib could not be ruled out. Attention should therefore be paid to the possible occurrence of ILD during treatment with gilteritinib. Thus, healthcare professionals in clinical practice should appropriately be informed of the incidence of ILD in clinical studies, via package insert etc.

7.R.4.10 Hypersensitivity

The applicant's explanation about the occurrence of hypersensitivity associated with gilteritinib:
As hypersensitivity-related adverse events, PTs in the MedDRA SMQ "hypersensitivity (narrow)" were counted.

The incidence of hypersensitivity in Studies 0301, 0102, and 0101 is shown in Table 38.

Table 38. Hypersensitivity reported by ≥2% of subjects in any study (Studies 0301, 0102, and 0101)

MedDRA PT (MedDRA/J ver.19.1)	n (%)					
	Study 0301 N = 168		Study 0102 N = 24		Study 0101 N = 252	
	All Grades	Grade 3 or higher	All Grades	Grade 3 or higher	All Grades	Grade 3 or higher
Hypersensitivity	58 (34.5)	14 (8.3)	6 (25.0)	0	77 (30.6)	10 (4.0)
Rash	18 (10.7)	0	3 (12.5)	0	25 (9.9)	1 (0.4)
Face oedema	9 (5.4)	1 (0.6)	0	0	8 (3.2)	0
Urticaria	7 (4.2)	3 (1.8)	0	0	3 (1.2)	0
Allergic transfusion reaction	7 (4.2)	0	1 (4.2)	0	1 (0.4)	0
Drug eruption	6 (3.6)	1 (0.6)	0	0	10 (4.0)	0
Drug hypersensitivity	5 (3.0)	2 (1.2)	0	0	1 (0.4)	0
Rash maculo-papular	5 (3.0)	1 (0.6)	0	0	14 (5.6)	1 (0.4)
Periorbital oedema	3 (1.8)	0	0	0	10 (4.0)	1 (0.4)
Rhinitis allergic	2 (1.2)	0	1 (4.2)	0	1 (0.4)	0
Erythema multiforme	1 (0.6)	0	1 (4.2)	0	2 (0.8)	0
Eyelid oedema	1 (0.6)	0	1 (4.2)	0	1 (0.4)	0
Rash pruritic	1 (0.6)	0	0	0	5 (2.0)	0
Epidermolysis	0	0	1 (4.2)	0	0	0

In Study 0301, no fatal hypersensitivity was reported. Serious hypersensitivity occurred in 8 subjects (4.8%) (anaphylactic reaction; and face oedema [2 subjects each]; anaphylactic transfusion reaction; dermatitis bullous; drug hypersensitivity; swelling face; and toxic skin eruption [1 subject each] [some subjects were counted more than once because more than one event occurred]), and a causal relationship to gilteritinib could not be ruled out for anaphylactic reaction; dermatitis bullous; drug hypersensitivity; and toxic skin eruption (1 subject each). Hypersensitivity leading to treatment discontinuation occurred in 1 subject (0.6%), hypersensitivity leading to dose interruption occurred in 4 subjects (2.4%), and hypersensitivity leading to dose reduction occurred in 2 subjects (1.2%).

In Study 0102, there was no fatal or serious hypersensitivity or hypersensitivity leading to treatment discontinuation or dose interruption/reduction.

In Study 0101, no fatal hypersensitivity was reported. Serious hypersensitivity occurred in 6 subjects (2.4%) (anaphylactic reaction; and angioedema [2 subjects each]; conjunctival oedema; and swollen tongue [1 subject each]), and a causal relationship to gilteritinib could not be ruled out for conjunctival oedema. Hypersensitivity leading to dose interruption occurred in 7 subjects (2.8%), and no hypersensitivity leading to treatment discontinuation or dose reduction was reported.

PMDA's discussion:
In Studies 0301 and 0101, there were multiple cases of serious hypersensitivity for which a causal relationship to gilteritinib could not be ruled out. Attention should therefore be paid to the possible occurrence of hypersensitivity during treatment with gilteritinib. Thus, healthcare professionals in clinical practice should appropriately be informed of the incidence of hypersensitivity in clinical studies, via package insert etc.

7.R.4.11 PRES

The applicant's explanation about the occurrence of PRES associated with gilteritinib:

As PRES-related adverse events, PTs in the MedDRA SMQ "noninfectious encephalopathy/delirium (narrow)" were counted.

The incidence of PRES in Studies 0301, 0102, and 0101 is shown in Table 39.

Table 39. Incidence of PRES (Studies 0301, 0102, and 0101)

MedDRA PT (MedDRA/J ver.19.1)	n (%)					
	Study 0301 N = 168		Study 0102 N = 24		Study 0101 N = 252	
	All Grades	Grade 3 or higher	All Grades	Grade 3 or higher	All Grades	Grade 3 or higher
PRES	5 (3.0)	3 (1.8)	1 (4.2)	1 (4.2)	9 (3.6)	5 (2.0)
Delirium	3 (1.8)	1 (0.6)	1 (4.2)	1 (4.2)	5 (2.0)	1 (0.4)
Encephalopathy	1 (0.6)	1 (0.6)	0	0	3 (1.2)	2 (0.8)
PRES	1 (0.6)	1 (0.6)	0	0	2 (0.8)	2 (0.8)

In Study 0301, no fatal PRES was reported. Serious PRES occurred in 1 subject (0.6%) (PRES), and its causal relationship to gilteritinib was ruled out. No PRES leading to treatment discontinuation or dose interruption/reduction was reported.

In Study 0102, no fatal or serious PRES was reported. PRES leading to treatment discontinuation occurred in 1 subject (4.2%) (delirium), and no PRES leading to dose interruption or reduction was reported.

In Study 0101, no fatal PRES was reported. Serious PRES occurred in 3 subjects (1.2%) (PRES [2 subjects]; encephalopathy [1 subject]), and a causal relationship to gilteritinib could not be ruled out for PRES (2 subjects). PRES leading to treatment discontinuation occurred in 1 subject (0.4%), and no PRES leading to dose interruption or reduction was reported.

PMDA's discussion:

In Study 0101, there were patients with serious PRES for which a causal relationship to gilteritinib could not be ruled out. Attention should therefore be paid to the possible occurrence of PRES during treatment with gilteritinib. Thus, healthcare professionals in clinical practice should be informed of the incidence of PRES in clinical studies. The package insert etc. should appropriately advise physicians to watch for the patient's state of consciousness, etc. during therapy so that gilteritinib can be discontinued and tests such as imaging can be performed if any abnormality is detected.

7.R.4.12 Others

The applicant's explanation about the occurrence of (a) rhabdomyolysis/myopathy, which were reported as serious adverse events in clinical studies, and (b) eye disorders, which may be related to toxicity findings (effects on the retina observed in non-clinical studies) that raised safety concerns for clinical use:

(a) Rhabdomyolysis/myopathy

As rhabdomyolysis/myopathy-related adverse events, PTs in the MedDRA SMQ "rhabdomyolysis/myopathy (narrow)" and MedDRA PTs "muscular weakness," "myalgia," "myositis," "Grade 3 or higher blood CK abnormality," "Grade 3 or higher blood CK increased," and "Grade 3 or higher blood CK-MM increased" were counted.

The incidence of rhabdomyolysis/myopathy in Studies 0301, 0102, and 0101 is shown in Table 40.

Table 40. Incidence of rhabdomyolysis/myopathy (Studies 0301, 0102, and 0101)

MedDRA PT (MedDRA/J ver.19.1)	n (%)					
	Study 0301 N = 168		Study 0102 N = 24		Study 0101 N = 252	
	All Grades	Grade 3 or higher	All Grades	Grade 3 or higher	All Grades	Grade 3 or higher
Rhabdomyolysis/Myopathy	41 (24.4)	9 (5.4)	4 (16.7)	3 (12.5)	46 (18.3)	20 (7.9)
Myalgia	23 (13.7)	1 (0.6)	0	0	21 (8.3)	2 (0.8)
Muscular weakness	15 (8.9)	1 (0.6)	1 (4.2)	0	14 (5.6)	5 (2.0)
Blood CK increased	6 (3.6)	6 (3.6)	3 (12.5)	3 (12.5)	13 (5.2)	13 (5.2)
Myopathy	2 (1.2)	0	0	0	1 (0.4)	1 (0.4)
Myositis	1 (0.6)	1 (0.6)	0	0	3 (1.2)	1 (0.4)
Rhabdomyolysis	0	0	0	0	1 (0.4)	1 (0.4)
Necrotising myositis	0	0	0	0	1 (0.4)	0

In Study 0301, serious rhabdomyolysis/myopathy occurred in 1 subject (0.6%) (muscular weakness), and its causal relationship to gilteritinib was ruled out. Rhabdomyolysis/myopathy leading to dose interruption occurred in 3 subjects (1.8%), and there was no rhabdomyolysis/myopathy leading to death, treatment discontinuation, or dose reduction.

In Study 0102, rhabdomyolysis/myopathy leading to treatment discontinuation occurred in 1 subject (4.2%), and rhabdomyolysis/myopathy leading to dose interruption occurred in 2 subjects (8.3%). There was no fatal or serious rhabdomyolysis/myopathy or rhabdomyolysis/myopathy leading to dose reduction.

In Study 0101, no fatal rhabdomyolysis/myopathy was reported. Serious rhabdomyolysis/myopathy occurred in 10 subjects[43)] (4.0%) (blood CK increased [4 subjects]; muscular weakness [2 subjects]; myalgia; myositis; rhabdomyolysis; and necrotising myositis [1 subject each]), and a causal relationship to gilteritinib could not be ruled out for blood CK increased (4 subjects); muscular weakness (2 subjects); myalgia; myositis; and rhabdomyolysis (1 subject each). Rhabdomyolysis/myopathy leading to treatment discontinuation occurred in 5 subjects (2.0%), rhabdomyolysis/myopathy leading to dose interruption occurred in 6 subjects (2.4%), and rhabdomyolysis/myopathy leading to dose reduction occurred in 2 subjects (0.8%).

(b) Eye disorders

As eye disorder-related adverse events, PTs in the MedDRA SOC "eye disorders" were counted.

[43)] In Study 0101, 1 of 10 subjects with serious rhabdomyolysis/myopathy had received gilteritinib at a higher dose (300 mg) than the proposed dose.

The incidence of eye disorders in Studies 0301, 0102, and 0101 is shown in Table 41.

Table 41. Eye disorders reported by ≥2% of subjects in any study (Studies 0301, 0102, and 0101)

MedDRA PT (MedDRA/J ver.19.1)	n (%)					
	Study 0301 N = 168		Study 0102 N = 24		Study 0101 N = 252	
	All Grades	Grade 3 or higher	All Grades	Grade 3 or higher	All Grades	Grade 3 or higher
Eye disorder	69 (41.1)	4 (2.4)	7 (29.2)	0	72 (28.6)	8 (3.2)
Retinal haemorrhage	12 (7.1)	0	1 (4.2)	0	4 (1.6)	0
Dry eye	11 (6.5)	1 (0.6)	1 (4.2)	0	16 (6.3)	0
Vision blurred	11 (6.5)	0	0	0	13 (5.2)	0
Conjunctival haemorrhage	8 (4.8)	0	0	0	8 (3.2)	0
Cataract	4 (2.4)	0	1 (4.2)	0	4 (1.6)	1 (0.4)
Conjunctivitis	4 (2.4)	0	0	0	5 (2.0)	1 (0.4)
Periorbital oedema	3 (1.8)	0	0	0	10 (4.0)	1 (0.4)
Photophobia	2 (1.2)	0	1 (4.2)	0	5 (2.0)	0
Vitreous floaters	2 (1.2)	0	0	0	8 (3.2)	0
Corneal erosion	1 (0.6)	0	4 (16.7)	0	0	0
Eyelid oedema	1 (0.6)	0	1 (4.2)	0	1 (0.4)	0
Seasonal allergy	1 (0.6)	0	1 (4.2)	0	4 (1.6)	0
Blepharitis	1 (0.6)	0	0	0	5 (2.0)	0
Macular fibrosis	0	0	1 (4.2)	0	1 (0.4)	0
Retinal disorder	0	0	1 (4.2)	0	0	0

In Study 0301, serious eye disorders occurred in 2 subjects (1.2%) (ocular hyperaemia; periorbital infection; and vision blurred [1 subject each] [some subjects were counted more than once because more than one event occurred]), and a causal relationship to gilteritinib was ruled out for all those events. Eye disorders leading to dose interruption occurred in 2 subjects (1.2%), and there were no eye disorders leading to death, treatment discontinuation, or dose reduction.

In Study 0102, there were no fatal or serious eye disorders or eye disorders leading to treatment discontinuation or dose interruption/reduction.

In Study 0101, serious eye disorders occurred in 3 subjects (1.2%) (conjunctival oedema; papilloedema; and periorbital infection [1 subject each]), and a causal relationship to gilteritinib could not be ruled out for conjunctival oedema. Eye disorders leading to dose interruption occurred in 6 subjects (2.4%), and there were no eye disorders leading to death, treatment discontinuation, or dose reduction.

PMDA's discussion:

At present, it is difficult to draw a definitive conclusion on the occurrence of rhabdomyolysis/myopathy and eye disorders associated with gilteritinib, for the reasons presented below. It is necessary to collect post-marketing information on the occurrence of these events and appropriately provide any new information to healthcare professionals in clinical practice.

- Rhabdomyolysis/myopathy

  In Study 0101, a subject experienced rhabdomyolysis for which a causal relationship to gilteritinib could not be ruled out, but the subject had been treated with gilteritinib at 300 mg, which was not the proposed dosage.

● Eye disorders

Retinal toxicity findings were observed in non-clinical studies. Ophthalmologic examinations were therefore performed periodically in clinical studies, but no serious retinal disorders were noted.

7.R.5 Indication

The proposed indication for gilteritinib was "*FLT3* mutation-positive relapsed or refractory acute myeloid leukemia." The following statement was included in the precautions for indication section of the proposed package insert.

● Gilteritinib should be used in patients with a confirmed *FLT3* (FMS-like tyrosine kinase 3) mutation. The approved *in vitro* diagnostic should be used for testing.

Based on Sections "7.R.3 Efficacy" and "7.R.4 Safety," and the following considerations in this section, PMDA concluded that the wording for the proposed indication should be modified slightly (the modification involves the original Japanese text only and does not affect the English translation), and that the following statements should be included in the precautions for indication section.

● Gilteritinib should be used in patients with a *FLT3* mutation as detected by testing performed by a pathologist or laboratory with adequate experience. The approved *in vitro* diagnostic should be used for testing.

● Eligible patients must be selected with a full understanding of the information presented in the “Clinical Studies” section and of the efficacy and safety of gilteritinib.

7.R.5.1 Target population and indication

The applicant's explanation about the target population and indication of gilteritinib:

Patients were eligible for Study 0301 if they were positive for *FLT3* mutation, as determined by Invivoscribe Technologies, Inc.'s PCR-based *in vitro* diagnostic test, "LeukoStrat CDx *FLT3* Mutation Assay" [see Section 6.1.1]. This test was designed to detect *FLT3*-ITD and *FLT3*-TKD mutations (D835 and I836) only.

The efficacy and safety results from Study 0301 by *FLT3* mutation type[44)] are shown in Table 42 and Table 43, respectively. Study 0301 showed no clear differences in the efficacy and safety of gilteritinib between the overall population and each subgroups based on *FLT3* mutation type, although this result has limitations because of the limited number of patients with *FLT3*-TKD,

Table 42. Efficacy results by *FLT3* mutation type (RAS, Study 0301)

FLT3 mutation type	N	CR+CRh (n) (CR+CRh rate [95% CI] (%))
Overall population*	142	40 (28.2 [20.9, 36.3])
FLT3-ITD	121	33 (27.3 [19.6, 36.1])
FLT3-TKD	12	2 (16.7 [2.1, 48.4])
FLT3-ITD and *FLT3*-TKD	5	3 (60.0 [14.7, 94.7])

* Including 4 patients negative for *FLT3* mutation based on central testing

44) In Study 0301, patients were allowed to start treatment with study drug based on *FLT3* mutation test results by local laboratory if they were unable to wait for the central test results due to rapidly progressive disease. Four patients were positive for *FLT3* mutation based on local testing, enrolled in Study 0301, and then identified as *FLT3*-negative based on central testing, of whom 3 patients received gilteritinib.

Table 43. Summary of safety data by *FLT3* mutation type (Safety analysis set, Study 0301)

	n (%)			
	Overall population*	Patients with *FLT3*-ITD	Patients with *FLT3*-TKD	Patients with *FLT3*-ITD and *FLT3*-TKD
	N = 168	N = 147	N = 13	N = 5
All adverse events	167 (99.4)	147 (100)	12 (92.3)	5 (100)
Grade 3 or higher adverse events	156 (92.9)	138 (93.9)	11 (84.6)	4 (80.0)
Adverse events leading to death	43 (25.6)	38 (25.9)	5 (38.5)	0
Serious adverse events	125 (74.4)	110 (74.8)	10 (76.9)	3 (60.0)
Adverse events leading to treatment discontinuation	34 (20.2)	30 (20.4)	3 (23.1)	1 (20.0)
Adverse events leading to dose interruption	66 (39.3)	58 (39.5)	5 (38.5)	2 (40.0)
Adverse events leading to dose reduction	15 (8.9)	14 (9.5)	1 (7.7)	0

* Including 3 patients who were identified as *FLT3*-negative based on central testing after the start of treatment with gilteritinib.

Based on the above, the applicant considered that the target population of gilteritinib should be the same as the population eligible for Study 0301 (i.e. patients with FLT3 mutation-positive relapsed or refractory AML). The applicant has therefore proposed the following indication: "*FLT3* mutation-positive relapsed or refractory acute myeloid leukaemia." As gilteritinib should be used in patients with a confirmed *FLT3* mutation, the following statement will be included in the precautions for indication section.

- Gilteritinib should be used in patients with a confirmed *FLT3* (FMS-like tyrosine kinase 3) mutation. The approved *in vitro* diagnostic should be used for testing.

PMDA's discussion:

Gilteritinib therapy should be limited to patients with a *FLT3* mutation as detected by appropriate testing. Therefore, types of *FLT3* mutations in patients enrolled in Study 0301 should be listed in the clinical studies section of the package insert, and the following statements should be included in the precautions for indication section:

- Gilteritinib should be used in patients with a *FLT3* mutation as detected by testing performed by a pathologist or laboratory with adequate experience. The approved *in vitro* diagnostic should be used for testing.
- Eligible patients must be selected with a full understanding of the information presented in the “Clinical Studies” section and of the efficacy and safety of gilteritinib.

Further, the wording for the proposed indication should be modified slightly. (The modification involves the original Japanese text only and does not affect the English translation.)

7.R.6 Dosage and administration

The proposed dosage and administration statement and the statements included in the precautions for dosage and administration section of the draft package insert are shown below.

Dosage and Administration

The usual adult dosage is 120 mg of gilteritinib administered orally once daily. According to the patient's condition, the dose may be increased up to 200 mg once daily, or reduced from 120 mg to 80 mg or from 200 mg to 120 mg.

Precautions for Dosage and Administration

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

● Dosage modifications for adverse reactions

● Dose increase for lack of efficacy after 4 weeks of therapy

Based on Sections "7.R.3 Efficacy" and "7.R.4 Safety," and the following considerations, PMDA concluded that the wording for the dosage and administration and precautions for dosage and administration, should be as follows.

Dosage and Administration

The usual adult dosage is 120 mg of gilteritinib administered orally once daily. The dosage may be adjusted according to the patient's condition, but should not exceed 200 mg once daily.

Precautions for Dosage and Administration

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

● In the event of adverse reactions, interrupt or reduce the dose of gilteritinib, or discontinue gilteritinib treatment, according to the symptoms and severity, as per the tables below.

Dose reduction levels for gilteritinib

Level	Dose
Usual dose	120 mg
Level −1	80 mg
Level −2	40 mg

Dosage modifications for adverse reactions

Adverse reaction	Severity	Recommended action
Prolonged QT interval	QT interval >500 ms	Interrupt dosing. Gilteritinib may be resumed at 1 dose level lower when QT interval returns to ≤480 ms or baseline.
Other non-hematologic toxicities	Grade 3	Interrupt dosing until toxicity resolves to Grade ≤1 or baseline. After resolution, gilteritinib may be resumed at 1 dose level lower.
	Grade 4	Discontinue treatment.

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

● If there is no response after 4 weeks of therapy, the dose may be increased to 200 mg once daily, after considering the patient's condition. When a patient receiving 200 mg requires a dose reduction, the dose should be reduced to ≤120 mg once daily.

7.R.6.1 Dosage and administration for gilteritinib

The applicant's explanation about the rationale for the proposed dosage and administration for gilteritinib:

Taking account of the following points, gilteritinib 120 mg QD was administered orally in 28-day cycles in Study 0301. If the criteria for dose reduction were met, the dose of gilteritinib was reduced to 80 mg, and a further dose reduction to 40 mg was allowed only when clinical benefit was observed. An increase in the

gilteritinib dose from 120 mg to 200 mg was allowed if no CRc was achieved after 1 cycle of therapy.

Study 0301 was conducted according to the above dose modification guidelines and demonstrated the clinical usefulness of gilteritinib [see Sections 7.R.2 and 7.R.3]. Thus, dosage and administration for gilteritinib was established based on this study.

- In Study 0101, the CRc rates in *FLT3* mutation-positive patients were 0% in the gilteritinib 40 mg group, 41.7% in the gilteritinib 80 mg group, 46.4% in the gilteritinib 120 mg group, and 40.4% in the gilteritinib 200 mg group, suggesting the efficacy of gilteritinib at doses of ≥80 mg/day.
- The applicant assessed the potential relationship between gilteritinib blood concentration and efficacy, and obtained the following results:
  (1) The CRc rates were 10.5% and 42.9% at gilteritinib steady-state trough concentrations of <100 ng/mL and ≥100 ng/mL, respectively, in Study 0101.
  (2) Simulations estimated that the percentages of patients with gilteritinib steady-state trough concentrations below 100 ng/mL were 38.3%, 0.6%, and 0% at doses of 80, 120, and 200 mg, respectively.

  These results support the efficacy of gilteritinib 120 mg.
- Although the MTD was determined to be 300 mg in Study 0101 [see Section 7.1.4], the incidences of DLTs were 5% in the 120 mg group, 8% in the 200 mg group, and 21% in the 300 mg group in Study 0101 at the time of planning Study 0301. Gilteritinib 200 mg was considered to be well-tolerated.

The efficacy and safety results in patients with or without dose increase in Study 0301 are shown in Table 44 and Table 45, respectively.

Table 44. Results of CR and CRh in patients with or without dose increase (RAS, Study 0301)

Best overall response	n (%)		
	120 mg	200 mg	
	N = 68	N = 46	
	No dose changes	Before dose increase	After dose increase
CR	15 (22.1)	1 (2.2)	2 (4.3)
CRh	7 (10.3)	0	2 (4.3)
CR+CRh	22	1	4
(CR+CRh rate [95% CI] (%))	(32.4 [21.5, 44.8])	(2.2 [0.1, 11.5])	(8.7 [2.4, 20.8])

Table 45. Summary of safety data in patients with or without dose increase (Study 0301)

	n (%)	
	120 mg	200 mg
	N = 118	N = 50
All adverse events	117 (99.2)	50 (100)
Grade 3 or higher adverse events	107 (90.7)	49 (98.0)
Adverse events leading to death	29 (24.6)	14 (28.0)
Serious adverse events	84 (71.2)	41 (82.0)
Adverse events leading to treatment discontinuation	25 (21.2)	9 (18.0)
Adverse events leading to dose interruption	46 (39.0)	20 (40.0)
Adverse events leading to dose reduction	11 (9.3)	4 (8.0)

PMDA's discussion:
PMDA largely accepted the applicant's explanation. However, the proposed dosage and administration statement and the statements in the precautions for dosage and administration section of the proposed package insert should be modified as follows.

Dosage and Administration
The usual adult dosage is 120 mg of gilteritinib administered orally once daily. The dosage may be adjusted according to the patient's condition, but should not exceed 200 mg once daily.

Precautions for Dosage and Administration
- Dosage modifications for adverse reactions
- If there is no response after 4 weeks of therapy, the dose may be increased to 200 mg once daily, after considering the patient's condition. When a patient receiving 200 mg requires a dose reduction, the dose should be reduced to ≤120 mg once daily.

7.R.6.2 Dosage modifications
The applicant's explanation about dosage modification guidelines:
Study 0301 used the guidelines for treatment discontinuation/dose interruption or reduction for adverse events, and patients following the guidelines were able to tolerate gilteritinib therapy. This is why the precautions for dosage and administration section, proposed by the applicant, includes a slightly revised version of the dosage modification guidelines used in Study 0301. The details of revision are shown below.

- None of the clinical studies (including Study 0301) had dosage modification guideline for PRES. On the other hand, the revised version states that gilteritinib treatment should be discontinued if PRES of any grade occurs, for the following reasons:
  (1) Serious PRES occurred in clinical studies (2 subjects in Study 0101, 1 subject in Study 0301).
  (2) PRES may lead to irreversible encephalopathy without early discontinuation of gilteritinib treatment.

- The dosage modification guidelines of Study 0301 states that, if the QTc interval has increased by >30 ms from baseline to Day 8 of Cycle 1, a confirmatory ECG should be performed on Day 9, and that if ECG on Day 9 revealed a >30 ms increase, dose reduction should be considered. In Study 0301, 3 patients had a dose reduction in accordance with this guideline, but their QTcF values on Day 9 were all ≤480 ms. Further, in clinical practice, dose reduction should be considered only when QTcF exceeds 500 ms. The revised version thus states that dosage modifications should be made only in patients with a QT interval >500 ms.

- Abnormal findings in the ocular tissues including the retina were observed in repeated-dose toxicity studies in dogs [see Section 5.2]. The protocols of clinical studies therefore included the dosage modification guideline for retinopathy, requiring subjects to undergo ophthalmologic examination. In Study 0301, however, no patients modified their doses in accordance with the guideline. The revised version therefore does not include the dosage modification guideline for retinopathy.

- At the time of planning Study 0301, the safety profile of gilteritinib was unknown in terms of adverse reactions other than described above. Study 0301 therefore included the following dosage modification guideline for non-hematologic toxicities: (1) if Grade 3 non-hematologic toxicity occurs, interrupt dosing for up to 14 days, and if toxicity improves to Grade ≤1 within 14 days, resume dosing at a reduced dose, and (2) if Grade 4 non-hematologic toxicity occurs, discontinue treatment. As a result of Study 0301, the safety profile of gilteritinib has been identified. On the basis of the identified safety profile and other information, the revised version specifies that, if Grade 3 or higher non-hematologic toxicity occurs, dosing should be interrupted until the toxicity resolves to Grade ≤1 or baseline.

Study 0301 had the following guideline, which was not a dosage modification guideline for adverse events:

> Gilteritinib therapy may delay hematologic recovery after inducing morphologic remission (i.e., <5% blasts in the bone marrow). Dose reduction should therefore be considered in patients with a CRp or CRi who meet all of the specified criteria.[45)]

Three patients with a CRp or CRi had a dose reduction, but whether the criteria were met was unknown.

PMDA's discussion:

PMDA largely accepted the applicant's explanation. However, the dosage modification guideline for non-hematologic toxicities other than prolonged QT interval should be the same as the guideline for Study 0301. The clinically significant adverse reactions section of the package insert, etc., should advise discontinuation of gilteritinib treatment in the event of PRES, and the precautions for dosage and administration section need not include any precautionary statement regarding PRES. Moreover, the dose reduction criteria for patients with a CRp or CRi in Study 0301 can be used as reference information for the use of gilteritinib; healthcare professionals should be informed about the criteria through information materials etc.

Based on the above, the following statement should be included in the precautions for dosage and administration section of the package insert.

Precautions for dosage and administration

- In the event of adverse reactions, interrupt or reduce the dose of gilteritinib, or discontinue gilteritinib treatment, according to the symptoms, severity, etc., as per the tables below.

Dose reduction levels for gilteritinib

Level	Dose
Usual dose	120 mg
Level −1	80 mg
Level −2	40 mg

Dosage modifications for adverse reactions

[45)] (1) received ≥2 cycles of gilteritinib, (2) an absolute neutrophil count ≤0.5×10^9/L and (or) a platelet count <25×10^9/L, (3) <5% blasts in bone marrow, (4) no evidence of extramedullary leukemia

Adverse reaction	Severity	Recommended action
Prolonged QT interval	QT interval >500 ms	Interrupt dosing. Gilteritinib may be resumed at 1 dose level lower when QT interval returns to ≤480 ms or baseline.
Other non-hematologic toxicities	Grade 3	Interrupt dosing until toxicity resolves to Grade ≤1 or baseline. After resolution, gilteritinib may be resumed at 1 dose level lower.
	Grade 4	Discontinue treatment.

Severity grade based on NCI-CTCAE

7.R.6.3 Gilteritinib in combination with other anti-neoplastic drugs

PMDA asked the applicant to explain the use of gilteritinib in combination with other anti-neoplastic drugs.

The applicant's response:

Since there are no clinical study data that demonstrated the clinical usefulness of gilteritinib in combination with other anti-neoplastic drugs, the use of gilteritinib in combination with other anti-neoplastic drugs is not recommended at present. Thus, the precautions for dosage and administration section of the package insert will states that the efficacy and safety of gilteritinib in combination with other anti-neoplastic drugs have not been established.

PMDA accepted the applicant's explanation.

7.R.7 Pediatric development

PMDA asked the applicant to explain the pediatric development of gilteritinib for *FLT3* mutation-positive AML.

The applicant's response:

Two clinical studies in pediatric patients with AML will be conducted outside Japan:

- A phase I/II study of gilteritinib in combination with chemotherapy in patients with *FLT3* mutation-positive relapsed or refractory AML who are aged ≥6 months and <18 years (to be conducted in Europe and the US).
- A phase II study of gilteritinib in combination with chemotherapy in treatment-naïve patients with *FLT3* mutation-positive AML who are aged ≥6 months and <18 years (to be conducted in Europe and the US).

The following studies will be conducted outside Japan, in order to initiate clinical studies in pediatric patients:

(a) A palatability study for the mini-tablet and the oral solution.
(b) A bioequivalence study of the proposed commercial formulation (the tablet), the mini-tablet, and the oral solution.

The pediatric development of gilteritinib in Japan is currently under consideration.

PMDA's discussion:

The applicant should collect and analyze information on the need for gilteritinib development for pediatric patients with *FLT3* mutation-positive AML, obtain information on gilteritinib development in non-Japanese

pediatric patients, and take appropriate actions regarding the development of dosage for Japanese pediatric patients.

7.R.8 Post-marketing investigations

The applicant's explanation about post-marketing surveillance plan:
The applicant is planning to conduct post-marketing surveillance, covering all patients treated with gilteritinib, to investigate the safety etc. of gilteritinib in clinical practice.

The safety specification for the surveillance includes PRES, prolonged QT interval, cardiac failure, pericarditis, and pericardial effusion, because these events require particular attention during gilteritinib therapy.

The planned sample size has been determined as 180 patients, based on the incidence of the above events (i.e., those included in the safety specification) in Study 0301 etc.

The observation period has been determined as 6 months, because in Study 0301 the above events (i.e., those included in the safety specification) mostly occurred within 6 months after the start of gilteritinib therapy, with no trend toward increasing incidence with prolonged gilteritinib treatment.

PMDA's discussion:
Since the safety information of gilteritinib in Japanese patients is limited, the applicant should conduct post-marketing surveillance covering all patients treated with gilteritinib over a certain period of time, in order to collect safety information in a prompt and unbiased manner, and provide the obtained safety information to healthcare professionals as soon as possible.

Based on the considerations in Section "7.R.4 Safety," PMDA considers that the safety specification should include myelosuppression, infection, hemorrhage, hepatic dysfunction, renal disorders, gastrointestinal perforation, ILD, and hypersensitivity, in addition to the events selected by the applicant.

The planned sample size and observation period should be reconsidered based on the incidence of the above events to be added to the safety specification (i.e., myelosuppression, infection, hemorrhage, hepatic dysfunction, renal disorders, gastrointestinal perforation, ILD, and hypersensitivity).

7.3 Adverse events etc. observed in clinical studies

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

7.3.1 Japanese phase I study (Study 0102)

Adverse events occurred in 24 of 24 subjects (100%), and those for which a causal relationship to gilteritinib could not be ruled out occurred in 22 of 24 subjects (91.7%). Adverse events reported by ≥20% of subjects were hepatic function abnormal; and blood CK increased (9 subjects each [37.5%]); blood LDH increased (8

subjects [33.3%]); diarrhoea; and pyrexia (7 subjects each [29.2%]); and febrile neutropenia; stomatitis; renal impairment; and hypertension (5 subjects each [20.8%]).

Serious adverse events occurred in 7 of 24 subjects (29.2%). Those reported by ≥2 subjects were subdural haematoma (2 subjects [8.3%]), and their causal relationship to gilteritinib could not be ruled out.

Adverse events leading to treatment discontinuation occurred in 6 of 24 subjects (25.0%). Those reported by ≥2 subjects were pneumonia (2 subjects [8.3%]), and their causal relationship to gilteritinib could not be ruled out.

7.3.2 Global phase III study (Study 0301)

Adverse events occurred in 167 of 168 subjects (99.4%), and those for which a causal relationship to gilteritinib could not be ruled out occurred in 139 of 168 subjects (82.7%). Adverse events reported by ≥20% of subjects are shown in Table 28 [see Section 7.R.4.1].

Serious adverse events occurred in 125 of 168 subjects (74.4%). Those reported by ≥2 subjects were febrile neutropenia (53 subjects [31.5%]); disease progression (29 subjects [17.3%]); pyrexia (18 subjects [10.7%]); pneumonia (15 subjects [8.9%]); lung infection (10 subjects [6.0%]); sepsis; and ALT increased (8 subjects each [4.8%]); bacteraemia; septic shock; and acute kidney injury (7 subjects each [4.2%]); anaemia; diarrhoea; and AST increased (6 subjects each [3.6%]); hypotension (5 subjects [3.0%]); staphylococcal bacteraemia; fall; dyspnoea; and respiratory failure (4 subjects each [2.4%]); pancytopenia; thrombocytopenia; cardiac arrest; cardiac failure; pericarditis; fatigue; bronchitis; cellulitis; device related infection; headache; and acute respiratory distress syndrome (3 subjects each [1.8%]); and disseminated intravascular coagulation; cardiac failure congestive; myocarditis; pericardial effusion; supraventricular tachycardia; abdominal pain; colitis; large intestine perforation; mouth haemorrhage; nausea; pancreatitis; asthenia; face oedema; cholecystitis; anaphylactic reaction; bronchopulmonary aspergillosis; clostridium difficile infection; enterocolitis infectious; Escherichia bacteraemia; influenza; neutropenic sepsis; pneumonia fungal; respiratory tract infection; sinusitis; tooth infection; urinary tract infection; urinary tract infection bacterial; viral upper respiratory tract infection; blood bilirubin increased; neutrophil count decreased; platelet count decreased; decreased appetite; dehydration; arthralgia; cerebral haemorrhage; depressed level of consciousness; cough; hypoxia; pleural effusion; pneumonia aspiration; and haematoma (2 subjects each [1.2%]). A causal relationship to gilteritinib could not be ruled out for febrile neutropenia (16 subjects); pneumonia; ALT increased; and AST increased (6 subjects each); anaemia (4 subjects); thrombocytopenia; and pericarditis (3 subjects each); acute kidney injury; cardiac failure; myocarditis; large intestine perforation; device related infection; neutrophil count decreased; and headache (2 subjects each); and pyrexia; sepsis; pancytopenia; hypotension; colitis; mouth haemorrhage; asthenia; cholecystitis; anaphylactic reaction; cardiac failure congestive; supraventricular tachycardia; bronchitis; cellulitis; influenza; respiratory tract infection; urinary tract infection; blood bilirubin increased; platelet count decreased; cerebral haemorrhage; syncope; and pneumonia aspiration (1 subject each).

Adverse events leading to treatment discontinuation occurred in 34 of 168 subjects (20.2%). Those reported by ≥2 subjects were disease progression (10 subjects [6.0%]); and lung infection; septic shock; cerebral haemorrhage; and acute kidney injury (2 subjects each [1.2%]), and a causal relationship to gilteritinib could not be ruled out for lung infection; cerebral haemorrhage; and acute kidney injury (1 subject each).

7.3.3 Foreign phase I/II study (Study 0101)

Adverse events occurred in (1) 17 of 17 subjects (100%) in the gilteritinib 20 mg group, (2) 16 of 16 subjects (100%) in the gilteritinib 40 mg group, (3) 23 of 24 subjects (95.8%) in the gilteritinib 80 mg group, (4) 67 of 69 subjects (97.1%) in the gilteritinib 120 mg group, (5) 103 of 103 subjects (100%) in the gilteritinib 200 mg group, (6) 20 of 20 subjects (100%) in the gilteritinib 300 mg group, and (7) 3 of 3 subjects (100%) in the gilteritinib 450 mg group, and those for which a causal relationship to gilteritinib could not be ruled out occurred in (1) 10 of 17 subjects (58.8%), (2) 8 of 16 subjects (50.0%), (3) 18 of 24 subjects (75.0%), (4) 55 of 69 subjects (79.7%), (5) 80 of 103 subjects (77.7%), (6) 15 of 20 subjects (75.0%), and (7) 3 of 3 subjects (100%). Adverse events reported by ≥20% of subjects in any of (1) to (6) groups are shown in Table 46 and Table 47. Adverse events reported by ≥2 subjects in (7) were AST increased (3 subjects [100%]); and diarrhoea; and hyperglycaemia (2 subjects each [66.7%]).

Table 46. Adverse events reported by ≥20% of subjects in any of gilteritinib 20 to 300 mg groups (Gilteritinib 20, 40, and 80 mg groups)

SOC PT (MedDRA/J ver.20.0)	n (%) 20 mg N = 17		40 mg N = 16		80 mg N = 24	
	All Grades	Grade 3 or higher	All Grades	Grade 3 or higher	All Grades	Grade 3 or higher
Any adverse event	17 (100)	12 (70.6)	16 (100)	15 (93.8)	23 (95.8)	22 (91.7)
Blood and lymphatic system disorders						
Febrile neutropenia	6 (35.3)	6 (35.3)	8 (50.0)	8 (50.0)	6 (25.0)	6 (25.0)
Anaemia	4 (23.5)	1 (5.9)	4 (25.0)	3 (18.8)	9 (37.5)	9 (37.5)
Gastrointestinal disorders						
Diarrhoea	1 (5.9)	0	2 (12.5)	0	7 (29.2)	1 (4.2)
Constipation	2 (11.8)	0	2 (12.5)	0	6 (25.0)	0
Nausea	3 (17.6)	0	3 (18.8)	0	6 (25.0)	0
Vomiting	3 (17.6)	0	1 (6.3)	0	7 (29.2)	2 (8.3)
General disorders and administration site conditions						
Fatigue	5 (29.4)	0	5 (31.3)	2 (12.5)	9 (37.5)	1 (4.2)
Oedema peripheral	4 (23.5)	0	3 (18.8)	0	5 (20.8)	0
Pyrexia	1 (5.9)	0	3 (18.8)	0	3 (12.5)	0
Infections and infestations						
Sepsis	0	0	2 (12.5)	2 (12.5)	8 (33.3)	7 (29.2)
Pneumonia	1 (5.9)	1 (5.9)	2 (12.5)	2 (12.5)	2 (8.3)	2 (8.3)
Bacteraemia	1 (5.9)	1 (5.9)	0	0	8 (33.3)	7 (29.2)
Investigations						
AST increased	1 (5.9)	1 (5.9)	1 (6.3)	0	4 (16.7)	1 (4.2)
ALT increased	1 (5.9)	1 (5.9)	1 (6.3)	0	4 (16.7)	1 (4.2)
Blood creatinine increased	1 (5.9)	0	2 (12.5)	0	5 (20.8)	1 (4.2)
Metabolism and nutrition disorders						
Hypokalaemia	6 (35.3)	1 (5.9)	2 (12.5)	1 (6.3)	3 (12.5)	2 (8.3)
Hypocalcaemia	1 (5.9)	1 (5.9)	2 (12.5)	0	3 (12.5)	1 (4.2)
Decreased appetite	1 (5.9)	0	1 (6.3)	0	5 (20.8)	1 (4.2)
Musculoskeletal and connective tissue disorders						
Arthralgia	0	0	0	0	5 (20.8)	1 (4.2)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)						
AML	3 (17.6)	3 (17.6)	5 (31.3)	5 (31.3)	5 (20.8)	5 (20.8)
Nervous system disorders						
Dizziness	1 (5.9)	0	2 (12.5)	0	6 (25.0)	0
Respiratory, thoracic and mediastinal disorders						
Dyspnoea	3 (17.6)	0	6 (37.5)	1 (6.3)	5 (20.8)	1 (4.2)
Cough	3 (17.6)	0	1 (6.3)	0	7 (29.2)	0
Epistaxis	3 (17.6)	0	4 (25.0)	0	4 (16.7)	1 (4.2)
Vascular disorders						
Hypotension	1 (5.9)	1 (5.9)	0	0	4 (16.7)	2 (8.3)

Table 47. Adverse events reported by ≥20% of subjects in any of gilteritinib 20 to 300 mg groups (Gilteritinib 120, 200, and 300 mg groups)

SOC PT (MedDRA/J ver.20.0)	n (%) 120 mg N = 69		200 mg N = 103		300 mg N = 20	
	All Grades	Grade 3 or higher	All Grades	Grade 3 or higher	All Grades	Grade 3 or higher
Any adverse event	67 (97.1)	60 (87.0)	103 (100)	101 (98.1)	20 (100)	16 (80.0)
Blood and lymphatic system disorders						
Febrile neutropenia	24 (34.8)	24 (34.8)	47 (45.6)	47 (45.6)	9 (45.0)	9 (45.0)
Anaemia	26 (37.7)	15 (21.7)	37 (35.9)	29 (28.2)	7 (35.0)	6 (30.0)
Gastrointestinal disorders						
Diarrhoea	31 (44.9)	4 (5.8)	47 (45.6)	6 (5.8)	6 (30.0)	0
Constipation	14 (20.3)	0	33 (32.0)	0	2 (10.0)	0
Nausea	15 (21.7)	1 (1.4)	30 (29.1)	4 (3.9)	1 (5.0)	0
Vomiting	13 (18.8)	2 (2.9)	23 (22.3)	1 (1.0)	1 (5.0)	0
General disorders and administration site conditions						
Fatigue	27 (39.1)	4 (5.8)	35 (34.0)	7 (6.8)	5 (25.0)	1 (5.0)
Oedema peripheral	18 (26.1)	0	31 (30.1)	4 (3.9)	2 (10.0)	0
Pyrexia	24 (34.8)	5 (7.2)	32 (31.1)	6 (5.8)	5 (25.0)	2 (10.0)
Infections and infestations						
Sepsis	10 (14.5)	10 (14.5)	19 (18.4)	19 (18.4)	0	0
Pneumonia	16 (23.2)	14 (20.3)	19 (18.4)	15 (14.6)	2 (10.0)	2 (10.0)
Bacteraemia	5 (7.2)	4 (5.8)	7 (6.8)	6 (5.8)	0	0
Investigations						
AST increased	20 (29.0)	4 (5.8)	36 (35.0)	9 (8.7)	3 (15.0)	1 (5.0)
ALT increased	16 (23.2)	3 (4.3)	26 (25.2)	8 (7.8)	3 (15.0)	1 (5.0)
Blood creatinine increased	13 (18.8)	1 (1.4)	21 (20.4)	3 (2.9)	1 (5.0)	0
Metabolism and nutrition disorders						
Hypokalaemia	10 (14.5)	1 (1.4)	25 (24.3)	4 (3.9)	1 (5.0)	0
Hypocalcaemia	11 (15.9)	3 (4.3)	24 (23.3)	10 (9.7)	1 (5.0)	0
Decreased appetite	11 (15.9)	0	19 (18.4)	2 (1.9)	1 (5.0)	0
Musculoskeletal and connective tissue disorders						
Arthralgia	11 (15.9)	0	17 (16.5)	1 (1.0)	1 (5.0)	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)						
AML	10 (14.5)	10 (14.5)	20 (19.4)	20 (19.4)	5 (25.0)	5 (25.0)
Nervous system disorders						
Dizziness	17 (24.6)	0	26 (25.2)	2 (1.9)	0	0
Respiratory, thoracic and mediastinal disorders						
Dyspnoea	19 (27.5)	4 (5.8)	30 (29.1)	9 (8.7)	2 (10.0)	0
Cough	18 (26.1)	0	27 (26.2)	0	3 (15.0)	0
Epistaxis	15 (21.7)	1 (1.4)	20 (19.4)	1 (1.0)	5 (25.0)	0
Vascular disorders						
Hypotension	12 (17.4)	4 (5.8)	29 (28.2)	11 (10.7)	1 (5.0)	0

Serious adverse events occurred in (1) 10 of 17 subjects (58.8%), (2) 14 of 16 subjects (87.5%), (3) 21 of 24 subjects (87.5%), (4) 53 of 69 subjects (76.8%), (5) 94 of 103 subjects (91.3%), (6) 16 of 20 subjects (80.0%), and (7) 2 of 3 subjects (66.7%). Serious adverse events reported by ≥3 subjects by dose level were (1) febrile neutropenia (4 subjects [23.5%]) and disease progression (3 subjects [17.6%]), (2) febrile neutropenia (8 subjects [50.0%]), disease progression (5 subjects [31.3%]), and acute kidney injury (3 subjects [18.8%]), (3) sepsis (8 subjects [33.3%]); disease progression; febrile neutropenia; and bacteraemia (6 subjects each [25.0%]); and septic shock; and acute kidney injury (3 subjects each [12.5%]), (4) febrile neutropenia (19 subjects [27.5%]); pneumonia (13 subjects [18.8%]); pyrexia; and sepsis (10 subjects each [14.5%]); disease progression (10 subjects [14.5%]); diarrhoea; pneumonia fungal; and acute kidney injury (5 subjects each [7.2%]); cellulitis (4 subjects [5.8%]); and atrial fibrillation; urinary tract infection; upper respiratory tract

infection; and hypotension (3 subjects each [4.3%]), (5) febrile neutropenia (37 subjects [35.9%]); disease progression (22 subjects [21.4%]); sepsis (19 subjects [18.4%]); pneumonia; and acute kidney injury (14 subjects each [13.6%]); respiratory failure (11 subjects [10.7%]); pyrexia (10 subjects [9.7%]); lung infection (7 subjects [6.8%]); clostridium difficile colitis (6 subjects [5.8%]); diarrhoea; bacteraemia; pneumonia fungal; syncope; and hypotension (5 subjects each [4.9%]); anaemia; multiple organ dysfunction syndrome; cellulitis; and septic shock (4 subjects each [3.9%]); and leukocytosis; atrial fibrillation; nausea; acute graft versus host disease in skin; bronchopulmonary aspergillosis; blood CK increased; hypoxia; and acute respiratory failure (3 subjects each [2.9%]), and (6) febrile neutropenia (6 subjects [30.0%]) and disease progression (5 subjects [25.0%]) [none in (7)]. A causal relationship to gilteritinib could not be ruled out for (2) acute kidney injury (1 subject), (3) febrile neutropenia; and septic shock (1 subject each), (4) acute kidney injury (2 subjects); and febrile neutropenia; pyrexia; sepsis; diarrhoea; and hypotension (1 subject each), and (5) febrile neutropenia; pyrexia; and blood CK increased (3 subjects each); acute kidney injury; diarrhoea; and hypotension (2 subjects each); and sepsis; clostridium difficile colitis; bacteraemia; syncope; nausea; acute graft versus host disease in skin; hypoxia; and acute respiratory failure (1 subject each).

Adverse events leading to treatment discontinuation occurred in (1) 4 of 17 subjects (23.5%), (2) 5 of 16 subjects (31.3%), (3) 12 of 24 subjects (50.0%), (4) 12 of 69 subjects (17.4%), (5) 48 of 103 subjects (46.6%), (6) 6 of 20 subjects (30.0%), and (7) 1 of 3 subjects (33.3%). Those reported by ≥3 subjects by dose level were (3) disease progression (4 subjects [16.7%]) and (5) disease progression (9 subjects [8.7%]), sepsis (7 subjects [6.8%]), and respiratory failure (4 subjects [3.9%]) [none in (1) (2) (4) (6) (7)], and a causal relationship to gilteritinib was ruled out for all those events.

7.3.4 Foreign phase I study (Study 0105)

Adverse events occurred in 6 of 6 subjects (100%), and those for which a causal relationship to gilteritinib could not be ruled out also occurred in 6 of 6 subjects (100%). Adverse events reported by ≥3 subjects were fatigue; and AST increased (4 subjects each [66.7%]); and anaemia; ALT increased; hyperglycaemia; and proteinuria (3 subjects each [50.0%]).

Serious adverse events occurred in 6 of 6 subjects (100%). Those reported by ≥2 subjects were overdose (2 subjects [33.3%]), and their causal relationship to gilteritinib could not be ruled out.

Adverse events leading to treatment discontinuation occurred in 2 of 6 subjects (33.3%). Those observed were anaemia; and dyspnoea (1 subject each [16.7%]), and a causal relationship to gilteritinib could not be ruled out for anaemia (1 subject).

7.3.5 Foreign phase I study (Study 0106)

Adverse events occurred in 7 of 8 subjects with mild hepatic impairment (87.5%), 6 of 8 subjects with moderate hepatic impairment (75.0%), and 3 of 8 subjects with normal hepatic function (37.5%), and those for which a causal relationship to gilteritinib could not be ruled out occurred in 6 of 8 subjects with mild hepatic impairment (75.0%), 5 of 8 subjects with moderate hepatic impairment (62.5%), and 3 of 8 subjects with normal hepatic

function (37.5%). Adverse events reported by ≥2 subjects by degree of hepatic impairment were headache (3 subjects [37.5%]) and blood thyroid stimulating hormone increased (2 subjects [25.0%]) in subjects with mild hepatic impairment and back pain; and headache (2 subjects each [25.0%]) in subjects with moderate hepatic impairment (none in subjects with normal hepatic function).

There were no serious adverse events or adverse events leading to treatment discontinuation in any of the groups.

7.3.6 Foreign phase I study (Study 0108)

Adverse events occurred in (1) 11 of 21 subjects (52.4%) in the gilteritinib alone group, (2) 4 of 20 subjects (20.0%) in the gilteritinib+itraconazole group (following administration of itraconazole alone), (3) 4 of 20 subjects (20.0%) in the gilteritinib+itraconazole group (following coadministration of gilteritinib with itraconazole), (4) 4 of 20 subjects (20.0%) in the gilteritinib+fluconazole group (following administration of fluconazole alone), (5) 7 of 20 subjects (35.0%) in the gilteritinib+fluconazole group (following coadministration of gilteritinib with fluconazole), (6) 11 of 20 subjects (55.0%) in the gilteritinib+rifampicin group (following administration of rifampicin alone), and (7) 6 of 20 subjects (30.0%) in the gilteritinib+rifampicin group (following coadministration of gilteritinib with rifampicin). Adverse events for which a causal relationship to study drug could not be ruled out occurred in (1) 9 of 21 subjects (42.9%), (2) 3 of 20 subjects (15.0%), (3) 2 of 20 subjects (10.0%), (4) 1 of 20 subjects (5.0%), (5) 6 of 20 subjects (30.0%), (6) 11 of 20 subjects (55.0%), and (7) 5 of 20 subjects (25.0%). Adverse events reported by ≥2 subjects by cohort were (1) constipation (4 subjects [19.0%]), muscle strain (2 subjects [9.5%]), and blister (2 subjects [9.5%]), (2) diarrhoea (2 subjects [10.0%]) and somnolence (2 subjects [10.0%]), (5) constipation (3 subjects [15.0%]) and headache (3 subjects [15.0%]), (6) chromaturia (9 subjects [45.0%]) and headache (3 subjects [15.0%]), and (7) headache (2 subjects [10.0%]) [none in (3) and (4)].

There were no serious adverse events or adverse events leading to treatment discontinuation in any cohort.

7.3.7 Foreign phase I study (Study 0110)

Adverse events occurred in 1 of 21 subjects (4.8%) in the gilteritinib new tablet group and 4 of 21 subjects (19.0%) in the gilteritinib reference tablet group, and those for which a causal relationship to study drug could not be ruled out occurred in 1 of 21 subjects (4.8%) in the gilteritinib new tablet group and 3 of 21 subjects (14.3%) in the gilteritinib reference tablet group. Adverse events reported by ≥2 subjects by group were headache (2 subjects [9.5%]) in the gilteritinib reference tablet group (none in the gilteritinib new tablet group).

There were no serious adverse events or adverse events leading to study drug discontinuation in either group.

7.3.8 Foreign phase I study (Study 0113)

Adverse events occurred in 5 of 16 subjects (31.3%) in the fed 40 mg gilteritinib group and 6 of 16 subjects (37.5%) in the fasted 40 mg gilteritinib group, and those for which a causal relationship to gilteritinib could not be ruled out occurred in 1 of 16 subjects (6.3%) in the fed 40 mg gilteritinib group (none in the fasted 40

mg gilteritinib group). There were no adverse events reported by ≥2 subjects, serious adverse events, or adverse events leading to treatment discontinuation in either group.

7.3.9 Foreign phase I study (Study 5101)

Adverse events occurred in 10 of 10 subjects (100%), and those for which a causal relationship to study drug could not be ruled out also occurred in 10 of 10 subjects (100%). Adverse events reported by ≥5 subjects were ALT increased; AST increased; and drug eruption (8 subjects each [80.0%]); diarrhoea (7 subjects [70.0%]); and constipation; and blood CK increased (5 subjects each [50.0%]).

Serious adverse events occurred in 5 of 10 subjects (50.0%). Those reported by ≥3 subjects were ALT increased (4 subjects [40.0%]) and AST increased (3 subjects [30.0%]), and a causal relationship to study drug could not be ruled out for all those events.

Adverse events leading to study drug discontinuation occurred in 4 of 10 subjects (40.0%). Those reported by ≥3 subjects were AST increased (3 subjects [30.0%]), and their causal relationship to study drug could not be ruled out.

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

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

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

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

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

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

On the basis of the data submitted, PMDA has concluded that gilteritinib has a certain level of efficacy in the treatment of *FLT3* mutation-positive relapsed or refractory AML, and that gilteritinib has acceptable safety in view of its benefits. Gilteritinib is a drug with a new active ingredient that inhibits tyrosine kinases including FLT3. It suppresses tumor growth by inhibiting FLT3 receptor signaling. Gilteritinib is clinically meaningful because it offers a treatment option for patients with *FLT3* mutation-positive relapsed or refractory AML. PMDA considers that the clinical positioning, efficacy, safety, indication, etc. of gilteritinib need to be further discussed.

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

Review Report (2)

August 2, 2018

Product Submitted for Approval

Brand Name	Xospata Tablets 40 mg
Non-proprietary Name	Gilteritinib Fumarate
Applicant	Astellas Pharma Inc.
Date of Application	March 23, 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 in the following. 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 Clinical positioning and efficacy

PMDA's conclusion:

Based on the considerations in Section "7.R.3 Efficacy" in the Review Report (1), PMDA considers that the results of the co-primary endpoint for a global phase III study (Study 0301) (i.e. the CR+CRh rate in the gilteritinib group at the time of the first interim analysis), demonstrated a certain level of efficacy of gilteritinib in patients with *FLT3* mutation-positive relapsed or refractory AML.

The above results of Study 0301 are clinically meaningful, and gilteritinib is positioned as a treatment option for Japanese patients with *FLT3* mutation-positive relapsed or refractory AML. PMDA has reached this conclusion based on the considerations in Section "7.R.2 Clinical positioning" in the Review Report (1), and for the following reasons.

- *FLT3* mutation-positive AML is a rare disease with a very poor prognosis.
- At present, no standard of care has been established for patients with *FLT3* mutation-positive relapsed or refractory AML, and treatment options are very limited.

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

1.2 Safety

PMDA's conclusion based on the considerations in Section "7.R.4 Safety" in the Review Report (1):
Adverse events that require particular attention during gilteritinib therapy are myelosuppression, infection, hemorrhage, cardiac disorders, hepatic dysfunction, renal disorders, gastrointestinal perforation, ILD, hypersensitivity, and PRES.

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

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

1.3 Indication

PMDA's conclusion based on the considerations in Section "7.R.5 Indication" in the Review Report (1):
The types of *FLT3* mutations in patients enrolled in Study 0301 should be listed in the clinical studies section of the package insert. The following statements should be included in the precautions for indication section. The wording for the proposed indication should be modified slightly. (The modification involves the original Japanese text only and does not affect the English translation.)

Precautions for indication

- Gilteritinib should be used in patients with a *FLT3* mutation as detected by testing performed by a pathologist or laboratory with adequate experience. The approved *in vitro* diagnostic should be used for testing.
- Eligible patients must be selected with a full understanding of the information presented in the “Clinical Studies” section and of the efficacy and safety of gilteritinib.

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

Based on the above, PMDA instructed the applicant to add words, "including data on the types of *FLT3* mutations in patients enrolled in a clinical study," to the second statement in the precautions for indication section and then amend the indication and precautions for indication sections accordingly. The applicant agreed.

1.4 Dosage and administration

PMDA’s conclusion based on the considerations in Section "7.R.6 Dosage and administration" in the Review Report (1):
The following statements and information should be included in the dosage and administration section and the precautions for dosage and administration section.

Dosage and administration

The usual adult dosage is 120 mg of gilteritinib administered orally once daily. The dosage may be adjusted according to the patient's condition, but should not exceed 200 mg once daily.

Precautions for Dosage and Administration

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

Dose reduction levels for gilteritinib

Level	Dose
Usual dose	120 mg
Level −1	80 mg
Level −2	40 mg

Dosage modifications for adverse reactions

Adverse reaction	Severity	Recommended action
Prolonged QT interval	QT interval >500 ms	Interrupt dosing. Gilteritinib may be resumed at 1 dose level lower when QT interval returns to ≤480 ms or baseline.
Other non-hematologic toxicities	Grade 3	Interrupt dosing until toxicity resolves to Grade ≤1 or baseline. After resolution, gilteritinib may be resumed at 1 dose level lower.
	Grade 4	Discontinue treatment.

Severity grade based on NCI-CTCAE

- If there is no response after 4 weeks of therapy, the dose may be increased to 200 mg once daily, after considering the patient's condition. When a patient receiving 200 mg requires a dose reduction, the dose should be reduced to ≤120 mg once daily.

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

Based on the above, PMDA instructed the applicant to amend the dosage and administration and precautions for dosage and administration sections accordingly. The applicant agreed.

1.5 Risk management plan (draft)

The applicant is planning to conduct post-marketing surveillance with a planned sample size of 180 and an observation period of 6 months, covering all patients treated with gilteritinib, in order to investigate the safety etc. of gilteritinib in clinical practice.

PMDA’s conclusion based on the considerations in Section "7.R.8 Post-marketing investigations" in the Review Report (1):

The applicant should conduct post-marketing surveillance covering all patients treated with gilteritinib over a certain period of time, in order to collect safety information in a prompt and unbiased manner, and provide the obtained safety information to healthcare professionals as soon as possible.

PMDA's conclusion on the surveillance plan:

- The safety specification should include myelosuppression, infection, hemorrhage, hepatic dysfunction, renal disorders, gastrointestinal perforation, ILD, and hypersensitivity, in addition to the events selected by the applicant (i.e., PRES, prolonged QT interval, cardiac failure, pericarditis, and pericardial effusion).
- The planned sample size and observation period should be reconsidered based on the incidence of the events to be added to the safety specification (i.e., myelosuppression, infection, hemorrhage, hepatic dysfunction, renal disorders, gastrointestinal perforation, ILD, and hypersensitivity).

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

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

The applicant's response:

- Myelosuppression, infection, hemorrhage, prolonged QT interval, cardiac failure, pericarditis, pericardial effusion, hepatic dysfunction, renal disorders, gastrointestinal perforation, ILD, hypersensitivity, and PRES will be added to the safety specification.
- The planned sample size will be changed to 270 with the observation period of 6 months, based on the clinical study incidence of the events to be included in the safety specification.

PMDA accepted the applicant's response.

In view of the discussion above, PMDA has concluded that the risk management plan (draft) for gilteritinib should include the safety and efficacy specifications presented in Table 48, and that the applicant should conduct additional pharmacovigilance activities, surveillance/study for efficacy, and additional risk minimization activities presented in Table 49 and Table 50.

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

Safety specification		
Important identified risks	Important potential risks	Important missing information
● Myelosuppression ● Infection ● Hemorrhage ● Prolonged QT interval ● Cardiac failure, pericarditis, pericardial effusion ● Hepatic dysfunction ● Renal disorders ● Gastrointestinal perforation ● ILD ● Hypersensitivity ● PRES	● Embryo-fetal toxicity	● None
Efficacy specification		
● Efficacy in patients with *FLT3* mutation-positive relapsed or refractory AML (overall survival etc.)		

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

Additional pharmacovigilance activities	Surveillance/studies for efficacy	Additional risk minimization activities
● Early post-marketing phase vigilance ● Use-results survey (all-case surveillance) ● Post-marketing clinical study (an extension study of Study 2215-CL-9100*)	● Post-marketing clinical study (an extension study of Study 0301)	● Disseminate data gathered during early post-marketing phase vigilance ● Develop information materials to be distributed to healthcare professionals

* An expanded access study (Study 0301 as the main study)

Table 50. Outline of post-marketing surveillance (draft)

Objective	To investigate the safety etc. of gilteritinib in post-marketing clinical practice.
Survey method	All-case surveillance
Population	All patients treated with gilteritinib
Observation period	6 months
Planned sample size	270 patients
Main survey items	Safety specification: myelosuppression, infection, hemorrhage, prolonged QT interval, cardiac failure, pericarditis, pericardial effusion, hepatic dysfunction, renal disorders, gastrointestinal perforation, ILD, hypersensitivity, PRES Other main survey items: patient characteristics (sex, age, disease stage, complications, prior treatment, etc.), the use of gilteritinib, 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 that the sponsor failed to ensure that all changes and corrections made in the case report forms (CRFs) completed by the investigator etc. via electronic data processing system could be reviewed by the investigator (some of the changes or corrections made in the CRFs could not be reviewed by the investigator). Although this problem was found, as the investigator checked and reviewed the final data entered in the CRFs, PMDA concluded that there were no obstacles to conducting its review based on the application documents submitted.

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

The new drug application data (CTD 5.3.5.1-1) were subjected to an on-site GCP inspection, in accordance with the provisions of the Act on Securing Quality, Efficacy and Safety of Pharmaceuticals, Medical Devices, Regenerative and Cellular Therapy Products, Gene Therapy Products, and Cosmetics. On the basis of the inspection, PMDA concluded that there were no obstacles to conducting its review based on the application documents submitted.

3. Overall Evaluation

As a result of the above review, PMDA has concluded that the product may be approved after modifying the proposed indication (Japanese text only) and dosage and administration as shown below, with the following conditions, provided that necessary precautionary statements are included in the package insert and information on the proper use of the product is properly disseminated after the market launch, and provided that the proper

use of the product is ensured under the supervision of physicians with adequate knowledge of and experience in the treatment of hematological malignancies at medical institutions that can provide adequate emergency medical care. As the product has been 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

FLT3 mutation-positive relapsed or refractory acute myeloid leukemia

Dosage and Administration

The usual adult dosage is 120 mg of gilteritinib administered orally once daily. The dosage may be adjusted according to the patient's condition, but should not exceed 200 mg once daily.

Conditions of Approval

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

Warnings

Gilteritinib should be administered only to patients eligible for gilteritinib therapy, under the supervision of a physician with adequate knowledge of and experience in the treatment of hematological malignancies at medical institutions with adequate facilities for the treatment of emergencies. Prior to initiation of treatment, patients or their families should be fully informed of its efficacy and risks, and their consent should be obtained.

Contraindication

Patients with a history of hypersensitivity to any of the ingredients in the product

Precautions for Indication

1. Gilteritinib should be used in patients with a *FLT3* mutation as detected by testing performed by a pathologist or laboratory with adequate experience. The approved *in vitro* diagnostic should be used for testing.
2. Eligible patients must be selected with a full understanding of the information presented in the “Clinical Studies” section, including data on the types of *FLT3* mutations in patients enrolled in a clinical study, and with a good understanding of the efficacy and safety of gilteritinib.

Precautions for Dosage and Administration

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

2. In the event of adverse reactions, interrupt or reduce the dose of gilteritinib, or discontinue gilteritinib treatment, according to the symptoms and severity, as per the tables below.

Dose reduction levels for gilteritinib

Level	Dose
Usual dose	120 mg
Level −1	80 mg
Level −2	40 mg

Dosage modifications for adverse reactions

Adverse reaction	Severity	Recommended action
Prolonged QT interval	QT interval >500 msec	Interrupt dosing. Gilteritinib may be resumed at 1 dose level lower when QT interval returns to ≤480 msec or baseline.
Other non-hematologic toxicities	Grade 3	Interrupt dosing until toxicity resolves to Grade ≤1 or baseline. After resolution, gilteritinib may be resumed at 1 dose level lower.
	Grade 4	Discontinue treatment.

Severity grade based on NCI-CTCAE

3. If there is no response after 4 weeks of therapy, the dose may be increased to 200 mg once daily, after considering the patient's condition. When a patient receiving 200 mg requires a dose reduction, the dose should be reduced to ≤120 mg once daily.

Appendix

List of Abbreviations

7-AAD	7-amino actinomycin D
AGP	α1-acid glycoprotein
ALK	anaplastic lymphoma kinase
ALP	alkaline phosphatase
ALT	alanine aminotransferase
AML	acute myeloid leukemia
Application	marketing application
APTT	activated partial thromboplastin time
Ara-C	cytarabine
AST	aspartate aminotransferase
ATP	adenosine triphosphate
BA	bioavailability
BCRP	breast cancer resistance protein
BID	bis in die
BMI	body mass index
BSA	body surface area
CHL cells	Chinese hamster lung cells
CHO cell line	Chinese hamster ovary cell line
CI	confidence interval
CK	creatine phosphokinase
CQA	critical quality attribute
CR	complete remission
CRc	composite complete remission
CRh	complete remission with partial hematologic recovery
CRi	complete remission with incomplete hematologic recovery
CRp	complete remission with incomplete platelet recovery
CYP	cytochrome P450
^{14}C-gilteritinib	^{14}C-labeled Gilteritinib Fumarate
DLT	dose limiting toxicity
DMSO	dimethylsulfoxide
ECOG	Eastern Cooperative Oncology Group
efflux ratio	the ratio of apparent permeability coefficient in the secretory direction to the absorptive direction
EGFR	epidermal growth factor receptor
EGFR-TKI	epidermal growth factor receptor-tyrosine kinase inhibitor
ELN	European LeukemiaNet
EML4	echinoderm microtubule-associated protein-like 4
ERK	extracellular signal-regulated kinase
Erlotinib	Erlotinib Hydrochloride
F_1	relative bioavailability
FLAG-IDA	The combination of fludarabine, Ara-C, and filgrastim (genetical recombination) with idarubicin
FLT3	FMS-like tyrosine kinase 3
Fludarabine	Fludarabine Phosphate
GC	gas chromatography
GGT	gamma-glutamyltransferase
Gilteritinib	Gilteritinib Fumarate
GVHD	graft versus host disease
HDL	high-density lipoprotein

hERG	human *ether-a-go-go*-related gene
HLT	high level terms
HPLC	high performance liquid chromatography
HSA	human serum albumin
HSCT	Allogeneic hematopoietic stem cell transplantation
5-HT	5-hydroxytryptamine
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
ICH Q1E guideline	Guideline on Evaluation of Stability Data (PMSB/ELD Notification No. 0603004 dated June 3, 2003)
IDA	Idarubicin Hydrochloride
IDMC	independent data monitoring committee
ILD	interstitial lung disease
IR	infrared absorption spectrum
ITD	internal tandem duplication
ITT	intent-to-treat
k_a	apparent absorption rate
LBM	lean body mass
LC-MS/MS	liquid chromatography/tandem mass spectrometry
LDH	lactate dehydrogenase
LDL	low-density lipoprotein
LTK	leukocyte tyrosine kinase
MATE	multidrug and toxin extrusion
MEC	The combination of mitoxantrone, etoposide, and Ara-C
MedDRA/J	Medical Dictionary for Regulatory Activities Japanese version
Mitoxantrone	Mitoxantrone Hydrochloride
MTD	maximum tolerated dose
mRNA	messenger ribonucleic acid
NADPH	nicotinamide adenine dinucleotide phosphate hydrogen
NCCN guidelines	National Comprehensive Cancer Network Clinical Practice Guidelines in Oncology, Acute Myeloid Leukemia
NCI-CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
NCI-ODWG	National Cancer Institute organ dysfunction working group
NE	not estimable
NMR	nuclear magnetic resonance spectrum
NOD/SCID mouse	non-obese diabetic/severe combined immunodeficient mouse
NPM1	nucleophosmin 1
NSCLC	non-small cell lung cancer
OAT	organic anion transporter
OATP	organic anion transporting polypeptide
OCT	organic cation transporter
OS	overall survival
$P_{app\ A \rightarrow B}$	apparent permeability in apical to basolateral direction
P-gp	P-glycoprotein
PK	pharmacokinetics
PMDA	Pharmaceuticals and medical devices agency
PPK	population pharmacokinetics
PRES	posterior reversible encephalopathy syndrome
PS	performance status
PT	preferred term
Q	inter-compartmental clearance
QbD	quality by design
QD	quaque die

QTcF	QT interval corrected using Fridericia's formula
ΔQTcF	Change from baseline in QTcF
RAS	Response analysis set
RET	rearranged during transfection
ROS	c-ros oncogene
RTRT	real time release testing
SMQ	standard MedDRA queries
SOC	system organ class
STAT5	signal transducer and activator of transcription 5
Study 0101	Study 2215-CL-0101
Study 0102	Study 2215-CL-0102
Study 0105	Study 2215-CL-0105
Study 0106	Study 2215-CL-0106
Study 0108	Study 2215-CL-0108
Study 0110	Study 2215-CL-0110
Study 0113	Study 2215-CL-0113
Study 0301	Study 2215-CL-0301
Study 5101	Study 2215-CL-5101
TKD	tyrosine kinase domain
TLS	tumor lysis syndrome
TRKA	tropomyosin receptor kinase A
Vc	central volume of distribution
Vp	peripheral volume of distribution