Report on the Deliberation Results

June 1, 2023
Pharmaceutical Evaluation Division, Pharmaceutical Safety and Environmental Health Bureau
Ministry of Health, Labour and Welfare

Brand Name	Lytgobi Tablets 4 mg
Non-proprietary Name	Futibatinib (JAN*)
Applicant	Taiho Pharmaceutical Co., Ltd.
Date of Application	July 28, 2022

Results of Deliberation

In its meeting held on May 29, 2023, the Second Committee on New Drugs concluded that the product may be approved and that this result should be presented to the Pharmaceutical Affairs Department of the Pharmaceutical Affairs and Food Sanitation Council.

The product is not classified as a biological product or a specified biological product. The re-examination period is 8 years, and the drug product and its drug substance are both classified as powerful drugs.

Approval Conditions

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

**Japanese Accepted Name (modified INN)*

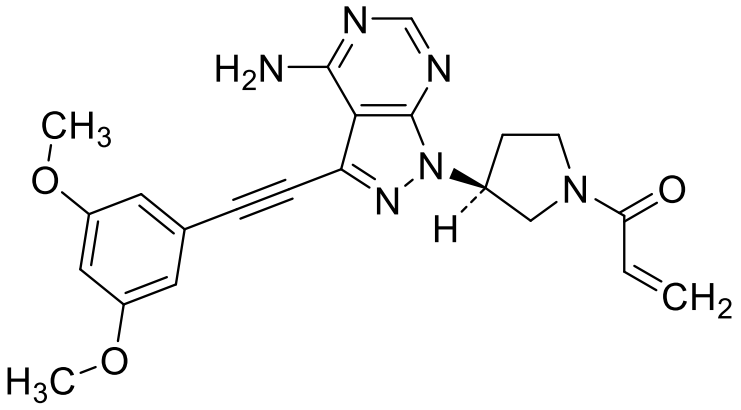
Review Report

May 17, 2023
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	Lytgobi Tablets 4 mg
Non-proprietary Name	Futibatinib
Applicant	Taiho Pharmaceutical Co., Ltd.
Date of Application	July 28, 2022
Dosage Form/Strength	Tablets, each containing 4 mg of futibatinib.
Application Classification	Prescription drug, (1) Drugs with a new active ingredient

Chemical Structure



Molecular formula: $C_{22}H_{22}N_6O_3$

Molecular weight: 418.45

Chemical name: 1-[(3*S*)-3-{4-Amino-3-[(3,5-dimethoxyphenyl)ethynyl]-1*H*-pyrazolo[3,4-*d*]pyrimidin-1-yl}pyrrolidin-1-yl]prop-2-en-1-one

Items Warranting Special Mention

None

Reviewing Office Office of New Drug V

Results of Review

On the basis of the data submitted, PMDA has concluded that the product has a certain level of efficacy in the treatment of unresectable *fibroblast growth factor receptor 2 (FGFR2)* gene fusion-positive biliary tract cancer that has progressed after cancer chemotherapy, and that the product has acceptable safety in view of its benefits (see Attachment).

As a result of its review, PMDA has concluded that the product may be approved for the indication and dosage and administration shown below, with the following approval conditions. Hyperphosphataemia, retinal detachment, eye disorders (except retinal detachment), nail disorders, palmar-plantar erythrodysaesthesia syndrome, and acute kidney injury as well as use in patients with hepatic impairment should be further investigated in post-marketing surveillance.

Indication

Unresectable *FGFR2* gene fusion-positive biliary tract cancer that has progressed after cancer chemotherapy

Dosage and Administration

The usual adult dosage is 20 mg of futibatinib administered orally once daily in the fasted state. The dose may be reduced according to the patient's condition.

Approval Conditions

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

Attachment

Review Report (1)

March 30, 2023

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

Product Submitted for Approval

Brand Name	Lytgobi Tablets 4 mg
Non-proprietary Name	Futibatinib
Applicant	Taiho Pharmaceutical Co., Ltd.
Date of Application	July 28, 2022
Dosage Form/Strength	Tablets, each containing 4 mg of futibatinib.
Proposed Indication	Previously treated, locally advanced or metastatic biliary tract cancer harboring *fibroblast growth factor receptor 2 (FGFR2*) gene fusion or other rearrangements

Proposed Dosage and Administration

The usual adult dosage is continuous oral dose of futibatinib 20 mg administered once daily. The dose may be reduced according to the patient's condition.

Table of Contents

List of Abbreviations

See Appendix.

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

1.1 Outline of the proposed product

Fibroblast growth factor receptor (FGFR)2, a receptor tyrosine kinase, forms dimers when a fibroblast growth factor (FGF) ligand binds to and thereby is activated, leading to activation of downstream signaling pathways such as mitogen-activated protein kinase (MAPK) pathway, which are deemed to be involved in cellular proliferation, survival, and other activities (*Cytokine Growth Factor Rev.* 2015;26:425-49, *J Biol Chem.* 2006;281:15694-700, etc.). In tumor cells harboring *FGFR2* gene fusion with other genes, FGFR2 is deemed to form dimers in a ligand-independent manner and thereby constitutively activate downstream signaling pathways, stimulating cellular proliferation (*Cancer Discov.* 2013;3:636-47, *J Hepatol.* 2021;75:351-62, etc.).

Futibatinib is a FGFR-inhibiting low-molecular-weight compound discovered by Taiho Pharmaceutical Co., Ltd. (the applicant) and is considered to inhibit FGFR2 phosphorylation and downstream signaling molecule phosphorylation, thereby inhibiting proliferation of tumor cells harboring *FGFR2* gene fusion.

1.2 Development history etc.

Outside Japan, the applicant initiated a phase I dose-escalation part of a global phase I/II study (Study TAS-120-101 [Study 101]) in patients with advanced solid cancers in July 2014. In April 2018, the applicant initiated a phase II part of the global phase I/II study (Study 101) in patients with unresectable, intrahepatic cholangiocarcinoma harboring *FGFR2* gene fusion or *FGFR2* gene rearrangement[1)] who had received prior chemotherapy.

In the US and EU, an application was submitted in January and [redacted] 2022, respectively, mainly based on results from the phase II part of Study 101. In the US, accelerated approval was granted for the following indication in September 2022: "LYTGOBI is indicated for the treatment of adult patients with previously treated, unresectable, locally advanced or metastatic intrahepatic cholangiocarcinoma harboring fibroblast growth factor receptor 2 (FGFR2) gene fusions or other rearrangements. This indication is approved under accelerated approval based on overall response rate and duration of response. Continued approval for this indication may be contingent upon verification and description of clinical benefit in a confirmatory trial(s)." In the EU, it is currently under review.

As of February 2023, futibatinib is approved for the indication of unresectable intrahepatic cholangiocarcinoma harboring *FGFR2* gene fusion or other rearrangements only in the US.

In Japan, the applicant initiated a Japanese phase I study (Study 10059010 [Study 010]) in patients with advanced solid cancers in July 2014. In addition, the applicant started patient registration for the phase II part of the global phase I/II study (Study 101) in [redacted] 20[redacted].

The application for marketing approval (application) for futibatinib has recently been submitted mainly based on results from the phase II part of Study 101.

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1) (a) "*FGFR2* gene fusion" was defined as a gene structure in which the breakpoint is at intron 17 or exon 18 of the *FGFR2* gene and a partner gene (gene fused with the *FGFR2* gene) is in the same reading frame as that of the *FGFR2* gene; and (b) "*FGFR2* gene rearrangement" was defined as a gene structure in which the breakpoint is at intron 17 or exon 18 of the *FGFR2* gene, and fusion occurred at an intergenic region or the partner gene is not in the same reading frame as that of the *FGFR2* gene. The status of *FGFR2* gene fusion or *FGFR2* gene rearrangement was tested using (i) "FoundationOne Assay for Clinical Study" of Foundation Medicine Inc. at a central laboratory, (ii) "FoundationOne CDx Cancer Genomic Profile" at a study site, or (iii) other examination methods at a study site ([1] next generation sequencing [NGS], [2] fluorescence *in situ* hybridization [FISH]).

2. Quality and Outline of the Review Conducted by PMDA

2.1 Drug substance

2.1.1 Characterization

The drug substance occurs as a white crystalline powder. Its general properties, including description, solubility, hygroscopicity, melting point, thermal analysis, pH, acid dissociation constant, partition coefficient, and optical rotation have been determined. For crystal polymorphism, the drug substance has been found in at least 3 crystal forms ([redacted], [redacted], and [redacted]), but only [redacted] is produced in the commercial manufacturing process. The stability tests [see Section 2.1.4] have demonstrated that no changes occur in the crystal form.

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

2.1.2 Manufacturing process

The drug substance is synthesized using [redacted],[2] [redacted],[3] [redacted],[4] and [redacted][5] as the starting materials.

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

- Identification of critical quality attributes (CQAs)
- Investigation of critical process parameters (CPPs) based on the risk evaluation and design of experiments, etc.

Table 1. Overview of control strategy for drug substance

CQA	Control method
Content	Manufacturing process and specification
Identification	Manufacturing process and specification
Related substances	Manufacturing process and specification
Enantiomers	Manufacturing process and specification
Residual solvents	Manufacturing process and specification
Elemental Impurities	Manufacturing process
Particle size distribution	Manufacturing process and specification
Crystalline polymorphism	Manufacturing process and specification

Processes for [redacted] of [redacted],[6] [redacted] of [redacted], and [redacted] of [redacted] have been defined as the critical steps. [redacted][7] and [redacted] have been controlled as critical intermediates.

2.1.3 Control of drug substance

The proposed specifications for the drug substance include content, description, identification (UV-VIS, IR, high-performance liquid chromatography [HPLC]), purity (related substances [HPLC], enantiomers

2) [redacted]
3) [redacted]
4) [redacted]
5) [redacted]
6) [redacted]
7) [redacted]

[HPLC], residual solvents [gas chromatography (GC)]), water content, residue on ignition, assay (HPLC), crystal forms, and particle size distribution.

2.1.4 Stability of drug substance

Table 2 lists the main stability tests conducted on the drug substance, and the results demonstrated the stability of the drug substance. A photostability testing showed that the drug substance is stable to light.

Table 2. Stability tests on drug substance

Test	Primary batches	Temperature	Humidity	Storage form	Storage period
Long-term	3 pilot scale batches	25°C	60%RH	Double-layered low-density polyethylene bag + high-density polyethylene drum	48 months
Accelerated		40°C	75%RH		6 months

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

2.2 Drug product

2.2.1 Description and composition of drug product and formulation development

The drug product is immediate-release film-coated tablets, each containing 4 mg of the drug substance. The drug product contains sodium lauryl sulfate, lactose hydrate, corn starch, hydroxypropylcellulose, D-mannitol, microcrystalline cellulose, crospovidone, magnesium stearate, hypromellose, macrogol 6000, and titanium oxide as excipients.

2.2.2 Manufacturing process

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

Based on the following investigations, the quality control strategy has been established (Table 3):

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

Table 3. Overview of control strategy for drug product

CQA	Control method
Description (appearance)	Specification
Identification	Specification
Related substances	Specification
Uniformity of dosage units (content uniformity)	Manufacturing process and specification
Dissolution	Manufacturing process and specification
Assay	Manufacturing process and specification
Microbial limit	Specification
Water content	Specification

2.2.3 Control of drug product

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

2.2.4 Stability of drug product

Table 4 lists the main stability tests conducted on the drug product, and the results demonstrated the stability of the drug product. A photostability testing showed that the drug product is stable to light.

Table 4. Stability tests on drug product

Test	Primary batches	Temperature	Humidity	Storage form	Storage period
Long-term	3 pilot scale batches	25°C	60%RH	Blister pack [redacted]	36 months
Accelerated		40°C	75%RH	[redacted]	6 months

Based on the above, a shelf life of 48 months has been proposed for the drug product when stored at room temperature in a blister pack [redacted] in accordance with the ICH Q1E guideline. Long-term testing will be continued up to [redacted] months.

2.R Outline of the review conducted by PMDA

On the basis of the data submitted, PMDA has concluded that the quality of the drug substance and drug product is appropriately controlled.

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

3.1 Primary pharmacodynamics

3.1.1 Inhibitory effect against FGFR kinase activity (CTD 4.2.1.1.1, 4.2.1.1.4)

The inhibitory effect of futibatinib against kinase activities of human FGFR1 to FGFR4 (recombinant proteins) was investigated by mobility shift assay using a fluorescein-labeled substrate. Table 5 shows concentrations that result in 50% inhibition (IC_{50}) of futibatinib against these FGFRs.

Table 5. Inhibitory effect of futibatinib against human FGFR1 to FGFR4

Kinase	IC_{50} (nmol/L)
FGFR1	1.8 ± 0.4
FGFR2	1.4 ± 0.3
FGFR3	1.6 ± 0.1
FGFR4	3.7 ± 0.4

Mean ± standard deviation (SD), n = 3

The inhibitory effect of futibatinib against FGFR2 phosphorylation was investigated using human embryonic kidney (HEK)-derived 293 cell line expressing wild-type FGFR2 kinase or one of 4 mutant FGFR2 kinases by enzyme-linked immunosorbent assay (ELISA). Table 6 shows IC_{50} of futibatinib against phosphorylation of various FGFR2 kinases.

Table 6. Inhibitory effect of futibatinib against phosphorylation of wild-type or mutant FGFR2 kinase

FGFR2	IC_{50} (nmol/L)
Wild-type	3.1 ± 1.3
N550H*1	12.0 ± 5.0
V565I*2	8.4 ± 3.1
E566G*3	5.5 ± 4.7
K660M*4	9.2 ± 7.0

Mean ± SD, n = 3,
*1 Asparagine at position 550 substituted by histidine,
*2 Valine at position 565 substituted by isoleucine,
*3 Glutamic acid at position 566 substituted by glycine,
*4 Lysine at position 660 substituted by methionine

3.1.2 Inhibitory effect against non-FGFR kinases (CTD 4.2.1.1.2)

The inhibitory effect of futibatinib against a panel of 287 kinases (recombinant proteins) other than FGFR1 to FGFR4 was investigated by mobility shift assay using a fluorescein-labeled substrate. Among these kinases, only mutant rearranged during transfection (RET) kinase (S891A[8)]) was inhibited by ≥50 % at 100 nmol/L of futibatinib, and the inhibitory rate was 72.9%.

3.1.3 Inhibitory effect against phosphorylation of FGFR signaling molecules (CTD 4.2.1.1.6)

The inhibitory effect of futibatinib against phosphorylation of FGFR2 and its downstream signaling molecules (fibroblast growth factor receptor substrate 2 [FRS2], protein kinase B [AKT], and extracellular signal-regulated kinase [ERK] 1/2) in tumor was investigated in nude mice (n = 3/group) subcutaneously transplanted with human endometrial carcinoma-derived AN3 CA cell lines expressing mutant FGFR2 (K310R/N549K[9)]) by Western blotting. When the tumor volume reached 558 to 777 mm^3, a single oral dose of futibatinib 5, 15, or 50 mg/kg was administered to nude mice. Phosphorylation of FGFR2, FRS2, AKT, and ERK1/2 was downregulated in the tumor at 3 and 6 hours post-dose irrespective of dose.

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

3.1.4.1 *In vitro* (CTD 4.2.1.1.3)

The inhibitory effect of futibatinib against proliferation of human malignant tumor-derived cell lines expressing wild-type or mutant FGFR was investigated using an amount of adenosine triphosphate (ATP) derived from viable cells as an indicator. Table 7 shows IC_{50} of futibatinib.

8) Serine at position 891 of RET substituted by alanine
9) Lysine at position 310 and asparagine at position 549 of FGFR2 substituted by arginine and lysine, respectively

Table 7. Inhibitory effect of futibatinib against proliferation of various cell lines

Cell line	Origin	FGFR	IC_{50} (nmol/L)
MKN45	Gastric cancer	Wild-type	>1,000
MCF-7	Breast cancer		>1,000
DMS 114	Small cell lung cancer	*FGFR1* gene amplification*1	2.22 ± 0.61
SNU-16	Gastric cancer	*FGFR2* gene amplification*2	1.40 ± 0.19
MFM-223	Breast cancer	*FGFR2* gene amplification*3	1.07 ± 0.04
AN3 CA	Endometrial cancer	*FGFR2* gene mutation (K310R/N549K)	3.65 ± 0.48
RT-4	Bladder cancer	*FGFR3-TACC3* gene fusion*4	10.31 ± 4.16

Mean ± SD, n = 3,
*1 ≥9 copies of the gene as detected by fluorescence *in situ* hybridization (FISH) method
*2 ≥4 copies of the gene as detected by Southern blot analysis
*3 Log2 value of signal intensity ratio as detected by comparative genomic hybridization (CGH) >0.45
*4 Exon 17 of *FGFR3* gene and exon 4 of transforming acidic coiled-coil containing protein 3 (*TACC3)* gene fused.

3.1.4.2 *In vivo* (CTD 4.2.1.1.5 and 4.2.1.1.7)

The inhibitory effect of futibatinib against tumor growth was investigated in nude mice (n = 5 or 6/group) subcutaneously transplanted with AN3 CA cell lines expressing mutant FGFR2 (K310R/N549K). When the tumor volume reached 57 to 113 mm^3, the study was started (Day 0). On Days 1 to 11, futibatinib 5, 15, or 50 mg/kg was administered orally once daily (QD), and the tumor volume was determined on Day 12. Relative tumor volumes[10] (mean ± standard error [SE]) in the futibatinib 5, 15, and 50 mg/kg groups were 8.53 ± 0.71, 5.90 ± 0.55, and 3.07 ± 0.53, respectively. Comparisons with the control (0.5% hydroxypropylmethylcellulose [HPMC] solution) indicated that futibatinib at all the doses inhibited tumor growth in a statistically significant manner ($P < 0.001$ for all the doses, Williams test).

The inhibitory effect of futibatinib against tumor growth was investigated in nude rats (n = 6/group) subcutaneously transplanted with human gastric carcinoma-derived SNU-16 cell lines with *FGFR2* gene amplification. When the tumor volume reached 205 to 731 mm^3, the study was started (Day 0). On Days 1 to 14, futibatinib 2.5, 5, or 10 mg/kg was administered orally QD, and the tumor volume was determined on Day 15. Relative tumor volumes[11] (mean ± SE) in the futibatinib 2.5, 5, and 10 mg/kg groups were 1.35 ± 0.25, 1.89 ± 0.36, and 1.24 ± 0.26, respectively. Comparisons with the control (0.5% HPMC solution) indicated that futibatinib at all the doses inhibited tumor growth in a statistically significant manner ($P < 0.025$ for 2.5 and 5 mg/kg; $P < 0.005$ for 10 mg/kg; Williams test for all the doses).

3.2 Safety pharmacology

3.2.1 Effects on central nervous system (CTD 4.2.1.3.3)

A single oral dose of futibatinib 3, 10, or 30 mg/kg was administered to rats (n = 5/group), and effects on the central nervous system were investigated according to the functional observational battery procedure. Futibatinib was found to have no effects.

3.2.2 Effects on cardiovascular system

3.2.2.1 Effects on hERG potassium current (CTD 4.2.1.3.1)

Effects of futibatinib 1, 10, and 30 μmol/L on human *ether-a-go-go* related gene (hERG) potassium current were investigated using HEK293 cell line transfected with hERG. Futibatinib 1, 10, and

[10] Relative tumor volume = (tumor volume on Day 12)/(tumor volume on Day 0)
[11] Relative tumor volume = (tumor volume on Day 15)/(tumor volume on Day 0)

30 μmol/L inhibited hERG potassium current by 9.2% ± 1.8%, 58.4% ± 4.7%, and 83.4% ± 4.8% (mean ± standard deviation (SD), n = 5), respectively, with the IC_{50} of 7.42 μmol/L. Comparisons with the control (0.1% dimethyl sulfoxide [DMSO]) indicated that futibatinib 10 and 30 μmol/L inhibited the current in a statistically significant manner ($P < 0.01$ for both doses, Dunnett test).

3.2.2.2 Effects on blood pressure, heart rate, and electrocardiogram (CTD 4.2.1.3.2)

A single oral dose of futibatinib 1, 3, and 10 mg/kg was sequentially administered to dogs (n = 4) once weekly (QW), and the effects on blood pressure (systolic, diastolic, and mean blood pressures), heart rate, and electrocardiogram (PR, QRS, QT, and QT interval corrected [QTc] intervals) were investigated. Futibatinib was found to have no effects.

3.2.3 Effects on respiratory system (CTD 4.2.1.3.4)

A single oral dose of futibatinib 3, 10, or 30 mg/kg was administered to rats (n = 6/group), and effects of futibatinib on respiratory rate, tidal volume, and minute ventilation were investigated. Futibatinib was found to have no effects.

3.R Outline of the review conducted by PMDA

On the basis of the data submitted, PMDA has concluded that applicant's explanation about non-clinical pharmacology of futibatinib is acceptable except the review presented in the section below.

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

The applicant's explanation about the mechanism of action of futibatinib and efficacy against biliary tract cancer harboring *FGFR2* gene fusion:

FGFR family proteins (FGFR1 to FGFR4) all bind to a FGF ligand and, via their downstream signaling molecules (phospholipase C-γ [PLC-γ], signal transducer and activator of transcription [STAT], phosphatidylinositol 3-kinase [PI3K]/AKT, MAPK, etc.), are involved in cellular proliferation (*Cytokine Growth Factor Rev.* 2015;26:425-49, *J Biol Chem.* 2006;281:15694-700, etc.).

FGFR gene fusion with another gene results in production of FGFR fusion protein, which can constitutively activate its downstream signaling pathways such as MAPK pathway (*Cancer Discov.* 2013;3:636-47, *J Hepatol.* 2021;75:351-62, etc.). In addition, the following finding suggests that *FGFR* gene fusion can be an oncogenic driver of proliferating tumor cells.

- In conditional knock-in mice in which Cre recombinase was designed to induce expression of *FGFR3-transforming acidic coiled-coil containing protein 3 (TACC3)* gene fusion, intratracheal administration of adenoviral vector that induced expression of Cre recombinase downstream of cytomegalovirus (CMV) promoter led to development of lung adenocarcinoma (*Oncogene.* 2018;37:6096-104).

Futibatinib is considered to inhibit tumor growth by inhibiting FGFR1 to FGFR4 kinases [see Section 3.1.1], which hinders phosphorylation of their downstream signaling molecules (FRS2, AKT, ERK1/2, etc.) [see Section 3.1.3]. In addition to the oncogenic mechanism driven by *FGFR* gene fusion, in view of the following point, futibatinib is expected to have efficacy in treatment of *FGFR2* gene fusion-positive biliary tract cancer.

- In NSG mice[12] subcutaneously transplanted with fragments of a xenograft derived from patients with cholangiocarcinoma with *FGFR2-KIAA1217*[13] gene fusion, futibatinib inhibited tumor growth (*Cancer Discov.* 2019;9:1064-79).

The applicant's explanation about differences in pharmacological attributes between futibatinib and pemigatinib, an FGFR inhibitor approved in Japan:
Both futibatinib and pemigatinib are inhibitors against FGFR family proteins but they differ in that futibatinib covalently binds to the cysteine residue of the ATP binding site (*Chem Med Chem.* 2019;14:494-500), while pemigatinib non-covalently binds to the ATP binding site (*Commun Chem.* 2022;5:100, *Cells.* 2019;8:614).

Mutations that render patients resistant to futibatinib and pemigatinib are reported as follows:
- Futibatinib inhibited proliferation of human cholangiocarcinoma-derived CCLP-1 cell line expressing FGFR2 fusion protein with mutations such as N550K/H,[14] L618V,[15] and K660M,[16] which were reported to render patients resistant to pemigatinib (*Cancer Discov.* 2021;11:326-39). On the other hand, CCLP-1 cell line expressing FGFR2 fusion protein with V565F[17] mutation was less sensitive to futibatinib than the cell line without V565F mutation (*Cancer Discov.* 2019;9:1064-79).

PMDA's view:
PMDA largely accepted the applicant's explanation. However, knowledge about pharmacological attributes of futibatinib including differences in such attributes between futibatinib and pemigatinib may be found important in predicting the efficacy of futibatinib in clinical use and selecting appropriate patients. The applicant is required to continue investigations and inform healthcare professionals of a new finding when it becomes available.

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

The pharmacokinetics (PK) of futibatinib in animals was investigated in dogs etc. Plasma protein binding, drug-metabolizing enzymes, and transporters of futibatinib were investigated using human or animal biological specimens.

4.1 Absorption

4.1.1 Single-dose study

A single oral dose of ^{14}C-labeled futibatinib (^{14}C-futibatinib) 10 mg/3.7 MBq/kg was administered to male dogs, and blood and plasma radioactivity concentrations were determined (Table 8).

12) Interleukin-2 (IL-2) receptor γ-deficient non-obese diabetic/severe combined immunodeficiency (NOD/SCID)-based mice
13) Exon 17 of *FGFR2* gene and exon 7 of *KIAA1217* gene fused.
14) Asparagine at position 550 substituted by lysine or histidine
15) Leucine at position 618 substituted by valine
16) Lysine at position 660 substituted by methionine
17) Valine at position 565 substituted by phenylalanine

Table 8. PK parameters of radioactivity (male dogs, single oral dose)

Specimen	n	C_{max} (μg Eq./mL)	t_{max}* (h)	AUC_{inf} (μg Eq.•h/mL)	$t_{1/2}$ (h)
Blood	3	0.903 ± 0.337	2.0 (2.0, 2.0)	83.6 ± 67.6	215 ± 133
Plasma	3	1.007 ± 0.405	2.0 (1.0, 2.0)	16.5 ± 5.40	146 ± 36.2

Mean ± SD, * Median (minimum, maximum)

4.1.2 Repeated-dose study

Repeated oral doses of futibatinib 0.3 or 3 mg/kg were administered QD for 4 weeks to male and female dogs, and plasma futibatinib concentrations were determined (Table 9). Repeated doses tended to increase exposure to futibatinib. No clear difference was noted in C_{max} or AUC_{24h} of futibatinib between males and females.

Table 9. PK parameters of futibatinib (female and male dogs, repeated oral doses for 4 weeks)

Day of measurement (Day)	Dose (mg/kg)	n	C_{max} (ng/mL)		t_{max}* (h)		AUC_{24h} (ng•h/mL)	
			Male	Female	Male	Female	Male	Female
1	0.3	3	48.4 ± 22.9	42.8 ± 20.0	2.0 (1.0, 2.0)	1.0 (1.0, 2.0)	143 ± 73.9	99.9 ± 58.0
	3	5	222 ± 67.5	218 ± 34.1	2.0 (1.0, 2.0)	1.0 (1.0, 1.0)	861 ± 342	751 ± 113
27	0.3	3	86.2 ± 16.6	29.6 ± 27.4	1.0 (1.0, 1.0)	1.0 (0.5, 1.0)	226 ± 53.4	70.5 ± 74.9
	3	5	405 ± 260	547 ± 167	2.0 (1.0, 2.0)	2.0 (2.0, 2.0)	1,570 ± 1,150	2,080 ± 531

Mean ± SD, * Median (minimum, maximum)

4.1.3 *In vitro* membrane permeability

Membrane permeability of futibatinib was investigated using human colon cancer-derived Caco-2 cell line. The apparent permeability in apical to basal direction ($P_{app\ A \rightarrow B}$) of futibatinib 6 and 60 μmol/L was 22.2 and 24.4 × 10^{-6} cm/s, respectively. The applicant explained that the membrane permeability of futibatinib is high in view of $P_{app\ A \rightarrow B}$ of highly membrane-permeable propranolol, which is 25.1 × 10^{-6} cm/s.

4.2 Distribution

4.2.1 Tissue distribution

A single oral dose of ^{14}C-futibatinib 10 mg/3.7 MBq/kg was administered to male pigmented rats and male albino rats, and tissue distribution of radioactivity was investigated by quantitative whole-body autoradiography. The radioactivity was shown to be extensively distributed in tissues of male pigmented and albino rats. In most of the tissues the radioactivity concentration peaked by 5 hours post-dose. In pigmented and albino rats, the maximum tissue radioactivity concentrations in small intestine (48,432 and 6,308 ng Eq./g, respectively) and liver (6,330 and 8,119 ng Eq./g, respectively) were especially higher than those in blood (787 and 823 μg Eq./g, respectively). The radioactivity was distributed in the pigmented skin in pigmented rats as done in albino rats, and the concentration was lower than that in blood. In the uvea and retina in pigmented rats, the radioactivity was detected even at 336 hours post-dose.[18)] Radioactivity concentrations in the uvea and retina in pigmented rats stayed high for a long time, suggesting that futibatinib and its metabolites might bind to melanin. The applicant, however, explained

[18)] In albino rats, radioactivity concentrations were determined at up to 48 hours post-dose. An amount of radioactivity distributed in eyeballs including uvea and retina could not be calculated.

that no toxicological findings were noted in either uvea or retina in repeated-dose toxicity studies in rats and dogs [see Section 5.2], and no safety concerns for eyes were raised in clinical studies. Safety of futibatinib in eyes is discussed in Sections "7.R.3.4 Retinal disorder" and "7.R.3.5 Eye disorders (except retinal disorder)."

4.2.2 Plasma protein binding

Futibatinib (0.2-5 μmol/L) was incubated with plasma specimens from mice, rats, dogs, and humans at 37°C for 8 hours, and plasma protein binding of futibatinib was investigated by an equilibrium dialysis method. Percentages of unbound (free) futibatinib in plasma specimens from mice, rats, dogs, and humans were 3.64% to 3.89%, 4.10% to 4.24%, 8.28% to 9.60%, and 4.41% to 4.83%, respectively.

Futibatinib (0.2-5 μmol/L) was incubated with human serum albumin (45 mg/mL), human α1-acid glycoprotein (0.75 mg/mL), or human γ-globulin (10 mg/mL) at 37°C for 8 hours, and binding of futibatinib to human serum albumin, human α1-acid glycoprotein, and human γ-globulin was investigated by an equilibrium dialysis method. Percentages of futibatinib bound to human serum albumin, human α1-acid glycoprotein, and human γ-globulin were 89.7% to 90.0%, 83.6% to 87.5%, and 9.06% to 11.5%, respectively. As shown above, the applicant explains that futibatinib was mainly bound to albumin and α1-acid glycoprotein in human plasma.

4.2.3 Distribution in blood cells

Futibatinib (0.2-5 μmol/L) was incubated with human blood at 37°C for 5 to 60 minutes, and the distribution of futibatinib in blood cells was investigated. The human blood/plasma ratio of futibatinib concentration ranged from 0.554 to 0.664. The applicant therefore explained that futibatinib was mainly distributed in plasma.

4.2.4 Placental and fetal transfer

Placental and fetal transfer of futibatinib have not been investigated. The applicant explained that futibatinib may cross the placenta and be distributed in fetuses in view of high membrane permeability of futibatinib [see Section 4.1.3] and teratogenicity found in an embryo-fetal development study in rats [see Section 5.5].

4.3 Metabolism

4.3.1 *In vitro*

Futibatinib (10 μmol/L) was incubated with liver microsomes from rats, dogs, and humans in the presence of nicotinamide adenine dinucleotide phosphate hydrogen (NADPH) at 37°C for 1 hour, and metabolites of futibatinib were investigated. No human-specific metabolites were detected.

Futibatinib (10 μmol/L) was incubated with human hepatocytes at 37°C for 2 hours, and metabolites of futibatinib were investigated. Major metabolites detected were M8 (cysteine conjugate) and M9 (glutathione conjugate).

Futibatinib (0.5 μmol/L) was incubated with liver microsomes from humans in the presence of a cytochrome P450 (CYP) isoform (CYP2C9, CYP2D6, or CYP3A) inhibitor and NADPH at 37°C for 1

hour, and metabolizing enzymes involved in metabolism of futibatinib were investigated. Metabolism of futibatinib was inhibited by 76.2% in the presence of an CYP3A inhibitor, while it was inhibited by ≤11% in the presence of other CYP isoform inhibitors investigated. Based on the above, the applicant explained that CYP3A was considered to play the main role in metabolism of futibatinib in humans. Pharmacokinetic interactions with CYP3A inhibitors and inducers are discussed in Sections "6.2.3.1 Drug interaction study with itraconazole and rifampicin" and "6.R.3 Pharmacokinetic interactions mediated by CYP3A."

4.3.2 *In vivo*

A single oral dose of ^{14}C-futibatinib 10 mg/3.7 MBq/kg was administered to non-bile duct-cannulated or bile-duct cannulated male rats, and its metabolites in plasma, urine, feces, and bile were investigated. The following results were obtained:

- In plasma collected from non-bile duct-cannulated male rats at up to 2 hours post-dose, unchanged futibatinib and M8 were mainly detected (accounting for 77.14% and 13.36%, respectively, of the total radioactivity in plasma).
- In urine collected from non-bile duct-cannulated male rats until 8 hours post-dose, M24 (*N*-acetyl cysteine conjugate) and M23 (*N*-acetyl cysteine conjugate of monoxide form) were mainly detected (accounting for 1.03% and 0.18%, respectively, of the radioactivity administered).
- In feces collected from non-bile duct-cannulated male rats until 24 hours post-dose, M8, M22 (hydroxide form), M24, and unchanged futibatinib were mainly detected (accounting for 7.37%, 6.58%, 4.47%, and 2.30%, respectively, of the radioactivity administered).
- In bile collected from bile-duct cannulated male rats until 4 hours post-dose, M8, M2 (glucuronate conjugate of *o*-desmethyl form), M24, M18 (glucuronate conjugate of monoxide form), and M13 (hydroxide form) were mainly detected (accounting for 9.55%, 3.00%, 2.93%, 1.43%, and 1.32%, respectively, of the radioactivity administered).

4.4 Excretion

4.4.1 Excretion in urine, feces, and bile

The applicant's explanation:

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

- A single oral dose of ^{14}C-futibatinib 10 mg/3.7 MBq/kg was administered to non-bile duct-cannulated male rats, and 4.8% and 92.2% of the radioactivity administered were excreted into urine and feces, respectively, until 120 hours post-dose.
- A single oral dose of ^{14}C-futibatinib 10 mg/3.7 MBq/kg was administered to bile-duct cannulated male rats, and 4.6% and 61.0% of the radioactivity administered were excreted into urine and bile, respectively, until 48 hours post-dose.

4.4.2 Excretion in milk

Although the excretion of futibatinib in milk has not been investigated, the applicant explained that futibatinib may be excreted in milk in view of physicochemical properties of futibatinib (molecular weight of 418.45, log *P* value of 2).

4.5 Pharmacokinetic interactions

4.5.1 Enzyme inhibition

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

In view of the following investigation results, the clinical use of futibatinib is unlikely to cause pharmacokinetic interactions mediated by the inhibitory effect of futibatinib against CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, and CYP2D6. On the other hand, the inhibitory effect of futibatinib against CYP3A may mediate pharmacokinetic interactions.

- Futibatinib (0.05-50 μmol/L) was incubated with human liver microsomes in the presence of each substrate of CYP isoforms (CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, and CYP3A)[19] and NADPH, and the inhibitory effect of futibatinib against each CYP isoform was investigated. Futibatinib inhibited the metabolism of substrates of CYP2C8, CYP2C9, and CYP2C19 with the IC_{50} of 8.14, 23.9, and 26.5 μmol/L, respectively. On the other hand, futibatinib did not clearly inhibit the metabolism of substrates of other CYP isoforms investigated.
- Futibatinib (0.05-50 μmol/L) was pre-incubated with human liver microsomes in the presence of NADPH followed by incubation with each substrate[19] of CYP isoforms (CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, and CYP3A), and time-dependent inhibitory effect of futibatinib against each CYP isoform was investigated. Futibatinib inhibited the metabolism of the CYP3A substrate in a time-dependent manner with concentration causing half-maximal inactivation (K_I) and maximum inactivation rate constant (k_{inact}) of 24.6 μmol/L and 0.0766 min^{-1}, respectively.[20] On the other hand, futibatinib did not clearly inhibit the metabolism of substrates of other CYP isoforms investigated in a time-dependent manner.

4.5.2 Enzyme induction

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

In view of the following investigation results, the clinical use of futibatinib is unlikely to cause pharmacokinetic interactions mediated by its induction of CYP2B6. On the other hand, the induction of futibatinib against CYP1A2 and CYP3A may mediate pharmacokinetic interactions.

- Futibatinib (0.5-50 μmol/L) was incubated with primary human hepatocytes for 3 days, and messenger ribonucleic acid (mRNA) expression of CYP isoforms (CYP1A2, CYP2B6, and CYP3A4) was investigated. Futibatinib induced mRNA expression of CYP1A2 and CYP3A4, increasing their levels to 204% to 284% and 141% to 285%, respectively, of those with the vehicle control. On the other hand, futibatinib did not clearly induce mRNA expression of CYP2B6.

Pharmacokinetic interactions of futibatinib with a CYP3A substrate are discussed in Section "6.2.3.2 Drug interaction study with midazolam."

4.5.3 Transporters

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

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

[20] K_I and k_{inact} against midazolam used as a substrate of CYP3A. When testosterone was used as a substrate of CYP3A, the K_I and k_{inact} were 62.4 μmol/L and 0.136 min^{-1}, respectively.

futibatinib:

The following investigation results indicated that futibatinib is not a substrate of organic anion transporting polypeptide (OATP)1B1 or OATP1B3 but a substrate of P-glycoprotein (P-gp) and breast cancer resistance protein (BCRP).

- Transport of futibatinib (0.3-30 μmol/L) mediated by P-gp was investigated using porcine kidney-derived LLC-PK1 cell line expressing human P-gp. The ratio of the efflux ratio (the ratio of secretion permeability coefficient in the secretive direction to that in the absorptive direction) of futibatinib in the cell line expressing P-gp relative to that in the cell line not expressing P-gp ranged from 2.73 to 6.85.
- Transport of futibatinib (0.3-30 μmol/L) mediated by BCRP was investigated using canine kidney-derived MDCKII cell line expressing human BCRP. The ratio of the efflux ratio of futibatinib in the cell line expressing BCRP relative to that in the cell line not expressing BCRP ranged from 1.77 to 1.81.[21)]
- Transport of futibatinib (0.1 μmol/L) mediated by OATP1B1 and OATP1B3 was investigated using HEK293 cell line expressing human OATP1B1 or OATP1B3. The ratio of futibatinib intake in the presence of an OATP1B1 or OATP1B3 inhibitor (cyclosporine A 10 μmol/L) relative to that in the absence of the inhibitor was <2 for either cell line.

The inhibitory effect of futibatinib (0.03-60 μmol/L[22)]) against the transport of substrates[23)] of transporter was investigated using LLC-PK1 cell line expressing human P-gp, MDCKII cell line expressing human BCRP, and HEK293 cell line expressing human organic anion transporter (OAT) 1, OAT3, organic cation transporter (OCT) 2, OATP1B1, OATP1B3, multidrug and toxin extrusion (MATE) 1, or MATE2-K. Futibatinib inhibited the transport of substrates of P-gp, BCRP, OATP1B1, OATP1B3, MATE1, and MATE2-K with IC_{50} of 0.296, 0.348, 2.85, 16.4, 5.69, and 5.97 μmol/L, respectively. On the other hand, futibatinib did not clearly inhibit the transport of substrates of OAT1, OAT3, and OCT2. In view of the above investigation results, the clinical use of futibatinib is unlikely to cause pharmacokinetic interactions medicated by the inhibitory effect against OAT1, OAT3, OCT2, OATP1B1, OATP1B3, MATE1, and MATE2-K. On the other hand, the clinical use of futibatinib may cause pharmacokinetic interactions mediated by the inhibitory effect against P-gp and BCRP. Pharmacokinetic interactions mediated by the inhibitory effect of futibatinib against P-gp and BCRP are discussed in Section "6.R.4 Pharmacokinetic interactions mediated by P-gp and BCRP."

4.R Outline of the review conducted by PMDA

On the basis of the data submitted and the review presented in the section below, PMDA has concluded that the applicant's explanation about the non-clinical pharmacokinetics of futibatinib is acceptable.

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21) Determined in the presence of futibatinib 0.3 and 1 μmol/L. The ratio of the efflux ratios determined in the presence of futibatinib 10 and 30 μmol/L ranged from 0.50 to 0.81, which were lower than those determined at 0.3 and 1 μmol/L. The applicant explained that the low values were caused by saturated efflux of futibatinib via BCRP in the presence of futibatinib ≥10 μmol/L.

22) For P-gp and BCRP, futibatinib was used at 0.03 to 30 μmol/L.

23) The following substrates were used: ^{3}H-verapamil (9.9 or 10.7 nmol/L) and ^{3}H-prazosin (11.3 or 12.5 nmol/L) for P-gp and BCRP, ^{3}H-estradiol-17β-glucuronide (28.6 or 29.5 nmol/L) for OATP1B1 and OATP1B3, ^{3}H-*p*-aminohippurate (229.9 nmol/L) for OAT1, ^{3}H-estrone-3-sulfate (18.8 nmol/L) for OAT3, and ^{14}C-tetraethylammonium (7.8, 7.9, or 8.1 μmol/L) for OCT2, MATE1, and MATE2-K.

4.R.1 Pharmacokinetic interactions

The applicant's explanation about pharmacokinetic interactions of futibatinib mediated by the induction of CYP1A2 as well as P-gp and BCRP:

In vitro study results suggested that the clinical use of futibatinib may cause pharmacokinetic interactions mediated by its induction of CYP1A2 as well as P-gp and BCRP [see Sections 4.5.2 and 4.5.3]. For the pharmacokinetic interactions mediated by CYP1A2, however, no safety concerns for concomitant use of futibatinib with substrates of CYP1A2 were observed in patients who received futibatinib 20 mg QD in a global phase I/II study (Study 101) and Japanese phase I study (Study 010). Combination of futibatinib in clinical use with the concerned substrates is unlikely to raise problems. For the pharmacokinetic interactions mediated by P-gp and BCRP, combination of futibatinib in clinical use with P-gp and BCRP inhibitors is also unlikely to raise problems in view of the absorption rate of futibatinib, which is estimated to be ≥70% [see Section 6.2.2.1].

The applicant plans to conduct a clinical study for pharmacokinetic interactions of futibatinib with a P-gp inhibitor.

PMDA's view:

PMDA largely accepted the above applicant's explanation. However, information about pharmacokinetic interactions of futibatinib mediated by its induction of CYP1A2 as well as P-gp and BCRP including results from the planned clinical study is important for ensuring the proper use of futibatinib. The applicant is required to appropriately provide the currently available information using the package insert to healthcare professionals, continue collecting relevant information, and appropriately inform them of useful information when it becomes available.

5. Toxicity and Outline of the Review Conducted by PMDA

5.1 Single-dose toxicity

No single-dose toxicity studies of futibatinib have been conducted. Acute toxicity and approximate lethal dose of futibatinib were evaluated based on results after the first dose in 3-week repeated oral dose studies for dose finding in rats and dogs and results from an *in vivo* micronucleus assay in rats. In either animal species, no acute toxicity was observed. An approximate lethal oral dose was determined to be >300 mg/kg in rats and >30 mg/kg in dogs.

5.2 Repeated-dose toxicity

Four- and 13-week repeated-dose toxicity studies in rats and dogs were conducted, and repeated-dose toxicity of futibatinib was evaluated from a viewpoint of tolerability (Table 10). Main toxicity findings noted in both rats and dogs were ectopic mineralization in organs and tissues throughout the body, bone/cartilage malformation, and abnormal values and findings related to ectopic mineralization and bone/cartilage malformation. In rats, corneal opacity was noted.

Table 10. Repeated-dose toxicity

Test system	Route of administration	Dosing period	Dose (mg/kg/day)	Main findings	NOAEL	Attached document CTD
Male and female rats (Sprague Dawley)	Oral	4 weeks + 4-week recovery	Every-other-day: 0,* 3, 10, 30 QD: 3	Every-other-day administration ≥3: Corneal opacity; increased urine calcium value; tissue mineralization (femur periosteum, cornea, and kidney medulla); aggregation of alveolar macrophages in the lung (male and female); increased urine inorganic phosphorus value; growth plate thickening, increased secondary trabecular bone, cortical bone ossification anomaly, and articular cartilage thickening in the femur; lingual arterial calcification (male); increased urine volume; and decreased osmotic pressure of urine (female) ≥10: Tissue mineralization (conjunctiva and tracheal mucosa); cornea epithelial atrophy (male and female); increased blood creatinine value; expanded Harderian gland cavity; tissue mineralization (aortic artery and arterial wall in the heart, arterial wall and cortex in the kidney, arterial wall in the lung, and arterial wall and mucosa in the stomach) (male); corneal endothelium adhesion; increased urine inorganic phosphorus value; decreased blood total protein and albumin values; thickening of growth plate and articular cartilage in the femur; femur cortical bone ossification anomaly; and lingual arterial calcification (female) 30: Increased blood inorganic phosphorus value; decreased urine pH value; decreased salivary gland weight; chondrosternal thickening; tissue mineralization (tunica muscularis ventriculi and spinal meninges) (male and female); decreased body weight and food consumption; corneal endothelium adhesion; increased urine volume; decreased osmotic pressure of urine; increased BUN value; decreased blood albumin value; tissue mineralization (thoracic aorta arterial wall, alveolar wall, and bronchiole); decreased femur osteoblasts; increased bone marrow adipocytes; mammary gland atrophy; glandular stomach accessory cell hyperplasia (male); corneal edema; increased blood ALP and total cholesterol; and tissue mineralization (aorta and arterial wall in the heart and kidney cortex, gastric mucosa, and tracheal muscle layer) (female) QD administration 3: Corneal opacity; decreased urine pH; increased urine calcium and inorganic phosphorus values; increased blood ALP and inorganic phosphorus values; decreased blood albumin value; decreased salivary gland weight; tissue mineralization (femur periosteum, cornea and conjunctiva in the eye, kidney cortex and medulla, gastric mucosa, lingual arterial wall, and tracheal mucosa); femur cortical bone ossification anomaly and articular cartilage thickening; cornea epithelial atrophy; expanded Harderian gland cavity; aggregation of alveolar macrophages in the lung (male and female); corneal endothelium adhesion; increased BUN and creatinine values; tissue mineralization (thoracic aorta arterial wall, aorta and arterial wall in the heart, kidney arterial wall, arterial wall in the lung, alveolar wall, bronchiole, arterial wall and muscle layer in the stomach); femur growth plate thickening, increased secondary trabecular bone, decreased osteoblasts, and bone marrow fibrogenesis; chondrosternal thickening; mammary gland atrophy; glandular stomach accessory cell hyperplasia (male); increased urine volume; decreased osmotic pressure of urine; and decreased blood total protein (female)	—	4.2.3.2.2
				After end of recovery period Corneal opacity and endothelial adhesion; and tissue mineralization (thoracic aorta arterial wall, cornea, aorta and arterial wall in the heart, arterial wall, cortex, and medulla in the kidney, arterial wall in the lung, bronchiole, arterial wall and mucosa in the stomach, lingual arterial wall, and tracheal mucosa)		

Test system	Route of administration	Dosing period	Dose (mg/kg/day)	Main findings	NOAEL	Attached document CTD
Male and female rats (Sprague Dawley)	Oral	13 weeks	Every-other-day: 0,* 1, 3, 10	≥1: Increased urine calcium and inorganic phosphorus values, increased blood creatinine value (male and female), decreased kidney weight (male), increased urine volume, and decreased osmotic pressure of urine (female) ≥3: Corneal opacity, increased BUN value (male and female), increased blood calcium value, femur articular cartilage thickening and increased diaphyseal trabecular bone, increased sternal secondary trabecular bone, tissue mineralization (gastric mucosa and lingual arterial wall) (male), and increased blood inorganic phosphorus value (female) 10: Decreased liver weight; cornea mineralization (male and female); increased urine volume; decreased osmotic pressure of urine; increased blood inorganic phosphorus value; decreased thyroid weight; tissue mineralization (thoracic aorta arterial wall, femur periosteum, aorta and arterial wall in the heart, medulla and arterial wall in the kidney, and spinal meninges); femur growth plate thickening, increased secondary trabecular bone, and decreased hypertrophy zone of growth plate; cornea epithelial atrophy; renal pelvis stone; aggregation of alveolar macrophages in the lung (male); increased blood AST and ALP values; decreased blood total protein and albumin values; decreased kidney weight; increased femur diaphyseal trabecular bone; increased sternal secondary trabecular bone; and lingual arterial calcification (female)	—	4.2.3.2.3
Male and female dogs (beagle)	Oral	4 weeks + 4-week recovery	Every-other-day: 0,* 1, 3, 10 QD: 0.3, 3	Every-other-day administration ≥1: Decreased femur bone marrow cells, thickening of the hypertrophy zone, thickening of the primary trabecular bone, ossification anomaly, thickening of the articular cartilage; sternal ossification anomaly (male and female); increased sternal osteoblasts; bronchial mineralization (male); decreased blood triglyceride value; thickening of femur proliferating zone; and thickening of sternal proliferating zone (female) ≥3: Increased blood inorganic phosphorus value (male and female); decreased body weight and food consumption; decreased blood triglyceride value; white foci at the aorta origin; arterial calcification, cell infiltration, and intimal edema at the aorta origin; thickening of femur proliferating zone; gastric mucosa mineralization (male); and increased sternal osteoblasts (female) 10: Decreased lymphocyte count (male and female); increased fibrinogen value; thickening of sternal proliferating zone (male); astasia; decreased body weight and food consumption; increased red blood cell count, hemoglobin value, hematocrit value, white blood cell count, neutrophil count, blood creatine kinase value, and glucose value; white foci at the aorta origin; arterial calcification, cell infiltration, and intimal edema at the aorta origin; and gastric mucosa mineralization (female) 3: Kidney pouch mineralization (male) QD administration ≥0.3: Decreased bone marrow cells, thickening of proliferating zone, thickening of hypertrophy zone, thickening of primary trabecular bone, and ossification anomaly in the femur; thickening of proliferating zone, ossification anomaly, and increased osteoblasts in the sternum (male and female); white foci at the aorta origin; and arterial calcification and cell infiltration at the aorta origin (male) 3: Decreased body weight and food consumption; increased blood fibrinogen, ALT, inorganic phosphorus, and CRP values; decreased blood triglyceride value; intimal edema at the aorta origin; thickening of femur articular cartilage (male and female); no feces; white foci on the left atrium; tissue mineralization (arterial wall in the kidney, coronary artery in the heart, and endocardium); arterial wall hemorrhage at the aorta origin; thickening of endocardium (male); decreased locomotor activity; increased white blood cell, neutrophil, and monocyte counts; decreased lymphocyte count; increased spleen weight; white foci at the aorta origin; arterial wall cell infiltration at the aorta origin; tissue mineralization (arterial wall at the aorta origin, mucosa and muscularis mucosae in the stomach); and endometrial hemorrhage (female) 0.3: Mineralization at the renal papilla (male) and bladder arterial calcification (female)	—	4.2.3.2.5

Test system	Route of administration	Dosing period	Dose (mg/kg/day)	Main findings	NOAEL	Attached document CTD
				After end of recovery period Tissue mineralization (arterial wall at the aorta origin, mucosa and muscularis mucosae in the stomach, and bladder arterial wall)		
Male and female dogs (beagle)	Oral	13 weeks	Every-other-day: 0,* 0.3, 1, 3	≥0.3: Thickening of proliferating zone, hypertrophy zone, and primary trabecular bone in the femur; increased femur trabecular bone and increased bone marrow cells; thinning of sternal hypertrophy zone (male and female); decreased blood triglyceride value; white foci at the aorta origin; arterial calcification at the aorta origin (male); and increased sternal bone marrow cells (male) ≥1: Intimal edema and cell infiltration at the aorta origin; thickening of sternal proliferating zone (male and female); increased blood inorganic phosphorus and ALT values (male); decreased blood triglyceride value; white foci at the aorta origin; and arterial calcification at the aorta origin (female) 3: Arterial wall hemorrhage at the aorta origin (male and female); increased eosinophil percentage; arterial wall cell infiltration at the aorta origin; tissue mineralization (arterial wall in the heart and gastric mucosa) (male); decreased lymphocyte percentage and neutrophil count; prolonged APTT; and increased blood inorganic phosphorus, ALT, and ALP values (female) 1: Arterial calcification at the aortic arch (male and female) and increased sternal bone marrow cells (female)	—	4.2.3.2.6

* 5 mg/mL HPMC solution

5.3 Genotoxicity

Bacterial reverse mutation assay (Ames test), chromosomal aberration assay in CHL/IU cells, *in vivo* micronucleus assay in rats, and *in vivo* comet assay using rat liver were conducted (Table 11). The chromosomal aberration assay in CHL/IU cells suggested that futibatinib induced structural chromosomal aberrations, but the *in vivo* micronucleus assay in rats and *in vivo* comet assay using rat liver showed the negative results. The applicant explained that futibatinib is therefore unlikely to raise concern about genotoxicity.

Table 11. Genotoxicity

Type of study		Test system	Metabolic activation (treatment)	Concentration or dose	Result	Attached document CTD
In vitro	Ames	*Salmonella typhimurium*: TA98, TA100, TA1535, TA1537 *Escherichia coli*: WP2*uvrA*	S9-	0,*1 39.1, 78.1, 156, 313, 625, 1,250, 2,500, 5,000 μg/plate	Negative	4.2.3.3.1.1
			S9+	0,*1 39.1, 78.1, 156, 313, 625, 1,250, 2,500, 5,000 μg/plate		
	Chromosomal aberration	Chinese hamster lung cells (CHL/IU cells)	S9- (6 hours)	0,*1 125, 250, 500 μg/mL	Positive	4.2.3.3.1.2
			S9- (24 hours)	0,*1 1.25, 2.5, 5 μg/mL	Negative	
			S9+ (6 hours)	0,*1 15.6, 31.3, 62.5, 125, 250, 500 μg/mL	Positive	
In vivo	Micronucleus	Male rat (Sprague Dawley), single, oral, bone marrow		0,*2 30, 100, 300 mg/kg	Negative	4.2.3.3.2.1
	Comet	Male rat (Sprague Dawley), QD, 2 days, oral, liver		0,*2 30, 100, 300 mg/kg	Negative	4.2.3.3.2.2

*1 DMSO, *2 5 mg/mL HPMC solution

5.4 Carcinogenicity

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

5.5 Reproductive and developmental toxicity

In the 13-week repeated-dose toxicity studies in rats and dogs, no effect on the male or female reproductive organ was noted.

A preliminary embryo-fetal development study was conducted in rats (Table 12). Visceral and skeletal malformations were noted at ≥0.05 mg/kg/day, and no no-observed-adverse-effect level (NOAEL) has been determined.

Exposure[24)] at 0.05 mg/kg/day, the lowest dose leading to the above findings, was below the clinical exposure,[25)] and biliary tract cancer is a disease with poor prognosis. In view of the above, the applicant explained that the following cautions would be provided to healthcare professionals appropriately using the package insert, etc.: (a) Futibatinib should be used in pregnant women or in women who may be pregnant only if the expected therapeutic benefits outweigh the possible risks associated with treatment; and (b) women of childbearing potential and men with a female partner of childbearing potential should be instructed to use appropriate contraception.

Table 12. Reproductive and developmental toxicity

Type of study	Test system	Route of administration	Dosing period	Dose (mg/kg/day)	Main findings	NOAEL	Attached document CTD
Embryo-fetal development	Female rats (Sprague Dawley)	Oral	Gestation Days 7-17	0,[*1] 0.05, 0.15, 0.5	Embryos and fetuses[*2]: ≥0.05: Membranous ventricular septal defect and absent thoracic vertebrae ≥0.15: Retroesophageal aortic arch; thoracic cartilage split; and supernumerary lumbar vertebrae 0.5: Decreased fetal body weight; interrupted aortic arch; aberrant subclavian artery at the origin; retroesophageal subclavian artery; absent kidney; small kidney; dilated renal pelvis; absent ureter; dilated ureter; convoluted ureter; malpositioned testis; malpositioned epididymis; small uterus; bipartite ossification of sternebra; fusion and misalignment of sternum; extra rib full; fused rib; fused and detached costal cartilage; absent, fused, misshapen, and small cervical arch; hemicentric cervical centrum and thoracic vertebra; and absent lumbar vertebra	—	4.2.3.5.2.2

*1 5 mg/mL HPMC solution, *2 Malformation finding

[24)] AUC_{24h} of unbounded futibatinib in plasma (0.78 ng•h/mL) calculated from AUC_{24h} of futibatinib (18.45 ng•h/mL) and a fraction of its unbounded form (0.0424) in rats [see Section 4.2.2].

[25)] AUC_{24h} of unbounded futibatinib in plasma (56.81 ng•h/mL) calculated from AUC_{24h} of futibatinib after oral administration of futibatinib 20 mg QD (1,176.23 ng•h/mL) in the phase I dose-escalation part of the global phase I/II study (Study 101) and a fraction of its unbounded form in humans (0.0483) [see Section 4.2.2].

5.6 Other toxicity studies

5.6.1 Photosafety

A phototoxicity testing was conducted using mouse fibroblasts (Table 13). The applicant explained that the study result indicated that futibatinib had no phototoxicity.

Table 13. Photosafety study

Type of study	Test system	Test method	Result	Attached document CTD
In vitro	Mouse fibroblasts (Balb/c 3T3)	Treatment at 0,* 0.391, 0.781, 1.56, 3.13, 6.25, 12.5, 25, and 50 µg/mL for 60 minutes followed by UV-A irradiation (5 J/cm^2) for 50 minutes	MPE: -0.048 No phototoxicity	4.2.3.7.7.1

* DMSO

5.R Outline of the review conducted by PMDA

On the basis of the data submitted and the review presented in the section below, PMDA has concluded that the applicant's explanation about toxicity of futibatinib is acceptable.

5.R.1 Ectopic mineralization and bone/cartilage malformation

The applicant's explanation about ectopic mineralization and bone/cartilage malformation noted in rats and dogs at doses (3 mg/kg every other day[26)] and 0.3 mg/kg QD[27)]) corresponding to exposure below the clinical exposure,[25)] and safety in humans related to the concerned toxicity findings:

Ectopic mineralization and bone/cartilage malformation noted in rats and dogs are considered attributable to effects of futibatinib on mineral homeostasis via its FGFR inhibition, including increased inorganic phosphorus and calcium values (*Toxicol Pathol.* 2005;33:449-55). Adverse drug reactions related to ectopic mineralization and bone/cartilage malformation reported in clinical studies of futibatinib included hyperphosphataemia, calciphylaxis, hypercalcaemia, arthralgia, and arthritis. Hyperphosphataemia, if it persists, may lead to hypercalcaemia, bone/cartilage disorders, and ectopic mineralization, but it can be managed by administration of anti-hyperphosphataemia drugs and dose reduction of futibatinib. Based on the above, the applicant plans to provide dose adjustment criteria for management of hyperphosphataemia in the package insert and take safety measures such as instructing measurement of serum phosphate levels. With the plan implemented, futibatinib in clinical use is unlikely to cause safety problems.

PMDA's view:

PMDA accepted the applicant's explanation. Safety in humans related to the concerned toxicity finding is discussed in Section "7.R.3.3 Hyperphosphataemia" in view of incidences of events including hyperphosphataemia in clinical studies.

26) AUC_{24h} of unbounded futibatinib in plasma (48.76 ng•h/mL) calculated from AUC_{24h} of futibatinib (1,150 ng•h/mL) and a fraction of its unbounded form (0.0424) in rats [see Section 4.2.2].

27) AUC_{24h} of unbounded futibatinib in plasma (14.23 ng•h/mL) calculated from AUC_{24h} of futibatinib (148.25 ng•h/mL) and a fraction of its unbounded form (0.0960) in dogs [see Section 4.2.2].

5.R.2 Effect on cornea

The applicant's explanation about corneal lesion noted in rats:

The change is considered attributable to inorganic phosphorus and calcium concentrations in blood affected by FGFR inhibition in rats in which corneal mineralization occurs more frequently than other animal species (*Ophthalmic Res.* 1994;26:296-303).

PMDA's view:

PMDA accepted the applicant's explanation. An effect on cornea in humans is discussed in Section "7.R.3.5 Eye disorders (except retinal disorder)" in view of incidences of eye disorders in clinical studies.

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

Futibatinib was provided in oral formulations of liquid, capsules, and film-coated tablets, and PK of futibatinib was investigated using these formulations (Table 14). Of note, a proposed commercial formulation is 4 mg film-coated tablets (b). Bioequivalence of the proposed commercial formulation and 4 mg film-coated tablets (a) used in Study 101 was verified by dissolution test.[28)]

Table 14. Oral formulations used in clinical studies

Formulation	Study ID
Oral liquid containing ^{14}C-futibatinib	Foreign phase I study (Study 106)
Capsules (4 and 20 mg)	Japanese phase I studies (Studies 010 and 020), global phase I/II study (Study 101)
Film-coated tablets (a) (4 and 20 mg)	Japanese phase I study (Studies 010 and 020), foreign phase I study (Studies 102, 103, 104, and 105), global phase I/II study (Study 101)
Film-coated tablets (b) (4 mg)	Foreign phase I study (Study 107)

6.1.1 Assay

Futibatinib in human plasma were determined by liquid chromatography-tandem mass spectrometry (LC-MS/MS), and the lower limit of quantification was 0.5 ng/mL.

6.1.2 Foreign clinical studies

6.1.2.1 Foreign phase I study (CTD 5.3.1.1.1, Study TAS-120-102 [Study 102], [redacted] to [redacted] 20[redacted])

A 2-treatment, 2-period crossover study was conducted to evaluate an effect of food on the PK of futibatinib in 17 healthy adults (17 subjects included in the PK analysis). A single oral dose of futibatinib 20 mg was administered in the fasted state[29)] or after a high-fat meal[30)] with a 7-day washout period between doses.

The geometric mean ratios [90% confidence interval (CI)] of C_{max} and AUC_{inf} of futibatinib taken after the high-fat meal relative to those under the fasted state were 0.576 [0.472, 0.703] and 0.888 [0.798, 0.989], respectively.

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28) The dissolution test was performed as defined in specifications for the 4 mg film-coated tablets (b), a test formulation. Of note, the dissolution test conditions defined in the specifications for the 4 mg film-coated tablets (b) and (a), a reference formulation, differ by only polysorbate 80 concentration (0.5 and 1.0 w/v%, respectively).

29) Administered after ≥10-hour fasting, followed by 4-hour fasting

30) A total of 900 to 1,000 kcal, of which ≥50% is from fat.

6.1.2.2 Foreign phase I study (CTD 5.3.3.4.2, Study TAS-120-104 [Study 104], [redacted] to [redacted] 20[redacted])

An open-label, uncontrolled study was conducted to evaluate an effect of a proton pump inhibitor (lansoprazole) on PK of futibatinib in 20 healthy adults (20 subjects included in the PK analysis). A single oral dose of futibatinib 20 mg was administered on Day 1 of Period 1 and Day 5 of Period 2, while multiple oral doses of lansoprazole 60 mg was administered QD on Days 1 to 5 of Period 2. Day 1 of Period 1 and Day 1 of Period 2 were separated by ≥2 days.

The geometric mean ratios [90% CI] of C_{max} and AUC_{inf} of futibatinib after co-administration of futibatinib with lansoprazole relative to those after administration of futibatinib alone were 1.08 [0.977, 1.20] and 1.05 [0.953, 1.16], respectively.

As shown above, the co-administered proton pump inhibitor had no definite effect on PK of futibatinib. The applicant therefore explained that no caution would be required for concomitant use of drugs impacting gastric pH such as proton pump inhibitors.

6.2 Clinical pharmacology

The PK of futibatinib in healthy adults and patients with cancer was investigated after administration of futibatinib alone and after co-administration of futibatinib with itraconazole or rifampicin. In addition, an effect of futibatinib on PK of midazolam was investigated.

6.2.1 Global study

6.2.1.1 Phase I dose-escalation part of global phase I/II study (CTD 5.3.5.2.1, Study TAS-120-101 [Study 101], July 2014 to [redacted] 20[redacted])

An open-label, uncontrolled study was conducted to investigate the PK of futibatinib in 86 non-Japanese patients with advanced solid cancers (86 patients included in the PK analysis). Futibatinib 4 to 24 mg was administered orally QD in the fasted state or futibatinib 8 to 200 mg was administered orally 3-times-a-week (QOD)[31] in the fasted state, and futibatinib concentrations in plasma were determined.

Table 15 shows the PK parameters of futibatinib. An accumulation ratio[32] of futibatinib after oral QD administration of futibatinib 20 mg ranged from 1.06 to 1.27.

[31] Monday, Wednesday, and Friday
[32] Ratio of AUC_{last} on Day 21 to that on Day 1

Table 15. PK parameters of futibatinib

Dosage regimen	Dose (mg)	Day of measurement	n	C_{max} (ng/mL)	t_{max}[*1] (h)	AUC_{last} (ng•h/mL)	$t_{1/2}$ (h)
QD	4	1	4	33.1 ± 20.4	0.960 (0.50, 2.02)	114 ± 85.9	1.75 ± 0.510
		21	3	52.5 ± 38.1	1.08 (1.00, 3.00)	134 ± 100	1.63 ± 0.748
	8	1	5	169 ± 150	2.00 (1.00, 25.5)	666 ± 505	2.26 ± 0.782[*2]
		21	5	98.2 ± 56.5	2.00 (1.00, 3.08)	550 ± 442	2.75 ± 0.594
	16	1	14	148 ± 67.0	2.00 (1.00, 3.00)	536 ± 284	2.73 ± 1.76
		21	9	172 ± 72.6	2.07 (0.93, 3.07)	737 ± 373	2.53 ± 1.13
	20	1	7	257 ± 70.1	1.92 (1.00, 3.00)	1,189 ± 648	2.94 ± 0.778[*3]
		21	2	133, 209	3.05, 3.98	843, 1,516	3.18, 3.69
	24	1	14	246 ± 113	1.98 (0.98, 3.08)	1,217 ± 656	3.13 ± 0.941[*4]
		21	3	194 ± 112	2.00 (1.98, 6.07)	1,416 ± 903	1.87, 4.36[*5]
QOD	8	1	6	85.5 ± 46.3	1.04 (1.00, 4.05)	304 ± 218	2.09 ± 0.902
		15-22[*7]	4	106 ± 35.9	1.49 (0.60, 2.08)	472 ± 329	2.01 ± 1.26
	16	1	3	207 ± 41.3	1.00 (1.00, 2.00)	736 ± 504	2.11 ± 1.12
		15-22[*7]	3	213 ± 99.8	1.00 (1.00, 1.92)	1,048 ± 958	2.75 ± 1.89
	24	1	3	258 ± 87.9	3.00 (1.00, 3.98)	1,792 ± 686	3.28, 3.75[*5]
		15-22[*7]	3	361 ± 246	1.05 (1.00, 2.33)	2,206 ± 1,545	5.77, 6.21[*5]
	36	1	3	556 ± 419	2.00 (1.00, 2.00)	2,673 ± 2,075	4.84 ± 2.25
		15-22[*7]	2	173, 1,299	2.05, 3.08	1,531, 7,451	6.00, 7.14
	56	1	3	695 ± 440	3.08 (2.27, 4.08)	3,291 ± 1,827	5.97 ± 2.20
		15-22[*7]	3	930 ± 597	2.00 (2.00, 3.08)	4,579 ± 1,595	6.24 ± 2.80
	80	1	4	964 ± 575	2.50 (1.50, 5.82)	7,472 ± 5,566	4.77 ± 1.69[*6]
		15-22[*7]	5	757 ± 246	3.00 (2.00, 4.00)	6,773 ± 3,129	5.28 ± 1.15
	120	1	4	713 ± 169	3.04 (2.05, 3.95)	6,636 ± 2,994	6.18 ± 1.02[*6]
		15-22[*7]	3	910 ± 645	3.17 (3.00, 6.08)	10,642 ± 10,684	10.6 ± 8.69
	160	1	8	819 ± 363	2.53 (2.00, 4.50)	7,983 ± 6,866	8.75 ± 3.28[*3]
		15-22[*7]	3	863 ± 296	5.57 (2.00, 8.00)	4,449, 13,822[*5]	3.99 ± 1.88
	200	1	7	1,292 ± 919	2.00 (2.00, 4.50)	10,084 ± 9,019	9.55 ± 5.72[*3]
		15-22[*7]	1	845	2.00	5,780	—

Mean ± SD (individual values for n = 1 or 2), [*1] Median (minimum, maximum), [*2] n = 4, [*3] n = 6, [*4] n = 13, [*5] n = 2, [*6] n = 3,
[*7] Determined on Day 15, 17, or 22; —, Not calculated

6.2.2 Foreign clinical studies

6.2.2.1 Foreign phase I study (CTD 5.3.3.1.1, Study TAS-120-106 [Study 106], [redacted] to [redacted] 20[redacted])

An open-label, uncontrolled study was conducted to investigate mass balance of futibatinib in 6 healthy adults (6 subjects included in the PK analysis). A single oral dose of ^{14}C-futibatinib 20 mg was administered, and radioactivity concentrations in blood, plasma, urine, and feces were determined.

In plasma at 24 hours post-dose, unchanged futibatinib, cysteinylglycine conjugate, cysteine conjugate, and glucuronate conjugate of monoxide form were mainly detected (accounting for 59.2%, 13.4%, 8.68%, and 8.97%, respectively, of the total radioactivity in plasma).

Until 336 hours post-dose, 6.47% and 63.6% of the radioactivity administered were excreted into urine and feces, respectively. In feces until 192 hours post-dose, *o*-desmethyl hydrogen adduct, di-*o*-desmethyl hydrogen adduct, and *o*-desmethyl hydrated hydrogen adduct were mainly detected (accounting for 17.0%, 8.98%, and 8.98%, respectively, of the radioactivity dose). The applicant explained that the amount of radioactivity excreted into urine and that excreted into feces as metabolites suggested that ≥70% of futibatinib administered was absorbed in humans.

6.2.3 Drug interaction studies

6.2.3.1 Drug interaction study with itraconazole and rifampicin (CTD 5.3.3.4.1, Study TAS-120-103 [Study 103], ■ to ■ 20■)

An open-label, uncontrolled study was conducted to evaluate effects of itraconazole (potent CYP3A inhibitor) and rifampicin (potent CYP3A inducer) on PK of futibatinib in 40 healthy adults (40 subjects included in the PK analyses). The following dosage regimens were used, and Day 1 of Period 1 and Day 1 of Period 2 were separated by ≥2 days.

Part 1: A single dose of futibatinib 20 mg was administered orally on Day 1 of Period 1 and Day 5 of Period 2, and itraconazole 200 mg was administered orally QD on Days 1 to 6 of Period 2.

Part 2: A single dose of futibatinib 20 mg was administered orally on Day 1 of Period 1 and Day 8 of Period 2, and rifampicin 600 mg was administered orally QD on Days 1 to 9 of Period 2.

The geometric mean ratios [90% CI] of C_{max} and AUC_{inf} of futibatinib after co-administration of futibatinib with itraconazole or with rifampicin to those after administration of futibatinib alone were 1.51 [1.28, 1.79] and 1.41 [1.22, 1.62], as well as 0.472 [0.411, 0.543] and 0.361 [0.305, 0.426], respectively.

6.2.3.2 Drug interaction study with midazolam (CTD 5.3.3.4.3, Study TAS-120-105 [Study 105], ■ to ■ 20■)

An open-label, uncontrolled study was conducted to evaluate an effect of futibatinib on PK of midazolam (CYP3A substrate) in 24 healthy adults (24 subjects included in the PK analysis). In this study, a single oral dose of midazolam 2 mg was administered on Day 1 of Period 1 and Day 7 of Period 2, while futibatinib 20 mg was administered orally QD on Days 1 to 7 of Period 2. Day 1 of Period 1 and Day 1 of Period 2 were separated by ≥1 day.

The geometric mean ratios [90% CI] of C_{max} and AUC_{inf} of midazolam after co-administration of midazolam with futibatinib to those after administration of midazolam alone were 0.946 [0.844, 1.06] and 0.911 [0.802, 1.04], respectively.

As shown above, the co-administered futibatinib had no definite effect on PK of the CYP3A substrate. The applicant therefore explained that no caution would be required for concomitant use of drugs potentially acting as a CYP3A substrate.

6.2.4 Foreign phase I study for an effect of hepatic impairment on PK of futibatinib (CTD 5.3.3.3, Study TAS-120-108 [Study 108], ■ 20■ to ■ 20■)

An open-label study was conducted to evaluate an effect of hepatic impairment on PK of futibatinib in 16 healthy adults (16 subjects included in the PK analysis) and 22 patients with hepatic impairment (including 8 with mild impairment [Child-Pugh score of 5-6], 8 with moderate impairment [Child-Pugh score of 7-9], and 6 with severe impairment [Child-Pugh score of 10-15]; 8, 8, and 6 patients, respectively, included in the PK analysis).

A single oral dose of futibatinib 20 mg was administered in the fasted state, and futibatinib concentrations in plasma were determined.

Table 16 shows the PK parameters of futibatinib.

Table 16. PK parameters of futibatinib by severity of hepatic impairment

Severity of hepatic impairment	n	C_{max} (ng/mL)	AUC_{inf} (ng•h/mL)	Geometric mean ratio [90% CI] (patients with hepatic impairment/healthy adults)	
				C_{max}	AUC_{inf}
Bound form + unbounded form					
Normal	16	108 (53.3)	417 (99.0)	—	—
Mild	8	123 (40.5)	357 (47.7)	1.14 [0.825, 1.56]	0.857 [0.547, 1.34]
Moderate	8	128 (51.1)	511 (108)	1.18 [0.820, 1.69]	1.22 [0.645, 2.33]
Severe	6	128 (29.9)	494 (68.6)	1.18 [0.874, 1.59]	1.19 [0.675, 2.08]
Unbounded form					
Normal	16	1.96 (50.8)	7.54 (94.8)	—	—
Mild	7	2.37 (28.1)	7.06 (42.0)	1.21 [0.922, 1.59]	0.937 [0.608, 1.44]
Moderate	8	2.95 (43.7)	11.8 (95.0)	1.50 [1.08, 2.09]	1.56 [0.861, 2.84]
Severe	6	4.51 (28.9)	17.5 (79.6)	2.30 [1.73, 3.07]	2.32 [1.27, 4.24]

Geometric mean (geometric coefficient of variation %); —, Not calculated

6.2.5 Use of futibatinib in patients with renal impairment

No clinical study have been conducted in patients with renal impairment to evaluate an effect of renal impairment on PK of futibatinib.

The applicant explanation:

In view of the following points, dose adjustment of futibatinib is not necessary for patients with renal impairment:

- The results of a foreign phase I study (Study 106) suggested that renal excretion contributes only minimally to the elimination of futibatinib [see Section 6.2.2.1].
- A pooled analysis of the global phase I/II study (Study 101) and Japanese phase I study (Study 010) showed that in patients who received futibatinib 20 mg QD and had normal renal function[33] (n = 153) or mild (n = 118) or moderate (n = 44) renal impairment, incidences of (a) adverse events leading to death, (b) serious adverse events, (c) adverse events leading to treatment discontinuation, (d) adverse events leading to interruption, and (e) adverse events leading to dose reduction were (a) 7.2%, 9.3%, and 11.4%, (b) 45.1%, 40.7%, and 45.5%, (c) 8.5%, 7.6%, and 13.6%, (d) 53.6%, 60.2%, and 63.6%, and (e) 37.9%, 36.4%, and 43.2%, respectively. No clear relationship between renal impairment and incidence of adverse events was noted. In the above pooled analysis, 1 patient with severe renal impairment was included but did not present any particular safety concerns.

6.2.6 Foreign phase I study (CTD 5.3.3.1.2, Study TAS-120-107 [Study 107], [redacted] to [redacted] 20[redacted])

A 4-treatment, 4-period crossover study was conducted to evaluate an effect of futibatinib on QT interval corrected using Fridericia's formula (QTcF) compared with those of placebo and moxifloxacin in 48 healthy adults (48 subjects included in the PK analysis).

[33] Renal function was classified according to the following criteria: Normal, CLcr ≥90 mL/min; mild impairment, CLcr ≥60 and <90 mL/min; moderate impairment, CLcr ≥30 and <60 mL/min; and severe impairment, CLcr ≥15 and <30 mL/min.

A single oral dose of futibatinib 20 mg, futibatinib 80 mg, placebo, or moxifloxacin 400 mg was administered with a ≥7-day washout period between doses.

The upper limit of two-sided 90% confidence interval of a difference of change in QTcF from baseline (ΔΔQTcF) after administration of futibatinib 20 or 80 mg was <10 ms at all measurement points. The lower limit of two-sided 97.5% CI of ΔΔQTcF after administration of moxifloxacin, a positive control, was >5 ms at 1.5 to 4 hours post-dose.

Based on the above result, the applicant explained that futibatinib in clinical use is unlikely to cause QT/QTc interval prolongation.

6.2.7 PPK analysis

The population pharmacokinetic (PPK) analysis was performed using a non-liner mixed-effects model (software, NONMEM Version 7.4.3) based on PK data (6,433 measuring time points from 491 subjects) on futibatinib from the Japanese phase I studies (Study 010 and Study 10059020 [Study 020]), global phase I/II study (Study 101), and foreign phase I studies (Studies 102, 103, 104, 105, and 107). The PK of futibatinib was described by a 2-compartment model combined with sequential zero- and first-order absorption and first-order elimination.

In this analysis, possible covariate of futibatinib for (1) relative bioavailability (F), first-order absorption rate constant (ka), duration of zero-order input (D1), and absorption lag time (ALAG), (2) CL/F, and (3) Vc/F of futibatinib, respectively, were (1) dosage form, food, dose, concomitant drugs,[34] and cycle, (2) baseline body weight, age, sex, race, region, subject status (healthy adult or patient with cancer), type of carcinoma, *FGFR* gene mutation status, Eastern Cooperative Oncology Group (ECOG) performance status (PS), serum albumin, alanine aminotransferase (ALT), aspartate aminotransferase (AST), total bilirubin, hepatic impairment,[35] renal impairment,[36] CLcr and cycle, and (3) baseline body weight, age, sex, race, region, subject status (healthy adult or patient with cancer), type of carcinoma, *FGFR* gene mutation status, ECOG PS, serum albumin, dosage form, food, dose, concomitant drugs, and cycle. As a result of assessments, (i) concomitant drugs, (ii) food, (iii) serum albumin and dose, and (iv) dose and baseline body weight were defined as covariates for (i) F, (ii) ka, (iii) CL/F, and (iv) Vc/F. Because effects of serum albumin, dose, and baseline body weight on exposure to futibatinib were limited, the applicant explained that dose would not have to be adjusted according to these covariates.

6.2.8 Relationships of exposure to efficacy and safety

6.2.8.1 Relationship of exposure to efficacy

On the basis of data from the phase II part of a global phase I/II study (Study 101), relationships of exposure to futibatinib[37] (C_{min}, C_{max}, C_{avg}, and AUC) to response rate, disease control rate, progression free survival (PFS), overall survival (OS), duration of response, and change in tumor size were investigated. No clear relationships were observed between the exposure to futibatinib and any of the above efficacy indicators.

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[34] Potent CYP3A inhibitors and moderate or potent CYP3A inducers
[35] Classified according to the criteria of NCI Organ Dysfunction Working Group.
[36] Classified according to FDA guidance.
[37] Estimated by the PPK analysis [see Section 6.2.7].

6.2.8.2 Relationship of exposure to safety

On the basis of data from the global phase I/II study (Study 101) and Japanese phase I study (Study 010), relationships of exposure to futibatinib[33] (C_{min}, C_{max}, C_{avg}, and AUC) to adverse events (all-grade hyperphosphataemia, Grade ≥3 hyperphosphataemia, retinal disorders, and nail disorders) were investigated. Incidences of all-grade hyperphosphataemia tended to increase with increasing C_{min} after the first dose, and C_{min} and AUC at steady state. Incidences of Grade ≥3 hyperphosphataemia and nail disorders tended to increase with increasing C_{min} and AUC after the first dose and at steady state.

6.2.9 Differences in PK between Japanese and non-Japanese patients

The applicant's explanation:

The PK parameters of futibatinib after the first dose in the oral administration of futibatinib 20 mg QD in the fasted state did not clearly differ between Japanese patients in the Japanese phase I study (Study 010) and non-Japanese patients in the global phase I/II study (Study 101) (Table 17). No clear difference was noted in the PK of futibatinib between Japanese and non-Japanese patients.

Table 17. PK parameters of futibatinib

Study ID	Population	n	C_{max} (ng/mL)	AUC_{last} (ng•h/mL)
Study 010	Japanese	7	253 ± 161	977 ± 714
Study 101	Non-Japanese	7	257 ± 70.1	1,189 ± 648

Mean ± SD

6.R Outline of the review conducted by PMDA

On the basis of the data submitted, PMDA has concluded that the applicant's explanation about clinical pharmacology of futibatinib is acceptable except the review presented in the section below.

6.R.1 Food effect

The applicant's explanation:

In the foreign phase I study (Study 102), a high-fat meal given before administration of futibatinib decreased the exposure [see Section 6.1.2.1], but no clear relationship of exposure to futibatinib to efficacy was noted [see Section 6.2.8.1]. The decreased exposure to futibatinib with administration in the fed state was considered to have a limited effect on the efficacy. Futibatinib, therefore, may be administered irrespective of the food intake status, and timing of a meal does not have to be specified in the dosage regimen of futibatinib.

PMDA's view:

In view of points below, futibatinib should be administered in the fasted state.

- In the global phase I/II study (Study 101), continuous oral dose of futibatinib 20 mg was administered QD in the fasted state (fasted ≥2 hours before and ≥1 hour after dosing), and the clinical usefulness of futibatinib was shown [see Sections 7.R.2 and 7.R.3].
- The relationship of futibatinib exposure to efficacy was analyzed based on data in the study population not including patients who received lower doses than the futibatinib 20 mg QD regimen. Therefore, the extent of decreased exposure on the efficacy after receiving futibatinib 20 mg QD in the fed state remains unknown.

In the package insert, therefore, Dosage and Administration section should clearly specify that futibatinib should be administered in the fasted state, and the Precautions Concerning Dosage and Administration section should caution that futibatinib should be taken on an empty stomach (2 hours after and 1 hour before a meal) [see Section 7.R.5.1].

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

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

- In view of exposure to futibatinib in patients with mild hepatic impairment [see Section 6.2.4] and the following points, no dose adjustment of futibatinib would be required for the concerned patient population:
  - A pooled analysis on safety in the global phase I/II study (Study 101) and Japanese phase I study (Study 010) showed that incidences of (a) adverse events leading to death, (b) serious adverse events, (c) adverse events leading to treatment discontinuation, (d) adverse events leading to interruption, and (e) adverse events leading to dose reduction in patients with normal hepatic function[38)] (n = 186) and patients with mild hepatic impairment (n = 129) both of whom received futibatinib 20 mg QD were (a) 6.5% and 11.6%, (b) 43.0% and 44.2%, (c) 7.0% and 11.6%, (d) 54.8% and 60.5%, and (e) 34.9% and 41.1%, respectively. No clear difference was noted in the incidence of adverse events between patients with normal hepatic function and patients with mild hepatic impairment.

- In view of exposure to futibatinib in patients with moderate or severe hepatic impairment [see Section 6.2.4], the use of futibatinib in the concerned patient population require attention. Such advice will be provided via the package insert.

PMDA's view:

PMDA accepted the above applicant's explanation about use of futibatinib in patients with mild hepatic impairment.

If futibatinib is used in patients with moderate or severe hepatic impairment, exposure to futibatinib may be increased, as indicated by the foreign phase I study (Study 108). For use of futibatinib in the concerned patients, therefore, dose reduction should be considered, and the treated patients should be carefully monitored with due attention paid to onset of adverse events. Accordingly, the applicant should inform healthcare professionals of investigation results about the effect of hepatic impairment on PK of futibatinib in the foreign phase I study (Study 108) via the package insert etc. appropriately and include the following cautionary statement in the Precautions Concerning Patients with Specific Backgrounds section:

- For patients with moderate or severe hepatic impairment, dose reduction of futibatinib should be considered, and the treated patients should be carefully monitored with due attention paid to onset of adverse drug reactions. Increased futibatinib concentrations in blood may occur, potentially intensifying adverse drug reactions.

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

6.R.3 Pharmacokinetic interactions mediated by CYP3A

The applicant's explanation about co-administration of futibatinib with a CYP3A inhibitor or inducer:
Futibatinib was suggested to be predominantly metabolized by CYP3A [see Section 4.3.1], and multiple doses of concomitant itraconazole (potent CYP3A inhibitor) or rifampicin (potent CYP3A inducer) impacted exposure to futibatinib [see Section 6.2.3.1]. The physiologically based pharmacokinetics (PBPK) model[39] was used to evaluate effects of the CYP3A inhibitors and inducers on PK of futibatinib. Table 18 shows the geometric mean ratios of AUC_{tau} of futibatinib after co-administration of futibatinib with the CYP3A inhibitor or inducer to that after administration of futibatinib alone.

Table 18. Effects of CYP3A inhibitors and inducers on PK of futibatinib

Concomitant drug	Measured or predicted value	Geometric mean ratio of AUC_{tau}
Itraconazole (potent CYP3A inhibitor)	Measured value*	1.41
Itraconazole (potent CYP3A inhibitor)	Predicted value	1.56
Clarithromycin (potent CYP3A inhibitor)		1.47
Fluconazole (moderate CYP3A inhibitor)		1.40
Fluvoxamine (moderate CYP3A inhibitor)		1.25
Cimetidine (weak CYP3A inhibitor)		1.13
Rifampicin (potent CYP3A inducer)	Measured value*	0.361
Rifampicin (potent CYP3A inducer)	Predicted value	0.383
Carbamazepine (potent CYP3A inducer)		0.646
Efavirenz (moderate CYP3A inducer)		0.521
Dexamethasone (weak CYP3A inducer)		0.840

* Results from the foreign phase I study (Study 103) [see Section 6.2.3.1].

The applicant explanation about co-administration of futibatinib with a CYP3A inhibitor or inducer, based on the above analysis results:

- Co-administration with moderate or potent CYP3A inhibitor is likely to increase futibatinib exposure. The package insert will include a cautionary statement that attention should be paid to the concomitant use with moderate or potent CYP3A inhibitors.
- Co-administration with weak CYP3A inhibitor is unlikely to have a clinically meaningful effect on futibatinib exposure. Therefore, it is unnecessary to include a cautionary statement concerning concomitant use with weak CYP3A inhibitors in the package insert.
- Co-administration with moderate or potent CYP3A inducer is likely to decrease futibatinib exposure. The package insert will include a cautionary statement that attention should be paid to the concomitant use with moderate or potent CYP3A inducers.
- Co-administration with weak CYP3A inducer is unlikely to have a clinically meaningful effect on futibatinib exposure. Therefore, it is unnecessary to include a cautionary statement concerning concomitant use with weak CYP3A inducers in the package insert.

[39] Simcyp version 19 was used to perform the PBPK model analysis. For absorption and distribution, the first-order absorption and Full PBPK models, respectively, were selected. On the basis of *in vitro* study results [see Section 4.3.1], contribution of CYP3A to metabolism was defined as 37%. For parameters for the CYP3A inhibitors and inducers, Simcyp defaults were used. Use of the PBPK model in the analysis for potential pharmacokinetic interactions of futibatinib via CYP3A was justified by approximate agreement between estimates obtained from the PBPK model and (a) exposure to futibatinib and changes in futibatinib concentration in plasma over time in the global phase I/II study (Study 101); (b) ratio of exposure to futibatinib after co-administration of futibatinib with rifampicin to that after administration of futibatinib alone in the foreign phase I study (Study 103); and (c) measured value of ratio of exposure to a CYP3A substrate such as midazolam after co-administration of this substrate with a CYP3A inhibitor or inducer to that after administration of CYP3A alone (*J Clin Pharmacol Ther.* 1996;34:400-5, etc.).

PMDA's view:
PMDA accepted the applicant's explanation. However, information about pharmacokinetic interactions of futibatinib mediated by CYP3A is important in justifying the cautionary statements concerning concomitant use with CYP3A inhibitors and inducers based on estimation results in the PBPK model. The applicant is required to continue collecting the concerned information and, when a new finding becomes available, provide it to healthcare professionals appropriately.

6.R.4 Pharmacokinetic interactions mediated by P-gp and BCRP

The applicant's explanation about pharmacokinetic interactions of futibatinib mediated by P-gp and BCRP:
Futibatinib inhibited P-gp and BCRP *in vitro* [see Section 4.5.3]. The PBPK model was used to evaluate an effect of futibatinib on PK of digoxin (P-gp substrate) and rosuvastatin (BCRP substrate). Simcyp version 19.1 was used to perform the PBPK model analysis. For absorption and distribution, the advanced dissolution absorption and metabolism (ADAM) and Full PBPK models, respectively, were selected. Inhibition constant (K_i) of futibatinib against P-gp and BCRP were defined as 0.296 μmol/L and 0.348 μmol/L, respectively, based on *in vitro* study results [see Section 4.5.3]. The appropriateness of the PBPK model of futibatinib was examined based on results from Studies 102, 106, and 107, and the appropriateness of the PBPK model of digoxin and rosuvastatin was examined based on publications (*Clin Pharmacol Ther.* 2001;70:311-16, *Clin Ther.* 2003;25:2215-24, etc.).

Using the above PBPK models, exposure to digoxin or rosuvastatin after a single dose of digoxin 0.5 mg or rosuvastatin 10 mg was estimated in healthy adults receiving futibatinib 20 mg QD. Table 19 (i) shows the geometric mean ratios of C_{max} and $AUC_{0\text{-}96h}$ of digoxin or rosuvastatin after co-administration of either substrate with futibatinib relative to those after administration of either substrate alone. Table 19 (ii) shows results from a sensitivity analysis using a conservative setting for K_i of futibatinib against P-gp and BCRP. As shown above, concomitant use of futibatinib may increase exposure to substrates of P-gp and BCRP. The package insert will include a cautionary statement that attention should be paid to the concomitant use with substrates of P-gp and BCRP.

Table 19. Changes in effects of futibatinib on PK of each substrates when K_i of futibatinib against P-gp and BCRP was varied

		(i)*1	(ii)*2
Digoxin (substrate of P-gp)	K_i (μmol/L)	0.296	0.0148
	Geometric mean ratio of $AUC_{0\text{-}96h}$*3	1.02	1.16
	Geometric mean ratio of C_{max}*3	1.07	1.54
Rosuvastatin (substrate of BCRP)	K_i (μmol/L)	0.348	0.0174
	Geometric mean ratio of $AUC_{0\text{-}96h}$*3	1.02	1.26
	Geometric mean ratio of C_{max}*3	1.04	1.92

*1 K_i was established based on *in vitro* study results [see Section 4.5.3]
*2 K_i was conservatively established.
*3 Co-administration of each substrate with futibatinib/administration of each substrate alone

The applicant plans to conduct a clinical study to investigate pharmacokinetic interactions of futibatinib with substrates of P-gp and BCRP.

PMDA's view:

PMDA accepted the applicant's explanation. However, when results from the above clinical study become available, the applicant should provide to healthcare professionals and reconsider whether caution is necessary.

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

The applicant submitted efficacy and safety evaluation data, in the form of results from a total of 4 studies including 1 Japanese phase I study, 1 global phase I/II study, and 2 foreign phase I studies, presented in Table 20. The applicant also submitted reference data, in the form of results from a total of 6 studies including 1 Japanese phase I study and 5 foreign phase I studies, presented in Table 20.

Table 20. List of clinical studies for efficacy and safety

Data category	Geographical location	Study ID	Phase	Study population	Number of patients enrolled	Dosage regimen	Main endpoints
Evaluation	Japan	Study 010	I	Dose-escalation part Patients with advanced solid cancers Dose-expansion part Patients with advanced solid cancers harboring *FGF* or *FGFR* gene abnormalities	Dose-escalation part 39 Dose-expansion part 44	Dose-escalation part Futibatinib 8, 16, 24, 36, 56, 80, 120, or 160 mg is orally administered QOD[*1] in the fasted state or continuous oral dose of futibatinib 16 or 20 mg is administered QD in the fasted state. Dose-expansion part Futibatinib 56, 80, or 120 mg is orally administered QOD[*1] in the fasted state or continuous oral dose of futibatinib 16 or 20 mg is administered QD in the fasted state.	Safety Tolerability PK
	Global	Study 101[*2]	II	Patients with unresectable, intrahepatic cholangiocarcinoma harboring *FGFR2* gene fusion or *FGFR2* gene rearrangement who had received prior chemotherapy	103	Continuous oral dose of futibatinib 20 mg is administered QD in the fasted state.	Efficacy Safety
	Foreign		I	Dose-expansion part: Patients with advanced solid cancers harboring *FGF* or *FGFR* gene abnormalities	197	Continuous oral dose of futibatinib 16 or 20 mg is administered QD in the fasted state.	Safety PK
		Study 102	I	Healthy adults	17	A single oral dose of futibatinib 20 mg is administered in the fasted state or in the fed state on Days 1 and 8.	PK
		Study 103	I	Healthy adults	Part 1 20 Part 2 20	Part 1 A single oral dose of futibatinib 20 mg is co-administered with itraconazole in the fasted state. Part 2 A single oral dose of futibatinib 20 mg is co-administered with rifampicin in the fasted state.	PK
Reference	Japan	Study 020	I	Healthy adults	24	A single oral dose of futibatinib (film-coated tablets [a]) 20 mg or futibatinib (capsules) 20 mg is administered in the fasted state on Days 1 and 8.	PK
	Foreign	Study 101[*2]	I	Dose-escalation part: Patients with advanced solid cancer	86	Futibatinib 8, 16, 24, 36, 56, 80, 120, 160, or 200 mg is administered QOD[*1] in the fasted state or continuous oral dose of futibatinib 4, 8, 16, 20, or 24 mg is administered QD in the fasted state.	Safety Tolerability PK
		Study 104	I	Healthy adults	20	A single oral dose of futibatinib 20 mg is co-administered with lansoprazole in the fasted state.	PK
		Study 105	I	Healthy adults	24	Continuous oral dose of futibatinib 20 mg is co-administered QD with midazolam in the fasted state for 7 days.	PK
		Study 106	I	Healthy adults	6	A single oral dose of ^{14}C-futibatinib (liquid) 20 mg is administered in the fasted state.	PK
		Study 107	I	Healthy adults	48	A single oral dose of futibatinib 20 or 80 mg, placebo, or moxifloxacin 400 mg is administered in the fasted state in a crossover manner.	PK

*1 Monday, Wednesday, and Friday, *2 Conducted as a phase I/II study. The phase I part was conducted outside Japan, and phase II part was conducted both in and outside Japan.

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

7.1 Evaluation data

7.1.1 Clinical pharmacology

The applicant submitted results from the following 2 clinical pharmacology studies in healthy adults [see Sections 6.1 and 6.2]. In these studies, no deaths occurred throughout the study treatment or within 7 (Study 102) or 14 (Study 103) days after the end of the treatment.

7.1.1.1 Foreign phase I study (CTD 5.3.1.1.1, Study TAS-120-102 [Study 102], [redacted] to [redacted] 20[redacted])

7.1.1.2 Foreign phase I study (CTD 5.3.3.4.1, Study 103, [redacted] to [redacted] 20[redacted])

7.1.2 Japanese studies

7.1.2.1 Japanese phase I study (CTD 5.3.3.2.1, Study 010, July 2014 to [redacted] 20[redacted] [data cutoff on [redacted] [redacted], 20[redacted] (dose-escalation part), [redacted] [redacted], 20[redacted] (dose-expansion part)])

An open-label, uncontrolled study was conducted to investigate the tolerability, safety, etc. of futibatinib in patients with advanced solid cancers[40] (maximum target sample size, 72 subjects in dose-escalation part, 70 subjects in dose-expansion part) at 4 study sites in Japan.

The dosage regimen was specified as provided below, and the study treatment was continued until disease progression or discontinuation criteria were met.

Dose-escalation part

- Futibatinib 8, 16, 24, 36, 56, 80, 120, or 160 mg was administered orally QOD.
- Continuous oral dose of futibatinib 16 or 20 mg was administered QD.

Dose-expansion part

- Futibatinib 56, 80, or 120 mg was administered orally QOD.
- Continuous oral dose of futibatinib 16 or 20 mg was administered QD.

All of 83 patients enrolled in this study (39 in dose-escalation part, 44 in dose-expansion part)[41] received futibatinib and were included in the safety analysis population.

In the dose-escalation part, dose-limiting toxicity (DLT) was evaluated until 21 days after the first dose of futibatinib. Evaluation of tolerability of 3-times-a-week dosing (QOD regimen) revealed that 2 of 5 patients receiving 80 mg experienced DLT (Grade 1 corneal opacity in 2 patients). At baseline, worsening of corneal disorder by ≥1 grade had been defined as DLT to evaluate the concerned event carefully in view of the findings including corneal disorder due to mineralization accompanied by hyperphosphataemia in repeated-dose toxicity studies in rats and dogs [see Section 5.2]. However, the Grade 1 corneal opacity in 2 patients was not accompanied by hyperphosphataemia and thus was not considered as corneal disorder due to mineralization. Then, the definition of DLT was revised so that only Grade ≥1 corneal disorder due to mineralization would be handled as DLT. With the revised

[40] The dose-escalation part included patients with advanced solid cancers, and the dose-expansion part included patients with advanced solid cancers harboring *FGF* or *FGFR* gene abnormalities.

[41] Futibatinib 20 mg was administered QD (continuous daily dosing) to 38 patients (7 in dose-escalation part, 31 in dose-expansion part).

definition, tolerability was evaluated at ≥80 mg, and no DLT was noted at doses up to 160 mg. Tolerability of QD continuous daily dosing (QD regimen) in the dose-escalation and dose-expansion parts was evaluated with the revised definition of DLT, and no DLT was noted at up to 20 mg. In addition, a recommended Phase 2 dose (RP2D) in the phase I dose-escalation part of Study 101 was determined to be 20 mg QD regimen [see Section 7.2.2.1]. In view of the above findings, an RP2D of futibatinib was also determined to be 20 mg QD regimen.

Deaths occurred in 5 of 39 patients (12.8%) (1 of 7 [14.3%] in the 56 mg QOD arm, 2 of 6 [33.3%] in the 80 mg QOD arm, 1 of 3 [33.3%] in the 16 mg QD arm, 1 of 7 [14.3%] in the 20 mg QD arm) in the dose-escalation part; and 5 of 44 patients (11.4%) (1 of 3 [33.3%] in the 80 mg QOD arm, 4 of 31 [12.9%] in the 20 mg QD arm) in the dose-expansion part throughout the futibatinib treatment or within 30 days after the end of the treatment and were all caused by disease progression.

7.1.3 Global study

7.1.3.1 Phase II part of the global phase I/II study (CTD 5.3.5.2.2, Study 101, April 2018 to [redacted] 20[redacted] [data cutoff on October 1, 2020])

An open-label, uncontrolled study was conducted to investigate the efficacy and safety of futibatinib in patients with unresectable, intrahepatic cholangiocarcinoma harboring *FGFR2* gene fusion or *FGFR2* gene rearrangement[42)] who had received prior chemotherapy[43)] (target sample size, 100 subjects[44)])[45)] at 48 study sites in 13 countries and regions including Japan.

Continuous oral dose of futibatinib 20 mg was administered QD, and the study treatment was continued until disease progression or discontinuation criteria were met.

All of 103 patients enrolled in the phase II part of the study received futibatinib and were included in the efficacy and safety analysis populations (of these, 14 patients were Japanese).

The primary endpoint in the phase II part of the study was the response rate as determined by an independent review committee (IRC) according to Response Evaluation Criteria in Solid Tumors (RECIST) ver.1.1, and the threshold response rate was 10%.[46)] In response to consultation with a foreign regulatory authority, timing of a final analysis was additionally specified after data cutoff for the final analysis of the phase II part of the study. The final analysis was performed when a majority of patients responding to futibatinib had ≥6 months of follow-up from onset of response (Statistical Analysis Plan

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42) (a) "*FGFR2* gene fusion" was defined as a gene structure in which the breakpoint is at intron 17 or exon 18 of the *FGFR2* gene and a partner gene (gene fused with the *FGFR2* gene) is in the same reading frame as that of the *FGFR2* gene; and (b) "*FGFR2* gene rearrangement" was defined as a gene structure in which the breakpoint is at intron 17 or exon 18 of the *FGFR2* gene, and fusion occurred at an intergenic region or the partner gene is not in the same reading frame as that of the *FGFR2* gene. The status of *FGFR2* gene fusion or *FGFR2* gene rearrangement was tested using (i) "FoundationOne Assay for Clinical Study" of Foundation Medicine Inc. at a central laboratory, (ii) "FoundationOne CDx Cancer Genomic Profile" at a study site, or (iii) other examination methods at a study site ([1] NGS, [2] FISH).

43) Patients who had received ≥1 line of prior chemotherapy including gemcitabine hydrochloride and a platinum antineoplastic agent were deemed eligible.

44) On the assumption that for response rate, the primary endpoint, a target value is 20% and the threshold is 10% (see Footnote 46) with a two-sided significance level of 5%, a sample size of 100 subjects in the phase II part will give the estimated power 81% (Protocol version 6, dated [redacted], 20[redacted]).

45) A scope of eligible patients was initially limited to patients harboring *FGFR2* gene fusion and then expanded by addition of patients harboring *FGFR2* gene rearrangement based on results from the phase I part of Study 101 (Protocol version 7, dated [redacted], 20[redacted]).

46) Established by referring to the response rate reported to be 7.7% in a pooled analysis of 22 reports on efficacy of second-line chemotherapy in patients with unresectable cholangiocarcinoma (*Ann Oncol.* 2014;25:2328-38).

version 2, dated [redacted], 20[redacted]). In addition, an interim analysis to generate preliminary data for consultation with foreign regulatory authorities was additionally planned after the start of this study. The analysis was performed when approximately 70% of all patients treated with futibatinib had 6 months of follow-up (Protocol version 9, dated [redacted], 20[redacted]) (data cutoff on [redacted], 20[redacted]; of 103 patients enrolled as of the concerned data cutoff date, 67 patients were included in the interim analysis).

Table 21 shows results of the final analysis on the response rate as determined by IRC according to RECIST ver.1.1, the primary endpoint, and the lower limit of 95% confidence interval exceeded the pre-determined threshold response rate (10%) (data cutoff on October 1, 2020).

Table 21. Best overall response and response rate
(determined by IRC per RECIST ver.1.1, efficacy analysis population, data cutoff on October 1, 2020)

Best overall response	Number of patients (%)
	Overall n = 103
CR	1 (1.0)
PR	42 (40.8)
SD	42 (40.8)
PD	16 (15.5)
NE	2 (1.9)
Response (CR + PR) (response rate [95% CI*] [%])	43 (41.7 [32.1, 51.9])

* Clopper-Pearson method

Deaths occurred in 6 of 103 patients (5.8%) throughout the futibatinib treatment or within 30 days after the end of the treatment (no deaths occurred in Japanese patients) and were all caused by disease progression.

7.1.3.2 Phase I dose-expansion part of the global phase I/II study (CTD 5.3.5.2.1, Study 101, July 2014 to [redacted] 20[redacted] [data cutoff on June 30, 2019])

An open-label, uncontrolled study was conducted to investigate the safety and PK of futibatinib in patients with advanced solid cancers harboring *FGF* or *FGFR* gene abnormalities[47)] (target sample size, approximately 185 subjects) at 37 study sites outside Japan.

47) The phase I dose-expansion part of Study 101 was comprised of Cohorts 1 to 8, each of which included patients as follows. *FGF or FGFR* gene abnormalities were determined on the basis of test results at the sponsor-designated central laboratory or study site.
Cohort 1: Patients with cholangiocarcinoma harboring *FGFR2* gene fusion
Cohort 2: Patients with cholangiocarcinoma harboring *FGFR2* gene fusion who (a) had not received chemotherapy or (b) had failed to complete 1 cycle of prior chemotherapy due to intolerance or patient refusal
Cohort 3: Patients with cholangiocarcinoma harboring *FGFR2* gene fusion and had received prior chemotherapy with an FGFR inhibitors
Cohort 4: Patients with cholangiocarcinoma harboring *FGFR* gene abnormalities other than *FGFR2* gene fusions
Cohort 5: Patients with primary central nervous system tumor harboring *FGFR* gene fusion or *FGFR1* activating mutation. Activating mutations are defined as mutations that are reported as somatic mutations in patients with cancer and to enhance tumor growth in non-clinical studies in publications (hereinafter, the same definition applies).
Cohort 6: Patients with advanced urothelial carcinoma harboring *FGFR3* gene fusion or *FGFR3* activating mutation
Cohort 7: Patients with advanced solid cancers harboring *FGFR2* gene amplification (except cholangiocarcinoma, primary central nervous system tumor, and urothelial carcinoma)
Cohort 8: Patients with advanced solid cancers harboring *FGFR* gene fusion or *FGFR* gene mutation (except cholangiocarcinoma, primary central nervous system tumor, and urothelial carcinoma)

Continuous oral dose of futibatinib 16[48)] or 20 mg was administered QD, and the study treatment was continued until disease progression or discontinuation criteria were met.

Of 201 patients enrolled in the study, 197 patients (27 on the 16 mg QD arm, 170 on the 20 mg QD arm) were included in the safety analysis, and 4 patients who did not receive futibatinib were excluded.

Deaths did not occur in patients on the 16 mg QD arm throughout the futibatinib treatment or within 30 days after the end of the treatment but occurred in 18 of 170 patients (10.6%) on the 20 mg QD arm (7 of 57 [12.3%] in Cohort 1, 3 of 15 [20.0%] in Cohort 3, 4 of 13 [30.8%] in Cohort 4, 2 of 24 [8.3%] in Cohort 5, 2 of 27 [7.4%] in Cohort 6) during the same period. Causes of the deaths other than disease progression in 15 patients were unknown in 2 patients and acute kidney injury in 1 patient, and a causal relationship to futibatinib was denied for both events.

7.2 Reference data

7.2.1 Clinical pharmacology

The applicant submitted results from the following 5 clinical pharmacology studies in healthy adults [see Section 6.2]. In these studies, no deaths occurred throughout the study treatment or within 6 days (Study 020) or 14 days (Studies 104, 105, 106, and 107) after the end of the treatment.

7.2.1.1 Japanese phase I study (CTD 5.3.1.2.1, Study 020, [redacted] to [redacted] 20[redacted])

7.2.1.2 Foreign phase I study (CTD 5.3.3.4.2, Study 104, [redacted] to [redacted] 20[redacted])

7.2.1.3 Foreign phase I study (CTD 5.3.3.4.3, Study 105, [redacted] to [redacted] 20[redacted])

7.2.1.4 Foreign phase I study (CTD 5.3.3.1.1, Study 106, [redacted] to [redacted] 20[redacted])

7.2.1.5 Foreign phase I study (CTD 5.3.3.1.2, Study 107, [redacted] to [redacted] 20[redacted])

7.2.2 Global study

7.2.2.1 Phase I dose-escalation part of the global phase I/II study (CTD 5.3.5.2.1, Study 101, July 2014 to [redacted] 20[redacted] [data cutoff on July 12, 2019])

An open-label, uncontrolled study was conducted to investigate the tolerability, safety, and PK of futibatinib in patients with advanced solid cancers (target sample size, approximately 60-120 subjects) at 6 study sites outside Japan.

Futibatinib 8, 16, 24, 36, 56, 80, 120, 160, or 200 mg was orally administered QOD, or continuous oral dose of futibatinib 4, 8, 16, 20, or 24 mg was administered QD, and the study treatment was continued until disease progression or discontinuation criteria were met.

All of 86 patients enrolled in the study (42 in the QOD arm, 44 in the QD arm) received futibatinib and were included in the safety analysis population.

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48) Until the 20 mg QD (continuous daily dosing) was confirmed to be tolerable in the phase I dose-escalation part of Study 101, the 16 mg QD (continuous daily dosing) had been used. After the 20 mg QD (continuous daily dosing) had been confirmed to be tolerable, patients on the 16 mg QD (continuous daily dosing) were allowed to make switchover to the 20 mg QD (continuous daily dosing) in consultation with the sponsor.

DLT was evaluated during a period of 21 days after the first dose of futibatinib. DLT was noted in 1 of 6 patients in the 8 mg QOD arm (Grade 4 blood creatine phosphokinase increased) and 3 of 9 patients in the 24 mg QD arm (Grade 3 ALT increased, Grade 3 AST increased, and Grade 3 blood bilirubin increased in 1 patient each), and an RP2D of futibatinib was determined to be 20 mg QD (continuous daily dosing).

Deaths occurred in 7 of 86 patients (8.1%) (1 of 4 [25.0%] in the 120 mg QOD arm, 1 of 8 [12.5%] in the 160 mg QOD arm, 2 of 7 [28.6%] in the 200 mg QOD arm, 2 of 14 [14.3%] in the 16 mg QD arm, 1 of 14 [7.1%] in the 24 mg QD arm) throughout the futibatinib treatment or within 30 days after the end of the treatment and were all caused by disease progression.

7.R Outline of the review conducted by PMDA

7.R.1 Data for review

PMDA determined that, among the evaluation data submitted, the pivotal study for evaluation of the efficacy of futibatinib was the phase II part of the global phase I/II study (Study 101) in patients with unresectable, intrahepatic cholangiocarcinoma harboring *FGFR2* gene fusion or *FGFR2* gene rearrangement who had received prior chemotherapy, and decided to evaluate the submitted data focusing on this study. PMDA, however, determined that the efficacy of futibatinib in the phase II part of Study 101 should be evaluated on the basis of results not only in the overall population, pre-determined primary analysis population, but also in populations of patients harboring *FGFR2* gene fusion and of patients harboring *FGFR2* gene rearrangement separately in view of their oncobiological meanings.

PMDA decided to evaluate the efficacy of futibatinib in Japanese patients systematically based on data from the phase II part of Study 101, etc. in accordance with “Basic Principles on Global Clinical Trials” (PFSB/ELD Notification No. 0928010, dated September 28, 2007), “Amendment to ‘Basic Principles on Global Clinical Trials (Reference Cases)’” (Administrative Notice, dated December 10, 2021), and “Guidelines on General Principles for Planning and Design of Multi-regional Clinical Trials” (PSEHB/PED Notification No. 0612-1, dated June 12, 2018). Efficacy results from the phase II part of Study 101 are discussed below. PMDA decided to evaluate the safety of futibatinib mainly based on results from the phase I and II parts of Study 101 and Japanese phase I study in patients with advanced solid cancers (Study 010).

7.R.2 Efficacy

On the basis of the following review, PMDA has concluded that futibatinib shows a certain level of efficacy in patients with unresectable, intrahepatic cholangiocarcinoma harboring *FGFR2* gene fusion or *FGFR2* gene rearrangement who received prior chemotherapy.

7.R.2.1 Efficacy endpoints and evaluation results

The applicant’s explanation about the patient population, the primary endpoint, and the efficacy of futibatinib in patients with unresectable, intrahepatic cholangiocarcinoma harboring *FGFR2* gene fusion or *FGFR2* gene rearrangement in Study 101:

In Study 101, the status of *FGFR2* gene fusion or *FGFR2* gene rearrangement was tested using (i) "FoundationOne Assay for Clinical Study" at a central laboratory, (ii) "FoundationOne CDx Cancer Genomic Profile" at a study site, or (iii) the next generation sequencing (NGS) or fluorescence *in situ* hybridization (FISH) method at a study site.

In the "FoundationOne Assay for Clinical Study" and "FoundationOne CDx Cancer Genomic Profile" test, (a) "*FGFR2* gene fusion" was defined as a gene structure in which the breakpoint is at intron 17 or exon 18 of the *FGFR2* gene and a partner gene (gene fused with the *FGFR2* gene) is in the same reading frame as that of the *FGFR2* gene; and (b) "*FGFR2* gene rearrangement" was defined as a gene structure in which the breakpoint is at intron 17 or exon 18 of the *FGFR2* gene, and fusion occurred at an intergenic region or the partner gene is not in the same reading frame as that of the *FGFR2* gene. *FGFR2* gene fusion and *FGFR2* gene rearrangement differ in mode of fusion with a partner gene, but in both gene structures, exons 9 to 17 coding the kinase domain are conserved, similarly allowing constitutive activation of its downstream signaling pathways when the C-terminal region essential in preventing FGFR2 dimerization is lost (*J Biol Chem.* 2009;284:6227-40, etc.). The applicant therefore considered it possible to evaluate the efficacy of futibatinib in one population of patients with intrahepatic cholangiocarcinoma harboring *FGFR2* gene fusion or *FGFR2* gene rearrangement irrespective of the mode of fusion.

A total of 9 patients were found to harbor *FGFR2* gene fusion or *FGFR2* gene rearrangement by the NGS or FISH method at a study site, but the breakpoint in *FGFR2* gene was not identified in 6 patients. The breakpoint in these 6 patients is considered highly likely to be at intron 17 or exon 18 of the *FGFR2* gene, because whole-genome sequencing or ribonucleic acid (RNA) sequencing in patients with biliary tract cancer harboring *FGFR2* gene fusion or *FGFR2* gene rearrangement revealed that the breakpoint was at intron 17 or exon 18 of the *FGFR2* gene in all the patients (*Nat Gene*t. 2015;47:1003-10 and *Cancer Discov.* 2017;7:1116-35). Inclusion of these 6 patients in Study 101 was thus justified.

In addition, if patients with unresectable intrahepatic cholangiocarcinoma who received prior chemotherapy respond to futibatinib, onset of obstructive jaundice associated with tumor growth can be delayed. The response in this patient population is considered clinically meaningful. Study 101 was therefore designed to evaluate the efficacy of futibatinib based on the response rate, which was specified as the primary endpoint.

The response rate [95% CI] in the overall population of Study 101 was 41.7% [32.1%, 51.9%], and the lower limit of the 95% confidence interval exceeded 10%, the threshold response rate [see Section 7.1.3.1]. Furthermore, the observed response rate was clinically meaningful, and results in the Japanese population were consistent with those in the overall population (Table 22). Futibatinib is therefore expected to have the efficacy in the target patient population in Study 101.

Table 22. Best overall response and response rate in the Japanese population (determined by IRC per RECIST ver.1.1, efficacy analysis population, data cutoff on October 1, 2020)

Best overall response	Number of patients (%)
	Japanese population n = 14
CR	0
PR	4 (28.6)
SD	9 (64.3)
PD	1 (7.1)
NE	0
Response (CR + PR) (response rate [95% CI*] [%])	4 (28.6 [8.4, 58.1])

* Clopper-Pearson method

The applicant's explanation about the efficacy of futibatinib in (a) patients with unresectable intrahepatic cholangiocarcinoma harboring *FGFR2* gene fusion and (b) patients with unresectable intrahepatic cholangiocarcinoma harboring *FGFR2* gene rearrangement:

(a) Efficacy in patients with unresectable intrahepatic cholangiocarcinoma harboring *FGFR2* gene fusion:

In view of the following points, futibatinib is expected to have the efficacy in patients with unresectable intrahepatic cholangiocarcinoma harboring *FGFR2* gene fusion who received prior chemotherapy: In the population of patients (n = 74) who were enrolled in Study 101 and determined to harbor *FGFR2* gene fusion by "FoundationOne Assay for Clinical Study" or "FoundationOne CDx Cancer Genomic Profile," the response rate [95% CI] was clinically meaningful 44.6% [33.0%, 56.6%]; and the *FGFR2* gene fusion is recognized as an oncogenic driver [see Section 3.R.1].

Figure 1 shows best percent changes in tumor diameter (target lesion) in the 74 patients as determined by IRC according to RECIST ver.1.1. The median duration [95% CI] of response[49)] in 33 patients with confirmed response (complete response [CR] or partial response [PR]) was 9.7 [7.6, 17.1] months.

49) Defined as a period from the initial documented response to progressive disease (PD) or death in patients with confirmed response (CR or PR), whichever occurred first. In the patient who did not experience PD or death or started new antitumor therapy, the data were censored at the last radiographic assessment.

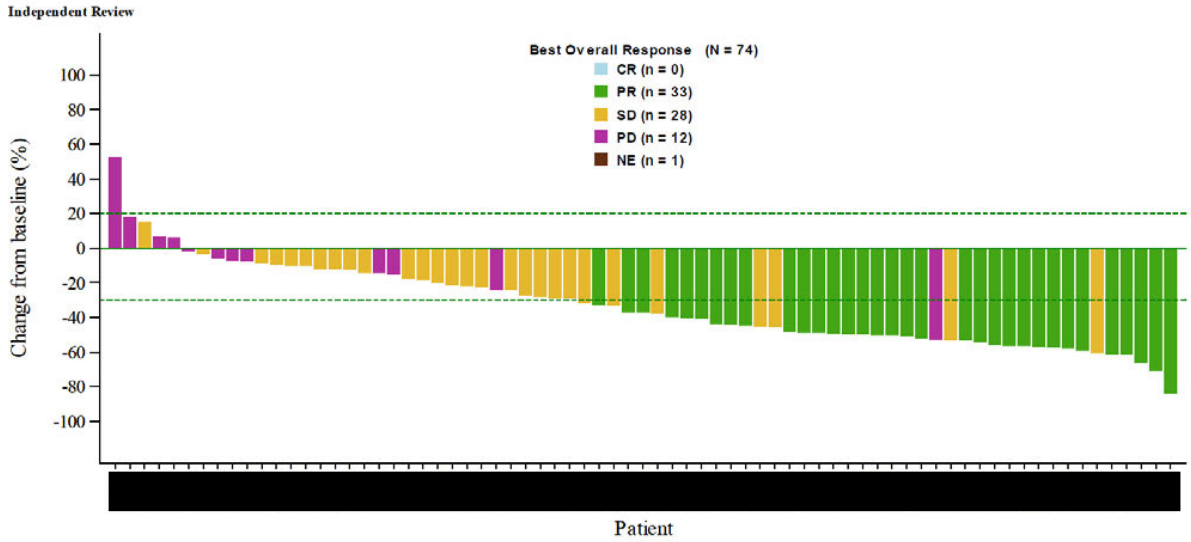

Figure 1. Best percent change in tumor diameter (target lesion)
(determined by IRC per RECIST ver.1.1, population of patients with intrahepatic cholangiocarcinoma harboring *FGFR2* gene fusion in Study 101, data cutoff on October 1, 2020)

(b) Efficacy in patients with unresectable intrahepatic cholangiocarcinoma harboring *FGFR2* gene rearrangement:

In view of the following points, futibatinib, an FGFR inhibitor, is expected to have the efficacy in patients with unresectable intrahepatic cholangiocarcinoma harboring *FGFR2* gene rearrangement who received prior chemotherapy: In the population of patients (n = 21) who were enrolled in Study 101 and determined to harbor *FGFR2* gene rearrangement by "FoundationOne Assay for Clinical Study " or "FoundationOne CDx Cancer Genomic Profile" or the NGS method at a study site, the response rate [95% CI] of 33.3% [14.6%, 57.0%] was clinically meaningful; and the *FGFR2* gene rearrangement is suggested to contribute to tumor growth as shown below.

- The *FGFR2* gene rearrangement can cause loss of the C-terminal region of FGFR2 protein, to which Grb2 binds to and thereby inhibits dimerization of FGFR2 protein. That is, loss of the Grb2 binding site of FGFR2 protein potentially enhances its dimerization, consequently activating downstream signaling pathways such as MAPK pathway (*J Biol Chem.* 2009;284:6227-40, etc.).
- A whole-genome sequencing study using specimens from 2,112 patients with solid cancers revealed that *FGFR2* gene abnormalities potentially causing loss of the C-terminal region of FGFR2 protein occurred in multiple cancer types including intrahepatic cholangiocarcinoma. The concerned loss contributes to tumor cell proliferation (*Nature.* 2022;608:609-17) and constitutive activation of downstream signaling pathways such as MAPK pathway (*Cytokine Growth Factor Rev.* 2020;52:56-67 and *J Biol Chem.* 2009;284:6227-40).

Figure 2 shows the best percent change in tumor diameter (target lesion) in the above 21 patients as determined by IRC according to RECIST ver.1.1. The median duration [95% CI] of response in 7 patients with confirmed response (CR or PR) was 14.0 [3.4, not evaluable (NE)] months.

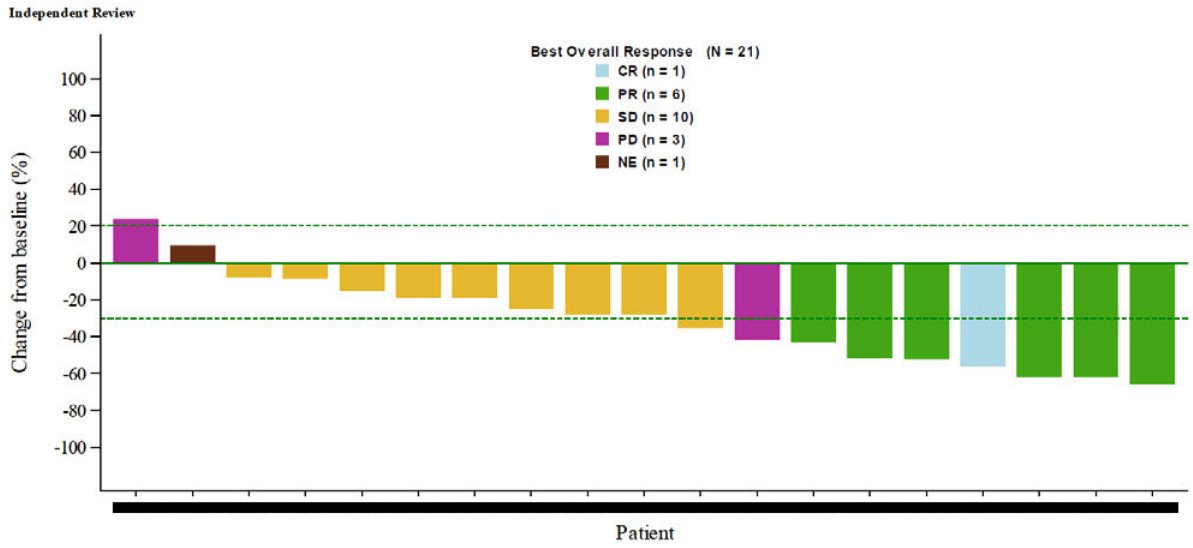

Figure 2. Best percent change in tumor diameter (target lesion)
(determined by IRC per RECIST ver.1.1, population of patients with intrahepatic cholangiocarcinoma harboring *FGFR2* gene rearrangement in Study 101, data cutoff on October 1, 2020)

PMDA's view:
Since the phase II part of Study 101 is the pivotal clinical study for this application, the change to study plan involving the statistical analysis plan should be carefully considered in terms of its impact on result interpretation. Especially, the change to timing of the final analysis in the statistical analysis plan [see Section 7.1.3.1] should have been defined in the protocol before the data cutoff. PMDA, however, considered it possible to evaluate the efficacy of futibatinib based on results from the phase II part of Study 101 submitted for this application, because 103 patients in the final analysis were already enrolled as of the data cutoff date for the interim analysis.

PMDA's view on the efficacy of futibatinib based on results from the phase II part of Study 101:
It is difficult to evaluate the survival benefits of futibatinib in patients with unresectable, intrahepatic cholangiocarcinoma harboring *FGFR2* gene fusion or *FGFR2* gene rearrangement based on results on the response rate, the primary endpoint in Study 101, because a relationship between OS, a true endpoint, and the response rate in the concerned patient population remains unclear. In addition, integrated efficacy evaluation of futibatinib in both (a) patients with unresectable intrahepatic cholangiocarcinoma harboring *FGFR2* gene fusion and (b) patients with unresectable intrahepatic cholangiocarcinoma harboring *FGFR2* gene rearrangement remains to be justified because differences between *FGFR2* gene fusion and *FGFR2* gene rearrangement in terms of contribution to tumor cell proliferation and the inhibitory effect of futibatinib against tumor growth have an unknown impact on the efficacy of futibatinib.

On the basis of results from Study 101, however, futibatinib is shown to have a certain level of efficacy in (a) patients with unresectable intrahepatic cholangiocarcinoma harboring *FGFR2* gene fusion, considering that the *FGFR2* gene fusion and futibatinib are an oncogenic driver [see Section 3.R.1] and an FGFR inhibitor, respectively.

Furthermore, PMDA considered that futibatinib is expected to have a certain level of efficacy in (b) patients with unresectable intrahepatic cholangiocarcinoma harboring *FGFR2* gene rearrangement in view of the above applicant's explanation and the following point, although the information about whether the *FGFR2* gene rearrangement can be positioned as an oncogenic driver is limited.

- Although the number of patients with *FGFR2* gene rearrangement enrolled in Study 101 was limited, a clinically meaningful response rate was achieved, and the response rate did not clearly differ between patients with *FGFR2* gene rearrangement and patients with *FGFR2* gene fusion.

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

PMDA's view:

On the basis of the following review, adverse events requiring particular attention during futibatinib treatment are hyperphosphataemia, retinal detachment, eye disorders (except retinal detachment), nail disorders, palmar-plantar erythrodysaesthesia syndrome, and acute kidney injury.

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

7.R.3.1 Safety profile

The applicant's explanation about the safety profile of futibatinib based on the safety data obtained from the phase II part of Study 101:

Table 23 shows the outline of the safety profile in the phase II part of Study 101.

Table 23. Outline of safety (phase II part of Study 101)

	Number of patients (%) n = 103
All adverse events	103 (100)
Grade ≥3 adverse events	79 (76.7)
Adverse events leading to death	5 (4.9)
Serious adverse events	40 (38.8)
Adverse events leading to treatment discontinuation	8 (7.8)
Adverse events leading to treatment interruption	68 (66.0)
Adverse events leading to dose reduction	60 (58.3)

All-grade adverse events with an incidence of ≥20% in the phase II part of Study 101 were hyperphosphataemia in 88 patients (85.4%), constipation in 40 patients (38.8%), diarrhoea in 37 patients (35.9%), dry mouth in 36 patients (35.0%), alopecia and fatigue in 35 patients (34.0%) each, dry skin in 30 patients (29.1%), AST increased in 26 patients (25.2%), nausea and stomatitis in 25 patients (24.3%) each, decreased appetite in 24 patients (23.3%), arthralgia in 23 patients (22.3%), dry eye, abdominal pain, and palmar-plantar erythrodysaesthesia syndrome in 22 patients (21.4%) each, and dysgeusia in 21 patients (20.4%). Similarly, Grade ≥3 adverse events with an incidence of ≥5% were hyperphosphataemia in 31 patients (30.1%), hyponatraemia in 11 patients (10.7%), AST increased in 10 patients (9.7%), fatigue in 8 patients (7.8%), and stomatitis and ALT increased in 6 patients (5.8%) each. Adverse events leading to death with an incidence of ≥2% were disease progression in 5 patients (4.9%).

Serious adverse events with an incidence of ≥2% were disease progression in 5 patients (4.9%), pyrexia in 4 patients (3.9%), and ascites, upper gastrointestinal haemorrhage, and bile duct obstruction in 3 patients (2.9%) each. Adverse events leading to treatment interruption with an incidence of ≥2% were hyperphosphataemia in 16 patients (15.5%), palmar-plantar erythrodysaesthesia syndrome in 11 patients (10.7%), ALT increased in 10 patients (9.7%), AST increased in 9 patients (8.7%), fatigue in 7 patients (6.8%), stomatitis and blood bilirubin increased in 5 patients (4.9%) each, anaemia, vomiting, pyrexia, and decreased appetite in 4 patients (3.9%) each, and nausea, blood alkaline phosphatase (ALP) increased, hyponatraemia, dyspnoea, and onycholysis in 3 patients (2.9%) each. Adverse events leading to dose reduction with an incidence of ≥2% were hyperphosphataemia in 20 patients (19.4%), palmar-plantar erythrodysaesthesia syndrome in 10 patients (9.7%), fatigue and ALT increased in 5 patients (4.9%) each, AST increased in 4 patients (3.9%), and stomatitis and nail disorder in 3 patients (2.9%) each. There were no adverse events leading to treatment discontinuation with an incidence of ≥2%.

PMDA's view:
Adverse events with a high incidence, Grade ≥3 adverse events, and serious adverse events in the phase II part of Study 101 are likely to occur during futibatinib treatment, and thus patients receiving futibatinib should be carefully monitored for these events in view of their association with futibatinib. Most of the reported events were manageable by the interruption or dose reduction of futibatinib. In view of the above points, futibatinib will be tolerable when appropriate measures, such as monitoring and controlling of adverse events and interruption or dose reduction of futibatinib, are taken by physicians with adequate knowledge and experience in cancer chemotherapy.

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

The applicant's explanation about difference in safety between Japanese and non-Japanese patients based on the safety data obtained from Studies 101 and 010:
Table 24 shows the outline of the safety in Japanese and non-Japanese patients with intrahepatic cholangiocarcinoma who received futibatinib 20 mg QD in Studies 101 and 010.

Table 24. Outline of safety
(patients with intrahepatic cholangiocarcinoma receiving futibatinib 20 mg QD in Studies 101 and 010)

	Number of patients (%)	
	Japanese patients Studies 101 and 010	Non-Japanese patients Study 101
	n = 16	n = 153
All adverse events	16 (100)	153 (100)
Grade ≥3 adverse events	11 (68.8)	118 (77.1)
Adverse events leading to death	0	11 (7.2)
Serious adverse events	6 (37.5)	66 (43.1)
Adverse events leading to treatment discontinuation	1 (6.3)	12 (7.8)
Adverse events leading to treatment interruption	10 (62.5)	93 (60.8)
Adverse events leading to dose reduction	10 (62.5)	71 (46.4)

All-grade adverse events with a ≥10% higher incidence in Japanese patients than in non-Japanese patients were hyperphosphataemia (16 Japanese patients [100%], 129 non-Japanese patients [84.3%]), constipation (8 patients [50.0%], 52 patients [34.0%]), dysgeusia (7 patients [43.8%], 24 patients [15.7%]), decreased appetite (5 patients [31.3%], 31 patients [20.3%]), nail discolouration (5 patients [31.3%], 13 patients [8.5%]), onychomadesis (4 patients [25.0%], 15 patients [9.8%]), paronychia (4

patients [25.0%], 8 patients [5.2%]), lymphocyte count decreased (4 patients [25.0%], 1 patient [0.7%]), epistaxis (3 patients [18.8%], 7 patients [4.6%]), trichomegaly (2 patients [12.5%], 3 patients [2.0%]), cystitis (2 patients [12.5%], 2 patients [1.3%]), overdosage (2 patients [12.5%], 2 patients [1.3%]), malaise (2 patients [12.5%], 1 patient [0.7%]), pneumothorax (2 patients [12.5%], 1 patient [0.7%]), skin ulcer (2 patients [12.5%], 1 patient [0.7%]), and dermatitis bullous (2 patients [12.5%], 0 patients). Similarly, Grade ≥3 adverse events with a ≥5% higher incidence in Japanese patients than in non-Japanese patients which occurred in ≥2 Japanese patients were anaemia (2 patients [12.5%], 7 patients [4.6%]) and lymphocyte count decreased (2 patients [12.5%], 0 patients). Similarly, adverse events leading to treatment discontinuation with a ≥2% higher incidence in Japanese patients than in non-Japanese patients were oesophagitis (1 patient [6.3%], 0 patient). Adverse events leading to treatment interruption with a ≥2% higher incidence in Japanese patients than in non-Japanese patients were hyperphosphataemia (3 patients [18.8%], 24 patients [15.7%]), decreased appetite (3 patients [18.8%], 1 patient [0.7%]), paronychia (2 patients [12.5%], 2 patients [1.3%]), fatigue (1 patient [6.3%], 6 patients [3.9%]), pyrexia (1 patient [6.3%], 5 patients [3.3%]), anaemia (1 patient [6.3%], 4 patients [2.6%]), blood creatinine increased (1 patient [6.3%], 2 patients [1.3%]), cholangitis (1 patient [6.3%], 1 patient [0.7%]), biliary tract infection (1 patient [6.3%], 1 patient [0.7%]), headache (1 patient [6.3%], 1 patient [0.7%]), intestinal obstruction (1 patient [6.3%], 0 patient), oesophagitis (1 patient [6.3%], 0 patient), malaise (1 patient [6.3%], 0 patient), malignant pleural effusion (1 patient [6.3%], 0 patient), nail discolouration (1 patient [6.3%], 0 patient). Adverse events leading to dose reduction with a ≥2% higher incidence in Japanese patients than in non-Japanese patients were stomatitis (1 patient [6.3%], 6 patients [3.9%]), fatigue (1 patient [6.3%], 5 patients [3.3%]), paronychia (1 patient [6.3%], 1 patient [0.7%]), decreased appetite (1 patient [6.3%], 1 patient [0.7%]), ulcerative keratitis (1 patient [6.3%], 0 patient), malaise (1 patient [6.3%], 0 patient), cholangitis (1 patient [6.3%], 0 patient), creatinine increased (1 patient [6.3%], 0 patient), and dermatitis bullous (1 patient [6.3%], 0 patient). There were neither adverse events leading to death with a ≥2% higher incidence in Japanese patients than in non-Japanese patients nor serious adverse events with a ≥2% higher incidence in Japanese patients than in non-Japanese patients and occurred in ≥2 Japanese patients.

PMDA's view:

Although the number of Japanese patients treated with futibatinib was small, and comparison of the safety profile between Japanese and non-Japanese patients has limitations, adverse events such as hyperphosphataemia were identified as events in which the incidence was higher in Japanese patients than in non-Japanese patients among patients with intrahepatic cholangiocarcinoma who received futibatinib 20 mg QD in Studies 101 and 010. Therefore, attention should be paid to these events during futibatinib treatment. Concerning hyperphosphataemia, however, incidences of the adverse event leading to death and serious adverse event did not tend to be clearly higher in Japanese patients than in non-Japanese patients. In addition, futibatinib is to be used by physicians with adequate knowledge and experience in cancer chemotherapy. In view of the above finding and proposed settings of use, futibatinib is tolerable in Japanese patients as well.

In the following sections, PMDA reviewed the safety results in Studies 101 and 010 with the focus on adverse events with a higher incidence for futibatinib, potential adverse events suspected from the

mechanism of action of futibatinib, and adverse events of special interest for pemigatinib, which targets *FGFR2* gene as with futibatinib.

7.R.3.3 Hyperphosphataemia

The applicant's explanation about hyperphosphataemia associated with futibatinib:
Adverse events classified into "hyperphosphataemia" and "blood phosphorus increased," preferred terms (PTs) in the Medical Dictionary for Regulatory Activities (MedDRA), were tabulated as hyperphosphataemia.

Table 25 shows incidences of hyperphosphataemia in patients who received futibatinib 20 mg QD in Studies 101 and 010.

Table 25. Incidences of hyperphosphataemia (patients with solid cancers who received futibatinib 20 mg QD in Studies 101 and 010)

PT (MedDRA ver.22.0)	Number of patients (%)					
	Phase I part of Study 101 n = 177		Phase II part of Study 101 n = 103		Study 010 n = 38	
	All Grades	Grade ≥3[*1]	All Grades	Grade ≥3[*1]	All Grades	Grade ≥3[*2]
Hyperphosphataemia[*3]	148 (83.6)	41 (23.2)	94 (91.3)	32 (31.1)	38 (100)	2 (5.3)
Hyperphosphataemia	145 (81.9)	39 (22.0)	88 (85.4)	31 (30.1)	38 (100)	2 (5.3)
Blood phosphorus increased	8 (4.5)	2 (1.1)	9 (8.7)	1 (1.0)	0	0

*1 Serum phosphate levels >7 mg/dL and ≤10 mg/dL were assessed as Grade 3, and serum phosphate levels >10 mg/dL were as Grade 4.
*2 NCI-CTCAE ver.4.03 (Grade 3, severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care activities of daily living: Grade 4, life-threatening consequences; urgent intervention indicated) was used for assessment
*3 Sum of events compiled

In patients who received futibatinib 20 mg QD in the phase I part of Study 101, hyperphosphataemia leading to treatment interruption occurred in 40 of 177 patients (22.6%; hyperphosphataemia in 36 patients and blood phosphorus increased in 4 patients) and hyperphosphataemia leading to dose reduction occurred in 16 of 177 patients (9.0%, hyperphosphataemia in 16 patients). There were no hyperphosphataemia leading to death, serious hyperphosphataemia, or hyperphosphataemia leading to treatment discontinuation.

In patients who received futibatinib 20 mg QD in the phase II part of Study 101, hyperphosphataemia leading to treatment interruption occurred in 18 of 103 patients (17.5%, hyperphosphataemia in 16 patients and blood phosphorus increased in 2 patients) and hyperphosphataemia leading to dose reduction occurred in 21 of 103 patients (20.4%, hyperphosphataemia in 20 patients and blood phosphorus increased in 1 patient). There were no hyperphosphataemia leading to death, serious hyperphosphataemia, or hyperphosphataemia leading to treatment discontinuation.

In patients who received futibatinib 20 mg QD in Study 010, hyperphosphataemia leading to treatment interruption occurred in 9 of 38 patients (23.7%, hyperphosphataemia in 9 patients) and hyperphosphataemia leading to dose reduction occurred in 4 of 38 patients (10.5%, hyperphosphataemia in 4 patients). There were no hyperphosphataemia leading to death, serious hyperphosphataemia, or hyperphosphataemia leading to treatment discontinuation.

Median time (minimum, maximum) to first onset of hyperphosphataemia was 7.0 (3, 117) days in the phase I part of Study 101, 5.0 (3, 106) days in the phase II part of Study 101, and 4.0 (3, 8) days in Study 010.

Table 26 shows a detailed description of patients with serious hyperphosphataemia for which a causal relationship to futibatinib could not be ruled out in other clinical studies of futibatinib including the above studies.

Table 26. List of patients with serious hyperphosphataemia (causally related to futibatinib)

Study	Age	Sex	Dosage regimen	PT[*1]	Grade	Time to onset (Day)	Duration (Day)	Action on futibatinib	Outcome
Study 201[*2]	7	[redacted]	20 mg QD	Hyperphosphataemia	3	28	5	Interruption	Resolved

*1 MedDRA ver.22.0
*2 Foreign phase II study in patients with inoperable or recurrent breast cancer harboring *FGFR* gene amplification

PMDA asked the applicant to explain the mechanism of onset of hyperphosphataemia associated with futibatinib and the management method.

The applicant's response:
Serum phosphate concentrations are regulated mainly through absorption of food-derived phosphorus from the gastrointestinal tract, release of phosphorus from the bone, uptake of phosphorus into the bone, reabsorption from the kidney, and its excretion into urine. FGFR inhibitors can increase serum phosphate concentrations by inhibiting phosphorylation of FGFR1 expressed in the kidney, which hinders FGFR1 from activating in response to FGF23 ligands and thereby precludes FGF23-induced phosphorus excretion into urine (*Am J Physiol Renal Physiol.* 2014;306:F351-8). In Studies 101 and 010, serum phosphate concentrations increased in many patients after the first dose of futibatinib, but measures for the management were taken including limitation of foods that are especially high in phosphate and medications for management of hyperphosphataemia such as lanthanum carbonate hydrate and sevelamer hydrochloride, as defined in the protocol [see Section 7.R.5.2]. Therefore, no hyperphosphataemia leading to treatment discontinuation of futibatinib occurred and hyperphosphataemia was manageable.

PMDA's view:
In the clinical studies included in the submitted data, there were no serious adverse events for which a causal relationship to futibatinib could not be ruled out. The clinical studies were conducted after specifying hyperphosphataemia management; hyperphosphataemia is an adverse event that can be predicted based on the mechanism of action of the FGFR inhibitor; and it is a known risk for other FGFR inhibitors. In view of the above, attention should be paid to onset of hyperphosphataemia associated with futibatinib. Accordingly, the applicant is required to raise caution among healthcare professionals by providing in the package insert the protocol-specified hyperphosphataemia management and incidence of hyperphosphataemia in the clinical studies.

7.R.3.4 Retinal disorder

The applicant's explanation about retinal disorder associated with futibatinib:
Adverse events classified into MedDRA PTs of "retinal detachment," "retinal disorder," "chorioretinopathy," "detachment of retinal pigment epithelium," "detachment of macular retinal pigment epithelium," "maculopathy," "serous retinal detachment," "macular oedema," "retinal oedema," "retinopathy," "retinal thickening," and "subretinal fluid" were tabulated as retinal disorder.

Table 27 shows incidences of retinal disorder in patients who received futibatinib 20 mg QD in Studies 101 and 010.

Table 27. Incidences of retinal disorder
(patients with solid cancers who received futibatinib 20 mg QD in Studies 101 and 010)

PT (MedDRA ver.22.0)	Number of patients (%)					
	Phase I part of Study 101 n = 177		Phase II part of Study 101 n = 103		Study 010 n = 38	
	All Grades	Grade ≥3	All Grades	Grade ≥3	All Grades	Grade ≥3
Retinal disorder*	9 (5.1)	0	8 (7.8)	0	10 (26.3)	0
Retinal detachment	4 (2.3)	0	0	0	0	0
Subretinal fluid	1 (0.6)	0	3 (2.9)	0	4 (10.5)	0
Chorioretinopathy	1 (0.6)	0	2 (1.9)	0	0	0
Serous retinal detachment	1 (0.6)	0	1 (1.0)	0	3 (7.9)	0
Macular oedema	1 (0.6)	0	0	0	2 (5.3)	0
Retinopathy	1 (0.6)	0	0	0	0	0
Detachment of retinal pigment epithelium	0	0	1 (1.0)	0	1 (2.6)	0
Maculopathy	0	0	1 (1.0)	0	0	0

* Sum of events compiled

In patients who received futibatinib 20 mg QD in the phase I part of Study 101, serious retinal disorder occurred in 1 of 177 patients (0.6%, retinal detachment), and a causal relationship to futibatinib could not be ruled out. Retinal disorder leading to treatment discontinuation occurred in 1 of 177 patients (0.6%, retinal detachment), retinal disorder leading to treatment interruption occurred in 1 of 177 patients (0.6%, retinal detachment), and retinal disorder leading to dose reduction occurred in 2 of 177 patients (1.1%, retinal detachment in 2 patients). There were no fatal retinal disorder.

In patients who received futibatinib 20 mg QD in the phase II part of Study 101, retinal disorder leading to treatment interruption occurred in 3 of 103 patients (2.9%, subretinal fluid, detachment of retinal pigment epithelium, and chorioretinopathy in 1 patient each), and retinal disorder leading to dose reduction occurred in 3 of 103 patients (2.9%, subretinal fluid, detachment of retinal pigment epithelium, and chorioretinopathy in 1 patient each). There were no fatal retinal disorder, serious retinal disorder, or retinal disorder leading to treatment discontinuation.

In patients who received futibatinib 20 mg QD in Study 010, there was no fatal retinal disorder, serious retinal disorder, or retinal disorder leading to treatment discontinuation, interruption, or dose reduction.

Median time (minimum, maximum) to first onset of retinal disorder was 43.0 (7, 902) days in the phase I part of Study 101, 42.0 (25, 362) days in the phase II part of Study 101, and 15.0 (14, 65) days in Study 010.

Table 28 shows a detailed description of patients with serious retinal disorder for which a causal relationship to futibatinib could not be ruled out in other clinical studies of futibatinib including the above studies.

Table 28. List of patients with serious retinal disorder (causally related to futibatinib)

Study	Age	Sex	Dosage regimen	PT*	Grade	Time to onset (Day)	Duration (Day)	Action on futibatinib	Outcome
Phase I part of Study 101	5[redacted]	[redacted]	20 mg QD	Retinal detachment	2	196	29	Discontinuation	Resolved

* MedDRA ver.22.0

PMDA asked the applicant to explain the mechanism of onset of retinal detachment associated with futibatinib and risk factors.

The applicant's response:
Adverse events related to retention of subretinal fluid such as retinal detachment are considered attributable to FGFR-mediated inhibition of the MAPK pathway, and these events are observed in the treatment with mitogen-activated protein kinase/extracellular signal-regulated kinase (MEK) or MAPK inhibitors (*Cancer Treat Rev.* 2013;39:664-72, etc.). FGFR1 or FGFR2 expressed in the retina plays a critical role in the function of retinal pigment epithelial cells. The inhibitory effect of futibatinib against FGFR1 or FGFR2 is suggested to impair the external blood-retinal barrier of retinal pigment epithelium, potentially causing retention of subretinal fluid. On the other hand, risk factors for retinal disorder associated with futibatinib have not been identified.

PMDA's view:
Attention should be paid to onset of retinal detachment associated with futibatinib in view of the following points: In the clinical studies included in the submitted data, serious retinal detachment for which a causal relationship to futibatinib could not be ruled out occurred; retinal disorder is an adverse event that can be predicted based on the mechanism of action of the FGFR inhibitor; and retinal disorder is a known risk for other FGFR inhibitors. Retinal detachment that occurred during futibatinib treatment were mostly reversible, and recovery can be expected with early detection and appropriate treatment. The applicant is required to raise caution among healthcare professionals by providing in the package insert incidence of retinal detachment in the clinical studies, recommendation of periodic ophthalmological examination, and measures to be taken in response to the onset.

7.R.3.5 Eye disorders (except retinal disorder)

The applicant's explanation about eye disorders (except retinal disorder) associated with futibatinib:
Adverse events classified into MedDRA system organ class (SOC) of "eye disorders"(except events classified into MedDRA PTs of "retinal detachment," "retinal disorder," "chorioretinopathy," "detachment of retinal pigment epithelium," "detachment of macular retinal pigment epithelium," "maculopathy," "serous retinal detachment," "macular oedema," "retinal oedema," "retinopathy," "retinal thickening," and "subretinal fluid") were tabulated as eye disorders.

Table 29 shows incidences of eye disorders reported by ≥3% of patients who received futibatinib 20 mg QD in either Study 101 or 010.

Table 29. Incidences of eye disorders reported by ≥3% of patients in either study (patients with solid cancers who received futibatinib 20 mg QD in Studies 101 and 010)

PT (MedDRA ver.22.0)	Number of patients (%)					
	Phase I part of Study 101 n = 177		Phase II part of Study 101 n = 103		Study 010 n = 38	
	All Grades	Grade ≥3	All Grades	Grade ≥3	All Grades	Grade ≥3
Eye disorders*	47 (26.6)	5 (2.8)	45 (43.7)	1 (1.0)	4 (10.5)	0
Dry eye	17 (9.6)	0	22 (21.4)	1 (1.0)	0	0
Vision blurred	12 (6.8)	0	8 (7.8)	0	0	0
Cataract	7 (4.0)	4 (2.3)	4 (3.9)	0	0	0
Lacrimation increased	1 (0.6)	0	6 (5.8)	0	0	0
Visual impairment	1 (0.6)	0	4 (3.9)	0	0	0
Trichomegaly	0	0	5 (4.9)	0	0	0

* Sum of events compiled

In patients who received futibatinib 20 mg QD in the phase I part of Study 101, serious eye disorders occurred in 3 of 177 patients (1.7%, ocular ischaemic syndrome, papilloedema, and cataract in 1 patient each), and a causal relationship of cataract to futibatinib could not be ruled out. Eye disorders leading to treatment discontinuation occurred in 1 of 177 patients (0.6%, cataract in 1 patient) and eye disorders leading to treatment interruption occurred in 7 of 177 patients (4.0%; cataract and vision blurred in 2 patients each, keratitis, blepharitis, ocular hyperaemia, papilloedema, and punctate keratitis in 1 patient each [some patients experienced multiple events]). There were neither fatal eye disorders nor eye disorders leading to dose reduction.

In patients who received futibatinib 20 mg QD in the phase II part of Study 101, eye disorders leading to treatment interruption occurred in 3 of 103 patients (2.9%, eye pain, punctate keratitis, dry eye, vision blurred, foreign body sensation in eyes, and lacrimation increased in 1 patient each [some patients experienced multiple events]) and eye disorders leading to dose reduction occurred in 1 of 103 patients (1.0%, ulcerative keratitis). There were no fatal eye disorders, serious eye disorders, or eye disorders leading to treatment discontinuation.

In the patients who received futibatinib 20 mg QD in Study 010, there was no fatal eye disorders, serious eye disorders, or eye disorders leading to treatment discontinuation, interruption, or dose reduction.

Median time (minimum, maximum) to first onset of eye disorders events was 39.0 (4, 693) days in the phase I part of Study 101, 64.0 (4, 322) days in the phase II part of Study 101, and 75.5 (25, 205) days in Study 010.

Table 30 shows a detailed description of patients with serious eye disorders for which a causal relationship to futibatinib could not be ruled out in other clinical studies of futibatinib including the above studies.

Table 30. List of patients with serious eye disorders (causally related to futibatinib)

Study	Age	Sex	Dosage regimen	PT*	Grade	Time to onset (Day)	Duration (Day)	Action on futibatinib	Outcome
Phase I part of Study 101	5[redacted]	[redacted]	20 mg QD	Cataract	3	613	1	Interruption	Resolved
				Cataract	3	627	1	Interruption	Resolved

* MedDRA ver.22.0

PMDA's view:

In the clinical studies included in the submitted data, serious eye disorders (except retinal disorder) for which a causal relationship to futibatinib could not be ruled out occurred, but many of the reported eye disorders (except retinal disorder) were Grade ≤2. Special caution about eye disorders (except retinal disorder) was not required at present, on the premise that incidences of eye disorders (except retinal disorder) in the clinical studies is communicated through the package insert etc., relevant information is collected further in the post-marketing settings, and the obtained safety information is provided to healthcare professionals.

7.R.3.6 Nail disorders

The applicant's explanation about nail disorders associated with futibatinib:

Adverse events classified into MedDRA PTs of "nail disorder," "nail discomfort," "nail dystrophy," "nail discolouration," "nail bed disorder," "nail hypertrophy," "nail pigmentation," "nail toxicity," "nail ridging," "nail infection," "nail bed tenderness," "nail bed bleeding," "onychomadesis," "onychoclasis," "onychalgia," "onycholysis," "onychomycosis," "paronychia," and "fungal paronychia" were tabulated as nail disorders-related events.

Table 31 shows incidences of nail disorders reported by ≥3% of patients who received futibatinib 20 mg QD in either Study 101 or 010.

Table 31. Incidences of nail disorders reported by ≥3% of patients in either study (patients with solid cancers who received futibatinib 20 mg QD in Studies 101 and 010)

PT (MedDRA ver.22.0)	Number of patients (%)					
	Phase I part of Study 101 n = 177		Phase II part of Study 101 n = 103		Study 010 n = 38	
	All Grades	Grade ≥3	All Grades	Grade ≥3	All Grades	Grade ≥3
Nail disorders*	42 (23.7)	2 (1.1)	48 (46.6)	2 (1.9)	4 (10.5)	0
Onycholysis	13 (7.3)	0	16 (15.5)	0	0	0
Nail disorder	11 (6.2)	1 (0.6)	16 (15.5)	0	1 (2.6)	0
Paronychia	7 (4.0)	0	8 (7.8)	1 (1.0)	3 (7.9)	0
Nail discolouration	6 (3.4)	0	14 (13.6)	0	0	0
Onychomadesis	5 (2.8)	0	15 (14.6)	1 (1.0)	0	0

* Sum of events compiled

In patients who received futibatinib 20 mg QD in the phase I part of Study 101, nail disorders leading to treatment discontinuation occurred in 1 of 177 patients (0.6%, onycholysis in 1 patient), nail disorders leading to treatment interruption occurred in 4 of 177 patients (2.3%; paronychia, onycholysis, onychalgia, and nail disorder in 1 patient each), and nail disorders leading to dose reduction occurred in 2 of 177 patients (1.1%, paronychia and onychalgia in 1 patient each). There were neither fatal nail disorders nor serious nail disorders.

In patients who received futibatinib 20 mg QD in the phase II part of Study 101, nail disorders leading to treatment interruption occurred in 8 of 103 patients (7.8%; onycholysis in 3 patients, paronychia in 2 patients, onychomadesis, nail disorder, and nail discolouration in 1 patient each), nail disorders leading to dose reduction occurred in 7 of 103 patients (6.8%; nail disorder in 3 patients, onychomadesis in 2 patients, paronychia, onycholysis, and onychalgia in 1 patient each [some patients experienced multiple events]). There were no fatal nail disorders, serious nail disorders, or nail disorders leading to treatment discontinuation.

In patients who received futibatinib 20 mg QD in Study 010, nail disorders leading to treatment interruption occurred in 1 of 38 patients (2.6%, paronychia in 1 patient) and nail disorders leading to dose reduction occurred in 1 of 38 patients (2.6%, paronychia in 1 patient). There were no fatal nail disorders, serious nail disorders, or nail disorders leading to treatment discontinuation.

Median time (minimum, maximum) to first onset of nail disorders was 76.5 (5, 547) days in the phase I part of Study 101, 106.0 (15, 280) days in the phase II part of Study 101, and 63.5 (34, 80) days in Study 010.

Table 32 shows a detailed description of patients with serious nail disorders for which a causal relationship to futibatinib could not be ruled out in other clinical studies of futibatinib including the above studies.

Table 32. List of patients with serious nail disorders (causally related to futibatinib)

Study	Age	Sex	Dosage regimen	PT*	Grade	Time to onset (Day)	Duration (Day)	Action on futibatinib	Outcome
Phase I part of Study 101	3[redacted]	[redacted]	16 mg QD	Paronychia	3	82	3	Dose reduction	Unknown

* MedDRA ver.22.0

PMDA's view:
In the clinical studies included in the submitted data, serious nail disorders for which a causal relationship to futibatinib could not be ruled out occurred, but many of the reported nail disorders were Grade ≤2. Special caution about nail disorders was not required at present, on the premise that incidences of nail disorders in the clinical studies is communicated through the package insert etc., relevant information is collected further in the post-marketing settings, and the obtained safety information is provided to healthcare professionals.

7.R.3.7 Skin disorders (except nail disorders)

The applicant's explanation about skin disorders (except nail disorders) associated with futibatinib:
Adverse events classified into MedDRA SOC of "skin and subcutaneous tissue disorders" (except events classified into MedDRA PTs of "nail disorder," "nail discomfort," "nail dystrophy," "nail discolouration," "nail bed disorder," "nail hypertrophy," "nail pigmentation," "nail toxicity," "nail ridging," "nail infection," "nail bed tenderness," "nail bed bleeding," "onychomadesis," "onychoclasis," "onychalgia," "onycholysis," "onychomycosis," "paronychia," and "fungal paronychia") were tabulated as skin disorders.

Table 33 shows incidences of skin disorders reported by ≥3% of patients who received futibatinib 20 mg QD in either Study 101 or 010.

Table 33. Incidences of skin disorders reported by ≥3% of patients in either study (patients with solid cancers who received futibatinib 20 mg QD in Studies 101 and 010)

PT (MedDRA ver.22.0)	Number of patients (%)					
	Phase I part of Study 101 n = 177		Phase II part of Study 101 n = 103		Study 010 n = 38	
	All Grades	Grade ≥3	All Grades	Grade ≥3	All Grades	Grade ≥3
Skin disorders*	75 (42.4)	6 (3.4)	72 (69.9)	5 (4.9)	11 (28.9)	0
Alopecia	34 (19.2)	0	35 (34.0)	0	1 (2.6)	0
Palmar-plantar erythrodysaesthesia syndrome	24 (13.6)	6 (3.4)	22 (21.4)	5 (4.9)	1 (2.6)	0
Dry skin	22 (12.4)	0	30 (29.1)	0	5 (13.2)	0
Pruritus	7 (4.0)	0	9 (8.7)	0	1 (2.6)	0
Rash	7 (4.0)	0	5 (4.9)	0	0	0
Rash maculo-papular	5 (2.8)	0	2 (1.9)	0	3 (7.9)	0
Urticaria	0	0	4 (3.9)	0	0	0

* Sum of events compiled

In patients who received futibatinib 20 mg QD in the phase I part of Study 101, skin disorders leading to treatment discontinuation occurred in 1 of 177 patients (0.6%, eczema in 1 patient), skin disorders leading to treatment interruption occurred in 5 of 177 patients (2.8%; palmar-plantar erythrodysaesthesia syndrome in 4 patients, hyperkeratosis and palmar erythema in 1 patient each [some patients experienced multiple events]), and skin disorders leading to dose reduction occurred in 8 of 177 patients (4.5%, palmar-plantar erythrodysaesthesia syndrome in 8 patients). There were neither fatal skin disorders nor serious skin disorders.

In patients who received futibatinib 20 mg QD in the phase II part of Study 101, skin disorders leading to treatment interruption occurred in 13 of 103 patients (12.6%; palmar-plantar erythrodysaesthesia syndrome in 11 patients, urticaria and skin disorder in 1 patient each) and skin disorders leading to dose reduction occurred in 12 of 103 patients (11.7%; palmar-plantar erythrodysaesthesia syndrome in 10 patients, dermatitis bullous and skin disorder in 1 patient each). There were no fatal skin disorders, serious skin disorders, or skin disorders leading to treatment discontinuation.

In the patients who received futibatinib 20 mg QD in Study 010, there was no fatal skin disorders, serious skin disorders, or skin disorders leading to treatment discontinuation, interruption, or dose reduction.

Median time (minimum, maximum) to first onset of skin disorders was 33.0 (3, 439) days in the phase I part of Study 101, 43.0 (1, 674) days in the phase II part of Study 101, and 43.0 (3, 116) days in Study 010.

In other clinical studies of futibatinib including the above studies, there were no serious skin disorders for which a causal relationship to futibatinib could not be ruled out.

PMDA's view:
In the clinical studies included in the submitted data, skin disorders such as palmar-plantar erythrodysaesthesia syndrome leading to treatment interruption or dose reduction of futibatinib occurred

at a certain incidence during futibatinib treatment, but there were no serious skin disorders for which a causal relationship to futibatinib could not be ruled out. Special caution about palmar-plantar erythrodysaesthesia syndrome was not required at present, on the premise that incidences of palmar-plantar erythrodysaesthesia syndrome in the clinical studies is communicated through the package insert etc., relevant information is collected further in the post-marketing settings, and the obtained safety information is provided to healthcare professionals.

7.R.3.8 Acute kidney injury

The applicant's explanation about acute kidney injury associated with futibatinib:
Adverse events classified into MedDRA standardised MedDRA queries (SMQ) of "acute renal failure (broad)" were tabulated as acute kidney injury.

Table 34 shows incidences of acute kidney injury in patients who received futibatinib 20 mg QD in Studies 101 and 010.

Table 34. Incidences of acute kidney injury
(patients with solid cancers who received futibatinib 20 mg QD in Studies 101 and 010)

PT (MedDRA ver.22.0)	Number of patients (%)					
	Phase I part of Study 101 n = 177		Phase II part of Study 101 n = 103		Study 010 n = 38	
	All Grades	Grade ≥3	All Grades	Grade ≥3	All Grades	Grade ≥3
Acute kidney injury*	26 (14.7)	3 (1.7)	17 (16.5)	0	8 (21.1)	1 (2.6)
Blood creatinine increased	21 (11.9)	0	15 (14.6)	0	7 (18.4)	0
Acute kidney injury	5 (2.8)	3 (1.7)	1 (1.0)	0	0	0
Renal failure	2 (1.1)	0	0	0	0	0
Creatinine renal clearance decreased	1 (0.6)	1 (0.6)	1 (1.0)	0	0	0
Proteinuria	1 (0.6)	1 (0.6)	1 (1.0)	0	0	0
Renal impairment	1 (0.6)	0	0	0	1 (2.6)	0
Blood urea increased	1 (0.6)	0	0	0	0	0

* Sum of events compiled

In patients who received futibatinib 20 mg QD in the phase I part of Study 101, fatal acute kidney injury was reported in 1 of 177 patients (0.6%, acute kidney injury in 1 patient), and a causal relationship to futibatinib was denied. Serious acute kidney injury occurred in 3 of 177 patients (1.7%, acute kidney injury in 3 patients), and a causal relationship to futibatinib was denied for all of the events. Acute kidney injury leading to treatment interruption occurred in 3 of 177 patients (1.7%; blood creatinine increased in 2 patients, acute kidney injury, creatinine renal clearance decreased and proteinuria in 1 patient each [some patients experienced multiple events]). There were neither acute kidney injury leading to treatment discontinuation nor acute kidney injury leading to dose reduction.

In patients who received futibatinib 20 mg QD in the phase II part of Study 101, acute kidney injury leading to treatment interruption occurred in 2 of 103 patients (1.9%; blood creatinine increased in 2 patients, creatinine renal clearance decreased in 1 patient [some patients experienced multiple events]), and acute kidney injury leading to dose reduction occurred in 2 of 103 patients (1.9%, blood creatinine increased and creatinine renal clearance decreased in 1 patient each). There were no fatal acute kidney injury, serious acute kidney injury, or acute kidney injury leading to treatment discontinuation.

In patients who received futibatinib 20 mg QD in Study 010, serious acute kidney injury occurred in 1 of 38 patients (2.6%, blood creatinine increased in 1 patient), and a causal relationship to futibatinib was denied. Acute kidney injury leading to treatment interruption occurred in 1 of 38 patients (2.6%, blood creatinine increased in 1 patient), and acute kidney injury leading to dose reduction occurred in 1 of 38 patients (2.6%, blood creatinine increased in 1 patient). There were neither fatal acute kidney injury nor acute kidney injury leading to treatment discontinuation.

Median time (minimum, maximum) to first onset of acute kidney injury was 23.0 (1, 315) days in the phase I part of Study 101, 22.0 (5, 496) days in the phase II part of Study 101, and 10.5 (3, 78) days in Study 010.

Table 35 shows a detailed description of patients with serious acute kidney injury for which a causal relationship to futibatinib could not be ruled out in other clinical studies of futibatinib including the above studies.

Table 35. List of patients with serious acute kidney injury (causally related to futibatinib)

Study	Age	Sex	Dosage regimen	PT[*1]	Grade	Time to onset (Day)	Duration (Day)	Action on futibatinib	Outcome
Study 201[*2]	7[redacted]	[redacted]	20 mg QD	Acute kidney injury	3	28	5	Interruption	Resolved
Study 202[*3]	6[redacted]	[redacted]	20 mg QD	Renal failure	1	26	2	Interruption	Resolved

*1 MedDRA ver.22.0
*2 Foreign phase II study in patients with inoperable or recurrent breast cancer harboring *FGFR* gene amplification
*3 Global phase II study in patients with advanced solid cancers harboring *FGFR* gene abnormalities

PMDA's view:
In the clinical studies included in the submitted data, acute kidney injury occurred at a certain level of incidence, but serious acute kidney injury for which a causal relationship to futibatinib could not be ruled out occurred in the limited number of patients. Special caution about acute kidney injury was not required at present, on the premise that incidences of acute kidney injury in the clinical studies is communicated through the package insert etc., relevant information is collected further in the post-marketing settings, and the obtained safety information is provided to healthcare professionals.

7.R.3.9 Others

(a) Gastrointestinal disorders

The applicant's explanation about gastrointestinal disorders associated with futibatinib:
Adverse events classified into MedDRA SOC of "gastrointestinal disorders" were tabulated as gastrointestinal disorders.

Table 36 shows incidences of gastrointestinal disorders reported by ≥3% of patients who received futibatinib 20 mg QD in either Study 101 or 010.

Table 36. Incidences of gastrointestinal disorders reported by ≥3% of patients in either study (patients with solid cancers who received futibatinib 20 mg QD in Studies 101 and 010)

PT (MedDRA ver.22.0)	Number of patients (%)					
	Phase I part of Study 101 n = 177		Phase II part of Study 101 n = 103		Study 010 n = 38	
	All Grades	Grade ≥3	All Grades	Grade ≥3	All Grades	Grade ≥3
Gastrointestinal disorders*	145 (81.9)	32 (18.1)	88 (85.4)	21 (20.4)	27 (71.1)	2 (5.3)
Diarrhoea	59 (33.3)	1 (0.6)	37 (35.9)	1 (1.0)	10 (26.3)	0
Constipation	58 (32.8)	2 (1.1)	40 (38.8)	0	14 (36.8)	0
Nausea	52 (29.4)	1 (0.6)	25 (24.3)	2 (1.9)	9 (23.7)	0
Vomiting	45 (25.4)	3 (1.7)	20 (19.4)	1 (1.0)	8 (21.1)	1 (2.6)
Abdominal pain	35 (19.8)	5 (2.8)	22 (21.4)	3 (2.9)	0	0
Dry mouth	31 (17.5)	0	36 (35.0)	0	3 (7.9)	0
Stomatitis	28 (15.8)	5 (2.8)	25 (24.3)	6 (5.8)	5 (13.2)	0
Gastrooesophageal reflux disease	17 (9.6)	0	6 (5.8)	0	0	0
Abdominal pain upper	11 (6.2)	2 (1.1)	8 (7.8)	0	0	0
Dyspepsia	11 (6.2)	0	7 (6.8)	0	0	0
Intestinal obstruction	6 (3.4)	5 (2.8)	1 (1.0)	1 (1.0)	1 (2.6)	1 (2.6)
Abdominal distension	4 (2.3)	0	6 (5.8)	0	0	0
Dysphagia	4 (2.3)	1 (0.6)	5 (4.9)	0	0	0
Ascites	3 (1.7)	2 (1.1)	6 (5.8)	5 (4.9)	0	0
Mouth ulceration	3 (1.7)	0	4 (3.9)	0	0	0

* Sum of events compiled

In patients who received futibatinib 20 mg QD in the phase I part of Study 101, fatal gastrointestinal disorders were reported in 3 of 177 patients (1.7%, gastrointestinal haemorrhage, pancreatitis acute, and small intestinal haemorrhage in 1 patient each), and a causal relationship to futibatinib was denied for all events. Serious gastrointestinal disorders occurred in 29 of 177 patients (16.4%; intestinal obstruction and abdominal pain in 5 patients each, vomiting, nausea, abdominal pain upper, upper gastrointestinal haemorrhage, colitis, and constipation in 2 patients each, gastric haemorrhage, gastrointestinal haemorrhage, obstruction gastric, ileus, pancreatitis acute, haematochezia, stomatitis, duodenal obstruction, small intestinal haemorrhage, oesophageal ulcer, inguinal hernia, ascites, and melaena in 1 patient each [some patients experienced multiple events]), and a causal relationship to futibatinib could not be ruled out for intestinal obstruction in 2 patients and abdominal pain upper and stomatitis in 1 patient each. Gastrointestinal disorders leading to treatment discontinuation occurred in 8 of 177 patients (4.5%; diarrhoea and intestinal obstruction in 2 patients each, gastrointestinal haemorrhage, vomiting, nausea, pancreatitis acute, stomatitis, duodenal obstruction, and oesophageal ulcer in 1 patient each [some patients experienced multiple events]), gastrointestinal disorders leading to treatment interruption occurred in 18 of 177 patients (10.2%; vomiting and stomatitis in 4 patients each, nausea and abdominal pain in 3 patients each, ileus, dry mouth, loose tooth, abdominal pain upper, upper gastrointestinal haemorrhage, varices oesophageal, inguinal hernia, colitis, intestinal obstruction, constipation, and melaena in 1 patient each [some patients experienced multiple events]), and gastrointestinal disorders leading to dose reduction occurred in 12 of 177 patients (6.8%; stomatitis in 6 patients, diarrhoea in 2 patients, nausea, abdominal pain upper, intestinal obstruction, and abdominal discomfort in 1 patient each).

In patients who received futibatinib 20 mg QD in the phase II part of Study 101, fatal gastrointestinal disorder was reported in 1 of 103 patients (1.0%, ascites in 1 patient), and a causal relationship to futibatinib was denied. Serious gastrointestinal disorders occurred in 11 of 103 patients (10.7%; upper gastrointestinal haemorrhage and ascites in 3 patients each, gastrointestinal haemorrhage, impaired

gastric emptying, vomiting, nausea, umbilical hernia, oesophagitis, oesophageal varices haemorrhage, intestinal obstruction, and abdominal pain in 1 patient each [some patients experienced multiple events]), and a causal relationship to futibatinib could not be ruled out for upper gastrointestinal haemorrhage, vomiting, nausea, and oesophagitis in 1 patient each. Gastrointestinal disorders leading to treatment discontinuation occurred in 2 of 103 patients (1.9%, oral dysaesthesia, stomatitis, and oesophagitis in 1 patient each [some patients experienced multiple events]), gastrointestinal disorders leading to treatment interruption occurred in 14 of 103 patients (13.6%; stomatitis in 5 patients, vomiting in 4 patients, nausea in 3 patients, diarrhoea, upper gastrointestinal haemorrhage, and abdominal pain in 2 patients each, gastrointestinal haemorrhage, impaired gastric emptying, oral pain, umbilical hernia, oesophagitis, and intestinal obstruction in 1 patient each [some patients experienced multiple events]), and gastrointestinal disorders leading to dose reduction occurred in 4 of 103 patients (3.9%, stomatitis in 3 patients and nausea in 1 patient).

In patients who received futibatinib 20 mg QD in Study 010, fatal gastrointestinal disorder was reported in 1 of 38 patients (2.6%, intestinal obstruction in 1 patient), and a causal relationship to futibatinib was denied. Serious gastrointestinal disorders occurred in 2 of 38 patients (5.3%, vomiting and intestinal obstruction in 1 patient each), and a causal relationship to futibatinib was denied for both events. Gastrointestinal disorders leading to treatment interruption occurred in 1 of 38 patients (2.6%, nausea in 1 patient), and gastrointestinal disorders leading to dose reduction occurred in 1 of 38 patients (2.6%, nausea in 1 patient). There were no gastrointestinal disorders leading to treatment discontinuation.

Median time (minimum, maximum) to first onset of gastrointestinal disorders was 10.0 (1, 358) days in the phase I part of Study 101, 13.0 (1, 315) days in the phase II part of Study 101, and 8.0 (2, 58) days in Study 010.

Table 37 shows a detailed description of patients with serious gastrointestinal disorders for which a causal relationship to futibatinib could not be ruled out in other clinical studies of futibatinib including the above studies.

Table 37. List of patients with serious gastrointestinal disorders (causally related to futibatinib)[*1]

Study	Age	Sex	Dosage regimen	PT[*2]	Grade	Time to onset (Day)	Duration (Day)	Action on futibatinib	Outcome
Phase I part of Study 101	5[redacted]	[redacted]	20 mg QD	Abdominal pain upper	3	9	7	Dose reduction	Resolved
	5[redacted]	[redacted]	20 mg QD	Stomatitis	3	54	5	Interruption	Resolved
	3[redacted]	[redacted]	20 mg QD	Intestinal obstruction	3	85	2	Unchanged	Resolved
	5[redacted]	[redacted]	20 mg QD	Intestinal obstruction	3	15	10	Dose reduction	Resolved
	8[redacted]	[redacted]	120 mg QOD	Nausea	3	56	3	Interruption	Resolved
				Vomiting	3	56	3	Interruption	Resolved
Phase II part of Study 101	4[redacted]	[redacted]	20 mg QD	Nausea	3	70	4	Interruption	Resolved
				Upper gastrointestinal haemorrhage	2	70	4	Interruption	Resolved
				Vomiting	3	70	4	Interruption	Resolved
	7[redacted]	[redacted]	20 mg QD	Oesophagitis	3	357	17	Interruption	Resolved
				Oesophagitis	3	386	28	Discontinuation	Resolved
				Oesophagitis	2	414	Unknown	Unchanged	Not resolved
Study 010	7[redacted]	[redacted]	160 mg QOD	Stomatitis	3	16	36	Unknown	Resolved
Study 201[*3]	5[redacted]	[redacted]	20 mg QD	Nausea	3	5	119	Dose reduction	Resolved

*1 Only patients treated with futibatinib alone presented in this table
*2 MedDRA ver.22.0
*3 Foreign phase II study in patients with inoperable or recurrent breast cancer harboring *FGFR* gene amplification

(b) Liver disorders

The applicant's explanation about liver disorders associated with futibatinib:

Adverse events classified into MedDRA PTs of "hepatic enzyme increased," "transaminases increased," "alanine aminotransferase (ALT) increased," "aspartate aminotransferase (AST) increased," "gamma-glutamyltransferase (GGT) increased," "bilirubin conjugated increased," "acute hepatic failure," "hepatic failure," "subacute hepatic failure," "drug-induced liver injury," "hepatotoxicity," and "hepatocellular injury" were tabulated as liver disorders.

Table 38 shows incidences of liver disorders in patients who received futibatinib 20 mg QD in Studies 101 and 010.

Table 38. Incidences of liver disorders
(patients with solid cancers who received futibatinib 20 mg QD in Studies 101 and 010)

PT (MedDRA ver.22.0)	Number of patients (%)					
	Phase I part of Study 101 n = 177		Phase II part of Study 101 n = 103		Study 010 n = 38	
	All Grades	Grade ≥3	All Grades	Grade ≥3	All Grades	Grade ≥3
Liver disorders*	57 (32.2)	24 (13.6)	28 (27.2)	13 (12.6)	9 (23.7)	1 (2.6)
AST increased	48 (27.1)	11 (6.2)	26 (25.2)	10 (9.7)	9 (23.7)	1 (2.6)
ALT increased	45 (25.4)	19 (10.7)	18 (17.5)	6 (5.8)	9 (23.7)	0
GGT increased	6 (3.4)	2 (1.1)	2 (1.9)	1 (1.0)	0	0
Bilirubin conjugated increased	3 (1.7)	0	0	0	0	0
Hepatic failure	2 (1.1)	2 (1.1)	0	0	0	0
Transaminases increased	1 (0.6)	0	0	0	0	0

* Sum of events compiled

In patients who received futibatinib 20 mg QD in the phase I part of Study 101, fatal liver disorders were reported in 2 of 177 patients (1.1%, hepatic failure in 2 patients), and a causal relationship to futibatinib

was denied for both events. Serious liver disorders occurred in 2 of 177 patients (1.1%, hepatic failure in 2 patients), and a causal relationship to futibatinib was denied for both events. Liver disorders leading to treatment interruption occurred in 13 of 177 patients (7.3%; ALT increased in 10 patients, AST increased in 8 patients [some patients experienced multiple events]), and liver disorders leading to dose reduction occurred in 13 of 177 patients (7.3%; ALT increased in 12 patients, AST increased in 8 patients [some patients experienced multiple events]). There were no liver disorders leading to treatment discontinuation.

In patients who received futibatinib 20 mg QD in the phase II part of Study 101, serious liver disorders occurred in 1 of 103 patients (1.0%, ALT increased, AST increased and GGT increased in 1 patient each [the patient experienced more than 1 event]), and a causal relationship to futibatinib was denied for all events. Liver disorders leading to treatment interruption occurred in 13 of 103 patients (12.6%; ALT increased in 10 patients, AST increased in 9 patients, GGT increased in 2 patients [some patients experienced multiple events]), and liver disorders leading to dose reduction occurred in 7 of 103 patients (6.8%; ALT increased in 5 patients, AST increased in 4 patients [some patients experienced multiple events]). There were neither fatal liver disorders nor liver disorders leading to treatment discontinuation.

In patients who received futibatinib 20 mg QD in Study 010, liver disorders leading to treatment interruption occurred in 3 of 38 patients (7.9%, ALT increased in 3 patients), and liver disorders leading to dose reduction occurred in 1 of 38 patients (2.6%, ALT increased in 1 patient). There were no fatal liver disorders, serious liver disorders, or liver disorders leading to treatment discontinuation.

Median time (minimum, maximum) to first onset of liver disorders was 16.0 (4, 609) days in the phase I part of Study 101, 38.0 (4, 504) days in the phase II part of Study 101, and 6.0 (3, 64) days in Study 010.

In other clinical studies of futibatinib including the above studies, there were no serious liver disorders for which a causal relationship to futibatinib could not be ruled out.

(c) Electrolyte abnormalities (except hyperphosphataemia)

The applicant's explanation about electrolyte abnormalities (except hyperphosphataemia) associated with futibatinib:

Adverse events classified into MedDRA PTs of "blood calcium increased," "blood chloride decreased," "blood phosphorus decreased," "blood sodium decreased," "hypercalcaemia," "hyperchloraemia," "hyperkalaemia," "hypernatraemia," "hypocalcaemia," "hypokalaemia," "hypomagnesaemia," "hyponatraemia," and "hypophosphataemia" were tabulated as electrolyte abnormalities.

Table 39 shows incidences of electrolyte abnormalities reported by ≥3% of patients who received futibatinib 20 mg QD in either Study 101 or 010.

Table 39. Incidences of electrolyte abnormalities reported by ≥3% of patients in either study (patients with solid cancers who received futibatinib 20 mg QD in Studies 101 and 010)

PT (MedDRA ver.22.0)	Number of patients (%)					
	Phase I part of Study 101 n = 177		Phase II part of Study 101 n = 103		Study 010 n = 38	
	All Grades	Grade ≥3	All Grades	Grade ≥3	All Grades	Grade ≥3
Electrolyte abnormalities*	47 (26.6)	19 (10.7)	41 (39.8)	20 (19.4)	9 (23.7)	6 (15.8)
Hypercalcaemia	21 (11.9)	2 (1.1)	16 (15.5)	2 (1.9)	2 (5.3)	1 (2.6)
Hypophosphataemia	15 (8.9)	9 (5.1)	13 (12.6)	5 (4.9)	2 (5.3)	1 (2.6)
Hypokalaemia	11 (6.2)	1 (0.6)	6 (5.8)	2 (1.9)	1 (2.6)	1 (2.6)
Hyponatraemia	8 (4.5)	6 (3.4)	16 (15.5)	11 (10.7)	6 (15.8)	4 (10.5)
Hyperkalaemia	2 (1.1)	1 (0.6)	4 (3.9)	2 (1.9)	1 (2.6)	0
Blood chloride decreased	1 (0.6)	0	0	0	2 (5.3)	0

* Sum of events compiled

In patients who received futibatinib 20 mg QD in the phase I part of Study 101, serious electrolyte abnormalities occurred in 2 of 177 patients (1.1%, hypercalcaemia and hyperkalaemia in 1 patient each), and a causal relationship to futibatinib was denied for both events. Electrolyte abnormalities leading to treatment interruption occurred in 4 of 177 patients (2.3%; hypercalcaemia in 3 patients, hypokalaemia in 1 patient), and electrolyte abnormalities leading to dose reduction occurred in 1 of 177 patients (0.6%, hyponatraemia in 1 patient). There were neither fatal electrolyte abnormalities nor electrolyte abnormalities leading to treatment discontinuation.

In patients who received futibatinib 20 mg QD in the phase II part of Study 101, serious electrolyte abnormalities occurred in 3 of 103 patients (2.9%, hypercalcaemia, hyperkalaemia, and hyponatraemia in 1 patient each), and a causal relationship to futibatinib was denied for all events. Electrolyte abnormalities leading to treatment interruption occurred in 4 of 103 patients (3.9%; hyponatraemia in 3 patients, blood sodium decreased in 1 patient), and electrolyte abnormalities leading to dose reduction occurred in 1 of 103 patients (1.0%, blood sodium decreased in 1 patient). There were neither fatal electrolyte abnormalities nor electrolyte abnormalities leading to treatment discontinuation.

In patients who received futibatinib 20 mg QD in Study 010, serious electrolyte abnormalities occurred in 1 of 38 patients (2.6%, hyponatraemia), and a causal relationship to futibatinib could not be ruled out. There were no fatal electrolyte abnormalities, electrolyte abnormalities leading to treatment discontinuation, treatment interruption, or dose reduction.

Median time (minimum, maximum) to first onset of electrolyte abnormalities was 41.0 (3, 675) days in the phase I part of Study 101, 64.0 (1, 474) days in the phase II part of Study 101, and 12.0 (6, 71) days in Study 010.

Table 40 shows a detailed description of patients with serious electrolyte abnormalities for which a causal relationship to futibatinib could not be ruled out in other clinical studies of futibatinib including the above studies.

Table 40. List of patients with serious electrolyte abnormalities (causally related to futibatinib)[*1]

Study	Age	Sex	Dosage regimen	PT[*2]	Grade	Time to onset (Day)	Duration (Day)	Action on futibatinib	Outcome
Study 010	7[redacted]	[redacted]	20 mg QD	Hyponatraemia	4	21	42	Unknown	Resolved

*1 Only patients treated with futibatinib alone presented in this table, *2 MedDRA ver.22.0

PMDA's view:

In the above (a) gastrointestinal disorders, (b) liver disorders, and (c) electrolyte abnormalities in clinical studies included in the submitted data, serious events for which a causal relationship to futibatinib could not be ruled out occurred at a certain incidence, but many of these events resolved shortly after treatment interruption etc. Special caution was not required at present, on premise that the incidence is monitored further in the post-marketing settings and new information is provided to healthcare professionals when it becomes available.

7.R.4 Clinical positioning and indication

The proposed indication of futibatinib was "Previously treated, locally advanced or metastatic biliary tract cancer harboring *fibroblast growth factor receptor 2 (FGFR2)* gene fusion or other rearrangements."

The following statements had been proposed for the Precautions Concerning Indication section:

- The efficacy and safety of futibatinib as the first-line therapy have not been established.
- The efficacy and safety of futibatinib have not been established for use in postoperative adjuvant chemotherapy.
- Appropriate patients should be selected by physicians with a full understanding of the information presented in the "Clinical Studies" section and of the efficacy and safety of futibatinib.
- Futibatinib should be used in patients harboring *FGFR2* gene fusion or other rearrangements confirmed by adequately experienced pathologists or testing at qualified laboratories. The testing should be performed using approved *in vitro* diagnostics or medical devices.

After submission of this application, however, the applicant expressed their intention of changing the proposed indication to "Locally advanced or metastatic biliary tract cancer harboring *FGFR2* gene fusion or other rearrangements that has progressed after cancer chemotherapy."

As a result of the review in Sections "7.R.2 Efficacy," "7.R.3 Safety," and the following subsections, PMDA has concluded that the indication of futibatinib should be "unresectable *FGFR2* gene fusion-positive biliary tract cancer that has progressed after cancer chemotherapy" with the following cautionary statements included in the "Precautions Concerning Indication" section:

- The efficacy and safety of futibatinib as the first-line therapy have not been established.
- The efficacy and safety of futibatinib have not been established for use in postoperative adjuvant chemotherapy.
- Appropriate patients should be selected by physicians with a full understanding of the information about the location of the primary lesion in patients enrolled in clinical studies presented in the "Clinical Studies" section and of the efficacy and safety of futibatinib.
- Futibatinib should be used in patients harboring *FGFR2* gene fusion confirmed by adequately experienced pathologists or testing at qualified laboratories. The testing should be performed using approved *in vitro* diagnostics or medical devices.

7.R.4.1 Clinical positioning of futibatinib and intended population

Japanese and foreign clinical practice guidelines and representative textbooks on clinical oncology were found to have the following descriptions about use of futibatinib in treatment of unresectable biliary tract cancer.

Clinical practice guidelines

- National Comprehensive Cancer Network Clinical Practice Guidelines in Oncology, Hepatobiliary Cancers (NCCN guidelines) (v.1.2023):
  Futibatinib is recommended as the second-line therapy in patients with cholangiocarcinoma harboring *FGFR2* gene fusion or *FGFR2* gene rearrangement.
- Biliary cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up (ESMO guidelines) (*Ann Oncol.* 2023;34:127-40):
  Futibatinib is strongly recommended as the second-line therapy in patients with biliary tract cancer harboring *FGFR2* gene fusion.

The applicant's explanation about the intended population and indication of futibatinib:
In view of results from Study 101 and oncobiological meanings of *FGFR2* gene fusion and *FGFR2* gene rearrangement [see Section 7.R.2.1], futibatinib can be positioned as a treatment option for patients with unresectable biliary tract cancer harboring *FGFR2* gene fusion or *FGFR2* gene rearrangement that has progressed after cancer chemotherapy.

Patients with some subtypes of biliary tract cancer, extrahepatic cholangiocarcinoma, gallbladder cancer, and papillary carcinoma, were not included in the phase II part of Study 101, and no clinical study results on the efficacy or safety of futibatinib in the concerned patient population are available. The applicant, however, considers it acceptable to use futibatinib in the concerned patient population in view of similar treatment strategies for unresectable cholangiocarcinoma, gallbladder cancer, and papillary carcinoma; and very rare cases of extrahepatic cholangiocarcinoma, gallbladder cancer, and papillary carcinoma harboring *FGFR2* gene fusion or *FGFR2* gene rearrangement (*Hepatology.* 2014;59:1427-34, *J Gastroenterol.* 2021;56:250-60, etc.). In addition, the Indication section should clearly state to the effect that futibatinib is intended for patients with cancer that has progressed after cancer chemotherapy, because Study 101 included patients who had received prior chemotherapy, and no clinical study results on the efficacy or safety of futibatinib in patients who had not received chemotherapy are available.

Because no clinical study results on the efficacy or safety of futibatinib are available for use in postoperative adjuvant chemotherapy, futibatinib is not recommended for postoperative adjuvant chemotherapy.

On the basis of the above, the package insert included details (e.g., location of the primary lesion) of the patients in the phase II part of Study 101 in the Clinical Studies section, provided the following cautionary statements in the Precautions Concerning Indication section, and specified the indication of futibatinib as "Locally advanced or metastatic biliary tract cancer harboring *FGFR2* gene fusion or other rearrangements that has progressed after cancer chemotherapy."

- The efficacy and safety of futibatinib as the first-line therapy have not been established.
- The efficacy and safety of futibatinib have not been established for use in postoperative adjuvant chemotherapy.
- Appropriate patients should be selected by physicians with a full understanding of the information presented in the "Clinical Studies" section and of the efficacy and safety of futibatinib.

The applicant's explanation about choice between futibatinib and pemigatinib for patients with locally advanced or metastatic biliary tract cancer harboring *FGFR2* gene fusion or *FGFR2* gene rearrangement that has progressed after cancer chemotherapy:
Futibatinib is a small molecule FGFR inhibitor that can be administered orally, similar to pemigatinib. It binds to the ATP binding site of FGFR and interferes with FGF/FGFR signaling, thereby inhibiting tumor growth. In addition, futibatinib was shown to inhibit proliferation of human cholangiocarcinoma-derived CCLP-1 cell line transfected with *FGFR2* gene fusion carrying N550K, L618V, or K660M mutation that was reported to render cancers resistant to pemigatinib after its treatment (*Cancer Discov.* 2021;11:326-39) (*Cancer Discov.* 2019;9:10645-1079). Futibatinib may have efficacy even in patients resistant to pemigatinib. However, no results from a clinical study comparing the efficacy and safety of futibatinib with those of pemigatinib are available, and choice between these drugs remains unclear at present.

PMDA's view:
PMDA accepted the applicant's explanation about patients with biliary tract cancer harboring *FGFR2* gene fusion.

Although whether *FGFR2* gene rearrangement contributes to tumor growth as the *FGFR2* gene fusion does remains unclear, the use of futibatinib in patients with biliary tract cancer harboring *FGFR2* gene rearrangement was acceptable in view of the applicant's explanation and the following points:
- A clinically meaningful response rate was achieved in patients with unresectable cholangiocarcinoma harboring *FGFR2* gene rearrangement enrolled in the phase II part of Study 101 [see Section 7.R.2.1].
- The number of patients with biliary tract cancer harboring *FGFR2* gene fusion or *FGFR2* gene rearrangement is limited as provided below, and it is thus considered difficult to evaluate the efficacy of futibatinib in patients harboring each of the concerned gene abnormalities.
  - *FGFR2* gene fusion or *FGFR2* gene rearrangement was found in 7.4% of intrahepatic cholangiocarcinoma and 3.6% of extrahepatic cholangiocarcinoma (hilar cholangiocarcinoma) (*J Gastroenterol.* 2021;56:250-60).

Gene fusion and gene rearrangement were separately evaluated in Study 101 [see Section 7.R.2.1] by defining the gene fusion narrowly as a gene structure in which the breakpoint is at intron 17 or exon 18 of the *FGFR2* gene and a partner gene is in the same reading frame as that of the *FGFR2* gene, as analyzed by NGS–based "FoundationOne Assay for Clinical Study." Of the approved drugs developed for specific patients identified by FISH, immunohistochemistry (IHC), and reverse transcription polymerase chain reaction (RT-PCR), however, the efficacy and safety were evaluated in patients harboring the "broadly defined gene fusion," which included gene rearrangement, because these analysis methods, owing to their analysis principles, do not have an ability to distinguish between the gene fusion

and gene rearrangement. For futibatinib, patients with biliary tract cancer harboring *FGFR2* gene fusion or *FGFR2* gene rearrangement identified according to the narrow definition were considered intended, based on results from Study 101. The indication may require the presence of broadly defined "*FGFR2* gene fusion-positive" as with that of the approved drugs. In view of the above decision and synonymous terms of "locally advanced or metastatic" and "unresectable," PMDA has concluded that the indication should be "unresectable *FGFR2* gene fusion-positive biliary tract cancer."

On the basis of the above, the package insert should include details (e.g., location of the primary lesion) of the patients in the phase II part of Study 101 in the Clinical Studies section, provide the following cautionary statements in the Precautions Concerning Indication section, and specify the indication of futibatinib as "unresectable *FGFR2* gene fusion-positive biliary tract cancer that has progressed after cancer chemotherapy."

- The efficacy and safety of futibatinib as the first-line therapy have not been established.
- The efficacy and safety of futibatinib have not been established for use in postoperative adjuvant chemotherapy.
- Appropriate patients should be selected by physicians with a full understanding of the information about the location of the primary lesion in patients enrolled in clinical studies presented in the "Clinical Studies" section and of the efficacy and safety of futibatinib.

7.R.4.2 Testing of *FGFR2* gene fusion

"OncoGuide NCC Oncopanel System" is a companion diagnostic in support of eligibility assessment of futibatinib. A partial change application for this product was submitted by Sysmex Corporation on August 31, 2022 and approved on February 28, 2023.

The applicant's explanation about testing of *FGFR2* gene fusion used to select intended patients for futibatinib:

In the phase II part of Study 101, "FoundationOne Assay for Clinical Study" or "FoundationOne CDx Cancer Genomic Profile" of Foundation Medicine was used at a central laboratory to identify patients harboring *FGFR2* gene fusion or *FGFR2* gene rearrangement, and the efficacy and safety of futibatinib were evaluated in this patient population [see Sections 7.1.3.1, 7.R.2.1, and 7.R.4.1]. "OncoGuide NCC Oncopanel System" is a test system that can detect *FGFR2* gene fusion and *FGFR2* gene rearrangement detected by "FoundationOne Assay for Clinical Study." A comparability study demonstrated that these test systems provided well-agreed assessment results. The NCC Oncopanel System is considered to appropriately identify patients in whom the efficacy and safety of futibatinib can be expected.

On the basis of the above, for futibatinib, intended patients should be selected using "OncoGuide NCC Oncopanel System," and this statement will be included in the Precautions Concerning Indication section to raise caution.

PMDA accepted the applicant's explanation.

7.R.5 Dosage and administration

The proposed dosage and administration of futibatinib was "The usual adult dosage is continuous oral dose of futibatinib 20 mg administered once daily. The dose may be reduced according to the patient's condition." The following statements were proposed for the Precautions Concerning Dosage and Administration section.

- The efficacy and safety of futibatinib have not been established for use in combination with other antineoplastic agents.
- Guide for treatment interruption, dose reduction, and treatment discontinuation of futibatinib in response to onset of adverse drug reactions

As a result of the review in Sections "6.R.1 Food effect," "7.R.2 Efficacy," "7.R.3 Safety," and the following subsection, PMDA has concluded that the "Dosage and Administration" of futibatinib should be "The usual adult dosage is 20 mg of futibatinib administered orally once daily in the fasted state. The dose may be reduced according to the patient's condition." with the following cautionary statements included in the Precautions Concerning Dosage and Administration section.

- The efficacy and safety of futibatinib have not been established for use in combination with other antineoplastic agents.
- C_{max} and AUC of futibatinib decrease when administered after a meal. To avoid food effect, futibatinib should be taken on an empty stomach (2 hours after and 1 hour before a meal).
- Guide for treatment interruption, dose reduction, and treatment discontinuation of futibatinib in response to onset of adverse drug reactions [see Section 7.R.5.2]

7.R.5.1 Dosage and administration of futibatinib

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

The phase II part of Study 101 was conducted using a dosage regimen based on the clinical study results presented below, and the efficacy and safety of futibatinib in this study population were demonstrated to a certain extent. On the basis of the dosage regimen in the phase II part of Study 101, the dosage regimen of futibatinib was specified.

- Of the global phase I/II study (Study 101), in the phase I dose-escalation part conducted overseas, the response rate was 9.3% (5 of 54 patients) on the QD regimen and 2.8% (2 of 71 patients) on the QOD regimen, indicating that the QD regimen achieved higher response rate.
- Of the global phase I/II study (Study 101), in the phase I dose-escalation part conducted overseas, patients who received futibatinib 20 mg QD did not experience DLT, and the regimen was well tolerated [see Section 7.2.2.1].
- In the Japanese phase I study (Study 010), patients who received futibatinib 20 mg QD did not experience DLT, and the regimen was well tolerated [see Section 7.1.2.1].
- In the foreign phase I study (Study 102), the geometric mean ratios [90% CI] of C_{max} and AUC_{last} of futibatinib 20 mg taken after the high-fat meal relative to those under the fasted state were 0.576 [0.47, 0.70] and 0.862 [0.77, 0.96], respectively. The exposures to futibatinib 20 mg taken after the high-fat meal were lower than those in the fasted state [see Section 6.1.2.1]. The decreased exposure to futibatinib noted after administration in the fed state was, however, considered to have a limited impact on the efficacy of futibatinib.

Of note, because no clinical study results on the efficacy or safety of futibatinib in combination with other antineoplastic agents are available at present, coadministration of futibatinib with other antineoplastic agents is not recommended.

PMDA's view:
As a result of the review in Section "6.R.1 Food effect," futibatinib should be administered in the fasted state.

The Dosage and Administration of futibatinib should be "The usual adult dosage is 20 mg of futibatinib administered orally once daily in the fasted state. The dose may be reduced according to the patient's condition." with the following cautionary statements included in the Precautions Concerning Dosage and Administration section.

- The efficacy and safety of futibatinib have not been established for use in combination with other antineoplastic agents.
- C_{max} and AUC of futibatinib decrease when administered after meal. To avoid food effect, futibatinib should be taken on an empty stomach (2 hours after and 1 hour before a meal).

7.R.5.2 Dose adjustment of futibatinib

The applicant's explanation about dose adjustment of futibatinib:
In the phase II part of Study 101, criteria for dose adjustment of futibatinib were specified with a numerical guide, and the efficacy and safety of futibatinib were demonstrated in patients who received futibatinib with the dose adjusted according to the above criteria. The Precautions Concerning Dosage and Administration section was therefore proposed to include criteria for dose adjustment based on those in the phase II part of Study 101 with the following modifications:

- The criteria for dose adjustment in response to serous retinal detachment were not separately specified in the phase II part of Study 101, and as done in response to other non-hematotoxicity events, treatment was interrupted in response to Grade 3 event and resumed at a 1-level reduced dose after the event resolved to Grade ≤1. In the phase I part of Study 101, retinal detachment occurred in 4 patients but resolved to Grade ≤1 in all of them after treatment interruption, dose reduction, or treatment discontinuation of futibatinib. Early treatment interruption, dose reduction, or treatment discontinuation is considered important. In view of the above finding and consideration, the criteria will be specified as follows: When the relevant symptom is present or worsening is noted at the examination, futibatinib should be interrupted irrespective of grade; and if no improvement is observed even after interruption, futibatinib should be discontinued.
- When serum phosphate concentration was ≥5.5 mg/dL and ≤7 mg/dL, it was re-measured within 1 week. When a continued raise was noted, a dose increase of a drug for treatment of hyperphosphataemia was considered. The criterion for re-measurement of serum phosphate concentrations was removed because the package insert of futibatinib is planned to advise periodic measurement of serum phosphate concentrations as a caution, and that of lanthanum carbonate, a drug for treatment of hyperphosphataemia, has advised the measurement of serum phosphate concentrations as a caution.

PMDA's view:

PMDA accepted the above applicant's explanation and concluded that the guide and criteria for dose adjustment should be modified as presented below and included in the Precautions Concerning Dosage and Administration section.

- If any adverse drug reaction occurs after use of futibatinib, futibatinib should be interrupted, reduced in dose, or discontinued in accordance with the following criteria.

Guide for dose reduction

Dose reduction level	Dose
Usual dose	20 mg
1-level reduced dose	16 mg
2-level reduced dose	12 mg
3-level reduced dose	Discontinuation

Criteria for interruption, dose reduction, and discontinuation in response to adverse drug reactions

Adverse drug reaction	Severity*	Action
Retinal detachment	—	• If symptoms are present or worsening in the ophthalmic evaluation, interrupt futibatinib. • If the symptoms resolve after interruption, resume futibatinib at a next lower dose. If symptoms do not resolve, discontinue futibatinib.
Hyperphosphataemia	Serum phosphate levels ≥5.5 mg/dL and ≤7 mg/dL	• Start phosphate lowering therapy in addition to limitation of phosphate-rich food intake.
	Serum phosphate levels >7 mg/dL and ≤10 mg/dL	• Reduce futibatinib to next lower dose and start phosphate lowering therapy in addition to limitation of phosphate-rich food intake. • If the serum phosphate resolves to ≤7 mg/dL within 2 weeks after 1-level dose reduction, continue futibatinib at this reduced dose. • If the serum phosphate level is not resolved to ≤7 mg/dL within 2 weeks after 1-level dose reduction, further reduce the dose to the next lower dose. • If the serum phosphate level is not resolved to ≤7 mg/dL within 2 weeks after the 2-level dose reduction, interrupt futibatinib until serum phosphate is ≤7 mg/dL. If resolved to ≤7 mg/dL after interruption, resume futibatinib at the dose prior to interruption.
	Serum phosphate levels >10 mg/dL	• Start phosphate lowering therapy in addition to limitation of phosphate-rich food intake. • Interrupt futibatinib until serum phosphate level is ≤7 mg/dL. If the serum phosphate level resolved to ≤7 mg/dL after interruption, resume futibatinib at a next lower dose. • If the serum phosphate level is >10 mg/dL after the 2-level dose reduction, discontinue futibatinib.
Other adverse drug reactions	Grade 3	• Interrupt futibatinib until toxicity resolves to Grade ≤1 or baseline. After recovery, resume futibatinib at a next lower dose. For hematological toxicities resolving within 1 week, resume futibatinib at the same dose prior to interruption.
	Grade 4	• Discontinue futibatinib.

* Graded according to NCI-CTCAE ver.4.03.

7.R.6 Post-marketing investigations

The applicant's explanation about post-marketing surveillance plan:

The applicant plans to conduct a post-marketing surveillance in all patients treated with futibatinib to investigate the safety of futibatinib etc. in post-marketing clinical use.

The safety specification in the surveillance includes the use of futibatinib in patients with moderate or severe hepatic impairment, in view of the limited safety information in these patient population, in

addition to hyperphosphataemia and serous retinal detachment, events requiring special attention during futibatinib treatment, based on incidences in the phase II part of Study 101.

The planned sample size and observation period in the surveillance are 120 patients and 1 year, respectively, based on incidences of hyperphosphataemia and serous retinal detachment in the phase II part of Study 101, which are included in the safety specification in the surveillance.

PMDA's view:
Because of the limited safety information in Japanese patients treated with futibatinib, the post-marketing surveillance should be conducted in all patients treated with futibatinib for a certain period after market launch, to collect the safety information etc. in a prompt and unbiased manner. Obtained safety information should be immediately provide to healthcare professionals.

On the basis of the review results in Section "7.R.3 Safety," the safety specification in the surveillance should include hyperphosphataemia, retinal detachment, eye disorders (except retinal detachment), nail disorders, palmar-plantar erythrodysaesthesia syndrome, and acute kidney injury, and information including the safety data of futibatinib in patients with hepatic impairment should be collected.

The planned sample size and observation period in the surveillance should be reconsidered in view of incidences of the above events to be specified in the safety specification.

7.3 Adverse events, etc. observed in clinical studies

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

7.3.1 Japanese phase I study (Study 010)

7.3.1.1 Dose-escalation part

Adverse events occurred in all patients, and adverse events for which a causal relationship to futibatinib could not be ruled out occurred in 0 of 1 patient in the 8 mg QOD arm, 0 of 1 patient in the 16 mg QOD arm, 1 of 1 patient (100%) in the 24 mg QOD arm, 3 of 3 patients (100%) in the 36 mg QOD arm, 6 of 7 patients (85.7%) in the 56 mg QOD arm, 6 of 6 patients (100%) in the 80 mg QOD arm, 4 of 4 patients (100%) in the 120 mg QOD arm, 6 of 6 patients (100%) in the 160 mg QOD arm, 3 of 3 patients (100%) in the 16 mg QD arm, and 7 of 7 patients (100%) in the 20 mg QD arm. Adverse events with an incidence of ≥40% in each arm were dental caries and cancer pain in 1 patient (100%) each in the 8 mg QOD arm, anaemia, nausea, oedema peripheral, blood creatinine increased, international normalised ratio increased, weight increased, hypoalbuminaemia, hypophosphataemia, cancer pain, and dry skin in 1 patient (100%) each in the 16 mg QOD arm, anaemia, malaise, decreased appetite, hypophosphataemia, pain in extremity, somnolence, and purpura in 1 patient (100%) each in the 24 mg QOD arm, hyperphosphataemia in 3 patients (100%), fatigue and nail disorder in 2 patients (66.7%) each in the 36 mg QOD arm, hyperphosphataemia in 6 patients (85.7%), insomnia in 4 patients (57.1%) in the 56 mg QOD arm, hyperphosphataemia in 6 patients (100%), decreased appetite in 4 patients (66.7%), constipation, diarrhoea and dyspnoea in 3 patients (50.0%) each in the 80 mg QOD arm, hyperphosphataemia in 4 patients (100%), constipation, ALT increased, AST increased, blood creatinine

increased, hypokalaemia, and hypophosphataemia in 2 patients (50.0%) each in the 120 mg QOD arm, hyperphosphataemia in 6 patients (100%), stomatitis and serous retinal detachment in 4 patients (66.7%) each, nausea and pyrexia in 3 patients (50.0%) each in the 160 mg QOD arm, nausea, decreased appetite, and hyperphosphataemia in 3 patients (100%) each, constipation, stomatitis, vomiting, influenza like illness, insomnia, and alopecia in 2 patients (66.7%) each in the 16 mg QD arm, and hyperphosphataemia in 7 patients (100%), constipation and nausea in 5 patients (71.4%) each, and decreased appetite in 3 patients (42.9%) in the 20 mg QD arm.

Serious adverse events occurred in 0 patients in the 8 mg QOD, 16 mg QOD, and 24 mg QOD arms, 1 of 3 patients (33.3%) in the 36 mg QOD arm, 3 of 7 patients (42.9%) in the 56 mg QOD arm, 4 of 6 patients (66.7%) in the 80 mg QOD arm, 2 of 4 patients (50.0%) in the 120 mg QOD arm, 3 of 6 patients (50.0%) in the 160 mg QOD arm, 2 of 3 patients (66.7%) in the 16 mg QD arm, and 2 of 7 patients (28.6%) in the 20 mg QD arm. Serious adverse events reported by ≥2 patients in each arm were disease progression in 2 patients (50.0%) in the 80 mg QOD arm (none in the 8 mg QOD, 16 mg QOD, 24 mg QOD, 36 mg QOD, 56 mg QOD, 120 mg QOD, 160 mg QOD, 16 mg QD, and 20 mg QD arms), and a causal relationship to futibatinib was denied.

There were no adverse events leading to treatment discontinuation of futibatinib.

7.3.1.2 Dose-expansion part

Adverse events occurred in all patients, and adverse events for which a causal relationship to futibatinib could not be ruled out occurred in 3 of 5 patients (60.0%) in the 56 mg QOD arm, 2 of 3 patients (66.7%) in the 80 mg QOD arm, 3 of 3 patients (100%) in the 120 mg QOD arm, 2 of 2 patients (100%) in the 16 mg QD arm, and 31 of 31 patients (100%) in the 20 mg QD arm. Adverse events with an incidence of ≥40% in each arm were pyrexia, weight decreased, hyperphosphataemia and dry skin in 3 patients (60.0%) each, nausea, vomiting and blood creatinine increased in 2 patients (40.0%) each in the 56 mg QOD arm, hyperphosphataemia and dyspnoea in 2 patients (66.7%) each in the 80 mg QOD arm, hyperphosphataemia in 3 patients (100%), nausea, decreased appetite, and cancer pain in 2 patients (66.7%) each in the 120 mg QOD arm, diarrhoea and hyperphosphataemia in 2 patients (100%) each, vision blurred, constipation, nausea, fatigue, paronychia, decreased appetite, hypophosphataemia, back pain, palmar-plantar erythrodysaesthesia syndrome, and rash in 1 patient (50.0%) each in the 16 mg QD arm, and hyperphosphataemia in 31 patients (100%) and decreased appetite in 18 patients (58.1%) in the 20 mg QD arm.

Serious adverse events occurred in 3 of 5 patients (60.0%) in the 56 mg QOD arm, 2 of 3 patients (66.7%) in the 80 mg QOD arm, 0 patients in the 120 mg QOD and 16 mg QD arms, and 9 of 31 patients (29.0%) in the 20 mg QD arm. Serious adverse events reported by ≥2 patients in each arm were bile duct obstruction in 2 patients (6.5%) in the 20 mg QD arm (none in the 56 mg QOD, 80 mg QOD, 120 mg QOD, and 16 mg QD arms). A causal relationship to futibatinib was denied.

Adverse events leading to treatment discontinuation of futibatinib occurred in 1 of 5 patients (20.0%) in the 56 mg QOD arm, 0 patients in the 80 mg QOD, 120 mg QOD, and 16 mg QD arms, and 1 of 31 patients (3.2%) in the 20 mg QD arm. Adverse events leading to treatment discontinuation of futibatinib

in each arm were duodenal obstruction in the 56 mg QOD arm and pulmonary tumour thrombotic microangiopathy in the 20 mg QD arm, and a causal relationship to futibatinib was denied for both events.

7.3.2 Global phase I/II study (Study 101)

7.3.2.1 Phase I dose-escalation part

Adverse events occurred in all patients, and adverse events for which a causal relationship to futibatinib could not be ruled out occurred in 5 of 6 patients (83.3%) in the 8 mg QOD arm, 3 of 3 patients (100%) in the 16 mg QOD arm, 2 of 3 patients (66.7%) in the 24 mg QOD arm, 2 of 3 patients (66.7%) in the 36 mg QOD arm, 3 of 3 patients (100%) in the 56 mg QOD arm, 5 of 5 patients (100%) in the 80 mg QOD arm, 3 of 4 patients (75.0%) in the 120 mg QOD arm, 8 of 8 patients (100%) in the 160 mg QOD arm, 6 of 7 patients (85.7%) in the 200 mg QOD arm, 4 of 4 patients (100%) in the 4 mg QD arm, 4 of 5 patients (80.0%) in the 8 mg QD arm, 12 of 14 patients (85.7%) in the 16 mg QD arm, 7 of 7 patients (100%) in the 20 mg QD arm, and 14 of 14 patients (100%) in the 24 mg QD arm. Adverse events with an incidence of ≥40% in each arm were diarrhoea in 3 patients (100%), asthenia in 2 patients (66.7%) in the 16 mg QOD arm, abdominal pain upper, dry mouth, and decreased appetite in 2 patients (66.7%) each in the 36 mg QOD arm, pyrexia, lipase increased, platelet count increased, and pruritus in 2 patients (66.7%) each in the 56 mg QOD arm, hyperphosphataemia in 4 patients (80.0%), nausea and hypomagnesaemia in 2 patients (40.0%) each in the 80 mg QOD arm, dry mouth and hyperphosphataemia in 3 patients (75.0%) each, anaemia, constipation, diarrhoea, nausea, vomiting, urinary tract infection, and hyponatraemia in 2 patients (50.0%) each in the 120 mg QOD arm, diarrhoea and hyperphosphataemia in 6 patients (75.0%) each, anaemia and constipation in 4 patients (50.0%) each in the 160 mg QOD arm, hyperphosphataemia in 6 patients (85.7%), abdominal pain, diarrhoea, nausea, and ALT increased in 3 patients (42.9%) each in the 200 mg QOD arm, dry mouth in 2 patients (50.0%) in the 4 mg QD arm, decreased appetite and hyperphosphataemia in 2 patients (40.0%) each in the 8 mg QD arm, hyperphosphataemia in 9 patients (64.3%) in the 16 mg QD arm, hyperphosphataemia in 6 patients (85.7%), constipation in 4 patients (57.1%), anaemia, diarrhoea, ALT increased, and AST increased in 3 patients (42.9%) each in the 20 mg QD arm, and hyperphosphataemia in 12 patients (85.7%), constipation and diarrhoea in 7 patients (50.0%) each, and ALT increased in 6 patients (42.9%) in the 24 mg QD arm (none in the 8 mg QOD and 24 mg QOD arms).

Serious adverse events occurred in 1 of 6 patients (16.7%) in the 8 mg QOD arm, 0 patients in the 16 mg QOD arm, 1 of 3 patients (33.3%) in the 24 mg QOD arm, 1 of 3 patients (33.3%) in the 36 mg QOD arm, 1 of 3 patients (33.3%) in the 56 mg QOD arm, 2 of 5 patients (40.0%) in the 80 mg QOD arm, 4 of 4 patients (100%) in the 120 mg QOD arm, 7 of 8 patients (87.5%) in the 160 mg QOD arm, 4 of 7 patients (57.1%) in the 200 mg QOD arm, 0 patients in the 4 mg QD arm, 1 of 5 patients (20.0%) in the 8 mg QD arm, 9 of 14 patients (64.3%) in the 16 mg QD arm, 3 of 7 patients (42.9%) in the 20 mg QD arm, and 6 of 14 patients (42.9%) in the 24 mg QD arm. Serious adverse events reported by ≥2 patients in each arm were abdominal pain in 2 patients (25.0%) in the 160 mg QOD arm and disease progression in 2 patients (28.6%) in the 20 mg QD arm (none in the 8 mg QOD, 16 mg QOD, 24 mg QOD, 36 mg QOD, 56 mg QOD, 80 mg QOD, 120 mg QOD, 200 mg QOD, 4 mg QD, 8 mg QD, 16 mg QD, and 24 mg QD arms). A causal relationship to futibatinib was denied for all events.

Adverse events leading to treatment discontinuation of futibatinib occurred in 1 of 4 patients (25.0%) in the 120 mg QOD arm and 2 of 14 patients (14.3%) in the 24 mg QD arm, and no such events occurred in other arms. Adverse events leading to treatment discontinuation of futibatinib were hemiparesis in 1 patient (25.0%) in the 120 mg QOD arm and nausea, vomiting, and spinal cord compression in 1 patient (7.1%) each in the 24 mg QD arm. A causal relationship to futibatinib could not be ruled out for nausea and vomiting in 1 patient (7.1%) each in the 24 mg QD arm.

7.3.2.2 Phase I dose-expansion part

Adverse events occurred in 27 of 27 patients (100%) in the 16 mg QD arm; and 57 of 57 patients (100%) in Cohort 1, 34 of 34 patients (100%) in Cohort 2, 15 of 15 patients (100%) in Cohort 3, 13 of 13 patients (100%) in Cohort 4, 23 of 24 patients (95.8%) in Cohort 5, 26 of 27 patients (96.3%) in Cohort 6 in the 20 mg QD arm, and adverse events for which a causal relationship to futibatinib could not be ruled out occurred in 27 of 27 patients (100%) in the 16 mg QD arm, 55 of 57 patients (96.5%) in Cohort 1, 33 of 34 patients (97.1%) in Cohort 2, 12 of 15 patients (80.0%) in Cohort 3, 13 of 13 patients (100%) in Cohort 4, 23 of 24 patients (95.8%) in Cohort 5, and 26 of 27 patients (96.3%) in Cohort 6 in the 20 mg QD arm. Adverse events with an incidence of ≥30% were hyperphosphataemia in 22 patients (81.5%), nausea in 12 patients (44.4%), diarrhoea in 10 patients (37.0%), and constipation in 9 patients (33.3%) in the 16 mg QD arm, hyperphosphataemia in 48 patients (84.2%), nausea in 22 patients (38.6%), and alopecia in 18 patients (31.6%) in Cohort 1, hyperphosphataemia in 30 patients (88.2%), ALT increased in 14 patients (41.2%), diarrhoea in 12 patients (35.3%) in Cohort 2, hyperphosphataemia in 9 patients (60.0%), and constipation in 5 patients (33.3%) in Cohort 3, hyperphosphataemia in 12 patients (92.3%), fatigue and AST increased in 5 patients (38.5%) each, and ALT increased in 4 patients (30.8%) in Cohort 4, hyperphosphataemia in 19 patients (79.2%), diarrhoea in 11 patients (45.8%), constipation in 9 patients (37.5%), and fatigue in 8 patients (33.3%) in Cohort 5, and hyperphosphataemia in 21 patients (77.8%), nausea in 13 patients (48.1%), constipation in 11 patients (40.7%), and diarrhoea in 10 patients (37.0%) in Cohort 6 in the 20 mg QD arm.

Serious adverse events occurred in 4 of 27 patients (14.8%) in the 16 mg QD arm, 26 of 57 patients (45.6%) in Cohort 1, 13 of 34 patients (38.2%) in Cohort 2, 10 of 15 patients (66.7%) in Cohort 3, 9 of 13 patients (69.2%) in Cohort 4, 11 of 24 patients (45.8%) in Cohort 5, and 13 of 27 patients (48.1%) in Cohort 6 in the 20 mg QD arm. Serious adverse events reported by ≥2 patients in each arm were abdominal pain and sepsis in 3 patients (5.3%) each, colitis, intestinal obstruction, hepatic failure, biliary tract infection, disease progression, dehydration, blood bilirubin increased, and acute renal failure in 2 patients (3.5%) each in Cohort 1, headache in 2 patients (5.9%) in Cohort 2, disease progression in 3 patients (20.0%) in Cohort 3, sepsis in 3 patients (11.1%) in Cohort 6 in the 20 mg QD arm (none in the 16 mg QD arm, and in Cohort 4 and 5 in the 20 mg QD arm), and a causal relationship to futibatinib could not be ruled out for intestinal obstruction in 2 patients (3.5%) and blood bilirubin increased in 1 patient (1.8%) in Cohort 1 in the 20 mg QD arm.

Adverse events leading to treatment discontinuation of futibatinib occurred in 1 of 27 patients (3.7%) in the 16 mg QD arm, 5 of 57 patients (8.8%) in Cohort 1, 3 of 34 patients (8.8%) in Cohort 2, 3 of 15 patients (20.0%) in Cohort 3, 2 of 13 patients (15.4%) in Cohort 4, 4 of 24 patients (16.7%) in Cohort 5, and 4 of 27 patients (14.8%) in Cohort 6 in the 20 mg QD arm. Adverse events leading to treatment

discontinuation of futibatinib reported in each arm were asthenia in 1 patient (3.7%) in the 16 mg QD arm, cholangitis acute, portal vein thrombosis, cataract, oesophageal ulcer, stomatitis, pyrexia, spinal compression fracture, and back pain in 1 patient (1.8%) each in Cohort 1, gait disturbance, general physical health deterioration, muscular weakness, and hemiparesis in 1 patient (2.9%) each in Cohort 2, diarrhoea, gastrointestinal haemorrhage, fatigue, decreased appetite, and onycholysis in 1 patient (6.7%) each in Cohort 3, intestinal obstruction and pancreatitis acute in 1 patient (7.7%) each in Cohort 4, retinal detachment, fatigue, decreased appetite, muscular weakness, eczema, and intestinal obstruction in 1 patient (4.2%) each in Cohort 5, and diarrhoea, duodenal obstruction, nausea, vomiting, fatigue, pulmonary embolism, and anaemia in 1 patient (3.7%) each in Cohort 6 in the 20 mg QD arm. A causal relationship to futibatinib could not be ruled out for stomatitis and cataract in 1 patient (1.8%) each in Cohort 1, diarrhoea, fatigue, decreased appetite, and onycholysis in 1 patient (6.7%) each in Cohort 3, retinal detachment and eczema in 1 patient (4.2%) each in Cohort 5, and diarrhoea, nausea, and vomiting in 1 patient (3.7%) each in Cohort 6 in the 20 mg QD arm.

7.3.2.3 Phase II part

Adverse events occurred in all the patients, and adverse events for which a causal relationship to futibatinib could not be ruled out occurred in 102 of 103 patients (99.0%). Table 41 shows adverse events with an incidence of ≥20%.

Table 41. Adverse events with incidence of ≥20%

SOC PT (MedDRA ver.22.0)	Number of patients (%) n = 103	
	All Grades	Grade ≥3
All adverse events	103 (100)	79 (76.7)
Eye disorders		
Dry eye	22 (21.4)	1 (1.0)
Gastrointestinal disorders		
Constipation	40 (38.8)	0
Diarrhoea	37 (35.9)	1 (1.0)
Dry mouth	36 (35.0)	0
Nausea	25 (24.3)	2 (1.9)
Stomatitis	25 (24.3)	6 (5.8)
Abdominal pain	22 (21.4)	3 (2.9)
General disorders and administration site conditions		
Fatigue	35 (34.0)	8 (7.8)
Investigations		
AST increased	26 (25.2)	10 (9.7)
Metabolism and nutrition disorders		
Hyperphosphataemia	88 (85.4)	31 (30.1)
Decreased appetite	24 (23.3)	3 (2.9)
Musculoskeletal and connective tissue disorders		
Arthralgia	23 (22.3)	0
Nervous system disorders		
Dysgeusia	21 (20.4)	0
Skin and subcutaneous tissue disorders		
Alopecia	35 (34.0)	0
Dry skin	30 (29.1)	0
Palmar-plantar erythrodysaesthesia syndrome	22 (21.4)	5 (4.9)

Serious adverse events occurred in 40 of 103 patients (38.8%). Serious adverse events reported by ≥2 patients were disease progression in 5 patients (4.9%), pyrexia in 4 patients (3.9%), ascites, upper gastrointestinal haemorrhage, and bile duct obstruction in 3 patients (2.9%) each, sepsis, urinary tract infection, fall, decreased appetite, dehydration, tumour pain, migraine, transient ischaemic attack, and

dyspnoea in 2 patients (1.9%) each. A causal relationship to futibatinib could not be ruled out for migraine in 2 patients (1.9%), pyrexia, upper gastrointestinal haemorrhage, urinary tract infection, and transient ischaemic attack in 1 patient (1.0%) each.

Adverse events leading to treatment discontinuation of futibatinib occurred in 8 of 103 patients (7.8%). Adverse events leading to treatment discontinuation of futibatinib were anaemia, oesophagitis, oral dysaesthesia, stomatitis, bile duct obstruction, hypoglycaemia, metastases to central nervous system, tumour pain, dizziness, and pharyngeal inflammation in 1 patient (1.0%) each. A causal relationship to futibatinib could not be ruled out for oesophagitis, oral dysaesthesia, stomatitis, and pharyngeal inflammation in 1 patient (1.0%) each.

7.3.3 Foreign phase I study (Study 102)

Adverse events occurred in 2 of 16 patients (12.5%) who received futibatinib in the fasted state and 1 of 16 subjects (6.3%) who received futibatinib after the high-fat meal. There were no adverse events for which a causal relationship to futibatinib could not be ruled out. There were no adverse events reported by ≥2 subjects after each dose.

There were no serious adverse events or adverse events leading to discontinuation of the study drug.

7.3.4 Foreign phase I study (Study 103)

7.3.4.1 Part 1

Adverse events occurred in 5 of 20 patients (25.0%) receiving futibatinib alone (Period A), 7 of 20 patients (35.0%) receiving itraconazole alone (Period B1), and 2 of 20 subjects (10.0%) receiving combination of futibatinib with itraconazole (Period B2), and adverse events for which a causal relationship to futibatinib could not be ruled out occurred in 1 of 20 patients (5.0%) in Period A, 0 patients in Period B1, and 0 patients in Period B2. In patients receiving futibatinib in Period A and Period B2, there were no adverse events with an incidence of ≥10%.

There were no serious adverse events or adverse events leading to discontinuation of the study drug.

7.3.4.2 Part 2

Adverse events occurred in 0 of 20 patients receiving futibatinib, 10 of 20 patients (50.0%) receiving rifampicin alone (Period D1), and 2 of 20 patients (10.0%) receiving combination of futibatinib with rifampicin (Period D2). There were no adverse events for which a causal relationship to futibatinib could not be ruled out. In patients receiving futibatinib and in Period D2, there were no adverse events with an incidence of ≥10%.

There were no serious adverse events or adverse events leading to discontinuation of the study drug.

7.3.4 Foreign phase I study (Study 020)

Adverse events occurred in 1 of 24 patients (4.2%), and adverse events for which a causal relationship to futibatinib could not be ruled out occurred in 1 of 24 subjects (4.2%). There were no adverse events with an incidence of ≥10%.

There were no serious adverse events or adverse events leading to discontinuation of the study drug.

7.3.5 Foreign phase I study (Study 104)

Adverse events occurred in 3 of 20 patients (15.0%) receiving futibatinib alone (Period A), 6 of 20 patients (30.0%) receiving lansoprazole alone (Period B1), and 5 of 20 patients (25.0%) receiving combination of futibatinib with lansoprazole (Period B2). There were no adverse events for which a causal relationship to futibatinib could not be ruled out. In patients receiving futibatinib in Period A and Period B2, adverse events with an incidence of ≥10% were headache in 2 patients (10.0%) in Period B2 (none in Period A).

There were no serious adverse events or adverse events leading to discontinuation of the study drug.

7.3.6 Foreign phase I study (Study 105)

Adverse events occurred in 4 of 24 patients (16.7%) receiving midazolam alone (Period A), 3 of 24 patients (12.5%) receiving futibatinib alone (Period B1), and 8 of 24 patients (33.3%) receiving combination of futibatinib with midazolam (Period B2). In patients receiving futibatinib, adverse events for which a causal relationship to futibatinib could not be ruled out occurred in 3 of 24 patients (12.5%) in Period B1 and 8 of 24 patients (33.3%) in Period B2. In patients in Period B1 and Period B2, adverse events with an incidence of ≥10% were diarrhoea in 5 patients (20.8%) and abdominal pain in 3 patients (12.5%) in Period B2.

There were no serious adverse events or adverse events leading to discontinuation of the study drug.

7.3.7 Foreign phase I study (Study 106)

Adverse events occurred in 2 of 6 patients (33.3%), and adverse events for which a causal relationship to futibatinib could not be ruled out occurred in 1 of 6 patients (16.7%). Adverse events reported by ≥2 patients were skin laceration in 2 patients (33.3%).

There were no serious adverse events or adverse events leading to discontinuation of the study drug.

7.3.8 Foreign phase I study (Study 107)

Adverse events occurred in 7 of 45 patients (15.6%) receiving futibatinib 20 mg (Period A), 7 of 47 patients (14.9%) receiving futibatinib 80 mg (Period B), 9 of 47 patients (19.1%) receiving placebo (Period C), and 6 of 47 patients (12.8%) receiving moxifloxacin (Period D), and adverse events for which a causal relationship to futibatinib could not be ruled out occurred in 3 of 45 patients (6.7%) in Period A, 1 of 47 patients (2.1%) in Period B, 2 of 47 patients (4.3%) in Period C, and 1 of 47 patients (2.1%) in Period D. There were no adverse events with an incidence of ≥10% during any period.

There were no serious adverse events or adverse events leading to discontinuation of the study drug.

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

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

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

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

The new drug application data (CTD 5.3.5.2.2) were subjected to an on-site GCP inspection, in accordance with the provisions of the Act on Securing Quality, Efficacy and Safety of Products Including Pharmaceuticals and Medical Devices. On the basis of the inspection, PMDA concluded that there were no obstacles to conducting its review based on the application documents submitted.

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

On the basis of the data submitted, PMDA has concluded that futibatinib has a certain level of efficacy in the treatment of unresectable *FGFR2* gene fusion-positive biliary tract cancer that has progressed after cancer chemotherapy, and that futibatinib has acceptable safety in view of its benefits. Futibatinib is a drug with a new active ingredient that is presumed to inhibit tyrosine kinase of FGFR and considered as a clinically meaningful treatment option for patients with unresectable *FGFR2* gene fusion-positive biliary tract cancer that has progressed after cancer chemotherapy. In addition, PMDA considers that the efficacy, indication, etc. need to be further investigated.

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

Review Report (2)

May 15, 2023

Product Submitted for Approval

Brand Name	Lytgobi tablets 4 mg
Non-proprietary Name	Futibatinib
Applicant	Taiho Pharmaceutical Co., Ltd.
Date of Application	July 28, 2022

List of Abbreviations

See Appendix.

1. Content of the Review

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

1.1 Efficacy

In view of the following results from the phase II part of the global phase I/II study (Study 101) in patients with unresectable, intrahepatic cholangiocarcinoma harboring *FGFR2* gene fusion or *FGFR2* gene rearrangement who received prior chemotherapy and oncobiological meanings of the *FGFR2* gene fusion and *FGFR2* gene rearrangement [see Section 7.R.2.1], PMDA has concluded that futibatinib has demonstrated a certain level of efficacy in the concerned patient population.

- The primary endpoint, the response rate [95% CI] as determined by IRC according to RECIST ver.1.1 was 41.7% [32.1%, 51.9%] (43 of 103 patients), and the lower limit of 95% confidence interval exceeded the threshold response rate (10%).
- The response rates [95% CI] in populations of patients harboring *FGFR2* gene fusion and of patients harboring *FGFR2* gene rearrangement were 44.6% [33.0%, 56.6%] (33 of 74 patients) and 33.3% [14.6%, 57.0%] (7 of 21 patients), respectively, and no distinct difference was noted in response rate between these populations.

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

1.2 Safety

As a result of the review in Section "7.R.3 Safety" of the Review Report (1), PMDA has concluded that adverse events requiring special attention during use of futibatinib in patients with unresectable, intrahepatic cholangiocarcinoma harboring *FGFR2* gene fusion or *FGFR2* gene rearrangement that has

progressed after cancer chemotherapy are hyperphosphataemia, retinal detachment, eye disorders (except retinal detachment), nail disorders, palmar-plantar erythrodysaesthesia syndrome, and acute kidney injury.

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

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

1.3 Clinical positioning and indication

As a result of the review in Sections "7.R.4 Clinical positioning and indication" of the Review Report (1), PMDA has concluded that the Indication of futibatinib should be defined as "unresectable *FGFR2* gene fusion-positive biliary tract cancer that has progressed after cancer chemotherapy" with the following cautionary statements included in the Precautions Concerning Indication section.

Precautions Concerning Indication

- The efficacy and safety of futibatinib as the first-line therapy have not been established.
- The efficacy and safety of futibatinib have not been established for use in postoperative adjuvant chemotherapy.
- Appropriate patients should be selected by physicians with a full understanding of the information about the location of the primary lesion in patients enrolled in clinical studies presented in the "Clinical Studies" section and of the efficacy and safety of futibatinib.
- Futibatinib should be used in patients harboring *FGFR2* gene fusion confirmed by adequately experienced pathologists or testing at qualified laboratories. The testing should be performed using approved *in vitro* diagnostics or medical devices.

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

PMDA thus instructed the applicant to specify the Indication and the Precautions Concerning Indication section as presented above and the applicant accepted it.

1.4 Dosage and administration

As a result of the review in Section "7.R.5 Dosage and administration" of the Review Report (1), PMDA has concluded that the Dosage and Administration of futibatinib should be "The usual adult dosage is 20 mg of futibatinib administered orally once daily in the fasted state. The dose may be reduced according to the patient's condition." with the following cautionary statements included in the Precautions Concerning Dosage and Administration section.

Precautions Concerning Dosage and Administration

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

- C_{max} and AUC of futibatinib decrease when administered after a meal. To avoid food effect, futibatinib should be taken on an empty stomach (2 hours after and 1 hour before a meal).
- If any adverse drug reaction occurs after use of futibatinib, futibatinib should be interrupted, reduced in dose, or discontinued in accordance with the following criteria.

Guide for dose reduction

Dose reduction level	Dose
Usual dose	20 mg
1-level reduced dose	16 mg
2-level reduced dose	12 mg
3-level reduced dose	Discontinuation

Criteria for interruption, dose reduction, and discontinuation in response to adverse drug reactions

Adverse drug reaction	Severity*	Action
Retinal detachment	—	• If symptoms are present or worsening in the ophthalmic evaluation, interrupt futibatinib. • If the symptoms resolve after interruption, resume futibatinib at a next lower dose. If symptoms do not resolve, discontinue futibatinib.
Hyperphosphataemia	Serum phosphate levels ≥5.5 mg/dL and ≤7 mg/dL	• Start phosphate lowering therapy in addition to limitation of phosphate-rich food intake.
	Serum phosphate levels >7 mg/dL and ≤10 mg/dL	• Reduce futibatinib to next lower dose and start phosphate lowering therapy in addition to limitation of phosphate-rich food intake. • If the serum phosphate resolves to ≤7 mg/dL within 2 weeks after 1-level dose reduction, continue futibatinib at this reduced dose. • If the serum phosphate level is not resolved to ≤7 mg/dL within 2 weeks after 1-level dose reduction, further reduce the dose to the next lower dose. • If the serum phosphate level is not resolved to ≤7 mg/dL within 2 weeks after the 2-level dose reduction, interrupt futibatinib until serum phosphate is ≤7 mg/dL. If resolved to ≤7 mg/dL after interruption, resume futibatinib at the dose prior to interruption.
	Serum phosphate levels >10 mg/dL	• Start phosphate lowering therapy in addition to limitation of phosphate-rich food intake. • Interrupt futibatinib until serum phosphate level is ≤7 mg/dL. If the serum phosphate level resolved to ≤7 mg/dL after interruption, resume futibatinib at a next lower dose. • If the serum phosphate level is >10 mg/dL after the 2-level dose reduction, discontinue futibatinib.
Other adverse drug reactions	Grade 3	• Interrupt futibatinib until toxicity resolves to Grade ≤1 or baseline. After recovery, resume futibatinib at a next lower dose. For hematological toxicities resolving within 1 week, resume futibatinib at the same dose prior to interruption.
	Grade 4	• Discontinue futibatinib.

* Graded according to NCI-CTCAE ver.4.03.

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

PMDA thus instructed the applicant to specify the Dosage and Administration and the Precautions Concerning Dosage and Administration section as presented above and the applicant accepted it.

1.5 Risk management plan (draft)

The applicant plans to conduct a post-marketing surveillance in all patients treated with futibatinib to evaluate the post-marketing safety, etc. of futibatinib in routine clinical practice. The safety specification includes hyperphosphataemia, serous retinal detachment, and use of futibatinib in patients with

moderate or severe hepatic impairment. The planned sample size is 120 patients and observation period is 1 year.

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

PMDA further concluded on the surveillance plan as follows:

- The safety specification in the surveillance should be hyperphosphataemia, retinal detachment, eye disorders (except retinal detachment), nail disorders, palmar-plantar erythrodysaesthesia syndrome, and acute kidney injury, and information including safety of futibatinib used in patients with hepatic impairment should also be collected.
- The planned sample size and observation period for the surveillance should be reconsidered in view of incidences of the events in clinical studies to be included in the safety specification.

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

On the basis of the above discussion, PMDA instructed the applicant to reconsider the surveillance plan.

The applicant's response:

- The safety specification of the surveillance will include hyperphosphataemia, retinal detachment, eye disorders (except retinal detachment), nail disorders, palmar-plantar erythrodysaesthesia syndrome, acute kidney injury, and use of futibatinib in patients with hepatic impairment.
- The planned sample size and observation period in the surveillance will be 107 patients and 1 year, respectively, based on incidences of the events in clinical studies 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 futibatinib should include the safety specification presented in Table 42, and that the applicant should conduct additional pharmacovigilance activities and additional risk minimization activities presented in Tables 43 and 44.

Table 42. Safety and efficacy specifications in the risk management plan (draft)

Safety specification		
Important identified risks	Important potential risks	Important missing information
• Hyperphosphataemia • Retinal detachment	• Eye disorders (except retinal detachment) • Nail disorders • Palmar-plantar erythrodysaesthesia syndrome • Acute kidney injury • Use in patients with hepatic impairment • Embryo-fetal toxicity	None
Efficacy specification		
None		

Table 43. Summary of additional pharmacovigilance activities, efficacy survey and studies, and additional risk minimization activities included under the risk management plan (draft)

Additional pharmacovigilance activities	Efficacy survey and studies	Additional risk minimization activities
• Early post-marketing phase vigilance • Use-results survey (all-case surveillance)	None	• Disseminate data gathered during early post-marketing phase vigilance • Organize and disseminate materials for healthcare professionals • Organize and disseminate materials for patients

Table 44. Outline of use-results survey (draft)

Objective	To investigate the post-marketing safety, etc. of futibatinib in routine clinical practice
Survey method	All-case surveillance
Population	All patients treated with futibatinib
Observation period	1 year
Planned sample size	107 patients
Main survey items	Safety specification: Hyperphosphataemia, retinal detachment, eye disorders (except retinal detachment), nail disorders, palmar-plantar erythrodysaesthesia syndrome, acute kidney injury and use in patients with hepatic impairment Other main survey items: Patient characteristics (age, sex, location of the primary lesion, prior treatment, medical history or complications, severity of hepatic impairment, etc.), details on the administration of futibatinib, adverse events, etc.

2. Overall Evaluation

As a result of the above review, PMDA has concluded that the product may be approved for the indication and dosage and administration shown below, with the following approval conditions, provided that the package insert includes appropriate cautionary statements; information about the proper use is appropriately communicated in post-marketing settings; and the product is properly used by physicians with adequate knowledge and experience in cancer chemotherapy at a medical institution capable of emergency response. The product is a drug with a new active ingredient, and the re-examination period is 8 years. The product is not classified as a biological product or a specified biological product. The drug product and its drug substance are both classified as powerful drugs.

Indication

Unresectable *FGFR2* gene fusion-positive biliary tract cancer that has progressed after cancer chemotherapy

Dosage and Administration

The usual adult dosage is 20 mg of futibatinib administered orally once daily in the fasted state. The dose may be reduced according to the patient's condition.

Approval Conditions

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

Warnings

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

Contraindication

Patients with a history of hypersensitivity to the product or any of the excipients

Precautions Concerning Indication

1. The efficacy and safety of futibatinib as the first-line therapy have not been established.
2. The efficacy and safety of futibatinib have not been established for use in postoperative adjuvant chemotherapy.
3. Appropriate patients should be selected by physicians with a full understanding of the information about the location of the primary lesion in patients enrolled in clinical studies presented in the “Clinical Studies” section and of the efficacy and safety of futibatinib.
4. Futibatinib should be used in patients harboring *FGFR2* gene fusion confirmed by adequately experienced pathologists or testing at qualified laboratories. The testing should be performed using approved *in vitro* diagnostics or medical devices.

Precautions Concerning Dosage and Administration

1. The efficacy and safety of futibatinib have not been established for use in combination with other antineoplastic agents.
2. C_{max} and AUC of futibatinib decrease when administered after a meal. To avoid food effect, futibatinib should be taken on an empty stomach (2 hours after and 1 hour before a meal).
3. If any adverse drug reaction occurs after use of futibatinib, futibatinib should be interrupted, reduced in dose, or discontinued in accordance with the following criteria.

Guide for dose reduction

Dose reduction level	Dose
Usual dose	20 mg
1-level reduced dose	16 mg
2-level reduced dose	12 mg
3-level reduced dose	Discontinuation

Criteria for interruption, dose reduction, and discontinuation in response to adverse drug reactions

Adverse drug reaction	Severity*	Action
Retinal detachment	—	• If symptoms are present or worsening in the ophthalmic evaluation, interrupt futibatinib. • If the symptoms resolve after interruption, resume futibatinib at a next lower dose. If symptoms do not resolve, discontinue futibatinib.
Hyperphosphataemia	Serum phosphate levels ≥5.5 mg/dL and ≤7 mg/dL	• Start phosphate lowering therapy in addition to limitation of phosphate-rich food intake.
	Serum phosphate levels >7 mg/dL and ≤10 mg/dL	• Reduce futibatinib to next lower dose and start phosphate lowering therapy in addition to limitation of phosphate-rich food intake. • If the serum phosphate resolves to ≤7 mg/dL within 2 weeks after 1-level dose reduction, continue futibatinib at this reduced dose. • If the serum phosphate level is not resolved to ≤7 mg/dL within 2 weeks after 1-level dose reduction, further reduce the dose to the next lower dose. • If the serum phosphate level is not resolved to ≤7 mg/dL within 2 weeks after the 2-level dose reduction, interrupt futibatinib until serum phosphate is ≤7 mg/dL. If resolved to ≤7 mg/dL after interruption, resume futibatinib at the dose prior to interruption.
	Serum phosphate levels >10 mg/dL	• Start phosphate lowering therapy in addition to limitation of phosphate-rich food intake. • Interrupt futibatinib until serum phosphate level is ≤7 mg/dL. If the serum phosphate level resolved to ≤7 mg/dL after interruption, resume futibatinib at a next lower dose. • If the serum phosphate level is >10 mg/dL after the 2-level dose reduction, discontinue futibatinib.
Other adverse drug reactions	Grade 3	• Interrupt futibatinib until toxicity resolves to Grade ≤1 or baseline. After recovery, resume futibatinib at a next lower dose. For hematological toxicities resolving within 1 week, resume futibatinib at the same dose prior to interruption.
	Grade 4	• Discontinue futibatinib.

* Graded according to NCI-CTCAE ver.4.03.

Appendix

List of Abbreviations

AKT	protein kinase B
ALAG	absorption lag time
ALP	alkaline phosphatase
ALT	alanine aminotransferase
Application	Application for marketing approval
APTT	activated partial thromboplastin time
AST	aspartate aminotransferase
ATP	adenosine triphosphate
BCRP	breast cancer resistance protein
BUN	blood urea nitrogen
CGH	comparative genomic hybridization
CI	confidence interval
CLcr	creatinine clearance
CMV	cytomegalovirus
CPP	critical process parameter
CQA	critical quality attribute
CR	complete response
CRP	C reactive protein
CYP	cytochrome P450
^{14}C-futibatinib	^{14}C-labeled futibatinib
D1	duration of zero-order input
DLT	dose-limiting toxicity
DMSO	dimethyl sulfoxide
ECOG	Eastern Cooperative Oncology Group
efflux ratio	The ratio of secretion permeability coefficient in the secretive direction to that in the absorptive direction
ELISA	enzyme-linked immunosorbent assay
ERK	extracellular signal-regulated kinase
ESMO guideline	Biliary cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up
F	relative bioavailability
FGF	fibroblast growth factor
FGFR	fibroblast growth factor receptor
FISH	fluorescence *in situ* hybridization
FRS2	fibroblast growth factor receptor substrate 2
Futibatinib	Futibatinib
GC	gas chromatography
GGT	γ-glutamyltransferase
hERG	human *ether-a-go-go* related gene
HPLC	high performance liquid chromatography

HPMC	hydroxypropylmethylcellulose
IC_{50}	concentration that results in 50% inhibition
ICH Q1E guideline	"Guideline on Evaluation of Stability Data" (PFSB/ELD Notification No. 0603004, dated June 3, 2003)
IHC	immunohistochemistry
IL-2	interleukin-2
IR	infrared absorption spectroscopy
IRC	independent review committee
ka	first-order absorption rate constant
K_I	concentration causing half-maximal inactivation
K_i	inhibition constant
k_{inact}	maximum inactivation rate constant
LC-MS/MS	liquid chromatography-tandem mass spectrometry
MAPK	mitogen-activated protein kinase
MATE	multidrug and toxin extrusion
MedDRA	Medical Dictionary for Regulatory Activities
MEK	mitogen-activated protein kinase/extracellular signal-regulated kinase kinase
MPE	mean photo effect
mRNA	messenger ribonucleic acid
MS	mass spectrometry
MTD	maximum tolerated dose
NADPH	nicotinamide adenine dinucleotide phosphate hydrogen
NCCN guideline	National Comprehensive Cancer Network Clinical Practice Guidelines in Oncology, Hepatobiliary Cancers
NE	not evaluable
NGS	next generation sequencing
NMR	nuclear magnetic resonance spectroscopy
NOD/SCID mouse	non-obese diabetic/severe combined immunodeficiency mouse
OAT	organic anion transporter
OATP	organic anion transporting polypeptide
OCT	organic cation transporter
OS	overall survival
$P_{app\ A \rightarrow B}$	apparent permeability in apical to basal direction
PBPK	physiologically based pharmacokinetics
PD	progressive disease
PFS	progression free survival
P-gp	P-glycoprotein
PI3K	phosphatidylinositol 3-kinase
PK	pharmacokinetics
PLC-γ	phospholipase C-γ
PMDA	Pharmaceuticals and Medical Devices Agency
PPK	population pharmacokinetics

PR	partial response
PS	performance status
PT	preferred term
PTP	press through packaging
QD	quaque die
QT	QT interval
QTc	QT interval corrected
QTcF	QT interval corrected using Fridericia's formula
ΔΔQTcF	Difference of change in QTcF from baseline between futibatinib and placebo
QW	quaque 1 week
RECIST	Response Evaluation Criteria in Solid Tumors
RET	rearranged during transfection
RP2D	recommended Phase 2 dose
RT-PCR	reverse transcription polymerase chain reaction
SD	stable disease
SMQ	standardised MedDRA queries
SOC	system organ class
STAT	signal transducer and activator of transcription
Study 010	Study 10059010
Study 020	Study 10059020
Study 101	Study TAS-120-101
Study 102	Study TAS-120-102
Study 103	Study TAS-120-103
Study 104	Study TAS-120-104
Study 105	Study TAS-120-105
Study 106	Study TAS-120-106
Study 107	Study TAS-120-107
Study 108	Study TAS-120-108
TACC3	transforming acidic coiled-coil containing protein 3
UV-A	ultraviolet light-A
UV-VIS	ultraviolet-visible spectroscopy
Vc/F	apparent central volume of distribution