CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

214801Orig1s000

MULTI-DISCIPLINE REVIEW

Summary Review
Clinical Review
Non-Clinical Review
Statistical Review
Clinical Pharmacology Review

NDA Multi-disciplinary Review and Evaluation

Disclaimer: FDA review was conducted in conjunction with other regulatory authorities under Project ORBIS. FDA collaborated with Australia's Therapeutic Goods Administration (TGA), and Health Canada (HC). While the conclusions and recommendations expressed herein reflect FDA's completed review of the application, the applications may still be under review at the other regulatory agencies.

In this document, the sections labeled as "Data" and "The Applicant's Position" are completed by the Applicant, which do not necessarily reflect the positions of the FDA or the other Regulatory Authorities.

Application Type	NDA
Application Number(s)	214801
Priority or Standard	Priority
Submit Date(s)	January 31, 2022
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Division/Office	Division of Oncology 3/ Office of Oncologic Diseases
Review Completion Date	Refer to electronic date stamp
Established Name	Futibatinib
(Proposed) Trade Name	Lytgobi
Pharmacologic Class	FGFR inhibitor
Code name	TAS-120
Applicant	Taiho Oncology, Incorporated
Formulation(s)	4 mg tablets
Dosing Regimen	20 mg daily
Applicant Proposed Indication(s)/Population(s)	Treatment of adult patients with previously treated, unresectable, locally advanced or metastatic cholangiocarcinoma harboring FGFR2 gene fusions or other rearrangements.
Recommendation on Regulatory Action	Approval
Recommended Indication(s)/Population(s) (if applicable)	Treatment of adult patients with previously treated, unresectable, locally advanced or metastatic intrahepatic cholangiocarcinoma harboring FGFR2 gene fusions or other rearrangements.

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OPQ=Office of Pharmaceutical Quality
OPDP=Office of Prescription Drug Promotion
OSI=Office of Scientific Investigations
OSE= Office of Surveillance and Epidemiology
DEPI= Division of Epidemiology
DMEPA=Division of Medication Error Prevention and Analysis
DRISK=Division of Risk Management

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Glossary

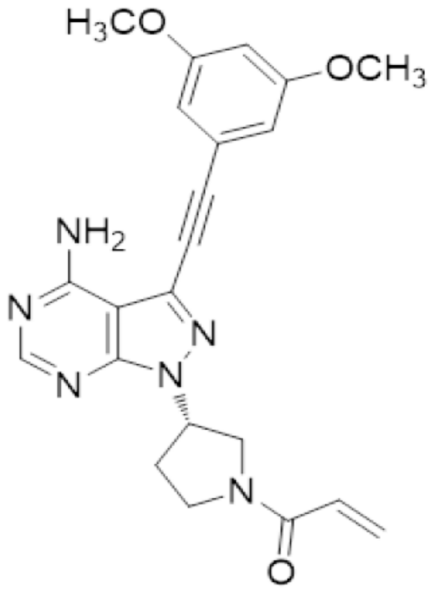
AC	advisory committee
ADME	absorption, distribution, metabolism, excretion
AE	adverse event
BLA	biologics license application
BPCA	Best Pharmaceuticals for Children Act
BRF	Benefit Risk Framework
CBER	Center for Biologics Evaluation and Research
CDER	Center for Drug Evaluation and Research
CDRH	Center for Devices and Radiological Health
CDTL	Cross-Discipline Team Leader
CFR	Code of Federal Regulations
CMC	chemistry, manufacturing, and controls
COSTART	Coding Symbols for Thesaurus of Adverse Reaction Terms
CRF	case report form
CRO	contract research organization
CRT	clinical review template
CSR	clinical study report
CSS	Controlled Substance Staff
DMC	data monitoring committee
ECG	electrocardiogram
eCTD	electronic common technical document
ETASU	elements to assure safe use
FDA	Food and Drug Administration
FDAAA	Food and Drug Administration Amendments Act of 2007
FDASIA	Food and Drug Administration Safety and Innovation Act
GCP	good clinical practice
GLP	good laboratory practice
GRMP	good review management practice
ICH	International Conference on Harmonization
IND	Investigational New Drug
ISE	integrated summary of effectiveness
ISS	integrated summary of safety
ITT	intent to treat
MedDRA	Medical Dictionary for Regulatory Activities
mITT	modified intent to treat
NCI-CTCAE	National Cancer Institute-Common Terminology Criteria for Adverse Event
NDA	new drug application

NME	new molecular entity
OCS	Office of Computational Science
OPQ	Office of Pharmaceutical Quality
OSE	Office of Surveillance and Epidemiology
OSI	Office of Scientific Investigation
PBRER	Periodic Benefit-Risk Evaluation Report
PD	pharmacodynamics
PI	prescribing information
PK	pharmacokinetics
PMC	postmarketing commitment
PMR	postmarketing requirement
PP	per protocol
PPI	patient package insert
PREA	Pediatric Research Equity Act
PRO	patient reported outcome
PSUR	Periodic Safety Update report
REMS	risk evaluation and mitigation strategy
SAE	serious adverse event
SAP	statistical analysis plan
SGE	special government employee
SOC	standard of care
TEAE	treatment emergent adverse event

1. Executive Summary

1.1.Product Introduction

Futibatinib (previously called TAS-120 or TAS-06-02985) is a small molecule kinase inhibitor of fibroblast growth factor receptor (FGFR) 1, 2, 3, and 4. The chemical name is 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. Futibatinib has a molecular formula of $C_{22}H_{22}N_6O_3$ and molecular mass of 418.45 g/mole. Futibatinib has the following chemical structure:



Futibatinib is supplied as 4 mg film-coated tablets for oral administration. The inactive ingredients are corn starch, crospovidone, hydroxypropyl cellulose, lactose monohydrate, magnesium stearate, mannitol, microcrystalline cellulose, and sodium lauryl sulfate. The film coating material contains hypromellose, magnesium stearate, polyethylene glycol, and titanium dioxide.

The proposed recommended dosage for futibatinib is 20 mg administered orally once daily until disease progression or intolerable toxicity.

Lytgobi (futibatinib) is a new molecular entity and has not been previously marketed.

1.2.Conclusions on the Substantial Evidence of Effectiveness

The review team agrees that the NDA for Lytgobi (futibatinib) tablets meets the statutory

standards for approval under 21 CFR 314, Subpart H (accelerated approval) for the following indication:

LYTGOBI is indicated for the treatment of adults with previously treated, unresectable locally advanced or metastatic intrahepatic cholangiocarcinoma harboring fibroblast growth factor receptor 2 (FGFR2) fusion 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).

This approval recommendation is primarily based on safety and efficacy results of a single trial, Study TAS-120-101 (NCT02052778). Study TAS-120-101 is an open label, non-randomized, multi-cohort trial that evaluated the efficacy of futibatinib in 103 patients with locally advanced unresectable or metastatic intrahepatic cholangiocarcinoma harboring an FGFR2 gene fusion or rearrangement, whose disease had progressed on or after at least 1 prior therapy (Phase 2 portion of the study). The safety of futibatinib is also supported by data from an additional 215 patients treated with futibatinib 20 mg daily as a single agent in the Phase 1 portion of Study TAS-120-101 and other clinical trials.

Study TAS-120-101 demonstrated a clinically meaningful and durable objective response rate (ORR) in patients with previously treated, locally advanced or metastatic intrahepatic cholangiocarcinoma with a FGFR2 gene fusion or rearrangement, a serious and life-threatening disease. Although pemigatinib and infigratinib are approved for use in the indicated population, both have been granted accelerated approval and as such there remains an unmet medical need for treatments for the indicated population. In the studied population of 103 patients with FGFR2 gene fusion/rearrangement intrahepatic cholangiocarcinoma who received at least one dose of futibatinib, the centrally reviewed estimated ORR was 42% (95% confidence interval [CI]: 32%, 52%). The median duration of response (DOR) was 9.7 months (95% CI: 7.6, 17.1); 31 of the 43 (72%) responders had a DOR lasting at least 6 months at the time of the analysis.

The review team considers the ORR and DOR results in Study TAS-120-101 reasonably likely to predict an effect on irreversible morbidity or mortality or other clinical benefit, and representative of a meaningful advantage over existing treatments for the proposed indication. The submitted data satisfies the requirements for accelerated approval. FDA requested and Taiho agreed to a postmarketing requirement to conduct a randomized clinical trial comparing dosages of futibatinib 20 mg or 16 mg daily to verify and describe the clinical benefit of futibatinib in patients with advanced or metastatic intrahepatic cholangiocarcinoma harboring an FGFR2 gene fusion or other rearrangement. The study endpoints will be ORR and DOR as per blinded independent review assessment and additional clinical outcomes that denote clinical benefit, such as patient reported outcomes will be assessed. In addition, this clinical trial will

provide a comparative analysis including dose- and exposure-response relationships for efficacy and safety of the 16 mg and 20 mg daily futibatinib dosages

APPEARS THIS WAY ON ORIGINAL

Benefit-Risk Assessment (BRA)

Benefit-Risk Summary and Assessment

Cholangiocarcinoma (CCA) is a rare cancer arising from epithelial cells of bile ducts and is the second most common primary liver tumor worldwide after hepatocellular carcinoma (Blechacz 2017). In the US, it is estimated that there are approximately 8,000 to 10,000 patients are diagnosed with CCA each year (American Cancer Society 2019); of these, approximately 65% have intrahepatic disease (Gad, 2020). Fibroblast growth factor receptor-2 (FGFR2) fusions have been detected in approximately 10-20% of intrahepatic CCA (iCCA) (Krook et al. 2020), and these fusions generally lead to ligand-independent constitutive activation of the receptor and downstream MAPK-ERK and JAK-STAT signaling pathways (Touat 2015; Babina 2017). Futibatinib is a small molecule kinase inhibitor of the fibroblast growth receptors (FGFRs) 1, 2, and 3.

There is no curative treatment for patients with advanced CCA. The standard of care for unresectable or metastatic disease is palliative chemotherapy with cisplatin in combination with gemcitabine. Use of this regimen is based on the results of the ABC-02 trial (Del Valle 2010) which was conducted in patients with biliary tract cancer (BTC) including CCA. This trial demonstrated a median survival of less than a year. In the randomized ABC-06 trial which evaluated chemotherapy consisting of fluorouracil/leucovorin in combination with oxaliplatin (FOLFOX) versus active symptom control in patients with BTC, patients receiving FOLFOX had a median OS benefit of 6.2 months compared to 5.3 months with in the control arm (hazard ratio [HR] 0.69; 95% CI: 0.50-0.97; p = 0.031) (Lamarca et al. 2019). For patients with FGFR2 fusions or other rearrangements who have progressed on at least 1 prior therapy, FDA granted accelerated approval to pemigatinib and infigratinib, which are also FGFR inhibitors. There are no other FDA-approved drugs indicated for the second-line treatment after disease progression on chemotherapy. Some patients (representing less than 5% of all CCA) may harbor genetic abnormalities for which there are tissue-agnostic therapies. For patients with tumors harboring neurotrophic tyrosine kinase (NTRK) gene fusions, FDA granted accelerated approvals for entrectinib and larotrectinib. For patients whose tumors have microsatellite instability-high (MSI-H) or tumor mutation burden-high (TMB-H), FDA granted accelerated approvals to pembrolizumab (both MSI-H and TMB-H) and dostarlimab (MSI-H only).

The safety and effectiveness of futibatinib for the treatment of patients with advanced, unresectable iCCA with FGFR2 fusions or other rearrangements and disease progression during or after systemic therapy is based on the results of the Phase 2 portion of Study TAS-120-101. The trial enrolled 103 patients in 13 countries in North America (46%), Europe (27%), Asia (26%), and Australia (1%). Patients received futibatinib in 28-day cycles at a dosage of 20 mg orally once daily until disease progression or unacceptable toxicity. The major efficacy

outcome measures were overall response rate (ORR) and duration of response (DOR) as determined by a blinded independent review committee (BIRC) according to RECIST v1.1.

Trial demographics were as follows: median age was 58 years (range: 22 to 79 years) and 22% were 65 years or older. 56% were female, 50% were White, 29% Asian, 8% African American, and 13% other races; 86% were not-Hispanic or Latino, 12% had unknown ethnicity, and 2% were Hispanic or Latino; baseline Eastern Cooperative Oncology Group (ECOG) performance status score was 0 (47%) or 1 (53%). Seventy-eight percent of patients had FGFR2 gene fusions and 22% had FGFR rearrangements. Among the patients with in-frame FGFR2 gene fusions, the most common FGFR2 fusion identified was FGFR2-BICC1 (23%). All patients had received at least 1 prior line of systemic therapy (including 91% with prior cisplatin and gemcitabine), and 30 and 23% had 2 or 3 prior lines of therapy, respectively.

The TAS-120-101 trial demonstrated a clinically meaningful and durable overall response rate (ORR) in patients with previously treated, locally advanced or metastatic intrahepatic cholangiocarcinoma with a FGFR2 gene fusion or other rearrangement, a serious and life-threatening disease. In the 103 patients with FGFR2 gene fusion/rearrangement-positive intrahepatic cholangiocarcinoma who received at least one dose of futibatinib, the estimated overall response rate (ORR) was 42% (95% confidence interval [CI]: 32%, 52%); all responses were partial responses. At the time of the analysis, the median duration of response (DOR) was 9.07 months (95% CI: 7.6, 17.7); 72% of patients had a response lasting at least 6 months.

The TAS-120-101 trial also provided the primary data to support the safety of futibatinib for the proposed indication. An additional 215 patients with a variety of cancers treated with futibatinib as a single agent in other cohorts of the TAS-120-101 trial provided additional, supportive safety data. Although assessment of a causal relationship between futibatinib and treatment-emergent reactions was limited given the single arm design of the trials providing safety data, the adverse reactions observed in patients treated with futibatinib were largely expected given the mechanism of action and the toxicity profile observed in preclinical studies. Among the 103 patients with intrahepatic cholangiocarcinoma enrolled in TAS-120-101, the most common adverse reactions to futibatinib (occurring at an incidence rate ≥ 20%) are arthralgia, nail toxicity, constipation, diarrhea, fatigue, dry mouth, alopecia, abdominal pain, dry skin, stomatitis, peripheral sensory neuropathy, nausea, dry eye, dysgeusia, decreased appetite, urinary tract infection, palmar-plantar erythrodysesthesia, vomiting, and weight decreased. The most common laboratory abnormalities were calcium-phosphate analyte abnormalities, increased glucose, increased creatinine, decreased hemoglobin, increased transaminases, decreased platelets, decreased leukocytes, and decreased neutrophils.

The serious risks of futibatinib include ocular toxicity (particularly retinal pigment epithelial detachment [RPED]) and hyperphosphatemia. Given

the lack of systematic optical coherence tomography (OCT) assessments in all patients, asymptomatic cases of RPED were undetected and therefore the incidence rate is likely an underestimate of this risk. Among the 318 patients who received futibatinib across clinical trials, RPED occurred in 9% of patients. The median time to first onset of RPED was 40 days. RPED led to futibatinib dose interruption in 1.3% of patients, futibatinib dose reduction in 1.6% of patients and permanent discontinuation in 0.3% of patients. In order to mitigate the risk of severe RPED, comprehensive ophthalmologic monitoring including ocular coherence tomography is recommended prior to initiation of futibatinib, at 6 weeks and every 3 months thereafter during treatment.
Among 103 patients who received futibatinib in TAS-120-101, hyperphosphatemia was reported in 97% of patients based on laboratory values above the upper limit of normal. Among 318 patients who received futibatinib across all cohorts in TAS-120-101, hyperphosphatemia was reported in 88% of patients based on laboratory values above the upper limit of normal. The median time to onset of hyperphosphatemia was 5 days (range 1-349). Phosphate binders were received by 83% of patients who received infigratinib. The median time to onset of hyperphosphatemia was 8 days (range 3-117).

Overall, the toxicity profile of futibatinib is considered acceptable when considering the anti-tumor effects (i.e., durable responses) in patients with previously treated intrahepatic cholangiocarcinoma harboring a FGFR2 fusion or other rearrangement, who have a poor life expectancy and limited treatment options. The risks of futibatinib are toxicities that oncologists and ophthalmologists are well-trained to manage, are largely reversible with dosage modification and supportive care, and overall are acceptable for a population with a serious and life-threatening condition.

Taken together, the review team concluded that the ORR and DOR results in TAS-120-101 provide evidence of futibatinib' s effectiveness and recommends accelerated approval as the conditions of 21 CFR Subpart H have been met. FDA requested and Taiho has agreed to a postmarketing requirement (PMR) to conduct a randomized clinical trial comparing dosages of futibatinib 20 mg or 16 mg daily to verify and describe the benefit of futibatinib in patients with advanced or metastatic intrahepatic cholangiocarcinoma harboring an FGFR2 gene fusion or other rearrangement. The study endpoints will be ORR and DOR as per blinded independent review assessment and additional clinical outcomes that denote clinical benefit, such as patient reported outcomes will be assessed. In addition, this clinical trial will provide a comparative analysis including dose- and exposure-response relationships for efficacy and safety of the 16 mg and 20 mg daily futibatinib dosages FDA requested additional PMRs related to further characterization of ocular toxicities and to study futibatinib in the pediatric population. FDA and Taiho also agreed to a post marketing commitment to develop a companion diagnostic test for the selection of patients with intrahepatic cholangiocarcinoma harboring an FGFR2 gene fusion or other rearrangements (commercial tests are available but not linked to futibatinib use).

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	Cholangiocarcinoma (CCA) is a rare cancer arising from epithelial cells of bile ducts. CCA is grouped based on location of origin in the biliary tract: intrahepatic (iCCA), perihilar, or extrahepatic. Extrahepatic and perihilar cholangiocarcinoma are the most common types, with 6% to 8% of CCA being intrahepatic, 50% to 67% perihilar and 27% to 42% distal extrahepatic (DeOliveira 2007); CCA accounts for approximately 3% of all gastrointestinal cancers and 10-25% of primary hepatic malignancies worldwide and the incidence appears to be rising (Rizvi et al. 2013). Fibroblast growth factor/fibroblast growth factor receptor (FGFR) fusions have been identified as an early driver of oncogenic events in iCCA (Nakamura et al. 2015). FGFR2 fusions are present in an estimated 10-20% of patients with iCCA (Krook et al. 2020). Patients with FGFR rearrangements appear to have a longer median overall survival compared to those with iCCA lacking a FGFR rearrangement. In a retrospective review of 377 patients with CCA, patients with FGFR rearrangements had a median survival of 37 months compared to 20 months in the unselected CCA population (Jain et al. 2018). The baseline demographic and disease characteristics of patients with FGFR rearrangements also appear to be prognostically favorable, including diagnosis at a younger age and an earlier stage of disease.	Cholangiocarcinoma is a serious and life threatening disease.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	Patients with FGFR fusion-positive CCA are also predominantly female (63%) and usually have iCCA (87%).	
Current Treatment Options	Treatment options are limited, and no treatment has received regular FDA approval for treatment of patients with relapsed CCA. In the randomized study ABC-06 exploring chemotherapy with fluorouracil/leucovorin in combination with oxaliplatin (FOLFOX) vs. standard of care for the second line treatment of patients with CCA, patients receiving FOLFOX had a median OS benefit of 6.2 months compared to 5.3 months with best supportive care (hazard ratio [HR] 0.69; 95% CI: 0.50-0.97; p = 0.031) (Lamarca et al. 2019). This OS difference is modest, accompanied by a 5% ORR and significant toxicities associated with multiagent chemotherapy. Other regimens include irinotecan in combination with a fluoropyrimidine, a platinum plus fluoropyrimidine, gemcitabine in combination with a platinum or fluoropyrimidine, or regorafenib (NCCN). Entrectinib and larotrectinib are approved for the treatment of patients with solid tumors that harbor NTRK gene fusions and who have no satisfactory alternative treatment options; however, NTRK gene fusions occur rarely in patients with CCA (i.e., in 1.3%)(Kheder et al 2018). Pembrolizumab is approved for the treatment of patients with microsatellite-high/mismatch repair deficient (MSI-high/dMMR) or tumor mutation-high (TMB-H) solid tumors that have progressed following prior treatment and who have no satisfactory treatment options; however, only approximately 4% of CCA are MSI-H/dMMR	Patients with CCA with a FGFR2 gene fusion or other rearrangement who have received at least one prior line of treatment have an unmet medical need. Current treatment options for patients with CCA are limited; pemigatinib and infigratinib, FGFR inhibitors, were approved under the accelerated approval pathway and therefore are not considered available therapy. No drugs or biologics hold regular FDA approval for the treatment of patients with CCA in the second-line setting, irrespective of whether the tumor harbors an FGFR2 gene fusion or rearrangement.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	(Goeppert et al. 2019). Pemigatinib and infigratinib are approved under the accelerated approval regulations for the second line treatment of patients with CCA that harbors an FGFR2 gene alteration. The pemigatinib approval was based on the demonstration of a clinically meaningful and durable overall response rate (ORR) in 107 patients. The ORR in the FIGHT-202 study was 36% (95% 27%, 45%), with a median duration of response of 9.1 months and 63% of responders had a DOR lasting at least 6 months. The infigratinib approval was based on the demonstration of a clinically meaningful and durable overall response rate (ORR) in 108 patients. The ORR in the CBGJ398X2204 study was 23.1% (95% 15.6%, 32.2%), with a median duration of response of 5.03 months and 32% of responders had a DOR lasting at least 6 months. As these approvals were granted under 21 CFR 314, pemigatinib and infigratinib are not considered available therapy for regulatory decision making.	
Benefit	Study TAS-120-101 (NCT02052778) provides the primary evidence demonstrating the effectiveness for futibatinib for the proposed indication. TAS-120-101 is an open label, non-randomized, 3-part trial; the Phase 2 part evaluated futibatinib in 103 patients with locally advanced unresectable or metastatic intrahepatic cholangiocarcinoma harboring an FGFR2 gene fusion or other rearrangement, whose disease had progressed on or after at least 1 prior systemic therapy (23% patients received at least 3 prior lines of therapy).	The magnitude of effect on ORR observed in Study TAS-120-101 in patients treated with futibatinib is higher than that observed with FOLFOX (5% in Study ABC-06, Lamarca et al 2019) or other chemotherapy agents or combinations (current standard of care for CCA). The duration of responses observed in patients with intrahepatic cholangiocarcinoma with a FGFR2 gene fusion who received prior

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	Patients received futibatinib 20 mg administered orally once daily until disease progression or unacceptable toxicity. The major efficacy outcome measures were overall response rate (ORR) and duration of response (DOR) as determined by an independent review committee (IRC) according to RECIST v1.1. Study TAS-120-101 demonstrated a clinically meaningful and durable ORR in 103 patients with previously treated, locally advanced or metastatic intrahepatic cholangiocarcinoma with a FGFR2 gene fusion or other rearrangement who received second line treatment with futibatinib. The estimated ORR was 42% (95% confidence interval [CI]: 32, 52) with a median duration of response (DOR) of 9.7 months (95% CI: 7.6, 17.1) by blinded independent central review (BICR). Of the 43 patients who achieved a confirmed partial response (PR) by BICR, 31 patients (72%) had a response duration ≥6 months.	treatment was clinically meaningful in the context of a disease with estimated survival of 5-6 months. The submitted evidence meets the statutory evidentiary standard for accelerated approval. Taiho has agreed to a postmarketing requirement to submit data from a randomized trial to verify and confirm the clinical benefit of futibatinib in patients with FGFR2 fusion/rearrangement-positive intrahepatic cholangiocarcinoma.
Risk and Risk Management	The primary data supporting the safety of futibatinib for the proposed indication was provided from data derived from 103 patients with previously treated, locally advanced or metastatic intrahepatic cholangiocarcinoma who received at least one dose of futibatinib in the Phase 2 part of Study TAS-120-101. The safety evaluation of futibatinib was also supported by data from an additional 215 patients with a variety of cancers treated with futibatinib 20 mg daily in Parts 1 and 2 of Study TAS-120-101. In FDA's analysis, the recommended dosage of futibatinib has not been adequately	The observed safety profile is acceptable when assessed in the context of the treatment of a life-threatening disease. Most of the adverse reactions to futibatinib were manageable with supportive care and dose modification as needed. The significant and potentially serious adverse reactions of hyperphosphatemia and ocular toxicity are adequately addressed in the

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	justified. The dosage was selected on the MTD of the first-in-human study and has not been optimized. Exploratory analyses suggest a negative exposure-response and a positive exposure-toxicity relationship; 66% patients needed dose interruptions and 58% patients needed dose reductions for the management of toxicity. In addition, characterization of the effects of infigratinib in patients with renal and hepatic impairment was insufficient. Although assessment of a causal relationship between futibatinib and adverse reactions was limited in the context of the single arm design of the trial providing safety data, the toxicity profile was consistent with the mechanism of action and the toxicity profile observed in preclinical studies and other drugs targeting the same pathway. The important identified risks related to futibatinib are ocular toxicity (including retinal detachment, dry eye, and vision blurred) and hyperphosphatemia. Among the 103 patients with intrahepatic cholangiocarcinoma enrolled in TAS-120-101, the most common adverse reactions and lab abnormalities to futibatinib (incidence ≥ 20%) were arthralgia, nail toxicity, constipation, diarrhea, fatigue, dry mouth, alopecia, abdominal pain, dry skin, stomatitis, peripheral sensory neuropathy, nausea, dry eye, dysgeusia, decreased appetite, urinary tract infection, palmar-plantar erythrodysesthesia, vomiting, and weight decreased. The most common laboratory abnormalities were calcium-phosphate analyte abnormalities, increased glucose, increased creatinine, decreased hemoglobin, increased transaminases, decreased platelets, decreased leukocytes, and decreased neutrophils.	Warnings and Precautions section and the dose modification recommendations included in product labeling. Although there were no significant safety concerns identified during the review of the application requiring risk management beyond labeling or warranting consideration for a Risk Evaluation and Mitigation Strategy(REMS), the review team identified issues with futibatinib dose optimization and potential drug-drug interactions, which are being addressed in labeling and for which post-marketing requirements and commitments have been negotiated to further inform labeling. In addition, a post-marketing requirement has been negotiated to further characterize the eye toxicity.

1.3.Patient Experience Data

Patient Experience Data Relevant to this Application (check all that apply)

X	The patient experience data that was submitted as part of the application, include:				Section where discussed, if applicable
	X	Clinical outcome assessment (COA) data, such as			
			X	Patient reported outcome (PRO)	8.1.2 Study Results
			□	Observer reported outcome (ObsRO)	
			□	Clinician reported outcome (ClinRO)	
			□	Performance outcome (PerfO)	
	□	Qualitative studies (e.g., individual patient/caregiver interviews, focus group interviews, expert interviews, Delphi Panel, etc.)			
	□	Patient-focused drug development or other stakeholder meeting summary reports			
	□	Observational survey studies designed to capture patient experience data			
	□	Natural history studies			
	□	Patient preference studies (e.g., submitted studies or scientific publications)			
	□	Other: (Please specify)			
□	Patient experience data that was not submitted in the application, but was considered in this review.				

Sandra J. Casak
Cross-Disciplinary Team Leader

2. Therapeutic Context

2.1.Analysis of Condition

The Applicant's Position:
Cholangiocarcinoma (CCA) is an aggressive malignancy of the biliary tract with poor overall prognosis and limited treatment options (Krook 2020; Rizvi 2017). CCAs are diverse epithelial tumors arising from the liver or large bile ducts with features of cholangiocyte differentiation. Anatomically, CCA is classified into extrahepatic, accounting for 80% to 90% of all CCAs, and intrahepatic (iCCA) forms (Blechacz 2008). Symptoms of CCA are not usually apparent until the disease is at an advanced stage; thus, the majority of patients with CCA (>65%) have nonresectable, incurable disease at the time of diagnosis.

CCAs represent the second-most common malignancy of the liver, accounting for approximately 15% of all primary liver cancers and approximately 3% of all gastrointestinal cancers (Banales 2020). The incidence of CCA is rare overall, with 1 to 3 patients per 100,000 in regions like the United States and Europe (Banales 2016; Khan 2019). However, its incidence varies by region and is exceptionally high in some countries, including Chile, Bolivia, South Korea, and North Thailand (Banales 2016). The incidence and mortality of CCA (in particular of iCCA) have been increasing in the past few decades worldwide (Banales 2020). For instance, the annual incidence of iCCA was 1.49 per 100,000 in the US in 2014, representing a 2-fold increase over the past 4 decades (Saha 2016). In the Western world, the median age at presentation of CCA is more than 65 years, and it is only rarely diagnosed in patients below 40 years of age (except in patients with pre-existing primary sclerosing cholangitis).

A number of risk factors for CCA have been recognized (eg, chronic liver disease including cirrhosis, viral and parasitic infections), although a specific risk factor cannot be identified for most patients.

Surgery is the preferred treatment option for patients when disease is resectable, including liver transplantation in highly selected cases, and is the only potential curative therapy for CCA (Banales 2020; Buettner 2017), but the rate of recurrence is high. When disease is unresectable, only palliative treatment is currently possible and those patients have a poor prognosis (Krook 2020; Rizvi 2017).

Fibroblast growth factor receptor 2 (*FGFR2*) rearrangements (including fusions) occur in about 10% to 16% of patients with iCCA (Krook 2020; Jain 2018), and at a much lower incidence in patients with eCCA (Arai 2014; Jain 2018). Baseline demographics of patients with CCA

harboring *FGFR2* rearrangements appear to differ from those without, with a lower median age of 52 years than the reported median age of the overall CCA population (~65 years) and a female preponderance (13% vs. 4%) (Graham 2014). Additionally, retrospective studies indicate a longer survival of CCA patients with *FGFR*2 rearrangements, suggesting the potential utility of *FGFR2* fusion identification as a prognostic marker (Graham 2014; Jain 2018).

Given the overall poor outcomes associated with currently available chemotherapy options in patients with CCA, there is an urgent need to develop novel targeted therapies for patients with this serious and life-threatening disease. Currently approved FGFR-targeting therapies, infigratinib and pemigatinib, have demonstrated anti-tumor activity in uncontrolled Phase 2 studies for CCA patients with *FGFR2* rearrangements (including fusions) and are awaiting confirmation in ongoing randomized Phase 3 studies as compared to standard of care chemotherapy in advanced CCA patients with *FGFR2* rearrangements (including fusions) receiving first-line treatment. Moreover, despite the 23% to 36% ORR reported for the ATP-competitive FGFR inhibitors infigratinib and pemigatinib, there is an unmet need for novel targeted therapies leading to an even higher number of responses with greater durability for advanced CCA patients with *FGFR2* rearrangement (including fusions). This also includes novel treatment options for patients with mutations in the FGFR2 kinase domain leading to conformational changes of the ATP pocket, and thereby causing resistance to ATP-competitive inhibitors (Goyal 2019; Sootome 2020).

The FDA's Assessment:

FDA agrees that there remains an unmet need to treat advanced or metastatic CCA, a rare disease with approximately 8,000 new cases diagnosed each year in the U.S. The majority (65%) of patients are diagnosed at an advanced stage and have a 5-year survival rate of less than 10% (Rizvi 2018, Fostea 2020). Historically, across the world, the distribution of CCA has been reported as presented by the Applicant, with the preponderance of cases being extrahepatic CCA. However, anatomic distribution varies by geographical region. In a more recent retrospective analysis of the Surveillance, Epidemiology, and End Results (SEER) database of CCA cases in the US during 2000-2015, a majority of patients (64.4%) had intrahepatic cholangiocarcinomas (iCCA) (Gad, 2020)". Furthermore, FGFR2 gene fusions are more common in patients with intrahepatic CCA. In the trial supporting the approval of the FGFR2 inhibitor pemigatinib for the treatment of patients with CCA (study eligibility criteria allowed enrollment in intrahepatic and extrahepatic CCA) harboring FGFR2 fusions or other rearrangements, 98% of the patients had intrahepatic CCA (Abou-Alfa 2020 and Pemazyre USPI).

In the SEER analysis (Gad, 2020), in the US, most patients with cholangiocarcinoma were White (78.4%), male (51.3%), and older than 65 years (63%).

The prognostic value of FGFR rearrangements is unclear; in a retrospective review of 377 patients with CCA, the reported median OS was 37 months in patients with FGFR gene fusion positive CCA compared to 20 months in the unselected CCA population (Jain 2018). However, in this retrospective analysis, the baseline demographic and disease characteristics of patients with FGFR rearrangements also appear to be prognostically favorable, including diagnosis at a younger age and an earlier stage of disease, which may be potentially confounding factors. Patients with FGFR fusion-positive CCA are also predominantly female (63%) and the location is intrahepatic for the majority of patients (87%).

FDA notes the Applicant's statements above regarding the potential advantage that treatment with futibatinib may provide over the referenced pemigatinib and infigratinib which are approved for the same indication, due to its 'novel' mechanism of action "leading to an even higher number of responses with greater durability for advanced CCA patients with FGFR2 rearrangement (including fusions)". FDA finds these statements to be potentially misleading as the Applicant has not provided any data supporting claims of superiority over other approved agents. Specifically, cross trial comparisons provide insufficient evidence to support the above statements.

2.2.Analysis of Current Treatment Options

In patients presenting with unresectable or metastatic disease, systemic chemotherapy remains the main palliative treatment modality (Banales 2020). The first-line, standard of care treatment for patients with unresectable/metastatic disease is gemcitabine and cisplatin (Valle 2010).

For patients who progress on first-line chemotherapy, there is no accepted standard of care chemotherapy. FOLFOX combination therapy (folinic acid, 5-fluorouracil, and oxaliplatin) is often recommended as second-line chemotherapy (Lamarca 2021; Banales 2020; NCCN 2021). However, the outcome reported showed limited clinical benefit with a median overall survival (OS) of 6.2 months (95% CI: 5.4, 7.6), median progression-free survival (PFS) of 4.0 months (95% CI: 3.2, 5.0), and a 5% objective response rate (ORR) (Lamarca 2021). In a retrospective meta-analysis including 22 studies with 761 patients undergoing second-line chemotherapy, the mean OS, PFS, and ORR were 7.2 months (95% CI: 6.2, 8.2), 3.2 months (95% CI: 2.7, 3.7), and 7.7% (95% CI: 4.6, 10.9), respectively (Lamarca 2014).

For patient with CCA and *FGFR2* rearrangements (including fusions), there is little information available regarding the treatment outcome of patients receiving chemotherapy. A retrospective analysis of 38 patients with advanced/metastatic CCA and tumors harboring *FGFR2* rearrangements (including fusions) receiving second-line treatment showed a median PFS of 4.4 months (95% CI: 3.0, 5.3) (Bibeau 2020), which is similar to the PFS reported for CCA patients overall receiving second-line chemotherapy (Lamarca 2014). Additionally, the ORR of 5.4% (95% CI: 0.7, 18.2) reported in another retrospective analysis of 71 CCA patients with *FGFR2* rearrangements receiving second-line chemotherapy was not apparently different from the one for CCA patients overall receiving second-line chemotherapy regardless of genomic status (Javle 2020).

Recently, the ATP-competitive FGFR inhibitors pemigatinib and infigratinib demonstrated efficacy in previously treated CCA patients with *FGFR2* rearrangements (including fusions) based on ORR (Abou-Alfa 2020; Javle 2021).

Pemigatinib is a small molecule tyrosine kinase inhibitor of FGFR1-3 approved in the US (accelerated approval), EU (conditional approval), and Japan for the second-line treatment of previously treated, unresectable, locally advanced or metastatic CCA patients with a *FGFR2* fusion or other rearrangement. These approvals were based on a single-arm Phase 2 study with 107 iCCA patients with *FGFR2* fusions or rearrangements showing an ORR of 35.5% (95% CI: 26.5, 45.4) and a median duration of response (DOR), PFS, and OS of 7.5 months (95% CI: 5.7, 14.5), 6.9 months (95% CI: 6.2, 9.6), and 21.1 months (95% CI: 14.8, NE), respectively (Abou-Alfa 2020).

Infigratinib is a small molecule kinase inhibitor of FGFR1-4 that received accelerated approval in the US for the treatment of adults with previously treated, unresectable locally advanced or metastatic cholangiocarcinoma with a *FGFR2* fusion or other rearrangement. This approval was based on a single-arm Phase 2 study with 108 CCA patients with *FGFR2* fusions or rearrangements showing an ORR of 23.1% (95% CI: 15.6, 32.2) and a median DOR, PFS, and OS of 5.0 months (range: 0.9-19.1), 7.3 months (95% CI: 5.6, 7.6), and 12.2 months (95% CI: 10.7, 14.9), respectively (Javle 2021).

Table 1: Applicant - Summary of Currently Available Treatments for Patients with Previously Treated Cholangiocarcinoma with *FGFR*2 Rearrangements (incl. fusions)

Product (s) Name	Relevant Indication	Year of Approval And Type of Approval *	Dosing/ Administration	Efficacy Information	Important Safety and Tolerability Issues
FDA Approved Treatments FGFR Inhibitors					
Pemigatinib (Pemazyre®)	For the treatment of adults with previously treated, unresectable locally advanced or metastatic cholangiocarcinoma with a fibroblast growth factor receptor 2 (*FGFR*2) fusion or other rearrangement as detected by an FDA-approved test.	2020 Accelerated Approval	13.5 mg/day for 14 days followed by 7 days off (21-day cycles)	ORR: 36% (95% CI: 27, 45); CR: 2.8%, PR: 33% Median DOR: 9.1 months (95% CI: 6.0,14.5) Patients with: DOR ≥ 6months: 24 (63%) DOR ≥ 12 months: 7 (18%)	Ocular Toxicity • Hyperphosphatemia • Embryo-fetal Toxicity
Infigratinib (Truseltiq®)	For the treatment of adults with previously treated, unresectable locally advanced or metastatic cholangiocarcinoma with a fibroblast growth factor receptor 2 (*FGFR*2) fusion or other rearrangement as detected by an FDA-approved test	2021 Accelerated Approval	125 mg/day for 21 days followed by 7 days off (28-day cycles)	ORR: 23.1% (95% CI: 15.6, 32.2) CR: 1 patient, PR: 24 patients Median DOR: 5.0 months (95% CI: 3.71, 9.26) Patients with: DOR ≥ 6months: 8 (32%) DOR ≥ 12 months: 1 (4%)	Ocular Toxicity • Hyperphosphatemia • Embryo-fetal Toxicity

Product (s) Name	Relevant Indication	Year of Approval And Type of Approval *	Dosing/ Administration	Efficacy Information	Important Safety and Tolerability Issues
Available Treatments for Patients with Cholangiocarcinoma Regardless of Presence of *FGFR2* Fusion or Rearrangement					
mFOLFOX NCCN Guidelines V3, 2020. Recommendation Category 2A	No relevant indications for CCA	N/A	No labeled dosing in this setting. However, in the ABC-06 trial, the regimen was administered as follows: Oxaliplatin 85 mg/m^2, L-folinic acid 175 mg (or folinic acid 350 mg), 5 FU 400 mg/m^2 (bolus), 5 FU 2400 mg/m^2 46h continuous infusion every 14 days for up to 12 cycles	In the Phase 2 randomized ABC-06 study (Lamarca 2021), in patients with advanced biliary tract cancer after disease progression to cisplatin + gemcitabine: Median OS: 6.2 months, adjusted HR 0.69 (95% CI 0.5 – 0.97; p=0.031) ORR: 5% (CR 1%, PR 4%)	Neutropenia Infections Peripheral neuropathy
FOLFIRI (NCCN Guidelines V3, 2020. Recommendation Category 2B)	No relevant indications for CCA	N/A	No labeled dosing in this setting. However, in the study supporting the Category 2B recommendation (Caparica 2019), FOLFIRI was administered per this institution's standard practice: fluorouracil 400 mg/m^2 bolus on D1 then 2400 mg/m^2 on a 48h protracted infusion D1-2; leucovorin 200 mg/m^2 on D1; irinotecan 180 mg/m^2 on D1 every 14 days, with each administration being considered 1 cycle	In a retrospective cohort study in patients with locally advanced or metastatic biliary tract cancer who progressed after at least one line of chemotherapy (Caparica 2019): Median PFS: 1.7 months (95% CI: 0.66 – 2.67) Median OS: 5 months (95% CI: 2.77 – 7.20)	Myelosuppression Diarrhea Renal impairment/ renal failure Embryo fetal toxicity

*Accelerated approval or full approval

The Applicant's Position:

Given the overall poor outcomes associated with currently available chemotherapy options in patients with CCA, there is an urgent need to develop novel targeted therapies for patients with this serious and life-threatening disease. Currently approved FGFR-targeting therapies have demonstrated clinical activity in uncontrolled Phase 2 studies for CCA patients with *FGFR2* rearrangements (including fusions) and will require confirmation of true clinical benefit in ongoing randomized Phase 3 studies as compared to standard of care chemotherapy in advanced CCA patients with *FGFR2* rearrangements (including fusions) receiving first-line treatment. Since this demonstration of true clinical benefit is not assured, there remains an ongoing unmet need for novel targeted therapies particularly ones with potential to generate an even higher number of responses with greater durability for advanced CCA patients with *FGFR2* rearrangement (including fusions). This also includes novel treatment options for patients with mutations in the FGFR2 kinase domain leading to conformational changes of the ATP pocket, and thereby causing resistance to ATP-competitive inhibitors (Goyal 2019; Sootome 2020).

The FDA's Assessment:

FDA generally agrees with the Applicant's summary of current treatment options for advanced cholangiocarcinoma.

Of note, although the above referenced ABC-06 trial demonstrated the superiority of mFOLFOX6 over placebo in terms of PFS prolongation, the benefit observed in the trial was modest and the use of mFOLFOX6 as second line therapy has not been universally adopted. While this application was under review, on September 2, 2022, FDA approved durvalumab (an immune checkpoint inhibitor) as an add-on to gemcitabine/cisplatin for the first-line treatment based on the results of the TOPAZ-1 trial. TOPAZ-1 demonstrated improved efficacy of combination chemo-immunotherapy in the first-line setting. The addition of durvalumab to gemcitabine and cisplatin increased median OS compared to gemcitabine and cisplatin only (HR of 0.80 [95% CI, 0.66-0.97; P = 0.021]) (Imfinzi US). These results were not available at the time of TAS-120-101 trial initiation or NDA submission.

As shown in Table 1, two drugs targeting *FGFR2* fusions or rearrangements (pemigatinib and infigratinib) are available for treatment of patients with advanced/metastatic CCA harboring *FGFR2* fusions or rearrangements. The efficacy of pemigatinib, an oral, selective FGFR1-3 kinase inhibitor, was investigated in a multicenter, open-labeled, single-arm trial with 107 patients with previously-treated CCA harboring *FGFR2* fusions/rearrangements and demonstrated an overall response rate (ORR) of 36% ((95% CI: 27%, 45%).

Similarly, the efficacy of infigratinib, an oral selective FGFR1-4 kinase inhibitor, was investigated in a multicenter, open-labeled, single-arm study with 108 patients with previously-treated CCA

harboring *FGFR2* fusions/rearrangements and demonstrated an ORR of 23% (95% CI: 15.6, 32.2).

3. Regulatory Background

3.1.U.S. Regulatory Actions and Marketing History

The Applicant's Position:
Futibatinib is not currently approved for marketing in the United States or in any other country.

The FDA's Assessment:
FDA concurs.

3.2.Summary of Presubmission/Submission Regulatory Activity

The Applicant's Position:
A summary of key interactions with the FDA regarding futibatinib is provided in Table 2 and Table 3 below.

Table 2: Applicant - Key FDA Interactions for IND 121062

Date	Description of Regulatory Activity
December 31, 2013	Taiho submitted an initial IND containing the clinical protocol for TPU-TAS-120-101 (Study 101), entitled "Dose-Finding Phase 1 Study of TAS-120 in Patients with Advanced Solid Tumors with or without Fibroblast Growth Factor/Receptor (FGF/FGFR)-Related Abnormalities Followed by a Phase 2 Study in Patients with Advanced Solid Tumors or Multiple Myeloma with FGF/FGFR-Related Abnormalities". On January 28, 2014, the IND was placed on a partial clinical hold for the Phase 2 portion of the study.
November 3, 2017	Partial clinical hold was removed by the FDA after Phase 1 results became available.
December 1, 2017	FDA issued final meeting minutes for a Type B / End of Phase 1 (EOP1) meeting to discuss Taiho's proposed development strategy for futibatinib.
May 23, 2018	FDA granted Orphan Drug Designation to futibatinib for the treatment of CCA.
August 20, 2018	FDA granted Fast Track Designation for the investigation of futibatinib for the first-line treatment of patients with unresectable or metastatic CCA harboring *FGFR* gene fusions to demonstrate a statistically significant improvement in overall survival for patients randomized to receive futibatinib as compared to those randomized to receive cisplatin and gemcitabine.

Date	Description of Regulatory Activity
January 25, 2019	FDA issued final meeting minutes for a Type B / product-quality only meeting to discuss the overall product quality development program and strategy to support an NDA.
December 4, 2019	FDA issued an advice letter containing FDA comments relating to Taiho's new clinical study, TAS-120-301, entitled "A Phase 3, Open-label, Randomized Study of Futibatinib Versus Gemcitabine-Cisplatin Chemotherapy as First-Line Treatment of Patients with Advanced Cholangiocarcinoma Harboring *FGFR2* Gene Rearrangements" submitted on September 23, 2019, a study intended to confirm the clinical benefit of futibatinib.
February 26, 2020	FDA issued Written Response to Type C guidance meeting to discuss Taiho's proposals relating to the presentation of efficacy and safety data, presentation of clinical pharmacology, and data standardization requirements in the planned NDA.
April 1, 2020	The expanded access protocol TAS-120-401, entitled "An Open-Label Expanded Access Program of Futibatinib (TAS-120) In Patients with Advanced Cholangiocarcinoma Harboring *FGFR2* Gene Rearrangements" (submitted on March 5, 2020) was allowed to proceed by the FDA.
June 17, 2020	FDA issued final meeting minutes for a Type B Pre-NDA meeting to discuss Taiho's proposed content and format of the planned NDA.
August 5, 2020	FDA issued final meeting minutes for a Type B CMC Pre-NDA meeting to discuss the content and format of the CMC section of the planned NDA.
February 11, 2021	FDA granted Breakthrough Therapy designation for futibatinib for the treatment of patients with previously treated locally advanced or metastatic cholangiocarcinoma harboring *FGFR2* gene rearrangements, including gene fusions.
April 23, 2021	FDA issued final meeting minutes for a pre-submission meeting with CDRH.
June 15, 2021	FDA issued final meeting minutes for a Type B Initial Multidisciplinary Breakthrough Therapy Designation meeting to discuss the proposed content and format of the planned NDA.
August 6, 2021	FDA issued an "Amended Agreed Initial Pediatric Study Plan - Agreement" letter for futibatinib indicated for the treatment of patients with previously treated locally advanced or metastatic cholangiocarcinoma harboring *FGFR2* gene rearrangements, including gene fusions.

Table 3: Applicant – Key FDA Interactions for NDA 214801

Date	Description of Regulatory Activity
August 3, 2021	Taiho submitted reviewable Unit #1 of the original NDA 214801 as a rolling submission, including: Request for Proprietary Name Review for the proposed tradename Lytgobi Request for Priority Review of the NDA
September 3, 2021	Taiho submitted rolling submission reviewable Unit #2 to the NDA 214801

The FDA's Assessment:

In addition to the information presented in Table 2 and Table 3, the following are key points included in the discussions between FDA and Taiho. The January 28, 2014, partial clinical hold on the IND was based on Study TAS-120-101. This partial hold was instituted because there was insufficient information to assess risks to human subjects with regard to product quality and due to clinical concerns relating to the proposed 20 mg strength capsule of TAS-120 (futibatinib). Taiho submitted a complete response addressing the clinical and product quality issues. Taiho's complete response to clinical hold relating to the clinical deficiencies, was based on safety data from 102 patients with unresectable solid tumors, preliminary efficacy data on 23 patients with cholangiocarcinoma (CCA), and a rationale for the selected dosage for the expansion cohorts and Phase 2 part of the study. FDA considered Taiho's response to be satisfactory and subsequently removed the partial clinical hold on November 3, 2017.

On December 1, 2017, FDA provided written comments regarding the development plan for futibatinib. In this EOP2 Written Response, FDA strongly recommended that Taiho request a pre-submission meeting with the Center for Devices and Radiological Health (CDRH) regarding the adequacy of the development of a companion diagnostic test (CDx) to identify patients with iCCA harboring FGFR2 gene fusions and the adequacy of the bridging strategy from the clinical trials assays to the companion diagnostic assay, prior to initiation of a trial intended to provide the substantial evidence of safety and effectiveness in support of a marketing application (e.g., Part 3 of the proposed trial). Taiho followed FDA's advice and on April 18, 2018, Taiho received written feedback from CDRH regarding development of a companion diagnostic test for futibatinib; FDA stated that ideally, a CDx is expected to be approved concurrently with the approval of the drug irrespective of the approval pathway; i.e., accelerated approval or full approval. FDA also conveyed a strong preference to have a pre-market approval (PMA) application for review at the time of the CDER submission of the New Drug Application to support concurrent approval of drug and CDx.

On December 4, 2019, FDA provided comments to Taiho regarding the study design and statistical plan for the confirmatory study TAS-120-301, entitled "A Phase 3, Open-Label, Randomized Study of Futibatinib Versus Gemcitabine-Cisplatin Chemotherapy as First-Line Treatment of Patients with Advanced Cholangiocarcinoma Harboring FGFR2 Gene Rearrangements (FOENIX-CCA3)." The study opened to enrollment on March 1, 2020 (https://clinicaltrials.gov/ct2/show/NCT04093362).

On February 26, 2020, FDA issued a written response only document for a Type C guidance meeting to discuss Taiho's proposals relating to the presentation of efficacy and safety data, presentation of clinical pharmacology, and data standardization requirements in the planned NDA. FDA also conveyed clear and specific comments to Taiho regarding need for dose

optimization and to clarify the basis for selecting the doses and dosing regimen used in the trial intended to support the NDA.

On June 17, 2020, as part of the Type B Pre-NDA meeting, FDA requested that Taiho provide specific rationale for recommendations for Section 2 (Dose Modifications) relating to retinal pigment epithelial detachment, Section 5 (Recommendations for Ocular Monitoring including optical coherence tomography), and provide justification for any deviations from the protocol procedures with regard to these recommendations. In this meeting, FDA also addressed the need for a companion diagnostic to help ensure the safe and effective use of futibatinib in the indicated population.

On April 23, 2021, FDA held a presubmission meeting with Taiho to discuss Clinical Trial Assay (CTA) to Detect FGFR2 Gene Fusions in intrahepatic cholangiocarcinoma. Taiho provided a brief update on futibatinib and Taiho's commitment to the futibatinib development plan with an NDA submission anticipated at the end of 2021, as well as the expectation of a post-approval commitment to support approval of the NDA without a contemporaneous CDx.

On July 9, 2021, a meeting was held between FDA, a patients advocacy group, and representatives from industry developing drugs for the treatment of advanced cholangiocarcinma harboring FGFR2 fusions or other rearrangements, including Taiho. The purpose of the meeting was to discuss an efficient trial design that could potentially provide evidence to verify the benefit of therapies indicated for the treatment of patients with cholangiocarcinoma harboring FGFR2 mutations (b) (4) FDA encouraged the development of the trial and supported its conduct. However, FDA was later informed that the trial would not be conducted.

On January 27, 2022, and April 22, 2022, FDA issued information requests (IR) inquiring about the status of Study FOENIX-CCA3. In response to both IRs, Taiho stated that (b) (4) On May 10, 2022, during the mid-cycle teleconference for this application, FDA raised concerns regarding the timely completion of the confirmatory trial to verify or refute clinical benefit. Given the low accrual on the trial to date, and the unclear efficacy of Taiho's

planned measures to improve enrollment, FDA recommended that Taiho consider potential alternative and feasible approaches to verify clinical benefit for the indicated population. FDA also recommended that Taiho consider further optimizing the dosage, potentially by evaluating the lower dosage of 16 mg QD.

In a correspondence received on June 21, 2022, Taiho summarized a plan to revise the FOENIX-CCA3 to increase the pool of eligible patients as a measure to improve accrual. FDA held a teleconference meeting with Taiho on July 15, 2022, to further clarify expectations for timely availability of data from a confirmatory trial. During this meeting, FDA again expressed concern that despite Taiho's planned measures, the FOENIX-CCA3 trial may not be completed in a reasonable timeframe and encouraged Taiho to consider an alternative approach to the ongoing randomized trial to further characterize the benefits of futibatinib. On August 3, 2022, Taiho submitted a response proposing the conduct of a randomized (1:1), open-label, uncontrolled study to confirm the clinical benefit of futibatinib 20 mg daily (QD) and to explore the safety and activity of 16 mg QD in (b) (4) patients with advanced, unresectable cholangiocarcinoma patients with *FGFR2* fusion or rearrangement.

(b) (4)

FDA inquired and Taiho clarified that the FOENIX-CCA3 trial, (b) (4) will continue enrollment but its viability will be assessed after an assessment of the impact of the measures to increase enrollment are implemented.

4. Significant Issues from Other Review Disciplines Pertinent to Clinical Conclusions on Efficacy and Safety

4.1.Office of Scientific Investigations (OSI)

The Office of Scientific Investigations (OSI) was consulted to conduct inspections of the study Contract Research Organization (CRO), Syneos Health and the two clinical sites with the highest rankings in the Inspections Tool. Site #01 had the highest patient enrollment and Site #21 had a high treatment effect compared to the study rate. OSI conducted on-site surveillance inspections of these three sites between March and April 2022. OSI concluded that the clinical data generated from the three inspected sites and submitted to the NDA by Taiho appear to be reliable and supportive of this NDA and the proposed indication for futibatinib.

4.2.Product Quality

The Office of Pharmaceutical Quality (OPQ) did not identify product quality issues that would preclude approval of futibatinib tablets under this NDA. Refer to the OPQ review of this application for additional information. No safety or efficacy concerns were identified during this review that related to Chemistry, Manufacturing, and Controls (CMC).

Pursuant to 21 CFR 25.31(b), Taiho submitted a Request for Categorical Exclusion from the preparation of an environmental assessment for futibatinib and submitted environmental assessment data to support this request. OPQ determined that this request could be granted, as the estimated concentration of the drug substance at the point of entry into the aquatic environment (EIC) is projected to be less than 1 part per billion (ppb), allowing an exclusion to be granted.

4.3.Clinical Microbiology

This NDA was reviewed by OPQ's Division of Microbiology Assessment. The microbiology reviewers did not identify issues that would preclude approval of futibatinib tablets. Infigratinib should be stored at room temperature 20°C - 25°C (68°F - 77°F); excursions permitted to 15°C - 30°C (59°F - 86°F).

4.4.Devices and Companion Diagnostic Issues

The final FGFR2 status used for the efficacy analyses of Study TAS120-101 was determined by the Applicant based on central or local test results. Sixty percent of patients (n=62) were enrolled based on local Next Generation Sequence (NGS) tests (i.e., FMI commercial F1CDx F1

(n=53), other tissue-based NGS (n=5), liquid-based NGS (n=3), FISH (n=1)], and 40% of patients (n=41) were enrolled based on a central NGS test (i.e., FMI Clinical Trial Assay [CTA]). Although CDER held several discussions with Taiho (e.g., on correspondence issued on December 1, 2017 and June 17, 2020; meeting held on June 14, 2021) regarding the need for a companion diagnostic for the selection of patients who may benefit from treatment with futibatinib, and CDRH also provided the same advice to Taiho, the Applicant submitted the NDA without a PMA application for the CDx. A PMC will be issued requesting the Applicant to conduct an analytical and clinical validation study, using clinical trial data, that is adequate to support labeling of an in vitro diagnostic device that is essential to the safe and effective use of futibatinib for patients with intrahepatic cholangiocarcinoma harboring FGFR2 gene fusions or rearrangements.

5. Nonclinical Pharmacology/Toxicology

5.1.Executive Summary

Futibatinib is a small molecule inhibitor of fibroblast growth factor receptor (FGFR) 1, 2, 3, and 4. The established pharmacological class for futibatinib is kinase inhibitor.

Constitutive FGFR signaling can support the proliferation and survival of malignant cells. Molecular irregularities like point mutations, gene amplifications, and/or chromosomal translocations of FGFR genes results in aberrative FGFR signaling.

Pharmacology assessments with futibatinib showed inhibitory activity against FGFR1-4 with IC50s in the nanomolar range (1.4 to 3.7 nM). Futibatinib had antitumor activity and inhibited FGFR2 phosphorylation and downstream AKT and ERK signaling in a human endometrial carcinoma mice model with an FGFR2 mutation. Antitumor activity was also observed in a nude rat model with human gastric carcinoma SNU-16 xenograft tumors (FGFR2 gene amplification). In a panel of 287 kinases, RET (S891A mutation) was the only kinase that was inhibited by more than 70%.

Safety pharmacology studies with futibatinib assessed the effects of cardiovascular, central nervous system (CNS), and respiratory function. Futibatinib had no toxicologically significant effects on cardiovascular function in telemetered dogs or on neurobehavioral and respiratory functions in rats.

The Applicant conducted general toxicology studies in rats and dogs. Futibatinib was dosed orally daily or every-other-day in 4-week and 13-week GLP repeat-dose studies. The oral route of administration is consistent with the intended clinical route of administration. Drug-related findings in both species were consistent with FGFR inhibition including increases in plasma phosphorus, ectopic mineralization in multiple tissues, and lesions in bone at exposure levels that are in range with human exposures at the recommended clinical dose of 20 mg. Microscopic findings of corneal opacity, atrophy, and mineralization were observed in rats. Evidence of recovery in rats and dogs was observed four weeks after cessation of dosing except for the ectopic mineralization.

Reproductive and developmental toxicology with futibatinib included dose-range finding and preliminary embryo-fetal development studies conducted in female rats with orally administered futibatinib. Once daily dosing for 11 days, between 7 and 17 days of pregnancy during the period of organogenesis, resulted in 100% embryofetal mortality due to post-

implantation loss at a dose of 10 mg/kg (approximately 5 times the recommended clinical dose of 20 mg based on body surface area, BSA). Fetal survival was unaffected at 0.5 mg/kg per day; however, once daily oral administration of futibatinib at the 0.5 mg/kg dose level (approximately 0.2 times the recommended clinical dose of 20 mg based on BSA) resulted in reduced mean fetal body weight and an increase in fetal skeletal and visceral malformations, major blood vessel variations, and reduced ossification.

Carcinogenicity studies have not been conducted with futibatinib and are not recommended for the proposed indication.

Futibatinib was not mutagenic in an in vitro bacterial reverse mutation (Ames) assay. Futibatinib was clastogenic in an in vitro chromosomal aberration assay after a 6 hour treatment. Futibatinib was not clastogenic in a rat bone marrow micronucleus assay or a rat DNA damaging (comet) assay. The totality of genotoxicity data, including negative in vivo studies evaluating up to 300 mg/kg (approximately 150 times the recommended clinical dose of 20 mg based on BSA) and a negative mutagenicity assay, indicate there is a low potential for futibatinib to be genotoxic in vivo. Therefore, futibatinib labeling is based on a determination of non-genotoxic.

FDA Nonclinical Pharmacology/Toxicology Review Summary	
Pharmacology	Kinase inhibitor of fibroblast growth factor receptor FGFR 1, 2, 3, and 4
General Toxicology	Main toxicology findings included increased plasma phosphorus, tissue mineralization, and bone findings, consistent with the class.
Genetic Toxicology	Totality of data indicates futibatinib is not genotoxic in vivo.
Reproductive and Developmental Toxicology	Futibatinib was embryofetal toxic in rats at clinically relevant exposures.

There are no approvability issues from a pharmacology/toxicology perspective.

5.2.Referenced NDAs, BLAs, DMFs

The Applicant's Position:
Not applicable.

5.3 Pharmacology

Primary pharmacology:

Futibatinib is a covalently binding kinase inhibitor of fibroblast growth factor receptor (FGFR) 1-4. In vitro-cell free biochemical enzyme assays showed inhibition of FGFR1 (IC_{50} of 1.8 nmol/L), FGFR2 (IC_{50} of 1.4 nmol/L), FGFR3 (IC_{50} of 1.6 nmol/L) and FGFR4 (IC_{50} of 3.7 nmol/L) (Table 4, Study No. TE2-11-18-001).

Table 4: Applicant - In Vitro IC_{50} Values of Futibatinib for Human FGFR1-4

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

Abbreviations: FGFR: fibroblast growth factor receptor; IC_{50}: half-maximal inhibitory concentration; SD: standard deviation.

To investigate selectivity of futibatinib for FGFRs over other protein kinases in vitro, inhibitory activity of futibatinib against 287 various human serine/threonine and tyrosine protein kinases other than FGFRs was examined. This selectivity profiling was conducted with a futibatinib concentration of 100 nmol/L. Futibatinib showed high selectivity for FGFR when tested against a panel of 287 kinases. Among the 287 kinases, RET (S891A mutation) was the only kinase that was inhibited by > 70% at 100 nmol/L (Study No. CBS-200263).

In vitro studies showed that futibatinib selectively inhibits cell proliferation of human cancer cell lines derived from gastric, breast, lung, endometrial, and bladder cancers that have *FGFR* gene abnormalities including gene amplification, point mutation, and gene translocation (Study No. BB12-18-002). Futibatinib inhibited in vitro proliferation of SNU-16 cells (gastric cancer), MFM-223 cells (breast cancer), DMS 114 cells (lung cancer), AN3 CA cells (endometrial cancer), and RT4 (urinary bladder cancer) with GI_{50} values of 1.40 ± 0.19, 1.07 ± 0.04, 2.22 ± 0.61, 3.65 ± 0.48, and 10.3 ± 4.2 nmol/L, respectively. In contrast, cell growth of MKN45 (gastric cancer) and MCF-7 (breast cancer) cells which had no genetic alterations of FGFR was not inhibited by futibatinib with GI_{50} values > 1000 nmol/L.

Futibatinib retained inhibitory activity against mutant FGFR2 including the V565I gatekeeper mutation with similar potency compared with wild-type FGFR. N550H and E566G mutations in the FGFR2 hinge region, which were reported to cause resistance to dovitinib, a multikinase inhibitor with inhibitory activity against FGFR, were also sensitive to futibatinib. Furthermore, futibatinib showed inhibition of FGFR2 K660M mutation in the activation loop of the kinase domain; (Study No. BB12-20-012).

Table 5: Applicant - Summary of IC_{50} Values for the Phosphorylation of Wild Type and Mutant FGFR2

Test compounds	Phospho-FGFR2 inhibition, IC_{50} (nmol/L), mean ± SD				
	Wild type	N550H	V565I	E566G	K660M
Futibatinib	3.1 ± 1.3	12 ± 5	8.4 ± 3.1	5.5 ± 4.7	9.2 ± 7.0

Abbreviations: FGFR: fibroblast growth factor receptor; IC_{50}: half-maximal inhibitory concentration; SD: standard deviation.
The IC_{50} values (mean ± standard deviation) were calculated by 3 independent experiments.

Futibatinib demonstrated antitumor efficacy in a nude mouse model bearing human endometrial carcinoma AN3 CA xenograft tumors (with FGFR2 mutation K310R + N549K) (Dutt 2008). The ratios of mean relative tumor volume (RTV) in each treatment group compared to the control group (T/C) were 22.4%, 15.5%, and 8.0% at the doses of 5, 15, and 50 mg/kg/day, respectively and indicated statistically significant antitumor efficacy at dose levels ≥ 5 mg/kg/day (Study No. 18TA01).

Inhibition of FGFR phosphorylation and its downstream signals by a single dose of futibatinib was evaluated using human endometrial carcinoma cell line AN3 CA xenografts (with FGFR2 mutation K310R + N549K) in nude mice. A single oral dose of futibatinib at 5, 15, or 50 mg/kg downregulated phosphorylation levels of FGFR and its downstream signaling pathway such as fibroblast growth factor receptor substrate 2 (FRS2), AKT, and extracellular signal-regulated kinase (ERK) (Study No. 18SA01).

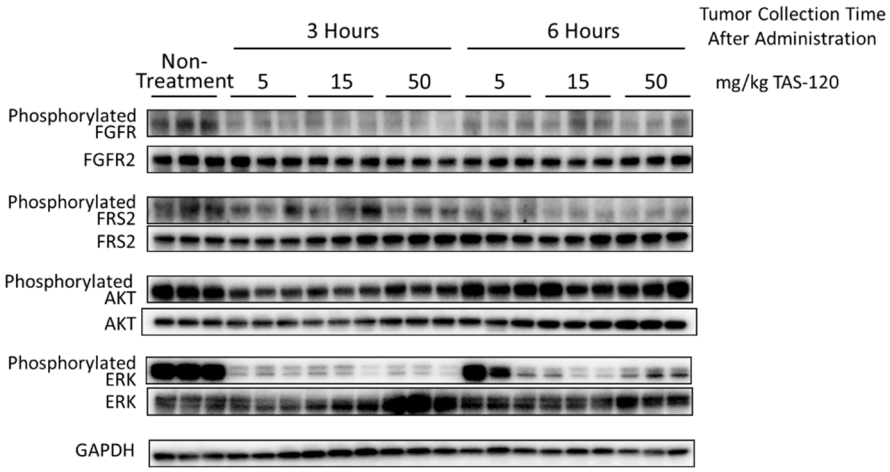


Figure 1: Applicant - Inhibition of FGFR Phosphorylation and Its Downstream Signals after a Single Dose of Futibatinib in AN3 CA Xenografted Tumor

Abbreviations: ERK: extracellular signal-regulated kinase; FGFR: fibroblast growth factor receptor; FRS2: fibroblast growth factor receptor substrate 2; GAPDH: glyceraldehyde 3-phosphate dehydrogenase.

Futibatinib demonstrated antitumor efficacy in a nude rat model bearing human gastric carcinoma SNU-16 xenograft tumors (*FGFR2* gene amplification) when orally administered once daily for 14 days. The T/C in animals treated with futibatinib at doses of 2.5, 5, and

10 mg/kg/day were 37.9%, 53.1%, and 34.8%, respectively, and indicated significant antitumor efficacy at dose levels ≥ 2.5 mg/kg/day (Study No. 18TA02).

The FDA's Assessment:
FDA generally agrees with the Applicant's position.

Secondary Pharmacology:

The Applicant's Position:
Futibatinib is a novel and highly selective fibroblast growth factor receptor (FGFR) 1-4 kinase inhibitor through its covalent mechanism of binding. Covalent binding imposes a higher degree of selectivity compared to conformational fitting of a chemical moiety into a receptor ATP pocket. In line, futibatinib demonstrated high selectivity for FGFR when tested against a panel of 287 human serine/threonine and tyrosine protein kinases other than FGFRs. Among the 287 kinases, RET (S891A mutation) was the only kinase that was inhibited by > 70% at 100 nmol/L, a futibatinib concentration > 50-fold higher than its IC_{50} values against FGFR1 (1.8 nmol/L), FGFR2 (1.4 nmol/L), and FGFR3 (1.6 nmol/L).

The FDA's Assessment:
FDA generally agrees with the Applicant's position.

Safety Pharmacology:
Nonclinical safety pharmacology studies conducted in rats and dogs identified no potential for futibatinib to cause cardiovascular, neurofunctional, or respiratory effects.

Futibatinib inhibited hERG current (Study No. 8215) but at concentrations that were much higher (IC_{50} value: 3105 ng/mL) than the C_{max} observed at a severely toxic dose (531 ng/mL) in dogs and the peak exposure in humans at the recommended clinical dose of futibatinib (20 mg QD). Furthermore, studies did not indicate that futibatinib would elicit a potential QTc prolongation at clinically meaningful exposures. This conclusion is in accordance with the lack of ECG changes noted in the single dose dog cardiovascular safety pharmacology study showing no effect on the cardiovascular system in conscious dogs at close to or above clinically relevant concentrations (Study No. 8214).

Futibatinib was considered to have no effect on the central nervous (Study No. 8212) or respiratory system (Study No. 8213) in rats after a single oral dose of up to 30 mg/kg.

The FDA's Assessment:
FDA generally agrees with the Applicant's position.

5.4 ADME/PK

The Applicant's Position:
The pre-clinical ADME/PK of futibatinib have been extensively characterized both in vitro and in vivo.

Absorption: Futibatinib was well absorbed with approximate 70% of radioactivity recovered in urine and bile after an oral administration of radiolabeled futibatinib ([^{14}C] futibatinib) to male rats with cannulated bile ducts. Approximately dose-proportional exposure increase was observed within the studied dose ranges in rats and dogs following single or multiple doses of futibatinib. No apparent futibatinib accumulation was observed in rats following daily dosing regimen up to 30 mg/kg dose level. In dogs, the accumulation was ~1.5x and ~2x in dogs following every other day and daily regimens, respectively, up to 30 mg/kg dose level. (Study No. AE-8214-G)

Distribution: Futibatinib exhibited rapid and extensive distribution based on quantitative whole-body autoradiography after a single oral dose of [^{14}C] futibatinib to pigmented rats. The concentration of radioactivity reached its peak in most of the tissues at 1 hr post-dosing. The blood-to-plasma drug concentration ratios (Rb) of futibatinib ranged from 0.554 to 0.664 over the futibatinib concentration 0.2 – 5 µM, indicating that futibatinib is unlikely to distribute in red blood cell. The plasma protein binding of futibatinib was high (> 90%) for all studied species, including mouse, rat, dog, and human. In human plasma, futibatinib was mainly bound to albumin and α1-acid glycoprotein. (Study Nos. AE-8076-G and 16DA)

Metabolism: No human specific metabolites were observed in the *in-vitro* liver microsomes and hepatocytes metabolite profiling from rat, dog, and human. The major metabolic pathways of futibatinib in humans are considered *O*-demethylation, oxidation, hydration, glutathione conjugation, and cysteine conjugation. CYP3A is a major enzyme involved in futibatinib hepatic metabolism. (Study Nos. 18DB26 and 18DB27)

Excretion: The orally absorbed drug-related material was predominantly excreted via feces in rats and dogs and via bile in bile-cannulated rats. (Study No. AE-8214-G).

Pharmacokinetic (PK) Drug Interaction: Results from *in-vitro* studies in human liver microsomes and hepatocytes indicated that futibatinib was a reversible inhibitor of CYP2C8, CYP2C9, and CYP2C19 but not of CYP1A2, CYP2B6, CYP2D6, or CYP3A. Time-dependent inhibition was observed for CYP3A but not CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, or CYP2D6. Futibatinib was a weak inducer of CYP1A2 but not CYP2B6 or CYP3A. Additionally, futibatinib was both a substrate and an inhibitor of P-gp and BCRP transporters. Futibatinib was an inhibitor of organic anion transporting polypeptide (OATP)1B1, OATP1B3, multidrug and toxin extrusion protein (MATE)1, and MATE2K but not of organic anion transporter (OAT)1,

OAT3, or organic cation transporter (OCT)2. Futibatinib was not a substrate of OATP1B1 or OATP1B3. (Study No. 16DA10)

The FDA's Assessment:
FDA generally agrees with the Applicant's position. CYP3A is the major CYP enzyme involved in futibatinib metabolism. In addition, FDA determined that CYP2C9 and CYP2D6 are also involved in futibatinib metabolism to a lesser extent compared to CYP3A (Table 6, Section 6.3.1).
FDA agrees with the Applicant's position that futibatinib does not inhibit CYP1A2, CYP2B6, CYP2D6, or CYP3A in vitro. While in vitro studies indicate futibatinib inhibits CYP2C8, CYP2C9, and CYP2C19, futibatinib is not expected to inhibit the CYP2C enzymes at clinically relevant concentrations (refer to Table 61, Appendix 19.5.3).
Additionally, in vitro studies indicate futibatinib inhibits OATP1B1, OATP1B3, MATE-1, and MATE2K, but futibatinib is not expected to inhibit these transporters at clinically relevant concentrations (refer to Table 62, Appendix 19.5.3).

5.5 Toxicology

5.5.1 General Toxicology

The Applicant's Position:
The nonclinical safety profile of futibatinib has been well characterized in rats and dogs, including oral repeated dose toxicity studies. The main toxicity findings of futibatinib in both species were increased values of phosphate and calcium in plasma, ectopic mineralization in multiple tissues, and lesions in both bone and cartilage. Most (if not all) of these toxicity findings were considered attributable to a mechanism-based effect of FGFR inhibition on mineral homeostasis and were confirmed as reversible except for ectopic mineralization. Species-specific findings of increased spontaneous corneal mineralization were noted in rats and were also considered to be affected by mineral imbalance because corneal mineralization is frequently observed in rats (Wegener 1994). Futibatinib was not genotoxic, but inhibited normal embryo-fetal development and resulted in embryo-fetal lethality.

The overall toxicity profile of futibatinib includes on-target related findings that are predictable, monitorable and considered clinically manageable in the intended patient population.

Rat Study:

4-Week Oral Repeated-Dosing Toxicity Study followed by 4-Week Recovery Period in Rats /B-7416, CTD location 4.2.3.2.2 Key Drug-related Adverse Findings

- The main toxicological findings were increased inorganic phosphorus in plasma, ectopic mineralization, bone/cartilage lesion, and increased corneal lesion. Reversibility of the toxicity findings was confirmed except for the ectopic mineralization.
- The severely toxic dose in 10% of the animals (STD10) of 10 mg/kg was established for the QOD regimen, but no STD10 was observed for QD dosing at the tested dose.

GLP compliance: Yes

Methods

Dose and frequency of dosing:	0, 3, 10, 30 mg/kg (QOD), 3 mg/kg (QD)
Route of administration:	Oral gavage
Formulation/Vehicle:	5 mg/mL/hypromellose solution
Species/Strain:	Rat/ Crl:CD(SD)
Number/Sex/Group:	10, including 6/sex/group for recovery
Age:	6 weeks old
Satellite groups:	Toxicokinetic: 6/sex/group for dosing groups, 3/sex/group for control groups

Dose (mg/kg)	**Toxicokinetics**		
	AUC_{0-24} (ng·hr/mL)		
	Analyte	**Males**	**Females**
0 (QOD)	TAS-120	BLQ/BLQ	BLQ/BLQ
3 (QOD)	(Day 1/27)	748/1030	741/1050
10 (QOD)		2660/3450	2490/2560
30 (QOD)		6640/7280	5450/5560
3(QD)		641/1120	862/953

Major Findings (Administration Period)

QOD	≥3 mg/kg: Increased inorganic phosphorus and calcium in urine, bone/cartilage lesion, increased corneal lesion, and ectopic mineralization ≥10 mg/kg: Increased creatinine and decreased total protein and albumin 30 mg/kg: Decreased body weight gain and food consumption; increased inorganic phosphorus in plasma; and increased BUN, ALP, and total cholesterol
QD	3 mg/kg: The treatment-related changes observed in-life and postmortem evaluations were mostly similar with those in the QOD dosing group. The severity of toxic changes was almost comparable or lower than that at 30 mg/kg (QOD); more severe than that at 3 and 10 mg/kg (QOD).
Recovery Period	
QOD	30 mg/kg: Toxicologic findings recovered except for ectopic mineralization
QD	3 mg/kg: Toxicologic findings recovered except for ectopic mineralization.

13-Week Oral Repeated-Dose Toxicity Study in Rats /B-8203, CTD location 4.2.3.2.3

Key Drug-related Adverse Findings

- The main toxicological findings were increased inorganic phosphorus in plasma, ectopic mineralization, bone/cartilage lesion, and increased corneal lesion. Reversibility of the toxicity findings was confirmed except for the ectopic mineralization.
- No new toxicologic findings or exacerbation compared with the 4-week study.

GLP compliance: Yes

Methods

Dose and frequency of dosing:	0, 1, 3, 10 mg/kg (QOD)

Route of administration:	Oral gavage
Formulation/Vehicle:	5 mg/mL/hypromellose solution
Species/Strain:	Rat/ Crl:CD(SD)
Number/Sex/Group:	10, including 6/sex/group for recovery
Age:	6 weeks old
Satellite groups:	Not applicable

Dose (mg/kg)	**Toxicokinetics**		
	AUC_{0-24} (ng·hr/mL)		
	Analyte	**Males**	**Females**
0 (QOD) 1 (QOD) 3 (QOD) 10 (QOD)	TAS-120 (Day 1/91)	BLQ/BLQ 205/293 909/1140 3080/3360	BLQ/BLQ 298/369 1020/1160 4050/3160

Major Findings (Administration Period)	
Male	≥1 mg/kg: Increase in one day's excretion of calcium and inorganic phosphorus in urine, increased creatinine in plasma. ≥3 mg/kg: Increased severity of focal corneal opacity, increased blood urea nitrogen, increased calcium, ectopic mineralization in various organs/tissues, bone lesion (thickening of the growth plate, increased secondary spongiosa, thickening of the joint cartilage, decreased hypertrophy zone of the growth plate, and increased trabecular bone of the diaphysis) in the femur and/or sternum. 10 mg/kg: Increased urine volume, decreased osmotic pressure of urine, increased inorganic phosphorus in plasma, mineralization-related change, atrophy of corneal epithelium, aggregation of the alveolar macrophages, decreased weights of the liver and thyroid, and mineralization of the aortic artery and arterial wall in the heart.
Female	≥1 mg/kg: Increase in one day's excretion of calcium and inorganic phosphorus in urine, increased urine volume, decreased osmotic pressure of urine, and increased creatinine in plasma. ≥3 mg/kg: Increased severity of focal corneal opacity, increased inorganic phosphorus in plasma, and increased blood urea nitrogen 10 mg/kg: Increased AST and ALP, decreased total protein and albumin, ectopic mineralization in various organs/tissues, bone lesion (thickening of the growth plate, increased secondary spongiosa, thickening of the joint cartilage, decreased hypertrophy zone of the growth plate and increased trabecular bone of the diaphysis) in the femur and/or sternum, and decreased weight of the liver.

Abbreviations: ALP: alkaline phosphatase; BLQ: below the lower limit of quantification (< 2.00 ng/mL); BUN: blood urea nitrogen; CTD: common technical document; GLP: Good Laboratory Practice; QD: once daily administration; QOD: every-other-day administration.

Dog Study:

4-Week Oral Repeated-Dosing Toxicity Study followed by and 4-Week Recovery Period in Dogs /B-7417, CTD location 4.2.3.2.5

Key Drug-related Adverse Findings

- The main toxicological findings were increased IP in plasma, ectopic mineralization, bone/cartilage lesion, and increased corneal lesion. Reversibility of the toxicity findings was confirmed except for the ectopic mineralization.

- The severely toxic dose in 10% of the animals (STD10) of 10 mg/kg was established in the QOD regimen, but no STD10 was observed for QD dosing at the tested dose.

GLP compliance: Yes

Methods

Dose and frequency of dosing:	0, 1, 3, 10 mg/kg (QOD), 0.3, 3 mg/kg (QD)
Route of administration:	Oral gavage
Formulation/Vehicle:	5 mg/mL/hypromellose solution
Species/Strain:	Dog, Beagle
Number/Sex/Group:	3, including 2/sex/group for recovery
Age:	6 months old
Satellite groups:	Not applicable

Dose (mg/kg)	Toxicokinetics		
	$AUC_{0\text{-}24}$ (ng·hr/mL)		
	Analyte	Males	Females
0 (QOD)	TAS-120 (Day 1/27)	BLQ/BLQ	BLQ/BLQ
1 (QOD)		528/585	390/379
3 (QOD)		984/1670	773/1050
10 (QOD)		1100/2320	1190/2110
0.3 (QD)		143/226	99.9/70.5
3 (QD)		861/1570	751/2080

Major Findings (Administration Period)	
QOD	≥1 mg/kg: Decreased triglyceride and bone/cartilage lesion ≥3 mg/kg: Suppression of body weight gain, slight decreased food consumption, increased inorganic phosphorus in plasma, and ectopic mineralization 10 mg/kg: Transit ananastasia (once) and moderate mineralization in aortic root
QD	≥0.3 mg/kg: Ectopic mineralization and bone lesion 3 mg/kg: Decreased locomotor activity, decreased body weight and food consumption, increased inorganic phosphorus in plasma, and moderate mineralization in aortic root
Recovery Period	
QOD	30 mg/kg: Toxicologic findings recovered except for ectopic mineralization
QD	3 mg/kg: Toxicologic findings recovered except for ectopic mineralization.

Abbreviations: BLQ: below the lower limit of quantification (< 2.00 ng/mL); CTD: common technical document; GLP: Good Laboratory Practice; QD: once daily administration; QOD: every-other-day administration

13-Week Oral Repeated-Dose Toxicity Study in Dogs/B-8204, CTD 4.2.3.2.6

Key Drug-related Adverse Findings

- The main toxicological findings were increased IP in plasma, ectopic mineralization, and bone/cartilage lesion. Reversibility of the toxicity findings was confirmed except for the ectopic mineralization.
- The highest non-severely toxic dose of 3 mg/kg in the QOD administration was established.
- There were no new toxicologic findings or exacerbation of known toxicities compared with the 4-week study.

GLP compliance: Yes

Methods

Dose and frequency of dosing:	0, 0.3, 1, 3 mg/kg (QOD)
Route of administration:	Oral gavage
Formulation/Vehicle:	5 mg/mL/hypromellose solution
Species/Strain:	Dog, Beagle
Number/Sex/Group:	3/sex/group for recovery
Age:	6 months old

Satellite groups:	Not applicable		
Dose (mg/kg)	**Toxicokinetics**		
	AUC_{0-24} (ng·hr/mL)		
	Analyte	**Males**	**Females**
0 (QOD) 0.3 (QOD) 1 (QOD) 3 (QOD)	TAS-120 (Day 1/91)	BLQ/BLQ 106/144 327/520 994/1470	BLQ/BLQ 133/135 477/445 1120/1610
Major Findings (Administration Period)			
Male	≥0.3 mg/kg: Mild mineralization in arterial walls of aortic root and related changes (cell infiltration etc.), bone lesion (elongation of proliferating zone, hypertrophic zone, and primary spongiosa; increased trabecular bone, and hypercellularity, etc.) ≥1 mg/kg: Increased ALT and inorganic phosphorus 3 mg/kg: Increased eosinophil ratio and moderate mineralization in arterial walls of the aortic root		
Female	≥0.3 mg/kg: Bone lesion (elongation of proliferating zone, hypertrophic zone and primary spongiosa, increased trabecular bone and hypercellularity, etc.) ≥1 mg/kg: Mild mineralization in arterial walls of aortic root and related changes (cell infiltration, edema, etc.) 3 mg/kg: Moderate mineralization in arterial walls of the aortic root; increased ALT, ALP, and inorganic phosphorus; and increased neutrophil count and ratio		

Abbreviations: ALP: alkaline phosphatase; BLQ: below the lower limit of quantification (< 2.00 ng/mL); BUN: blood urea nitrogen; CTD: common technical document; GLP: Good Laboratory Practice; QD: once daily administration; QOD: every-other-day administration

The FDA's Assessment:

FDA generally agrees with the Applicant's position. Plasma calcium levels increases were not remarkable across the 4-week and 13-week studies in rats and dogs.

	Male					Female				
Rat 4-week study (B-7416)	QD	QOD	QOD	QOD		QD	QOD	QOD	QOD	
Dose (mg/kg)	3	3	10	30		3	3	10	30	
P	23	.	.	12		17	.	.	19	
Ca	.	.	.	.		.	.	.	.	
Rat 13-week study (B-8203)	QOD	QOD	QOD			QOD	QOD	QOD		
Dose (mg/kg)	1	3	10			1	3	10		
P	10	11	36			.	27	43		
Ca	.	.	.			.	.	.		
Dog 4-week study (B-7417)	QD	QD	QOD	QOD	QOD	QD	QD	QOD	QOD	QOD
Dose (mg/kg)	0.3	3	1	3	10	0.3	3	1	3	10
P	.	.	14	18	24	16	.	.	.	16
Ca	.	5	.	.	.	.	.	.	.	.
Dog 13-week study (B-8204)	QOD	QOD	QOD			QOD	QOD	QOD		
Dose (mg/kg)	0.3	1	3			0.3	1	3		
P	20	38	46			18	19	36		
Ca	.	.	.			.	.	.		

"." indicates values below +5% change
QD=once daily; QOD=every-other-day

Detailed histopathology findings for 13-week rat and dog toxicology studies are below. Cartilage findings were not observed in the 13-week dog study.

Rat 13-week study (B-8203) Histophatology			Male				Female			
		Dose (mg/kg every-other-day)	0	1	3	10	0	1	3	10
Tissue		# Animals	10	10	10	10	10	10	10	10
Eye	Corneal opacity, focal	Minimal	7	8	7	4	6	7	5	6
		Mild			2	5			1	4
	Mineralization, corneal	Minimal		1	3	5				4
	Atrophy, corneal epithelium	Minimal				6				
	Retinal dysplasia, unilateral	Mild				1				
	Keratitis, unilateral	Minimal				1				
Thoracic aorta	Mineralization, arterial wall	Minimal				1				
Femur	Mineralization, periosteum	Minimal		3	4	10		2	2	3
	Thickening, growth plate	Mild				1				
	Decreased hypertrophic zone, growth plate	Minimal				2				
	Increased secondary spongiosa	Minimal				1				
	Thickening, joint cartilage	Minimal			2	3				
	Increased trabecular bone, diaphysis	Minimal			2	6				3
Sternum	Increased secondary spongiosa	Minimal			4	10				3
Heart	Mineralization, aortic artery	Minimal				2				
		Mild				1				
	Mineralization, arterial wall	Minimal				1				
	Myocarditis, focal, left, and right ventricles	Minimal	3	1	2	2				1
Kidney*	Calculus, renal pelvic	Minimal				2				
	Mineralization, arterial wall	Minimal				2				
	Mineralization, cortical total	Minimal	4	8	7	7	1	2	1	1
		Mild			1	2				
	Mineralization, medullary total	Minimal	5	6	8	5	6	9	8	8
		Mild				4				
Lung, bronchus	Aggregation, alveolar macrophage	Minimal	3	4	6	6	5	6	7	8
		Mild				4	1			
	Metaplasia, osseous	Minimal			1	2		1	1	
	Mineralization, arterial wall	Minimal	1			3	1		1	
Liver	Necrosis, focal	Minimal				1				
Stomach	Mineralization, mucosal glandular stomach	Minimal			1	4				
	Cyst, squamous, forestomach	Minimal				1				
	Hyperplasia, squamous focal, forestomach	Minimal				1				
Small intestine, duodenum	Erosion	Minimal				1				
Spinal cord	Mineralization, meninx	Minimal				2		1		2
Tongue	Mineralization, arterial wall	Minimal			2	7				2
		Mild				3				

Dog 13-week study (B-8204) Histophatology			Male				Female			
		Dose (mg/kg every-other-day)	0	0.3	1	3	0	0.3	1	3
Tissue		# Animals	3	3	3	3	3	3	3	3
Aorta, Aortic root	Mineralization, arterial wall	Mild		2	2	1			1	
		Moderate				1				1
	Cell infiltration, arterial wall	Minimal		1		1				
		Mild				1				
	Edema, Tunica intima	Minimal			1	2			1	1
	Cell infiltration, tunica intima	Minimal			1	2			1	1
	Hemorrhage, arterial wall	Minimal				1				1
Aorta, Arch	Mineralization, arterial wall	Minimal			1				1	
Femur, Bone marrow	Elongate, proliferating zone	Minimal		2	3	1		1	1	
		Mild				2				2
	Elongate, hypertrophic zone	Minimal		2	3	1		1	1	1
		Mild				1				
	Elongate, primary spongiosa	Minimal		1	2	1		1	2	
		Mild			1	2				1
	Increased, trabecular bone	Minimal		1	1	2		1	3	2
		Mild			2	1				1
	Hypercellularity	Minimal		1	1			2	2	2
		Mild			1				1	1
		Moderate		1		3				
Sternum, Bone marrow	Elongate, proliferating zone	Minimal			2	1			1	2
		Mild				2			1	1
	Thinning, hypertrophic zone	Minimal		1	2			2	2	
		Mild			1	1				1
		Moderate				1			1	1
		Severe				1				1
	Hypercellularity	Minimal		2		2				
		Mild		1		1			1	
Heart	Mineralization, arterial wall	Minimal				1				
Stomach	Mineralization, mucosal	Minimal				1				
	Cell infiltration, inflammation, lamina propria	Minimal						1		
Lung, Bronchus	Thickening, alveolar wall	Minimal							1	

5.5.2 Genetic Toxicology

The Applicant's Position:

Futibatinib had tested negative in an in vitro reverse mutation assay in bacteria. Futibatinib induced chromosomal aberrations in vitro although, in an in vivo micronucleus test, futibatinib did not exhibit clastogenic potential. In an in vivo comet assay, futibatinib did not exhibit DNA damaging potential.

In Vitro Reverse Mutation Assay in Bacterial Cells (Ames)

Study title/number/eCTD	Reverse Mutation Test in Bacteria/13CA16/4.2.3.3.1.1
Key findings	Futibatinib was not mutagenic

GLP compliance	Yes
Test system	Bacterial Ames Test: *Salmonella typhimurium*: TA98, TA100, TA1535, TA1537; with or without S9
Test validity	Yes

In Vitro Assays in Mammalian Cells

Study title/number/eCTD	Chromosomal Aberration Test in CHL/IU Cells/13CA17/4.2.3.3.1.2
Key findings	Futibatinib induced clastogenicity with or without S9 in short-term, but not induced in continuous treatment
GLP compliance	Yes
Test system	Chromosome aberration; CHL/IU Cells
Test validity	Yes

In Vivo Clastogenicity Assay in Rodent (Micronucleus Assay)

Study title/number/eCTD	Micronucleus Test in Rats/M-1504/4.2.3.3.2.1
Key findings	Futibatinib was not clastogenic
GLP compliance	Yes
Test system	Induction of bone marrow micronuclei in polychromatic erythrocytes from Wistar Han rats, Doses of 0, 30, 100, 300 mg/kg
Test validity	Yes

In Vivo DNA Damage Assay in Rat Liver (Commet Assay)

Study title/number/eCTD	In Vivo Comet Assay of Futibatinib in Rat Liver/ M-1592/4.2.3.3.2.2
Key findings	Futibatinib did not affect DNA
GLP compliance	Yes
Test system	Doses of 0, 30, 100, 300 mg/kg
Test validity	Yes

The FDA's Assessment:
FDA generally agrees with the Applicant's position. In the in vitro chromosomal aberration test (Study No. 13CA17), the short-term treatment was 6 hours. In the continuous treatment, cells were treated for 24 hours in the absence of metabolic activation.

The totality of genotoxicity data, including negative in vivo studies evaluating up to 300 mg/kg (approximately 150 times the recommended clinical dose of 20 mg based on BSA) and a negative mutagenicity assay, indicate there is a low potential for futibatinib to be genotoxic in vivo. Therefore, labeling is based on a determination that futibatinib is non-genotoxic.

5.5.3 Carcinogenicity

The Applicant's Position:
No carcinogenicity studies have been conducted with futibatinib and are not required for the proposed indication.

The FDA's Assessment:
Carcinogenicity studies are not recommended for the proposed indication.

5.5.4 Reproductive and Developmental Toxicology

The Applicant's Position:
Embryo-fetal developmental toxicity studies of futibatinib demonstrated that futibatinib has teratogenic effects on the rat embryo-fetus under the conditions of these studies.

Reproductive and Developmental Toxicity Studies				
Embryo-fetal development -Dose-range finding study	Oral	Rat	Futibatinib	18CC01 (Non-GLP)
Embryo-fetal development -Preliminary study for GLP study	Oral	Rat	Futibatinib	18CB09 (Non-GLP)

Oral Dose-Range Finding Study for Effects of Futibatinib on Embryo-Fetal Development in Rats (Study No. 18CC01)
Key Study Findings
- Effects on the Dams (F0): No death, moribundity, or abortion occurred in any group.
- Effects on the Fetuses (F1): The dose of 10 mg/kg was assumed to be the lethal dose for embryos/fetuses.
- It was concluded that a dose of <1 mg/kg was appropriate for highest dose to evaluate for the effects of futibatinib on embryo-fetal development in rats because live fetuses were obtained.

GLP compliance: Yes

Methods	
Dose and frequency of dosing:	0, 1, 10, mg/kg
Route of administration:	Oral gavage
Formulation/Vehicle:	5 mg/mL/hypromellose solution
Species/Strain:	Rat/ Crl:CD(SD)
Number/Sex/Group:	6 dams
Age:	12 weeks old
Satellite groups:	Not applicable

Abbreviations: GLP: Good Laboratory Practice; QD: once daily administration

Oral Preliminary Study for Effects of futibatinib on Embryo-Fetal Development in Rats (Study No. 18CB09)
Key Drug-related Adverse Findings
- Effects on the Dams (F0): No death, moribundity, or abortion occurred in any group.
- Effects on the Fetuses (F1): A dose of 0.5 mg/kg, enough live fetuses were obtained, however fetuses with visceral and skeletal anomalies were detected.
- Futibatinib has teratogenic effects in the rat embryo-fetus under the conditions of this study

GLP compliance: No

Prenatal and Postnatal Development

The Applicant's Position:
No pre- or postnatal studies have been conducted with futibatinib.

The FDA's Assessment:
In the preliminary study (Study No. 18CB09) where futibatinib was orally administered to pregnant rats once a day from Day 7 to Day 17 of the gestation period, the incidence of visceral or skeletal anomalies observed in fetuses (F1) was less than 5% at doses ≤ 0.15 mg/kg. A futibatinib dose of 0.5 mg/kg resulted in ~30% visceral anomalies and ~26% skeletal anomalies.

Summary of Visceral and Skeletal Anomalies in F1 Fetuses from Embryo-Fetal Development in Rats Study

Visceral anomalies	Cardiovascular	≥ 0.05 mg/kg	Membranous ventricular septal defect (VSD)
	Angiectopia	≥ 0.15 mg/kg	Interrupted aortic arch, malpositioned subclavian branch, retroesophageal subclavian or retroesophageal aortic arch
	Urogenital Anomalies (accompanied by transposed umbilical artery)	≥ 0.5 mg/kg	Absent kidney; small kidney; dilated renal pelvis; absent, dilated, convoluted ureter; malpositioned testis and/or epididymis;
Skeletal anomalies	Numerical anomalies	≥ 0.05 mg/kg	Absence or supernumerary of the thoracic and lumbar vertebrae or rib
		≥ 0.5 mg/kg	Fusion, absence, misalignment or misshape mainly in the sternabrae, rib, cervical, thoracic, and lumbar vertebrae

5.5.5 Other Toxicology Studies

The Applicant's Position:
In vitro, futibatinib did not induce phototoxic response in Balb/3T3 clone A31 cells under the conditions of this study.

In Vitro 3T3 NRU Phototoxicity Test (Study No. B190598)

Key Drug-related Adverse Findings
- Cell growth was not inhibited by >50% under any treatment conditions.
- The mean photo effect was <0.15 (actual value: -0.048).

Futibatinib did not induce phototoxic response to Balb/3T3 clone A31 cells under the conditions of this study

Test	Strains	GLP Compliance	Study Number
In Vitro Phototoxicity	BALB/3T3 clone A31 cells	Yes	B190598
Treatment:	0.391, 0.781, 1.56, 3.13, 6.25, 12.5, 25, and 50 µg/mL Incubation with futibatinib 60 minutes; Irradiation: 50 minutes		

The FDA's Assessment:
FDA agrees with the Applicant's position.

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Dubravka Kufrin
Primary Reviewer

Matthew Thompson
Supervisor

6 Clinical Pharmacology

6.1 Executive Summary

The FDA's Assessment:

The Applicant seeks approval of LYTGOBI (futibatinib) for the treatment of adult patients with previously treated, unresectable, locally advanced or metastatic cholangiocarcinoma (CCA) harboring fibroblast growth factor receptor 2 (FGFR2) gene fusions or other rearrangements. The proposed LYTGOBI dosing regimen is 20 mg orally once daily (QD), with or without food.

The Clinical Pharmacology section of the NDA is includes data to support the characterization of single and repeat dose pharmacokinetics (PK) of futibatinib, evaluation of effect of food on futibatinib PK, evaluation of drug-drug interactions (DDI) between futibatinib and dual P-gp and cytochrome P450 (CYP) 3A modulators and acid reducing agents, and physiologically-based PK (PBPK) modeling and simulations of DDI with moderate CYP3A modulators, assessment of potential for QT/QTc prolongation, population PK (popPK) analysis, and exploratory exposure-response (E-R) relationships for efficacy and safety.

The proposed LYTGOBI dosing regimen of 20 mg QD with the dose modification schema in the event of adverse reactions (AR) is supported by the efficacy and safety results from the Phase 2 portion of Study TAS-120-101 in patients with intrahepatic CCA harboring FGFR2 gene fusions or other rearrangement (n=103). The overall response rate (ORR) was 42% (95% CI: 32, 52) with a median duration of response of 9.7 months (95% CI: 7.6, 17.1). At the 20 mg QD dosing regimen, a flat E-R relationship was observed for ORR. However, positive E-R relationships were identified for safety endpoints with increasing futibatinib exposure resulting in higher probability of Grade ≥3 and serious AR, nail disorders, and AR leading to dose reductions and dose interruptions.

The key review questions focused on dose recommendations for the general population and in patients taking concomitant dual P-gp and strong CYP3A modulators, and the assessment of response to futibatinib based on the FGFR2 alteration type. The DDI studies support the recommendation to avoid concomitant administration of LYTGOBI with dual P-gp and strong CYP3A modulators. The popPK analyses did not identify clinically important covariates influencing futibatinib PK, including mild hepatic impairment and mild or moderate renal impairment; therefore, no dose adjustments are recommended based on the presence of mild or moderate hepatic impairment. Although nominally higher in the subset of patients with fusions, responses were observed in patients with either FGFR2 fusions or non-fusion rearrangements.

While the proposed 20 mg QD is efficacious, this dosing regimen may not be optimal as the limited data from the expansion phase of Phase 1 portion of Study TAS-120-101 suggest that 16 mg QD provides a potentially improved safety profile compared to the 20 mg QD (maximum tolerated dose, MTD) dosing regimen, with what appears to be similar efficacy. Hence,

investigation of the 16 mg QD dosing regimen within ongoing or planned trials to further optimize the recommended dose is recommended as a postmarketing requirement (PMR).

Recommendations
The proposed LYTGOBI dosage of 20 mg orally administered once daily for the proposed indication and the associated dose modification schema in the event of adverse reactions is generally acceptable. The Clinical Pharmacology review team has reviewed the information contained in NDA 214801 and recommends approval. The key review issues with specific recommendations and/or comments are summarized below. Post-marketing requirements and commitments are detailed in Section 13.

Review Issue	Recommendations and Comments
Pivotal or supportive evidence of effectiveness[†]	Phase 2 portion of Trial TAS-120-101 (patients with CCA with FGFR2 gene fusions or other rearrangements) demonstrated an ORR of 42% with a median duration of response of 9.7 months.
General dosing instructions	20 mg orally once daily, with or without food. This dosage needs further optimization from a clinical pharmacology perspective for the following reasons: • 20 mg QD is the MTD determined in the dose escalation phase. • High rates of Grade ≥ 3 (77%) and serious (39%) ARs, and dose adjustments due to ARs (77%: dose reductions 58% and dose interruptions 66%) were observed at 20 mg QD. • Data from expansion phase of Phase 1 portion of Study TAS-120-101 suggest that 16 mg QD may also be as efficacious, possibly with an improved safety profile for patients who met the selection criteria of the Phase 2 portion based on the following findings: the 16 mg QD cohort (n=11) had an ORR (95% CI) of 36% (15, 65) compared to 22% (6, 46) in the 20 mg QD cohort (n=19) based on independent assessor, and had a lower incidence of Grade ≥3 and serious ARs, dose reductions due to ARs, and late onset of first toxicity events compared to the 20 mg QD cohort. Of note, higher response rate (42%) at 20 mg QD was observed in the pivotal trial.

	• Positive exposure-safety relationships were identified for any grade, Grade ≥3, and serious ARs, and dose reductions, drug interruptions and dose discontinuations due to ARs, and ARs leading to Grade ≥3 hyperphosphatemia, any grade eye disorders, and any grade nail disorders.
Dosing in patient subgroups (intrinsic and extrinsic factors)	• Avoid concomitant use of dual P-gp and strong CYP3A inhibitors and inducers. • No dose adjustment is recommended for concomitant use of gastric acid reducing agents. • No dose adjustments are recommended in patients with mild hepatic impairment, and mild to moderate renal impairment.
Labeling	• Avoid concomitant use of dual P-gp and strong CYP3A inhibitors and inducers. • Consider more frequent monitoring for adverse reactions associated with concomitantly administered drugs that are sensitive substrates of P-gp or BCRP and reduce the dose of these drugs per their Prescribing Information.
Bridge between the to-be-marketed and clinical trial formulations	The pharmacokinetic exposures of the earlier capsule formulation , and the subsequent tablet formulation, and the to-be approved tablet formulation used during clinical development of futibatinib were found to be comparable.

Postmarketing Requirements and Commitments

The Applicant is requested to conduct the following clinical pharmacology studies as postmarketing requirements (PMRs) or postmarketing commitments (PMCs). The PMR and PMC studies will be included in the Approval letter with milestones agreed upon after negotiation with the Applicant.

PMC or PMR	Key Issue(s) to be Addressed	Rationale	Key Considerations for Design Features
☐ PMC ☒ PMR	Determination of an optimal futibatinib dose from a safety perspective	High rates of Grade ≥3 AR (77%), serious AR (39%) and dose reductions due to ARs (58%) were observed with the proposed LYTGOBI 20 mg QD dosing regimen. Expansion phase of Study TAS-120-101 suggests that 16 mg QD of	Randomized study that compares the recommended dosage of 20 mg daily to a lower dosage (e.g., 16 mg). The study should provide a comparative analysis including dose- and exposure-response relationships for efficacy and safety, overall response rate and

		futibatinib may also be as efficacious, possibly with a better safety profile, for patients who met the selection criteria of the Phase 2 portion. The 16 mg QD cohort (n=11) had an ORR (95% confidence intervals) of 36% (15, 65) compared to 22% (6, 46) in the 20 mg QD cohort (n=19) based on independent assessor, and had a lower incidence of Grade ≥3 and serious AR, dose reductions due to AR, and late onset of first toxicity events compared to 20 mg QD cohort. Positive exposure-safety relationships were identified for any grade, Grade ≥3 and serious ARs, and dose reductions, drug interruptions and dose discontinuations due to AR, and AR leading to Grade ≥3 hyperphosphatemia, any grade eye disorders, and any grade nail disorders.	duration of response, the rates of Grade ≥3 adverse reactions, serious adverse reactions, dose reductions, interruptions, and discontinuations due to adverse reactions. The study should incorporate systematically assessed patient- reported outcome assessments to evaluate tolerability. Core outcomes should include patient-reported symptomatic adverse event data, overall side effect bother, physical function, and role function. .
☐ PMC ☒ PMR	Determination of an appropriate futibatinib dose for patients with moderate and severe hepatic impairment.	Majority (92%) of the total recovered radioactivity was found in the feces, indicating that hepatic elimination is the major elimination pathway for futibatinib.	Single dose of futibatinib in otherwise healthy subjects with moderate and severe hepatic impairment compared to healthy subjects on PK and safety.
☐ PMC ☒ PMR	Determination of the effect of a P-gp inhibitor on the PK and safety of futibatinib.	Futibatinib is a substrate of P-gp in vitro. Modeling and simulations suggest possible involvement of P-gp in its ADME. The extent of involvement is unknown.	Single dose of futibatinib with and without a concomitant P-gp inhibitor.
☒ PMC ☐ PMR	Identification of potential mechanisms of primary and acquired resistance to futibatinib	Emergence of secondary FGFR2 mutations have been associated with resistance to FGFR inhibitors in patients with cholangiocarcinoma. In TAS-120-101 and TAS-120-301, ctDNA samples were planned to be collected to	ctDNA sample collection and analysis as described in TAS-120-101 and TAS-120-301 protocols.

		evaluate FGFR2 alterations, including analysis of FGFR2 mutations potentially associated with resistance to FGFR2 inhibition. Molecular characterization of tumors (tissue and/or cell free DNA) at baseline, on-treatment and at the time of progression may allow for uncovering primary and acquired resistance mechanisms to futibatinib and help to inform sequence of FGFR2 inhibitors and therapy combinations, and to optimize patient selection.	

6.2 Summary of Clinical Pharmacology Assessment

6.2.1 Pharmacology and Clinical Pharmacokinetics

Data:
Refer to Table 6 in Section 6.3.1 for a summary of clinical pharmacology characteristics for futibatinib.

The Applicant's Position:
The development program of futibatinib included a comprehensive clinical pharmacology package to support the use of futibatinib 20 mg once daily (QD) for the treatment of CCA.

Clinical studies in cancer patients (TAS-120-101 and 10059010) collectively allowed for a characterization of the PK of futibatinib in the intended patient population, population PK (PopPK) analyses for potential sources of intrinsic and extrinsic PK variability, exposure-response (ER) analyses for outcome measures for both efficacy and patient safety, and ultimately a justification of the proposed dosage regimen of 20 mg QD for futibatinib (Study TONC-PMX-TAS-120-1718).

In addition, 7 clinical pharmacology studies in healthy subjects have been completed and are included in the initial submission. Single-dose studies evaluated bioequivalence of 2 different clinical formulations (10059020), food effect (TAS-120-102), mass balance excretion and metabolism (TAS-120-106), and gastric pH dependency (TAS-120-104) of futibatinib. Multiple dose studies assessed the clinical DDI potential of futibatinib either as a victim or perpetrator (TAS-120-103, TAS 120-105) and cardiac safety (TAS-120-107). Physiologically based

pharmacokinetic (PBPK) analyses predicted DDI potential with cytochrome P450 (CYP) 3A perpetrators or transporter substrates (Studies 20DC01 and 20DC09). Lastly, there is an ongoing clinical pharmacology study (TAS 120-108) for evaluation of PK and safety of futibatinib in patients with chronic hepatic impairment (HI) and matched healthy subjects.

Overall, the results of the clinical pharmacology program provided sufficient information to support the use of futibatinib for the treatment of CCA.

The FDA's Assessment:
FDA generally agrees with the Applicant's position that the clinical pharmacology studies support the use of futibatinib for the indicated population. However, the 20 mg QD dosing regimen had high rates of Grade ≥3 AR (77%), serious AR (39%) and dose reductions due to AR (58%). Therefore, there is the need to further optimize dosage post-approval. A postmarketing requirement study to evaluate a lower dosage of 16 mg QD regimen within ongoing or planned trials for dose optimization may provide additional information to support dosing (refer to Sections 6.2.2.3 and 6.3.2.2 for details). Refer to Table 6 in Section 6.3.1 regarding the pharmacokinetic characteristics of futibatinib.

6.2.2 General Dosing and Therapeutic Individualization

6.2.2.1 General Dosing

Data:
The Phase 1 clinical trials (Study 10059010 and Study TAS-120-101) explored QOD and QD dosing schedules in their dose escalation parts. Based on safety, PK/pharmacodynamic, and preliminary efficacy results, futibatinib 20 mg once daily dosing (QD) as the maximum tolerated dose (MTD) for futibatinib was selected as the recommended Phase 2 dose (RP2D) for further futibatinib monotherapy development.

In the Phase 2 portion of study TAS-120-101, the futibatinib 20 mg QD regimen demonstrated a clinically meaningful benefit in patients with iCCA with a confirmed ORR of 41.7% (95% CI: 32.1, 51.9) and a median DOR of 9.7 months as assessed by independent central radiology review committee (IRC), as well as a generally predictable, monitorable and manageable safety profile.

The effect of food on futibatinib PK was evaluated in Study TAS-120-102 in healthy adult subjects. Consumption of a high-fat and high-calorie meal had minimum impact on the overall exposure (14% and 11% reductions in AUC_{last} and AUC_{inf}, respectively) of futibatinib in plasma although the 42% decrease in Cmax was observed. Considering the variability of PK and results of the exposure-efficacy response analyses, the food effect is considered to have no clinically meaningful effect, and therefore futibatinib may be administered with or without food.

The Applicant's Position:
The recommended dose of futibatinib is 20 mg (five 4-mg tablets) taken orally once daily until disease progression or unacceptable toxicity occurs. Futibatinib can be taken with or without food at approximately the same time each day. Refer also to Section 6.3.2.2 for the regimen selection rationale.

The FDA's Assessment:
FDA agrees with the Applicant's position that 20 mg QD is efficacious based on the results of Phase 2 portion of Study TAS-120-101. However, this dosage may not be optimal as available data from Phase 1 portion of Study TAS-120-101, although limited, suggests that a 16 mg QD may be as efficacious with a more tolerable safety profile compared to 20 mg QD (refer to Sections 6.2.2.3 and 6.3.2.2 for details).
FDA agrees with the Applicant's position on administration of LYTGOBI with or without food as there was no clinically meaningful effect of a high fat meal on futibatinib exposure (Refer to Section 6.3.2.4).

6.2.2.2 Therapeutic Individualization

Data:
The PK population analyses showed age, patient status (healthy volunteers vs patients with advanced solid tumors), liver enzymes, sex, race, cancer type, Eastern Cooperative Oncology Group (ECOG) score, cycle, and FGFR abnormality were not found to have a significant effect on futibatinib PK. No significant effects of hepatic impairment (mild) or renal impairment (mild and moderate) on futibatinib CL/F were identified.

Although high body weight was found to be associated with larger Vc/F, it has no effect on overall exposure at steady state (AUCss) as shown in Figure 2. Low serum albumin was associated with lower CL/F. Patients at the 5th percentile of baseline albumin were predicted to have 36% higher AUCss as compared to patients with median value of baseline albumin.

Additionally, population PK analysis confirmed that co-administration with CYP3A4 inducer was predicted to result in ~ 60% decrease in futibatinb AUCss; co-administration with CYP3A4 inhibitor was predicted to result in ~ 30% increase in futibatinb AUCss. These findings were generally consistent with the results obtained from non-compartment analysis in Study TAS-120-103.

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Covariate	Percentile	Value	Ratio [95% CI]
Weight (kg)	5%	49	1 [1, 1]
	25%	60	1 [1, 1]
	50%	70	1 [1, 1]
	75%	83	1 [1, 1]
	95%	105	1 [1, 1]
Albumin (g/dL)	5%	31	1.36 [1.28, 1.44]
	25%	38	1.11 [1.09, 1.13]
	50%	42	1 [1, 1]
	75%	46	0.913 [0.897, 0.928]
	95%	49	0.857 [0.832, 0.882]
CYP3A4 Inducer	---	Yes	0.395 [0.34, 0.449]
CYP3A4 Inhibitor	---	Yes	1.3 [1.18, 1.42]
High dose	---	>36 mg	1.11 [1.05, 1.17]
Fed status	---	Yes	1 [1, 1]
Study 20	---	Yes	0.428 [0.341, 0.514]
Other studies	---	Yes	0.769 [0.679, 0.861]

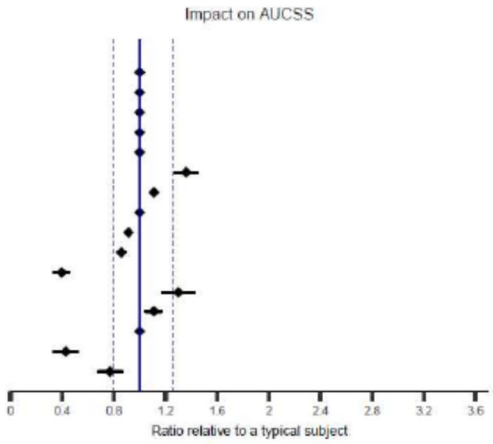


Figure 2: Forest Plot of Covariate Effects on AUCss

Source: Figure 5-5 in Report TONC-PMX-TAS120-1718

The Applicant's Position:

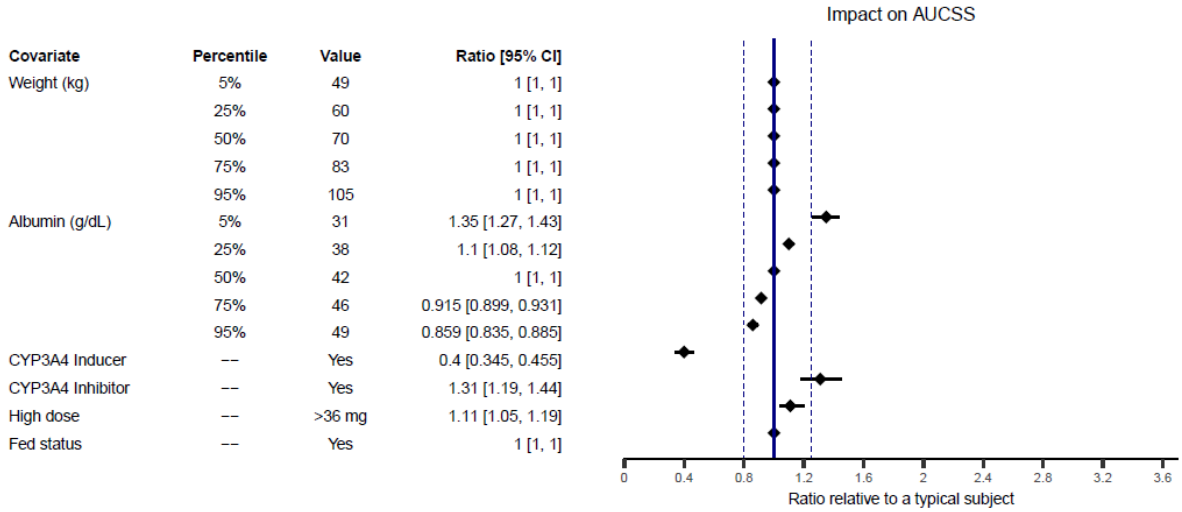
No therapeutic individualization is needed in the proposed indication based on intrinsic factors, including age, sex, race/ethnicity, body weight, mild to moderate renal impairment, or mild hepatic impairment, as no clinically relevant impact in exposure was identified in the population PK analysis. Considering the variability of PK and results of the exposure-efficacy response analyses, also the effect of albumin on exposure is not considered to be clinically meaningful and does not require therapeutic individualization.
Concomitant uses of moderate-to-strong CYP3A inhibitors and moderate-to-strong CYP3A inducers with futibatinib should be avoided.

The FDA's Assessment:

FDA agrees with the Applicant's position that dose modifications are not needed based on age (18 to 82 years), sex, race (White, Asian, and African American), body weight (36 to 152 kg), mild hepatic impairment (total bilirubin ≤ upper limit of normal (ULN) and aspartate transaminase (AST) > ULN, or total bilirubin >1 to 1.5× ULN and any AST), and mild to moderate renal impairment (creatinine clearance ≥30 mL/min) (refer to Section 6.3.2.3). The effect of moderate to severe hepatic impairment and severe renal impairment on the PK of futibatinib have not been investigated.
FDA recommends that concomitant use of medications that are dual P-gp and strong CYP3A modulators should be avoided with LYTGOBI. FDA disagrees with the Applicant's position on avoiding strong and moderate CYP3A modulators with LYTGOBI as the Applicant's modeling and simulations are deemed unreliable (refer to Section 6.3.2.4). The effect of a P-gp modulator (without CYP3A modulation), or a strong CYP3A modulator (without P-gp modulation) on the exposure of futibatinib has not been investigated. Therefore, no dose recommendations can be

provided for P-gp modulator (without CYP3A modulation), or a strong CYP3A modulator (without P-gp modulation) at this time.
The effect of moderate and severe hepatic impairment, and P-gp inhibitors on the PK and safety of futibatinib should be assessed to inform corresponding dose recommendations (see 6.2.2.3 and 6.3.2.3). The effect of P-gp inhibitors that are not CYP3A modulators will inform the contribution of CYP3A towards the observed changes in exposure of futibatinib with strong CYP3A modulators that are not P-gp modulators.

Figure 3: Forest Plot of Covariate Effects on AUCss



Source: Reviewer generated based on response to Information Request received on 12/08/2021

6.2.2.3 Outstanding Issues

Data:
Not Applicable.

The Applicant's Position:
The PK and safety of futibatinib in patients with moderate to severe hepatic impairment have not been studied. A dedicated Phase 1 study with subjects with mild, moderate, and severe hepatic impairment and matched-control subjects is ongoing.

The FDA's Assessment:
While the proposed 20 mg QD dosing regimen is efficacious, it may not be optimal. Evaluation of a lower dose of 16 mg QD within ongoing or planned trials for dose optimization is required as a postmarketing requirement (PMR) (Section 13).

Moderate to severe hepatic impairment has not been investigated. Evaluation of the effect of moderate and severe hepatic impairment on the PK and safety of futibatinib is required as a PMR (Section 13).

Futibatinib is a substrate of P-gp and the modeling and simulations suggest possible involvement of P-gp transporter in its ADME; however, the extent of P-gp involvement is unknown. This needs to be assessed as a PMR (Section 13).

6.3 Comprehensive Clinical Pharmacology Review

6.3.1 General Pharmacology and Pharmacokinetic Characteristics

Data:
General pharmacological and pharmacokinetic characteristics of futibatinib can be found in Table 6 below.

Table 6: Applicant – General Pharmacology and Pharmacokinetic Characteristics of Futibatinib

Pharmacology	
Mechanism of Action	Futibatinib is a structurally novel, irreversible inhibitor of FGFR 1–4. Selective inhibitor of FGFR1–4 with 50% inhibitory concentration (IC_{50} values) against a panel of 287 human kinases FGFR1: 1.8 ± 0.4 nmol/L FGFR2: 1.4 ± 0.3 nmol/L FGFR3: 1.6 ± 0.1 nmol/L FGFR4: 3.7 ± 0.4 nmol/L
Active moiety	The main circulating component in plasma was futibatinib (59.19% of the total sample radioactivity), and as primary circulating metabolites in plasma, a glucuronide of monohydroxy futibatinib (8.97%), a cysteine conjugate (TAS-06-22947) (8.68%), and a cysteinylglycine conjugate (TAS-06-22952) (13.37%) were observed. TAS-06-22947 and TAS-06-22952 inhibited FGFR1–4 with >70-fold higher IC_{50} than futibatinib.
QT/QTc prolongation	Based on results of the thorough QT study, at the recommended dose of 20 mg and supratherapeutic dose of 80 mg, futibatinib does not result in increase of the QTc interval more than 5 msec.
General Information	
Bioanalytical assay	Futibatinib bioanalytical assays (LC-MS/MS) were developed to measure the concentration of futibatinib in the clinical studies in this NDA.
Healthy vs. Patients	Patient status (healthy volunteers vs subjects with advanced solid tumors) is not a significant covariate for futibatinib PK in the popPK analysis.
Steady-state exposure at the proposed dosing regimen	Futibatinib exposures in patients (N=203) following multiple-dose oral administration of futibatinib (20 mg QD) were predicted by the PopPK analysis. Geometric mean $C_{min,ss}$ (gCV%): 1.67 ng/mL (117%) Geometric mean $C_{max,ss}$ (gCV%): 144 ng/mL (50.3%) Geometric mean AUC_{ss} (gCV%) 790 ng·hr/mL (44.7%)

Minimal effective dose or exposure	12 mg
Maximum tolerated dose	20 mg QD
Dose-proportionality	Following single-dose and multiple-dose oral administrations, C_{max} and AUCs of futibatinib were dose proportional in the dose range of 4 to 24 mg QD.
Accumulation	Steady state was achieved after the 1st dose and there was no accumulation with the geometric mean accumulation ratio (gCV%) of 1.03 (2.3%).
Absorption	
Bioavailablity	Futibatinib has low solubility and high permeability (BCS Class II compound). Absolute oral bioavailability has not been determined. Based on results of the mass balance study, the absorption ratio of futibatinib is expected to be over 70%. The bioavailability of liquid filled hard capsule and film coated tablet clinical trial formulations for futibatinib is equivalent.
T_{max}	Median T_{max} is 2 (range: 1.2 to 22.8) hours.
Food effect	Consumption of a high-fat and high-calorie meal resulted in decreases in C_{max} and AUC_{inf} of futibatinib by approximately 42% and 11%, respectively.
Distribution	
Volume of distribution	The geometric mean (gCV%) apparent central volume of distribution (Vc/F) was 72.59 L (32.9%) at steady state. FDA Assessment: The geometric mean (gCV%) for Vc/F was 66 L (18%) for patients who received 20 mg QD based on final popPK model.
Plasma protein binding	Futibatinib was 95% bound to in human plasma protein, primarily to albumin and α1-acid glycoprotein, independent of drug concentration. FDA Assessment: FDA disagrees with Applicant's position that futibatinib protein binding is independent of concentrations, as protein binding was tested only from 0.2 to 5 µmol/L and futibatinib Cav,ss and Cmin,ss levels were below 0.2 µmol/L.
Elimination	
Half-life	The mean (CV%) elimination half-life ($T_{1/2}$) of futibatinib was 2.94 hours (26.5%).
Clearance	The geometric mean (gCV%) apparent clearance (CL/F) was 18.474 L/h (43.9%). FDA Assessment: The geometric mean (gCV%) for CL/F is 20 L/hr (23%) for patients who received 20 mg QD based on final popPK model.
Metabolism	Futibatinib is predominantly metabolized by CYP3A in vitro. FDA Assessment: While futibatinib is primarily metabolized by CYP3A, in vitro studies indicate that CYP2C9 and CYP2D6 are also involved in futibatinib metabolism, however, to a lesser extent compared to CYP3A.
Excretion	Following a single oral dose of 20 mg radiolabeled futibatinib, approximately 64% of the dose was recovered in feces and 6% in urine. Futibatinib excretion in unchanged form was negligible in either urine or feces. FDA Assessment: Based on total radioactivity recovered in the mass balance study, 91% of recovered radioactivity was observed in feces and 9% in urine.
Drug interaction liability	
As victim	• Itraconazole, a strong CYP3A inhibitor, increased futibatinib C_{max} by 51% and increased AUC by 41% following a single dose of 20 mg futibatinib.

	• Concomitant use of moderate CYP3A inhibitors is predicted to increase futibatinib exposure by approximately 25-40%. • Rifampin, a strong CYP3A inducer, decreased futibatinib C_{max} by 53% and AUCs by 64% following a single dose of 20 mg futibatinib. • Concomitant use of a moderate CYP3A inducer is predicted to decrease futibatinib exposure by approximately 48%. • Co-administrations of multiple doses of lansoprazole, a proton pump inhibitor, has no clinically significant impact on the potentially pH-dependent absorption of futibatinib PK. • Futibatinib is a substrate of P-gp and BCRP not a substrate of organic anion transporting polypeptide (OATP1B1 and OATP1B3). P-gp or BCRP inhibitors are not expected to affect futibatinib exposure at clinically relevant concentrations. FDA Assessment: FDA disagrees with Applicant's determination that strong and moderate CYP3A modulators should be avoided with LYTGOBI as the Applicant's PBPK modeling and simulations suggested possible involvement of transporters in the absorption of LYTGOBI , and itraconazole and rifampin are dual P-gp and strong CYP3A modulators. FDA also disagrees with Applicant's determination that P-gp and BCRP inhibitors are not expected to affect futibatinib exposures as the Applicant's PBPK modeling and simulations suggested possible involvement of transporters although the extent of involvement is unknown.
As perpetrator	• Futibatinib has no clinically significant impact on C_{max} and AUCs of midazolam as a sensitive CYP3A substrate. • Futibatinib does not inhibit CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6 or CYP3A, and does not induce CYP1A2, CYP2B6, or CYP3A4 at clinically relevant concentrations. • Futibatinib inhibits P-gp and BCRP in vitro, but does not inhibit OAT1, OAT3, OCT2, OATP1B1, OATP1B3, MATE1, or MATE2K at clinically relevant concentrations.
Population PK and Exposure-Response Analyses	
Population PK	Age, patient status (healthy volunteers vs cancer patients), liver enzymes, sex, race, cancer type, Eastern Cooperative Oncology Group (ECOG) score, cycle, and FGFR abnormality were not found to impact futibatinib PK. No clinically meaningful differences in the systemic exposure of futibatinib were observed based on mild-to-moderate renal impairment or mild hepatic impairment.
Efficacy Exposure-Response relationship	In patients with CCA harboring *FGFR2* rearrangements (including fusions) who received 20 mg futibatinib QD, there were no statistically significant exposure-efficacy relationships for ORR, DCR, DoR, OS, PFS, or CTS. However, a statistically nonsignificant trend toward higher ORR with increased $C_{min,ss}$ was noted. FDA Assessment: FDA notes that the E-R for efficacy should be interpreted with caution because of the limited sample size and narrow exposure range of exposures from a single dose level (20 mg QD).
Safety Exposure-Response relationship	In cancer patients receiving futibatinib QD, statistically significant exposure-safety relationships were observed for hyperphosphatemia and nail disorders. FDA Assessment: Positive E-R relationships were observed for multiple safety endpoints including any grade and Grade ≥3 hyperphosphatemia, any grade nail disorders, any grade retinal disorders, any grade retinal detachment, any Grade ≥3 ARs, serious ARs, ARs leading to dose discontinuations, ARs leading to dose reductions, and ARs leading to study drug

	interruptions. FDA notes that the positive E-R relationships for any grade and grade ≥3 hyperphosphatemia are likely confounded by the frequent use and early initiation of the phosphate-lowering therapies.

The Applicant's Position:
Futibatinib is a selective irreversible inhibitor of FGFR 1-4. There are no circulating active metabolites and the active moiety among futibatinib-relevant compounds is futibatinib. At the recommended dose of 20 mg QD, futibatinib reached C_{max} at 2 hours after oral administration to cancer patients then declined with a half-life of 2.94 hours. Futibatinib does not accumulate over multiple doses. Futibatinib PK is dose-proportional in the dose range of 4 to 24 mg QD. Absorption of futibatinib is expected to be at least 70%. Almost all of futibatinib administered is metabolized and subsequently excreted into mainly feces. CYP3A is a metabolizing enzyme responsible for futibatinib in vitro. This is consistent with the DDI observation that a strong inhibitor and a strong inducer of CYP3A significantly altered futibatinib exposures. In addition, the PBPK analysis suggested moderate CYP3A perpetrators may also affect futibatinib exposures. On the other hand, futibatinib does not have potential to affect PK of any CYP enzyme substrates in the clinical setting. In the PopPK analysis, clinically meaningful intrinsic factors were not identified. E-R analyses showed there was no significant relationship between exposures and efficacy endpoints; however, a nonsignificant trend of increase in ORR was observed with C_{min} at steady state. Significant exposure-safety relationships were observed for hyperphosphatemia and nail disorders. Futibatinib does not prolong QTc interval at dose levels up to 80 mg.

The FDA's Assessment:
FDA's assessments are provided in Table 6 above.

6.3.2 Clinical Pharmacology Questions

6.3.2.1 Does the clinical pharmacology program provide supportive evidence of effectiveness?

Data:
The results from the futibatinib development program provide evidence for the following key benefits of futibatinib in the treatment of patients with previously treated locally advanced or metastatic CCA harboring *FGFR2* gene rearrangements, including gene fusions:

In the Phase 2 portion of TAS-120-101, futibatinib demonstrated a significant and clinically meaningful benefit in patients with CCA harboring *FGFR2* gene rearrangements (including fusions) with a confirmed ORR of 41.7% (95% CI: 32.1, 51.9) as assessed by IRC according to RECIST version 1.1. This exceeded the target of 20% for the primary endpoint of the Phase 2

portion of TAS-120-101. Tumor responses were durable with a 9.7-month (95% CI: 7.62, 17.05) median DOR as a key secondary endpoint of the Phase 2 portion of TAS-120-101. A total of 31 of 43 responders (72%) had a response duration of over 6 months and 6 responders (14.0%) had DOR lasting at least 12 months. At the time of the data cut, 13 patients (30.2%) had an ongoing response of ≥6 months.

Further secondary efficacy endpoints corroborate the efficacy of futibatinib, including a median PFS of 9.0 months (95% CI: 6.9, 13.1) and a median OS of 21.7 months (95% CI: 14.5, NE). Quality of life data show that the overall health status of patients was maintained during the treatment period.

The exposure-response (ER) analyses were conducted to evaluate ER relationships for efficacy and safety to support dose selection of futibatinib in adult subjects with CCA harboring *FGFR2* rearrangements (including fusions). In the exposure-efficacy analyses including patients in the Phase 2 portion, no statistically significant exposure-efficacy relationships for ORR, DCR, DoR, OS, PFS, or CTS were observed within the exposure range produced by the 20 mg QD regimen although there was a nonsignificant trend (p=0.145) toward higher ORR with an increase of $C_{min,ss}$ (Figure 4).

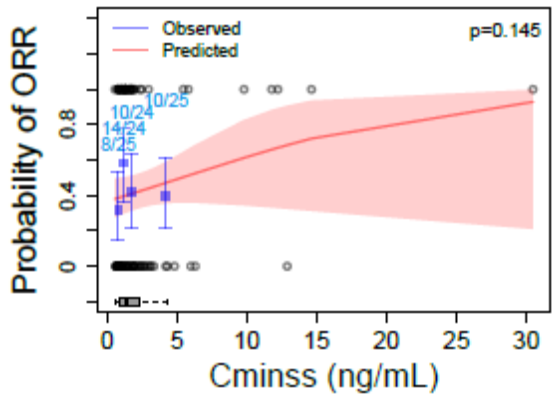


Figure 4: Applicant - Relationship Between Exposure and ORR

Source: Figure 17 in Module 2.7.2

The exposure-safety response analyses were conducted in patients from Study 10059010 and Study TAS-120-101. The results showed a significant increase in the probability of any grade and Grade ≥3 hyperphosphatemia with increasing futibatinib exposure for the QD dosing regimen. The probability of nail disorders (any grade) increased modestly with increasing futibatinib exposures after QD dosing.

Model-based dose-response projections were performed to predict probabilities of key efficacy and safety endpoint rates (ORR, hyperphosphatemia any grade, hyperphosphatemia Grade ≥3,

nail disorders any grade) for doses ranging from 16 to 24 mg QD (Table 7). Model-based projections of ORR showed a modest increase in objective response (<3%) over the dose range of 16 to 24 mg QD. Hyperphosphatemia observed at a dose of 20 mg QD was manageable while there was a steep increase in Grade ≥3 hyperphosphatemia for the 24 mg QD regimen relative to the 20 mg QD regimen (51.2% versus 24.9%).

Table 7: Applicant – Model predicted Probabilities of Key Efficacy and Safety Endpoints by Dose Group

Futibatinib Dose (mg QD)	Model-predicted Rate (%) Estimate (90% CI)			
	ORR	Hyperphosphatemia Any Grade	Hyperphosphatemia Grade ≥3	Nail disorders Any Grade
16	41.7 (33.3 – 50.3)	46.1 (29.1 – 66.4)	10.4 (6.1 – 20.1)	34.9 (29.1 – 41.1)
20	42.9 (34.5 – 51.4)	75.4 (68.0 – 81.2)	24.9 (18.1 – 33.3)	37.0 (30.8 – 43.4)
24	44.0 (35.6 – 52.7)	91.8 (82.1 – 96.3)	51.2 (30.1 – 69.9)	38.9 (32.2 – 45.4)

Sources: Table 51 in Module 2.7.2

The Applicant's Position:
Clinical pharmacology studies including the E-R analyses support the recommended dosing regimen of 20 mg QD is effective for the treatment of patients with CCA.

The FDA's Assessment:
FDA agrees with the Applicant that 20 mg QD of LYTGOBI is efficacious based on the results of Phase 2 portion of Study TAS-120-101. However, the 16 mg QD dose also appeared to be efficacious and potentially with a more tolerable safety profile compared to 20 mg QD dosage based on the results of the expansion phase of Phase 1 portion of Study TAS-120-101 (refer to Sections 6.2.2.3 and 6.3.2.2).

6.3.2.2 Is the proposed dosing regimen appropriate for the general patient population for which the indication is being sought?

Data:
The recommended dose of futibatinib monotherapy is 20 mg orally once daily (QD). In vivo, futibatinib demonstrated sustained inhibition of FGFR signaling and potent antitumor activity in *FGFR* alteration-driven human tumor xenograft models. Futibatinib exhibited statistically significant and dose-dependent antitumor activity with once daily administration. Intermittent futibatinib dosing schedules (QOD or twice weekly) resulted in antitumor activity in some but not all FGFR-deregulated xenograft models. On the other hand, in nonclinical toxicology studies, futibatinib QD dosing resulted in more pronounced hyperphosphatemia compared to QOD dosing. While hyperphosphatemia is a known on-target effect of FGFR inhibition, prolonged and

pronounced hyperphosphatemia may cause precipitation of calcium-phosphate crystals that can lead to soft tissue mineralization.

Based on these nonclinical results, the Phase 1 clinical trials (Study 10059010 and Study TAS-120-101) explored QOD and QD schedules in their dose escalation parts.

- From a safety perspective, there was no MTD defined up to the highest dose of 200 mg QOD evaluated, as there was a single DLT reported (10059010 CSR, Module 5.3.5.2). For QD dosing, the MTD was established as 20 mg QD due to 3 out of 9 evaluable patients experiencing DLTs when dosed at a starting dose of 24 mg QD futibatinib (TAS-120-101 Part 1 CSR, Module 5.3.5.2).
- When comparing reported adverse events (AEs) other than DLTs at the system organ class (SOC) level, the incidence of AEs in most SOCs was numerically lower in the QD population than in the QOD population, including the SOCs for skin and subcutaneous disorders, nervous system disorders, general and administration site disorders, and blood and lymphatic system disorders (all ≤10% lower incidence). The only SOC ≥10% more frequent with QD dosing was nutrition and metabolism, largely driven by asymptomatic hyperphosphatemia manageable by phosphate binders and/or futibatinib dose adjustments.
- From a PK/pharmacodynamic perspective, both futibatinib QD and QOD dosing led to dose-proportional exposure and increased serum phosphate concentrations after repeated doses. However, a stronger exposure-pharmacodynamic response relationship was observed in the QD cohort compared to the QOD cohorts, suggesting more profound FGFR target engagement with QD dosing.
- From a preliminary efficacy perspective, a higher frequency of confirmed PRs was observed for QD dosing (5 / 54 patients) compared to QOD dosing (2 / 71 patients) across the 2 Phase 1 clinical trial dose escalation portions.

Based on safety, PK/pharmacodynamic, and preliminary efficacy results, dosing at 20 mg daily (QD) as the MTD for futibatinib was selected as the RP2D for futibatinib monotherapy development. In addition to the efficacy data and manageable safety profile observed for 20 mg QD futibatinib dosing in the Phase 2 portion of Study TAS-120-101, model-based dose projections for futibatinib support selection of the 20 mg QD dosing (refer to Table 6 in Section 6.3.2.1).

Consumption of a high-fat and high-calorie meal slightly decreased bioavailability of futibatinib, however it is not expected to have a clinically meaningful effect on futibatinib efficacy and therefore futibatinib may be administered without regard to meals (refer to Section 6.3.2.4).

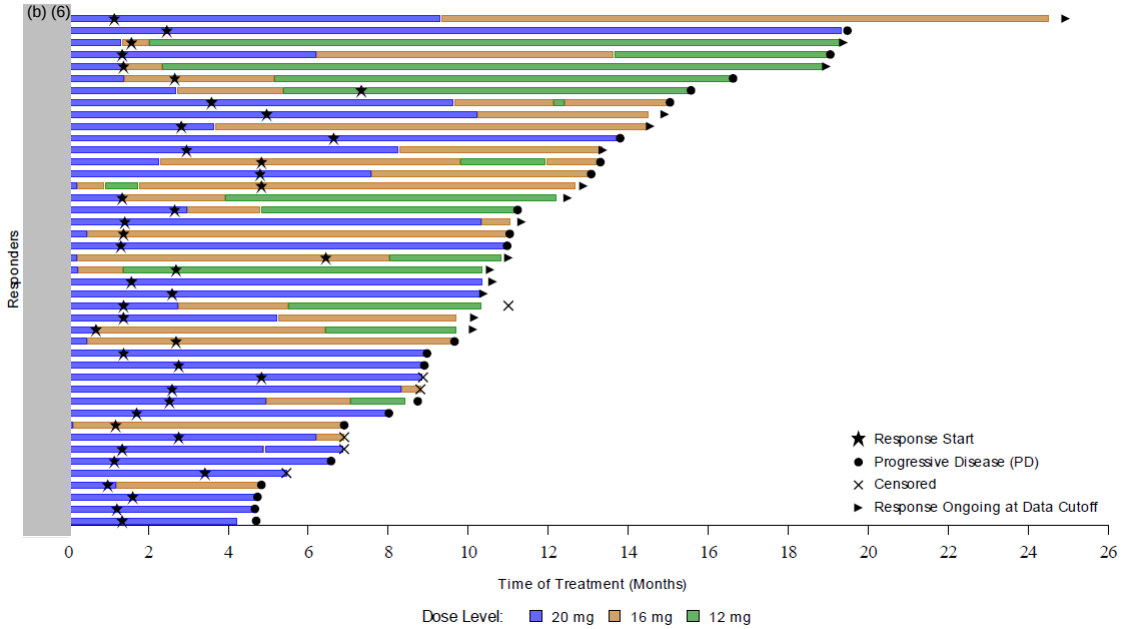
The Applicant's Position:

Based on the collective study results, the recommended dosing regimen of 20 mg QD futibatinib monotherapy is safe and efficacious for the treatment of patients with CCA.

The FDA's Assessment:

The FDA agrees with the Applicant's position that the 20 mg QD dose of LYTGOBI is efficacious (ORR of 42%, 95 CI: 32, 52) based on the results of the Phase 2 portion of Study TAS-120-101 (Table 9 and Section 8.1.2). Majority (72%) of patients were on 20 mg at the time of response (Figure 5). However, there was a high incidence of Grade≥3 adverse reactions (AR: 77%), serious ARs (39%) and dose adjustments due to ARs (77%: dose reductions 58% and dose interruptions 66%) (Table 9).

Figure 5: Swimmers Plot: Dose distribution of futibatinib at the time of response through duration of response for responders assessed by IRC in 20 mg QD cohort (n=43) in Phase 2 portion of Study TAS-120-101



Source: Figure 4, Information Request (IR) Response 2/7/22. SDN 12

Table 8: Comparison of ORR at 16 mg QD and 20 mg QD in Expansion Phase and at 20 mg QD in Phase 2 of Study TAS-120-101

	TAS-120-101				
	Expansion Phase of Phase 1				**Phase 2**
	16 mg QD (iCCA, n=19)	**20 mg QD** (iCCA/FGFR2, n=42)	**16 mg QD** (iCCA/FGFR2 & meet criteria of Pivotal trial, n=11)	**20 mg QD** (iCCA/FGFR2 & meet criteria of Pivotal trial, n=19)	20 mg QD (iCCA/FGFR2 **Pivotal**, n=103)

ORR % (95% CI)	32% (13, 57)	17% (7, 31)	**36% (15, 65)**	**21% (6, 46)**	**42% (32, 52)**

Efficacy data based on independent assessors were used for the analysis
Source: Appendix 19.5.8, Table 75 and Table 76; IR response 4/11/22, SDN 19; IR Response 6/2/22, SDN27

Table 9: Comparison of Safety at 16 mg QD and 20 mg QD in Expansion Phase and 20 mg QD in Phase 2 Portions of Study TAS-120-101

	TAS-120-101				
	Expansion Phase of Phase 1				**Phase 2**
	16 mg QD (iCCA, n=19)	**20 mg QD** (iCCA/FGFR2, n=42)	**16 mg QD** (iCCA/FGFR2 & meet criteria of Pivotal trial, n=12)	**20 mg QD** (iCCA/FGFR2 & meet criteria of Pivotal trial, n=19)	**20 mg QD** (iCCA/FGFR2 **Pivotal**, n=103)
Grade ≥3 ARs	58	**76**	**64**	**74**	**77**
Serious ARs	16	**45**	**27**	**47**	**39**
Dose Modifications due to ARS	63	62	82	63	77
Dose reductions due to ARs	5	31	9	**37**	**58**
Dose interruptions due to ARs	63	50	82	63	66
Discontinuations due to ARs	5	7	0	0	8

Source: Table 14.3.2.1.1.1 to 4, IR Response 6/2/22, SDN 27; Table 10, Part 2, CSR, SDN 3

Table 10: Comparison of Time to First Events for Safety at 16 mg QD and 20 mg QD in Expansion Phase and 20 mg QD in Phase 2 Portions of Study TAS-120-101

	TAS-120-101				
	Expansion Phase of Phase 1				**Phase 2**
	16 mg QD (iCCA, n=19)	**20 mg QD** (iCCA/FGFR2, n=42)	**16 mg QD** (iCCA/FGFR2 & meet criteria of Pivotal trial, n=11)	**20 mg QD** (iCCA/FGFR2 & meet criteria of Pivotal trial, n=19)	**20 mg QD** (iCCA/FGFR2 **Pivotal**, n=103)
Grade ≥3 ARs	16	**2**	--	--	--
Serious ARs	25	**12**	--	--	--
Dose reductions due to ARs	NE	**15.8** (5.2, NE)	NE (2.6, NE)	**8.8** (1.7, NE)	**6.2** (3.7, 9.7)
Dose interruptions due to ARs	NE (2.4, NE)	NE (1.4, NE)	NE (0.4, NE)	**2.1** (0.3, NE)	**3.9** (1.7, 6.0)

Discontinuations due to ARs	NE	NE	NE	NE	NE

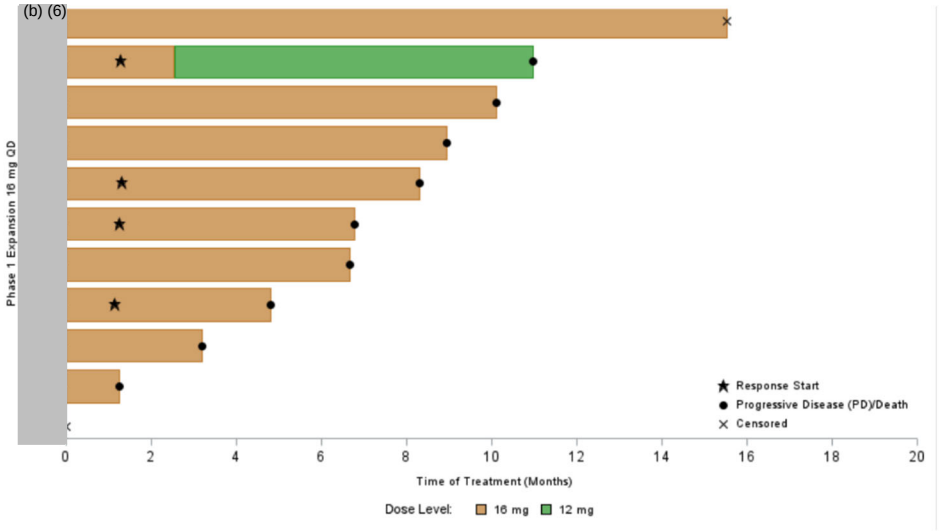
Source: Table 14.2.4.4.3.1.1 to 4, IR Response 6/2/22, SDN 27; Figure 13, IR Response, 2/7/22, SDN 12

FDA's position based on the limited Expansion Phase data is that the 16 mg QD dose also appeared efficacious, potentially with a better safety profile compared to 20 mg QD. This is supported by the following data:

- ORR in the 16 mg QD cohort (n=11) was 36% (15, 65) versus 22% (6, 46) in the 20 mg QD cohort (n=19) in patients in the Expansion Phase of Study TAS-120-101 who met the selection criteria of the Phase 2 portion of the study (Table 8). All 4 responders at 16 mg QD cohort (n=11) were on 16 mg QD at the onset of the response (Figure 6).
- A flat E-R relationship for efficacy (Figure 15, Appendix 19.5.8) was observed at 20 mg QD. FDA notes that the E-R for efficacy should be interpreted with caution because of the limited sample size and narrow exposure range of exposures from a single dose level (20 mg QD).
- Lower incidence of Grade ≥3 and serious ARs and dose reductions due to ARs in the 16 mg QD cohort compared to 20 mg QD cohorts, and time to first toxicity events was generally earlier for the 20 mg QD cohort versus 16 mg QD cohort in patients in the Expansion Phase of the study (Table 9 and Table 10).
- Positive E-R relationships were observed for multiple safety endpoints including any grade and Grade ≥3 hyperphosphatemia, any grade nail disorders, any grade retinal disorders, any grade retinal detachment, any Grade ≥3 ARs, serious ARs, ARs leading to dose discontinuations, ARs leading to dose reductions, and ARs leading to study drug interruptions: Figure 19, Appendix 19.5.8).
- The efficacy and safety results in the 16 mg QD and 20 mg QD cohorts in the Expansion Phase do not appear to be confounded by demographic factors (Table 11). See detailed evaluation below.
- Additionally, population PK analysis suggested that age (18–82 years), sex, race, cancer type, ECOG score, and FGFR abnormality were not found to be predictors of futibatinib PK. Exposures between Asian and non-Asian population were comparable (Appendix 19.5.7).

The above data, although limited, suggest that the 16 mg QD may potentially have a better safety profile and be equally efficacious as 20 mg QD; therefore, more data is necessary to determine that the futibatinib dose is optimized. Consequently, we recommend evaluation of the 16 mg QD dosage within ongoing or planned trials for dose optimization as a PMR.

Figure 6: Swimmers Plot: Dose distribution of futibatinib over treatment period assessed by independent assessors in 16 mg QD cohort (n=11) in patients in the Expansion phase of Study TAS-120-101 and who met the selection criteria in Phase 2 portion of the study



Source: Reviewer generated based on response to FDA information request received on 05/13/2022.

Table 11: Comparison of Demographic Factors at 16 mg QD and 20 mg QD Cohorts in Expansion Phase and 20 mg QD in Phase 2 Portions of Study TAS-120-101

Demographics, Median (range)	**16 mg QD** (iCCA, n=19) (%)	**20 mg QD** (iCCA with FGFR2 , n=42) (%)	**16 mg QD** (iCCA/FGFR2 & meet PT criteria) (N=11)	**20 mg QD** (iCCA/FGFR2 & meet PT criteria) (N=19)	**20 mg QD** (iCCA/FGFR2 **Pivotal Trial,** N=103
Age (years)*	52 (34,68)	55 (8, 83)	56 (34, 64)	56 (35, 80)	58 (22, 79)
<65 yrs (%)	95%	81%	100%	64%	78%
Female (%)	74%	79%	73%	79%	56%
Weight (kg)*	78 (52, 134)	69 (45, 101)	82 (55, 134)	69 (45, 95)	70 (43, 152)
% ECOG 0	58%	45%	46%	53%	47%
Height (cm)*	165 (152, 180)	166 (155, 185)	165 (152, 180)	166 (160, 178)	166 (152, 190)
Race (%) Caucasians Asian Blacks	 84% 5% 5%	 60% 14% 2%	 82% 0 9%	 58% 11% 5%	 50% 29% 8%
1 & ≥3 Prior Therapies (%)	32% & 47%	14% & 45%	46% & 18%	21% & 21%	47% & 23%

*Median (range)
Source: Table 14.1.5.1.1, IR Response 6/2/22, SDN 27; Table 14B.1.10.1, Pt 2 CSR, SDN 3

The following evaluation, based on limited data, supports the FDA's position that the efficacy and safety results in the 16 mg QD and 20 mg QD cohorts in Expansion Phase do not appear to be confounded by patient demographic factors (Table 11):

- Demographics for 16 mg and 20 mg cohorts in the Expansion Phase showed similar trend for age, sex, ECOG score, and height.
- The higher proportion of patients <65 years in the 16 mg QD cohort does not explain the observed difference in efficacy and safety, as subgroup analyses (see Figure 8, Section 8.1.2 and Table 64, Appendix 19.5.5) indicated that age patients ≥65 years had better ORR with no clinically significant differences in safety.
- The higher proportion of Caucasians and less Asians in 16 mg cohorts does not explain the observed difference in safety and efficacy as subgroup analyses (see Figure 8, Section 8.1.2 and Table 64, Appendix 19.5.5) indicated that safety and efficacy between the two racial groups were similar for both 16 mg QD and 20 mg QD cohorts.
- The higher proportion of patients with 1 prior therapy and comparable proportion of patients with ≥3 prior therapy were observed in the 16 mg cohort compared to 20 mg cohort. Nonetheless, subgroup analyses (see Figure 8, Section 8.1.2 and Table 64, Appendix 19.5.5) indicated that efficacy was better for ≥3 prior therapies with no trend for safety.

6.3.2.3 Is an alternative dosing regimen or management strategy required for subpopulations based on intrinsic patient factors?

Data:

As described in detail in Section 6.2.2, no patient intrinsic factors were found to have clinically meaning effect on futibatinib exposure.

In addition, futibatinib exposures were comparable between subjects with mild hepatic impairment and normal hepatic function. Only 1 subject (of 203 subjects on 20 mg QD) was classified as having moderate hepatic impairment and had exposures comparable to subjects with normal hepatic function.

Results of the mass balance study showed that the mean urinary excretion of radioactivity was approximately 6.5% of the dose during 336 hours following a single dose of [^{14}C]-futibatinib solution (20 mg). Similarly, for patients with advanced solid tumors following a single dose of futibatinib (8 to 200 mg QOD), less than 0.1% of the dose was excreted in urine as unchanged form. Thus, renal function is not expected to have effect on futibatinib exposure.

The Applicant's Position:

No alternative dosing regimen or management strategy is recommended for subpopulations based on intrinsic patient factors. No dose adjustment is recommended for patients with mild hepatic impairment and mild to moderate renal impairment. However, the recommended dose of futibatinib has not been established for patients with moderate to severe hepatic impairment. Effects of moderate to severe hepatic impairment will be determined from the ongoing study.

The FDA's Assessment:

FDA agrees with the Applicant's position to not implement dose adjustments for patients with mild hepatic impairment and mild to moderate renal impairment (Appendix 19.5.7). However, the effect of moderate to severe hepatic impairment and severe renal impairment have not been investigated. The effects of moderate and severe hepatic impairment on the PK and safety of futibatinib need to be investigated as a PMR to inform appropriate dose recommendation in this specific patient population.

FGFR2 Fusions or Rearrangements and Response to Futibatinib

Of 103 patients comprising the efficacy population, FGFR2 status was analyzed in tumor tissue in 96% [n=99/103; primary tumor site: (n=55); metastatic tumor site: (n=44)], in liquid samples in 3% (n=3) and in unspecified tissue in 1% (n=1) of patients. Sixty percent (n=62) of patients were enrolled based on local NGS tests [FMI commercial F1CDx F1 (n=53), other tissue-based NGS (n=5), liquid-based NGS (n=3), FISH (n=1)] and 40% (n=41) were enrolled based on a central NGS test (FMI Clinical Trial Assay [CTA]). Of the 62 patients enrolled with local tests, 27 had tumor samples retrospectively retested with the FMI CTA. Of these, results were concordant in 21 samples. The 6 discordant results were due to differences in fusion vs non-fusion rearrangement calls.

The final FGFR2 status used for analyses was determined by the Applicant based on central or local test results using the following precedence rules: (1st) results of the FMI CTA; (2nd), results of local FMI F1CDx; and (3rd), results of local tests. Seventy seven percent (n=79) of samples had fusions and 22% (n=24) had other rearrangements (Table 12).

Table 12: Distribution of Final FGFR2 Status per Applicant Rules of Precedence (N=103)

FGFR2 Alteration	Central test	Local test	Total
Fusion	49	30[1]	79
Rearrangement	19	5[2]	24
Total	68	35	103

Source: Reviewer's analysis of adsl dataset. Per precedence rules, when FMI CTA results were discordant with local results, final FGFR2 alteration classification was based on FMI CTA.

The FMI CTA and FMI commercial F1CDx assays used the following definitions for fusions or other rearrangements:

An FGFR2 rearrangement predicted to be a fusion: Breakpoint is within the FGFR2 intron 17/ exon 18 hotspot and the gene partner is known in the literature or is a novel partner;

An FGFR2 rearrangement, which cannot be conclusively predicted to be a fusion: Breakpoint is within the FGFR2 intron 17/exon 18 hotspot, and the partner gene is out of frame or out of strand with exon 17 of FGFR2. Alternatively, the downstream end of the breakpoint may be in an intergenic region and not within another gene.
1. Fusions identified with local tests (N=30): FMI CDx (n=23), local FMI liquid test (n=2), other local NGS-based tests (n=4), and local NGS-based liquid test (n=1).
2. Rearrangements identified with local tests (N=5): Local FISH (n=1), local FMI CDx (n=2), and other local NGS-based test (n=1).

In the subset of FGFR2 fusions (n=79), 46 unique partners were identified, most (n=37) occurring only once. BICC1 was the most common partner (n=24) (Table 13), which is consistent with results previously reported for FGFR2 fusion positive-iCCA. Confirmed partial responses were observed in patients with either FGFR2 fusions (including a variety of non-BICC1 partners) or non-fusion rearrangements, although responses were nominally higher in the subset of patients with fusions (Table 13).

Table 13: Exploratory analyses of response by FGFR2 status (N=103)

FGFR2 Fusions or Other Rearrangements		Number of Patients	Number of Confirmed Responses
Fusions (N=79; ORR 44.3%)			
FGFR2 fusion gene partners	BICC1	24	10 PR
	WAC	3	0
	KIAA1217	3	2 PR
	SHROOM3	2	0
	SMARCC1	2	1 PR
	SHTN1	2	1 PR
	VCL	2	2 PR
	CTNNA3	2	1 PR
	MACF1	2	1 PR
	Other FGFR2 partners, one patient each[1]	37	17 PR
Rearrangements (N=24; ORR 33.3%)			
		24	8 PR

Source: Reviewer's exploratory analysis using adsl and adrs datasets. Responses are IRC-confirmed best overall response. PR= Partial Response. FGFR2 status correspond to Applicant's determined final FGFR2 status. Gene partners identified in local enrollment test but not identified in retrospective FMI CTA test: MYPN (n=1), CEP55 (n=1), BICC1 (n=1) i.e., fusion on local test and rearrangement on FMI CTA are not included in the table.
1. FGFR2 fusion partners identified once (N=37), those associated with response are bolded: TBC1D4, CEP131, **RBM20**, **CIP2A**, SORBS1, **CIT**, **CFAP58**, CREB5, SEC23IP, **BEND3**, SLMAP, **CUX1**, **TACC1**, **DDX21**, **TUFT1**, EVI5, PUM1, **GPHN**, **RXRG**, INA, **SH3KBP1**, **BFSP2**, CEP44, LRBA, CEP55, **AXDND1**, SYNPO2, CA10, **TACC2**, NRBF2, TRIM8, OFD1, TXLNA, **PDE3B**, POC1B, **ARHGAP22**, MYH9.

FGFR2 kinase domain mutations and sensitivity to futibatinib
In vitro studies showed that futibatinib demonstrated inhibitory activity against FGFR2 kinase domain mutations previously associated with resistance to FGFR2 inhibition (Section 5.3). In response to an FDA information request (May 18, 2022), the Applicant indicated that the planned exploratory analysis to assess the presence of FGFR2 mutations in plasma samples collected at baseline and end of treatment has not been conducted. A PMC to identify potential mechanisms of primary and acquired resistance to futibatinib will be requested so as to further characterize the impact of FGFR2 alterations on futibatinib response (Section 13).

6.3.2.4 Are there clinically relevant food-drug or drug-drug interactions, and what is the appropriate management strategy?

Data:

Food effect:

Futibatinib PK was assessed in healthy adult subjects following a single oral dose of futibatinib (5 × 4 mg tablets) under fasted and fed conditions. Consumption of a high-fat and high-calorie meal resulted in statistically significant decreases in C_{max}, AUC_{last}, and AUC_{inf} of futibatinib by approximately 42%, 14%, and 11%, respectively. However, the extent of decrease in AUCs was smaller than gCV% values of $C_{min,ss}$ and AUC_{ss} (44.7% and 117%, respectively), and the effect of food on futibatinib bioavailability is considered to be marginal. Given that no clear relationships between futibatinib exposures ($C_{min,ss}$ and AUC_{ss}) and efficacy endpoints were observed, consumption of a high-fat and high-calorie meal is not expected to have a clinically meaningful effect on futibatinib efficacy and therefore futibatinib may be administered without regard to meals.

Effects of other drugs on futibatinib:

A significant drug-drug interaction was observed when futibatinib was coadministered with itraconazole (a strong inhibitor of CYP3A and P-gp). Coadministration of a single oral 20-mg dose of futibatinib with itraconazole 200 mg QD increased futibatinib C_{max} by approximately 51% and AUCs by approximately 41%, relative to a 20-mg dose of futibatinib administered alone. PBPK model analyses predicted that coadministration of strong, moderate, and weak inhibitors of CYP3A potentially increase futibatinib AUC_{tau} by around 50%, 25 to 40%, and 10%, respectively.

Coadministration of futibatinib with a strong CYP3A and P-gp inducer (rifampicin 600 mg QD) resulted in approximately 53% and 64% decreases in C_{max} and AUCs of futibatinib following a single dose, respectively, in healthy adult subjects. PBPK analyses predicted that carbamazepine (strong CYP3A inducer), rifampicin (strong CYP3A inducer), and efavirentz (moderate CYP3A

inducer) would decrease AUC_{tau} of futibatinib 20 mg QD by approximately 35%, 60%, and 50%, respectively.

A proton pump inhibitor, lansoprazole 60 mg QD, had no clinically significant impact on the potentially pH-dependent absorption of futibatinib in healthy adult subjects. Futibatinib is a substrate of P-gp and BCRP. However, considering the expected high absorption ratio of futibatinib and saturable efflux transport activities, inhibitors of P-gp and BCRP are not expected to affect futibatinib exposure to a clinically relevant extent.

Potential for futibatinib to affect other drugs:
Futibatinib is a potential time-dependent inhibitor of CYP3A enzymes in vitro; however, futibatinib (20 mg QD) had no clinically significant impact on C_{max} and AUCs of a single-dose of oral midazolam, a sensitive CYP3A substrate, in healthy adult subjects.

Futibatinib reversibly inhibited activities of CYP2C8, CYP2C9, and CYP2C19 in vitro. Basic model analyses indicated that coadministration of futibatinib 20 mg QD is unlikely to cause clinical DDIs with CYP2C substrates. Futibatinib had potential for the weak induction of mRNA of CYP1A2, CYP2B6, and CYP3A4 in vitro; however, considering the expected concentration of futibatinib in the liver, it is unlikely that futibatinib would have a clinically significant impact on PK of substrates for CYP1A2, CYP2B6, and CYP3A4.

Futibatinib is an inhibitor of P-gp and BCRP in vitro. Results of PBPK analyses suggested that futibatinib is unlikely to have a clinically significant impact on exposures of clinical substrates for P-gp. On the other hand, only under the most conservative modelling assumptions, futibatinib was predicted to have potential to increase exposures of clinical BCRP substrates when coadministered simultaneously, in particular of hepatic BCRP. PBPK simulations incorporating a 2-hour dosing interval between futibatinib PO and the clinical BCRP substrate rosuvastatin decreased the potential risk for a clinically important drug-drug interaction to unlikely. Under all other conditions, futibatinib was predicted to have no clinically significant effect on rosuvastatin. Futibatinib is an inhibitor of OATP1B1, OATP1B3, MATE1, and MATE2K in vitro. Basic model analyses indicated that coadministration of futibatinib 20 mg QD is unlikely to cause clinical DDIs with substrates of OATP1B1, OATP1B3, MATE1, or MATE2K.

<u>The Applicant's Position:</u>
A strong CYP3A inhibitor and a strong CYP3A inducer significantly altered futibatinib exposures. The PBPK analysis predicted a potential DDI with moderate CYP3A inhibitor and inducer. Based on these results, concomitant uses of moderate-to-strong CYP3A inhibitors and moderate-to-strong CYP3A inducers with futibatinib should be avoided. A slight change of bioavailability by food consumption was not expected to be clinically meaningful and therefore futibatinib can be taken with or without food.

The FDA's Assessment:

FDA agrees with the Applicant's position that there is no clinically meaningful effect of high fat meal on futibatinib exposure (Appendix 19.5.2). Clinical DDI studies with itraconazole and rifampin (dual P-gp and strong CYP3A modulators) and PBPK analysis suggest that the involvement of the transporters in the absorption of futibatinib cannot be excluded and P-gp modulators may alter systemic exposure of futibatinib. FDA disagrees with Applicant's position on avoiding strong and moderate CYP3A modulators with LYTGOBI. Instead, FDA recommends that dual P-gp and strong CYP3A modulators be avoided with LYTGOBI based on the DDI studies with itraconazole (dual P-gp and strong CYP3A inhibitor) and rifampin (dual P-gp and strong CYP3A inducer) (Appendix 19.5.3). The effect of a P-gp modulator (without CYP3A modulation), or a strong CYP3A modulator (without P-gp modulation) on the exposure of futibatinib has not been investigated. Therefore, no dose recommendations can be provided for P-gp modulator (without CYP3A modulation), or a strong CYP3A modulator (without P-gp modulation) at this time. Also, FDA recommends frequent monitoring of ARs for concomitant use of drugs that are substrates of P-gp and BCRP and reducing the dose of these drugs per their Prescription Information, as futibatinib inhibits P-gp and BCRP in vitro.

In addition, a drug-drug interaction study of LYTGOBI with a P-gp inhibitor is requested as a PMR, as futibatinib is a substrate of P-gp and the Applicant's PBPK modeling and simulations indicated the possible involvement of P-gp transporter but did not reliably address the relative contributions of CYP3A and P-gp towards the change in futibatinib exposure with dual CYP3A and P-gp modulators (Appendix 19.5.6). This PMR should address the contributions of P-gp, consequently, inform the contribution of CYP3A, towards change in futibatinib exposure with a P-gp modulator (without CYP3A modulation), or a strong CYP3A modulator (without P-gp modulation).

Does this drug prolong the QT or QTc interval?

At the proposed dose of 20 mg and a supratherapeutic dose of 80 mg futibatinib was not associated with significant QTc prolongation effect, the upper bound 90% confidence interval was less than 5 ms (DARRTS ID 4888313, 11/15/2021).

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7 Sources of Clinical Data

7.1 Table of Clinical Studies

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Data:
An overview of the clinical studies supporting the efficacy and safety of futibatinib is presented in Table 14.

Table 14: Applicant – Listing of Clinical Trials Relevant to this NDA

Type of Study	Study Identifier	Objective(s) of the Study	Study Design and Type of Control	Test Product(s); Dosage Regimen;	Number of Subjects	Healthy Subjects or Diagnosis of Patients	Duration of Treatment	Study Status; Type of Report
Studies to Support Efficacy and Safety								
Efficacy/ safety	TAS-120-101	Phase 1 Expansion: evaluate the safety and efficacy of futibatinib in multiple tumor types harboring specific FGF/FGFR aberrations.	Open-label, non-randomized study	Futibatinib: 16 or 20 mg QD (continuous daily dosing)	20 mg: 170	Patients aged ≥18 years with multiple tumor types	Patients may continue until discontinuation criteria were met.	Complete; Full
		Phase 2: assess the antitumor efficacy (ORR) and safety of futibatinib.	Open-label, non-randomized study	Futibatinib: 20 mg QD (continuous daily dosing)	103	Patients aged ≥18 years with iCCA harboring *FGFR2* gene rearrangements	Patients may continue until discontinuation criteria were met.	Ongoing; Full
Studies to Support Safety								
Efficacy/ safety	TAS-120-101	Phase 1 Dose Escalation: establish the MTD/RP2D.	Open-label, non-randomized study	Futibatinib: escalating dose levels of 8-200 mg QOD and 4-24 mg QD.	QD: 44	Patients aged ≥18 years with advanced solid tumors	Patients may continue until discontinuation criteria were met.	Complete; Full

Type of Study	Study Identifier	Objective(s) of the Study	Study Design and Type of Control	Test Product(s); Dosage Regimen;	Number of Subjects	Healthy Subjects or Diagnosis of Patients	Duration of Treatment	Study Status; Type of Report
Phase 1 PK	10059010	Phase 1 Dose Escalation: establish the MTD and/or RP2D of futibatinib.	Open-label, non-randomized study	Futibatinib: escalating dose levels of 8-160 mg QOD and 16-20 mg QD	QD: 10	Japanese patients aged ≥20 years with advanced solid tumors	Patients may continue until discontinuation criteria were met.	Complete; Full
		Phase 1 Expansion: evaluate the safety, efficacy, PK, and PD	Open-label, non-randomized study	Futibatinib: escalating dose levels of 56-120 mg QOD and 16-20 mg QD.	QD: 33	Japanese patients aged ≥20 years with FGFR2+ gastric cancer and other FGFR+ solid tumors	Patients may continue until discontinuation criteria were met.	Complete; Full

The Applicant's Position:

The primary evidence of efficacy and safety of futibatinib in the treatment of CCA is based on data from the Phase 2 portion of Study TAS-120-101 with a primary efficacy and safety data cut-off date of October 1, 2020. Supportive evidence for efficacy and safety is from the Phase 1 expansion portion of Study TAS-120-101. Additional supportive evidence for safety analyses are provided by the Phase 1 escalation portion of Study TAS-120-101 and Study 10059010.

The FDA's Assessment:

FDA generally agrees with Applicant's description of the clinical trials considered in this review. In TAS-120-101 Phase 1 Expansion portion of the study, 27 patients received futibatinib 16 mg QD (19 patients had CCA and 8 patients had other tumor types). Of the 170 patients in TAS-120-101 Phase 1 Expansion portion who received futibatinib 20 mg QD, 57 had cholangiocarcinoma.

8 Statistical and Clinical Evaluation

8.1 Review of Relevant Individual Trials Used to Support Efficacy

8.1.1 Phase 2 Portion of Study TAS-120-101

Trial Design

The Applicant's Description:
The Phase 2 portion of Study TAS-120-101 was a multinational, open-label, nonrandomized, single-arm study evaluating the efficacy and safety of futibatinib in patients with iCCA with *FGFR2* rearrangements (including gene fusions) after progression on at least 1 prior line of systemic therapy with gemcitabine plus cisplatin. The study was conducted at 36 sites (including 21 sites in the US) in 13 countries.

Key eligibility criteria included the following main inclusion criteria:

- Patient has histologically or cytologically confirmed, locally advanced, metastatic, unresectable iCCA harboring *FGFR2* gene fusions or other *FGFR2* rearrangements based on results from either of the following:
    - a. Testing by Foundation Medicine
    - b. Local laboratory testing using next generation sequencing [NGS], fluorescence in situ hybridization [FISH], or other assays that can determine *FGFR2* gene fusions or other *FGFR2* rearrangements on tumor tissues or from ctDNA
- Prior treatment with at least one systemic gemcitabine and platinum-based chemotherapy
- Documentation of radiographic disease progression on the most recent prior therapy
- Measurable disease as defined by RECIST 1.1
- Eastern Cooperative Oncology Group (ECOG) performance status 0 or 1

Main exclusion criteria were prior treatment with another FGFR inhibitor and history and/or current evidence of clinically significant ectopic mineralization/calcification or alteration of calcium-phosphorus homeostasis.

Study treatment: Patients received futibatinib continuous oral dosing at a starting dose of 20 mg once daily (QD) on a 21-day cycle. This recommended Phase 2 dose of futibatinib was selected based on safety, PK/PD and preliminary efficacy results observed in the Phase 1 studies. Futibatinib study treatment was continued until progressive disease, unacceptable toxicity, or any other discontinuation criterion were met.

Dose modifications for safety reasons were permitted for patients who did not tolerate the protocol-specified dosing schedule. Each patient was allowed 2 serial dose reductions for AEs, with dose-level (DL) reductions to 16 mg (DL -1) and 12 mg (DL -2). Dose reductions below 12 mg were not allowed. All dose modifications were based on the worst preceding toxicity. Following resolution of toxicity to baseline or Grade ≤1, treatment was resumed at either the same or lower dose of study drug as per the criteria in the protocol. In addition, the study protocol included a tabular dose reduction guideline for management of toxicities.

Study procedures included at least weekly clinical monitoring for the first cycle, every 3 weeks thereafter, at the end of treatment, and 30 days following the end of treatment. Ophthalmological examinations were conducted at screening, 4-6 weeks after first dose of futibatinib, and as clinically indicated based on visual signs and symptoms or physician judgment. Tumor assessments by computed tomography (CT) or magnetic resonance imaging (MRI) were performed at baseline, every 2 cycles through Cycle 4, and then every 3 cycles. A schedule of laboratory assessments is shown below in Table 15.

Table 15: Schedule of Laboratory Assessments

	Screening	Treatment Period (1 cycle = 21 days)					Safety Follow-up		Notes
		Cycle 1				Cycles ≥2			
		Day				Day			
		1	4 (±1d)	8 (±3d)	15 (±3d)	1 (±3d)	End of Tx (+0-7 days)	30 (±3) days After Last Dose	
Hematology and coagulation	X	X		X	X	X	X	X	Within 24 hours prior to treatment on D1 of each cycle, any time on C1D8 and C1D15, and as clinically indicated.
Chemistry (Serum or plasma)	X	X	(X)	X	X	X	X	X	Within 24 hours prior to treatment on D1 of each cycle, any time on C1D8 and C1D15, and as clinically indicated. Additional collection for phosphorus only at C1D4.

The FDA's Assessment:

FDA generally agrees with the applicant's description of the trial design of Study TAS-120-101. Confirmation of *FGFR2* gene fusions or other FGFR2 rearrangements in patients with iCCA was required based on testing using a central Clinical Trial Assay by Foundation Medicine or by local laboratory testing using next generation sequencing [NGS], fluorescence in situ hybridization [FISH], or other assays that can determine FGFR2 gene fusions or other FGFR2 rearrangements on tumor tissues or from circulating tumor DNA (ctDNA). Patients who enrolled using local

testing had to provide tumor tissue to Foundation of Medicine (archival tissue if available of fresh tumor sample) for central testing. Additional key eligibility criteria were

- Patients with prior adjuvant gemcitabine-platinum chemotherapy were eligible if the patient had recurrence within 6 months of the last dose of the regimen.
- Adequate organ function defined as follows: AST and ALT ≤ 3.0 x ULN (if liver function abnormalities are due to underlying liver metastasis, AST and ALT ≤ 5 × ULN); total bilirubin ≤ 1.5 × ULN, or ≤ 3.0 mg/dL for patients with Gilbert's syndrome; INR <1.3 (or < 3.0 on anticoagulants), ANC ≥ 1000/mm^3, platelet count ≥ 75,000/mm^3, hemoglobin ≥ 9.0 g/dL; phosphorus ≤ ULN; creatinine clearance ≥ 40 mL/min.
- Patients with QTc >470 msec, history and/or current evidence of clinically significant retinal disorder confirmed by retinal examination, and other serious comorbidities were not eligible.

The exclusion criteria for TAS-120-101 were appropriate given the known toxicity profile of FGFR2 inhibitors. Hyperphosphatemia is a class effect of FGFR inhibition due to increased phosphate reabsorption in the proximal tubule of the kidney.
Management of hyperphosphatemia is summarized in Table 42 (Appendices Section). No special instructions were given for ophthalmologic events.

Study Endpoints:

The Applicant's Description:
The primary endpoint of the study was overall response rate (ORR) per RECIST 1.1 guidelines, defined as the proportion of patients who had best overall response (BOR) of complete response (CR) or partial response (PR) as assessed by IRC. The IRC was comprised of two primary reviewers, and a third blinded reviewer was the adjudicator for discordant cases of the two primary reviewers.

Secondary endpoints included duration of response (DOR), disease control rate (DCR), progression-free survival (PFS) per RECIST 1.1 as assessed by the IRC, overall survival (OS), and patient reported outcomes based on European Organization for Research and Treatment of Cancer Quality-of-Life Questionnaire (EORTC QLQ-C30) and EuroQol- 5 Dimension (EQ-5D) for measuring quality of life.

The FDA's Assessment:
FDA agrees with the applicant's description of the study endpoints. FDA's efficacy evaluation is based on the primary endpoint of overall response rate (ORR) by IRC according to RECIST v1.1, accompanied with the duration of response (DOR). FDA considers DCR to be exploratory in nature and not supportive of registration. Additionally, time-to-event endpoints of OS and PFS

are not interpretable in a single arm study. Similarly, patient reported outcomes (PRO) are difficult to interpret in the absence of PRO data from a control arm.

Statistical Analysis Plan and Amendments

The Applicant's Description:
The assessment of efficacy for the NDA was conducted using pre-specified timing of the final analysis timepoint when a majority of patients responding to futibatinib had at least 6 months of follow-up from onset of response. At the data cut-off date of October 1, 2020, a minimum of 10 months of follow-up was performed for all patients and a minimum of 6 months of follow-up from time of initial response for 98% of responders.

The statistical analysis plan (v2.0) dated October 15, 2020 was finalized prior to the database lock date of October 30, 2020. The study was designed to have 81% power to rule out a historical control rate of 10% by the lower limit of the 95% confidence interval (CI), with an assumed target response rate of 20%. Approximately 100 patients were to be enrolled into the study.

The primary efficacy analysis for objective response rate (ORR), defined as the proportion of patients who achieved best overall response of partial response (PR) or complete response (CR) per RECIST 1.1 based on IRC in the Efficacy Population, were summarized by a binomial response rate. The corresponding 95% confidence interval for ORR was constructed using Clopper-Pearson exact method. Patients who have not had a confirmed response prior to the data cutoff date were considered as non-responders. The sensitivity analyses for ORR were also conducted per investigator assessment and in Per-Protocol population.
Secondary endpoints included:

- Efficacy:
    - Duration of Response (DOR) was defined as the time between the date of first response and the subsequent date of objectively documented progression of disease or death. If a patient was still responding, the patient's data were censored at the date of the patient's last available disease assessment.
    - Progression free survival (PFS) was defined as the time from the first dosing date to the date of the first documented progression or death due to any cause, whichever occurred first. If the patient did not experience disease progression or death, the data were censored at the date of last disease assessment.
    - OS was defined as number of days from the date of first dose to the date of death for all dosed patients. For patients who did not die, their data were censored at the date of last study visit or the last known date to be alive, whichever was later.

  - DOR, PFS, and OS were analyzed using Kaplan-Meier methodology using data from all treated patients. Median time was estimated and 95% confidence interval for the median time survival was presented.
- Safety and Tolerability: Including incidence and severity of adverse events, physical examination, vital sign measurements, and dose modifications.
- Patient-Reported Outcomes (PROs): EQ-5D and EORTC QLQ-C30

Subgroup analyses of the ORR were performed for selected demographic and disease characteristics as specified in the SAP: age (<65, ≥65 years), gender (female, male), race (White, Black, Asian, Other), baseline ECOG score (0, 1), prior systemic therapy (1, 2, and ≥3), region (North America, Europe, Asia Pacific (excluding Japan), Japan), prior surgical resection of primary tumor (Yes, No), Baseline *FGFR* status (*FGFR*2 fusion, *FGFR*2 rearrangements) and prior (neo) adjuvant treatment (Yes, No).

SAP Amendment:
The initial statistical analysis plan (SAP) for the Phase 2 portion of Study TAS-120-101 was approved on August 2, 2019 and was amended on October 15 2020, prior to the database lock for the primary efficacy analysis for this study.

- Timing of analysis was added to ensure that the majority of treated patients responding to futibatinib had at least 6 months of follow-up from onset of response.
- Additional subgroup analyses were added.
- Added additional analyses of hyperphosphatemia toxicities based on CTCAE v5.0 criteria and liver toxicity analysis were added.

The FDA's Assessment:
FDA agrees with the applicant's description of the analysis methods used in this study. Note that FDA does not consider inferential procedures to evaluate results from single-arm studies. Instead the efficacy decision was based on the lower limit of a 95% confidence interval of the response rate in the trial to exceed a clinically relevant response rate with adequate duration of response.

Protocol Amendments

The Applicant's Description:
The study protocol was amended 9 times prior to the primary analysis (cut-off date of October 1, 2020). None of the changes impacted trial integrity or interpretation of the results. Table 16 describes each amendment with key changes made for the Phase 2 portion of TAS-120-101 study.

Table 16: Applicant – TAS-120-101 Phase 2 Protocol Amendments Summary

Version/Date	Summary of Major Changes and Rationale

NA / 09 Dec 2013	Original protocol
03 / 19 Feb 2016	Sample size was revised from approximately 570 patients to up to 150 response-evaluable patients in Phase 2.
04 / 15 May 2017	Sample size of 120 efficacy-evaluable patients to confirm the antitumor activity in the selected tumor type(s) for the proposed Phase 2 portion.
05 / 29 Aug 2017	Updated the study design to reflect that the Phase 2 portion would be used to confirm the ORR of futibatinib in iCCA patients with tumors harboring *FGFR2* gene fusions. Updated the primary study endpoint for Phase 2 to include determination of ORR in iCCA patients with *FGFR* gene fusions, and updated the Phase 2 secondary endpoints to include evaluation of DCR, DOR, PFS, OS, safety, and tolerability of futibatinib Added inclusion criterion further defining patients in Phase 2 as those with histologically or cytologically confirmed advanced or metastatic iCCA patients with *FGFR2* gene fusions. FGFR status was to be confirmed by testing of archived or fresh tumor biopsy samples for *FGFR2* gene fusions prior to enrollment into Phase 2. Updated definition of Efficacy population to include all patients in the safety population with measurable disease at baseline and at least 1 post-baseline disease assessment. Revised the sample size for Phase 2 to N=60 with a target of 53 tumor response-evaluable patients and provided a sample size justification based on target response rate of 25% and the historical response rate of 10%.
06 / 31 Jan 2018	Clarified the primary Phase 2 objective by adding independent central radiology review requirement to ORR confirmation. Made evaluation of DOR a key secondary objective. Updated the inclusion criteria to require the following: Patients must have locally advanced, metastatic, unresectable iCCA harboring *FGFR2* gene fusions based on results from a next generation sequencing (NGS) assay by a central laboratory. Patients have been treated with and failed at least 1 prior systemic gemcitabine and platinum-based chemotherapy for the advanced disease. Documentation of radiographic progression of disease on prior systemic therapy. Updated sample size determination for the Phase 2 part to approximately 100 patients with iCCA with confirmed *FGFR2* gene fusions will be treated, and provided detailed assumptions and statistical considerations.
07 / 28 Sep 2018	Expanded eligibility criteria to allow enrollment of all patients with *FGFR2* rearrangements, rather than patients with *FGFR2* gene fusions only. Clarified requirements for tumor testing to determine and/or confirm study eligibility on the basis of *FGFR2* rearrangement or fusion status based on testing conducted by Foundation Medicine Inc. (FMI) or local laboratory testing using NGS, or other specified testing methods.
09 / 01 Aug 2019	Removed the requirement to have *FGFR2* rearrangements be centrally confirmed prior to enrollment. A formal interim analysis was added, to be performed when approximately 70% of all treated patients had 6 months of follow-up.

The FDA's Assessment:
FDA agrees with the Applicant's summary of protocol amendments.

8.1.2 Study Results

Compliance with Good Clinical Practices

Data:
Not applicable.

The Applicant's Position:
The clinical studies were conducted in accordance with the International Council for Harmonisation (ICH) Harmonised Tripartite Guidelines for Good Clinical Practice (GCP), with applicable local regulations (including European Directive 2001/20/EC and US Code of Federal Regulations Title 21), and with the ethical principles laid down in the Declaration of Helsinki.

The FDA's Assessment:
FDA acknowledges the Applicant's statement above as stated in the cover page of the clinical study report.

Financial Disclosure

Data:
Not applicable.

The Applicant's Position:
Details of financial disclosure are provided in Section 19.2.

The FDA's Assessment:
In accordance with 21 CFR 54, the Applicant submitted information for all 758 principal investigators and sub-investigators participating in study TAS-120-101. According to the Applicant, none of these investigators had financial information to disclose (as documented in FDA's Form 3454 included in the NDA). The Applicant also certified that: 1) the Sponsor has not entered into any financial arrangement whereby the value of compensation to the investigator could be affected by the outcome of the study; 2) no listed investigator disclosed a proprietary interest in the product or a significant equity in the Sponsor; and 3) no listed investigator was the recipient of significant payments of other sorts.

Patient Disposition

Data:
Overall patient disposition for the Phase 2 portion of Study TAS-120-101 is provided in Table 17.

Table 17: Applicant - Patient Disposition and Reasons for Discontinuation from Treatment

	TAS-120-101-Phase 2 20 mg QD (N=103) n (%)
All Treated	
Treatment Ongoing at Data Cutoff Date	31 (30.1)
Discontinued Treatment	72 (69.9)
Primary Reason for Discontinuation from Treatment	
Adverse Event/Serious Adverse Event	5 (4.9)
Radiologic Progression	59 (57.3)
Clinical Disease Progression	5 (4.9)
Patient Withdrew Consent	2 (1.9)
Investigator Decision	1 (1.0)

Source: TAS-120-101 Part 2 CSR In-text Table 1 ; ADSL
Abbreviations: N=number of patients in group; n=number of patients with event

The Applicant's Position:
A total of 103 patients received at least 1 dose of futibatinib in the Phase 2 portion of Study TAS-120-101. As of the data cutoff date of October 1, 2020, 72 patients (69.9%) had discontinued treatment, including 59 patients (57.3%) due to radiologic disease progression. No patients discontinued study treatment due to death, pregnancy, or loss to follow-up. Treatment was ongoing for 31 patients (30.1%).

The FDA's Assessment:
FDA agrees with Applicant's presentation of patient disposition. Upon review, patients who discontinued treatment after withdrawal of consent had concomitant adverse events at the time of withdrawal and one of these patients had disease progression confirmed two weeks later.

Protocol Violations/Deviations

Data:
Important protocol deviations in the Phase 2 portion of Study TAS-120-101 are presented in Table 18.

Table 18: Applicant - Important Protocol Deviations

	TAS-120-101 Phase 2/ 20 mg QD (N=103) n (%)
Patients with at least 1 Important Protocol Deviation	**24 (23.3)**
Deviation – Laboratory	1 (1.0)
Deviation - Dosing	3 (2.9)
Deviation - Enrollment Criteria	7 (6.8)
Deviation - Visit/Procedure Requirement	18 (17.5)

Source: TAS-120-101 Part 2 CSR, In-text Table 2; ADDV

The Applicant's Position:

A total of 24 (23.3%) patients had important protocol deviations during the course of the study, including visit/procedure requirement (18 patients, 17.5%), enrollment criteria (7 patients, 6.8%), dosing (3 patients, 2.9%), and laboratory (1 patient, 1.0%). No coronavirus disease-2019 (COVID-19)-related protocol deviations were reported.

For the 7 patients with deviations of enrollment criteria, these deviations included:

- 4 patients with FGFR2 testing deviations (enrollment based on local testing only and/or liquid biopsy with no tissue submitted for central confirmation prior to approval of Amendment 9 allowing this); 1 of these 4 patients had a PR with a DOR of 2.1 months (i.e., patient with liquid biopsy results only)
- 2 patients with laboratory deviations (1 patient each with Hb and Ca out of allowed range); 1 of these 2 patients had a PR with a DOR of 11.5 months (i.e., patient with calcium > ULN)
- 1 patient with less than 3 weeks from last cancer treatment and no laboratory results repeated on C1D1. This patient had a PR with a DOR of 8.54 months.

The Sponsor does not consider any deviations to have a meaningful effect on the overall safety or efficacy conclusions.

The FDA's Assessment:

FDA agrees with the Applicant's presentation of protocol deviations. FDA reviewed data is summarized in Table 18 for the 24 patients who had at least one protocol deviation. It is FDA's assessment that the protocol deviations related to missing laboratory assessments and to dosing that did not follow protocol guidelines for dose modifications are unlikely to have an impact on the study efficacy results. Protocol deviations in enrollment criteria included:

- Enrollment of two patients based on the local test only for confirmation of FGFR2 gene fusion prior (i.e., no confirmation using a central test was performed).
- Enrollment despite calcium level and hemoglobin level outside the normal limits.

- Screening labs assessed outside the protocol-specified required period of 72 hours prior to first dose and labs were not repeated in the correct time window.
- Incorrect washout period (< 3 weeks) between prior gemcitabine/cisplatin and initiation of this study.

Protocol deviations regarding visit/procedure requirement included

- Imaging studies not performed as scheduled in 6 patients;
- EKG not completed as scheduled in 1 patient;
- Quality of life surveys not completed as indicated in 10 patient;
- Failure to discontinue patient from study despite radiographic progression occurred in 1 patient.

Based on their nature, it is unlikely that the protocol violations had an impact on the observed efficacy outcomes of the study. All other protocol violations may have had an impact on tolerability of the drug or increase the risk for a particular patient, but have no major impact on the ability to assess the safety of futibatinib. The reported protocol deviations/violations do not appear to be a significant cause of bias influencing the study results.

Table of Demographic Characteristics

Data:

Patient demographics and baseline characteristics for patients enrolled in the Phase 2 portion of Study TAS-120-101 are presented in Table 19.

Table 19: Applicant - Demographics and Baseline Characteristics

	TAS-120-101 Phase 2 20 mg QD (N=103) n (%)
Age (years)	
Mean (SD)	55.7 (12.23)
Median (min, max)	58.0 (22, 79)
Age Groups	
<65 years	80 (77.7)
≥65 years	23 (22.3)
Sex, n (%)	
Male	45 (43.7)
Female	58 (56.3)
Race, n (%)	
Caucasian/White	51 (49.5)
Black or African American	8 (7.8)
Asian/Oriental	30 (29.1)
Native Hawaiian or Other Pacific Islander	1 (1.0)
Unknown	13 (12.6)

	TAS-120-101 Phase 2 20 mg QD (N=103) n (%)
Region, n (%)	
North America	47 (45.6)
Europe	28 (27.2)
Asia Pacifica	14 (13.6)
Japan	14 (13.6)
Ethnicity, n (%)	
Hispanic or Latino	2 (1.9)
Not Hispanic or Latino	89 (86.4)
Unknown	12 (11.7)
ECOG Performance Status, n (%)	
0	48 (46.6)
1	55 (53.4)

Source: 2.5 Clinical Overview, In-text Table 3 Table 14b.1.5.1 and TAS-120-101 Part 2 CSR Table 14b.1.10.1; ADSL
Abbreviations: ECOG PS= Eastern Cooperative Oncology Group Performance Status; N=number of patients in group; n=number of patients with event; SD=standard deviation
[a] Excluding Japan

The Applicant's Position:

The median age of enrolled patients was 58 years (range: 22 to 79 years) and the majority were female (56.3%). Most patients were White/Caucasian (49.5%) or Asian/Oriental (29.1%), and were enrolled in North America (45.6%) or Europe (27.2%). A majority of patients (53.4%) had an ECOG Performance Status of 1.

The FDA's Assessment:

FDA generally agrees with Applicant's summary of main demographic and baseline disease characteristics. ECOG Performance Status was roughly distributed in half. Although the population may slightly differ from the general U.S. CCA population (i.e., minorities are underrepresented), it appears consistent with the subset of patients with *FGFR2* altered CCA: majority of the patients were White (50%), there was a higher percent of female patients (56%), and a higher percentage of those younger than 65 years of age (78%) with the median age being 58 years. As noted above in Section 2.1, patients with CCA harboring *FGFR2* rearrangements have a female preponderance and are younger than the overall CCA population (48% female and median age of 65 years). However, overall, the patient population in the Phase 2 portion of Study TAS-120-101 appear to be adequately representative of the intended treatment population.

Other Baseline Characteristics (e.g., disease characteristics, important concomitant drugs)

Data:

Summary of cancer diagnosis, *FGFR*2 status, and prior therapy are in Table 20, Table 21 and Table 22, respectively.

Cancer Diagnosis:

Table 20: Applicant - Cancer Diagnosis

	TAS-120-101- Phase 2 20 mg QD
Time since initial diagnosis (months)	
N	103
Mean (SD)	17.46 (13.116)
Median (min, max)	12.70 (2.0, 61.4)
Age at initial diagnosis (years)[a]	
N	90
Mean (SD)	55.2 (11.81)
Median (min, max)	57.5 (21, 78)
Time since most recent progression (months) to first dose date[a]	
N	100
Mean (SD)	2.81 (4.427)
Median (min, max)	1.50 (0.2, 28.3)
Age at most recent progression (years)[a]	
N	87
Mean (SD)	56.5 (11.65)
Median (min, max)	60.0 (22, 78)

Source: 2.7.3 Summary of Clinical Efficacy In-text Table 3; ADMH
Abbreviations: N=number of patients in group; n=number of patients with event; SD=standard deviation
[a] For patients with available data

Fibroblast Growth Factor Receptor Status at Baseline:

Table 21: Applicant - Summary of *FGFR*2 Status

	TAS-120-101- Phase 2 20 mg QD (N=103) n (%)
Patients with sample for *FGFR2* status	**103 (100.0)**
FGFR*2* Status	
FGFR2 fusion	80 (77.7)
FGFR2 rearrangement	23 (22.3)
Results by FMI local	
FGFR2 fusion	23 (22.3)
FGFR2 rearrangement	2 (1.9)

	TAS-120-101- Phase 2 20 mg QD (N=103) n (%)
Results by FMI central	
FGFR2 fusion	49 (47.6)
FGFR2 rearrangement	19 (18.4)
Source of sample	
Primary tumor site	55 (53.4)
Metastatic tumor site	44 (42.7)
Liquid Sample	4 (3.9)
Not applicable	1 (1.0)

Source: 2.7.3 Summary of Clinical Efficacy, In-text Table 4; ADXB
Abbreviations: FGF=fibroblast growth factor; FGFR=fibroblast growth factor receptor; FMI=Foundation Medicine, Inc.; N=number of patients in group; n=number of patients with event
Note: One patient had both liquid sample and tissue sample from the primary tumor site. *FGFR2* final status was derived from the results by FMI central, results by FMI local, and results by local laboratory, in order of precedence

Prior Therapies:

Table 22: Applicant – Prior Anticancer Therapy

	TAS-120-101- Phase 2 20 mg QD (N=103) n (%)
Patients having at least 1 prior anticancer therapy	**103 (100.0)**
Treatment type	
Neoadjuvant	4 (3.9)
Adjuvant	14 (13.6)
Advanced	101 (98.1)
Maintenance therapy	3 (2.9)
Number of regimens	
1	48 (46.6)
2	31 (30.1)
≥3	24 (23.3)
Time from the last prior anticancer therapy to the first dose date of futibatinib (months)	
N	103
Mean (SD)	2.96 (3.464)
Median (min, max)	1.51 (0.1, 22.5)

Source: 2.7.3 Summary of Clinical Efficacy, In-text Table 5; ADSL, ADCM
Abbreviation: N=number of patients in group; n=number of patients with event; SD=standard deviation

The Applicant's Position:
All patients had received at least 1 prior systemic anticancer therapy. Most of the patients (101/103) had received at least 1 prior systemic anticancer therapy for advanced/metastatic disease, including 94 (91.3%) patients who received the combination of gemcitabine plus cisplatin.

More than half of patients had received ≥2 prior lines of treatment. Best response to the last prior line of treatment was most often stable disease (34.0%), followed by progressive disease (33.0%), and PR (17.5%). The median time from last dose of prior anticancer therapy to the first dose of futibatinib was 1.51 months (range: 0.1 to 22.5 months).

*FGFR*2 genomic status was assessed by next-generation sequencing (NGS) in 102 out of 103 patients enrolled, including 93 patients with FMI reports available. Eighty patients (77.7%) had *FGFR*2 fusions with detectable partner genes, and the remaining 23 patients (22.3%) had *FGFR*2 rearrangements other than fusions. The most frequently identified *FGFR*2 fusion partner was BICC1, reported in 24 (23.3%) patients.

The FDA's Assessment:
FDA agrees with Applicant's assessment of FGFR2 status and of prior anticancer therapy. All patients received a combination treatment with gemcitabine and platinum-based therapy, including 94 (91%) patients who received the combination of gemcitabine plus cisplatin; other chemotherapy regimens included combinations of gemcitabine with carboplatin, paclitaxel, fluoropyrimidines or platinum agents with fluoropyrimidines, taxanes, topoisomerases, , anthracyclines, and alkylant agents.

Treatment Compliance, Concomitant Medications, and Rescue Medication Use

Data:
Treatment compliance in the Phase 2 portion of Study TAS-120-101 was 90.29% determined by median relative dose intensity. A summary of concomitant medication use in the Phase 2 portion of Study TAS-120-101 is provided in Table 23.

Table 23: Applicant - Concomitant Medications Reported for > 15% of the Safety Population

Anatomical Therapeutic Chemical Class WHO Drug Name (Preferred Term)	TAS-120-101 Phase 2 20 mg QD (N=103) n (%)
Patients Who Took at Least 1 Concomitant Medication	**103 (100.0)**
All Other Therapeutic Products	96 (93.2)

Anatomical Therapeutic Chemical Class WHO Drug Name (Preferred Term)	TAS-120-101 Phase 2 20 mg QD (N=103) n (%)
Sevelamer	66 (64.1)
Lanthanum Carbonate	27 (26.2)
Analgesics	76 (73.8)
Paracetamol	56 (54.4)
Oxycodone	18 (17.5)
Drugs for Acid Related Disorders	64 (62.1)
Omeprazole	20 (19.4)
Drugs for Constipation	55 (53.4)
Sennoside A+B	16 (15.5)
Diuretics	48 (46.6)
Acetazolamide	30 (29.1)
Furosemide	16 (15.5)
Blood Substitutes and Perfusion Solutions	41 (39.8)
Sodium Chloride	23 (22.3)
Antiemetics and Antinauseants	39 (37.9)
Ondansetron	27 (26.2)
Anti-inflammatory and Antirheumatic Products	38 (36.9)
Ibuprofen	16 (15.5)

Source: TAS-120-101 Part 2 CSR In-Text Table 6 ; ADCM
Abbreviation: WHO = World Health Organization
Notes: Patients with 2 or more medications within a class level and drug name are counted only once within that class level and drug name. Concomitant medications include medications that either (1) started before first dose of study drug and were continuing at the time of first dose of study drug, or (2) started on or after first dose of study drug. Medications terms were coded using WHO Drug Dictionary version 2016 or current.

No rescue medications were used.

The Applicant's Position:

All 103 (100%) patients enrolled reported the use of concomitant medications. The types of concomitant medications used were consistent overall with medications expected to be administered to patients with advanced cancer, with the exception of phosphate binders (eg, sevelamer) administered for the treatment of hyperphosphatemia as a known on-target effect of FGFR inhibitors.

The FDA's Assessment:

FDA replicated the Applicant's analysis. With the exception of a higher than expected use of diuretic drugs (47%), other concomitant medications are generally reflective of medications

often used in the disease setting. In Study TAS-120-101, acetazolamide, a phosphoturic diuretic, was used to treat hyperphosphatemia in 31% of patients, which may explain the increased incidence of use of this class of drugs.

Efficacy Results – Primary Endpoint (Including Sensitivity Analyses)

Data:

Efficacy results for the primary endpoint of ORR by Independent Review are presented in Table 24 and Figure 7. Sensitivity analyses for the primary endpoint of ORR were based on Investigator review. Subgroup analysis of ORR by independent review is presented in Figure 8.

Table 24: Applicant - Primary Endpoint of ORR assessed by Independent Review Committee

	Independent Review (N=103)
Objective response rate (ORR), n (%)	**43 (41.7)**
95% CI	(32.1, 51.9)
Best overall response, n (%)	
Complete response (CR)	1 (1.0)
Partial response (PR)	42 (40.8)
Unconfirmed CR or PR, n (%)	7 (6.8)

Source: TAS-120-101 CSR In-Text Table 31, ADRS
Abbreviations: CI=confidence interval; CR=complete response; N=number of patients in group; n=number of patients with event; PR=partial response
Notes: Objective response rate is based on confirmed PR/CR. The exact 95% of tumor response rate are 2-sided and calculated using the Clopper–Pearson method.

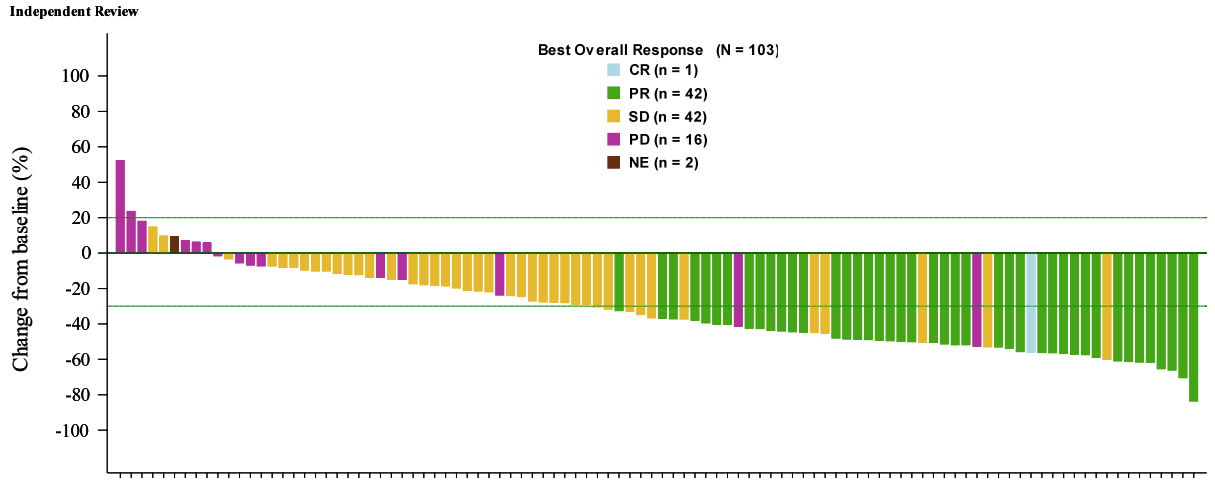

Figure 7: Applicant - Waterfall Plot of Patients Target Lesion Sum of Diameters Percent Change from Baseline and Best of Response

Source: TAS-120-101 CSR Phase 2, Figure 2, ADRS & ADTR
Abbreviations: CR=complete response; NE=not estimable; PD=progressive disease; PR=partial response; SD=stable disease
Note: The one patient with CR had one remaining nodal lesion which was found to be PET-CT negative

Pre-planned sensitivity analyses for the primary endpoint of ORR included an assessment of ORR based on investigator assessment (ORR: 36.9% [95% CI: 27.6, 47.0]), the per-protocol analysis set (ORR: 43.0% [95% CI: 33.1, 53.3]), and the subset of patients with dose modifications (ORR: 40.0% [95% CI: 29.8, 50.9]).

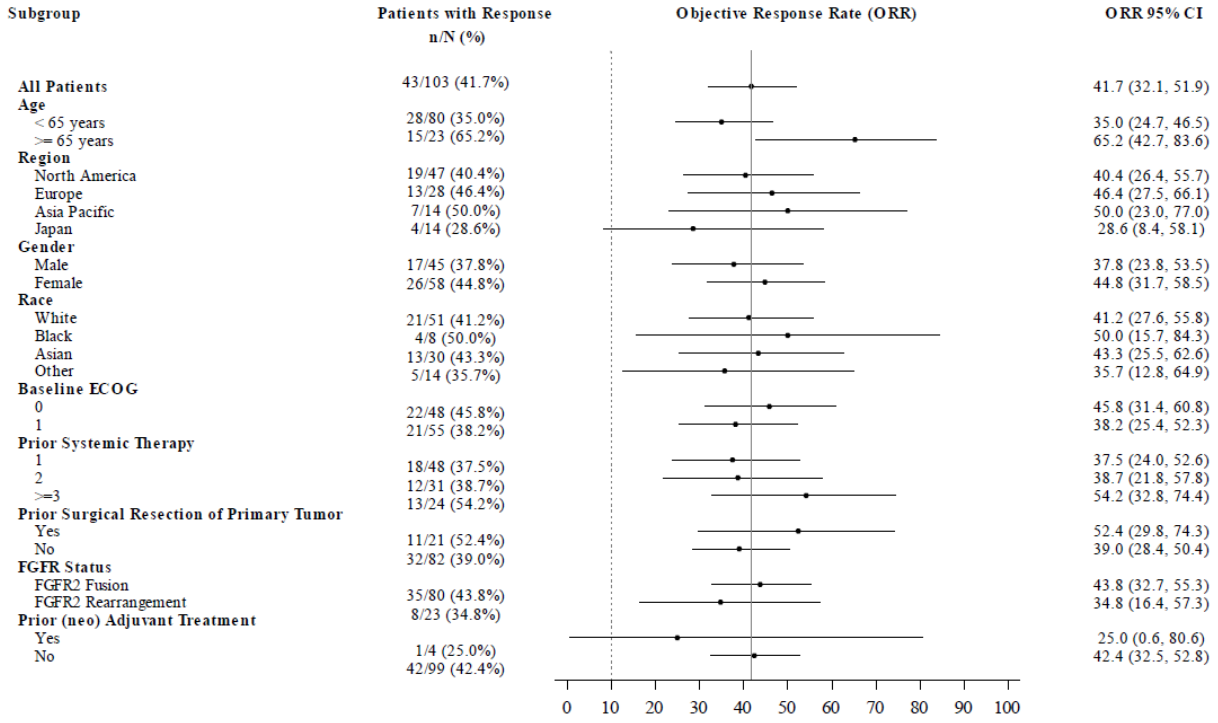

Figure 8: Applicant - Subgroup Analysis of ORR Based on Independent Review

Source: 2.7.3 Summary of Efficacy, Figure 5, ADCL,ADRS

The Applicant's Position:

Futibatinib demonstrated a clinically meaningful confirmed ORR of 41.7% (95% CI: 32.1, 51.9), as assessed by IRC according to RECIST 1.1. The effect size observed for the primary endpoint of ORR was more than 4-fold higher relative to historically reported ORR for chemotherapy in previously treated patients with CCA (Lamarca 2014) and thereby constitutes a clinically significant improvement over currently available treatment options. The pre-planned sensitivity

analyses confirmed the robustness of the primary analysis by showing similar ORR results based on investigator assessment (ORR: 36.9% [95% CI: 27.6, 47.0]), the per-protocol analysis set (ORR: 43.0% [95% CI: 33.1, 53.3]), and the subset of patients with dose modifications (ORR: 40.0% [95% CI: 29.8, 50.9]).

The primary endpoint of ORR was consistent across subgroups (i.e., gender, race, ECOG performance score, lines of prior systemic therapy, region, prior surgical resection of primary tumor, prior (neo)adjuvant treatment, type of FGFR rearrangement). This included patients >65 years of age, a population of particular relevance as in most regions of the world (eg, Western countries), the population is aging.

The observed primary endpoint of ORR was also consistent regardless of whether patients were enrolled based on local or central FGFR*2* status testing. Exploratory analysis of samples from patients enrolled based on central NGS testing (FMI clinical trial assay; N=68) confirmed the *FGFR2* rearrangement status and demonstrated a very similar ORR of 39.7% (95% CI: 28.0, 52.3) based on independent review. The data further support the robustness of the results observed for the primary endpoint of ORR and the generalizability of the study results across subgroups and different healthcare settings.

The FDA's Assessment:

FDA does not agree with the Applicant's presentation of the efficacy results based on the primary endpoint of ORR by IRC. Information about unconfirmed responses is not considered for the assessment of efficacy and FDA verified that data displayed in Figure 5 does not include unconfirmed responses.

In addition, on September 12, 2022, FDA sent an information request regarding patient (b) (6), who Taiho singled out in a note below Figure 5 as achieving a complete response despite having one remaining nodal lesion which was found to be PET-CT negative. Taiho clarified that there were no enlarged lymph nodes assessed as nodal target lesions for patient (b) (6) As RECIST 1.1 clearly states that complete disappearance is required for qualifying a response as complete in a non-target, non-nodal lesion (irrespective of PET scan results), FDA disagreed with Taiho's assessment of the response in patient (b) (6); this should be considered a partial response. Therefore, all responses observed were partial responses and Taiho agreed to describe in the Lytgobi UPSI all responses as partial.

The concordance rate of ORR was 82% between the investigator based response assessments and independent review. This was considered to be adequately high and no further investigation was performed by FDA to evaluate the differences.

FDA considers the subgroup analyses of ORR to be exploratory.

Data Quality and Integrity

Data:
Not applicable.

The Applicant's Position:
There are no concerns regarding data integrity and submission quality.

The FDA's Assessment:
FDA's review of the application did not raise concerns regarding data integrity. Although the quality of the application generally supported FDA's review, the review team requested several Information Requests to clarify the missing or confusing elements in the datasets provided by Taiho.

Efficacy Results – Secondary and other relevant endpoints

Data:
Results for the secondary endpoints are presented in Table 25 below.

Table 25: Applicant - Secondary Efficacy Endpoints

	TAS-120-101 Phase 2 20 mg QD (N=103)
Duration of response (months)[a]	
Median (95% CI)	9.69 (7.62, 17.05)
Number of patients with duration of response of at least, n (%)	
6 Months	31 (72.1)
9 Months	12 (27.9)
12 Months	6 (14.0)
Summary of Progression-free Survival	
Disease progression or deaths, n (%)	64 (62.1)
Censored patients, n (%)	39 (37.9)
PFS (months)	
Median (95% CI)	9.0 (6.9, 13.1)
Summary of Overall Survival	
Deaths, n (%)	40 (38.8)
Censored patients, n (%)	63 (61.2)
Overall survival (months)	

	TAS-120-101 Phase 2 20 mg QD (N=103)
Median (95% CI)	21.7 (14.5, NE)
Disease control rate (DCR), n (%)	**85 (82.5)**
95% CI	(73.8, 89.3)

Source: 2.7.3 Summary of Efficacy, In-text Tables 13 and 14, ADSL, ADRS, ADTTE
Abbreviations: CI=confidence interval; N=number of patients in group; n=number of patients with event; PFS=progression-free survival
Note: Responders are patients with confirmed partial response or complete response.
[a] Kaplan-Meier Analysis
PFS is calculated from the date of the first dose of study drug to the date of 1st objective evidence of disease progression or date of death due to any cause, whichever occurs first. Point estimates of PFS rate are based on Kaplan-Meier method and 95% confidence intervals are based on the Greenwood Formula.

The Applicant's Position:

The secondary endpoint of DOR demonstrated that responses observed in the Phase 2 portion of TAS-120-101 were durable. The median DOR of 9.69 months (95% CI: 7.62, 17.05) is clinically meaningful in the targeted patient population in light of the limited efficacy of available alternative treatment options. With a median follow-up of 11.76 months from the onset of response, and 42 out of the 43 patients responding to futibatinib followed for more than 6 months, the data for this key secondary endpoint are mature. Fifteen patients had ongoing responses as of the data cutoff date.

The further secondary endpoints of PFS and OS support the efficacy of futibatinib in the Phase 2 portion of TAS-120-101. The observed median PFS (9.0 months) and OS (21.7 months) appear to be favorable in the context of current treatment options (refer to Section 1). Thus, the efficacy results of futibatinib in the Phase 2 portion of TAS-120-101 are clinically meaningful and address a significant unmet medical need of patients who have only limited effective therapeutic options available.

The FDA's Assessment:

FDA agrees with the Applicant's interpretation of durability of response observed in the patients treated with futibatinb. However, given that only 18/103 patients enrolled in this single-arm study had a duration of response >6 months, the toxicity profile of futibatinib, and uncertainty regarding futibatinib optimimal dosage, a confirmatory study will be needed to verify the clinical benefit of futibatinib.

Regarding the PFS and OS results presented above, as stated previously, in the absence of data on PFS and OS from control arm within same study, the results are uninterpretable.

Dose/Dose Response

Data:

Not applicable.

The Applicant's Position:
Data on dose-response are presented in Section 6.2.2 (Clinical Pharmacology).

The FDA's Assessment:
As summarized in Section 6.2.2, the FDA clinical pharmacology team concluded that although futibatinib 20 mg daily is efficacious, limited data from the Phase 1 portion of Study TAS-120-101 suggest that a 16 mg QD dosing could be as efficacious and with improved tolerability. A PMR to further study the 16 mg QD dosage will be requested.

Durability of Response

Data:
Duration of response data are presented in the "Efficacy Results – Secondary and other relevant Endpoints" in section above (Table 25).

The Applicant's Position:
Durability of response was demonstrated in the secondary endpoint of DOR. A median duration of response of 9.69 months, with the majority of responders (31 patients [72.1%]) having response durations of ≥6 months, demonstrated clinically meaningful benefit in previously treated patients with advanced CCA.

The FDA's Assessment:
FDA agrees with the Applicant's position above regarding the durability of response.

Persistence of Effect

Data:
Not applicable

The Applicant's Position:
Persistence of effect was demonstrated based on the observed duration of response.

The FDA's Assessment:
FDA agrees.

Efficacy Results – Secondary or exploratory COA (PRO) endpoints

Data:
Patient reported outcomes (PRO) measures included the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30 (EORTC-QLQ-C30; 5 functional

and 9 physical measures) and the EuroQol-5D measure of health-related quality of life EQ-5D-3L (utility index and 5 dimensions: anxiety/depression, mobility, pain/discomfort, self-care, and usual activity). Ninety-two of 103 (89%) enrolled patients had PRO data at baseline and at least 1 follow-up assessment; 48 patients had PRO data at Cycle 13. Baseline mean (SD) EORTC QLQ-C30 global health status score was 70.1 (19.4) and EuroQoL visual analog scale (EQ VAS) score was 71.7 (20.3). Mean EORTC QLQ-C30 global health status scores did not change from baseline to Cycle 13 (approximately 9 months on treatment) with no ≥10-point changes in functional measures. EORTC QLQ-C30 scores across symptom measures were stable from baseline to Cycle 13. Constipation was the only component with a mean 10.0-point worsening at only Cycle 4. Mean EQ VAS scores did not change from baseline to Cycle 13 (mean change -1.8 to +4.8 across cycles).

The Applicant's Position:
The observed quality-of-life data from the Phase 2 portion of TAS-120-101 showed that physical, cognitive, and emotional functioning, and overall health status were maintained among patients with advanced iCCA receiving futibatinib. Mean EORTC QLQ-C30 scores on global health status and functional scales were maintained from baseline to Cycle 13, with no clinically meaningful (≥10-point) changes. Mean EQ VAS scores were sustained from baseline to Cycle 13, with values maintained within the population norm range from across 20 countries. Changes from baseline in individual EQ-5D-3L dimensions showed that 72–94% of patients' status remained the same or improved over time. These findings were consistent with ECOG PS scores, which remained generally stable from baseline to Cycle 13.

The FDA's Assessment:
The study design did not support an assessment of treatment benefit based on patient reported outcomes. The PRO analyses presented above are considered descriptive and exploratory. Mean change from baseline analyses can obscure important individual level changes. FDA did not conduct additional in-depth analyses of clinical outcomes assessments and no conclusions should be drawn from the PRO analyses results presented above.

Additional Analyses Conducted on the Individual Trial

Data:
Not applicable.

The Applicant's Position:
No additional analyses were conducted on individual trial.

The FDA's Assessment:
Not applicable.

8.1.3 Integrated Review of Effectiveness

The FDA's Assessment:
FDA conducted independent analysis of the efficacy data from Study TAS-120-101 and in general concurs with Taiho's analysis of the primary endpoint of ORR by IRC and durability of response. There were no notable statistical issues with the study design, statistical analysis plan, or efficacy results for patients with intrahepatic cholangiocarcinoma harboring an FGRFR2 fusion or rearrangement who received at least one dose of futibatinib (Phase 2 of the trial) in Study TAS-120-101. Results from Study TAS-120-101 indicate that treatment with futibatinib 20 mg QD in patients with previously treated, unresectable, locally advanced or metastatic intrahepatic cholangiocarcinoma with an FGFR2 fusion/rearrangement leads to a clinically meaningful and durable response. The ORR of 41.7% (95% CI: 32.1, 51.9), as assessed by IRC according to RECIST 1.1, with a median duration of response of 9.7 months (95% CI: 7.6, 17.1) is clinically meaningful in the context of life expectancy in this setting of 5-6 months. The efficacy evaluation was based on the magnitude of response rate and adequate duration of response. Although PFS and OS results were summarized, FDA notes that time-to-event endpoints are uninterpretable without a comparator arm. PRO data is also considered to be exploratory in nature and difficult to interpret in this single-arm study.

8.1.4 Assessment of Efficacy Across Trials

Data:
Not applicable.

The Applicant's Position:
Efficacy was assessed based on data from a single clinical trial TAS-120-101 presented in Section 8.1.

The FDA's Assessment:
FDA agrees.

8.1.5 Integrated Assessment of Effectiveness

Data:
In addition to the results of Phase 2 portion of TAS-120-101, there is supportive evidence for the antitumor activity of futibatinib in patients with CCA harboring *FGFR2* rearrangements (including fusions) from the Phase 1 Expansion portion of TAS-120-101. Among the 197 patients enrolled in this Phase 1 expansion, there were:

- 42 patients with iCCA harboring *FGFR2* rearrangements who received a starting dose of futibatinib 20 mg QD. The confirmed ORR for these patients (including 17 patients with

prior FGFR inhibitor treatment) was 14.3% (95% CI: 5.4, 28.5) according to RECIST 1.1, with a median DOR by Kaplan-Meier analysis of 4.3 months (95% CI: 2.8, 6.9).

- For the subset of patients (N=19) with *FGFR2* rearrangement after failure of at least one systemic treatment with gemcitabine plus platin and no prior FGFR inhibitor treatment, the confirmed ORR was 21.1% (95% CI: 6.1, 45.6) with a median DOR by Kaplan-Meier analysis of 5.2 months (95% CI: 3.5, 6.9).
- 3 patients with extrahepatic CCA (eCCA) harboring *FGFR*2 rearrangements (including fusions) who received a starting dose of futibatinib 20 mg QD. Of these 3 eCCA patients, 1 patient had a confirmed PR according to RECIST 1.1 lasting for 3.5 months.

The Applicant's Position:

There has been no formal integrated assessment of efficacy conducted for patients receiving futibatinib due to differences in futibatinib dosing schedules, tumor types, and prior treatment of patient populations across the different portions of TAS-120-101 and other studies.

However, there is supportive evidence from the Phase 1 expansion of TAS-120-101 showing anti-tumor activity of futibatinib in CCA. In patients with iCCA harboring *FGFR2* rearrangements and prior systemic treatment with gemcitabine/platin but no prior FGFR inhibitor (i.e. equivalent to the population enrolled in the Phase 2 portion of TAS-120-101), the 95% confidence interval around the 21.1% response rate overlaps that reported for the 103 patients in the Phase 2 portion of the study. In addition, futibatinib demonstrated anti-tumor activity in patients with CCA with extrahepatic disease and *FGFR2* rearrangements as evidenced by 1 out of 3 patients experiencing a confirmed partial response. While *FGFR2* rearrangements are rare in patients with eCCA (<1% of eCCA) (Jain 2018, Lowery 2018), these supportive data indicate that the efficacy of futibatinib is likely to be seen in all types of CCAs with *FGFR2* rearrangements regardless of intrahepatic or extrahepatic localization.

The FDA's Assessment:

FDA's analysis of the efficacy results of the Phase 2 portion of Study TAS-120-101 generally concurs with the Applicant's analyses of the primary endpoints of ORR and DOR. There were no notable statistical issues with the study design, statistical analysis plan, or efficacy results for patients with FGFR2 gene fusions who received at least one dose of futibatinib in the Phase 2 of Study TAS-120-101. The study showed an ORR of 41.7% (95% CI: 32.1, 51.9), as assessed by ICR according to RECIST v1.1. in FDA's primary analysis population of patients with FGFR2 gene fusions who received at least one dose of futibatinib. The efficacy evaluation was based on the magnitude of response rate and adequate duration of response, which are considered clinically meaningful. Although PFS and OS results were summarized, FDA notes that time-to-event endpoints are uninterpretable without a comparator arm.

The review team disagrees with Taiho's statement that the supportive data on eCCA indicates that the efficacy of futibatinib is likely seen in all types of CCA with FGFR2 irresepctive of tumor localization. Although data from 3 patients in the Phase 1 of the TAS-120-101 study were available while Phase 2 was being conducted, Taiho restricted enrollment to patients with iCCA in the Phase 2 portion, limiting the availability of additional data to support the claim.

FDA notes the data from additional patients with FGFR2 fusions/rearrangements and acknowledges that no integrated review of effectiveness has been undertaken. The primary efficacy data has been derived solely from Phase 2 portion of Study TAS-120-101 and the indication in the futibatinib label reflects the population studied in the Phase 2 portion of Study TAS-120-101.

8.2 Review of Safety

The Applicant's Position:
The safety profile of futibatinib for patients with CCA with *FGFR2* rearrangement (including fusions) is primarily derived from the safety results of the Phase 2 portion of Study TAS-120-101 (TAS-120-101 Part 2 CSR).

As supportive safety information, data from the Phase 1 portions of Study TAS-120-101 (Dose Escalation and Expansion), and the Japanese Phase 1 Study 10059010 conducted in cancer patients with various types of tumors were pooled with patients in the TAS-120-101 Phase 2 portion as an integrated safety population to allow assessment of the safety of 20 mg QD futibatinib in a broader patient population relative to the Phase 2 population (N=103). These integrated populations summarize data for patients with iCCA who received 20 mg QD futibatinib (N=145) and patients with any tumor type who received futibatinib, including patients with a starting dose of 20 mg QD futibatinib (N=318).

In safety analysis sets (which included both the safety analysis and integrated safety population as described above), all patients had received futibatinib at a dose of 20 mg QD orally. Safety analysis data provided an assessment of the safety profile for futibatinib and an overall benefit-risk evaluation in patients with CCA. The safety population was considered appropriate for detecting common AEs and for providing guidance on toxicity management.

The FDA's Assessment:
FDA notes the studies above and that the primary safety analysis for this application is based on 103 patients from Phase 2 portion of Study TAS-120-101. FDA also clarifies that the safety data provided in this package support an overall benefit-risk assessment in the indicated population (i.e., patients with advanced intrahepatic cholangiocarcinoma harboring FGFR2 fusions or other rearrangements).

8.2.1 Safety Review Approach

Data:
Not applicable.

The Applicant's Position:
The clinical assessment of the safety of futibatinib is based on data from the Phase 2 portion of Study TAS-120-101 (TAS-120-101 Part 2 CSR). The duration of exposure to study treatment was determined by the number of months exposed to futibatinib. Demographics, baseline disease characteristics, and prior anticancer therapies were summarized by treatment groups. Prior anticancer therapies were summarized by ATC code (WHO Drug Dictionary Version 01Mar2019-b3). All adverse events (AEs) are treatment-emergent AEs, defined as an AE that started on or after the first dose date and up to 30 days after last dose date of futibatinib.

Adverse events of special interest (AESIs) evaluated include event categories based on class effect, mechanism of action, and the clinical experience to date with futibatinib: serous retinal detachment, hyperphosphatemia, hepatotoxicity, nail disorders, Palmar-planter erythrodysesthesia syndrome (PPES), and rash.

The FDA's Assessment:
FDA agrees with the Applicant's description of the safety review approach.

8.2.2 Review of the Safety Database

Overall Exposure

Data:
Overall futibatinib exposure is presented in Table 26 below.

Table 26: Applicant – Treatment Duration and Exposure

	TAS-120-101 Phase 2 20 mg QD (N=103)	All iCCA 20 mg QD (N=145)	Any Tumor Type 20 mg QD (N=318)
Duration of Treatment (months)			
Mean (SD)	9.35 (5.274)	8.82 (5.763)	5.91 (5.829)
Median (Min, Max)	9.07 (0.5, 24.5)	8.87 (0.5, 31.7)	3.65 (0.1, 34.5)
No. of Cycles Treated			
Mean (SD)	13.4 (7.41)	12.7 (8.14)	8.6 (8.18)
Median (Min, Max)	13.0 (1, 36)	12.0 (1, 46)	5.0 (1, 49)
Number of Patients with Duration of Treatment, n (%)			
≥6 months	72 (69.9)	92 (63.4)	116 (36.5)

	TAS-120-101 Phase 2 20 mg QD (N=103)	All iCCA 20 mg QD (N=145)	Any Tumor Type 20 mg QD (N=318)
≥12 months	25 (24.3)	34 (23.4)	41 (12.9)
≥18 months	9 (8.7)	12 (8.3)	17 (5.3)
≥24 months	1 (1.0)	2 (1.4)	5 (1.6)
Relative Dose Intensity (%)			
N	103	145	318
Mean (SD)	83.26 (15.675)	84.77 (15.383)	84.64 (16.965)
Median (Min, Max)	85.71 (46.3, 100.0)	88.37 (41.1, 100.0)	90.29 (19.0, 100.0)

Source: 2.5 Clinical Overview, In-text Table 6 ; ADSL, ADEX
Abbreviations: max=maximum; min=minimum; n=number of patients with at least 1 event; N=number of patients in treatment group; QD=once daily; SD=standard deviation

The Applicant's Position:

The median duration of treatment for patients with iCCA who received a starting dose of 20 mg QD futibatinib in the TAS-120-101 Phase 2 population (N=103) was 9.07 months. Patients received a median of 13 treatment cycles, and the duration of treatment in the majority of patients (n=72, 69.9%) was ≥6 months, with treatment duration lasting for ≥12 months in 24.3% of patients. Median relative dose intensity was 85.71%.

Extent of exposure to futibatinib for patients with iCCA who received 20 mg QD within the integrated safety population was comparable to that reported for the Phase 2 population. For patients with any tumor type in the integrated safety population who received a starting dose of 20 mg QD futibatinib (N=318), treatment duration was shorter overall (median 3.65 months), consistent with the generally lower antitumor activity observed in other tumor types. However, the median relative dose intensity (90.29%) of futibatinib was similar to those reported for patients with iCCA in the TAS-120-101 Phase 2 and integrated safety populations.

The FDA's Assessment:

FDA confirms that the median exposure of 9.07 months (min, max: 0.5, 24.5) in the 103-patient primary safety analysis set . As summarized in Table 17, 70% of patients had discontinued treatment at the time of the primary analysis; 57% of patients discontinued due to disease progression. The shorter duration of exposure in the pooled population likely reflects a heterogeneous population, particularly regarding tumor types, FGFR alteration, and prior lines of therapy.

Relevant characteristics of the safety population:

Data:

A summary of the demographics and baseline characteristics of the safety population are provided in Table 27.

Table 27: Applicant – Demographics and Baseline Characteristics

	TAS-120-101 Phase 2 20 mg QD (N=103)	All iCCA 20 mg QD (N=145)	Any tumor type 20 mg QD (N=318)
Age (Years)			
n	103	145	318
Mean (SD)	55.7 (12.23)	55.4 (12.30)	56.8 (12.77)
Median (Min, Max)	58.0 (22, 79)	57.0 (22, 83)	59.0 (20, 83)
Age Groups			
<65 years	80 (77.7)	114 (78.6)	229 (72.0)
≥65 and <75 years	19 (18.4)	25 (17.2)	71 (22.3)
≥75 years	4 (3.9)	6 (4.1)	18 (5.7)
Sex, n (%)			
Male	45 (43.7)	54 (37.2)	151 (47.5)
Female	58 (56.3)	91 (62.8)	167 (52.5)
Race, n (%)			
Caucasian/White	51 (49.5)	76 (52.4)	157 (49.4)
Black	8 (7.8)	9 (6.2)	12 (3.8)
Asian/Oriental	30 (29.1)	36 (24.8)	90 (28.3)
Other	1 (1.0)	1 (0.7)	2 (0.6)
Unknown	13 (12.6)	23 (15.9)	57 (17.9)
Region, n (%)			
North America	47 (45.6)	75 (51.7)	124 (39.0)
Europe	28 (27.2)	38 (26.2)	112 (35.2)
Asia Pacific (excluding Japan)	14 (13.6)	18 (12.4)	30 (9.4)
Japan	14 (13.6)	14 (9.7)	52 (16.4)
Ethnicity, n (%)			
Hispanic or Latino	2 (1.9)	4 (2.8)	5 (1.6)
Not Hispanic or Latino	89 (86.4)	119 (82.1)	252 (79.2)
Unknown	12 (11.7)	22 (15.2)	61 (19.2)
ECOG Performance Status, n (%)			
0	48 (46.6)	67 (46.2)	130 (40.9)
1	55 (53.4)	78 (53.8)	188 (59.1)

Source: 2.7.4 Summary of Clinical Safety, In-text Table 3; ADSL
Abbreviations: N=number of patients in group; n=number of patients with event; SD=standard deviation

The Applicant's Position:

In the Phase 2 of Study TAS-120-101 (N=103), the median age of all patients was 58 years (range: 22 to 79 years) and the majority were female (56.3%). Most patients were White/Caucasian (49.5%) or Asian/Oriental (29.1%), and were enrolled in North America (45.6%) or Europe (27.2%). A majority of patients (53.4%) had an ECOG Performance Status of 1. All patients reported receiving at least 1 prior systemic anticancer therapy, with more than half of patients receiving ≥2 prior lines of treatment. Most patients (101/103) had received at least 1 prior systemic anticancer therapy for advanced/metastatic disease, including 91.3% who received gemcitabine/cisplatin as treatment.

There are no significant differences of demographic profiles among these patients' groups.

The FDA's Assessment:
FDA agrees with the Applicant's description of the study population for the primary safety analysis set above. All patients enrolled in Phase 2 portion of Study TAS-120-101 had received at least one dose of futibatinib, therefore the safety population and efficacy populations are the same. See Section 7 for FDA analysis of the adequacy of the study population to characterize the effect of futibatinib.

Adequacy of the safety database:

Data:
The evaluation of safety is primarily based on data from the pivotal study TAS-120-101 Phase 2 (N=103) patients with iCCA who received futibatinib at a dose of 20 mg QD with a median exposure of 9.07 months. Supportive safety information was from the Phase 1 portions of Study TAS-120-101 (Dose Escalation and Expansion) and the Japanese Phase 1 Study 10059010 conducted in cancer patients with various types of tumors pooled with patients in the TAS-120-101 Phase 2 portion as an integrated safety population. These data allow assessment of the safety of 20 mg QD futibatinib in a broader patient population relative to the Phase 2 CCA population. These integrated populations include supportive data for patients with iCCA who received 20 mg QD futibatinib (N=145) with a median exposure of 8.87 months, and patients with any tumor types who received 20 mg QD futibatinib (N=318) with a median exposure of 3.65 months were also evaluated. In these 3 analysis sets for primary assessment (TAS-120-101 Phase 2 portion) and supportive assessment described above, all patients received futibatinib 20 mg QD as a starting dose. The exposures in all analysis sets are also considered appropriate to allow for an adequate assessment of safety in patients who were representative of the intended target population.

The Applicant's Position:
The safety database is adequate for an informed assessment of the safety profile of futibatinib and an informed evaluation of the overall risk-benefit in subjects with advanced or metastatic CCA harboring *FGFR2* gene fusions or other *FGFR2* rearrangements.

The FDA's Assessment:
FDA concurs with the Applicant's assessment of the adequacy of the safety database.

8.2.3 Adequacy of Applicant's Clinical Safety Assessments

Issues Regarding Data Integrity and Submission Quality

Data:
Not applicable.

The Applicant's Position:
No meaningful concerns are anticipated in the quality and integrity of the submitted datasets and individual case narratives; these were sufficiently complete to allow for a thorough review of safety.

The FDA's Assessment:
FDA acknowledges the Applicant's position; the review did not uncover any data integrity issues. FDA agrees the NDA submission was complete. Taiho provided additional information to further characterize the toxicity as requested by FDA through information requests.

Categorization of Adverse Event

The Applicant's Position:
Adverse events (AEs) were graded based on the National Cancer Institute's Common Terminology Criteria for Adverse Events (CTCAE) Version 4.03 with the exception of hyperphosphataemia (see below). Grading scale ranges from 1 to 5 corresponding to mild, moderate, severe, life threatening and fatal events. Categories of adverse events included death, serious AE, AE leading to discontinuation of study drug, AE leading to dose modification, and all AEs.

An AE was defined as any untoward medical condition that occurs in a patient while participating in this clinical study. AEs were coded according to the Medical Dictionary for Regulatory Activities (MedDRA 22.0) terminology.

The severity of hyperphosphatemia was not defined in CTCAE v4.03; thus severity was evaluated based on the laboratory values as defined in the protocol (TAS-120-101).
The adverse events of special interest (AESI) consisted of a list of preferred terms (PTs) grouped by specific category (for example, hyperphosphatemia) and/or by subcategory (for example, diabetes). Search strategies for predefined AESI used sponsor-defined grouped PTs. The predefined AESI categories were retinal disorders (serous retinal detachment),

hyperphosphatemia, hepatotoxicity, nail disorders, palmar-plantar erythrodysesthesia syndrome, and rash.

The FDA's Assessment:
FDA agrees with the Applicant's summary. For Study TAS-120-101 Phase 2, AEs (except for hyperphosphatemia – see definitions below, in the Routine Clinical Test subsection) were assessed by the investigator according to CTCAE v4.03 criteria and were coded using MedDRA version 22.0.

Adverse events were assessed during the treatment period and for 30 days after the last dose of study drug or until the start of new antitumor therapy, whichever was earlier.

FDA conducted an audit of the safety datasets. Verbatim terms for safety events were accurately coded using the MedDRA dictionary; differences between the verbatim terms and the preferred terms are mostly related to differences in spelling or the use of common medical terms. FDA also agrees with the grading of events.

Routine Clinical Tests

Data:
Not Applicable.

The Applicant's Position:
Laboratory values were graded programmatically using CTCAE version 4.03, or as otherwise specified in the SAP. Laboratory results were summarized using SI units. The maximum and minimum observed postbaseline values, last observed values, and changes from baseline were summarized. All post-baseline assessments (including unscheduled visits) were used to determine the maximum (most severe) post-baseline CTCAE grade. A baseline laboratory value was defined as the last assessment performed on or prior to the date and time of the first dose of study treatment. Laboratory test results were categorized by CTCAE criteria V4.03 with the exception of hyperphosphatemia. Ophthalmologic assessments were summarized.

The FDA's Assessment:
FDA agrees with the Applicant's description. Patients were tested for routine clinical tests (hematology and coagulation, chemistry) at screening, on Days 1, 8, and 15 of Cycle 1, and on Day 1 of each cycle thereafter. Urinalysis was done at screening and Day 1 of each cycle Phosphorus was tested 4 days (±24 hours) after Day 1 of Cycle 1 to initiate early intervention for hyperphosphatemia.

All clinical tests were performed at end of treatment and at 30-day safety visit after treatment termination.

As CTCAE v4.03 does not specifically describe hyperphosphatemia, the Applicant classified serum phosphate levels as follows:

- Grade 1: Upper limit of normal to 5.5 mg/dL (1.78 mmol/L)
- Grade 2: 5.5 to 7 mg/dL (1.78 to 2.26 mmol/L)
- Grade 3: 7 to 10 mg/dL (2.26 to 3.23 mmol/L)
- Grade 4: >10 mg/dL (>3.23 mmol/L)

8.2.4 Safety Results

Deaths

Data:
Table 28 below summarizes the deaths that occurred during the study. The on-treatment period was defined as the period of time from the day of first dose to the day of last dose administered.

Table 28: Applicant – Overview of On-Study Deaths

	TAS-120-101 Phase 2 20 mg QD (N=103) n (%)	All iCCA 20 mg QD (N=145) n (%)	Any tumor type 20 mg QD (N=318) n (%)
All Deaths	**40 (38.8)**	**71 (49.0)**	**182 (57.2)**
Time from first dose date to death (month)			
N	40	71	182
Mean (SD)	9.91 (5.505)	10.03 (5.901)	8.39 (5.739)
Median (Min, Max)	10.02 (1.4, 26.4)	9.03 (1.0, 26.4)	6.74 (0.7, 26.4)
The period in which death occurred			
Deaths on-treatment and during 30-day safety follow-up	6 (5.8)	9 (6.2)	29 (9.1)
Deaths >30 days of last dose date	34 (33.0)	62 (42.8)	153 (48.1)
Reasons for all study deaths			
Radiological or clinical disease progression	36 (35.0)	61 (42.1)	160 (50.3)
Adverse event	0	0	2 (0.6)
Unknown[a]	2 (1.9)	8 (5.5)	17 (5.3)
Other	2 (1.9)	2 (1.4)	3 (0.9)
Reasons for deaths on-treatment and during 30 days safety follow-up			

	TAS-120-101 Phase 2 20 mg QD (N=103) n (%)	All iCCA 20 mg QD (N=145) n (%)	Any tumor type 20 mg QD (N=318) n (%)
Radiological or clinical disease progression	6 (5.8)	8 (5.5)	25 (7.9)
Adverse event	0	0	1 (0.3)
Unknowna	0	1 (0.7)	3 (0.9)
Other	0	0	0

Source: 2.7.4 Summary of Clinical Safety, In-text Table 9; ADSL
Abbreviations: iCCA=intrahepatic cholangiocarcinoma; max=maximum; min=minimum; n=number of patients with at least 1 event; N=number of patients in treatment group; QD=once daily; SD=standard deviation
[a] Unknown includes all cases where no reason is given (missing), no other information was given, no cause of death was specified, or the reason contained the word "unknown"

The Applicant's Position:
In the TAS-120-101 Phase 2 study, 6 patients (5.8%) died within 30 days of their last dose of futibatinib as of the cutoff date (October 1, 2020) (TAS-120-101 CSR Part 2 Section 11.2.4.1). No patients died while receiving study treatment. The most common reasons for death were clinical or radiological disease progression. There was no death due to a TEAE reported in the Phase 2 patient population.

No patients with iCCA (N=145) and no patients with any tumor type who received a starting dose of 20 mg QD (N=318) in the integrated safety population died while receiving study treatment; 6.2% of patients with iCCA, and 9.1% of patients with any tumor type who received a 20 mg QD starting dose died during the 30-day safety follow-up period, primarily due to disease progression. Deaths of 2 patients (0.6%) with any tumor type who received a starting dose of 20 mg QD in the integrated population were attributed to AEs. These included 1 patient each with acute pulmonary edema and renal failure acute (both after discontinuation of study treatment). Neither of these events were assessed by the investigators as treatment-related.

The FDA's Assessment:
FDA agrees with Taiho's summary of deaths and, after review of the narratives, concludes that based on the information provided in the application for all seven patients (7%) who died within 30 days of receiving last treatment dose, the cause of death was disease progression. Overall, 39 out of 103 (38%) patients in the Phase 2 portion of the study died due to clinical or radiological disease progression. One patient (1%) died due to pneumonia associated with esophageal perforation 70 days after discontinuing futibatinib due to esophagitis.

Serious Adverse Events

Data:

Table 29 presents summary of SAE that occurred in more than 2 patients in TAS-120-101 Phase 2 study.

Table 29: Applicant - Summary of Serious Adverse Events by System Organ Class and Preferred Term: Preferred Terms Reported for ≥ 2.0 of Total Patients (Safety Population)

SOC PT	TAS-120-101 Phase 2 20 mg QD (N=103)		All iCCA 20 mg QD (N=145)		Any tumor type 20 mg QD (N=318)	
	Total n (%)	Grade ≥3 n (%)	Total n (%)	Grade ≥3 n (%)	Total n (%)	Grade ≥3 n (%)
Patients with at Least 1 AE	**40 (38.8)**	**34 (33.0)**	**59 (40.7)**	**52 (35.9)**	**139 (43.7)**	**121 (38.1)**
Blood and lymphatic system disorders	**1 (1.0)**	**1 (1.0)**	**1 (0.7)**	**1 (0.7)**	**3 (0.9)**	**3 (0.9)**
Anaemia	1 (1.0)	1 (1.0)	1 (0.7)	1 (0.7)	3 (0.9)	3 (0.9)
Gastrointestinal disorders	**11 (10.7)**	**10 (9.7)**	**20 (13.8)**	**17 (11.7)**	**42 (13.2)**	**36 (11.3)**
Abdominal pain	1 (1.0)	0	4 (2.8)	2 (1.4)	6 (1.9)	3 (0.9)
Ascites	3 (2.9)	3 (2.9)	3 (2.1)	3 (2.1)	4 (1.3)	4 (1.3)
Intestinal obstruction	1 (1.0)	1 (1.0)	3 (2.1)	3 (2.1)	7 (2.2)	7 (2.2)
Nausea	1 (1.0)	1(1.0)	2 (1.4)	1 (0.7)	3 (0.9)	2 (0.6)
Upper gastrointestinal haemorrhage	3 (2.9)	2 (1.9)	4 (2.8)	3 (2.1)	5 (1.6)	4 (1.3)
Vomiting	1 (1.0)	1(1.0)	2 (1.4)	1 (0.7)	4 (1.3)	3 (0.9)
General disorders and administration site conditions	**5 (4.9)**	**5 (4.9)**	**12 (8.3)**	**8 (5.5)**	**29 (9.1)**	**23 (7.2)**
Disease progression	4 (3.9)	0	6 (4.1)	6 (4.1)	15 (4.7)	15 (4.7)
Pyrexia	4 (3.9)	0	4 (2.8)	0	6 (1.9)	1 (0.3)
Hepatobiliary disorders	**4 (3.9)**	**3 (2.9)**	**9 (6.2)**	**8 (5.5)**	**17 (5.3)**	**16 (5.0)**
Bile duct obstruction	3 (2.9)	2 (1.9)	4 (2.8)	3 (2.1)	6 (1.9)	5 (1.6)
Cholangitis	1 (1.0)	1 (1.0)	2 (1.4)	2 (1.4)	4 (1.3)	4 (1.3)
Infections and infestations	**13 (12.6)**	**12 (11.7)**	**18 (12.4)**	**17 (11.7)**	**33 (10.4)**	**32 (10.1)**
Biliary tract infection	1 (1.0)	1 (1.0)	4 (2.8)	3 (2.1)	3 (0.9)	3 (0.9)
Pneumonia	1 (1.0)	1(1.0)	1 (0.7)	1 (0.7)	3 (0.9)	3 (0.9)
Sepsis	2 (1.9)	2 (1.9)	4 (2.8)	4 (2.8)	11 (3.5)	11 (3.5)
Urinary tract infection	2 (1.9)	2 (1.9)	2 (1.4)	2 (1.4)	3 (0.9)	3 (0.9)
Metabolism and nutrition disorders	**7 (6.8)**	**6 (5.8)**	**9 (6.2)**	**7 (4.8)**	**15 (4.7)**	**13 (4.1)**
Decreased appetite	2 (1.9)	2 (1.9)	2 (1.4)	2 (1.4)	4 (1.3)	4 (1.3)
Dehydration	2 (1.9)	2 (1.9)	3 (2.1)	2 (1.4)	6 (1.9)	5 (1.6)
Nervous system disorders	**10(9.7)**	**4 (3.9)**	**12 (8.3)**	**4 (2.8)**	**23 (7.2)**	**11 (3.5)**
Transient ischaemic attack	2 (1.9)	0	3 (2.1)	0	4 (1.3)	0
Renal and urinary disorders	**0**	**0**	**1 (0.7)**	**1 (0.7)**	**6 (1.9)**	**5 (1.6)**
Acute kidney injury	0	0	1 (0.7)	1 (0.7)	3 (0.9)	3 (0.9)
Respiratory, thoracic and mediastinal disorders	**3 (2.9)**	**1 (1.0)**	**3 (2.1)**	**1 (0.7)**	**10 (3.1)**	**7 (2.2)**
Dyspnoea	2(1.9)	0	2 (1.4)	0	3 (0.9)	1 (0.3)
Vascular disorders	**0**	**0**	**0**	**0**	**6 (1.9)**	**3 (0.9)**

SOC PT	TAS-120-101 Phase 2 20 mg QD (N=103)		All iCCA 20 mg QD (N=145)		Any tumor type 20 mg QD (N=318)	
	Total n (%)	Grade ≥3 n (%)	Total n (%)	Grade ≥3 n (%)	Total n (%)	Grade ≥3 n (%)
Deep vein thrombosis	0	0	0	0	3 (0.9)	1 (0.3)

Source: 2.7.4 Summary of Clinical Safety, In-text Table 10, ISS Table 14.3.2.2.1.1; ADSL, ADAE
Abbreviations: AE=adverse event; iCCA=intrahepatic cholangiocarcinoma; n=number of patients with at least 1 event; N=number of patients in treatment group; PT=preferred term; QD=once daily; SOC=system organ class.

The Applicant's Position:

In the TAS-120-101 Phase 2 study, SAEs were reported for 40 patients (38.8%), including 34 patients (33.0%) who experienced a Grade ≥3 SAE. The most frequently reported SAEs other than disease progression were pyrexia (3.9%), and ascites, upper gastrointestinal hemorrhage, and bile duct obstruction (2.9% each). One patient experienced adverse reactions of ascites, decreased appetite, and dehydration with outcome of death associated with clinical disease progression. Treatment-related SAEs were reported for 10 patients (9.7%), including 7 patients (6.8%) with a Grade ≥3 SAE. The only treatment-related SAE reported for more than 1 patient was migraine (n=2, 1.9%).
For patients with iCCA (N=145) and patients with any tumor type (N=318) who received a starting dose of 20 mg QD in the integrated safety population, frequency (40.7% / 43.7%) and severity (Grade ≥3: 35.9% / 38.1%) of SAEs were comparable to those observed in the TAS-120-101 Phase 2 population.

The FDA's Assessment:

FDA replicated Taiho's summary of SAEs in Table 29 and agrees that the nature of the reported SAEs are consistent with what would be expected based on the disease under study, an advanced cancer population, and with an FGFR2 kinase inhibitor like futibatinib.Table 29

Dropouts and/or Discontinuations Due to Adverse Effects

Data:

Table 30 below describes subject disposition in the TAS-120-101 Phase 2 study. Patients discontinued the study treatment most often due to radiologic progression (57.3%).

Table 30: Applicant - Patient Disposition and Reasons for Discontinuation from Treatment

	TAS-120-101-Phase 2 20 mg QD (N=103) n (%)
All Treated	
Treatment Ongoing at Data Cutoff Date	31 (30.1)
Discontinued Treatment	72 (69.9)
Primary Reason for Discontinuation from Treatment	
Adverse Event/Serious Adverse Event	5 (4.9)
Radiologic Progression	59 (57.3)
Clinical Disease Progression	5 (4.9)
Patient Withdrew Consent	2 (1.9)
Investigator Decision	1 (1.0)

Source: 2.5 Clinical Overview, In-text Table 2; ADSL
Abbreviations: N=number of patients in group; n=number of patients with event

Table 31 below presents subject incidence of AEs that led to treatment discontinuation in TAS-120-101 Phase 2 study.

Table 31: Applicant - Adverse Events With the Outcome of Treatment Discontinuation by System Organ Class, Preferred Term, and Worst Grade on Treatment (Safety Population)

	TAS-120-101-Phase 2 20 mg QD (N=103)	
System Organ Class Preferred Term	**Total (N %)**	**≥Grade 3 (N %)**
Patients with at least 1 adverse event	**8 (7.8)**	**7 (6.8)**
Blood and lymphatic system disorders	**1 (1.0)**	**1 (1.0)**
Anaemia	1 (1.0)	1 (1.0)
Gastrointestinal disorders	**2 (1.9)**	**2 (1.9)**
Oesophagitis	1 (1.0)	1 (1.0)
Oral dysaesthesia	1 (1.0)	1 (1.0)
Stomatitis	1 (1.0)	0
Hepatobiliary disorders	**1 (1.0)**	**1 (1.0)**
Bile duct obstruction	1 (1.0)	1 (1.0)
Metabolism and nutrition disorders	**1 (1.0)**	**1 (1.0)**
Hypoglycaemia[a]	1 (1.0)	1 (1.0)
Neoplasms benign, malignant and unspecified (incl. cysts and polyps)	**2 (1.9)**	**2 (1.9)**
Metastases to central nervous system[a]	1 (1.0)	1 (1.0)

	TAS-120-101-Phase 2 20 mg QD (N=103)	
System Organ Class Preferred Term	**Total (N %)**	**≥Grade 3 (N %)**
Tumour pain[a]	1 (1.0)	1 (1.0)
Nervous system disorders	**1 (1.0)**	**0**
Dizziness	1 (1.0)	0
Respiratory, thoracic and mediastinal disorders	**1 (1.0)**	**0**
Pharyngeal inflammation	1 (1.0)	0

Source:TAS-120-101 Part 2 CSR; In-text Table 24; ADSL, ADAE

[a] These patients discontinued study treatment due to these adverse events, which the Investigator subsequently determined were associated with disease progression.

Notes: Summary includes all events reported between first dose and 30 days after last dose of study drug. If a subject had 2 or more adverse events in the same system organ class (or with the same preferred term) with different Common Terminology Criteria for Adverse Events (CTCAE) grades, then the event with the highest grade was used for that subject. Adverse Events terms were coded using Medical Dictionary for Regulatory Activities (MedDRA) version 22.0. Adverse events were graded using CTCAE Version 4.03 per Protocol.

The Applicant's Position:

In the TAS-120-101 Phase 2 study, most patients (57.3%) discontinued futibatinib study treatment due to radiologic disease progression rather than an AE (Table 30). Eight patients (7.8%), including 2 patients (1.9%) with treatment-related adverse events (TRAE) discontinued treatment due to an AE (Table 31).

The FDA's Assessment:

FDA agrees with Taiho's analysis summarized in Table 30. Five patients (5%) discontinued futibatinib due to AEs. One patient each had hypoglycemia, metastases to central nervous system, and tumor pain, which FDA agrees are not AEs related to treatment but are effects of tumor progression. FDA also agrees with data presented in Table 31 except to note that metastases to CNS is not considered an AE .

Dose Interruption/Reduction Due to Adverse Effects

Data:

Dose modification of futibatinib in the form of dose interruptions or dose reductions were reported for 68 patients (66.0%) and 60 patients (58.3%), respectively (TAS-120-101 Phase 2 (Part 2) CSR, Section 11.2.1).

Table 32 and Table 33 below present AEs that led to dose interruption and dose reduction, respectively, in TAS-120-101 Phase 2 study.

Table 32: Applicant - Adverse Events Leading to Dose Interruptions by System Organ Class, and Preferred Term (Safety Population) – Preferred Terms Reported for > 2 Patients

System Organ Class Preferred Term	TAS-120-101-Phase 2 20 mg (N=103) n (%)
Patients with any adverse event leading to dose interruption	**68 (66.0)**
Blood and lymphatic system disorders	**6 (5.8)**
Anaemia	4 (3.9)
Thrombocytopenia	2 (1.9)
Gastrointestinal disorders	**14 (13.6)**
Nausea	3 (2.9)
Stomatitis	5 (4.9)
Vomiting	4 (3.9)
General disorders and administration site conditions	**13 (12.6)**
Fatigue	7 (6.8)
Pyrexia	4 (3.9)
Investigations	**22 (21.4)**
Alanine aminotransferase increased	10 (9.7)
Aspartate aminotransferase increased	9 (8.7)
Blood alkaline phosphatase increased	3 (2.9)
Blood bilirubin increased	5 (4.9)
Metabolism and nutrition disorders	**22 (21.4)**
Decreased appetite	4 (3.9)
Hyperphosphataemia	16 (15.5)
Hyponatraemia	3 (2.9)
Respiratory, thoracic and mediastinal disorders	**3 (2.9)**
Dyspnoea	3 (2.9)
Skin and subcutaneous tissue disorders	**16 (15.5)**
Onycholysis	3 (2.9)
Palmar-plantar erythrodysaesthesia syndrome	11 (10.7)

Source: TAS-120-101 Phase 2 CSR; In-text Table 23; ADSL, ADAE
Note: Summary includes all events reported between first dose and 30 days after last dose of study drug.

Table 33: Applicant - Adverse Events Leading to Dose Reductions by System Organ Class, and Preferred Term (Safety Population)

System Organ Class Preferred Term	TAS-120-101-Phase 2 20 mg QD (N=103) n (%)
Patients with any adverse events leading to dose reduction	**60 (58.3)**

System Organ Class Preferred Term	TAS-120-101-Phase 2 20 mg QD (N=103) n (%)
Gastrointestinal disorders	**4 (3.9)**
Stomatitis	3 (2.9)
General disorders and administration site conditions	**6 (5.8)**
Fatigue	5 (4.9)
Investigations	**14 (13.6)**
Alanine aminotransferase increased	5 (4.9)
Aspartate aminotransferase increased	4 (3.9)
Blood creatine phosphokinase increased	2 (1.9)
Metabolism and nutrition disorders	**21 (20.4)**
Hyperphosphataemia	20 (19.4)
Nervous system disorders	**4 (3.9)**
Skin and subcutaneous tissue disorders	**17 (16.5)**
Nail disorder	3 (2.9)
Onychomadesis	2 (1.9)
Palmar-plantar erythrodysaesthesia syndrome	10 (9.7)

Source: TAS-120-101 phase 2 CSR, In -text Table 22; ADSL, ADAE
Note: Summary includes all events reported between first dose and 30 days after last dose of study drug

The Applicant's Position:

As shown in Table 32, 68 (66.0%) patients experienced AEs leading to dose interruption; 52 (50.5%) patients experienced events considered related to study drug (TAS-120-101 Phase 2 CSR). The five most frequently reported preferred terms were hyperphosphatemia (16 patients, 15.5%), PPES (11 patients, 10.7%), ALT increased (10 patients, 9.7%), AST increased (9 patients, 8.7%), and fatigue (7 patients, 6.8%).

As shown in Table 33, 60 (58.3%) patients experienced AEs leading to dose reduction; 56 (54.4%) patients experienced events considered related to study drug. The most frequently reported (> 2 patients) preferred terms were hyperphosphatemia (20 patients, 19.4%), PPES (10 patients, 9.7%), fatigue, ALT increased (5 patients, 4.9% each), AST increased (4 patients, 3.9%), stomatitis, and nail disorder (3 patients, 2.9% each).

The FDA's Assessment:

FDA replicated the analysis in Table 32 and Table 33 but grouped PTs, which resulted in the most common AEs leading to dose interruptions being hyperphosphatemia (17%), AST/ALT increased (9%), fatigue (8%), nail disorders (6%), hyperbilirubinemia (5%), and palmar plantar erythrodysesthesia syndrome (5%). Ocular toxicity accounted for 6% of dose interruptions (1% each for detachment of retinal pigment epithelium, eye pain, foreign body sensation in eyes, lacrimation increased, punctate keratitis, and vision blurred).

For Table 33 (dose reductions), FDA grouped the terms "fatigue" and "malaise" to yield an incidence of 6% (with 4% incidence of Grade 3 fatigue), "AST increased" and "ALT increased" to yield an incidence of 7% and the terms "nail disorder", "paronychia", "onychomadesis", "onycholysis", and "onychalgia" to yield an incidence of 7%. FDA also notes that ocular toxicity let do dose reduction in 4% of patients (3% with retinal pigment epithelium detachment and 1% with ulcerative keratitis). The incidence of other AEs that led to dose reduction were <2%.

Significant Adverse Events

Data:
Adverse events of special interest (AESI) are included in Section 8.2.5 of this document.

The Applicant's Position:
Adverse events of special interest (AESI) are discussed in Section 8.2.5 of this document.

The FDA's Assessment:
FDA has reviewed AESI in Section 8.2.5.

Treatment Emergent Adverse Events and Adverse Reactions

Data:
Frequently reported (preferred terms of any grade reported for >15%) AEs are summarized in Table 34. Adverse events by system organ class, preferred term (reported for >15% of patients), and worst Common Terminology Criteria for Adverse Events (CTCAE) grade are summarized in

Table 35.

Table 34: Applicant - Most Frequently Reported (> 15% Any Grade Incidence) Adverse Events by Preferred Term (Safety Population)

	TAS-120-101-Phase 2 20 mg QD	
MedDRA Preferred Term	**Any Grade Incidence N = 103 n (%)**	**Grade ≥3 Incidence N = 103 n (%)**
Patients with any adverse event	**103 (100.0)**	**79 (76.7)**
Hyperphosphataemia	88 (85.4)	31 (30.1)
Constipation	40 (38.8)	0
Diarrhoea	37 (35.9)	1 (1.0)
Dry mouth	36 (35.0)	0
Alopecia	35 (34.0)	0

	TAS-120-101-Phase 2 20 mg QD	
MedDRA Preferred Term	**Any Grade Incidence N = 103 n (%)**	**Grade ≥3 Incidence N = 103 n (%)**
Fatigue	35 (34.0)	8 (7.8)
Dry skin	30 (29.1)	0
Aspartate aminotransferase increased	26 (25.2)	10 (9.7)
Nausea	25 (24.3)	2 (1.9)
Stomatitis	25 (24.3)	6 (5.8)
Decreased appetite	24 (23.3)	3 (2.9)
Arthralgia	23 (22.3)	0
Abdominal pain	22 (21.4)	3 (2.9)
Dry eye	22 (21.4)	1 (1.0)
Palmar-plantar erythrodysaesthesia syndrome	22 (21.4)	5 (4.9)
Dysgeusia	21 (20.4)	0
Urinary tract infection	20 (19.4)	3 (2.9)
Vomiting	20 (19.4)	1 (1.0)
Weight decreased	19 (18.4)	4 (3.9)
Alanine aminotransferase increased	18 (17.5)	6 (5.8)
Back pain	17 (16.5)	2 (1.9)
Anaemia	16 (15.5)	5 (4.9)
Hypercalcaemia	16 (15.5)	2 (1.9)
Hyponatraemia	16 (15.5)	11 (10.7)
Nail disorder	16 (15.5)	0
Onycholysis	16 (15.5)	0

Source: TAS-120-101 phase 2 CSR ,In-text Table 11; ADSL, ADAE
Notes: Summary includes all events reported between first dose and 30 days after last dose of study drug. Patient with 2 or more adverse events in the same preferred term is counted only once for that preferred term. Adverse events terms were coded using Medical Dictionary for Regulatory Activities (MedDRA) version 22.0. Adverse events were graded using Common Terminology Criteria for Adverse Events (CTCAE) Version 4.03 except for hyperphosphatemia and blood phosphorus increased.

Table 35: Applicant - Summary of Adverse Events by System Organ Class, Preferred Term, and Worst CTCAE Grade: Preferred Terms Reported for > 15% of Total Patients (Safety Population)

	TAS-120-101-Phase 2 20 mg QD (N=103)	
Adverse Reaction	**All Grades[a] (%)**	**Grade 3[b] (%)**
Metabolism and nutrition disorders		
Decreased appetite	24 (23.3)	3 (2.9)
Skin and subcutaneous tissue disorders		
Nail toxicity[c]	48 (46.6)	2 (1.9)
Alopecia	35 (34.0)	0
Dry skin	30 (29.1)	0
Palmar-plantar erythrodysesthesia syndrome	22 (21.4)	5 (4.9)
Gastrointestinal disorders		
Constipation	40 (38.8)	0
Diarrhea	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)
Vomiting	20 (19.4)	1 (1.0)
General disorders		
Fatigue	35 (34.0)	8 (7.8)
Musculoskeletal and connective tissue disorders		
Arthralgia	23 (22.3)	0
Back pain	17 (16.5)	2 (1.9)
Eye disorders		
Dry eye	22 (21.4)	1 (1.0)
Nervous system disorders		
Dysgeusia	21 (20.4)	0
Infections and infestations		
Urinary tract infection	20 (19.4)	3 (2.9)
Investigations		
Weight decreased	19 (18.4)	4 (3.9)

Source: 2.5 Clinical Overview In-Text Table 12; ADSL, ADAE

[a] Graded per NCI CTCAE 4.03.

[b] Events of Grade 3 only (no Grade 4 or 5 occurred)

[c] Includes nail toxicity, nail disorder, nail discoloration, nail dystrophy, nail hypertrophy, nail infection, nail pigmentation, onychalgia, onychoclasis, onycholysis, onychomadesis, onychomycosis, and paronychia.

The Applicant's Position:

Frequently reported TEAEs:

At least 1 AE of any grade was reported for 100% of patients. The most frequently reported (≥25%) AEs (preferred term) of any grade were: hyperphosphatemia (85.4%), constipation (38.8%), diarrhea (35.9%), dry mouth (35.0%), fatigue, alopecia (34.0% each), dry skin (29.1%), and aspartate aminotransferase (AST) increased (25.2%).

Severity of TEAEs:

Grade 3 or higher AEs were reported for 76.7% of patients (predominantly Grade 3, 66.0%). The most frequently (≥5%) reported Grade ≥3 events included hyperphosphatemia (30.1%; defined by serum phosphate level ≥7 mg/dL irrespective of any clinical symptoms), hyponatremia (10.7%), AST increased (9.7%), fatigue (7.8%), stomatitis (5.8%), and alanine aminotransferase (ALT) increased (5.8%).

Seven Grade 4 AEs were reported for 6 (5.8%) patients, and included 1 event each of hyponatremia, hypophosphatemia, hypercalcemia, bile duct obstruction, sepsis, ALT increased, and hypoglycemia (CSR Table 14b.3.2.5.1). The hyponatremia, hypercalcemia, bile duct obstruction, and hypoglycemia were considered by the Investigator as due to disease under study/disease progression, the causes of sepsis and hypophosphatemia were unspecified, and the ALT increased was considered related to study treatment (CSR Listing 16b.2.7.1).

Adverse drug reactions (ADRs):

TAS-120-101 was a single arm study; therefore, all TEAEs regardless of relationship to futibatinib are considered to be ADRs. Overall, futibatinib was safe and tolerable at the recommended dose of 20 mg QD with a generally predictable, monitorable, and manageable safety profile in cancer patients. TEAEs were manageable with supportive treatment and/or futibatinib dose modifications. Treatment discontinuations due to adverse reactions were rare.

The FDA's Assessment:

FDA analyzed AEs by preferred terms (as grouped below) and the results are summarized in Table 36. AEs that occurred with frequency > 5% were hyperphosphatemia (31%), AST/ALT increased (12%), hyponatremia (12%), fatigue (11%), hypophosphatemia (7%), palmar-plantar erythrodysesthesia syndrome (6%), anemia (6%), and stomatitis (6%). Overall, FDA agrees that the observed safety profile is consistent with futibatinib' s mechanism of action and the patient population studied. Although the majority of AEs were Grade 1-2, 66% of patients needed treatment interruption and 58% of patients needed dose reductions for toxicity management.

A revised table of AEs is included in labeling.

Table 36. FDA's Analysis of Adverse Events by Preferred Term (Safety Population).

Preferred Term (AEDCOD)	All grades %	Grade 3 and 4 %
Hyperphosphatemia[1]	91	31
Arthralgia[2]	50	4
Nail disorder[3]	46	2
Constipation	41	0
Diarrhea[4]	39	1
Fatigue[5]	38	11
Dry mouth	36	0
Alopecia	34	0
Abdominal pain[6]	30	3
Dry skin	29	0
Stomatitis[7]	29	6
AST/ALT increased	27	12
Peripheral sensory neuropathy[8]	27	1
Nausea	26	2
Dysgeusia[9]	25	0
Decreased appetite	24	2
Dry eye [10]	24	1
Urinary tract infection[11]	23	3
Palmar-plantar erythrodysesthesia syndrome	22	6
Vomiting[12]	20	1
Weight decreased	20	4
Hypercalcemia[13]	17	2
Hyponatremia[14]	17	12
Hemorrhage[15]	17	3
Anemia	16	6
Blood creatinine increased	16	0
Hypophosphatemia	16	7
Pyrexia	16	0
Edema[16]	16	0
Oropharyngeal pain[17]	16	1
Blood alkaline phosphatase increased	15	3
Muscle spasms	15	1
Rash[18]	14	0
Thrombocytopenia[19]	13	2
Dizziness[20]	12	1
Headache[21]	11	1
Blood creatine phosphokinase increased	10	3
Blood bilirubin increased[22]	10	1
Dehydration	9	3

Pruritus	9	0
Vision blurred	9	1
Neutropenia[23]	9	1
Cataract	8	3
Insomnia	8	0
White blood cell count decreased	8	1
Abdominal distension	7	0
Dyspepsia	7	0
Troponin T increased	7	1
Ascites	6	4
Gastroesophageal reflux disease	6	0
Hypertension	6	3
Hypoalbuminemia	6	1
Hypokalemia	6	2
Lacrimation increased	6	0
Nasopharyngitis	6	0
Upper respiratory tract infection	6	0

1. Hyperphosphatemia and blood phosphorous increased
2. Arthralgia, arthritis, back pain, bone pain, musculoskeletal chest pain, musculoskeletal discomfort, musculoskeletal pain, musculoskeletal stiffness, myalgia, neck pain, non-cardiac chest pain, pain in extremity, and spinal pain.
3. Nail disorder, nail discoloration, nail dystrophy, nail hypertrophy, nail pigmentation, nail toxicity, onychalgia, onychoclasis, onycholysis, onychomadesis, and paronychia.
4. Diarrhea, colitis, and gastroenteritis.
5. Fatigue and asthenia.
6. Abdominal Pain, abdominal discomfort, abdominal pain lower, gastrointestinal pain, and hepatic pain.
7. Stomatitis, glossitis, mouth ulceration, mucosal inflammation, pharyngeal inflammation, and tongue ulceration.
8. Peripheral sensory neuropathy, burning sensation, hyperesthesia, hypoesthesia, neuralgia, neuropathy peripheral, and paresthesia.
9. Dysgeusia, ageusia, and taste disorder.
10. Includes dry eye, keratitis (Grade 1, 1%), lacrimation increased, and punctate keratitis.
11. Urinary tract infection, cystitis, and dysuria.
12. Vomiting and hematemesis.
13. Hypercalcemia and blood calcium increased.
14. Hyponatremia and blood sodium decreased.
15. Hemorrhage, anal hemorrhage, epistaxis, gastrointestinal ulcer hemorrhage, hematochezia, hematuria, lower gastrointestinal hemorrhage, esophageal varices hemorrhage, rectal hemorrhage, upper gastrointestinal hemorrhage, vaginal hemorrhage, and vitreous hemorrhage.
16. Edema and peripheral swelling.
17. Oropharyngeal pain, oral pain, tooth pain, pain in jaw, glossodynia, and gingival pain.
18. Rash, dermatitis, dermatitis acneiform, dermatitis bullous, rash macular, rash maculo-papular, rash papular, and skin exfoliation.
19. Thrombocytopenia and platelet count decreased.
20. Dizziness and vertigo.
21. Headache and migraine.
22. Blood bilirubin increased and hyperbilirubinemia.

23. Neutropenia and neutrophil count decreased.

Laboratory Findings

Data:
Results outside of normal limits were graded according to NCI-CTCAE v 4.03 and were recorded as AEs as appropriate, with the exception of Grade ≥3 hyperphosphatemia, which was defined as serum phosphate >7 mg/dL irrespective of clinical symptoms. Select laboratory abnormalities (≥10%) worsening from Baseline are summarized in Table 37.

Table 37: Applicant - Select Laboratory Abnormalities (≥10%) Worsening from Baseline in Patients Receiving Futibatinib in Phase 2 of TAS-120-101

	TAS-120-101-Phase 2 20 mg QD (N=103)	
Laboratory Abnormality[a]	**All Grades**[b] **(%)**	**Grade ≥3 (%)**
Hematology		
Decreased hemoglobin	52.4	5.8
Decreased lymphocytes	46.3	10.0
Decreased platelets	42.0	1.0
Decreased leukocytes	33.0	1.1
Decreased neutrophils	31.3	1.6
Chemistry		
Increased phosphate[c]	96.7	38.5
Increased creatinine[d]	58.1	0
Increased glucose	52.0	4.9
Increased calcium	51.2	1.2
Decreased sodium	50.5	14.6
Decreased phosphate	49.5	19.6
Increased alanine aminotransferase	49.5	7.4
Increased alkaline phosphatase	46.6	4.9
Increased aspartate aminotransferase	45.6	12.6
Increased creatine kinase	30.7	5.3
Decreased albumin	30.6	2.4
Increased bilirubin	28.4	0
Decreased glucose	25.4	0
Decreased potassium	21.9	2.1
Increased potassium	16.2	2.0
Coagulation		

	TAS-120-101-Phase 2 20 mg QD (N=103)	
Laboratory Abnormality[a]	**All Grades**[b] **(%)**	**Grade ≥3 (%)**
Increased activated partial thromboplastin time	36.4	8.0
Increased prothrombin Intl. Normalized Ratio	25.3	0

Source: 2.5 Clinical Overview, In-text Table13; ADSL, ADLB

[a] Graded per NCI CTCAE 4.03.

[b] Percentages are based on the number of subjects with nonmissing data at both baseline and at least one relevant post-baseline data value

[c] NCI CTCAE 4.03 does not define grades for increased phosphate. Laboratory value shift table categories were used to assess increased phosphorus levels (Grades ≥3 defined as >7 mg/dL).

[d] Graded based on comparison to upper limit of normal.

The Applicant's Position:

Hematology and Coagulation:

In the TAS-120-101 Phase 2 study, no patient had a Grade 4 post-baseline hematologic laboratory result. The most frequently reported (≥5.0%) Grade 3 results were lymphocyte count decreased (12.0%), prolonged aPTT (8.0%), and anemia (5.8%).

Chemistry:

Grade 4 post-baseline clinical chemistry laboratory results were reported for 1 patient each for the laboratory parameters of ALT increased, hypercalcemia, hypophosphatemia, and hyponatremia. The most frequently reported (≥5.0%) Grade 3 results were hyperphosphatemia (35.0%), hypophosphatemia (19.2%), AST increased (12.6%), hyponatremia (15.5%), ALP increased 6.8%), and ALT increased, and hyperglycemia (5.8% each).

The FDA's Assessment:

FDA replicated the analysis of laboratory abnormalities summarized in Table 37 and generally agrees with Taiho's assessment. Lab abnormalities with incidence > 30% included decreased hemoglobin, increased glucose, increased creatinine, decreased sodium, increased calcium, decreased phosphate, increased alkaline phosphatase, , increased ALT, increased AST, decreased lymphocytes, decreased platelets, increased activated partial thromboplastin time, decreased leukocytes, and decreased albumin. Hyperphosphatemia is discussed further in Section 8.2.5.2. Overall, the laboratory abnormalities observed in the Phase 2 of Study TAS-120-101 are consistent with the expected abnormalities in patients with advanced intrahepatic cholangiocarcinoma and with the mechanism of action of futibatinib. Hypophosphatemia was a result of phosphate lowering therapy treatment and not direct effect of futibatinib.

Vital Signs

Data:

Refer to applicant's position below.

The Applicant's Position:
No clinically meaningful trends from baseline were observed in heart rate, respiratory rate, body weight, systolic and diastolic blood pressure, or body temperature of patients in the TAS-120-101 Phase 2 population.

The FDA's Assessment:
FDA's review of vital signs data in the CSR did not raise any specific safety concerns.

Electrocardiograms (ECGs)

Data:
Nine patients in the TAS-120-101 Phase 2 population had a normal or abnormal not clinically significant ECG at Screening visit and an abnormal but clinically significant result at a subsequent visit. Abnormal and clinically significant ECG results are reported as AEs as assessed by the investigators.

The Applicant's Position:
Futibatinib did not appear to have any clinically significant adverse effects on HR or ECG parameters including PR interval, QRS interval, QT interval, HR corrected QT interval (QTcF), or ECG morphology.

The FDA's Assessment:
FDA review of ECG data in the CSR did not raise any specific safety concerns.

QT

Data:
Table 38 presents abnormal QTcF results in safety population who had both baseline and post-baseline data.

Table 38: Applicant – Summary of QTc Assessment

QTc Assessment Results	TAS-120-101-Phase 2 20 mg QD (N=103)
Patients with both baseline and post-baseline data	100
Maximum Increase from Baseline (msec)	
≤ 30	59 (59.0)
>30 - 60	16 (16.0)

>60	6 (6.0)
Maximum Post Baseline Value (msec)	
≤470	92 (92.0)
>470 - 480	2 (2.0)
>480 - 500	2 (2.0)
>500	4 (4.0)
QTc Value	
New >450 (msec)	20 (20.0)
New >480 (msec)	6 (6.0)
New >500 (msec)	4 (4.0)

Source: TAS-120-101 Phase 2 CSR Table 14b.3.5.3; ADSL, ADEG

The Applicant's Position:
Among the CCA patients in TAS-120-101 Phase 2 study, Electrocardiogram QT prolongation was reported in 2 patients, Grade 1 and Grade 2 in one each. Both events resolved without corrective treatment or dose modification. (TAS-120-101 Phase 2 Table 14b.3.2.5.1)
Based on the result of a thorough TQT study (TAS-120-107), futibatinib did not appear to have any clinically significant adverse effects on HR or ECG parameters including PR interval, QRS interval, QT interval, HR corrected QT interval, or ECG morphology in healthy volunteers. (IB v7)

The FDA's Assessment:
FDA agrees with Taiho's assessment. As summarized in the Interdisciplinary Review Team for Cardiac Safety Studies (uploaded to darrts on November 15, 2021), futibatinib does not cause significant QTcF prolongation. The effect of futibatinib was evaluated in a TQT study (Study # TAS-120-107). This was a randomized, double-blind, single-dose, placebo- and positive-controlled, crossover (4-period) study evaluating the effect of futibatinib on the QT/QTc interval in healthy subjects. The highest dose studied was 80 mg, which is the supratherapeutic dose and provides a Cmax approximately 4-fold the RP2D. Data were analyzed using the by-time analysis as the primary analysis. This analysis did not suggest that futibatinib is associated with significant QTc prolonging effect – see Table 38 for overall results. The findings of this analysis are further supported by the exposure-response analysis and categorical analyses.

Immunogenicity

Data:
Not Applicable

The Applicant's Position:
Not Applicable

The FDA's Assessment:
Not Applicable.

8.2.5 Analysis of Submission-Specific Safety Issues/Adverse event of special interest

Adverse events of special interest (AESIs) were defined based on nonclinical data and prior clinical experience with futibatinib, as well as known class effects of FGFR inhibitors, and included retinal disorders, hyperphosphatemia, hepatotoxicity, nail disorders, PPES, and rash. The list of preferred terms used to define each of the AESIs is provided below.

AESI Category	AESI	MedDRA PT Included[a]
Eye toxicity	Retinal disorders	Retinal detachment, retinal disorder, chorioretinopathy, detachment of retinal pigment epithelium, detachment of macular retinal pigment epithelium, maculopathy, serous retinal detachment, macular oedema, retinal edema, retinopathy, retinal thickening, subretinal fluid
Hyperphosphatemia	Hyperphosphatemia	Hyperphosphataemia, blood phosphorous increased
Hepatotoxicity	Hepatotoxicity	Hepatic enzyme increased, transaminases increased, alanine aminotransferase increased, aspartate aminotransferase increased, gamma-glutamyltransferase increased, bilirubin conjugated increased, acute hepatic failure, hepatic failure, subacute hepatic failure, drug-induced liver injury, hepatotoxicity, hepatocellular injury
Nail disorders	Nail disorders	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, fungal paronychia
Skin toxicity	Palmar-plantar erythrodysesthesia	Palmar-plantar erythrodysaesthesia syndrome, plantar erythema, palmar erythema
	Rash	Rash, rash erythematous, rash maculo-papular, rash papular, rash macular, rash pustular

Abbreviations: AESI = adverse event of special interest; MedDRA = Medical Dictionary for Regulatory Activities; PT = preferred term.
[a] Preferred terms coded using MedDRA version 22.0

8.2.5.1 Retinal disorders

Data:
In the Phase 2 portion of TAS-120-101, AESIs in the category of retinal disorders were infrequent, with 8 patients (7.8%) experiencing retinal disorder, including 3 patients (2.9%) with

subretinal fluid, 2 patients (1.9%) with chorioretinopathy, and one patient (1.0%) each with detachment of retinal pigment epithelium, maculopathy, and serous retinal detachment. There were no Grade ≥3 events of retinal disorders.

A total of 27 patients (8.5%) with any tumor type who received a starting dose of 20 mg QD futibatinib (N=318) experienced an AESI of retinal disorders; most of these (n=25, 7.9%) were assessed as treatment-related by the investigator. No Grade ≥3 AEs were reported.

The Applicant's Position:
Retinal disorders are an AESI for futibatinib and have also been reported for other FGFR inhibitors (Alekseev 2021; Goyal 2021; Morales-Barrera 2020). Median time to onset of retinal disorder was 42 days. In the 3 patients (2.9%) with Grade 2 retinal disorders, all events resolved to Grade <2 following dose reduction and/or interruption (TAS-120-101 Phase 2 CSR Listing 16b.2.7.7). There were no SAEs reported, and no AEs led to discontinuation of futibatinib, although 3 patients (2.9%) experienced AEs leading to dose interruption and/or reduction (TAS-120-101 Part 2 CSR, Section 11.2.4.3.1.2).

The FDA's Assessment:
This review included an ophthalmologic consult (CDER/OND/OSM/DO) to assess the adequacy of the monitoring guidelines and to evaluate ophthalmologic toxicities. Although FDA confirmed the incidence of retinal disorders as summarized by the Applicant, Taiho's monitoring plan for ocular toxicity included only a baseline ophthalmologic examination and subsequently, a single protocol mandated on-treatment examination on Cycle 2. Additional exams were triggered by the observation of symptoms or due to physician concern. The ophthalmologic monitoring plan did not include routine examination of all eye structures. For example, optical coherence tomography (OCT) was not included during visits at baseline or at Cycle 2 unless practitioners considered these assessments necessary). Therefore, FDA does not consider that the ophthalmologic toxicity of futibatinib has been adequately characterized, as some pathology, particularly retinal pigment epithelial detachment (RPED) may occur in the absence symptoms.

In addition, there was a large number of missing examinations: examinations of the anterior ocular structures are missing in 29% of patients at Cycle 2 (the visit with the most examinations) and less than 20% of patients had an end of treatment assessment. Given the monitoring frequency, lack of systematic assessments, lack of serial optical coherence tomographies, and incomplete assessments, it appears that the ophthalmological events described above represent mostly events of retinal pathology that were symptomatic and prompted examination.
Additionally, there is greater than a 20% incidence of dry eye, which is a significant concern because this condition can lead to ulcerative keratitis. Despite the limitations of the data, the reported eye toxicities are within the expected toxicities observed in the pharmacological class. Because ocular toxicity is an important risk for patients, Section 5.1 of the Lytgobi USPI was revised to follow standard of care recommendations for agents in the pharmacological class.

The labels states: " Perform a comprehensive ophthalmic examination including OCT prior to initiation of Lytgobi, every 2 months for the first 6 months of treatment and every 3 months thereafter. Refer patients for ophthalmic evaluation urgently for onset of visual symptoms, and follow-up every 3 weeks until resolution or discontinuation of LYTGOBI"

The review team considers that post marketing studies are required to further characterize the ophthalmologic toxicity of futibatinib.

8.2.5.2 Hyperphosphatemia

Data:
In the Phase 2 portion of TAS-120-101, hyperphosphatemia was the most frequently reported AESI (91.3% of patients); Grade 3 events were reported for 31.1% of patients. Of note, hyperphosphatemia was not graded according to CTCAE; Grade ≥3 was defined as serum phosphate level >7 mg/dL irrespective of clinical symptoms.

The Applicant's Position:
Hyperphosphatemia is a known on-target effect of FGFR inhibitors due to FGFR inhibition and its effect on phosphate homeostasis (Javle 2018; Mazzaferro 2019). Median time to onset was 5.0 days (Grade 3: 5.0 days) and all Grade 3 events resolved with a median time to resolution of 7.0 days (range: 2.0 to 26.0 days).

Hyperphosphatemia was manageable with use of concomitant phosphate lowering medication(s) (85.1% of patients) and/or futibatinib dose modifications (20.4% reductions/17.5% interruptions). Eighty (85.1%) of 94 patients with hyperphosphatemia were receiving at least 1 concomitant medication for hyperphosphatemia management (eg, were sevelamer/sevelamer carbonate/sevelamer hydrochloride (66.0%/14.9%/4.3%), acetazolamide (30.9%), calcium carbonate (3.2%), and calcitonin/salmon calcitonin (2.1%)). There were no SAEs, and no patient discontinued due to hyperphosphatemia (TAS-120-101 Part 2 CSR, Section 11.2.4.3.1.1).
Among patients who received a starting dose of 20 mg QD futibatinib (N=318), there were 75 patients (23.6%) with a Grade ≥3 AESI of hyperphosphatemia. No Grade 4 or Grade 5 events were reported.

The FDA's Assessment:
Hyperphosphatemia and related mineral metabolism issues (hypocalcemia, hypophosphatemia and hypercalcemia secondary to treatment to manage hyperphosphatemia, tissue calcification, etc.) are a class effect of FGFR inhibitors. In the Phase 2 portion of Study TAS-120-101, hyperphosphatemia was managed by the use of phosphate-lowering therapies (sevelamer, acetazolamide, or lanthanum carbonate), dose modifications, and limitation of phosphate-rich food intake. It is important to note that the protocol allowed the use of diuretics

(acetazolamide and furosemide) to manage hyperphosphatemia, a practice that is not commonly implemented in the U.S. The protocol also allowed local practices and clinical judgement to guide the use of phosphate-lowering agents. The protocol did not recommend any prophylactic use of phosphate-lowering therapy. Dose modification occurred as summarized in Table 39 below.

Table 39. Hyperphosphatemia Management in Study TAS-120-101

Phosphate level	Futibatinib dose modification	Phosphate-lowering therapy
Upper limit of normal (ULN) up to <5.5 mg/dL (1.78 mmol/L)	No futibatinib dose modification	Consider early phosphate-lowering therapy in case serum phosphate level rapidly increases within 1 week
5.5 mg/dL (1.78 mmol/L) to ≤7.0 mg/dL (2.26 mmol/L)	No futibatinib dose modification	Implement/intensify phosphate-lowering therapy (monotherapy or in combination)
>7.0 mg/dL (2.26 mmol/L) to ≤10.0 mg/dL (3.23 mmol/L)	Dose reduce futibatinib to the next lower dose level.	Implement/intensify phosphate-lowering therapy. If serum phosphate has resolved to ≤7.0 mg/dL (2.26 mmol/L) within 14 days after dose reduction, continue futibatinib at the same dose level; if not, further reduce futibatinib from the last reduced dose level. If serum phosphate has not resolved to ≤7.0 mg/dL (2.26 mmol/L) after 14 days of the second dose reduction of futibatinib, dose interrupt futibatinib until it is resolved to ≤7.0 mg/dL (2.26 mmol/L)
>10.0 mg/dL (3.23 mmol/L)	Interrupt futibatinib until serum phosphate is ≤7.0	Intensify phosphate-lowering therapy.

	mg/dL (2.26 mmol/L), then resume futibatinib at the next lower dose level	If after 2 dose interruptions and 2 dose reductions, serum phosphorus level is not resolved to ≤7.0 mg/dL (2.26 mmol/L) after 14 days, permanently discontinue futibatinib.

FDA generally agrees with Taiho's summary of hyperphosphatemia onset and management. FDA could not replicate Taiho's analysis of the use of phosphate-lowering agents and on April 12, 2022, FDA requested Taiho to submit a comprehensive analysis of hyperphosphatemia management, including phosphate binders, diuretics, and other drugs used to lower blood phosphate. On the revised analysis that Taiho submitted on April 26, 2022, a total of 96 (93%) patients received at least 1 phosphate-lowering treatment and the median serum phosphorus level at the time of initiating the first phosphate-lowering therapy was 5.87 mg/dL with a range from 3.0 to 8.4. Initiation of the first phosphate-lowering therapy occurred at a median of 6.0 days (range: 0, 302) following the start of treatment with futibatinib.

Due to the incidence of hyperphosphatemia following treatment with futibatinib, and the need for early identification and intervention to avoid clinical sequelae, hyperphosphatemia is described in the Warnings and Precautions section of product labeling for futibatinib and management guidelines are included in the dosage modification table in Section 2.

Hypophosphatemia was reported in 14 patients (14 %) and hypocalcemia was seen in 2 patients (1.9%).There were no reported events of phosphate metabolism-related clinical events such as calcinosis/calciphylaxis, stress fracture/compression fracture, myocardial calcification, or vascular calcification. An event of Grade 3 peripheral ischemia, which can occur due to arterial calcification from hyperphosphatemia was reported in 1 patient.

8.2.5.3 Hepatotoxicity

Data:
In the Phase 2 portion of TAS-120-101 (N=103), 28 patients (27.2%) had an AESI in the category of hepatotoxicity, including 13 patients (12.6%) with Grade ≥3 events. None of these events were serious, and there were no cases of Hy's Law.

The Applicant's Position:
All of these events were increases in transaminases with a median time to onset of 38 days (Grade ≥3: 64 days). All Grade ≥3 events resolved with a median time to resolution to Grade <3

of 5.0 days, Grade <2 of 5.0 days, and Grade <1 of 8.0 days (ISS Table 14.3.2.5.8.1). One patient experienced 3 AESIs which were considered serious (Grade 3 ALT increased, Grade 3 AST increased, and Grade 2 GGT increased); all resolved, and none were considered treatment-related by the investigator. Seven patients (6.8%) had AESIs resulting in dose reduction and 13 patients (12.6%) had events leading to dose interruption. De-/re-challenge information was not available for the majority of events. When reported, de-challenge was positive (yes) in the majority of events: 20 of 53 events for ALT increased, 24 of 61 events for AST increased, and 4 of 5 events for GGT increased (ISS Table 14.3.2.6.1). No AESI in this category resulted in treatment discontinuation (TAS-120-101 Part 2 CSR, Section 11.2.4.3.1.3).

A total of 94 patients (29.6%) with any tumor type who received a starting dose of 20 mg QD futibatinib (N=318) experienced an AESI of hepatotoxicity, 74 (23.3%) of which were assessed as treatment-related by the investigator (ISS Table 14.3.2.5.3.2). There were 38 patients (11.9%) with a Grade ≥3 AESI of hepatotoxicity, including 2 Grade 5 AEs of hepatic failure (n=2, 0.6%; both considered not related to study treatment).

The FDA's Assessment:
As described in Table 36, AST/ALT levels were increased in 27% of patients (12% were Grade > 3), blood alkaline phosphatase was increased in 15% of patients (3% were Grade > 3), and blood bilirubin was increased in 10% of patients (1% were Grade > 3). FDA disagrees with Taiho statement that none of the transaminase increases were considered related to treatment; as stated above, there is no information on de-/re-challenge for the majority of events, but when available, dechallenge was positive in the majority of events.

8.2.5.4 Nail disorders

Data:
In the Phase 2 portion of TAS-120-101, 48 patients (46.6%) had an AESI of nail disorders. Common AEs reported were onycholysis, nail disorders (both 15.5%), onychomadesis (14.6%), and nail discoloration (13.6%).

The Applicant's Position:
Most AEs were Grade 1 or Grade 2; 2 patients experienced Grade 3 AEs (1 event each of onychomadesis and paronychia). AEs such as nail discoloration were primarily Grade 1 (n=12, 11.7%), and may have little clinical impact. Median time to onset was 106 days (Grade ≥3: 155.5 days; ISS Table 14.3.2.5.7.1). No AESIs in this category were Grade 4 or 5, were serious, or led to treatment discontinuation. Nail disorders were manageable with use of concomitant medication(s) (87.5% of patients) and/or futibatinib dose modifications (6.8% reductions/7.8% interruptions) (TAS-120-101 Part 2 CSR, Section 11.2.4.3.1.4).

A total of 94 patients (29.6%) with any tumor type who received a starting dose of 20 mg QD futibatinib (N=318) experienced an AESI of nail disorders (ISS Table 14.3.2.5.2.2); the majority of these (n=91, 28.6%) were assessed as treatment-related by the investigator (ISS Table 14.3.2.5.3.2). There were 4 patients (1.3%) with a Grade ≥3 AESI of nail disorders. No Grade 4 or Grade 5 events were reported.

The FDA's Assessment:
FDA agrees with Taiho's summary of nail disorders.

8.2.5.5 Palmar-Plantar Erythrodysesthesia Syndrome (PPES)

Data:
In the Phase 2 portion of TAS-120-101, 22 patients (21.4%) had an AESI of palmar-plantar erythrodysesthesia syndrome (PPES), including 5 patients (4.9%) with Grade 3 events.

The Applicant's Position:
Median time to onset was 129 days (Grade 3: 190 days) and all Grade 3 events resolved with a median time of 7.0 days. No AESIs in this category were Grade 4 or 5, were serious, or led to treatment discontinuation. PPES were manageable with use of concomitant medication(s) (95.5% of patients) and/or futibatinib dose modifications (9.7% reductions/10.7% interruptions) (TAS-120-101 Part 2 CSR, Section 11.2.4.3.1.5).

A total of 48 patients (15.1%) with any tumor type who received a starting dose of 20 mg QD futibatinib (N=318) experienced an AESI of PPES; all but 1 of these were assessed as treatment-related by the investigator (ISS Table 14.3.2.5.3.2). There were 11 patients (3.5%) with a Grade ≥3 AESI of PPES. No Grade 4 or Grade 5 events were reported.

The FDA's Assessment:
FDA agrees with Taiho's summary of palmar-plantar erythrodysesthesia syndrome.

8.2.5.6 Rash

Data:
In the Phase 2 portion of TAS-120-101, 9 patients (8.7%) had an AESI of rash.

The Applicant's Position:
The median time to onset of rash was 54 days and there were no Grade ≥3 events, SAEs, or events leading to modification of study treatment. Four patients (44.4%) received at least 1 concomitant medication for management of rash (n=1 each, 11.1%) (TAS-120-101 Phase 2 CSR).

A total of 27 patients (8.5%) with any tumor type who received a starting dose of 20 mg QD futibatinib (N=318) experienced an AESI of rash; 14 of these (4.4%) were assessed as treatment related by the investigator (ISS Table 14.3.2.5.3.2). No Grade ≥3 AEs were reported.

The FDA's Assessment:
Taiho's analysis included only the terms "rash, rash erythematous, rash maculo-papular, rash papular, rash macular, rash pustular". FDA conducted an analysis of AE that have similar pathophysiology and added the following preferred terms to the grouped analysis: dermatitis, dermatitis acneiform, dermatitis bullous, and skin exfoliation. The overall incidence of rash was 14% (no Grade ≥ 3 events).

8.2.6 Clinical Outcome Assessment (COA) Analyses Informing Safety/Tolerability

Data:
Not applicable.

The Applicant's Position:
Not applicable.

The FDA's Assessment:
Not applicable.

8.2.7 Safety Analyses by Demographic Subgroups

Data:

Table 40 summarizes the overview of AE by demographic subgroups.

Table 40: Applicant - Overview of Adverse Events by Demographic Subgroups

	TAS-120-101 Phase 2 20 mg QD (N=103)	
	All Grades n (%)	**Grade ≥3 n (%)**
Race		
Caucasian/White	51 (100.0)	37 (72.5)
Black	8 (100.0)	8 (100.0)
Asian/Oriental	30 (100.0)	24 (80.0)

	TAS-120-101 Phase 2 20 mg QD (N=103)	
	All Grades n (%)	**Grade ≥3 n (%)**
Other or unknown	14 (100.0)	10 (71.4)
Age		
Age <65	80 (100.0)	63 (78.8)
Age ≥65	23 (100.0)	16 (69.6)
Sex		
Male	45 (100.0)	33 (73.3)
Female	58 (100.0)	46 (79.3)

Source: ISS Table 14.3.2.230.1, ISS Table 14.3.2.234.1, ISS Table 14.3.2.238.1; ADSL, ADAE

The Applicant's Position:
The AE profiles were similar between age groups (<65 years old vs. ≥65 years old), genders, and among the racial groups.

The FDA's Assessment:
FDA agrees with Taiho's assessment. FDA notes the Applicant's reference to a group of patients (i.e., Asian/Oriental) who would be appropriately described as "Asian" based on U.S. standards and FDA guidance for reporting and presenting race data and information.

8.2.8 Specific Safety Studies/Clinical Trials

Data:
No specific safety studies were performed.

The Applicant's Position:
Not applicable.

The FDA's Assessment:
Not applicable.

8.2.9 Additional Safety Explorations

Human Carcinogenicity or Tumor Development

Data:
No human carcinogenicity study was performed.

The Applicant's Position:

Not applicable.

The FDA's Assessment:
Not applicable.

Human Reproduction and Pregnancy

Data:
There is no clinical data on use of futibatinib in pregnant women.

The Applicant's Position:
The effect on a pregnant woman is unknown. Females of reproductive potential should be instructed to use effective contraception during treatment with futibatinib and for 1 week after the final dose. Males with female partners of reproductive potential should be instructed to use effective contraception during treatment with futibatinib and for 1 week after the final dose.

The FDA's Assessment:
The USPI will reflect that futibatinib has not been studied in individuals who are pregnant or lactating and that, based on animal studies and its mechanism of action, it can cause fetal harm. Contraception is advised for women and men for the duration of treatment and for 1 week after the final dose.

Pediatrics and Assessment of Effects on Growth

Data:
No study was performed in a pediatric population.

The Applicant's Position:
The effect on pediatric patients is unknown.

The FDA's Assessment:
Not applicable.

Overdose, Drug Abuse Potential, Withdrawal, and Rebound

Data:
In the Phase 2 TAS-120-101 study, five cases of overdose with futibatinib have been reported.

The Applicant's Position:
All 5 reported cases of overdose with futibatinib were due to patients taking a higher-than-planned dose of futibatinib for 1 day. Only 1 patient reported an adverse event (Grade 1

nausea) associated with the overdose. This patient accidentally self-administered 40 mg for 1 day only. The event was nonserious and resolved without sequelae the following day. There is no antidote to an overdose with futibatinib.

The FDA's Assessment:
FDA agrees with the Applicant's position.

Safety in the Postmarket Setting

Safety Concerns Identified Through Postmarket Experience

Data:
Not applicable.

The Applicant's Position:
Futibatinib has not been marketed anywhere in the world.

The FDA's Assessment:
Not applicable.

Expectations on Safety in the Postmarket Setting

Data:
None

The Applicant's Position:
The safety profile of futibatinib has been adequately represented and characterized in the Phase 2 portion of TAS-120-101 study. Routine risk mitigation measure will be provided in the proposed USPI. Routine pharmacovigilance will be conducted to monitor for unexpected adverse events.

The FDA's Assessment:
Routine pharmacovigilance will be important to monitor for expected toxicities (including mineral-metabolism and ocular toxicity) and to monitor for any unexpected adverse events. The review team determined that a REMS is not required to ensure safe and effective use of futibatinib but a PMR to further characterize ophthalmologic toxicities has been agreed with Taiho. Futibatinib will be prescribed by oncologists who are trained in how to monitor, diagnose, and manage serious adverse reactions caused by anti-neoplastic drugs in accordance with FDA-approved labeling. Additionally, standard practice in oncology dictates informed consent prior to prescribing or administering anti-neoplastic drugs.

8.2.10 Integrated Assessment of Safety

The Applicant's Position:
The overall safety review is focused on data from the primary safety analysis set of 103 patients with iCCA from Phase 2 portion of study TAS-120-101 (median exposure of 9.07 months), safety analysis set of 145 patients with iCCA from Phase 1 and 2 portions of study TAS-120-101 (median exposure of 8.87 months), and safety analysis set of 318 patients with any solid tumor from studies TAS-120-101 and 10059010 (median exposure of 3.65 months). In all analysis sets, patients received 20 mg QD as the starting dose.

Overall, the proportions of patients who experienced TEAEs (including Grade ≥3) and treatment-emergent SAEs were similar between the patients in the TAS-120-101 Phase 2 population and patients with iCCA in the integrated population who received 20 mg QD futibatinib. Additionally, TEAEs leading to treatment discontinuation were reported at similar frequency (<10%) for all populations.

In the Phase 2 portion of TAS-120-101, 6 patients (5.8%) died within 30 days of their last dose of futibatinib as of the cutoff date (October 1, 2020) (TAS-120-101 Part 2 CSR, Section 11.2.4.1). No patients died while receiving study treatment. The most common reasons for death were clinical or radiological disease progression. There was no death due to a TEAE reported in the Phase 2 patient population. No patients with iCCA (N=145) and no patients with any tumor type who received a starting dose of 20 mg QD (N=318) in the integrated safety population died while receiving study treatment; 6.2% of patients with iCCA and 9.1% of patients with any tumor type who received a 20mg QD starting dose died during the 30-day safety follow-up period, primarily due to disease progression. Deaths of 2 patients (0.6%) with any tumor type who received a starting dose of 20 mg QD in the integrated population were attributed to AEs.

The safety profile of futibatinib in the TAS-120-101 Phase 2 population was largely consistent with the profile observed for patients with iCCA in the integrated safety population (N=145) and patients with any tumor type who received a starting dose of 20 mg in the integrated safety population (N=318). Compared to the TAS-120-101 Phase 2 patient population, incidence rates for some TEAEs were numerically lower (>10% difference) for patients with any tumor type who received a 20-mg starting dose in the integrated population, including dry mouth (35.0% vs. 22.0%), alopecia (34.0% vs. 22.0%), and dry skin (29.1% vs. 17.9%). This may be due in part to the shorter duration of study treatment given the generally lower antitumor activity observed in other tumor types included in that integrated population.

Ocular toxicity is on-target effect of FGFR inhibitors. Ophthalmologic examination at screening and 4-6 weeks after initiation of futibatinib was implemented in the protocol. Retinal pigment epithelial detachment has been reported in 7.8% of Phase 2 TAS-120-101 patients, 6.2% of patients with iCCA who received 20 mg QD, and 8.5% of patients with any solid tumor who

received 20 mg QD. All events were Grade 1 and 2 (majority Grade 1) (2.5 and 2.7.4, ISS table 14.3.2.5.2.2). Time to onset was similar among the groups, approximately 6 weeks (median; 42 days, 43 days, 40 days).

An ophthalmological exam was performed prior to initiation of futibatinib, repeated 6 weeks after the first dose, and at any time as needed based on physician's judgment. Retinal disorders are considered an important risk and are proposed to be included in the "Warnings and Precautions" with recommendations for monitoring and dose modification in the respective product label sections.

Hyperphosphatemia is a known on-target effect of FGFR inhibitors due to FGFR inhibition and its effect on phosphate homeostasis. Approximately 90% of patients experienced hyperphosphatemia and 30% experienced Grade ≥3 hyperphosphatemia across the groups. Of note, hyperphosphatemia was not graded according to CTCAE; Grade ≥3 was defined as serum phosphate level >7 mg/dL irrespective of clinical symptoms. Median time to onset was 5.0 days (Grade 3: 5.0 days) and all Grade 3 events resolved with a median time to resolution of 7.0 days (range: 2.0 to 26.0 days) in the Phase 2 study of TAS-120-101. Hyperphosphatemia was manageable with use of phosphate lowering therapy (85.1% of patients) and/or futibatinib dose modifications (20.4% reductions/17.5% interruptions). Hyperphosphatemia is proposed to be included in the "Warnings and Precautions" with recommendations for monitoring, dose modification, and corrective treatment in the respective product label sections.

Nail disorders and PPES were manageable and largely reversible with dosage modification and supportive care. Considering the nature of both AESIs in the context of the intended target population, nail disorders and PPES are not considered important risks. Recommendations for dose modification will follow the standard criteria for adverse reactions in the respective product label sections.

Hepatotoxicity, reported in 27.2% of patients in the TAS-120-101 Phase (part 2) population, is considered a potential risk for futibatinib. Reported hepatotoxicity events were almost completely comprised of PTs of elevated transaminases/bilirubin; the PT of hepatic failure was reported for 4 patients (0.9%), which were considered not related to study treatment. TEAEs were generally manageable with dose modifications and no patient discontinued treatment due an AESI of hepatotoxicity. Considering most patients had underlying advanced CCA with liver metastases and reported elevated liver enzymes, this AESI is not considered an important risk and will continue to be monitored.

Futibatinib was safe and tolerable at the recommended dose of 20 mg QD with a generally predictable, monitorable, and manageable safety profile in cancer patients. TEAEs were manageable with supportive treatment and/or futibatinib dose modifications. Treatment discontinuations due to adverse reactions were rare.

The FDA's Assessment:
FDA generally agrees with Taiho's assessment of safety and treatment-related adverse events. The primary safety analysis set of 103 patients with iCCA from Phase 2 portion of study TAS-120-101 is adequate to characterize the safety of futibatinib 20 mg QD dosing in this patient population. The safety analysis set of 318 patients with any solid tumor from Study TAS-120-101 and Study 10059010 provides adequate supportive data for most adverse events with the exception of ophthalmologic toxicities. The observed toxicities are consistent with the mechanism of action and toxicity profile of FGFR2 inhibitors. AEs of special interest include ophthalmologic toxicity (RPED, dry eye, and keratitis) and hyperphosphatemia, which are adequately addressed in the Warnings and Precautions and Dosage Modifications sections of product label. The monitoring of ocular toxicity, including frequency and types of ocular examinations as well as missing examinations are considered insufficient to characterize the effects of futibatinib in eye structures and will require post-marketing studies for complete characterization. Although insufficiently characterized, the observed toxicity profile in the eye is consistent with the pharmacologic class and the label was revised to provide adequate guidelines for monitoring and management of these adverse reactions.
Serious risks associated with futibatinib are described in the Warnings and Precautions and Dosage Modifications sections of futibatinib product labeling and will additionally be monitored in patients through post-marketing pharmacovigilance efforts and postmarketing studies. The major safety risks of futibatinib are toxicities that oncologists frequently manage and the toxicity profile of futibatinib is considered acceptable when considering the anti-tumor effects observed (e.g., durable responses) in a patient population with a serious and life-threatening condition.

SUMMARY AND CONCLUSIONS

8.3 Statistical Issues

The FDA's Assessment:
There were no major statistical issues in the review of this NDA. FDA does not consider inferential procedures in the evaluation of single arm study results. Instead, the efficacy evaluation is based on the magnitude of response rate and adequate duration of response, compared with the available therapies at time of approval. Results of time-to-event endpoints such as PFS and OS were not interpretable without a control.

8.4 Conclusions and Recommendations

The FDA's Assessment:
Results from Study TAS-120-101 indicate that treatment with futibatinib 20 mg QD in patients with previously treated, unresectable, locally advanced or metastatic intrahepatic cholangiocarcinoma with an FGFR2 fusion/rearrangement provides a clinically meaningful and

durable response. The ORR of 41.7% (95% CI: 32.1, 51.9), as assessed by IRC according to RECIST 1.1., with a median duration of response of 9.69 months (95% CI: 7.62, 17.05) is meaningful in the context of a life expectancy in this setting of 5-6 months based on historical controls.

The primary safety analysis consisted of results from 103 patients from Phase 2 portion of study TAS-120-101. In general, the toxicities seen with futibatinib are consistent across FGFR2 inhibitors and include (incidence > 20%) hyperphosphatemia, arthralgia, nail disorders, constipation, diarrhea, fatigue, dry mouth, alopecia, abdominal pain, dry skin, stomatitis, AST/ALT increased, peripheral sensory neuropathy, nausea, dysgeusia, decreased appetite, dry eye, urinary tract infection, palmar-plantar erythrodysesthesia syndrome, vomiting, and weight decreased. The most common relevant laboratory abnormalities (incidence >20%) were increased phosphate, increased creatinine, decreased hemoglobin , decreased lymphocyte, decreased platelets, decreased leukocytes, decreased neutrophils, increased glucose, increased calcium, decrease sodium, decreased phosphate, increased ALT, increased alkaline phosphatase, increased AST, increased creatine kinase, decreased albumin, increased activated partial thromboplastin time, increased prothrombin/INR, increased bilirubin, decreased glucose, and decreased potassium. These are acceptable given the anti-tumor effects observed in a patient population with a serious and life-threatening condition. AEs of special interest include ophthalmologic toxicity (RPED, dry eye, and keratitis) and hyperphosphatemia, which are adequately addressed in the Warnings and Precautions and Dosage Modifications sections of product label.

Key review issues included:

- Inadequate characterization of ocular toxicity.
- Inadequate exploration of futibatinib dosage. There was a high rate (77%) of dose modifications/interruptions, which in the context of a similar response rate with an improved safety profile observed in an earlier phase of the study in a limited number of patients suggest that further dose evaluation is needed.

The serious risks of eye toxicity and hyperphosphatemia are adequately addressed in the Warnings and Precautions and Dosage Modifications sections of futibatinib product labeling. The major safety risks of futibatinib are toxicities that oncologists frequently manage in consultation with ophthalmologists and the toxicity profile of futibatinib is considered acceptable when considering the anti-tumor effects observed (e.g., durable responses in 41.7% of patients) in a patient population with a serious and life-threatening condition.

The review team concludes that overall, the results of Study TAS-120-101 Phase 2 portion are reasonably likely to predict a clinically meaningful benefit and represent a meaningful advantage over existing treatments for the proposed indication, meeting the requirements for accelerated approval. As a condition of accelerated approval, a post marketing study will be required to verify the clinical benefit of futibatinib.

X	X
Sirisha Mushti Primary Statistical Reviewer	Joyce Cheng Statistical Team Leader
X	X
Shruti Gandhy Primary Clinical Reviewer	Sandra J. Casak Clinical Team Leader

9 Advisory Committee Meeting and Other External Consultations

The FDA's Assessment:

The FDA did not obtain the advice of the Oncologic Drug Advisory Committee (ODAC) for this NDA because no review issues were identified that raised significant public health questions regarding the risk:benefit assessment of futibatinib for the proposed indication. Futibatinib is the fourth in-class product reviewed by FDA for the treatment of cancer and the third one for the treatment of FGFR2-mutated intrahepatic cholangiocarcinoma.

10 Pediatrics

The Applicant's Position:
Futibatinib was granted Orphan Designation on May 23, 2018 for the treatment of CCA and in accordance with 21 CFR 314.55(5)(d), orphan drugs are exempt from the pediatric study requirements under 21 CFR 314.55.

To fulfill the pediatric requirements in Section 505B of the FD&C Act as amended by Title V of FDARA regarding pediatric evaluation of certain molecularly targeted oncology drugs, Taiho submitted an initial pediatric study plan (iPSP) that includes a Phase 1 study in the US in children age 1 to 17 years of age, including PK/dose confirmation in Part 1 in children who are unable to swallow adult tablets and will be dosed with minitablets, and a clinical effectiveness and safety study in Part 2 in children age 1 to 17. The other pediatric study that will be conducted is the European Proof of Concept Therapeutic Stratification Trial of Molecular Anomalies in Relapsed or Refractory Tumors in Children (ESMART) study in Europe which will enroll children who can swallow adult tablets. Due to the small number of patients in any one of the pediatric tumors where FGF/FGFR has been shown to play a role, a broad-based, tumor-agnostic approach will be employed in clinical studies in children age 1-17 years with relapsed/refractory pediatric cancers harboring *FGFR* alterations. FDA issued a written response agreeing with Taiho's amended Agreed iPSP submitted on July 16, 2021.

A deferral for the submission of results of pediatric studies in pediatric patients 1 year of age or older is requested with this NDA submission as the planned study has not been initiated.

A request for a partial waiver for the conduct of a molecularly targeted investigation in patients less than 1 year of age is requested, given tumors harboring *FGFR* alterations occur so rarely in this age group that studies would be impossible or highly impractical.

The FDA's Assessment:
FDA agrees with Taiho's statement that futibatinib is exempted from the PREA requirements to study futibatinib in pediatric patients with cholangiocarcinoma.

To fulfill the pediatric requirements in Section 505B of the FD&C Act as amended by Title V of FDARA regarding pediatric evaluation of certain molecularly targeted oncology drugs, Taiho submitted a pediatric study plan (PSP), described above. On July 16, 2021, FDA issued a written response acknowledging Taiho's submission of the amended Agreed initial Pediatric Study Plan. A deferral for the submission of results of pediatric studies in pediatric patients 1 year of age or older is requested with this NDA submission as the results of Cohort O of the eSMART trial are not available and the second pediatric clinical study planned study has not been initiated. FDA

agrees with this request and a PMR for the submission of the pediatric study results was agreed.

A request for a partial waiver for the conduct of a molecularly targeted investigation in children 1 year of age or younger is requested, given FGFR1-3 genetically altered, refractory solid tumors occur so rarely in this age group that studies would be impossible or highly impractical. FDA agrees with this request.

11 Labeling Recommendations

Table 41 summarizes changes to the proposed prescribing information (PI) made by FDA. See the final approved prescribing information for LYTGOBI (futibatinib) accompanying the approval letter for more information.

Table 41. Summary of Significant Labeling Changes

Summary of Significant Labeling Changes (High level changes and not direct quotations)		
Section	**Applicant's Proposed Labeling**	**FDA's proposed Labeling**
Full Prescribing Information		
Section 1: Indications and Usage	(b) (4)	Indication revised to reflect study population and reference to companion diagnostic removed: 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 rearrangement.
Section 2: Dosage and Administration		2.1 Removed (b) (4) and inserted statement that FDA-approved test for detection of FGFR2 gene fusions or other rearrangements in patients with unresectable, locally advanced, or metastatic intrahepatic cholangiocarcinoma for selecting patients for treatment with LYTGOBI is not available

Section 5: Warnings and Precautions	(b) (4)	Added "and Soft Tissue Mineralization" to Hyperphophatemia. Revised content for consistency with pharmacologic class.
Section 6: Adverse Reactions		Revisions throughout this section to align with OOD preferred approach for the presentation of safety data.
Section 7: Drug Interactions		Revised based on study results to include interactions with and on dual CYP3A and P-gp inhibitors and inducers.
Section 8: Use in Specific Populations		Removed (b) (4) as there are no actionable items.
Section 12: Clinical Pharmacology		12.1 Edited to be consistent with EPC, 12.2 Statement on ERR added, description of impact on QTc interval prolongation revised to align with current labeling practices
Section 13: Nonclinical Toxicology		Removed (b) (4)
Section 14: Clinical Studies		Specifics of testing used to determine presence of FGFR2 fusions or rearrangements added; additional trial population characteristics were added

12 Risk Evaluation and Mitigation Strategies (REMS)

The FDA's Assessment:
The risks of futibatinib are acceptable in the indicated patient population with a serious and life-threatening condition. The safe use of futibatinib can be adequately implemented in the post-marketing setting through product labeling. No additional risk management strategies are recommended.

13 Postmarketing Requirements and Commitment

Taiho agreed to the following clinical postmarketing requirements (PMR) and commitments (PMC):

PMR #1: Conduct a randomized clinical trial comparing dosages of futibatinib 16 mg and 20 mg once daily to verify and describe the clinical benefit of futibatinib in patients with advanced or metastatic cholangiocarcinoma harboring an FGFR2 gene fusion or other rearrangement. The overall response rate and duration of response should be assessed by a blinded independent review. The study should also evaluate other clinical outcomes that denote clinical benefit, such as patient reported outcomes. This study should enroll a minimum of 120 patients and all responders should have a minimum of 6 months from the date of initial response (or until disease progression, whichever comes first). Ensure that racial and ethnic minorities are adequately represented in the trial population, at a minimum, proportional to the prevalence of FGFR2 alterations in these subgroups in the US population.

Draft Protocol Submission:	10/2022
Final Protocol Submission:	12/2022
Trial Completion:	02/2027
Final Report Submission:	10/2027

PMR #2: Conduct a clinical trial of futibatinib 20 mg once daily in a sufficient number of patients with cholangiocarcinoma harboring a FGFR2 fusion or other rearrangement, that incorporates prospectively specified, scheduled ophthalmologic assessments that include optic coherence tomography (OCT), for all patients (symptomatic or asymptomatic), at baseline and during treatment with futibatinib, to further characterize the incidence and severity of futibatinib-related ocular adverse events.

Draft Protocol Submission:	10/2022
Final Protocol Submission:	12/2022
Trial Completion:	02/2027
Final Report Submission:	10/2027

With the final report submission, submit the datasets from the study.

PMR #3: Conduct a clinical trial of futibatinib in pediatric patients to further characterize the safety, pharmacokinetics, and anti-tumor activity of futibatinib for pediatric patients 1 year of age or older with advanced or metastatic solid tumors harboring FGFR gene alterations, deferred until the results of the non-clinical in vitro and in vivo efficacy studies in human cell line-derived mouse xenografts of rhabdomyosarcoma, submitted to and reviewed by FDA, have

been found to support a clinical investigation in the pediatric population. In addition, include the results of Arm O of the eSMART trial, which will also be used to support the decision for the pediatric investigation.

Draft Protocol Submission: 03/2023
Final Protocol Submission: 06/2023
Trial Completion: 12/2029
Final Report Submission: 12/2030

With the final report(s) submission, submit the datasets from the study(ies).

PMR #4: Conduct a randomized study that compares the recommended dosage of 20 mg daily to a lower dosage (e.g., 16 mg) to provide a comparative analysis of dose- and exposure-response relationships for safety including further characterization of the rates of Grade ≥3 adverse reactions, Grade ≥3 hyperphosphatemia, serious adverse reactions, and dose reductions, interruptions, and discontinuations due to adverse reactions. Incorporate systematically assessed patient-reported outcome assessments to evaluate tolerability. Core outcomes should include patient-reported symptomatic adverse event data, overall side effect bother, physical function, and role function. The study should also provide a comparative analysis of dose- and exposure-response relationships for efficacy, including overall response rate and duration of response.

Draft Protocol Submission: 10/2022
Final Protocol Submission: 12/2022
Trial Completion: 02/2027
Final Report Submission: 10/2027

With the final report submission, submit the datasets from the study.

PMR #5: Conduct a clinical pharmacokinetic trial to determine an appropriate dosage of futibatinib to minimize toxicity in subjects with moderate and severe hepatic impairment. Design and conduct the trial in accordance with the FDA guidance for industry entitled, Pharmacokinetics in Patients with Impaired Hepatic Function: Study Design, Data Analysis, and Impact on Dosing and Labeling.

Final Report Submission: 10/2022

PMR #6: Conduct a drug interaction study to evaluate the effect of a P-gp inhibitor on the pharmacokinetics of futibatinib to assess the magnitude of increased drug exposure and determine appropriate dosage recommendations when futibatinib is administered concomitantly with P-gp inhibitors. Design and conduct the study in accordance with the FDA

Guidance for Industry titled Clinical Drug Interaction Studies —Cytochrome P450 Enzyme- and Transporter-Mediated Drug Interactions.

Draft Protocol Submission:	12/2022
Final Protocol Submission:	03/2023
Study Completion:	03/2024
Final Report Submission:	09/2024

PMC #1: Establish, through the use of clinical trial data, an in-vitro diagnostic device that is essential to the safe and effective use of futibatinib for patients with advanced unresectable or metastatic cholangiocarcinoma harboring an FGFR2 gene fusions or other alterations.

Draft Protocol Submission:	10/2022
Final Protocol Submission:	12/2022
Trial Completion:	02/2027
Final Report Submission:	10/2027

PMC #2: Conduct exploratory analyses aimed at identifying potential mechanisms of primary and acquired resistance to futibatinib using longitudinal ctDNA samples collected at baseline and at the end of treatment or time of progression from patients treated with futibatinib in TAS-120-101 and in the randomized clinical trial to verify and describe the clinical benefit of futibatinib in patients with advanced or metastatic cholangiocarcinoma harboring an FGFR2 gene fusion or other rearrangement. Include a discussion of the results in the context of the available published literature.

Study Completion:	02/2027
Final Report Submission:	10/2027

PMC #3: Conduct Study TAS-120-301 (FOENIX-CCA3), investigating futibatinib for the first line treatment of patients with locally advanced or metastatic cholangiocarcinoma harboring an FGFR2 fusion or other rearrangement, and submit the final progression-free survival results.

Study Completion:	12/2026
Final Report Submission:	12/2027

14 Division Director (DHOT) (NME ONLY)

X

APPEARS THIS WAY ON ORIGINAL

15 Division Director (OCP)

X

APPEARS THIS WAY ON ORIGINAL

16 Division Director (OB)

X

APPEARS THIS WAY ON ORIGINAL

17 Division Director (Clinical)

I concur with the the review team's assessment of the the CMC, non-clinical pharmacology/toxicology, clinical pharmacology, clinical, statistical, review teams with respect to the approvability of this NDA. The submitted data package meets the evidentiary requirements for accelerated approval for the indication, as amended by FDA, based on a favroable benefit:risk assessment. The Applicant submitted data from an adequate and well controlled study (Study TAS-120-101 (NCT02052778)) which demonstrated that treatment with futibatinib results in a clinically meaningful durable overall response rate of 42% (95% confidence interval [CI]: 32%, 52%) with a median duration of response of 9.7 months (95% CI: 7.6, 17.1); 31 of the 43 (72%) responders had sustained response a for at least 6 months. These results were observed in the context of an acceptable safety profile but I agree with the review team's conclusion that further studies are needed including to further optimize the dosage of futibatinib, and to further chacterize its ocular toxicity profile. Overall, the benefit:risk assessment is favorable for the indicated population with an unmet need for effective therapies.

As a condition of accelerated approval, confirmatory studies may be required to verify clinical benefit. FDA guidance states that such trials should be underway at the time of accelerated approval to help ensure timely verification or refutation of clinical benefit. For this application, the Applicant initiatilly proposed a randomized controlled clinical trial (FOENIX-CCA3) to compare the survival of patients with previously untreated cholangiocarcinoma with an FGFR2 fusion or rearrangement who are randomized to receive futibatinib to those randomized to receive gemcitabine plus cisplatin. The FOENIX-CCA3 was initiated well before the NDA was submitted but has had poor accrual as noted in the review. Based on enrollment trends to date, it is unclear whether this trial can be completed in a timely fashion such that the results would be interpreted in the context of the treatment landscape for adult patients with previously treated, unresectable, locally advanced or metastatic intrahepatic cholangiocarcinoma harboring FGFR2 gene fusions or other rearrangements, at the time of trial completion. It is in this setting (See also FDA Assessment in Section 3) that FDA and the Applicant considered an alternative study to verify the benefit of futibatinib in the indicated population; the postmarkeing requirement for is described in Section 8 and Section 13 of the review.

X

Lola A. Fashoyin-Aje, MD, MPH

APPEARS THIS WAY ON ORIGINAL

18 Office Director (or designated signatory authority)

This application was reviewed by the Oncology Center of Excellence (OCE) per the OCE Intercenter Agreement. My signature below represents an approval recommendation for the clinical portion of this application under the OCE.

X _____

APPEARS THIS WAY ON ORIGINAL

19 Appendices

19.1 References

The Applicant's References:

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The FDA's Additional References:

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19.2 Financial Disclosure

The Applicant's Position:

The Applicant provided a summary of financial disclosure for all 758 clinical investigators involved in Study TAS-120-101. Signed financial disclosure forms could not be obtained for four sub-investigators. Due diligence was conducted to attempt to obtain financial disclosures forms from these sub-investigators. There were no principal investigators with disclosable financial arrangements.

The FDA's Assessment:

In accordance with 21 CFR 54, the Applicant submitted information for all 758 principal investigators and sub-investigators participating in study TAS-120-101. According to the Applicant, none of these investigators had financial information to disclose (as documented in FDA's Form 3454 included in the NDA). The Applicant also certified that: 1) the Applicant has not entered into any financial arrangement whereby the value of compensation to the investigator could be affected by the outcome of the study; 2) no listed investigator disclosed a proprietary interest in the product or a significant equity in the Sponsor; and 3) no listed investigator was the recipient of significant payments of other sorts.

Covered Clinical Study (Name and/or Number):* 1

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from Applicant)
Total number of investigators identified: 758		
Number of investigators who are Sponsor employees (including both full-time and part-time employees): 0		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 0		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: _____ Significant payments of other sorts: _____ Proprietary interest in the product tested held by investigator: _____ Significant equity interest held by investigator in study: _____ Sponsor of covered study: _____		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes ☐	No ☐ (Request details from Applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes ☐	No ☐ (Request information from Applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) 0		
Is an attachment provided with the reason:	Yes ☐	No ☐ (Request explanation from Applicant)

*The table above should be filled by the applicant, and confirmed/edited by the FDA.

19.3 Additional Clinical Tables/Figures

Table 42. Hyperphosphatemia management recommendations

Serum Phosphorus Result[a] (mg/dL and mmol/L)[b]	Grade[c]	TAS-120 Dose Interruption and Modification	Recommended phosphate binder for the management of hyperphosphatemia[d]
ULN < P < 5.5 (mg/dL) ULN < P < 1.78 (mmol/L)	Grade 1	• No Interruption, consider phosphate binder once serum phosphorus level is > ULN • Should serum phosphorus level rapidly increase within 1 week, consider early phosphate lowering therapy, eg, Sevelamer oral tablets 800 mg TID	• 800 mg tablets Sevelamer TID • 1600 mg tablets Sevelamer TID • 2400 mg tablets Sevelamer TID • Acetazolamide 250 mg QD (and titrate up to BID or TID if required) • Lanthanum carbonate (Fosrenol) 1.0 g QD (and titrate up to BID or TID if required)[e]
5.5 ≤ P ≤ 7.0 (mg/dL) 1.78 ≤ P ≤ 2.26 (mmol/L)	Grade 2	• No interruption, implement phosphate binder (monotherapy or in combination) • Start with Sevelamer monotherapy (range from 800 mg TID to 2400 mg TID). • Re-assess serum phosphate within 7 days, and plan to escalate Sevelamer or add treatment with acetazolamide 250 mg QD or TID and/or lanthanum carbonate 1.0 g QD or TID, and further titration, if phosphate level continues to increase.	
7.0 < P ≤ 10.0 (mg/dL) 2.26< P ≤ 3.23 (mmol/L)	Grade 3	• Dose reduce TAS-120 to the next lower dose level and intensify phosphate lowering therapy. • If serum phosphorus level has resolved to ≤ Grade 2 within 14 days after dose reduction, continue TAS-120 at the same dose level. • If serum phosphorus level not resolved to ≤ Grade 2 after 14 days, further reduce TAS-120 from the last reduced dose level (or no lower than 12 mg) • If serum phosphorus level not resolved to ≤ Grade 2 after 14 days of the second dose reduction of TAS-120 (or no lower than 12 mg), dose interrupt TAS-120 until it is resolved to ≤ Grade 2 before resuming TAS-120 at the reduced dose prior to dose interruption.	
P > 10.0 (mg/dL) P > 3.23 (mmol/L)	Grade 4	Interrupt TAS-120 until serum phosphorus level is resolved to ≤Grade 2, then resume TAS-120 at the next lower dose level and intensify phosphate lowering therapy. If after 2 dose interruptions and 2 dose reductions, serum phosphorus level is not resolved to ≤Grade 2 after 14 days, permanently discontinue TAS-120.	

Abbreviations: BID = twice a day; P = Phosphorus; QD = once a day; TID = three times a day; ULN = upper limit of normal

19.4 Nonclinical Pharmacology/Toxicology

Data:
See Section 1.

The Applicant's Position:
All relevant nonclinical and pharmacology assessments are provided in Section 1.

19.5 OCP Appendices (Technical documents supporting OCP recommendations)

19.5.1 General Information

Table 43: List of clinical studies

Study Type	Study Number	Formulation	Study Description
Phase 1/2	TAS-120-101	EF. LF	Multiple dose, dose escalation/expansion/Phase 2 in patients
	10059010	EF, LF	Multiple dose, dose escalation/expansion in Japanese patients
Bioavailability and Food Effect	10059020	LF	Bioavailability in Japanese healthy subjects
	TAS-120-102	LF	Food effect in healthy subjects
Drug-Drug Interaction Studies	TAS-120-103	LF	Drug-drug interaction study with strong CYP3A modulators, itraconazole and rifampin in healthy Subjects
	TAS-120-104	LF	PPI study in healthy subjects
	TAS-120-105	LF	CYP3A substrate, midazolam, in healthy subjects
Mass Balance	TAS-120-106	Oral solution	in healthy subjects.
QT Study	TAS-120-107	CF	in healthy subjects
Organ Impairment	TAS-120-108	NA	Single dose hepatic impairment study in healthy subjects (ongoing)
Modeling and Simulations	20DC01	--	PBPK for DDI with CYP3A modulators
	20DC09	--	PBPK for DDI with transporters
	TONC-PMX-TAS120-1718	--	PBPK for DDI with CYP3A modulators

EF = early formulation Hypromellose capsules (4 or 20 mg); LF = Late film coated tablets (FCT: 4, 20 mg); CF = Commercial FCT Tablet (4 mg) same as LF except (b) (4) with same manufacturing process but change of manufacturing site; NA=Not available

Source: SBS and SCP, Modules 2.7.1 and 2.7.2

Single and multiple dose Pharmacokinetics and Dose proportionality
Population PK analysis predictions following once daily futibatinib (20 mg) dosing in patients are summarized in Table 44. No accumulation was observed for Cmax or AUC with repeat dosing.

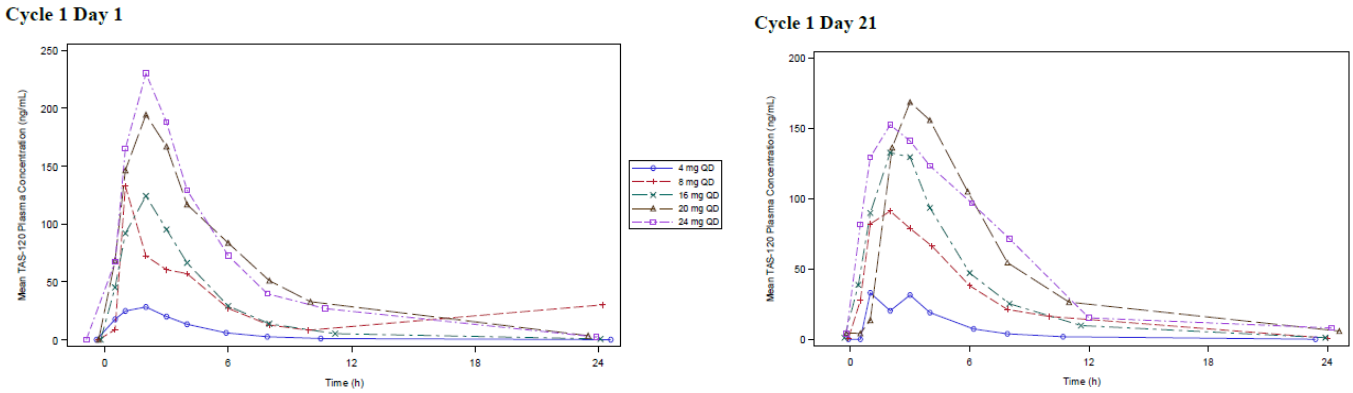
Futibatinib was rapidly absorbed with median Tmax of 2 hours. Futibatinib exposure was dose proportional between 4 and 24 mg QD (Figure 9, Table 45): the 90% confidence intervals (CIs) of the slopes of Cmax and AUClast contained 1.

Table 44: Dose Proportionality of Futibatinib PK in Patients (n=203)

PK Parameter	Geometric Mean (geometric CV%) (95% CI)	Median (range)
Cmin Day 1 (ng/mL)	1.39 (121%) (1.22 – 1.58)	1.08 [0.261 – 36.9]
Cmax Day 1 (ng/mL)	142 (50.1%) (133 – 152)	147 [20.3 – 534]
AUCtau Day 1 (ng · hr/mL)	769 (43.5%) (726 – 814)	702 [279 – 3334]
Cav Day 1 (ng/mL)	32.0 (43.5%) (30.2 – 33.9)	29.3 [11.6 – 139]
Cmin,ss (ng/mL)	1.68 (117%) (1.47 – 1.90)	1.31 [0.322 – 45.3]
Cmax,ss (ng/mL)	144 (50.3%) (135 – 154)	148 [20.5 – 537]
AUCss (ng · hr/mL)	790 (44.7%) (745 – 838)	721 [286 – 3840]
Cav,ss (ng/mL)	32.9 (44.7%) (31.1 – 34.9)	30.0 [11.9 – 160]
Accumulation ratio, Rac	1.03 (2.30%) (1.025 – 1.031)	1.02 [1.01 – 1.16]
Individual CL/F (L/hr)	19.8 (23.0%) (19.2 – 20.5)	20.8 [9.13 – 33.8]
Individual Vc/F (L)	66.1 (17.5%) (64.6 – 67.7)	65.8 [40.1 – 98.9]
Tmax (hour) Day 1	2.27 (53.9%) (2.12 – 2.44)	2.00 [1.20 – 22.8]
Tmax (hour) SS	2.27 (53.9%) (2.12 – 2.43)	2.00 [1.20 – 22.8]
Half-life (alpha) (hour)	2.14 (31.6%) (2.05 – 2.23)	2.03 [0.814 – 5.19]
Half-life (beta) (hour)	10.5 (3.04%) (10.4 – 10.5)	10.4 [10.0 – 12.4]
T1/2eff (hour)	4.45 (16.5%) (4.35 – 4.55)	4.20 [3.46 – 8.30]

AUCss=area under the plasma concentration-time curve at steady state; AUCtau=AUC over the dosing interval; Cav=average plasma concentration; Cav,ss=Cav at steady state; CL/F=oral clearance; Cmax=maximum plasma concentration; Cmax,ss=Cmax at steady state; Cmin=minimum plasma concentration; Cmin,ss=Cmin at steady state; CI=confidence interval; Rac=accumulation ratio of AUC (Day 1/D21); SD=standard deviation; SS=steady state; T1/2eff=effective half-life; Tmax=time to reach Cmax; Vc/F=apparent central volume of distribution
Source: Table 45, SCP, Module 2.7.2

Figure 9: Mean futibatinib concentrations vs. time for Cycle 1 Day 1 (left) and Cycle 1 Day 21 (right) with once daily dosing (TAS-120-101)



Source: Figure 1 of SCP, Module 2.7.2

Table 45: Dose Proportionality Analysis (regression analysis using power model) for Futibatinib PK Parameters, Cycle 1 Day 1 and Cycle 1 Day 21, QD Schedule (Study TAS-120-101)

Regression Parameters (Power Model)							
			Regression Parameter	Estimate	90% CI		P Value
Visit	PK Parameter	n	[1]		Lower	Upper	
Day 1	C_{max} (ng/mL)	44	α	1.853	0.958	2.748	0.0012
			β	1.141	0.819	1.462	<0.0001
	AUC_{inf} (ng·hr/mL)	41	α	2.325	1.226	3.424	0.0010
			β	1.467	1.072	1.861	<0.0001
	AUC_{last} (ng·hr/mL)	44	α	2.581	1.476	3.686	0.0003
			β	1.374	0.977	1.771	<0.0001
Day 21	C_{max} (ng/mL)	22	α	2.592	1.617	3.568	0.0002
			β	0.859	0.478	1.239	0.0009
	AUC_{last} (ng·hr/mL)	22	α	3.030	1.604	4.456	0.0015
			β	1.265	0.709	1.821	0.0008

AUCinf=area under the plasma concentration-time curve from time 0 to infinity; AUClast=area under the plasma concentration-time curve from time 0 to time of the last quantifiable plasma concentration; CI=confidence interval; Cmax=maximum plasma concentration; n=number of observations; PK=pharmacokinetic; QD=once daily dosing. The regression analysis uses power model: log(AUC or Cmax) = α + β × log(dose)

Source: Table 5 of SCP, Module 2.7.2

Intersubject variability

The inter-subject variability was in the range of 19% to 52% and intra-subject variability was in the range of 16% to 36% in healthy subjects. The inter-patient CV in the Study TAS-120-101 was 31% to 53%. The geometric CV values of Cmax and AUC at steady state in patients following 20 mg QD predicted by the population PK analysis were similar to those in the Study TAS-120-101.

19.5.2 Absorption, Distribution, and Elimination

Absorption
Futibatinib is rapidly absorbed in the fasted state with a median time to peak concentration (T_{max}) of 2 hours (range 1 to 23 hours) following a 20 mg oral once daily in patients (Table 46).

Comparability of Early and Late Formulations
The "Late formulation" (LF) and the "Early formulation" (EF) were bioequivalent for AUC and Cmax.

10059020 Compared the PK parameters of the "Late formulation" (LF) and the "Early formulation" (EF) in a Phase 1, open-label, randomized, 2-period, 2-sequence, 2 single-dose, crossover study in 24 healthy male subjects. Subjects were randomized to Group A (LF: 1x20 mg, n=12) or Group B (EF: 1 x 20 mg, n=12) with a washout period of 6 days between doses. Intensive PK blood samples were collected up to 48 hours.

Table 46: Point Estimates and 90% Confidence Intervals of Pharmacokinetic Parameters of Futibatinib of Early and Late Formulations

Comparison	Geometric Mean Ratio (90% CI)	
	$AUC_{0\text{-}inf}$ (ng*hr/mL)	Cmax (ng/mL)
Late vs. Early Formulations	1.09 (0.97, 1.23)	0.99 (0.83, 1.18)

Source: Table 16 of SCP, Module 2.7.2

Table 47: Pharmacokinetic Parameters of Futibatinib of Early and Late Formulation

Formulation	Descriptive statistics	$T_{1/2}$* (hr)	T_{max} (hr)**	C_{max} (ng/mL)	$AUC_{0\text{-}48h}$ (ng*hr/mL)	AUC_{inf} (ng*hr/mL)
Early formulation	N	24	24	24	24	24
	Mean	2.3	2	95.3	358	354
	gCV (%)	46.2	1-4	52.2	67.4	67.3
Late formulation	N	22	24	24	24	22
	Mean	2.2	2	94.4	376	401
	CV (%)	60.1	1-2	47.9	48.8	39.4

*Arithmetic mean, ** median (range)
Source: Table 15 of SCP, Module 2.7.2

Comparability of Commercial and Late Formulations
PK parameters of Commercial and Late (FCT) tablet formulations were compared from five single dose (20 mg: 5 x 4 mg) PK studies in healthy subjects (Table 48). The point estimate indicates a ~10% difference in exposure, and 90% confidence intervals (CIs) of the point estimate of C_{max}, AUC_{last} and AUC_{inf} contained 1 (Table 49).

Table 48: Study Information

Study	Description	Population	Dosing Formulation (# of Units)	N
TAS-120-102	Food Effect	Healthy Subjects	Clinical FCT (5 × 4 mg)	16
TAS-120-103 Part 1	DDI with Itraconazole	Healthy Subjects	Clinical FCT (5 × 4 mg)	20
TAS-120-103 Part 2	DDI with Rifampin	Healthy Subjects	Clinical FCT (5 × 4 mg)	20
TAS-120-104	DDI with Lansoprazole	Healthy Subjects	Clinical FCT (5 × 4 mg)	20
TAS-120-107	Thorough QT	Healthy Subjects	Commercial FCT (5 × 4 mg)	45

Source: Table 5 of IR Response 5/13/22, SDN 24

Table 49: Comparison of Single-dose PK Parameters of Futibatinib in Healthy Subjects between Late Formulation and Commercial FCTs (5 × 4 mg)

PK Parameters	Late (Reference)		Commercial (Test)		GMR (T/R)	90% CI	
	Mean (%CV)*	N	Mean (%CV)*	N		Lower	Upper
Cmax (ng/mL)	190 (48)	76	165 (52)	45	0.87	0.75	1.01
AUC_{0-t} (hr*ng/mL)	789 (56)	76	704 (69)	45	0.89	0.75	1.07
AUC_{0-inf} (hr*ng/mL)	796 (56)	76	714 (68)	45	0.90	0.75	1.07

*geometric mean (geometric CV); GMR=geometric mean ratio; CI=confidence interval
Source: Table 6 of IR Response 5/13/22, SDN 24

Food Effect

TRADENAME can be administered without regards to meal (Table 50).

In the Phase 2 portion of TAS-120-101, futibatinib was administered under modified fasted conditions (2 hours after and 1 hour before a meal). The Applicant proposes to administer futibatinib with or without food.

The effect of food on futibatinib PK was evaluated with a single dose (5 x 4 mg) in 17 healthy subjects using "Late" tablet formulation under fasted and fed (high-fat: 900 to 1000 calories with 50% of total caloric content as fat) conditions in Study TAS-120-102. This was an open-label, randomized, 2-treatment crossover study with a minimum 7-day washout between treatments. PK samples were collected over 168 hour in both periods.

Table 50: Point Estimates and 90% Confidence Intervals of Pharmacokinetic Parameters of Futibatinib under Fasted and Fed States.

Comparison (N=16)	Geometric Mean Ratio (90% CI)	
	AUC_{0-inf} (ng*hr/mL)	Cmax (ng/mL)
Fed vs. Fasted	0.89 (0.80, 0.99)	0.58 (0.47, 0.70)

Source: Table 18 of SBS, Module 2.7.1

Table 51: Pharmacokinetic Parameters of Futibatinib under Fasted and Fed states

Formulation	Descriptive statistics	$T_{1/2}$* (hr)	C_{max} (ng/mL)*	T_{max} (hr)**	AUC_{0-48h} (ng*hr/mL)	AUCinf (ng*hr/mL)
Early formulation	N	24	16	16	16	16
	Mean	2.3	155	1	618	626
	CV (%)	46.2	35	1 - 3	41	40
Late formulation	N	22	16	16	16	15
	Mean	2.2	91	2	529	551
	CV (%)	60.1	36	2 - 8	43	42

*Arithmetic mean, ** median (range)
Source: Table 17 of SBS, Module 2.7.1

Distribution

Futibatinib is 95% bound to human plasma protein at 0.2 to 5 µmol/L in vitro, primarily to albumin and α1-acid glycoprotein.

The human blood cell distribution of futibatinib is low (Rb <0.67) in vitro (Study 16DA16).

The volume of distribution (V/F) at steady state in patients was 66 L (18%). (Appendix 19.5.7).

Elimination

Study TAS-120-106 assessed mass balance, total radioactivity (TRA), metabolism and excretion of futibatinib. This was an open-label, single-dose study in 6 healthy adult male subjects. On Day 1, subjects received a single dose of 20 mg [^{14}C]-futibatinib oral solution (~100 µCi): [^{14}C]-futibatinib (20 mg/45 mL oral solution) following an overnight fast. Whole blood, plasma, urine, and fecal samples were analyzed for at least 168 hours post-dose (Day 8) to measure TRA, plasma futibatinib concentrations, and for metabolic profiling and identification (plasma, urine, and fecal samples).

Table 52: Summary of the PK Parameters for Plasma Futibatinib, and Total Radioactivity in Plasma and Whole Blood following Administration of a Single Oral Solution Dose of 20 mg (~100 µCi) [^{14}C]

Pharmacokinetic Parameters	Futibatinib in Plasma	n	Total Radioactivity in Plasma	n	Total Radioactivity in Whole Blood	n
AUC_{0-last} (ng eq·hr/mL)	548 (59)	6	1279 (53)	6	925 (63)	6
AUC_{0-8} (ng eq·hr/mL)	511 (54)	6	913 (33)	6	NC	
AUC_{0-inf} (ng eq·hr/mL)	550 (59)	6	1337 (56)	5	1512 (66)	5
C_{max} (ng /mL)	172 (37)	6	253 (28)	6	140 (26)	6
T_{max} (hr)	1.0 (1.0, 2.0)	6	1.0 (1.0, 2.0)	6	1.0 (1.0, 2.0)	6
T1/2 (hr)	2.3 ± 1.1	6	11.9 ± 8.8	5	29.0 ± 13.6	5

Source: Table 21 of SCP, Module 2.7.2

Metabolism

Study TAS-120-106 found that the predominant circulating radioactivity in plasma was from futibatinib. The major metabolites observed in healthy subjects were derivatives of desmethyl and mono-hydroxy products (M408,M610, M392, M424, M597, M406) and derivatives of reduced glutathione (GSH) conjugates (M539, M596, M725, M581). The primary circulating metabolites in plasma were a glucuronide conjugate of mono-oxidized product (P1: 8.97%), a cysteine conjugate (P5: 8.68%), and a cysteinylglycine conjugate (P7: 13.37%). Majority of radioactivity (64% of dose) following a single oral dose of [^{14}C]futibatinib solution was excreted in feces as metabolites. The derivatives of dimethyl and mono-hydroxy products (F5 + F8 + F14 + F16) in feces, which are formed via oxidation pathways including CYP enzymes, represented approximately 54% of the total sample radioactivity. The derivatives of GSH conjugates in feces (F18 + F20) represented approximately 5% of the total sample radioactivity. Per Applicant, the remaining 40% of the total sample radioactivity in fecal samples was not structurally identified.

In vitro metabolism study was performed using human hepatocytes with futibatinib at lower concentrations (0.1 and 1 µmol/L) than that used in Study 18DB26 (10 µmol/L). The elimination of [^{14}C]-radiolabeled futibatinib and metabolite profile after incubation for 120 minutes were evaluated and the effect of a pan-CYP inhibitor, 1-aminobenzotriazole (1 mmol/L) on the overall metabolism of futibatinib was examined to estimate the contribution of CYP enzymes. The result suggests that CYP enzymes accounted for approximately 50% of futibatinib metabolism under the linear condition (Table 53).

Table 53: Contribution of CYP/non-CYP Enzymes to Metabolism of Futibatinib in Human Hepatocytes

Futibatinib concentration (µmol/L)	Group	Elimination (%)	Ke (1/hr)	Non-CYP Contribution (%)	CYP Contribution (%)
0.1	Control	48.0	0.326	50.1	49.9
	ABT	27.9	0.164		
1	Control	40.2	0.257	61.2	38.8
	ABT	27.0	0.157		

Source: Table 10, IR Response 4/1/22, SDN 18

In vitro experiments with recombinant human CYP enzymes and liver microsomes indicate that CYP3A was major CYP enzyme involved in futibatinib metabolism (80-95%), and CYP2C9 and CYP2D6 contributed to a lesser extent (~ 5-10% each).

Excretion

Study TAS-120-106 found that following administration of a single oral dose of 20 mg (~100 µCi) [14C]-futibatinib, the average (±SD) total recovery of the administered radioactivity was about 70% ± 25%, of which 64% ± 25% (92% of recovered radioactivity) and 6% ± 1.4% (9% of recovered radioactivity) were recovered in feces and urine, respectively. Futibatinib was present at negligible levels in urine and feces.

19.5.3 Drug Interaction Studies

In Vivo Drug-Drug Interactions

Effects on Futibatinib

Effect of P-gp and Strong CYP3A Modulators
Dual P-gp and CYP3A modulators should be avoided with TRADENAME (Table 54).

Effect of dual P-gp and CYP3A modulators was evaluated in Study TAS-120-103. This was a 2-part study and each part was conducted as an open-label, fixed sequence, 2-period study. A total of 40 healthy adult subjects were enrolled (20 subjects/ part). Each subject participated in only one study part.

- Part 1: to determine the effect of multiple-dose itraconazole, a strong CYP3A and P-gp inhibitor, on the single-dose PK of futibatinib.

On Day 1 of Period 1, a single oral dose of 20 mg futibatinib was administered. In Period 2, 200 mg PO itraconazole was administered QD for 6 consecutive days (Day 1 to Day 6) with a single dose of 20 mg futibatinib PO coadministered on Day 5. Blood samples for plasma futibatinib concentrations were collected through 48 hours after futibatinib administration on Day 1 and 5. There was a washout period of at least 2 days between the futibatinib dose in Period 1 and the first dose of itraconazole in Period 2.

- Part 2: to determine the effect of multiple-dose rifampin, a strong CYP3A and P-gp inducer.

On Day 1 of Period 1, a single PO dose of 20 mg futibatinib was administered. In Period 2, an oral dose of 600 mg rifampin was administered QD for 9 consecutive days (Day 1 to Day 9) with a single PO dose of 20 mg futibatinib coadministered on Day 8. Blood samples for plasma futibatinib concentrations were collected through 48 hours after futibatinib administration on Day 1 and 8. There was a washout period of at least 2 days between the futibatinib dose in Period 1 and the first dose of rifampin in Period 2.

Table 54: Point Estimates and 90% Confidence Intervals of Pharmacokinetic Parameters of Futibatinib under Fasted and Fed States.

Comparison (N=20)	Geometric Mean Ratio (90% CI)	
	$AUC_{0\text{-}inf}$ (ng*hr/mL)	Cmax (ng/mL)
Futbatinib with and without Itraconazole	1.41 (1.22, 1.63)	1.51 (1.28, 1.79)
Futbatinib with and without rifampin	0.36 (0.31, 0.43)	0.47 (0.41, 0.54)

Source: Tables 27 and 29 of SCP, Module 2.7.2

Table 55: Pharmacokinetic Parameters of Futibatinib With and Without Itraconazole and Rifampin

PK Parameters	Part 1		Part 2	
	Itraconazole + Futibatinib (n=20)	Futibatinib Alone (n=20)	Rifampin + Futibatinib (n=20)	Futibatinib Alone (n=20)
AUC_{last} (ng*hr/mL)	951 (46)	674 (70)	341 (61)	947 (36)
AUC_{inf} (ng*hr/mL)	957 (46)	679 (70)	344 (61)	955 (36)
Cmax (ng/mL)	253 (34)	167 (49)	105 (44)	222 (45)
Tmax (hr)	1.0 (0.7, 4.0)	1.5 (1.0, 6.0)	1.8 (0.7, 4.0)	1.3 (0.7, 6.0)
$T_{1/2}$ (hr)	3.5 ± 1.1	2.6 ± 0.9	2.0 ± 1.3	2.8 ± 0.7

Source: Tables 26 and 28 of SCP, Module 2.7.2

Effect of Gastric Acid Reducing Agents

There was no effect of acid reducing agents (ARAs) on fedratinib exposure (Table 56).

The effect of ARAs was evaluated in Study INT12894, an open-label, fixed sequence, 2-period study in 20 healthy subjects receiving a single dose of Late formulation of futibatinib (5 x 4 mg). A single oral dose of 20 mg futibatinib was administered on Day 1 in Period 1 (Reference). Multiple oral doses of 60 mg lansoprazole were administered QD on Days 1 - 5 with administration of a single oral dose of 20 mg futibatinib one hour after administration of lansoprazole on Day 5 in Period 2 (Test). PK samples for plasma futibatinib concentrations were collected over 48 hours in both periods.

Table 56: Point Estimates and 90% Confidence Intervals of Pharmacokinetic Parameters of Futibatinib under Fasted and Fed States.

Comparison (N=20)	Geometric Mean Ratio (90% CI)	
	$AUC_{0\text{-}inf}$ (ng*hr/mL)	Cmax (ng/mL)
Futbatinib with and without Lanzoprazole	1.05 (0.95 to 1.16)	1.08 (0.98 to 1.20)

Source: Table 20 of SBS, Module 2.7.1

Table 57: Pharmacokinetic Parameters of Futibatinib With and Without Lanzoprazole

PK Parameters	Lansoprazole + Futibatinib (n=20)	Futibatinib Alone (n=20)
AUC_{last} (ng*hr/mL)	983 (52)	934 (60)
AUC_{inf} (ng*hr/mL)	991 (52)	942 (59)
Cmax (ng/mL)	234 (43)	216 (52)
Tmax (hr)	1.5 (0.7, 4.0)	1.7 (0.7, 3.1)
$T_{1/2}$ (hr)	2.5 ± 1.3	3.1 ± 0.9
CL/F (L/hr)	22.7 ± 12.5	25.5 ± 21.8

Source: Table 19 of SBS, Module 2.7.1

DDI Effects of Futibatinib

Effect of CYP3A substrate
No major effect of futibatinib on CYP3A substrates (Table 58).

Effect of futibatinib on CYP3A substrate was evaluated in Study TAS-120-105, an open-label, fixed-sequence, 2-period study in 24 healthy subjects. On Day 1 of Period 1, a single oral dose of 2 mg midazolam was administered. In Period 2, an oral dose of 20 mg futibatinib was administered QD for 7 consecutive days (Days 1 to 7 of Period 2) with a single oral dose of 2 mg midazolam coadministered on Day 7. Blood samples for plasma midazolam and 1-hydroxymidazolam (1-OH-midazolam) concentrations were collected through 24 hours post-dose on Day 1 and 7. Blood samples for plasma futibatinib concentrations were collected pre-dose on Day 5 and Day 6 and through 12 hours post-dose on Day 7. There was a washout period of at least 1 day between the midazolam dose in Period 1 and the first futibatinib dose in Period 2.

Table 58: Point Estimates and 90% Confidence Intervals of Pharmacokinetic Parameters of Midazolam With and Without Futibatinib.

Comparison (N=24)	Geometric Mean Ratio (90% CI)	
	$AUC_{0\text{-}inf}$ (ng*hr/mL)	Cmax (ng/mL)
Midazolam with and without Futibatinib	1.05 (0.95 to 1.16)	1.08 (0.98 to 1.20)

Source: Table 32 of SCP, Module 2.7.2

Table 59: Pharmacokinetic Parameters of Midazolam With and Without Futibatinib

Pharmacokinetic Parameters	Futibatinib + Midazolam (n=24)	Midazolam Alone (n=24)
AUC_{last} (ng·hr/mL)	25 (39)	27 (45)
AUC_{inf} (ng·hr/mL)	26 (39)	28 (45)
C_{max} (ng/mL)	9 (31)	10 (39)
T_{max} (hr)	0.5 (0.5, 0.8)	0.8 (0.3, 1.5)
$T_{1/2}$ (hr)	5.2 ± 1.9	5.3 ± 1.8
CL/F (L/hr)	83 ± 33	77 ± 35

Source: Table 31 of SCP, Module 2.7.2

In Vitro Drug-Drug Interactions

DDI Effects of Futibatinib

On CYP Inhibition
Futibatinib is a time-dependent inhibitor of CYP3A (Table 60) and is not expected to inhibit CYP2C8,CYP2C9, and CYP2C19 at clinically relevant concentrations (Table 61).

Table 60: Time-dependent Inhibition Potential of Futibatinib on CYP3A

Substrates	kobs (min-1)	kdeg (min-1)	R2	R2 (Worst case)	Criteria for ruling out DDI potential

Midazolam	0.00494	0.00032	16.45	41.34	R_2 <1.25
Testosterone	0.00360	0.00032	12.26	32.45	

R_2 = (kobs + kdeg) / kdeg, where kobs = (Kinact × 50 × Imax,u) / (KI,u + 50 × Imax,u).
kobs is the observed (apparent first order) inactivation rate of the affected enzyme.
kdeg is the apparent first-order degradation rate constant of the hepatic CYP3A enzymes.
Imax,u= fu,p x Cmax = 0.0193 µmol/L, where Cmax=170.6 ng/mL and fu,p=0.0474 at 1 µmol/L.
KI,u is the unbound inhibitor concentration causing half-maximal inactivation = KI,u = KI × fu,mic, where KI is the inhibitor concentration causing half-maximal inactivation, and fu,mic is the unbound fraction in microsomes (0.57 at 1 mg/mL microsomal protein) was estimated using fu,mic = 1 / [1 + C × 10 ^ (0.072 × logP ^ 2 + 0.067 × logP – 1.126)], where C is the microsomal protein concentration used in the in vitro study for the IC_{50} determination for reversible inhibition. Kinact is the maximal inactivation rate constant.
Source: Table 48 of SCP, Module 2.7.2

Table 61: DDI Potential of Futibatinib on Other CYP2C8, 2C9, and 2C19

CYP isoforms	Ki,u (µmol/L)	R1	Criteria for ruling out DDI potential
CYP2C8	3.42	1.01	<1.02
CYP2C9	10.05	1.00	
CYP2C19	11.14	1.00	

Source: Table 49 of SCP, Module 2.7.2

On CYP Induction

Futibatinib has a low potential to induce CYP1A2, CYP2B6, and CYP3A4 in vitro.

The mean increase of CYP1A2, 2B6 and 3A4 mRNA levels were 2 to 2.85 at futibatinib concentrations of 0.5 and 5 µmol/L , respectively, in human hepatocytes. Increases in activities and mRNA levels of CYP enzymes were mostly < 20% of positive control in majority of cell lines tested. Treatment with futibatinib at up to 5 µmol/L did not cause an increase in either CYP2B6 activity or CYP3A activity.

On Transporters

Futibatinib is an inhibitor of P-gp and BCRP, but is not expected to inhibit other transporters at clinically relevant concentrations in vitro (Table 62).

Table 62: DDI Potential of Futibatinib on Transporters

Transporters	IC_{50} (µmol/L)	R	Criteria for ruling out DDI potential
P-gp	0.296	646	<10
BCRP	0.348	549	<10
OATP1B1	2.845	1.09	<1.1
OATP1B3	16.418	1.02	<1.1
OAT1	>60	<0.0003	<0.1
OAT3	>60	<0.0003	<0.1

OCT2	>60	<0.0003	<0.1
MATE1	5.687	0.0034	<0.1
MATE2K	5.969	0.0032	<0.1

Source: Table 50 of SCP, Module 2.7.2

Substrates of Futibatinib

Transporters

Futibatinib is a substrate of P-gp and BCRP (Study 16DA10).

The net efflux ratio (P-gp expressing versus control cells) were 6.05, 6.85, 2.73, and 2.73 at futibatinib concentrations of 0.3, 1, 10, and 30 µmol/L, respectively. Likewise, net efflux ratio (BCRP expressing versus control cells) were 1.81, 1.77, 0.81, and 0.50 at futibatinib concentrations of 0.3, 1, 10, and 30 µmol/L, respectively. Although net efflux ratio <2, the flux ratio in BCRP expressing cells was greater than that in control cells and saturated with increasing the futibatinib concentrations.

19.5.4 Summary of Bioanalytical Method Validation and In-Study Performance

Method Validation

The Applicant used a liquid-liquid extraction with tandem mass spectrometric detection (LC/MS/MS) for quantitation of futibatinib in human plasma. Three bioanalytical sites were used for the estimation of fedratinib in human plasma. The bioanalytical methods were validated as described in Table 63:.

Table 63: Method Validation Parameters

Validation Parameters	**8291169**	(b) (4)	(b) (4)
Facility	(b) (4)		
Analyte	Futibatinib		
Internal Standard (IS)	d^6-futibatinib		
Detection	LC/MS/MS		
Extraction	Protein Precipitation	Liquid-Liquid	Protein Precipitation
Anticoagulant	K_2EDTA		
Range	0.5 to 500 ng/mL	0.5 to 250 ng/mL	0.5 to 1000 ng/mL
Quality Controls	0.5, 1.5, 25, 400 ng/mL		ng/mL
Inter/Intra-assay Precision at LLOQ	2.2 to 6.8%	5.6 to 8.4%	0.4 to 3.3%
Inter/Intra-assay Accuracy at LLOQ	0.6 to 15.6%	-5.6 to 4.8%	-3.7 to 2.6%
Selectivity (accuracy %)	-2.0 to 4.0% at 1.5 ng/mL	No interference in 10 lots	No interference in 6 lots
Inter/Intra-assay Precision	1.5% to 6.1%	2% to 6.9%	0.4% to 3.3%
Inter/Intra-assay Accuracy	-4.3% to 10.7%	-4.9 to 11.3%	-3.7% to 2.6%

Dilution %Bias (%CV)	2500 ng/mL (100x): <6%	2500 ng/mL (20X & 100x): ≤10% (≤6%)	4000 ng/mL (100x): 0.8% (2.2%)
Stock stability for futibatinib	6 hrs at RT 106 days at 2°C to 8°C	202 days at -20°C 6 hours at RT	92 days at 2 to 8°C
Stock stability for IS	6 hrs at RT	6 hours at RT	92 days at 2 to 8°C
Bench-top stability	9 hours at RT & wet ice		6 hours at RT
Matrix Factpr	1	1-1.3	1
Extract stability	163 hours at 2°C to 8°C	220 hours at 5°C	48 hours at 10°C
Long-term Stability	245 days at -30°C to -10°C* 492 days at -80°C to -60°C*	214 days at -20°C 406 days at -80°C	182 days at -30°C to -15°C† 365 days at ≤-70°C†
Freeze-Thaw Stability	5 cycles at -30°C to -10°C and -80°C to -60°C	6 cycles at -20°C and -80°C	5 cycles at ≤-70°C
Hemolysis, %Bias (%CV)	<3% (≤4%)	<6% (<2%)	--
Hyperlipidaemic	<6% (CV: <5%)	<8% (≤5.3%)	--
Recovery, % (%CV)	98-99% (0.7-4.6%)	99-102% (1.2-4.3%)	--
Whole blood stability	2 hrs at RT & wet ice	2.4 hours in wet ice	--
Assay used in Clinical Studies	TAS-120-101 and TAS-120-102	TAS-120-103, -104, -105, -106, and -107	10059010 and 10059020

RT=room temperature
Source: Validation reports 8291169, (b) (4), *Addendum to 8291169, and † (b) (4)
Module 5.3.1.4.

In-Study Assay Performance:

In Studies 10059010 and 10059020, TAS-120-101 and TAS-120-102, and TAS-120-103, -104, -105, -106, and -107, the precision was ≤10% (except for Study 10059010 where ≤13%) and accuracy was ≤10%. Majority (75-100%) of the analytical runs in the studies were successful. The incurred sample reanalysis (ISR) was performed in all studies, and were within acceptable limits, with ≥95% of samples within 20% different.

The study samples were reported as analyzed within the validated storage and handling conditions (i.e., within 69 days at -20°C, 34 days at -70°C, or 468 days at -80°C to -60°C) . All patient samples in Study TAS-120-101 were analyzed at the same bioanalytical facility, with total duration from 1st sample collection to last sample analysis of 2058 days. However, patient samples in the study were analyzed in multiple subsets with all patient samples analyzed within 468 days of storage at -80°C to -60°C.

19.5.5 Subgroup Analysis

Table 64: Subgroup analysis of safety in Study TAS-120-101

	Safety Data Grp 1 (n=145)	**Phase 1** (n=42)	**Phase 2** (n=103)
Adverse Reactions (%)	**20 mg QD**		

Age	<65 yrs	≥65 yrs	<65 yrs	≥65 yrs	<65 yrs	≥65 yrs
Grade ≥3	77	74	73	70	68	63
Serious	42	36	45	42	42	45
Sex	Male	Female	Male	Female	Male	Female
Grade ≥3	76	77	67	76	66	68
Serious	50	35	47	41	46	40
Race	Caucs.	Asians	Caucs.	Asians	Caucs.	Asians
Grade ≥3	78	78	75	66	70	62
Serious	35	33	46	42	45	42
Prior Therapy	1	≥3	1	≥3	1	≥3
Grade ≥3	76	68	76	71	70	67
Serious	31	50	39	37	35	33

19.5.6 Physiologically-based Pharmacokinetic Modeling

Executive Summary

The objective of this review is to evaluate the adequacy of the Applicant's following PBPK reports to support the intended uses.

- 20DC01 PK Analysis Report: Physiologically based pharmacokinetic modeling using Simcyp to evaluate drug-drug interaction potential of TAS-120 (futibatinib) as a victim of CYP3A inhibitors and inducers.
- 20DC09 PK Analysis Report: Physiologically based pharmacokinetic modeling using Simcyp to evaluate drug-drug interaction potential of TAS-120 (futibatinib) as a perpetrator of P-gp and BCRP substrates.

The Division of Pharmacometrics reviewed the PBPK reports, supporting modeling files, and the Applicant's responses to FDA's information requests (IRs) submitted on March 04th, 2022 and April 21st, 2022, and reached the following conclusions.

- The futibatinib PBPK model was able to capture the clinically observed futibatinib PK profiles following a single oral dose (20 mg) or multiple oral dose administration (4, 8, 16, 20 and 24 mg QD) of futibatinib in healthy subjects and cancer patients.
- The futibatinib PBPK model is inadequate to predict the effect of clarithromycin (a strong CYP3A4 and P-gp inhibitor), fluconazole (a moderate CYP3A4 and CYP2C9 inhibitor), fluvoxamine (a moderate CYP3A4 inhibitor, a weak CYP2C9 and CYP2D6 inhibitor and a P-gp inhibitor), carbamazepine (a strong CYP3A4 and P-gp inducer) and efavirenz (a moderate CYP3A4 and P-gp inducer) on the PK of futibatinib in healthy subjects, because the fractions metabolized by individual enzymes and magnitude of transporters involved in the

absorption of futibatinib could not be reliably quantified based on current available data and PBPK analysis.
- In vitro study and PBPK analysis suggested that the DDI potential of futibatinib as a perpetrator with digoxin (a P-gp substrate) or rosuvastatin (a BCRP substrate) cannot be excluded.

Applicant's PBPK Modeling

PBPK software

Simcyp V19 (Certara, UK) was used by the Applicant to develop the futibatinib PBPK models and predict the PK of futibatinib with and without CYP3A modulators, and the effect of futibatinib on the PK of digoxin and rosuvastatin. The review team used the same software and version for analyses.

Model development

Futibatinib Model 1

Futibatinib model 1 was used to assess the DDI potential of futibatinib as a victim with CYP3A modulators.

As shown in Table 65, the first order absorption model was used to describe the absorption of futibatinib and a full PBPK model was used to simulate the distribution phase of futibatinib PK profiles.

In vitro metabolism studies involving recombinant enzymes indicated that CYP3A4, CYP2C9 and CYP2D6 were responsible for the oxidative metabolism of futibatinib. The contribution of CYP3A (fmCYP3A4=0.37) to the overall clearance of futibatinib was estimated based on clinical DDI study with itraconazole. The relative contributions of CYP2C9 (0.05) and CYP2D6 (0.05) to the total clearance of futibatinib was calculated based on the estimated fmCYP3A4 value (0.37) and in vitro determined contributions of CYP2C9 (10.5%), CYP2D6 (11.2%), and CYP3A (78.3%) to the overall CYP mediated metabolism in human liver microsomes.

After oral administration, futibatinib is excreted into feces (64%) and urine (6%). Unchanged futibatinib was not detected either in urine or feces (Study TAS-120-106).

Futibatinib Model 2

Futibatinib model 2 was used to evaluate the DDI potential of futibatinib as a perpetrator with digoxin and rosuvastatin.

In futibatinib model 2, the absorption model was changed from first order absorption model (futibatinib model 1) to Advanced Dissolution, Absorption and Metabolism (ADAM) absorption model. The absorption model parameter values are shown in Table 66 and Table 66. The model structure and parameter values in Model 2 remained the same as those in Model 1 with respect to the characterization of futibatinib distribution, metabolism, and elimination processes.

Futibatinib has been identified as a P-gp and BCRP inhibitor in vitro. The in vitro obtained inhibition parameter values (Ki) were used in the model to evaluate the DDI potential of futibatinib as a perpetrator with digoxin and rosuvastatin.

Table 65: Parameter values implemented in futibatinib model 1

	Parameters and model	**Value**	**Source**
Physiochemical Properties	Molecular weight (g/mol)	418.45	Investigator's Brochure
	Compound type	Monoprotic base	Not applicable
	Log P	3.3	Study PCA19100
	pKa	3.24	Study PCA19100
	B/P ratio	0.55	Study 16DA16
	fu,p	0.044	Study 16DA16
Absorption	Absorption model	First-order	Not applicable
	fa	1	Study TAS-120-106
	*k*a (hr_{-1})	0.818	Parameter estimation
	Lag time (hr)	0.655	Parameter estimation
	Papp across Caco-2 cells (cm/sec)	24.4×10-6	Propranolol: 25.1×10^{-6} cm/sec Study 20DB01
	fu,gut	0.044	Assumed equal to fu,p
	Qgut (L/hr)	14.8	Predicted within Simcyp
Distribution	Distribution model	Full PBPK	Not applicable
	Vss (L/kg)	0.646	Predicted with method 2
	Kp scalar	0.162	Parameter estimation
Elimination	Clearance type	Enzyme kinetics	Not applicable
	CYP2C9 CLint (µL/min/pmol)	0.116	Retrograde calculation
	CYP2D6 Clint (µL/min/pmol)	0.916	Retrograde calculation
	CYP3A4 Clint (µL/min/pmol)	0.402	Retrograde calculation
	Additional CL for human liver microsomes (µL/min/mg protein)	73.5	Retrograde calculation

	CLr (L/hr)	0	Study TAS-120-106
Interaction	CYP2C8 Ki (µmol/L)	4.07	Study 18DB18
	CYP2C9 Ki (µmol/L)	11.95	Study 18DB18
	CYP2C19 Ki (µmol/L)	13.25	Study 18DB18
	CYP3A TDI KI (µmol/L)	24. 6	Study 18DB18
	CYP3A TDI Kinact (hr-1)	4.596	Study 18DB18
	P-gp Ki (µmol/L)	0.296	Study 16DA10
	BCRP Ki (µmol/L)	0.348	Study 16DA10

ADAM = advanced dissolution, absorption and metabolism; BCRP = breast cancer resistance protein; B/P = blood to plasma ratio; CL = clearance; CLint = intrinsic clearance; CLr = renal clearance; CSR = critical supersaturation ratio; CYP = cytochrome P450; fu,gut = unbound fraction in enterocytes; fu,p = unbound fraction in plasma; Ki = inhibition constant; KI = inhibitor concentration causing half-maximal inactivation; Kinact = maximal inactivation rate constant; Km:w = micelle: buffer partition coefficient; Kp = tissue-plasma partition coefficient; Log P = octanol-water partition coefficient; MechPeff = mechanistic permeability; Peff = effective permeability; P-gp = P-glycoprotein; pKa = acid dissociation constant; PRC = precipitation rate constant; Ptrans,0 = intrinsic permeability; Vss = distribution volume at steady state.
Source: PBPK report 20DC01

Table 66: Parameter values implemented in futibatinib model 2

Absorption	Absorption model	ADAM	Not applicable
	Formulation	Solution with precipitation (simulation for Study TAS-120-106), immediate release (simulations for other studies and scenarios)	Not applicable
	pH-solubility profile in aqueous buffer	684.9 µg/mL (pH 1.2)	In vitro (IND 121062)
		11.0 µg/mL (pH 3.0)	
		4.2 µg/mL (pH 4.5)	
		3.9 µg/mL (pH 5.0)	
		3.4 µg/mL (pH 6.8)	
		3.5 µg/mL (pH 7.5)	
	log *K*m:w (neutral)	3.846	Estimated using SIVA
	log *K*m:w (un-ionized)	6.318	Estimated using SIVA
	Particle size monodispersed radius	(b) (4)	Assumed as Simcyp default

	Particle density	(b) (4) g/mL	Assumed as Simcyp default
	CSR	36	Parameter estimation
	PRC	0.38 hr-1	Parameter estimation
	Diffusion coefficient	4.037 × 10-4 cm2/sec	Predicted within Simcyp
	MechPeff, Ptrans,0	684 × 10-6 cm/sec	Parameter estimation
	Peff in duodenum	3.28 × 10-4 cm/sec	Predicted within Simcyp
	Peff in jejunum I	8.44 × 10-4 cm/sec	Predicted within Simcyp
	Peff in jejunum II	5.91 × 10-4 cm/sec	Predicted within Simcyp
	Peff in ileum I and II	1.40 × 10-4 cm/sec	Predicted within Simcyp
	Peff in ileum III	1.37 × 10-4 cm/sec	Predicted within Simcyp
	Peff in ileum IV	1.32 × 10-4 cm/sec	Predicted within Simcyp
	Peff in colon	0.72 × 10-4 cm/sec	Predicted within Simcyp

Source: PBPK report 20DC09

Cancer patients

Simcyp cancer patient population was used to predict the exposure of futibatinib. The differences in patient demographics and physiology compared to healthy subjects have been integrated in Simcyp cancer patient population. For instance, cancer patients have different levels of blood and plasma binding proteins and hepatic transporters. The perpetrator DDI liability of futibatinib with digoxin and rosuvastatin was also evaluated in cancer population.

Victim and perpetrator drug models

The default PBPK models of itraconazole, clarithromycin, fluconazole, fluvoxamine, cimetidine, rifampicin, carbamazepine, efavirenz, digoxin and rosuvastatin in Simcyp (V19) were used for DDI prediction.

FDA's assessment

1. A solution formulation of itraconazole was used in Study TAS-120-103 to evaluate its effect on the PK of futibatinib. Hydroxypropyl-β-cyclodextrin (HP-β-CD) is used as an excipient in the itraconazole solution (Sporanox®) for oral dosing. It has been shown that HP-β-CD may have impact on the rate and extent of the drug absorption when co-administered with itraconazole solution, leading to potential underestimation of the DDI with itraconazole[1],[2]. An information request was issued requesting the Applicant to evaluate the potential impact of HP-β-CD in the itraconazole solution on the observed DDI between itraconazole and futibatinib.
2. The contributions of CYP and non-CYP pathways to the overall metabolism of futibatinib were estimated to be 0.47 and 0.53, respectively. An information request was issued

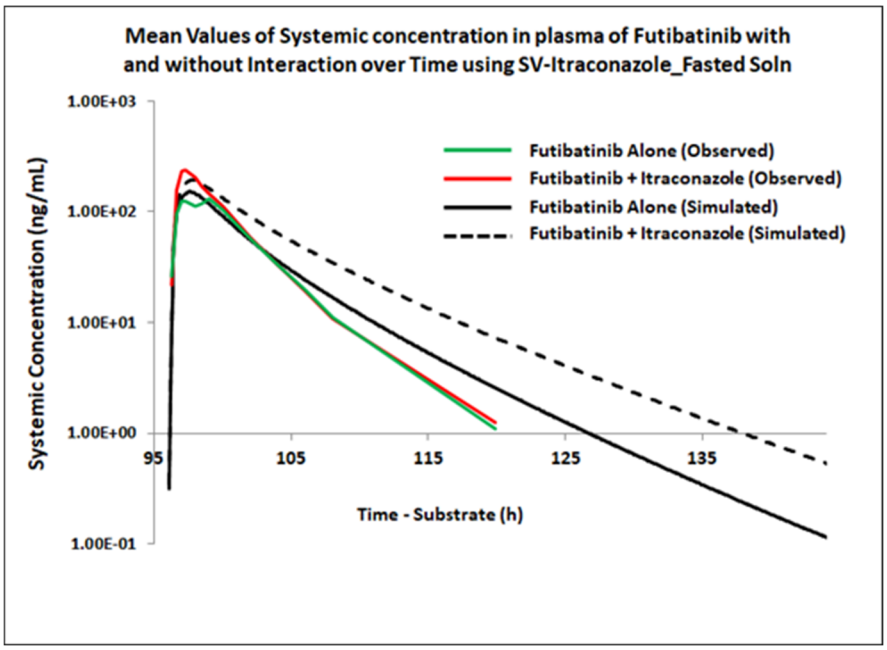
requesting the Applicant to provide adequate justification for the assigned fmCYP value of 0.47 in the model.

3. The Applicant's model predicted geometric mean ratios of Cmax (1.27) and AUC (1.57) in the presence and absence of itraconazole were not consistent with the observed data (CmaxR=1.51 and AUCR=1.41), which showed Cmax had higher fold changes compared to AUC fold changes with itraconazole. In addition, the clinical study showed that futibatinib elimination half-lives were not significantly impacted by itraconazole, whereas the Applicant's model predicted a prolonged terminal half-life of futibatinib with itraconazole (Figure 10). In vitro study indicated that futibatinib was a P-gp and BCRP substrate. Transporters mediated drug efflux was not incorporated in the futibatinib PBPK model. An information request was issued requesting the Applicant to evaluate the effect of transporter on the PK of futibatinib.
4. The futibatinib metabolites of CoF8 (8.98% of dose), F16 (16.99% of dose) and F5 (3.47% of dose) were only present in the feces (Study TAS-120-106) and have not been detected in in vitro metabolism studies with liver microsome and hepatocytes and in vivo plasma samples. An information request was issued requesting the Applicant to discuss the possibility that futibatinib was metabolized by the gut microbiota.

Applicant's response to FDA's IR and FDA's assessment

1. In the response to the FDA's IR, the Applicant provided binding constant data ($k_{complex}$=2738 mol/L^{-1}) and in vitro permeability of futibatinib in the presence of HP-β-CD. The permeability of futibatinib was decreased by approximately 2.4-fold at the molar ratio between futibatinib and HP-β-CD similar to the clinical setting. Based on the findings in the literature[3] [4], these data and information suggested that the likelihood that HP-β-CD in the itraconazole solution would impact futibatinib absorption was low.
2. The Applicant conducted an in vitro human hepatocyte incubation study with futibatinib. The effect of a pan-CYP inhibitor on the overall metabolism of futibatinib was evaluated. The study results suggested that CYP enzyme accounted for about 50% of futibatinib metabolism.
3. In the response to the FDA's IR, the DDI potential between futibatinib and itraconazole was reevaluated by using a PBPK model that incorporated P-gp-mediated efflux transport in the intestine. The modeling analysis results suggested that the involvement of the transporters in the absorption of futibatinib cannot be excluded. The DDI with P-gp inhibitors may result in higher systemic PK exposure of futibatinib and increased safety risk.
4. In the response to the FDA's IR, the Applicant discussed the metabolic pathways that were involved in the formation of CoF8, F16 and F5 metabolites. The analysis showed that the conversion from an O-demethylated metabolite of futibatinib (desmethyl futibatinib) to its reduced form F16 and subsequent CoF8 and then F5 is a possible metabolic pathway mediated by gut microbiota.

Figure 10: Simulated and observed mean plasma concentration-time profiles of futibatinib in the absence and presence of itraconazole.



Source: Observed data were from TAS-120-103 study report and simulated data were from PBPK report 20DC09

PBPK model application

The developed futibatinib model 1 was used to simulate the DDI for futibatinib as a victim in the following scenarios.

- To predict the effect of clarithromycin (a strong CYP3A4 and P-gp inhibitor) and fluvoxamine (a moderate CYP3A4, a weak CYP2C9 and CYP2D6 inhibitor and a P-gp inhibitor) on the PK of futibatinib following multiple oral dose administration in healthy subjects.
- To predict the effect of fluconazole (a moderate CYP3A4 and CYP2C9 inhibitor) on the PK of futibatinib following multiple oral dose administration in healthy subjects.
- To predict the effect of carbamazepine (a strong CYP3A4 and P-gp inducer) and efavirenz (a moderate CYP3A4 and P-gp inducer) on the PK of futibatinib following multiple oral dose administration in healthy subjects.
- To predict the effects of pure moderate or weak CYP3A4 inhibitors on the PK of futibatinib following multiple oral dose administration in healthy subjects.

The developed futibatinib model 2 was used to simulate the DDI for futibatinib as a perpetrator in the following scenarios.

- To predict the effect of futibatinib on the PK of digoxin (P-gp substrate) and rosuvastatin (BCRP substrate) following multiple oral dose administration of futibatinib in healthy subjects.

Results

1. **Can futibatinib PBPK model (first order absorption model) reasonably describe the PK of futibatinib?**

Yes. The futibatinib PBPK model with a first-order absorption model (model 1) was able to capture the observed futibatinib PK profiles following a single oral dose (20 mg) or multiple oral dose administration (4, 8, 16, 20 and 24 mg, QD) of futibatinib in healthy subjects and cancer patients (Figure 11 and Table 67).

2. **Can futibatinib PBPK model (ADAM absorption model) reasonably describe the PK of futibatinib?**

Yes. The futibatinib PBPK model with an ADAM absorption model (model 2) was able to capture the observed futibatinib PK profiles following a single oral dose (20 mg) administration of futibatinib in healthy subjects (Figure 12 and Table 68).

3. **Can futibatinib PBPK model predict the effect of clarithromycin (a strong CYP3A4 and P-gp inhibitor), fluvoxamine (a moderate CYP3A4, a weak CYP2C9 and CYP2D6 inhibitor and a P-gp inhibitor), carbamazepine (a strong CYP3A4 and P-gp inducer) and efavirenz (a moderate CYP3A4 and P-gp inducer) on the PK of futibatinib following multiple oral dose administration in healthy subjects?**

No. As stated in previous sections, the involvement of P-gp transporter in the absorption of futibatinib cannot be excluded. The fractions metabolized by individual enzymes and magnitude of transporters involved in the absorption of futibatinib could not be reliably quantified based on current available data and PBPK analysis. Therefore, the current PBPK model is inadequate to predict the magnitude of exposure changes of futibatinib when co-administered with clarithromycin, fluvoxamine, carbamazepine and efavirenz.

4. **Can futibatinib PBPK model predict the effects of fluconazole (a moderate CYP3A4 and CYP2C9 inhibitor) on the PK of futibatinib following multiple oral dose administration in healthy subjects?**

No. As stated in previous sections, the fractions metabolized by individual enzymes could not be reliably quantified for futibatinib based on current available data and PBPK analysis. Therefore, the current PBPK model is inadequate to predict the magnitude of exposure changes of futibatinib when co-administered with fluconazole.

5. **Can futibatinib PBPK model predict the effects of pure moderate or weak CYP3A4 inhibitors on the PK of futibatinib following multiple oral dose administration in healthy subjects?**

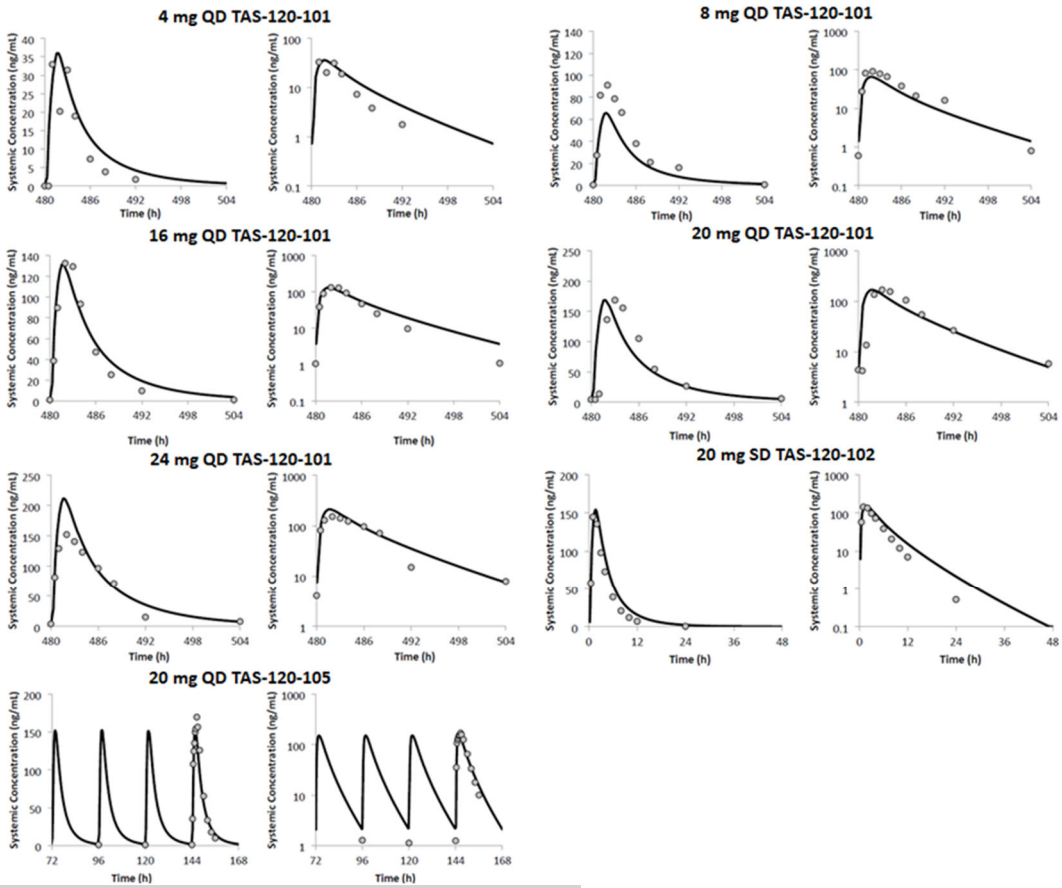
No, but provided supporting information. The Applicant's original model analysis assumed that the observed DDI between futibatinib and itraconazole was driven by the itraconazole mediated inhibition effect on CYP3A4 only. The fmCYP3A4 value in the Applicant's original model estimated based on clinical DDI study with itraconazole may represent the highest possible contribution of CYP3A4 to the overall clearance of futibatinib. In addition, the

fluvoxamine and cimetidine mediated inhibition effect on CYP3A4 was only considered in the Applicant's original model analysis for the DDI evaluation of futibatinib with fluvoxamine and cimetidine. Thus, the applicant's original model predicted exposure changes of futibatinib with fluvoxamine (↑25%) and cimetidine (↑13%) may represent the worst-case scenarios for the DDI potential with pure moderate and weak CYP3A4 inhibitors. Therefore, the model analysis suggested that co-administration of pure moderate and weak CYP3A4 inhibitors may result in a ≤25% and 13% increase in the exposure of futibatinib at steady state, respectively.

6. Can the PBPK model predict the effect of futibatinib on the PK of digoxin (a P-gp substrate) and rosuvastatin (a BPCR substrate) in healthy subjects?

No, but provided supportive information. The Applicant used the in vitro obtained Ki values of 0.296 µmol/L and 0.348 µmol/L in the model to predict the effect of futibatinib on the PK of digoxin and rosuvastatin, respectively. A sensitivity analysis of Ki values was conducted to further assess the effect of futibatinib on the PK of digoxin and rosuvastatin. The simulated AUCRs were about 1.3 and 1.8 for digoxin and rosuvastatin, respectively, with 100-fold reduction of Ki values in the presence and absence of futibatinib (Table 69). In addition, the reviewer's model analysis showed that the effect of futibatinib on the PK of digoxin and rosuvastatin in cancer patients and healthy subjects appeared to be comparable. Due to the uncertainties regarding the in vitro to in vivo extrapolation of the Ki values of P-gp or BCRP inhibitors, the futibatinib model was not considered adequate to accurately predict the effect of futibatinib on the PK of digoxin or rosuvastatin. However, the analysis indicated that the potential DDI risk between futibatinib and digoxin or rosuvastatin cannot be excluded.

Figure 11: Simulated and observed plasma concentration–time profiles of futibatinib following a single (20 mg) or multiple dose administrations of futibatinib at a dose range of 4 to 24 mg in healthy subjects and cancer patients. The black line represents predicted mean concentrations, and the gray circles represent observed mean concentrations. The left panel is the linear scale, and the right panel is the semi-logarithmic scale.



Source: Applicant's response to FDA's IR dated April 01st, 2022

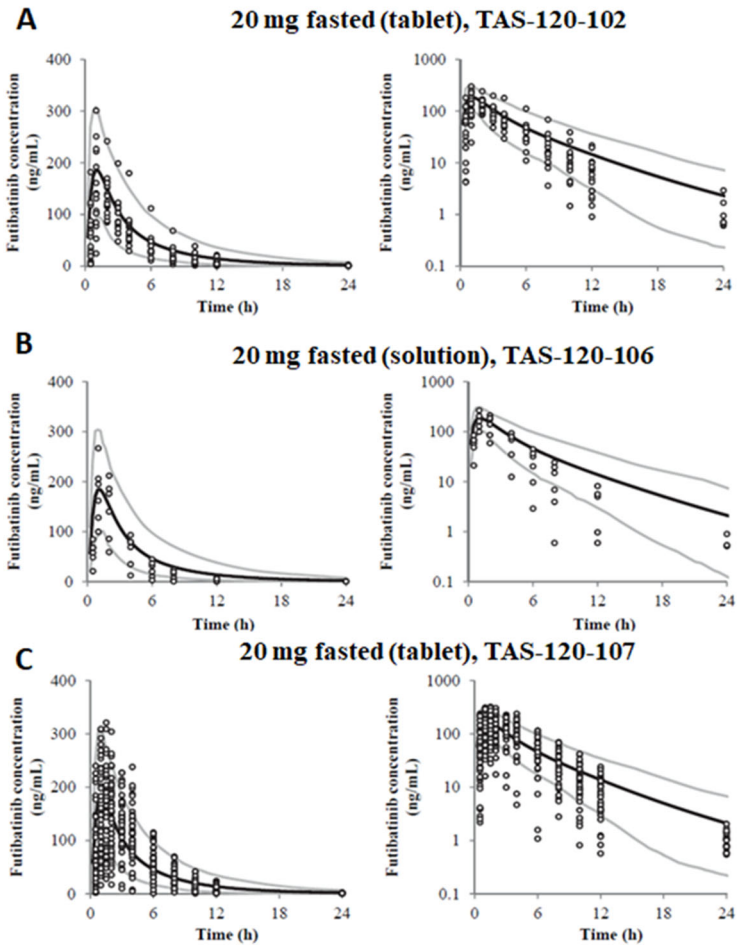
Table 67: Simulated and Observed Geometric Mean PK Parameters and C_{max} and AUC_{inf} Ratios for Futibatinib

Trial	Dosage	Visit	Observed		Population	Predicted		Pred/Obs ratio (acceptance criteria)	
			C_{max} (ng/mL)	$AUC_{(0,t)}$ (ng.h/mL)		C_{max} (ng/mL)	$AUC_{(0,t)}$ (ng.h/mL)	C_{max}	AUC
TAS-120-101	4 mg QD	Day 1	24.3	70.3	Cancer	35.5	181	1.46 (0.30-3.35)	2.57 (0.24-4.11)
		Day 21	39.1	94.3		36.1	187	0.93 (0.20-4.96)	1.98 (0.20-5.11)
	8 mg QD	Day 1	100	406		63.9	335	0.64 (0.23-4.27)	0.83 (0.30-3.32)
		Day 21	86.2	437		65.4	349	0.76 (0.36-2.77)	0.80 (0.28-3.63)
	16 mg QD	Day 1	134	469		128	693	0.96 (0.61-1.63)	1.48 (0.57-1.76)
		Day 21	153	599		133	737	0.87 (0.56-1.78)	1.23 (0.51-1.97)

	20 mg QD	Day 1	247	1100		166	909	0.67 (0.65-1.54)	0.83 (0.46-2.18)
		Day 21	166	1130		173	976	1.04	0.86
	24 mg QD	Day 1	223	1050		205	1140	0.92 (0.61-1.65)	1.09 (0.57-1.77)
		Day 21	175	1120		216	1250	1.24 (0.27-3.77)	1.11 (0.24-4.19)
TAS-120-102	20 mg SD	Day 1	155	626	HV	159	792	1.03 (0.69-1.45)	1.27 (0.64-1.56)
TAS-120-105	20 mg QD	Day 7	192	836		159	784	0.83 (0.71-1.41)	0.94 (0.72-1.40)

SD = single dose; QD = once daily.
Source: Observed data were from Study TAS-120-101, TAS-120-102 and TAS-120-105. Simulated data were from PBPK report 20DC01.

Figure 12: Simulated and observed plasma concentration-time profiles of futibatinib following a single dose administration of 20 mg futibatinib solution and tablets. The black line represents predicted mean concentrations, and the gray lines represent the 5th and 95th percentiles. The circle represents individual observed concentrations. The left panel is the linear scale, and the right panel is the semi-logarithmic scale.



Source: PBPK report 20DC09

Table 68: Simulated and Observed Geometric Mean PK Parameters and C_{max} and AUC_{inf} Ratios for Futibatinib in Healthy Subjects

Trial	Dosage	Observed		Population	Predicted		Pred/Obs ratio	
		C_{max} (ng/mL)	$AUC_{(0,t)}$ (ng.h/mL)		C_{max} (ng/mL)	$AUC_{(0,t)}$ (ng.h/mL)	C_{max}	AUC
TAS-120-102	20 mg SD (fasted, tablet)	154.6	625.7	HV	183.9	805.2	1.19	1.29
TAS-120-106	20 mg SD (fasted, solution)	172.4	550.1		182.9	795.5	1.06	1.45
TAS-120-107	20 mg SD (fasted, tablet)	165.2	713.5		182.3	787.3	1.10	1.10

Source: Observed data were from Study TAS-120-102, TAS-120-106 and TAS-120-107. Simulated data were from PBPK report 20DC09.

Table 69: Simulated C_{max} and AUC_{0-96h} Ratios for Digoxin and Rosuvastatin in the Presence and Absence of Multiple Dose Administrations of 20 mg QD Futibatinib in Healthy Subjects

Substrate	Input Ki Value	Predicted ratio (90% CI)	
		C_{max}	AUC
Digoxin	0.296 µmol/L (in vitro Ki)	1.07 (1.07-1.07)	1.02 (1.02-1.02)
	0.0296 µmol/L (0.1-fold Ki)	1.39 (1.36-1.41)	1.11 (1.10-1.12)
	0.00296 µmol/L (0.01-fold Ki)	1.84 (1.78-1.90)	1.28 (1.25-1.32)
Rosuvastatin	0.348 µmol/L (in vitro Ki)	1.04 (1.04-1.04)	1.02 (1.02-1.02)
	0.0348 µmol/L (0.1-fold Ki)	1.50 (1.45-1.54)	1.15 (1.14-1.16)
	0.00348 µmol/L (0.01-fold Ki)	3.61 (3.41-3.83)	1.79 (1.73-1.86)

Source: PBPK report 20DC09

[1] Durk MR, Jones NS, Liu J, Nagapudi K, et al. Understanding the Effect of Hydroxypropyl-β-Cyclodextrin on Fenebrutinib Absorption in an Itraconazole-Fenebrutinib Drug-Drug Interaction Study. Clin Pharmacol Ther. 2020; 108: 1224-1232.
[2] Tachibana T, Kitamura S, Kato M, Mitsui T, et al. Model Analysis of the Concentration Dependent Permeability of P-gp Substrates. Pharm Res. 2010; 27: 442-446.
[3] Durk MR, Jones NS, Liu J, Nagapudi K, et al. Understanding the Effect of Hydroxypropyl-β-Cyclodextrin on Fenebrutinib Absorption in an Itraconazole-Fenebrutinib Drug-Drug Interaction Study. Clin Pharmacol Ther. 2020; 108: 1224-1232.
[4] Tachibana T, Kitamura S, Kato M, Mitsui T, et al. Model Analysis of the Concentration Dependent Permeability of P-gp Substrates. Pharm Res. 2010; 27: 442-446.

19.5.7 Population PK Analysis

19.5.7.1 Executive Summary

The FDA's Assessment:

The applicant's population PK analysis is acceptable for characterization of PK of futibatinib. Intrinsic (body weight, serum albumin) and extrinsic (fed, dose, CYP3A inhibitors/inducers) factors were identified as covariates on F, Ka, CL/F and Vc/F in PK models of futibatinib. Amongst the identified covariates, none was found to have a clinically meaningful effect on futibatinib exposure.

19.5.7.2 PPK Assessment Summary

The Applicant's Position:

General Information	
Objectives of PPK Analysis	• To develop a PPK model for futibatinb in healthy volunteers and patients with advanced solid tumors • To assess the impact of potential covariates on futibatinib PK

Study Included		*Seven Phase 1 studies (TAS-120-102, TAS-120-103, TAS-120-104, TAS-120-105, TAS-120-107, 10059010, and 10059020) and one Phase 1/2 study (TAS-120-101)*
Dose(s) Included		*4, 8, 12, 16, 20, 24, 36, 56, 80, 120, 160, and 200 mg*
Population Included		*Healthy adults, adult patients with advanced solid tumors, patientswith CCA harboring FGF/FGFR aberrations*
Population Characteristics (Table 5-2, Table 5-3)	General	*Age: 51 (18–82)* *Weight: 70.5 (36.0–152)* *Sex: 255 (51.9%) Male, 236 (48.1%) Female* *Race:* *284 (57.8%) White* *35 (7.1%) Black or African American* *107 (21.8%) Asian* *2 (0.4%) American Indian or Alaska Native* *2 (0.4%) Native Hawaiian or other Pacific Islander* *7 (1.4%) Others* *54 (11.0%) Missing*
	Organ Impairment	*Hepatic function:* *Normal hepatic function (NCI): 432 (88.0%)* *Mild hepatic impairment (NCI): 56 (11.4%)* *Moderate hepatic impairment (NCI): 3 (0.6%)* *Renal function:* *Normal renal function (CLcr): 328 (66.8%)* *Mild renal impairment (CLcr): 127 (25.9%)* *Moderate renal impairment (ClCr): 36 (7.3%)*
	Pediatrics (if any)	
No. of Patients, PK Samples, and BLQ		There were a total of 7690 PK samples collected from 496 subjects across the eight studies. Of these samples, the following samples were excluded prior to model development: • 30 (0.390%) samples because of missing data about dose or blood withdrawal time • 781 (10.2%) post-dose samples with futibatinib concentration BLQ • 446 (5.80%) pre-dose samples collected on Day 1 of first dose
Sampling Schedule	Healthy adults Rich Sampling	• Day 1 and Day 8: pre-dose, 0.5, 1, 2, 3, 4, 6, 8, 10, 12, 24, and 48 hours post-dose • Day 1 and Day 8: pre-dose, 0.5, 1, 2, 3, 4, 6, 8, 12, 24, and 48 hours post-dose • Day 1, Day 5, and Day 8: pre-dose, 0.333, 0.667, 1, 1.333, 1.667, 2, 2.5, 3, 4, 6, 8, 10, 12, 24, and 48 hours post-dose • Day 7: pre-dose, Day 8: pre-dose, Day 9: pre-dose, 0.333, 0.667, 1, 1.333, 1.667, 2, 2.5, 3, 4, 6, 8, 10, and 12 hours post-dose • Day 1: pre-dose, 0.5, 1, 1.5, 2, 3, 4, 6 , 8, 10, 12, and 24 hours post-dose
	Patients	• Cycle 1 Day 1 and Last Wednesday: pre-dose, 0.5, 1, 2, 3, 4, 6, 8, 12, 24, and 48 hours post-dose • Cycle 1 Day 1 and Day 21: pre-dose, 0.5, 1, 2, 3, 4, 6, 8, 12, and 24 hours post-dose

		• Cycle 2 Day 1: pre-dose (Cycle 3 and Cycle 4 also), 1, and 3 hours post-dose
Covariates Evaluated	Static	• Baseline body weight, age, sex, race, ethnicity, patient status (healthy versus patient), cancer type, FGFR mutation status, ECOG, and serum albumin • Formulation, food, dose, time/cycle, and concomitant medications (strong CYP3A and P-gp inhibitors and moderate/strong inducers) • ALT, AST, TBIL, hepatic impairment by the NCI-ODWG, CLCR, renal impairment as defined by FDA Guidance, and cycle
	Time-varying	*Not applicable*

Final Model	**Summary**	**Acceptability [FDA's comments]**
Software and Version	• NONMEM (version 7.4.3), a software package for non-linear mixed-effects analysis (ICON, Hanover, MD, US) • Perl Speaks NONMEM® (version 4.8.1) (Department of Pharmaceutical Biosciences, Uppsala University, Uppsala,Sweden), R (version 4.0.0 or higher) • NONMEM analyses were run on a grid of Intel Xeon servers running the CentOS 7 Linux with Open Grid Scheduler, GNU Fortran Compiler (version 4.8.5).	Acceptable.
Model Structure	• A two-compartment model combined with sequential zero- and first-order absorption and first-order elimination. • Random effects included inter-individual variability (IIV) on the apparent clearance (CL/F), the apparent central volume of distribution (Vc/F), and duration of the zero-order input (D1) on the F.	Acceptable.
Model Parameter Estimates	*Table 5-6*	The table and figure numbers in this table refer to applicants' population PK and E-R analysis report (tonc-pmx-tas-120-1718-002) , and not tables and figures in current assessment aid.
Uncertainty and Variability (RSE, IIV, Shrinkage, Bootstrap)	• Residual error was modelled with a proportional error structure stratified by subject status. The residual error was estimated to be 39.3% for healthy	Acceptable.

	subjects and 48.0% for patients. The shrinkage on residual error was 6.54%. • The shrinkage on IIV and proportional residual error was within reasonable range. Median shrinkage for IIV on CL/F of 23%, IIV on D_1 of 18%, and IIV on F of 19% and higher shrinkage of 37% for Vc/F were noted. Due to the large shrinkage on Vc/F, covariate relationships for Vc/F should be interpreted with caution.	
BLQ for Parameter Accuracy	• If more than 15% of post-dose observations over the entire study population were BLQ, likelihood-based approaches to handle these BLQ observations would have been considered. • 781 (10.2%) post-dose samples with futibatinib concentration BLQ was less than 15%.	Acceptable.
GOF, VPC	• Figure 5-3 • Figure 5-4	See above.
Significant Covariates and Clinical Relevance	Figure 5-5	See above.
Analysis Based on Simulation (optional)	• Table 5-7 • Table 5-8	See above.
Labeling Language	**Description**	**Acceptability [FDA's comments]**
12.3 PK	Specific Populations No clinically meaningful differences in the systemic exposure of futibatinib were observed based on age (18 - 82 years), sex, race/ (b) (4), body weight (36 - 152 kg), mild to moderate renal impairment, or mild hepatic impairment. The effect of severe renal impairment, renal dialysis in end-stage renal disease, or moderate or severe hepatic impairment on futibatinib exposure is unknown.	Acceptable.

Table 5-6: Parameters of the Final TAS-120 PPK Model (Run085)
Table 5-7: Model-Predicted Exposure Metrics after 20 mg QD in Patients (N=203)
Table 5-8: Summary of Model-Predicted Steady-State TAS-120 Exposure for Patients Receiving 20 mg QD (N=203) Stratified for Subgroups of Interest
Figure 5-3: GOF Diagnostics of the TAS-120 Final Model (Run085)
Figure 5-4: pcVPC for the TAS-120 Final Model (Run085)
Figure 5-5: Forest Plot of Covariate Effects on Drug Exposure

The FDA's Assessment:

Demographic data and laboratory values for subjects in each of the studies are shown in Table 70 and Table 71 below.

Table 70: Summary of Baseline Continuous Covariates by Study

Covariate Statistics	Study TAS-120-102 N=17	Study TAS-120-103 N=40	Study TAS-120-104 N=20	Study TAS-120-105 N=24	Study TAS-120-107 N=48	Study TAS-120-101 N=279	Study 10059010 N=39	Study 10059020 N=24	Overall N=491
Age (y)									
Mean (SD)	41.5 (9.77)	40.5 (10.3)	39.5 (10.3)	39.2 (9.45)	38.6 (10.5)	56.2 (12.7)	61.3 (12.0)	30.5 (5.26)	50.3 (14.7)
Median [Min–Max]	44.0 [25.0–55.0]	44.0 [19.0–55.0]	41.0 [20.0–54.0]	37.5 [23.0–54.0]	40.0 [20.0–55.0]	58.0 [18.0–82.0]	64.0 [27.0–79.0]	30.5 [22.0–38.0]	51.0 [18.0–82.0]
Body weight (kg)									
Mean (SD)	77.1 (15.5)	76.6 (11.3)	71.7 (14.4)	88.4 (11.2)	77.3 (13.2)	73.0 (19.9)	58.3 (10.6)	62.3 (6.08)	72.9 (17.9)
Median [Min–Max]	77.7 [57.8–110]	75.9 [55.1–106]	71.1 [43.8–95.2]	88.8 [65.5–111]	76.8 [52.2–106]	69.0 [36.0–152]	55.3 [39.7–81.3]	62.3 [53.3–77.7]	70.5 [36.0–152]
CLCR (mL/min)									
Mean (SD)	107 (26.9)	120 (24.8)	115 (19.5)	129 (21.9)	126 (25.3)	99.9 (39.7)	86.3 (30.8)	114 (16.2)	106 (36.0)
Median [Min–Max]	92.5 [70.1–161]	116 [77.6–176]	117 [84.7–169]	123 [91.6–180]	121 [76.8–206]	92.5 [37.8–353]	78.2 [33.6–184]	112 [87.3–148]	103 [33.6–353]
Body surface area (m^2)									
Mean (SD)	1.91 (0.252)	1.86 (0.187)	1.76 (0.211)	2.07 (0.162)	1.87 (0.199)	1.81 (0.246)	1.61 (0.168)	1.72 (0.104)	1.82 (0.237)
Median [Min–Max]	1.93 [1.58–2.45]	1.85 [1.41–2.36]	1.73 [1.38–2.12]	2.07 [1.67–2.45]	1.86 [1.47–2.34]	1.79 [1.28–2.68]	1.60 [1.31–1.97]	1.74 [1.55–1.99]	1.80 [1.28–2.68]
Albumin (g/L)									
Mean (SD)	44.4 (2.50)	46.6 (2.51)	45.9 (3.18)	48.5 (2.54)	46.1 (3.00)	38.9 (4.97)	39.4 (5.55)	47.0 (1.98)	41.6 (5.67)
Median [Min–Max]	45.0 [39.0–48.0]	47.0 [42.0–53.0]	46.0 [37.0–52.0]	48.0 [43.0–52.0]	46.0 [36.0–51.0]	40.0 [21.0–50.0]	41.0 [27.0–51.0]	47.0 [43.0–51.0]	42.0 [21.0–53.0]
ALT (U/L)									
Mean (SD)	20.2 (7.54)	17.7 (7.62)	21.5 (12.4)	25.8 (12.9)	22.3 (10.0)	27.7 (20.2)	17.4 (13.2)	19.1 (7.88)	24.5 (17.1)
Median [Min–Max]	20.0 [10.0–34.0]	15.0 [9.00–39.0]	15.5 [7.00–46.0]	22.0 [9.00–56.0]	19.0 [10.0–54.0]	22.0 [5.00–157]	14.0 [6.00–77.0]	17.0 [10.0–37.0]	19.0 [5.00–157]
AST (U/L)									
Mean (SD)	21.5 (5.30)	19.6 (4.56)	20.8 (5.75)	22.8 (6.25)	19.9 (4.78)	40.0 (27.8)	26.7 (14.9)	18.9 (3.79)	32.0 (23.5)
Median [Min–Max]	21.0 [13.0–31.0]	18.0 [13.0–28.0]	20.0 [13.0–34.0]	23.5 [13.0–36.0]	19.0 [12.0–30.0]	30.0 [7.00–169]	24.0 [11.0–71.0]	19.0 [14.0–31.0]	24.0 [7.00–169]
ALP (U/L)									
Mean (SD)	63.6 (14.7)	73.3 (20.0)	73.0 (21.7)	67.3 (9.98)	79.3 (18.8)	188 (209)	352 (192)	196 (49.3)	167 (183)
Median [Min–Max]	60.0 [43.0–87.0]	69.5 [29.0–120]	73.5 [34.0–122]	64.0 [56.0–93.0]	75.0 [40.0–118]	121 [40.0–2260]	285 [173–974]	179 [121–318]	102 [29.0–2260]
Bilirubin (mg/dL)									
Mean (SD)	0.435 (0.200)	0.553 (0.279)	0.495 (0.228)	0.454 (0.144)	0.490 (0.202)	0.614 (0.334)	0.593 (0.254)	0.896 (0.363)	0.590 (0.311)
Median [Min–Max]	0.400 [0.200–0.900]	0.500 [0.200–1.40]	0.400 [0.300–1.00]	0.500 [0.200–0.700]	0.500 [0.200–1.10]	0.500 [0.100–2.00]	0.580 [0.210–1.27]	1.00 [0.300–1.70]	0.500 [0.100–2.00]

Source: Table 5-2 in PopPK and ER Report TONC-PMX-TAS120-1718 (\\CDSESUB1\evsprod\nda214801\0001\m5\53-clin-stud-rep\533-rep-human-pk-stud\5335-popul-pk-stud-rep\tonc-pmx-tas-120-1718-002\tonc-pmx-tas-120-1718-002.pdf)

Table 71: Summary of Baseline Categorical Covariates by Study

Covariate Category	Study TAS-120-102 N=17	Study TAS-120-103 N=40	Study TAS-120-104 N=20	Study TAS-120-105 N=24	Study TAS-120-107 N=48	Study TAS-120-101 N=279	Study 10059010 N=39	Study 10059020 N=24	Overall N=491
Sex									
Male	11 (64.7%)	18 (45.0%)	5 (25.0%)	22 (91.7%)	28 (58.3%)	122 (43.7%)	25 (64.1%)	24 (100%)	255 (51.9%)
Female	6 (35.3%)	22 (55.0%)	15 (75.0%)	2 (8.3%)	20 (41.7%)	157 (56.3%)	14 (35.9%)	0 (0%)	236 (48.1%)
Subject status									
Healthy	17 (100%)	40 (100%)	20 (100%)	24 (100%)	48 (100%)	0 (0%)	0 (0%)	24 (100%)	173 (35.2%)
Patients	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	279 (100%)	39 (100%)	0 (0%)	318 (64.8%)
Race									
White	11 (64.7%)	34 (85.0%)	16 (80.0%)	16 (66.7%)	42 (87.5%)	165 (59.1%)	0 (0%)	0 (0%)	284 (57.8%)
Black or African American	6 (35.3%)	4 (10.0%)	3 (15.0%)	5 (20.8%)	5 (10.4%)	12 (4.3%)	0 (0%)	0 (0%)	35 (7.1%)
Asian	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	44 (15.8%)	39 (100%)	24 (100%)	107 (21.8%)
American Indian or Alaska Native	0 (0%)	1 (2.5%)	1 (5.0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	2 (0.4%)
Native Hawaiian or other Pacific Islander	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	2 (0.7%)	0 (0%)	0 (0%)	2 (0.4%)
Others	0 (0%)	1 (2.5%)	0 (0%)	3 (12.5%)	1 (2.1%)	2 (0.7%)	0 (0%)	0 (0%)	7 (1.4%)
Missing	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	54 (19.4%)	0 (0%)	0 (0%)	54 (11.0%)
FGFR mutation									
No	17 (100%)	40 (100%)	20 (100%)	24 (100%)	48 (100%)	3 (1.1%)	30 (76.9%)	24 (100%)	206 (42.0%)
Yes	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	253 (90.7%)	9 (23.1%)	0 (0%)	262 (53.4%)
Missing	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	23 (8.2%)	0 (0%)	0 (0%)	23 (4.7%)
Formulation									
Tablet	17 (100%)	40 (100%)	20 (100%)	24 (100%)	48 (100%)	191 (68.5%)	23 (59.0%)	12 (50.0%)	375 (76.4%)
Capsule	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	88 (31.5%)	16 (41.0%)	12 (50.0%)	116 (23.6%)
Dose (mg)									
4	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	4 (1.4%)	0 (0%)	0 (0%)	4 (0.8%)
8	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	11 (3.9%)	1 (2.6%)	0 (0%)	12 (2.4%)
12	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	1 (0.4%)	0 (0%)	0 (0%)	1 (0.2%)
16	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	33 (11.8%)	4 (10.3%)	0 (0%)	37 (7.5%)
20	17 (100%)	40 (100%)	20 (100%)	24 (100%)	23 (47.9%)	183 (65.6%)	7 (17.9%)	24 (100%)	338 (68.8%)
24	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	17 (6.1%)	1 (2.6%)	0 (0%)	18 (3.7%)
36	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	3 (1.1%)	3 (7.7%)	0 (0%)	6 (1.2%)
56	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	3 (1.1%)	7 (17.9%)	0 (0%)	10 (2.0%)
80	0 (0%)	0 (0%)	0 (0%)	0 (0%)	25 (52.1%)	5 (1.8%)	6 (15.4%)	0 (0%)	36 (7.3%)
120	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	4 (1.4%)	4 (10.3%)	0 (0%)	8 (1.6%)
160	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	8 (2.9%)	6 (15.4%)	0 (0%)	14 (2.9%)
200	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	7 (2.5%)	0 (0%)	0 (0%)	7 (1.4%)
ECOG performance status									
0	17 (100%)	40 (100%)	20 (100%)	24 (100%)	48 (100%)	102 (36.6%)	27 (69.2%)	24 (100%)	302 (61.5%)
1	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	177 (63.4%)	12 (30.8%)	0 (0%)	189 (38.5%)
Regimen									
SD	17 (100%)	40 (100%)	20 (100%)	0 (0%)	48 (100%)	0 (0%)	0 (0%)	24 (100%)	149 (30.3%)
QD	0 (0%)	0 (0%)	0 (0%)	24 (100%)	0 (0%)	237 (84.9%)	10 (25.6%)	0 (0%)	271 (55.2%)
QOD/TIW	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	42 (15.1%)	29 (74.4%)	0 (0%)	71 (14.5%)
Renal function									
Normal	12 (70.6%)	36 (90.0%)	19 (95.0%)	24 (100%)	47 (97.9%)	153 (54.8%)	14 (35.9%)	23 (95.8%)	328 (66.8%)
Mild impairment	5 (29.4%)	4 (10.0%)	1 (5.0%)	0 (0%)	1 (2.1%)	95 (34.1%)	20 (51.3%)	1 (4.2%)	127 (25.9%)

Covariate Category	Study TAS-120-102 N=17	Study TAS-120-103 N=40	Study TAS-120-104 N=20	Study TAS-120-105 N=24	Study TAS-120-107 N=48	Study TAS-120-101 N=279	Study 10059010 N=39	Study 10059020 N=24	Overall N=491
Moderate impairment	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	31 (11.1%)	5 (12.8%)	0 (0%)	36 (7.3%)
Hepatic function									
Normal	17 (100%)	40 (100%)	20 (100%)	24 (100%)	48 (100%)	226 (81.0%)	36 (92.3%)	21 (87.5%)	432 (88.0%)
Mild impairment	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	50 (17.9%)	3 (7.7%)	3 (12.5%)	56 (11.4%)
Moderate impairment	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	3 (1.1%)	0 (0%)	0 (0%)	3 (0.6%)
Strong CYP3A and P-gp inhibitor*									
Without inhibitor	17 (100%)	40 (100%)	20 (100%)	24 (100%)	48 (100%)	274 (97.8%)	38 (97.4%)	24 (100%)	485 (98.6%)
With inhibitor	0 (0%)	20 (50%)	0 (0%)	0 (0%)	0 (0%)	8 (2.9%)	1 (2.6%)	0 (0%)	29 (5.89%)
Strong CYP3A and P-gp inducer*									
Without inducer	17 (100%)	40 (100%)	20 (100%)	24 (100%)	48 (100%)	278 (99.6%)	38 (97.4%)	24 (100%)	489 (99.4%)
With moderate inducer	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	1 (0.4%)	1 (2.6%)	0 (0%)	2 (0. 407%)
With strong inducer	0 (0%)	20 (50%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	20 (4.07%)
Food status*									
Fasted	16 (94.1%)	40 (100%)	20 (100%)	24 (100)	48 (100%)	279 (100%)	39 (100%)	24 (100%)	490 (99.6%)
Fed	17 (100%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	00 (0%)	17 (3.46%)

Source: Table 5-3 in PopPK and ER Report TONC-PMX-TAS120-1718 (\\CDSESUB1\evsprod\nda214801\0001\m5\53-clin-stud-rep\533-rep-human-pk-stud\5335-popul-pk-stud-rep\tonc-pmx-tas-120-1718-002\tonc-pmx-tas-120-1718-002.pdf)

In applicant's final PopPK model, study effect was included as a covariate for bioavailability (F), given the lack of physiological explanation, FDA requested applicant to conduct a sensitivity analysis to compare the results with and without studies as a covariate for bioavailability. The comparison of the parameters obtained from the final model and the sensitivity analysis model was presented in Table 73. Changes in parameter estimates were generally minimal, except for CL/F, Vc/F, Vp/F and Q/F, where 25.4-26.8% differences were observed after removing the study effect. Predicted exposures obtained from the final model and the sensitivity analysis was compared to evaluate effect of the changes in parameter estimates, results are shown in Table 74. Overall, the results from the sensitivity analysis showed that inclusion/exclusion of the study effect in the PopPK model have no meaningful effect on model performance, exposure estimation and therefore no meaningful effect on exposure-response analyses.
Model-predicted TAS-120 exposures for patients receiving 20 mg QD were compared among specific subgroups of interest, such as renal impairment and hepatic impairment, as shown in Table 72. Overall, mild/moderate renal impairment and mild hepatic impairment have no clinically meaningful effect on PK of futibatinib, which is consistent with applicant's conclusion.

Table 72: Summary of Model-Predicted Steady-State TAS-120 Exposure for Patients Receiving 20 mg QD Stratified by Organ Functions

Subgroup	N	Statistic	AUCss (ng•h/mL)	Cmax,ss (ng/mL)	Cmin,ss (ng/mL)

Hepatic impairment					
Normal	167	GM (95% CI)	802 (747, 859)	144 (133, 155)	1.7(1.5, 2.0)
Mild	35	GM (95% CI)	756 (672, 849)	149(133, 168)	1.4(1.1,1.8)
Moderate	1	GM (95% CI)	984	204	1.6
Renal Impairment					
Normal	104	GM (95% CI)	749(688, 814)	137(126,149)	1.5(1.3,
Mild	72	GM (95% CI)	839(760,928)	157(140,178)	1.7(1.4,2.1)
Moderate	27	GM (95% CI)	857(716,1024)	143(118, 174)	2.3(1.5,3.4)

Note: Hepatic impairment was classified by NCI-ODWG criteria, Renal impairment was classified based on CLCr.
Source: Reviewer generated after excluding study effect in the final PopPK model.

Table 73: Comparison of Parameters of the Final TAS-120 PPK Model (Run085) to the Parameters from the Sensitivity Analysis Model (Run085s)

Parameter	Final Model (run085)		Sensitivity Analysis Model (Run085s)		Difference in %[c] (Estimate/IIV)
	Estimate (RSE[a] (%))	IIV[b] (CV%) (RSE (%))	Estimate (RSE[a] (%))	IIV[b] (CV%) (RSE (%))	
Fixed effects					
CL/F (L/h)	21.2 (7.46)	28.9 (30.2)	26.7 (2.90)	25.3 (31.3)	25.9 / -12.5
V_c/F (L)	66.0 (6.09)	28.4 (39.5)	83.2 (2.80)	26.5 (36.5)	26.1 / -6.69
V_p/F (L)	16.4 (12.0)		20.8 (7.90)		26.8
Q/F (L/h)	1.18 (14.5)		1.48 (9.20)		25.4
k_a, fasted state (h)	1.55 (4.46)		1.56 (3.90)		0.645
D_1 (h)	0.885 (4.98)	128.2 (11.1)	0.885 (4.20)	127.2 (10.5)	0 / -0.55
F	1 (fixed)	41.8 (15.2)	1 (fixed)	48.6 (10.4)	- / 16.3
Residual error					
Proportional residual error - HV (%)	39.3 (2.79)		39.4 (2.60)		0.254
Proportional residual error - PAT (%)	48.0 (2.70)		48.0 (2.70)		0
Covariate effects					
F relative when on CYP3A4 Inhibitors	0.394 (8.26)		0.400 (8.40)		1.52
k_a, fed state (/h)	0.275 (25.7)		0.274 (19.4)		-0.364
F relative when on CYP3A4 Inducers	1.30 (5.62)		1.31 (5.70)		0.769
F relative for study 10059020	0.428 (12.2)		-		-
F relative for study TAS-120-101, 102, 107	0.768 (7.23)		-		-
Albumin effect on CL/F	1.01 (11.6)		0.982 (11.8)		-2.77
Dose ≥36 mg effect on CL/F	-0.0951 (33.1)		-0.106 (33.3)		11.5
Dose ≥36 mg effect on V_c/F	0.441 (11.5)		0.420 (17.9)		-4.76
Body weight effect on V_c/F	0.367 (24.6)		0.323 (26.5)		-12.0

Source: Response to Information Request received on 12/08/2021.

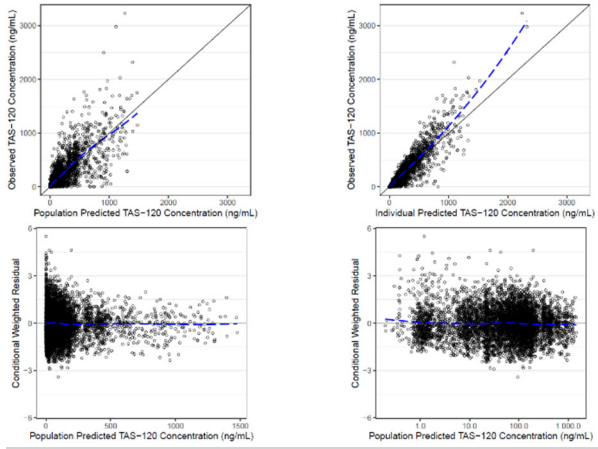
Table 74: Model-Predicted Exposure Metrics after 20 mg QD in Patients (N=203) Based on the Final TAS-120 PPK Model (Run085) and the Sensitivity Analysis Model (Run085s)

Exposure Metric	Final Model (run085) Geometric mean (gCV%)	Sensitivity Analysis Model (Run085s) Geometric mean (gCV%)
Cmin Day 1 (ng/mL)	1.39 (121)	1.39 (120)
Cmax Day 1 (ng/mL)	142 (50.1)	143 (51.8)
AUC Day 1 (ng•h/mL)	769 (43.5)	770 (45.4)
Cav Day 1 (ng/mL)	32.0 (43.5)	32.1 (45.4)
Cmin,ss (ng/mL)	1.68 (117)	1.68 (116)
Cmax,ss (ng/mL)	144 (50.3)	145 (52.0)
AUCss (ng•h/mL)	790 (44.7)	792 (46.5)
Cav,ss (ng/mL)	32.9 (44.7)	33.0 (46.5)

Source: Response to Information Request received on 12/08/2021.

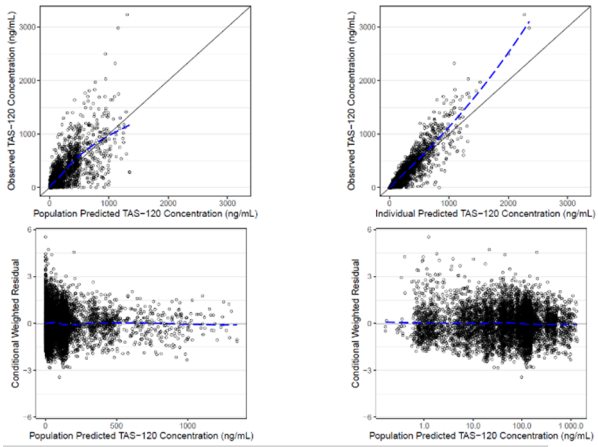
Figure 13: GOF Diagnostics for Futibatinib PPK Model

a: Applicant's Final Model (run085)



Source: Figure 5-3 in PopPK and ER Report TONC-PMX-TAS120-1718

b: Sensitivity Analysis Model (run085s)

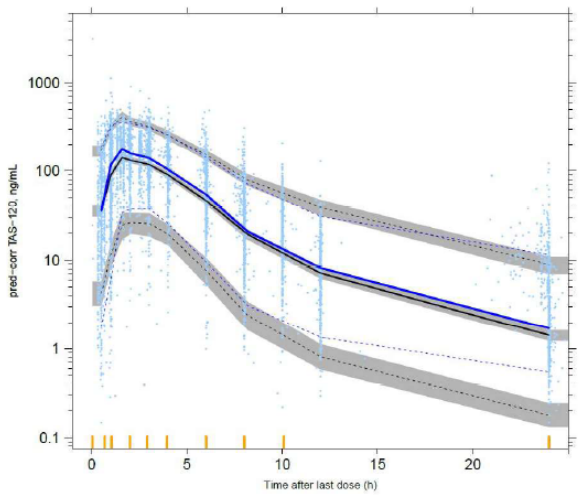


Source: Reviewer generated based on response to Information Request received on 12/08/2021

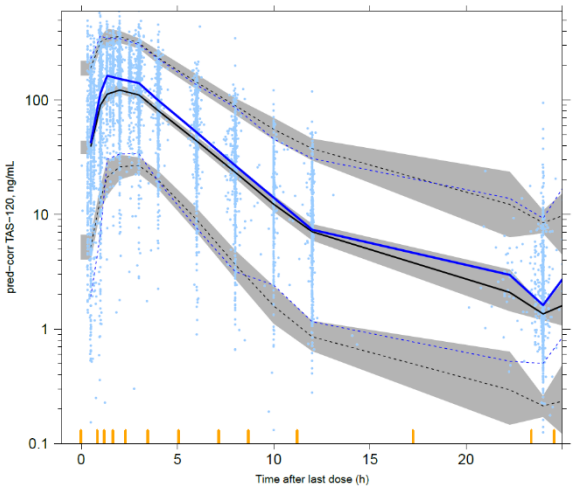
Figure 14: VPC for Futibatinib PPK Model

a: Applicant's Final Model (run085)

b: Sensitivity Analysis Model (run085s)



Source: Figure 5-4 in PopPK and ER Report TONC-PMX-TAS120-1718



Source: Reviewer generated based on response to Information Request received on 12/08/2021

19.5.8 Exposure-Response Analysis

19.5.8.1 ER (efficacy) Executive Summary

The FDA's Assessment:

No significant exposure response relationships were observed for ORR, DCR, DoR, PFS, OS, or change in tumor size (CTS) based on data obtained from a single dose level, 20 mg QD. Interpretation should be taken with caution because of the limited sample size and narrow exposure range from a single dose level (20 mg QD).

19.5.8.2 ER (efficacy) Assessment Summary

The Applicant's Position:

General Information	
Goal of ER analysis	• To characterize E-R efficacy relationships in patients with CCA • To evaluate covariate relationships to explain potential differences in efficacy among subgroups of patients • To integrate the E-R relationships and support dose justification for the treatment of CCA patients based on the PPK and E-R analyses
Study Included	*All efficacy-evaluable CCA patients in the Phase 2 part of StudyTAS-120-101 in whom futibatinib exposures could be estimated*
Endpoint	*Confirmed ORR, DCR, DoR, PFS, OS, CTS (maximum percent change from baseline of target lesion)*

No. of Patients (total, and with individual PK)		*A total of 98 patients in the exposure-efficacy analysis population*
Population Characteristics (Table 5-9)	General	*Age: 58 (22–78)* *Weight: 69.9 kg (43.3–152)* *Sex: 44 (44.9%) male, 54 (55.1%) female* *Race:* *48 (49.0%) White* *8 (8.2%) Black* *29 (29.6%) Asian* *1 (1.0%) Pacific Islander* *12 (12.2%) Unknown*
	Pediatrics (if any)	*Not Applicable*
Dose(s) Included		*20 mg QD*
Exposure Metrics Explored (range)		*C_{min}, C_{max}, C_{av}, and AUC on Cycle 1 Day 1 and at steady-state.* *Table 8-7 (Summary of Covariates)*
Covariates Evaluated		*Baseline body weight, age (<65 and ≥65 years), sex, race, and ECOG status*

Final Model Parameters	**Summary**	**Acceptability [FDA's comments]**
Model Structure	*For ORR and DCR, a linear logistic regression model:* *logit(Prob) = Intercept + Slope × Exposure* *For PFS, DoR, and OS, a Cox proportional-hazards regression model:* *$h(t) = h_0(t) \times exp(Slope \times Exposure)$* *For CTS, linear or inhibitory Emax models:* *Maximum %CfB = Intercept + Slope × Exposure* *Maximum %CfB = $I_0 \times (1 - Imax \times Exposure/(Exposure + IC_{50}))$*	Acceptable.
Model Parameter Estimates	*Table 5-12*	The table and figure numbers in this table refer to applicants' population PK and E-R analysis report (tonc-pmx-tas-120-1718-002) , and not tables and figures in current assessment aid.
Model Evaluation	*Table 5-13*	See above.
Covariates and Clinical Relevance	*No significant covariate*	Acceptable.
Simulation for Specific Population	*Table 5-14*	See above.
Visualization of E-R relationships	*Figure 8-19* *Figure 8-20* *Figure 8-21* *Figure 8-22* *Figure 8-23* *Figure 8-24*	See above.

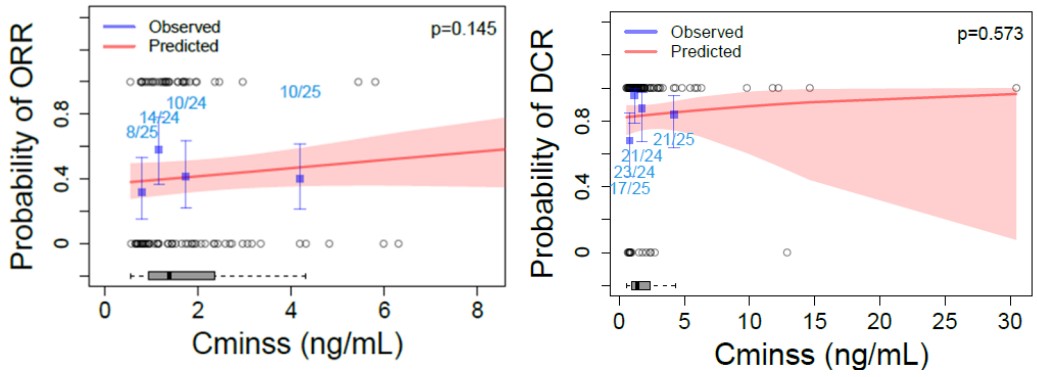
Overall Clinical Relevance for ER	*There were no statistically significant exposure-efficacy relationships observed for ORR, DCR, DoR, OS, PFS, or CTS and any PK exposure metric (C_{min}, C_{max}, C_{av}, and AUC on Cycle 1 Day 1 or at steady-state), although the dose range and subject numbers were limited. However, there was a trend noted toward increasing ORR with increasing $C_{min,ss}$ (P=0.145).*	Acceptable.
Labeling Language	**Description**	**Acceptability [FDA's comments]**
12.2 Pharmacodynamics	*No specific description*	

Table 5-14: Model-Predicted ORR by Dose
Table 8-7: Summary of Covariates by TAS-120 $C_{min,ss}$ Quartiles in the Exposure-Efficacy Dataset Figure 8-19: Model-Estimated Exposure-ORR Relationship
Figure 8-20: Model-Estimated Exposure-DCR Relationship
Figure 8-21: Kaplan-Meier Curves for DoR by Quartile of TAS-120 Exposures
Figure 8-22: Kaplan-Meier Curves for PFS by Quartile of TAS-120 Exposures
Figure 8-23: Kaplan-Meier Curves for OS by Quartile of TAS-120 Exposures
Figure 8-24: Exposure-Change in Tumor Size Relationship

The FDA's Assessment:

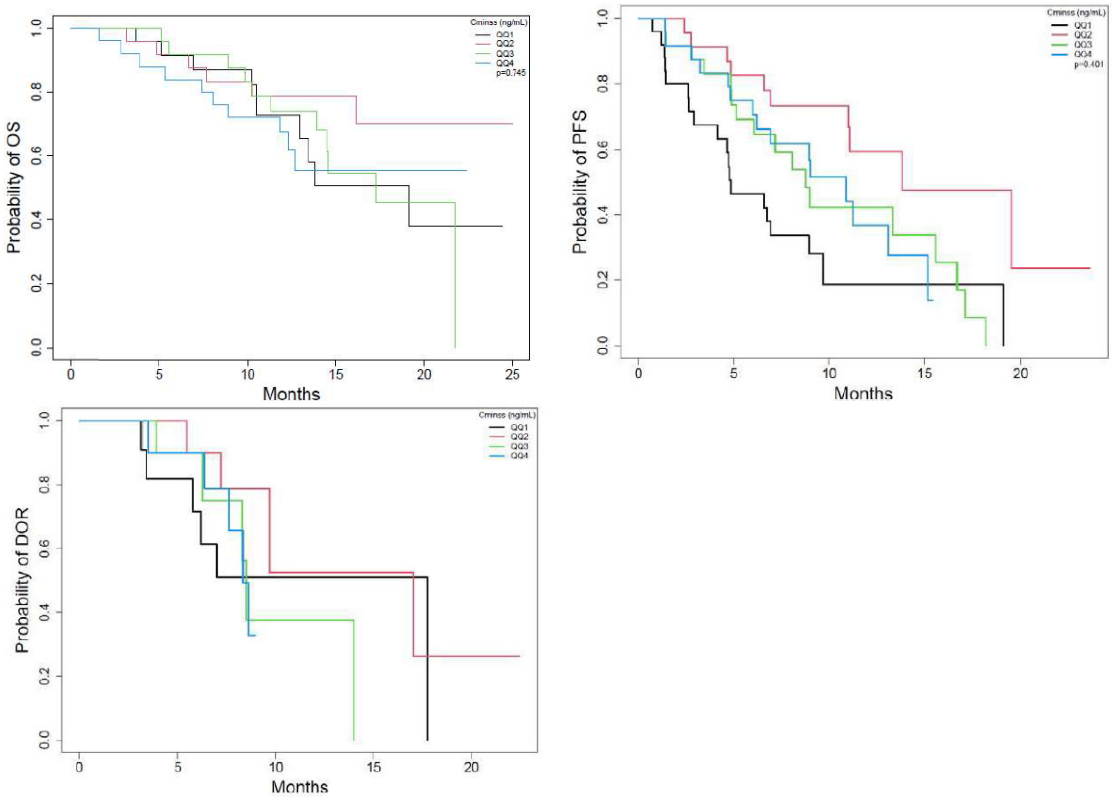
FDA generally agrees with applicant's assessment. There were no statistically significant exposure-efficacy relationships observed for ORR, DCR, DoR, OS, PFS, or CTS and any PK exposure metric, see Figure 15, Figure 16 and Figure 17 below. Of note, in applicant's ER analysis, dose interruptions and reductions were not taken into consideration, exposures at steady state were comparable to that in cycle 1 due to the minimal accumulations following 20 mg QD dosing regimen. Overall, the ER analysis for efficacy was considered exploratory and the flat relationship should be interpreted with caution as it was derived based on the exposure range from a single dosing regimen 20 mg QD.

Figure 15: Model-predicted Probability of Overall Response and Disease Control Rate versus Exposures



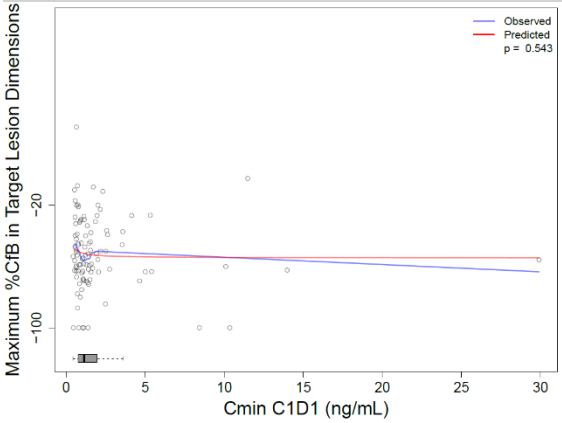
Source: Figure 5-8 and 5-10 in PopPK and ER Report TONC-PMX-TAS120-1718 (re-plotted by reviewer) (\\CDSESUB1\evsprod\nda214801\0001\m5\53-clin-stud-rep\533-rep-human-pk-stud\5335-popul-pk-stud-rep\tonc-pmx-tas-120-1718-002\tonc-pmx-tas-120-1718-002.pdf)

Figure 16: Probability of OS, PFS and DOR by Exposure Quartiles of Cmin,ss



Source: Figure 5-11, 5-12 and 5-13 in PopPK and ER Report TONC-PMX-TAS120-1718 (\\CDSESUB1\evsprod\nda214801\0001\m5\53-clin-stud-rep\533-rep-human-pk-stud\5335-popul-pk-stud-rep\tonc-pmx-tas-120-1718-002\tonc-pmx-tas-120-1718-002.pdf)

Figure 17: Retationship between Change in Tumor Size (CTS) and Cmin,ss



Source: Figure 5-14 in PopPK and ER Report TONC-PMX-TAS120-1718 (\\CDSESUB1\evsprod\nda214801\0001\m5\53-clin-stud-rep\533-rep-human-pk-stud\5335-popul-pk-stud-rep\tonc-pmx-tas-120-1718-002\tonc-pmx-tas-120-1718-002.pdf)

Comparison of 20 mg QD vs 16 mg QD

It should be noted that, in study TAS-120-101, after the determination of MTD at 20 mg QD in dose escalation cohort, two dose levels 16 mg QD and 20 mg QD were selected and evaluated in the subsequent dose expansion cohort. However, it was unclear in the original submission that why 20 mg QD was selected in the pivotal study, as efficacy data was only provided for 20 mg QD. FDA requested applicant to clarify the rationales for the selection of 20 mg QD during the NDA review.

Based on applicant's response to information request received on 04/11/2022, the objective response data for the 19 and 42 iCCA patients treated at 16 and 20 mg QD, respectively, were not considered in the dose selection since these data only became available in July 2019, whereas the decision to use 20 mg QD dose for further clinical investigations was made in October 2017. A comparison of the ORR at 16 mg and 20 mg QD in the expansion cohorts is shown in Table 75.

Table 75: ORR at 16 mg and 20 mg QD in the Expansion Cohort in Study TAS-120-101

	16 mg QD (iCCA/FGFR2, N=19)	20 mg QD (iCCA/FGFR2, N=42)
ORR% (95% CI)[a]	32% (13, 57)	17% (7, 31)

[a] ORR was evaluated by Independent Assessors.

Applicant further evaluated the ORR in the two dose groups, in subsets of patients who met criteria established for the intended pivotal Phase 2 target population. The findings were consistent with the broader population with higher ORR at 16 mg QD.

- Of the 19 iCCA patients treated at the 16-mg QD dose in the Phase 1 dose expansion portion, there were 11 patients who were consistent with the intended Phase 2 patient population.
- Of the 42 iCCA pts with FGFR2 rearrangement treated at the 20-mg QD dose in Phase 1 dose expansion portion, there were 19 patients who were consistent with the intended Phase 2 patient population.

A comparison of the ORR in this subset of patients at 16 mg and 20 mg QD in the expansion cohorts, as well as ORR observed in pivotal phase 2 trial are shown in Table 76.

Table 76: ORR at 16 mg and 20 mg QD in the expansion cohort in study TAS-120-101

	16 mg QD	20 mg QD	20 mg QD

	(iCCA/FGFR2, & meet criteria of pivotal trial, N=11)	(iCCA/FGFR2 & meet criteria of Pivotal trial, N=19)	(Pivotal trial, iCCA/FGFR2, N=103)
ORR % (95% CI) [a]	36% (15, 65)	21% (6, 46)	42% (32, 52)

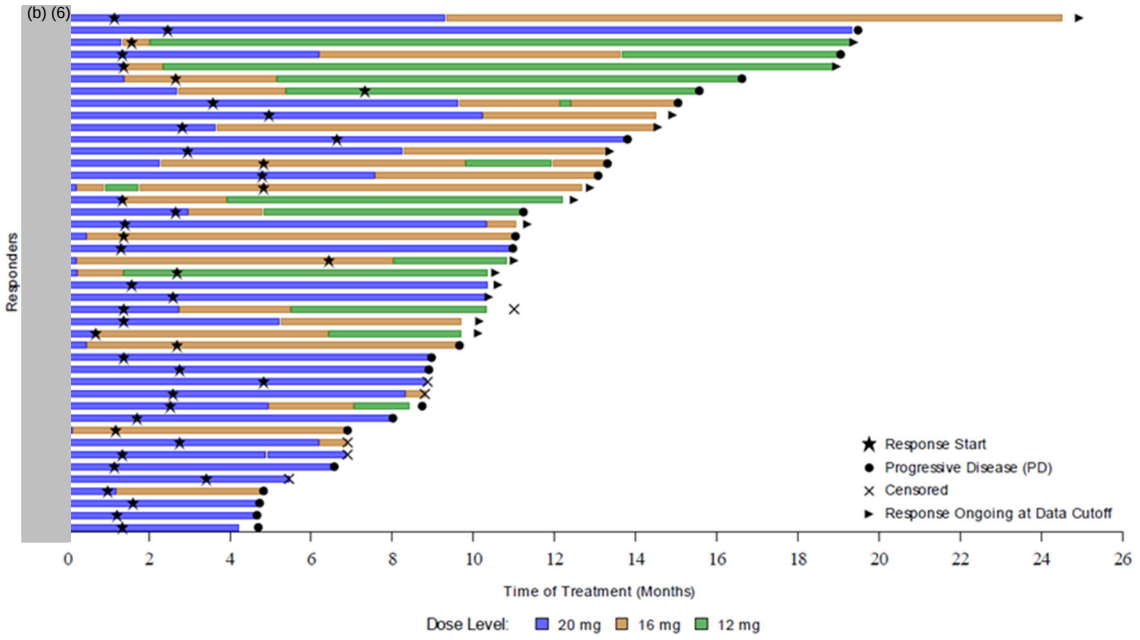
[a] ORR was evaluated by Independent Assessors.

A further ER analysis for ORR based on data from 16 and 20 mg QD also showed a flat relationship; however, such analysis is considered exploratory and should be interpreted with caution due to the differences in sample size between the two dose cohorts.

Dose Distribution at the Time of First Recorded Response

A swimmer plot of treatment exposure and treatment duration presented for responders (N=43) in pivotal phase 2 portion of study TAS-120-101 is shown in Figure 18 below. The median time to first recorded response is 2.5 month (range 0.7 to 7.4 months).

Figure 18: Swimmer Plot Showing Dose Distribution at the Time of Response through Duration of Response for Responders per RECIST 1.1 Assessed by IRC (N=43)



In addition, the distribution of the actual administered dose(s) at the time of first recorded response showed that majority of patients (72.1%) were on 20 mg dose when first recorded as responders, see Table 77.

Table 77: Dose Distribution at the Time of First Recorded Response in Pivotal Phase 2 of Study TAS-120-101

Endpoint	20 mg	16 mg	12 mg
ORR n(%)	31 (72.1%)	10 (23.3%)	2 (4.7%)

Source: Figure 4 in response to FDA information request received on 02/07/2022

19.5.8.3 ER (safety) Executive Summary

The FDA's Assessment:

Positive exposure response relationships were observed for multiple safety endpoints, such as any grade and Grade ≥3 hyperphosphatemia, any grade nail disorders, any grade retinal disorders, any grade retinal detachment, any AE Grade ≥3, SAE, AEs leading to discontinuation of study drug, AEs leading to dose reduction and AEs leading to study drug interruption. The ER relationship for hyperphosphatemia maybe confounded by the common use of phosphate lowering agents.

19.5.8.4 ER (safety) Assessment Summary

The Applicant's Position:

General Information		
Goal of ER analysis		• To characterize E-R safety relationships in patients with advanced solid tumors • To evaluate covariate relationships to explain potential differences in safety among subgroups of patients • To integrate the E-R relationships and support dose justification for the treatment of CCA patients based on the PPK and E-R analyses
Study Included		*Studies 10059010 and TAS-120-101*
Population Included		*All safety-evaluable patients from Studies 10059010 and TAS-120-101 in whom futibatinib exposures could be estimated*
Endpoint		*Major common AE/SAE, AE of interest*
No. of Patients (total, and with individual PK)		*A total of 318 patients in the exposure-safety analysis population including 39 patients from Study 10059010 and 279 patients from Study TAS-120-101*
Population Characteristics (Table 5-19, Table 5-20)	General	*Age: 59 (18–82)* *Weight: 67.0 (36.0–152)* *Sex: 147 (46.2%) Male, 171 (53.8%) Female* *Race:* *165 (51.9%) White* *12 (3.77%) Black or African American* *83 (26.1%) Asian*

		2 (0.629%) Native Hawaiian or other Pacific Islander *2 (0.629%) Other* *54 (17.0%) Unknown* *Dosing schedule: 247 (77.7%) QD, 71 (22.3%) QOD*
	Organ impairment	*Not Applicable*
	Pediatrics (if any)	*Not Applicable*
	Geriatrics (if any)	*223 (70.1%) < 65 yr, 95 (29.9%) ≥ 65 yr*
Dose(s) Included		*QD: 4, 8, 16, 20, and 24 mg* *QOD: 8, 16, 24, 36, 56, 80, 120, 160, and 200 mg*
Exposure Metrics Explored (range)		*C_{min}, C_{max}, C_{av}, and AUC on Cycle 1 Day 1 and at steady-state* *Table 8-12 (Summary of Covariates)* *Table 8-13 (Summary of Covariates)*
Covariates Evaluated		• Baseline body weight, age (<65 and≥65 years), sex, race, diagnosis, and ECOG status • Baseline serum phosphate and calcium (<median value versus ≥median value)

Final Model Parameters	**Summary**	**Acceptability [FDA's comments]**
Model Structure	*For the safety endpoints, a linear logistic regression model* *logit(Prob) = Intercept + Slope × Exposure* *For maximum change from baseline (CfB) in phosphate and calcium, a linear or inhibitory Emax model* *CfB = Intercept + Slope × Exposure* *$CfB = I_0 \times (1 - I_{max} \times Exposure/(Exposure + IC_{50}))$*	Acceptable.
Model Parameter Estimates	*Table 5-25* *Table 5-29* *Table 5-33* *Table 5-37* *Table 5-41* *Table 5-44*	The table and figure numbers in this table refer to applicants' population PK and E-R analysis report (tonc-pmx-tas-120-1718-002) , and not tables and figures in current assessment aid.
Model Evaluation	*Table 5-26* *Table 5-30* *Table 5-34* *Table 5-38* *Table 5-42*	See above.
Covariates and Clinical Relevance	Any grade of hyperphosphatemia: baseline serum phosphate concentration Grade ≥3 hyperphosphatemia: baseline serum phosphate concentration and sex Nail disorder: ECOG score	Acceptable.
Simulation for Specific Population	*Table 5-27* *Table 5-31*	See above.

	Table 5-35 *Table 5-43*	
Visualization of E-R relationships	*Figure 5-26* *Figure 8-28*	See above.
Overall Clinical Relevance for ER	Significant exposure-safety relationships were observed for any grade of hyperphosphatemia and for Grade ≥3 hyperphosphatemia.	See FDA's assessment.
Labeling Language	**Description**	**Acceptability [FDA's comments]**
12.2 Pharmacodynamics	Futibatinib increased serum phosphate levels as a consequence of FGFR inhibition. In patients, serum phosphate increased with increased exposure across the dose range of 4 to 24 mg once daily (0.2 to 1.2 times the recommended dose), with increased risk of hyperphosphatemia with higher futibatinib exposure.	Acceptable.

Table 5-25: Parameters of Exposure-Any Grade of Hyperphosphatemia Final Model
Table 5-26: Numerical Predictive Check of Exposure-Any Grade of Hyperphosphatemia Final Model
Table 5-27: Model-Predicted Mean Probability of Any Grade of Hyperphosphatemia by Dose Group
Table 5-29: Parameters of Exposure-Any Grade of Hyperphosphatemia Final Model
Table 5-30: Numerical Predictive Check of Exposure-Any Grade of Hyperphosphatemia Final Model
Table 5-31: Model-Predicted Mean Probability of Any Grade of Hyperphosphatemia by Dose Group
Table 5-33: Parameters of Exposure-Grade ≥3 Hyperphosphatemia Final Model
Table 5-34: Numerical Predictive Check of Exposure-Grade ≥3 Hyperphosphatemia Final Model
Table 5-35: Model-Predicted Mean Probability of Grade ≥3 Hyperphosphatemia by Dose Group
Table 5-37: Parameters of Exposure-Any Grade of Retinal Disorders Model
Table 5-38: Numerical Predictive Check of Exposure-Any Grade of Retinal Disorder Final Model
Table 5-41: Parameters of Exposure-Any Grade of Nail Disorders Final Model
Table 5-42: Numerical Predictive Check of Exposure - Any Grade of Nail Disorder Final Model
Table 5-43: Model-Predicted Mean Probability of Any Grade of Nail Disorder by Dose Group
Table 5-44: Parameters of Exposure-Response Analysis for Greatest %CfB in Corrected Blood Phosphate and in Corrected Calcium
Table 8-12: Summary of Covariates by TAS-120 AUC_{ss} Quartiles in the Exposure-Safety Dataset - QD
Table 8-13: Summary of Covariates by TAS-120 AUC_{ss} Quartiles in the Exposure-Safety Dataset - QOD
Figure 5-26: Model-Based Exposure-Response Analysis for the Greatest %CfB in Corrected Blood Phosphate and in Corrected Calcium
Figure 8-28: Probability of Any Grade and Grade ≥3 Hyperphosphatemia, Any Grade of Retinal Disorders and Any Grade of Nail Disorders Versus TAS-120 Exposure by Regimen

The FDA's Assessment:

In applicant's exposure response analyses for safety, the two dosing regimens (QOD and QD) were assessed separately, and the following safety endpoints were evaluated:

- Hyperphosphatemia, any grade
- Hyperphosphatemia, Grade ≥3
- Hepatotoxicity, any grade
- Nail Disorders, any grade
- Palmar-plantar erythrodysaesthesia syndrome (PPE), any grade

- Rash, any grade
- Retinal Disorders, any grade
- Phosphate level changes from baseline
- Calcium level changes from baseline

For the QD dosing regimen, significant correlations with futibatinib exposures were identified for Any Grade of Hyperphosphatemia, Grade ≥3 Hyperphosphatemia, Nail Disorders, Phosphate level changes from baseline.

For the QOD dosing regimen, significant correlations with futibatinib exposures were identified for Any Grade of Hyperphosphatemia, Retinal Disorders, Phosphate level changes from baseline.

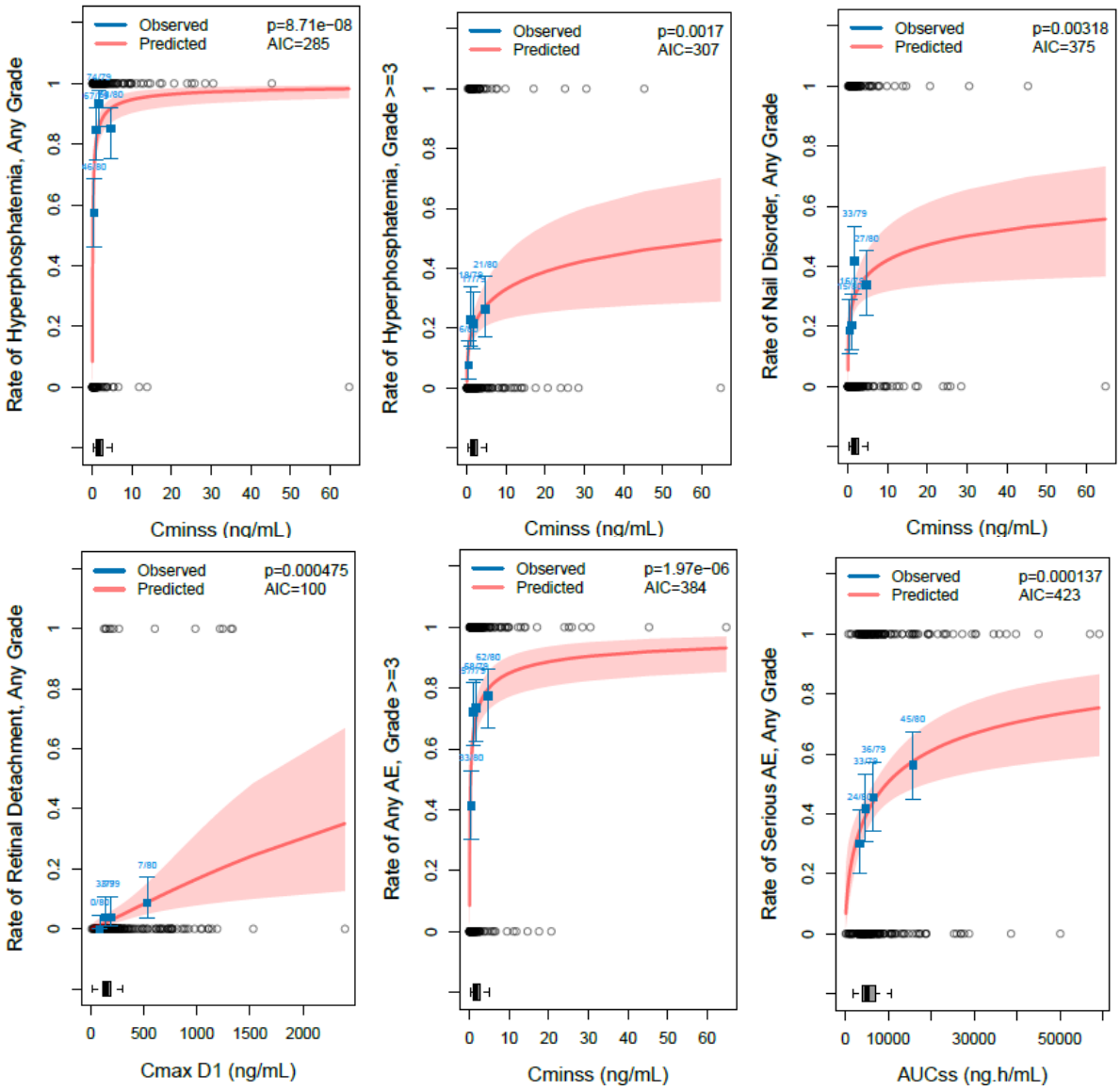
In order to evaluate the ER relationship over a wide range of exposures, QD and QOD dosing regimens were combined, and the following additional safety endpoints were also evaluated during the review:

- Retinal detachment, any grade
- Any AE Grade ≥3
- SAE
- AEs leading to discontinuation of study drug
- AEs leading to dose reduction
- AEs leading to study drug interruption

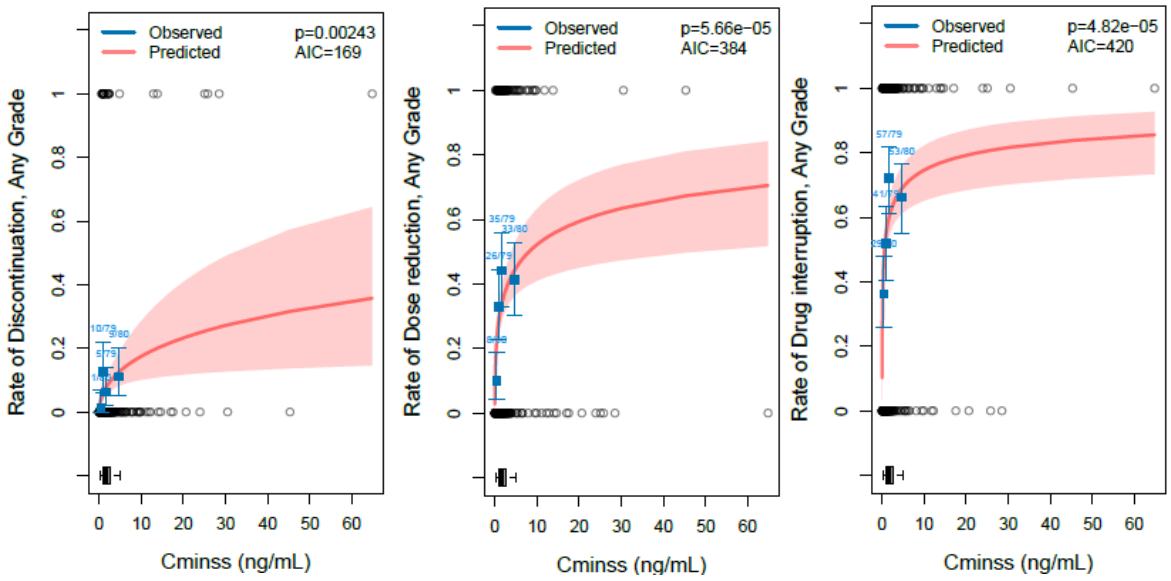
Additional sensitivity analyses based on either QD dosing only or QOD dosing only were conducted. Results showed that increasing futibatinib exposure was found to be associated with increased risk of any AE Grade ≥3, SAE, AEs leading to discontinuation of study drug, AEs leading to dose reduction and AEs leading to study drug interruption, regardless of QD or QOD dosing regimen. For any grade retinal detachment, a positive ER relationship was observed for the pool dataset (QD+QOD) with Cmax as the best predictor; however, no trends were observed for the QD only dataset, possibly due to the low incidence rate of retinal detachment (2.4%) in the QD only dataset. It should be noted that ER analysis for retinal disorders and retinal detachment should be interpreted with caution due to the large number of missing ophthalmic examinations, see details in section 8.2.5.1.

See Figure 19 below demonstrating the statistically significant relationships between the exposure metric and safety endpoints (with the lowest p-value) using the pooled datasets (QD+QOD).

Figure 19: Model-predicted vs. observed relationship of futibatinib exposure and safety endpoints



Disclaimer: In this document, the sections labeled as "Data" and "The Applicant's Position" are completed by the Applicant and do not necessarily reflect the positions of the FDA.



Note: The horizontal boxplot below shows the exposure distribution (where the whiskers represent 1.5 × interquartile range) for the 20 mg QD dose group.
Source: Reviewer generated based on response to FDA information request received on 03/11/2022.

Hyperphosphatemia

Given hyperphosphatemia is an on-target effect of FGFR inhibitors, phosphate-lowering therapies were commonly used. In the pivotal study, TAS-120-101 Phase 2 study part, 96 out of the 103 patients received at least 1 phosphate-lowering treatment, initiation of the first phosphate-lowering therapy occurred at a median of 6.0 days (range: 0, 302) following the start of treatment with futibatinib. Most (88.5%) patients began a phosphate-lowering therapy during the first cycle of futibatinib treatment, with 76.0% and 12.5% of patients starting therapy within 0-7 days and 8-21 days of initiating treatment with futibatinib, respectively.

Due to the frequent use and early initiation of the phosphate-lowering therapies, the identified ER relationship for hyperphosphatemia is likely confounded.

In addition, a time to event analysis was conducted to understand the dose modifications/treatment discontinuations overtime. As shown in Figure 20, the median time to first dose reduction and first dose interruption due to any AE were 6.2 months and 3.9 months, respectively. For the most common AE leading to dose modifications hyperphosphatemia, the dose modifications/treatment discontinuations occurred almost exclusively in the first month of futibatinib treatment, see Figure 21. In addition, the median time to first incidence of any Grade ≥3 AEs including/excluding hyperphosphatemia was 1.4 months (95% CI 0.7, 3.5) and 4.9 months (95% CI 2.9, 6.2), respectively.

Figure 20: Kaplan-Meier Plot of Time to First Dose Reduction, Dose Interruption or Treatment Discontinuation Due to Any AE

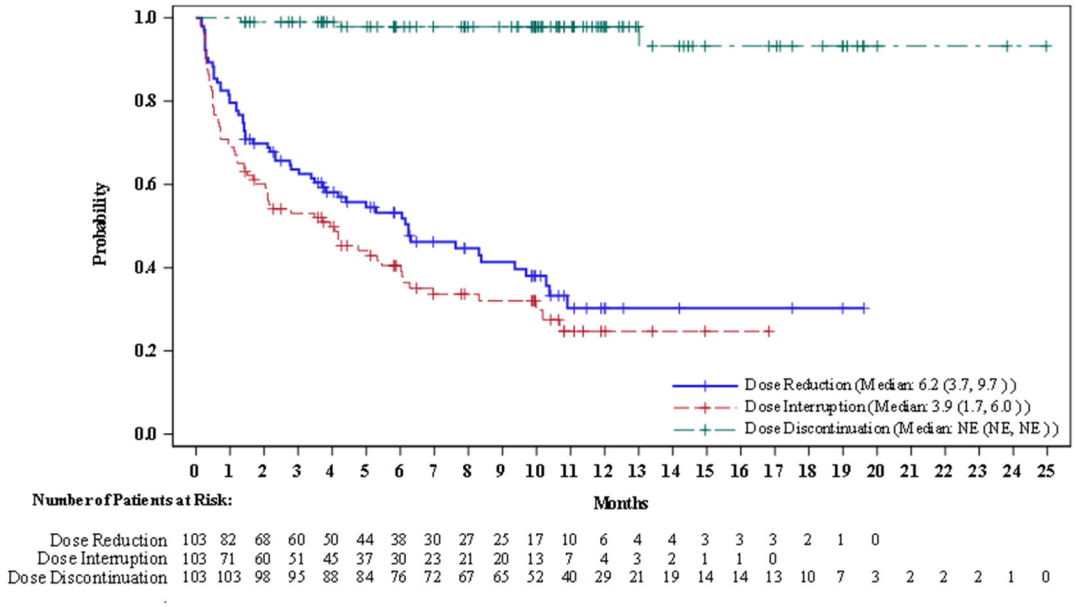
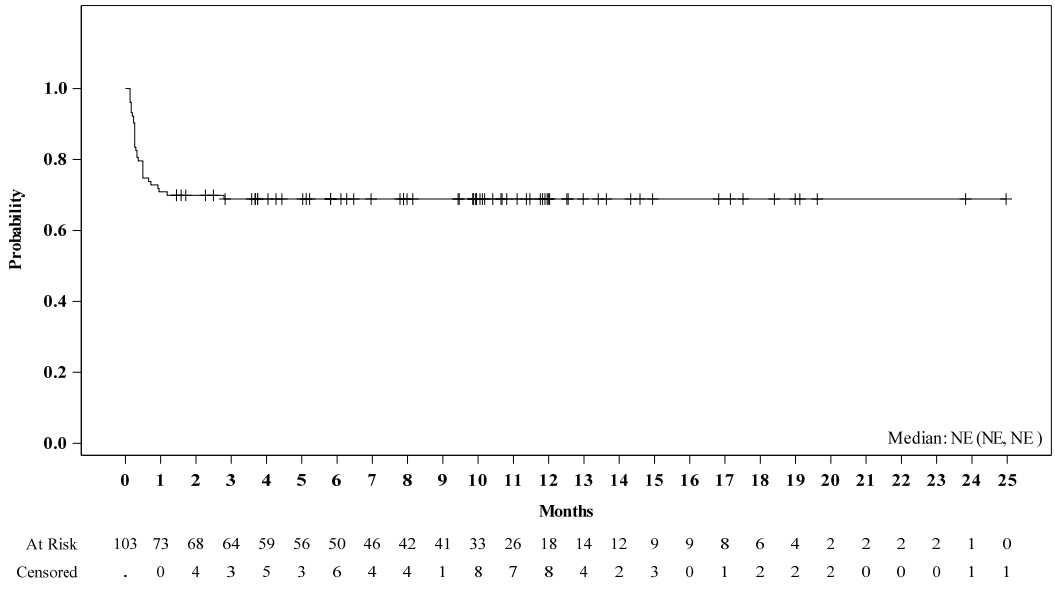


Figure 21: Kaplan-Meier Plot of Time to First Incidence of Hyperphosphataemia Leading to Dose Modification or Treatment Discontinuation



Source: Figure 13 and 8 in response to FDA information request received on 02/07/2022.

19.5.8.5 Overall benefit-risk evaluation based on E-R analyses

The Applicant's Position:
Exposure-response analyses indicated a modest, statistically nonsignificant increase in ORR (<3%) over the 16-24-mg QD dose range with a model predicted ORR of 52% for patients within the highest exposure quartile. Exposure-safety analyses showed a statistically significant exposure-safety relationships for hyperphosphatemia (any grade and Grade ≥3) as a known on-target effect. Nail disorders (any grade) were the only other AESI statistically significant increasing with futibatinib exposures. Acceptable incidence of hyperphosphatemia AEs was observed at a dose of 20 mg QD, while there was a steep increase in Grade ≥3 hyperphosphatemia at the 24-mg QD dose relative to the 20 mg QD dose (51.2% vs. 24.9%).

In conclusion and based on the collective study results, the E-R analyses support 20 mg orally once daily (QD) as the recommended starting dose of futibatinib monotherapy by providing the numerically highest probability of clinical efficacy with a predictable, monitorable, and manageable safety profile and dose adjustments as needed for the management of AEs (i.e. hyperphosphatemia).

The FDA's Assessment:
The exposure response analyses for efficacy were considered exploratory and the identified flat relationship should be interpreted with caution.

20 mg QD is an acceptable dosing regimen with demonstrated efficacy and manageable safety profile in the pivotal study. For majority of the patients (72.1%), first response was recorded while receiving 20 mg QD dosing regimen, and the median time to first recorded response (2.5 months) is shorter than the median time to First Dose Reduction (6.2 month), Dose Interruption (3.9 month) or Treatment Discontinuation (not reached) due to any AE. However, a lower dose level of 16 mg QD also appears efficacious based on efficacy results from expansion cohort in study TAS-120-101. Given the positive exposure response relationship for multiple safety endpoints, including any grade and Grade ≥3 hyperphosphatemia, any grade nail disorders, any grade retinal disorders, any grade retinal detachment, any AE Grade ≥3, SAE, AEs leading to discontinuation of study drug, AEs leading to dose reduction and AEs leading to study drug interruption, a lower dose 16 mg QD may provide a better safety profile.

Signatures
NDA 214801 Assessment Aid

DISCIPLINE	REVIEWER	OFFICE/DIVISION	SECTIONS	AUTHORED/ APPROVED
Nonclinical Division Director	John Leighton	Office of Oncologic Diseases	Sections: 5	___Authored X_Approved
	Signature: John K. Leighton -S Digitally signed by John K. Leighton -S Date: 2022.08.08 15:03:10 -04'00'			
Nonclinical Reviewer	Dubravka Kufrin	Office of Oncologic Diseases	Sections: 5	X Authored X_Approved
	Signature: Denali D. Kufrin -S Digitally signed by Denali D. Kufrin -S Date: 2022.08.15 12:21:17 -04'00'			
Nonclinical Team Leader	Matthew Thompson	Office of Oncologic Diseases	Sections: 5	X Authored X_Approved
	Signature: Matthew D. Thompson -S Digitally signed by Matthew D. Thompson -S Date: 2022.08.25 07:00:05 -04'00'			
Clinical Pharmacology Division Director	Atiqur Nam Rahman	Office of Clinical Pharmacology	Sections: 6 and 18	___Authored X_Approved
	Signature: Nam A. Rahman -S Digitally signed by Nam A. Rahman -S Date: 2022.08.24 08:12:12 -04'00'			
Clinical Pharmacology Reviewer	Sriram Subramaniam	Office of Clinical Pharmacology	Sections: 6 and 18	X Authored _Approved
	Signature: Sriram Subramaniam -S Digitally signed by Sriram Subramaniam -S Date: 2022.08.08 15:46:00 -04'00'			
Clinical Pharmacology Team Leader	Hong Zhao	Office of Clinical Pharmacology	Sections: 6 and 18	_X_Authored X_Approved
	Signature: Hong Zhao -S Digitally signed by Hong Zhao -S Date: 2022.08.08 15:20:31 -04'00'			
Pharmacometrics reviewer	Miao Zhao	Office of Clinical Pharmacology	Sections: 6 and 18	X Authored _Approved
	Signature: Miao Zhao -S Digitally signed by Miao Zhao -S Date: 2022.08.29 10:53:22 -04'00'			
Pharmacometrics team lead	Youwei Bi	Office of Clinical Pharmacology	Sections: 6 and 18	___Authored X_Approved
	Signature: Youwei Bi -S Digitally signed by Youwei Bi -S Date: 2022.08.25 11:59:21 -04'00'			

Signatures
NDA 214801 Assessment Aid

DISCIPLINE	REVIEWER	OFFICE/DIVISION	SECTIONS	AUTHORED/ APPROVED
Physiological Based Pharmacokinetics (PBPK) reviewer	Guansheng Liu	Office of Clinical Pharmacology	Sections: 6 and 18	X Authored _Approved
	Signature: Guansheng Liu -S Digitally signed by Guansheng Liu -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Guansheng Liu -S, 0.9.2342.19200300.100.1.1=2003130570 Date: 2022.08.25 11:17:48 -04'00'			
Physiological Based Pharmacokinetics (PBPK) team lead	Jianghong Fan	Office of Clinical Pharmacology	Sections: 6 and 18	___Authored X Approved
	Signature: Jianghong Fan -S Digitally signed by Jianghong Fan -S Date: 2022.08 24 09:50:42 -04'00'			
Genomics reviewer	Oluseyi Adeniyi	Office of Clinical Pharmacology	Sections: 6	X Authored _Approved
	Signature: Oluseyi Adeniyi -S Digitally signed by Oluseyi Adeniyi -S Date: 2022.08.23 23:32:02 -04'00'			
Genomics team lead	Rosane Charlab Orbach	Office of Clinical Pharmacology	Sections: 6	___Authored X Approved
	Signature: Rosane Charlaborbach -S Digitally signed by Rosane Charlaborbach -S Date: 2022.08.08 15:16:59 -04'00'			
Statistical Reviewer	Sirisha Mushti	Office of Biostatistics	Sections: 1 and 8.1, 8.3, 8.4	X Authored X Approved
	Signature: Sirisha Mushti -S Digitally signed by Sirisha Mushti -S Date: 2022.08.09 10:13:36 -04'00'			
Statistical Team Leader	Joyce Cheng	Office of Biostatistics	Sections: 1 and 8.1, 8.3, 8.4	___Authored X Approved
	Signature: Joyce Cheng -S Digitally signed by Joyce Cheng -S Date: 2022.08.08 14:57:49 -04'00'			
Division Director, OB/DB-V	Shenghui Tang	Office of Biostatistics	Sections: 1 and 8.1, 8.3, 8.4	___Authored X Approved
	Signature: Shenghui Tang -S Digitally signed by Shenghui Tang -S Date: 2022.08.08 14:58:47 -04'00'			

Signatures

NDA 214801 Assessment Aid

DISCIPLINE	REVIEWER	OFFICE/DIVISION	SECTIONS	AUTHORED/ APPROVED
Clinical Reviewer	Shruti Gandhy	Office of Oncologic Diseases	Sections: All	X Authored X Approved
	Signature: Shruti U. Gandhy -S Digitally signed by Shruti U. Gandhy -S Date: 2022.08.15 11:59:55 -04'00'			
Cross-Disciplinary Team Leader (CDTL)	Sandra Casak	Office of Oncologic Diseases	Sections: All	___Authored X Approved
	Signature: Refer to final assessment aid			
Associate Director for Labeling (ADL)	Doris Auth	Oncology Center of Excellence	Sections: All	X Authored X Approved
	Signature: Doris Auth -S Digitally signed by Doris Auth -S Date: 2022.08.15 12:55:44 -04'00'			
Deputy Division Director (Clinical)	Lola Fashoyin-Aje	Office of Oncologic Diseases	Sections: All	___Authored X Approved
	Signature: Refer to final assessment aid			
Deputy Center Director	Paul Kluetz	Oncology Center of Excellence	Sections: All	___Authored X Approved
	Signature: Refer to final assessment aid			

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/s/

SANDRA J CASAK
09/29/2022 12:39:52 PM

IBILOLA A FASHOYIN-AJE
09/29/2022 12:55:16 PM

PAUL G KLUETZ
09/29/2022 02:33:35 PM