26 April 2023
EMA/218116/2023
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Lytgobi

International non-proprietary name: futibatinib

Procedure No. EMEA/H/C/005627/0000

Note

Assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

Official address Domenico Scarlattilaan 6 ● 1083 HS Amsterdam ● The Netherlands
Address for visits and deliveries Refer to www.ema.europa.eu/how-to-find-us
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List of abbreviations

ADAM	advanced dissolution, absorption, and metabolism
ADME	absorption, distribution, metabolism, and excretion
AE	adverse event
AESI	Adverse events of special interest
ALT	alanine aminotransferase
AST	aspartate aminotransferase
AUC	area under the curve
BCS	Biopharmaceutics Classification System
CCA	Cholangiocarcinoma
CHMP	Committee for Medicinal Products for Human use
CIS	cisplatin
CMA	conditional marketing authorization
C_{max}	maximal concentration
CQA	critical quality attribute
CR	complete response
CTCAE	Common Terminology Criteria for Adverse Events
ctDNA	circulating tumour DNA
DCO	data cut-off date
DCR	disease control rate
DOR	duration of response
EC	European Commission
ECOG	Eastern Cooperative Oncology Group
EU	European Union
FCT	Film-coated tablet
FGFR2	fibroblast growth factor receptor 2
FISH	fluorescence in situ hybridization
GC	Gas chromatography
GEM	gemcitabine
GGT	gamma-glutamyl transferase
GI50	half maximal cell growth-inhibitory concentration
GSH	glutathione
HDPE	High density polyethylene
HPLC	High performance liquid chromatography
iCCA	intrahepatic CCA
ICH	International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use
IDH1/2	isocitrate dehydrogenase
INR	International normalized ratio
IR	Infrared
IRC	Independent Review Committee

LDPE	low-density polyethylene
LF	Late formulation
LSC	liquid scintillation counter
MAA	Marketing Authorisation Application
MTD	maximum tolerated dose
N/A	not applicable
NCI	National Cancer Institute
NDEA	*N*-Nitrosdiethylamine
NDMA	*N*-Nitrosodimethylamine
NGS	next generation sequencing
NMR	Nuclear magnetic resonance
NOAEL	no observed adverse effect level
ORR	objective response rate
OS	overall survival
PBPK	physiologically based pharmacokinetic
PBT	persistent, bioaccumulative and toxic
PCTFE	Polychlorotrifluoroethylene
PFS	progression free survival
Ph. Eur.	European Pharmacopoeia
PK	pharmacokinetic
PO	oral
PPES	Palmar-plantar erythrodysesthesia syndrome
PR	partial response
PRO	Patient-reported Outcomes
PSD	particle size distribution
PT	preferred term
PVC	Polyvinyl chloride
QC	quality control
QD	daily dosing
QOD	dosing every other day
QTcF	Fridericia's corrected QT interval
QWBA	quantitative whole-body autoradiography
RANO	Response Assessment in Neuro-Oncology
RDT	repeat dose toxicity
RECIST	Response Evaluation Criteria in Solid Tumours
RH	Relative humidity
RP2D	recommended phase II dose
rpm	Revolutions per minute
SD	Sprague Dawley
SDG	safety data group
SIRT	selective internal radiotherapy

SLS	Sodium lauryl sulfate
SmPC	Summary of Product Characteristics
SOC	system organ class
STD	severely toxic dose
TACE	transarterial chemoembolization
TEAE	treatment-emergent adverse event
TK	toxicokinetic
TRAE	treatment-related adverse event
TSE	Transmissible spongiform encephalopathy
ULN	upper limit of normal
XRPD	X-ray powder diffraction

1. Background information on the procedure

1.1. Submission of the dossier

The applicant Taiho Pharma Netherlands B.V. submitted on 29 April 2022 an application for marketing authorisation to the European Medicines Agency (EMA) for Lytgobi, through the centralised procedure falling within the Article 3(1) and point 4 of Annex of Regulation (EC) No 726/2004. The eligibility to the centralised procedure was agreed upon by the EMA/CHMP on 30 April 2020.

Lytgobi was designated as an orphan medicinal product EU/3/19/2146 on 01 April 2019 in the following condition: Treatment of biliary tract cancer.

Following the CHMP positive opinion on this marketing authorisation and at the time of the review of the orphan designation by the Committee for Orphan Medicinal Products (COMP), this product was withdrawn from the Community Register of designated orphan medicinal products on 16 May 2023 on request of the sponsor. The relevant orphan designation withdrawal assessment report can be found under the 'Assessment history' tab on the Agency's website.
https://www.ema.europa.eu/en/medicines/human/EPAR/Lytgobi

The applicant applied for the following indication:

Lytgobi monotherapy is indicated for the treatment of adult patients with locally advanced or metastatic cholangiocarcinoma with a fibroblast growth factor receptor 2 (FGFR2) fusion or rearrangement that have progressed after at least one prior line of systemic therapy.

1.2. Legal basis

The legal basis for this application refers to:

Article 8.3 of Directive 2001/83/EC - complete and independent application

The application submitted is composed of administrative information, complete quality data, non-clinical and clinical data based on applicants' own tests and studies and/or bibliographic literature substituting/supporting certain test(s) or study(ies).

1.3. Information on Paediatric requirements

Pursuant to Article 7 of Regulation (EC) No 1901/2006, the application included an EMA Decision (P/0045/2020) on the granting of a product-specific waiver.

1.4. Information relating to orphan market exclusivity

1.4.1. Similarity

Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the applicant did submit a critical report addressing the possible similarity with authorised orphan medicinal products.

1.5. Applicant's request(s) for consideration

1.5.1. Conditional marketing authorisation

The applicant requested consideration of its application for a Conditional marketing authorisation in accordance with Article 14-a of the above-mentioned Regulation.

1.5.2. New active Substance status

The applicant requested the active substance futibatinib contained in the above medicinal product to be considered as a new active substance, as the applicant claims that it is not a constituent of a medicinal product previously authorised within the European Union.

1.6. Protocol assistance

The applicant received the following Scientific Advice on the development relevant for the indication subject to the present application:

Date	**Reference**	**SAWP co-ordinators**
26 April 2018	EMEA/H/SA/3800/1/2018/II	Paolo Foggi and Daniel O'Connor
16 September 2021	EMA/SA/0000063252	Anders Lignell and Fernando de Andrés Trelles

The applicant received Scientific Advice on the development of futibatinib (TAS-120) for the treatment of cholangiocarcinoma from the CHMP on 26 April 2018 (EMEA/H/SA/3800/1/2018/II). The Scientific Advice pertained to the following Clinical aspects:

- Eligibility for Conditional Marketing Authorization.
- Adequacy of the Phase II part of Phase I/II study to fulfil the criteria for Conditional Marketing Authorization.
- Design of Phase II part of Phase I/II open-label, single-arm study in patients with advanced solid tumours harbouring FGF/FGFR aberrations including study population, inclusion/exclusion criteria, sample size, statistical analysis.

The applicant received Scientific Advice on the development of futibatinib (TAS-120) for the treatment of biliary tract cancer from the CHMP on 16 September 2021 *(*EMA/SA/0000063252). The Scientific Advice pertained to the following Quality aspects:

- Starting materials, testing for elemental impurities, particle size testing, control strategy for mutagenic impurities, and risk assessment process for the presence of nitrosamines.
- Testing for elemental impurities, adequacy of stability data and equivalence of the formulation used in the pivotal Phase I/II study with the proposed Phase III study commercial formulation.

1.7. Steps taken for the assessment of the product

The Rapporteur and Co-Rapporteur appointed by the CHMP were:

Rapporteur: Johann Lodewijk Hillege Co-Rapporteur: Alexandre Moreau

The application was received by the EMA on	29 April 2022
The procedure started on	19 May 2022
The CHMP Rapporteur's first Assessment Report was circulated to all CHMP and PRAC members on	08 August 2022
The CHMP Co-Rapporteur's critique was circulated to all CHMP and PRAC members on	22 August 2022
The PRAC Rapporteur's first Assessment Report was circulated to all PRAC and CHMP members on	22 August 2022
The CHMP agreed on the consolidated List of Questions to be sent to the applicant during the meeting on	15 September 2022
The applicant submitted the responses to the CHMP consolidated List of Questions on	21 December 2022
The CHMP Rapporteurs circulated the CHMP and PRAC Rapporteurs Joint Assessment Report on the responses to the List of Questions to all CHMP and PRAC members on	30 January 2023
The PRAC agreed on the PRAC Assessment Overview and Advice to CHMP during the meeting on	09 February 2023
The CHMP agreed on a list of outstanding issues in writing to be sent to the applicant on	23 February 2023
The applicant submitted the responses to the CHMP List of Outstanding Issues on	24 March 2023
The CHMP Rapporteurs circulated the CHMP and PRAC Rapporteurs Joint Assessment Report on the responses to the List of Outstanding Issues to all CHMP and PRAC members on	12 April 2023
The CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a positive opinion for granting a marketing authorisation to Lytgobi on	26 April 2023
The CHMP adopted a report on similarity of Lytgobi with Pemazyre and Tibsovo on	26 April 2023
Furthermore, the CHMP adopted a report on New Active Substance (NAS) status of the active substance contained in the medicinal product on	26 April 2023

2. Scientific discussion

2.1. Problem statement

2.1.1. Disease or condition

The initially applied indication was:

Lytgobi is indicated as monotherapy for the treatment of adult patients with previously treated locally advanced or metastatic cholangiocarcinoma harbouring FGFR2 gene rearrangements, including gene fusions.

2.1.2. Epidemiology

Cholangiocarcinoma (CCA) 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). Liver fluke and other parasitic infections give rise to a much higher incidence in Southeast Asia (113 per 100,000 person-years in men and 50 per 100,000 person-years in women; Bergquist and von Seth 2015). The incidence and mortality of CCA (in particular of intrahepatic CCA (iCCA)) have been increasing in the last 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).

The incidence of iCCA in Europe has also increased over the past decades (1971-2009) in Austria, Germany, Italy, and the United Kingdom (Banales 2016), but not in Denmark (Bridgewater 2014; Cardinale 2018). This overall increase in incidence has been linked (to an extent) to several emerging risk factors of the disease, including the rising prevalence of obesity (Banales 2016).

There are some risk factors and pathological conditions that have been clearly associated with CCA development, including infectious and inflammatory diseases, but despite the advancements in the knowledge of CCA etiology, approximately 50% of cases in Western countries are still diagnosed without any identifiable risk factor (Banales 2016; Banales 2020). General risk factors include age >65 years, obesity and diabetes mellitus. The main risk factors are primary sclerosing cholangitis and fibropolycystic liver disease (e.g., choledochal cysts) in the United States and Europe. There is a clear association between chronic intrahepatic stone disease (hepatolithiasis, also called recurrent pyogenic cholangitis) and CCA. Chronic liver disease (cirrhosis and viral infection) is now recognised as a risk factor, particularly for iCCA. Finally, at least four genetic conditions, Lynch syndrome, BRCA-associated protein-1 tumour predisposition syndrome, cystic fibrosis and biliary papillomatosis, appear to increase the risk for CCA. About 50% of cases are still diagnosed without any identifiable risk factor despite the advancements in the knowledge of CCA aetiology in Western countries. Other still undefined etiologic factors are likely to be responsible for the recent increase of CCA (especially iCCA) incidence worldwide. (Khan et al, 2019)

2.1.3. Aetiology and pathogenesis

CCA is a heterogeneous disease arising from a complex interaction between host- specific genetic background and multiple risk factors.

CCA is a malignancy originating in the epithelial lining of the biliary tree and it is commonly classified based on anatomical location. Extrahepatic (eCCA) includes hilar and distal tumours and accounts for the majority of cases (DeOliveira et al 2007, Nakeeb et al 1996). Approximately 5 to 10 percent of CCAs are intrahepatic (UpToDate visited 06JUL22).

The knowledge of the molecular pathogenesis of CCA is less advanced than that of other gastrointestinal cancers. Molecularly, the precursors of carcinoma remain poorly characterised. With emerging technologies, including next-generation sequencing (NGS), actionable mutations in the isocitrate dehydrogenase (IDH1/2), FGFR2, BRAF, and HER2/neu genes have been identified for targeted therapeutics in CCA and gallbladder cancer.

The FGFR family consists of four transmembrane receptors (FGFR1 to FGFR4), 18 FGF ligands, and a heparan sulfate proteoglycan that stabilises and sequesters the FGFs. The ligand-receptor combination is responsible for the activation of downstream RAS/RAF/MEK, JAK/STAT, and PI3K/AKT pathways. Genetic aberrations such as activating mutations, amplifications, or chromosomal translocations/fusions in the FGFR pathway contribute to malignant transformation (EPAR Pemazyre EMA/CHMP/105411/2021, Krook 2020).

2.1.4. Clinical presentation, diagnosis and prognosis

The prognosis of patients with Stage III or IV CCA is poor, with 5-year survival rates of 10% and 0%, respectively (Lamarca et al. 2014) and a median overall survival (OS) of 8-12 months (Goral 2017). The majority of patients with cholangiocarcinoma (> 65%) have nonresectable disease at the time of diagnosis, and the rate of recurrence is high among patients in the minority who are able to undergo potentially curative surgery.

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). The prognostic role of coexisting GAs, and the outcome with FGFR-targeted inhibitors are still under discussion (EPAR Pemazyre EMA/CHMP/105411/2021).

2.1.5. Management

First line treatment

CCA is a fatal disease for which there is significant unmet need for new therapies.

The ESMO guideline recommends cisplatin–gemcitabine–durvalumab for first-line treatment of patients with unresectable and metastatic disease (ESMO 2022). On 10 November 2022, the CHMP adopted a positive opinion recommending a new indication to include first-line treatment of biliary tract cancer for durvalumab.

Durvalumab plus chemotherapy was evaluated in the phase 3 TOPAZ-1 trial. The primary objective was to assess overall survival. Patients with advanced biliary tract cancer were randomly assigned to receive durvalumab (n=341) or placebo (n=344) in combination with gemcitabine plus cisplatin for up to eight cycles, followed by durvalumab or placebo monotherapy until disease progression or unacceptable toxicity. The median overall survival was 12.8 months (95% CI, 11.1 to 14.0) in the durvalumab group and 11.5 months (95% CI, 10.1 to 12.5) in the placebo treatment group (Oh Do-Youn et al. 2022).

Gemcitabine/cisplatin was the standard first-line chemotherapy regimen for patients with locally advanced or metastatic CCA at the time of study conduct (ESMO 2016). This was based on a randomized-controlled study comparing gemcitabine plus cisplatin versus gemcitabine alone in 410 patients with newly diagnosed or recurrent biliary tract cancer where the median mPFS was 8.0 months in the gemcitabine/cisplatin group and 5.0 months in the gemcitabine-only group (Valle 2010). In other prospective studies published between 2004 and 2013 in patients with advanced biliary tract cancers, treatment with gemcitabine/cisplatin as first-line treatment resulted in median progression free survival (PFS) ranging from 4.0 to 8.0 months and median overall survival (OS) ranging from 4.6 to 11.7 months (Park 2015).

Second line treatment

Therapeutic options for patients who progress on standard therapy are limited. There is no established systemic therapy once CCA has progressed on first-line therapy. A systematic review including 761 patients showed disappointing median PFS (3.2 months; 95% CI: 2.7–3.7) and response rates (7.7%; 95% CI: 4.6–10.9); the mean OS was 7.2 months (95% CI: 6.2–8.2) in the second-line treatment with chemotherapy (ESMO Guideline biliary cancer and Lamarca et al. 2014). Patients are therefore encouraged to participate in clinical trials per ESMO 2016 guidelines. According to clinical data collected in a database of the Hannover Medical School (Germany), patients received different chemotherapy regimens in second- and third-line treatment (e.g. FOLFOX and FOLFIRI). On 28 January 2021, the CHMP adopted a positive opinion, recommending the granting of a conditional marketing authorisation for the medicinal product Pemazyre (pemigatinib), intended for the second and later line of treatment of advanced or metastatic cholangiocarcinoma characterized by fusion or rearrangements of fibroblast growth factor receptor 2. The objective response rate (ORR) was 37.0% (95 CI%: 27.94, 46.86) in the Efficacy Evaluable Population (N=108) (SmPC Pemazyre). The median DOR was 8.08 months (95 % CI: 5.65, 13.14) (EPAR Pemazyre EMA/CHMP/105411/2021). Most recently, the IDH1-inhibitor Tibsovo (ivosidenib) was approved for the treatment of adult patients with locally advanced or metastatic cholangiocarcinoma with an IDH1 R132 mutation who were previously treated by at least one prior line of systemic therapy.

Locoregional therapies, including transarterial chemoembolisation, hepatic arterial infusion, percutaneous ablation, external beam radiation therapy, and radioembolisation (Koay 2017), are not recommended for routine use due to a lack of prospective data (Labib et al 2017).

2.2. About the product

Futibatinib is a small molecule tyrosine kinase inhibitor that irreversibly inhibits FGFR 1, 2, 3, and 4 by covalent binding with IC_{50} values of less than 4 nM. Futibatinib inhibited FGFR phosphorylation and downstream signalling and decreased cell viability in cancer cell lines with activating FGFR alterations, including FGFR fusions/rearrangements, amplifications, or mutations. Constitutive FGFR signalling can support the proliferation and survival of malignant cells. Futibatinib exhibited *in vitro* antiproliferative activity against cancer cell lines harbouring FGFR2 resistance mutations in the kinase domain (*N550H, V565I, E566G, K660M*). Futibatinib demonstrated anti-tumour activity in mouse and rat xenograft models of human tumours with activating FGFR genetic alterations.

The proposed Pharmacological classification is: antineoplastic agents, protein kinase inhibitors; ATC code: L01EN04.

The indication as adopted by CHMP is:

Lytgobi monotherapy is indicated for the treatment of adult patients with locally advanced or metastatic cholangiocarcinoma with a fibroblast growth factor receptor 2 (FGFR2) fusion or rearrangement that have progressed after at least one prior line of systemic therapy.

The film-coated tablet contains 4 mg of futibatinib.

The recommended starting dose is 20 mg Lytgobi taken orally once daily. Treatment should be continued until disease progression or unacceptable toxicity.

2.3. Type of Application and aspects on development

The applicant requested consideration of its application for a Conditional Marketing Authorisation in accordance with Article 14-a of the above-mentioned Regulation, based on the following criteria:

- The benefit-risk balance is positive.
- It is likely that the applicant will be able to provide comprehensive data.

  The applicant proposes the 'single-arm' Phase 2 Study TAS-120-205 as SOB, to provide comprehensive clinical data within an appropriate timeframe confirming that the benefit-risk balance is positive. This proposal entails replication of the single-arm efficacy (and safety) data from the pivotal Study TAS-120-101 in a new and independent single-arm study cohort to in time provide a comprehensive overall data package.

  This study will be a global, open-label Phase 2 study in patients with advanced, unresectable cholangiocarcinoma with FGFR2 fusions or rearrangements who have received at least one prior systemic therapy. A total of 120 patients will be randomized (1:1) to receive futibatinib at a starting dose of either 20 mg (Arm A) or 16 mg (Arm B) orally QD. The primary endpoint will be ORR according to RECIST 1.1 as determined by blinded independent central review with DOR being a key secondary endpoint. The primary analysis will be based on the 20 mg treatment arm.
- Unmet medical needs will be addressed.

  Therapeutic options for patients who progress on standard therapy are very limited. In second line and beyond, currently available chemotherapy treatments are largely ineffective, with a collective median ORR of less than 8% observed in a retrospective review covering 761 patients (Lamarca 2014). Of note, recent retrospective analyses have shown that the outcomes of post-first-line chemotherapy among the subset of patients with *FGFR2* rearrangements/fusions were similarly poor as those seen in the overall population, including a response rate <6% (Javle 2020).

  Multiple FGFR inhibitors are in development for CCA. The oral FGFR1-3 inhibitor pemigatinib has received accelerated approval in the United States and conditional approval in the European Union (EU) for the treatment of patients with previously treated CCA harbouring *FGFR2* rearrangements/fusions. However, options for patients with CCA with a clearly established and positive benefit/risk profile remain limited. Pemigatinib (as the only currently approved FGFR- targeting therapy for CCA in the EU) has demonstrated clinical benefit in an uncontrolled Phase 2 study for CCA patients with *FGFR2* rearrangements (including fusions) and is awaiting confirmation in an ongoing randomized Phase 3 study as compared to standard of care chemotherapy in first-line advanced CCA patients with *FGFR2* rearrangements (including fusions). Moreover, despite the 36% ORR reported for the ATP-competitive FGFR inhibitor pemigatinib, there is an unmet need for novel targeted therapies leading to an even higher number of responses with greater durability for patients with advanced CCA 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).

In the primary analysis (n=103) of the Phase 2 portion of Study TAS-120-101, treatment with futibatinib resulted in the numerically highest confirmed ORR (41.7%) and numerically longest median duration of response (9.7 months) for previously treated patients with advanced iCCA with FGFR2 rearrangement reported so far. Median PFS (9.0 months) also exceeded historical controls by a substantial margin. Furthermore, expression of FGFR4 correlates with disease progression and poor prognosis in CCA (Xu 2014).

For patients who progress on standard chemotherapy with gemcitabine/cisplatin(2L+), prognosis is even more dismal, with life expectancy of 6-7 months, response rates below 10%, and mPFS of only 3 months (Lamarca 2014). On 23 February 2023 the CHMP adopted a positive opinion recommending the granting of a MA for the IDH1-inhibitor Tibsovo (ivosidenib) for the treatment of adult patients with locally advanced or metastatic cholangiocarcinoma with an IDH1 R132 mutation who were previously treated by at least one prior line of systemic therapy. FGFR2 alterations occur in roughly 10% to 15% of cholangiocarcinoma, however, they rarely co-occur with IDH1 mutations (co-occurrence in approximately 2% to 5%) (Battaglin et al, 2020; Jain et al, 2018; Valle et al, 2017; Saborowski et al, 2020). While the EU specific obligations for pemigatinib to demonstrate clinical benefit in a randomized controlled Phase 3 study compared to standard of care are ongoing, it is not yet possible to confirm the full benefit of this conditionally authorised product. Therefore, according to section 4c of the EMA CMA guideline EMA/CHMP/509951/2006, Rev.1 (2016) guideline, futibatinib can be recommended for CMA as another medicinal product if it is addressing the same unmet medical need of patients with CCA to a similar or greater extent than what is understood for the already conditionally authorised product pemigatinib.

Based on the above considerations and on the results from the pivotal Phase 2 portion of study TAS-120-101, futibatinib has the potential to address a significant unmet medical need in this patient population.

- The benefits to public health of the immediate availability outweigh the risks inherent in the fact that additional data are still required.

  Unfortunately, few treatment options (with the exception of pemigatinib) are available in the EU to CCA patients with FGFR2 gene rearrangements, including gene fusions who progress on standard chemotherapy with gemcitabine/cisplatin. In the 2L+ setting prognosis is even more dismal, with life expectancy of 6-7 months, response rates below 10%, and mPFS of only 3 months (Vienot and Neuzillet 2018; Lamarca 2014). The specific obligations for pemigatinib to demonstrate clinical benefit in a randomized controlled Phase 3 study compared to standard of care are ongoing and as such, it is not yet possible to confirm the full benefit of this conditionally authorised product.

  Futibatinib is the first agent to irreversibly inhibit all 4 subtypes of FGFR, expected to result in a clear advantage in terms of possible clinical benefit for treated patients. Furthermore, futibatinib treatment was associated with a generally predictable, monitorable, and manageable toxicity profile with low incidence of severe adverse events and quality of life scores maintained during futibatinib treatment.

2.4. Quality aspects

2.4.1. Introduction

The finished product is presented as film-coated tablets containing 4 mg of futibatinib as active substance.

Other ingredients are:

Core tablet: mannitol (E421), maize starch, lactose monohydrate, sodium lauryl sulfate, microcrystalline cellulose, crospovidone, hydroxypropyl cellulose (E463) and magnesium stearate.

Film-coating: hypromellose (E464), macrogol and titanium dioxide (E171).

Lustering agent: magnesium stearate.

The product is available in polyvinyl chloride (PVC)/polychlorotrifluoroethylene (PCTFE) laminated blisters with aluminium foil back as described in section 6.5 of the SmPC.

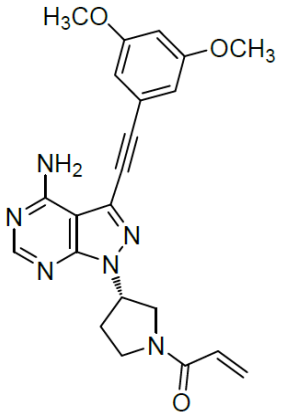
2.4.2. Active Substance

General information

The dossier contains full information on the active substance.

The chemical name of futibatinib 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 corresponding to the molecular formula $C_{22}H_{22}N_6O_3$. It has a relative molecular mass 418.45 g/mol and the following structure:

Figure 1. Active substance structure



The chemical structure of futibatinib was inferred from its route of synthesis and confirmed by a combination of elemental analysis, mass spectrometry, UV spectroscopy IR spectroscopy NMR spectroscopy (^{1}H NMR, H-D exchange,^{13}C NMR, DEPT135, HSQC, COSY, HMBC, NOESY) and single crystal X-ray diffraction. The single chiral centre is in the (*S*) configuration. Enantioselectivity is confirmed by chiral HPLC analysis of relevant materials and the active substance.

The solid-state properties of the active substance were measured by thermal analysis, X-ray powder diffraction, IR spectroscopy, and by measuring water content. Several anhydrous and hydrated forms were identified. It was confirmed that the intended commercial polymorphic form is routinely produced under the applied recrystallisation conditions and is thermodynamically stable.

The active substance is a non-hygroscopic white to light yellow crystalline powder. It is classified as BCS class 2 compound, i.e. low solubility/high permeability.

Manufacture, characterisation and process controls

Futibatinib is synthesized by a convergent process using well defined starting materials with acceptable specifications.

Adequate in-process controls are applied during the synthesis. The specifications and control methods for intermediate products, starting materials and reagents have been presented. The final crystallisation conditions ensure the correct polymorphic form and particle size distribution (PSD).

The characterisation of the active substance and its impurities are in accordance with the EU guideline on chemistry of new active substances. Potential and actual impurities were well discussed with regards to their origin and characterised. Given the indication of the product in advanced cancer, ICH M7 does not apply. Limits for impurities have been set accordingly.

The commercial manufacturing process for the active substance was developed in parallel with the clinical development program. The overall synthetic route has remained the same and minor changes to reagents, solvents, and the overall process have been presented in sufficient detail and have been justified. The quality of the active substance used in the various phases of the development is considered to be comparable with that produced by the proposed commercial process.

The active substance is packaged in triple low-density polyethylene (LDPE) sealed in a polyethylene liner. The bag is placed into a high-density polyethylene (HDPE) drum with a secure fitting lid. The relevant materials comply with the EC directive 2002/72/EC and EC 10/2011 as amended.

Specification

The active substance specification includes tests for appearance (visual), identity (IR, UV, HPLC), impurities (HPLC), enantiomeric impurity (chiral HPLC), residual solvents (GC), water content (Ph. Eur.), residue on ignition (Ph. Eur.), polymorphic form (XRPD), particle size distribution (Ph. Eur.), and assay (HPLC),

Limits for impurities have been set according to ICH Q3A and the limit for total impurities is considered acceptable. The justification, based on historical batch data, for not including test for elemental impurities and microbiological purity is considered acceptable.

The analytical methods used have been adequately described and non-compendial methods appropriately validated in accordance with the ICH guidelines. Satisfactory information regarding the reference standards used for assay and impurities testing has been presented.

Batch analysis data for seven production scale batches of the active substance were provided. The results are within the specifications and consistent from batch to batch.

Stability

Stability data from 6 production scale batches of active substance from the proposed manufacturer stored in a container closure system representative of that intended for the market for up to 36 months under long term conditions (25 ºC / 60% RH) and for up to 6 months under accelerated conditions (40 ºC / 75% RH) according to the ICH guidelines were provided. The following parameters were tested: appearance, identity, impurities, enantiomer, water content, assay, polymorphic form and microbial limits. The analytical methods are the same as for release except the microbial limit test which is pharmacopoeial. All tested parameters during the stability studies remained within specifications and or trends or significant changes were observed. No agglomeration or particle growth occurs during storage and the polymorphic form remains unchanged.

Photostability testing following the ICH guideline Q1B was performed on one batch. Forced degradation studies demonstrate the that the analytical methods are stability

The stability results indicate that the active substance manufactured by the proposed supplier is sufficiently stable. The stability results justify the proposed retest period and storage conditions.

2.4.3. Finished Medicinal Product

Description of the product and pharmaceutical development

Lytgobi film-coated tablets contain 4 mg of futibatinib as active substance. The finished product is presented as white, round, film-coated tablets debossed with "4MG" on one side, and "FBN" on the other. The tablets have a nominal diameter of 6.1 mm and a nominal thickness of 3.0 mm.

The development target was a solid oral dosage form containing 4 mg futibatinib. Various formulations were investigated during clinical development. The physicochemical characteristics of active substance were discussed. Futibatinib is a weakly ionizable compound (pKa=3.24) which is classified as BCS Class 2 due to its low solubility and high Caco-2 cell membrane permeability. Futibatinib exhibits polymorphism and the most thermodynamically stable form is consistently produced by the manufacturing process. No further transformation of the polymorphic form occurs on formulation.

The PSD of futibatinib active substance may influence the performance of the finished product as futibatinib is a low solubility compound. The specification for PSD for active substance is set based on the PSDs of batches used in clinical studies.

The compatibility of futibatinib active substance with a range of excipients was assessed using mixtures of the drug substance and excipients under stress conditions in line with ICH Q8. The choice, characteristics and function of the excipients in the commercial formulation has been adequately discussed. The inclusion of SLS has been adequately justified. All excipients are well known pharmaceutical ingredients and their quality is compliant with Ph. Eur. standards. There are no novel excipients used in the finished product formulation. The list of excipients is included in section 6.1 of the SmPC.

Based on the Quality Target Product Profile for the finished product, appearance, identity, impurities, content uniformity, dissolution, assay, microbiological quality, and water content were identified as critical quality attributes (CQAs).

Development of the dissolution method was adequately discussed. The discriminatory power was demonstrated for relevant CQAs of the product.

The manufacturing process was developed according to ICH principles and has been discussed extensively. The applied process is standard for this type of dosage form. The optimization of the process has been described as well as the development of the control strategy.

The primary packaging is polyvinyl chloride PVC/PCTFE laminated blisters with aluminium foil lidding. The materials comply with Ph. Eur. and EC requirements. The choice of the container closure system has been validated by stability data and is adequate for the intended use of the product.

Manufacture of the product and process controls

The manufacturing process consists of six main steps: granulation, blending and lubrication, tableting, film-coating, lustering and packaging. The process is considered to be a standard manufacturing process.

It has been demonstrated that the manufacturing process is capable of producing the finished product of intended quality in a reproducible manner during manufacture. Formal process validation will take place before commercialization and an acceptable validation protocol has been provided. The in-process controls are adequate for this type of manufacturing process and pharmaceutical form.

Product specification

The finished product release specifications include appropriate tests for this kind of dosage form and include tests for appearance (visual), identity (HPLC, UV), assay (HPLC), related substances (HPLC), dissolution (Ph. Eur.), uniformity of dosage units (Ph. Eur.), water content (Ph. Eur.) and microbiological examination (Ph. Eur.).

The specifications proposed for the finished product contain tests typical for this type of pharmaceutical form. The justifications for the proposed specification are supported by the release and stability data.

A risk assessment on elemental impurities in line with ICH Q3D has been performed on bulk tablet batches and it is confirmed that levels of elemental impurities in futibatinib FCT are adequately controlled and no additional controls in the drug product specifications are required.

The applicant has adequately mitigated all risks pertaining to nitrosamines. Furthermore, since Lytgobi has an advanced cancer indication in the scope of ICH S9, ICH Q3B limits would apply. The risk assessment is considered acceptable, and no specific controls are required.

The analytical methods used have been adequately described and appropriately validated in accordance with the ICH guidelines. Satisfactory information regarding the reference standards used for assay and impurities testing has been presented.

Batch analysis results are provided for 24 historical batches including 6 production scale batches of the proposed commercial formulation confirming the consistency of the manufacturing process and its ability to manufacture to the intended product specification.

The finished product is released on the market based on the above release specifications, through traditional final product release testing.

Stability of the product

Stability data from production scale batches of finished product stored for up to 36 months under long term conditions (25 ºC / 60% RH), up to 36 months under intermediate conditions (30 ºC / 75% RH), and for up to 6 months under accelerated conditions (40 ºC / 75% RH) according to the ICH guidelines were provided. The batches of finished product are representative of those proposed for marketing and were packed in the primary packaging proposed for marketing.

Samples were tested for appearance, identification, related substances, assay, water content, dissolution, content uniformity and microbiological examination. The analytical procedures used are stability indicating. There were no trends or significant changes to any of the measured parameters were observed, other than a slight increase in water content which had no impact on the other properties. All parameters remained within specifications.

In addition, one batch was exposed to light as defined in the ICH Guideline on Photostability Testing of New Drug Substances and Products. The finished product is photostable.

Studies on the bulk finished product in bulk packaging were conducted and the results justify the proposed bulk storage time.

Based on available stability data, the proposed shelf-life of 48 months without special storage conditions as stated in the SmPC (section 6.3 and 6.4) is acceptable.

Adventitious agents

It is confirmed that the lactose is produced from milk from healthy animals in the same condition as those used to collect milk for human consumption and that the lactose has been prepared without the use of ruminant material other than calf rennet according to the Note for Guidance on Minimising the Risk of Transmitting Animal Spongiform Encephalopathy Agents Via Human and veterinary medicinal products.

No other excipients derived from animal or human origin have been used.

2.4.4. Discussion on chemical, pharmaceutical and biological aspects

Information on development, manufacture and control of the active substance and finished product has been presented in a satisfactory manner. The results of tests carried out indicate consistency and uniformity of important product quality characteristics, and these in turn lead to the conclusion that the product should have a satisfactory and uniform performance in clinical use. No major objections on quality aspects were raised during the procedure.

2.4.5. Conclusions on the chemical, pharmaceutical and biological aspects

The quality of this product is considered to be acceptable when used in accordance with the conditions defined in the SmPC. Physicochemical and biological aspects relevant to the uniform clinical performance of the product have been investigated and are controlled in a satisfactory way. Data has been presented to give reassurance on viral/TSE safety.

2.4.6. Recommendations for future quality development

Not applicable.

2.5. Non-clinical aspects

2.5.1. Introduction

Futibatinib (hereafter also referred to as TAS-120) is a novel, highly potent and selective fibroblast growth factor receptor (FGFR) inhibitor developed for treatment of advanced cancers with activations of fibroblast growth factor/FGFR pathway including intrahepatic cholangiocarcinoma (iCCA) harbouring FGFR2 gene rearrangements.

2.5.2. Pharmacology

2.5.2.1. Primary pharmacodynamic studies

To investigate whether futibatinib inhibits FGFR1, FGFR2, FGFR3 and FGFR4, the IC_{50} values of futibatinib against these FGFRs were determined using *in vitro* assays. The cytoplasmic domains of recombinant human FGFR1, FGFR2, FGFR3 and FGFR4 proteins, expressed as N-terminal glutathione S-transferase-fusion proteins, were used as enzymes. Futibatinib inhibited the activity of all 4 types of FGFR: the mean (± standard deviation) IC_{50} values of futibatinib against human FGFR1, FGFR2, FGFR3 and FGFR4 were calculated to be 1.8 ± 0.4, 1.4 ± 0.3, 1.6 ± 0.1, and 3.7 ± 0.4 nmol/L, respectively.

The effect of futibatinib on cell proliferation was investigated using a panel of 7 human cancer cell lines with various genetic alterations of FGFRs. After exposure of cells to futibatinib for 3 days, cell viability was determined by quantitation of ATP and the half maximal cell growth-inhibitory concentration (GI_{50}) values were calculated. Futibatinib potently inhibited the *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 cells (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, MKN45 (gastric cancer) and MCF-7 (breast cancer) cells had no genetic alterations of FGFR and the cell growth of these cell lines was not inhibited by futibatinib.

To evaluate the effect of futibatinib on mutant forms of FGFR2 in comparison with ATP-competitive inhibitors, 4 mutant forms of FGFR2 (N550H, V565I, E566G, and K660M) were constructed and subsequently transfected into HEK293 cells. Then, the effect of futibatinib on FGFR2 autophosphorylation was determined by phospho-FGFR2 enzyme-linked immunosorbent assay. Futibatinib showed potent inhibitory activity against all mutants tested, with IC_{50} values (mean ± standard deviation) of 12 ± 5 nmol/L for N550H, 8.4 ± 3.1 nmol/L for V565I, 5.5 ± 4.7 nmol/L for E566G, and 9.2 ± 7.0 nmol/L for K660M, which was similar to its inhibitory potency against wild-type FGFR2 (3.1 ± 1.3 nmol/L).

In contrast, the inhibitory potency of ATP-competitive FGFR inhibitor AZD4547 against these FGFR2 mutant forms was reduced compared with wild-type FGFR, whereas ATP-competitive inhibitor BGJ398 demonstrated limited activity only against the mutant FGFR forms V565I and K660M.

The antitumour effects of futibatinib were evaluated *in vivo* using two animal models with subcutaneously implanted human cancer cells with FGFR2 mutation or amplification.

In the first *in vivo* study, the antitumour effect of futibatinib was evaluated using nude mice implanted with the human endometrial carcinoma cell line AN3 CA, expressing FGFR2 with K310R and N549K point mutations. AN3 CA fresh tumour fragments were subcutaneously implanted into female nude mice. Futibatinib was administered orally once daily for 11 days at doses of 5, 15 and 50 mg/kg/day. No deaths, 10% or greater losses of body weight, or other clinical observations caused by futibatinib

were observed in any of the futibatinib dose groups. Therefore, these doses of futibatinib were deemed tolerable. Relative tumour volumes (volume at day 12/ volume at day 1) in all of the futibatinib dose groups were significantly lower than the control group. The relative tumour volume values in the 5, 15 and 50 mg/kg/day groups were 8.5%, 5.9% and 3.1%, respectively, whereas untreated mice showed 38% relative tumour volume. These results indicate antitumour activity of futibatinib in this model. In addition, the effect of futibatinib on FGFR-related signals in AN3 CA xenografts was evaluated in AN3 CA xenograft tumours following single-dose administration of futibatinib at 5, 15 and 50 mg/kg in nude mice. The tumour samples were collected 3 and 6 hours after dosing and were homogenized and protein lysates were then extracted from the tissues. The protein expression levels of FGFR2, FRS2, AKT and ERK, and the phosphorylation levels of FGFR, FRS2, AKT and ERK were determined by Western blot. The expression levels of total proteins as FGFR2, FRS2, AKT and ERK were nearly the same among all samples. Phosphorylation of FGFR, FRS2 and ERK was decreased dose-dependently until 6 hours after futibatinib administration. Phosphorylation of AKT was decreased slightly after 3 hours, but not after 6 hours.

In a second *in vivo* study, the antitumour effect of futibatinib was evaluated using nude rats injected subcutaneously with the human gastric carcinoma cell line SNU-16 carrying the amplified FGFR2 gene. Futibatinib was administered orally once daily for 14 days at doses of 2.5, 5 and 10 mg/kg/day. No deaths, 20% or greater losses of body weight, or other clinical observations caused by futibatinib were observed in any of the futibatinib administration groups. Therefore, these doses of futibatinib were deemed tolerable. After 14 days of dosing, the relative tumour volume values in the 2.5, 5 and 10 mg/kg/day groups were 1.4%, 1.9%, and 1.2%, respectively, whereas untreated mice showed 3.6% relative tumour volume. Statistically significant decreases in relative tumour volume growth were observed for all three dose levels when compared to control rats.

2.5.2.2. Secondary pharmacodynamic studies

The selectivity of futibatinib for FGFRs over other protein kinases was explored *in vitro* using 287 various human serine/threonine and tyrosine protein kinases other than FGFRs. This selectivity profiling was run with a futibatinib concentration of 100 nmol/L. The test concentration of 100 nM is regarded well chosen as it is sufficiently exceeding the human unbound C_{max} of ~28 nM futibatinib.

All kinases except one showed inhibition ≤30% at 100 nmol/L, not indicative of a concern (although Sootome *et al* in 2020 reported that MAPKAPK2 and CK1α also were inhibited >30% by futibatinib). Only RET kinase (S891A mutation) was inhibited by >70% at 100 nmol/L.

2.5.2.3. Safety pharmacology programme

hERG channel transfected HEK293 cells were exposed to 0, 1, 10 and 30 µmol/L of futibatinib to evaluate the effects on hERG current. No suppression of the hERG current was observed at 1 µmol/L, but the hERG current was significantly suppressed at 10 and 30 µmol/L (the relative peak tail currents were 41.6% and 16.6%, respectively). The concentration where no significant effect was observed (1 µM) was ~35-fold higher than the free fraction of futibatinib observed at C_{max} in human volunteers (~28 nM), indicating that no effects are to be expected in humans.

Four increasing doses of futibatinib were administered orally once a week at 0, 1, 3 and 10 mg/kg to conscious male Beagle dogs with an implanted telemetry device. The animals' blood pressures (systolic, diastolic, and mean blood pressure), heart rate, electrocardiographic parameters (PR interval, QRS duration, QT interval, and QTc interval) and respiration rate were measured before administration and at 1, 2, 4, 8 and 24 hours after administration. Futibatinib was not considered to have an effect on the cardiovascular system in conscious dogs up to 10 mg/kg. The C_{max} values on day 1 in a 4-week

dog toxicology study with 10 mg/kg dosing were 280 ng/mL (669 nM) for males and 321 ng/mL (767 nM) for females, corresponding to a free fraction of ~59-68 nM (using 91.2 % plasma protein binding in dog). Therefore, the findings from this cardiovascular study indicate that no effects are to be expected in humans, where the free fraction at C_{max} for MRHD was ~28 nM.

With regard to the effects of futibatinib in the central nervous system, futibatinib was administered orally once to male rats (Crl:CD[SD]) at 0, 3, 10 and 30 mg/kg; and the effects on general condition and behavior were evaluated at 1, 2, 4, 8 and 24 hours after administration using the functional observational battery method. Futibatinib was considered to have no effect on the central nervous system in rats after a single oral dose of up to 30 mg/kg. The average C_{max} values on day 1 in a 4 week rat toxicology study with 30 mg/kg dosing for both sexes was 1005 ng/mL (2402 nM), corresponding to a free fraction of ~103 nM (using 95.7% plasma protein binding in rat). Therefore, the findings from this central nervous system study indicate that no effects are to be expected in humans, where the free fraction at C_{max} for MRHD was ~28 nM.

The effects of futibatinib on the respiratory system were investigated by orally dosing male rats (Crl:CD[SD]) once at 0, 3, 10 and 30 mg/kg, and the effects on the respiratory system (respiration frequency, tidal volume, and minute volume) were evaluated at 1, 2, 4, 8 and 24 hours after administration. Futibatinib was considered to have no effect on the respiratory system in rats after a single oral dose of up to 30 mg/kg. The average C_{max} values on day 1 in a 4-week rat toxicology study with 30 mg/kg dosing for both sexes was 1005 ng/mL (2402 nM), corresponding to a free fraction of ~103 nM (using 95.7% plasma protein binding in rat). Therefore, the findings from this respiratory study indicate that no effects are to be expected in humans, where the free fraction at C_{max} for MRHD was ~28 nM.

2.5.2.4. Pharmacodynamic drug interactions

No studies were provided. This is agreed, as it is expected that no other FGFR-modulating drugs will be used during futibatinib treatment.

2.5.3. Pharmacokinetics

Futibatinib (TAS-120) was investigated in a range of *in vitro* and *in vivo* pharmacokinetic (PK) and toxicokinetic (TK) studies in Sprague Dawley (SD) rats and Beagle dogs, which are the nonclinical safety species. These studies were conducted to define the absorption, distribution, metabolism, and excretion (ADME) of futibatinib. Oral administration, which is the route of clinical administration, was selected for the pharmacokinetic studies in animals. Data from these studies were used to characterize the PK and TK properties of futibatinib to support nonclinical toxicology evaluations.

2.5.3.1. Methods of analysis

Liquid chromatography with tandem mass spectrometry (LC-MS/MS) methods were employed to analyse plasma samples from both GLP and non-GLP nonclinical studies in rat and dog. In general, heparin plasma was deproteinized using acetonitrile, centrifuged and in the supernatant futibatinib and an internal standard (futibatinib-D_6) were analysed with a Sciex API 4000 LC-MS-MS equipped with an HPLC column. The analytical range (LLOQ – ULOQ) for plasma samples was 2.0 to 1000 ng/mL. The bioanalytical methods met all validation criteria with respect to intra- and inter-day accuracy, precision, sensitivity, linearity, reproducibility, matrix effect and stability (up to 92 d). Incurred sample reproducibility for nonclinical sample analysis was conducted once per method per species.

Radioactivity levels of radiolabeled compounds in samples were measured by a liquid scintillation counter (LSC). Quantitative whole-body autoradiography was used for the measurement of radioactivity levels in tissues in the distribution studies.

2.5.3.2. Absorption

The PK/TK of futibatinib was studied using Sprague Dawley (SD) rats (n=3/time point) following oral (PO) gavage daily dosing (QD) and every other day dosing (QOD), in three multiple dose safety studies, including a non-GLP 3 week study (10, 20 and 30 mg/kg QD; 30, 60 mg/kg QOD) in male rats, a 4 week GLP study (3 mg/kg QD; 3, 10, 30 mg/kg QOD) in male and female rats and a 13 week GLP study (1, 3, 10 mg/kg QOD) in male and female rats. The single dose PK was only studied on day 1 of multiple dosing, which is acceptable given the fast clearance of the compound from plasma.

Following oral administration in rats, futibatinib was quickly absorbed reaching maximal plasma concentration after 1 – 2 hrs, whereafter it declined quickly in a bidirectional fashion leaving ~10% in plasma at 8 hours after dosing. In general, C_{max} and AUC_{0-24} values increased dose proportionally with increasing dose. Upon multiple dosing for 4 or 13 weeks in the rat safety studies, no apparent accumulation of futibatinib was found yielding similar C_{max} and AUC_{0-24} values as on day 1. No clear sex differences were observed for any parameter. Distribution volume and clearance were not determined as no intravenous dosing was performed. Terminal elimination half-life ($t_{1/2}$) values were not determined but are expected to be less than 2 h.

The fraction absorbed (Fpo) was not investigated in rats, however, the male SD rat excretion study (see section 3.2.2.5) suggests that the oral absorption in the rat is at least 65%.

The PK/TK of futibatinib was studied using Beagle dogs following oral (PO) gavage daily dosing (QD) and every other day dosing (QOD), in three multiple dose safety studies, including a non-GLP 3 week study (5, 10 and 30 mg/kg QD; 10, 30 mg/kg QOD, n=2) in male dogs, a 4 week GLP study (0.3, 3 mg/kg QD; 1, 3, 10 mg/kg QOD, n=3-5) in male and female dogs and a 13 week GLP study (0.3, 1, 3 mg/kg QOD, n=3) in male and female dogs. The single dose PK was only studied on day 1 of multiple dosing, which is acceptable given the fast clearance of the compound from plasma.

Following oral administration in dogs, futibatinib was quickly absorbed reaching maximal plasma concentration after 1 – 2 hrs, whereafter it declined quickly in a bidirectional fashion leaving ~10% in plasma at 8 hours after dosing. In general, C_{max} and AUC_{0-24} values increased dose proportionally with increasing dose. Upon multiple dosing for 4 or 13 weeks in the dogs safety studies, no apparent accumulation of futibatinib was found yielding similar C_{max} and AUC_{0-24} values as on day 1. No clear sex differences were observed in any parameter. Distribution volume and clearance were not determined as no intravenous dosing was performed. Terminal elimination half-life ($t_{1/2}$) values were not determined but are expected be less than 2 h.

After a single oral administration of [^{14}C]futibatinib (10 mg/kg) to fasting male Beagle dogs (n=3), absorption was fast yielding a T_{max} at 1.7 - 2 h, whereafter it declined quickly in a bidirectional fashion leaving 41% and 16% in blood and plasma, respectively, at 8 hours after dosing. Thereafter, however, radioactivity was eliminated very slowly, displaying a terminal elimination half-life ($T_{1/2}$) of 214 hrs and 146 hrs for blood and plasma, respectively, yielding after 168 hrs still 19% and 2.6% of C_{max} present.

2.5.3.3. Distribution

Protein binding studies with futibatinib were performed *in vitro* with plasma from human, dog, rat and mouse at 0.2, 1 and 5 µM using an equilibrium dialysis method and determined by LC-MS/MS. Plasma protein binding of futibatinib was ~91.2% in dog, 96.3% in mouse, 95.7% in rat and 95.3% in human

plasma. Futibatinib had a similar binding affinity to human serum albumin (90%) as to alpha-1-acid glycoprotein (86%). This means that the unbound futibatinib concentration (F_u) is about 2-fold higher in dog than in human, rat or mouse.

The partitioning of futibatinib into plasma and blood was determined *in vitro* with plasma from human only. The blood/plasma (B/P) ratio, using 0.2, 1 and 5 µM futibatinib concentrations, was found to be 0.66 after 5 min incubation and 0.55 after 60 min, indicating futibatinib is distributed mainly in plasma.

The *in vivo* tissue distribution of [^{14}C]futibatinib was investigated in the male albino SD rat and the partially-pigmented Long Evans rat after oral administration of 10 mg/kg (3.7 MBq/kg) using quantitative whole-body autoradiography (QWBA) at 1h up to 48 h (albino SD) and up to 336 h (Long Evans) post dosing. Tissue distribution in non-pigmented rats was generally comparable to that in the pigmented male rats. Following oral administration, radioactivity was quickly distributed to most tissues studied but was absent (albino) or very low (LE) in eyeball, brain and spinal cord. The highest [^{14}C]-related radioactivity was found at 1 to 5 hours post dose. Tissue to blood ratios (T/B) were generally found to be <4 for all tissues during the first 5 hours post dose except in liver (13.9) small intestine (7.7), kidney (5.1) and adrenal (5.9). Thereafter, radioactivity decreased in most tissues but continued to increase in the skin and uveal tract (pigmented only, probably due to melanin binding) until 12 hours after administration. At 48 hours after administration, the radioactivity was relatively high in skin and also still present in liver, kidney, thyroid, heart, adrenal and harderian gland. At 336 hrs post dose, radioactivity was still high in the uveal tract and retinal epithelial cells and low but measurable in blood, kidney, heart and skin (pigmented).

2.5.3.4. Metabolism

Metabolism in vitro

The *in vitro* metabolite profile of futibatinib was obtained following incubation with Sprague-Dawley rat, beagle dog, and human liver microsomes and hepatocytes. [^{14}C]Futibatinib, studied at 10 µM, was moderately metabolized in liver microsomes (31% to 66% after 1 hr) and hepatocytes (24% to 58% after 2 hrs), yielding Phase I metabolites (*O*-demethylation, mono & di-oxidations and reductions) and Phase II metabolites (glutathione, cysteine or glucuronide conjugation). Seventeen metabolites (M1 to M17) were identified in total, and no unique metabolite was observed from human liver microsomes or hepatocytes that was not also formed by rat and/or dog microsomes or hepatocytes.

In vitro metabolism studies using human liver microsomes and recombinant enzymes are consistent with futibatinib elimination by mainly CYP3A4 and 3A5 enzymes and a minor contribution by CYP2C9 and 2D6. The estimated contribution of rhCYPs to the total metabolism (fmCYP) in human liver microsomes was approximately 72% for CYP3A4, 23% for CYP3A5, 5% for CYP2C9 and 0% for CYP2D6. With respect to Phase II metabolism pathway, the contribution of glutathione (GSH) was evaluated by using human liver S9 fraction and fraction metabolized by GST (fmGST) was found to be minor (13%).

Metabolism in vivo

Following a single oral administration of 10 mg/kg [^{14}C]futibatinib to male Sprague-Dawley rats (n=3) unchanged futibatinib was the major source of radioactivity (77%) and the cysteine conjugate (M8) was the most abundant metabolite (13%) in plasma at 2 hr post-dose, leaving ~9.5% of label unaccounted. In bile (0-4 hrs post-dose), containing a quarter of the radioactive dose, unchanged futibatinib was not present and most of the identified excreted radioactivity was associated with M8 (9.6%) and four metabolites, of which M2 / M24 (~3%) and M18 / M13 (~1.4%) were above 1% of

the radioactive dose, while 6.7% was unknown. In faeces, containing two third of the radioactive dose, unchanged futibatinib was slightly present (2.3% of the radioactive dose) and most of the identified radioactivity was associated with M8 (7.4%), M22 (6.5%), M21+M11 (7.3%) and M24 (4.5%) (unknown 28%). In urine, containing about 3% of the radioactive dose, unchanged futibatinib was not present and six metabolites were found, of which M24 (1%) was the largest and the other five (M21, M11, M23, M13, M14) were below 1% of the radioactive dose.

Following a single oral administration of 10 mg/kg [^{14}C]futibatinib to male Beagle dogs (n=3), unchanged futibatinib was the major source of circulating radioactivity (84.6%) and the cysteine conjugate (M8) was the most abundant metabolite (8%) in plasma at 1 hr post-dose, leaving 7.4% of label unaccounted. [^{14}C]Futibatinib was metabolized by both phase I and phase II biotransformation. In faeces, containing ~80% of the radioactive dose, unchanged futibatinib was present (28% of the radioactive dose) and most of the identified radioactivity was associated with M8 (13.7%), M19 (4.3%), M10 (4.0%) and M20 (3.0%) (unknown 23%). In urine, containing about 0.7% of the radioactive dose, unchanged futibatinib was not present and two metabolites were found, which all (M8, M20) were below 0.4% of the radioactive dose.

In summary, in both rat and dog [^{14}C] futibatinib was metabolized by both phase I (*O*-demethylation, mono- or di-oxidation, hydration) and phase II (cysteine or *N*-acetylcysteine conjugation, sulfation, glucuronidation) biotransformation.

In human, an AME study (CLN01) indicated that unchanged futibatinib was the main component (59%) present in plasma, while P7 (a cysteinylglycine conjugate) was identified as a major circulating metabolite in plasma accounting for 13.4% of the total radioactivity. In addition, P1 (a glucuronide of a mono-oxidized product, named as M18 in rat and dog), and P5 (named as M8 in rat and dog) were also found in human plasma, accounting for 9% and 8.7% of total radioactivity, respectively. P5 (M8) was the main metabolite detected in rat and dog plasma and also found in their faeces. P1 (M18) was found in rat bile, but at low levels. P7, however, which is the major metabolite in human plasma, was not detected in rat or dog plasma and also not present in faeces, bile or urine.

2.5.3.5. Excretion

The excretion of radioactivity was investigated in fasting male SD rats (intact and Bile Duct Cannulated) and Beagle dogs (n=3) after a single oral dose of [^{14}C]futibatinib (10 mg/kg). The excretion of radioactivity was predominantly through the faecal (biliary) pathway and, for the intact rat, and dog, it accounted after five days for 92% and 99% of the radioactivity dose, while the urinary route contributed 4.8% and 1.3%. The total recovery of radioactivity, two days after dosing, was high in the rat (95%) and dog (99%). Excretion to expired air was not found in the rat.

In bile duct-cannulated rats, at two days following oral administration, excretion into the bile and urine was 61% and 4.8% of the radioactivity dose, respectively, indicating a predominant biliary clearance. The recovery data indicate that the fraction absorbed upon oral administration was at least 0.65.

In conclusion, following oral administration, futibatinib was primarily cleared upon metabolism via biliary excretion and faecal elimination in the tested preclinical species (rat and dog). Renal clearance plays a lesser role.

2.5.4. Toxicology

2.5.4.1. Single dose toxicity

Single dose toxicity studies with futibatinib were not performed.

2.5.4.2. Repeat dose toxicity

Pivotal 4-weeks and 13-weeks repeat dose toxicity (RDT) studies were preceded by non-GLP range finding studies in both rat and dog. Lot KMBH271 was used for all repeat dose toxicology studies. Every other day treatment was generally better tolerated than daily treatment. Higher doses (>20 mg/kg) pivotal 4-weeks and 13-weeks RDT studies were preceded by non-GLP range finding studies in both rat and dog. Lot KMBH271 was used for all repeat dose toxicology studies. Every other day treatment was generally better tolerated than daily treatment. Higher doses (>20 mg/kg) in the dose range finding (DRF) studies were poorly tolerated leading to moribundity in both rats and dogs. In the DRF studies, main drug-related effects in rats were increased inorganic phosphorus (IP) and calcium in plasma, ectopic mineralisation, bone and cartilage lesions and increased corneal lesions, likely as a result of FGFR inhibition. In dogs, increased plasma IP, ectopic mineralisation in aortic root and bone and cartilage changes were observed. The comparable toxicity profile was also confirmed in the pivotal repeat dose toxicity studies.

In all pivotal studies a severely toxic dose could be identified. There is no appreciable clinical exposure multiple even for the severe toxic dose that has been established in the pivotal toxicology studies. It is considered that findings in the lowest dose groups of these studies, irrespective of the dosing schedule, are also adverse. Therefore, a NOAEL was not established.

In the pivotal 4-week and 13-week toxicology studies in rats and dogs, no mortality was observed during the treatment window or in the recovery period. Every other day (QOD) administration was better tolerated than daily administration (QD). Nevertheless, comparable and severe toxicity was still observed with the QOD administration schedule albeit at higher doses.

In rats, males appeared to be more sensitive to effects of futibatinib although no pharmacokinetic differences are apparent. Nevertheless, most toxicologically relevant findings were also observed in females at higher doses. In the 4-week study, decreased body weight gain was observed in male animals receiving 30 mg/kg futibatinib. Increased urinary calcium and inorganic phosphate was noted from 3 mg/kg onwards, but IP was increased in females from 10 mg/kg onwards. Target organs of toxicity in rat were eye (increased corneal opacity, secondary to corneal mineralisation), bone and cartilage and various organ tissues including heart and vasculature as a result of ectopic mineralization. Ectopic mineralisation was consistently observed in both males and females at all doses and tissues including aortic artery and arterial wall in the heart; arterial wall, cortex, and medulla in the kidney; arterial wall, alveolar wall, and bronchioles in the lung; arterial wall, mucosa, and muscle in the stomach; meninx in the spinal cord; arterial wall in the tongue and submucosa; and muscle in the trachea. Mineralisation in heart of males from 10 mg/kg and in females from 30 mg/kg was considered a severe toxicological finding. Except for the conjunctiva in the eye and mucosa in the glandular stomach, ectopic mineralisation was non-recoverable. Bone lesions were observed in males from 3 mg/kg onwards and in females from 10 mg/kg onwards, including thickening of growth plate, increased secondary spongiosa with cartilage material, abnormal ossification of the cortical bone, thickening of the joint cartilage, and decreased osteoblasts. Thickening of the cartilage in the sternum was observed. A NOAEL was not established. A severely toxic dose (STD_{10}) was determined for QOD dosing of 10 mg/kg based on the cardiac mineralisation. There is no exposure multiple as this exposure corresponds to approximately the clinical exposure. Exposures up to 14-weeks did not lead to

a further exacerbation of the findings in the short term study and confirmed the previously observed toxicities. In the 13-week study, 10 mg/kg was also considered to be the STD_{10}, and a NOAEL was not established.

In the 4-week dog study, dogs received 1, 3 or 10 mg/kg futibatinib every other day or 0.3 and 3 mg/kg every day. No deaths occurred during the study or in the recovery period. Body weight loss was observed in the 3 mg/kg QD only, which correlated with decreased food consumption. Gross pathology revealed white focus in the aortic root in all animals in the 3 mg/kg QD group and one male in the 10 mg/kg QOD group. Absolute and relative spleen weights were increased in the 3 mg/kg QD group. Mineralisation of various tissues was observed, which included mineralization of the coronary artery and endocardium in the heart; arterial wall, papillary, and capsule in the kidney; bronchus in the lung; mucosa and muscularis mucosa in the stomach; or arterial wall in the urinary bladder at 1 mg/kg in the QOD groups and at 0.3 mg/kg in the QD groups. Decreased cartilage ossification was observed in femur and sternum of all test-article related groups. All findings were reversible with exception of ectopic mineralisation of the arterial wall in the aortic root, arterial wall in the heart, mucosa and muscularis mucosa in the stomach, and arterial wall in the urinary bladder. A NOAEL was not established in this study, and white focus in the aortic root, which correlated with mineralisation in the arterial wall, decreased locomotor activity, body weight loss associated with decreased food consumption were considered severe toxicities. Based on the findings, a non-severely toxic dose of 3 mg/kg QOD or 0.3 mg/kg QD was established.

The 13-week dog study, in which animals received 0.3, 1 or 3 mg/kg futibatinib every other day, confirmed the findings of the 4-week study. Severe toxicity was identified as mineralisation of the aortic root at the highest dose tested, 3 mg/kg. There is no clinical exposure multiple at this dose. Notably, the white focus that was observed previously was absent in this study. Other toxicologically relevant findings that were not previously observed included cell infiltration in arterial walls of the aortic root in males at 0.3 and 3 mg/kg; oedema and cell infiltration of the tunica intima and haemorrhage of arterial walls of the aortic root in males and females at 1 and 3 mg/kg; bone lesions of the femur (*i.e.*, elongation of the proliferating zone, hypertrophic zone, and primary spongiosa, increased trabecular bone, and hypercellularity [including bone marrow]) in both sexes at 0.3 mg/kg; and bone lesions of the sternum (*i.e.*, elongation of proliferating zone, thinning of hypertrophic zone, and hypercellularity, including in bone marrow) in both sexes from 0.3 mg/kg onwards. Considering the absence of a NOAEL, and the STD falling within clinical exposure, all findings are considered to be clinically relevant.

2.5.4.3. Genotoxicity

Futibatinib did not increase revertant colonies in a panel of salmonella and E.coli strains. However, in mammalian cells (CHL/IU cells), in presence or absence of metabolic activation, frequencies of cells with structural chromosome aberrations frequencies were dose dependently increased compared to controls. At lower doses there was also an increased frequency of structural chromosomal aberration, but this change was not statistically significant. There was no evidence of statistically significantly increased polyploidy. Therefore, futibatinib is considered to induce chromosomal aberrations in mammalian cells. A micronucleus test in rats receiving up to 300 mg/kg futibatinib did not reveal an increase in frequency of micronucleated reticulocytes. In contrast, the positive control mitomycin C markedly increased the frequency of micronucleated reticulocytes. Therefore, futibatinib is not considered to be clastogenic in rats. A comet assay was performed to evaluate the potential to induce DNA damage. Rats received up to 300 mg/kg futibatinib. No change in percentage of the tail DNA was observed compared to the negative control group receiving the vehicle. In contrast, administration of

the positive control, ethylmethanesulfonate, resulted in a marked increase in tail DNA. Therefore, futibatinib is not considered to induce DNA damage in rats.

Based on the negative results of the AMES and *in vivo* micronucleus and COMET assays in rat, futibatinib is not a genotoxicant.

2.5.4.4. Carcinogenicity

Carcinogenicity studies with futibatinib have not been conducted.

2.5.4.5. Reproductive and developmental toxicity

In line with ICH S9, no fertility, PPND or juvenile animals studies were performed. An EFD dose range finding study revealed considerable maternal toxicity from the lowest dose (1 mg/kg/day) onward, leading to low foetal body weight or total litter loss in the 10 mg/kg dose group. In the 1 mg/kg group, all foetuses were recoded as having anomalies. Subsequently, the GLP EFD study used doses below 1 mg/kg.

In the GLP EFD study, pregnant rats received 0.05, 0.15, or 0.5 mg/kg/day between GD7 and GD17. All dams survived to the end of the study. No treatment related changes were observed in clinical observations, body weight, food consumption, necropsy findings, and caesarean sections such as the number of corpora lutea and implantation, the rate of pre-implantation loss, implantation, and post-implantation loss in any group. In dams, the NOAEL was considered to be 0.5 mg/kg/day. A NOAEL for foetuses could not be established. Foetal body weight was decreased in the high dose group, which correlated to delayed ossification. Visceral and skeletal anomalies were observed in all dose groups, including in heart and vasculature, were observed at all doses. Therefore, futibatinib is teratogenic in rats at clinically relevant doses.

2.5.4.6. Toxicokinetic data

For rat, increases in futibatinib dose resulted in dose-proportional increases in AUC values (except for doses >10 mg/kg QOD. In dog, dose-proportional increases in AUC were observed for all QOD doses except the highest dose of 10 mg/kg. No evidence of accumulation was observed for both species. In the 13-weeks rat study, the exposure multiples ranged from 0.14-1.6 for AUC values. In the 13-weeks dog study, exposure multiples based on AUC values ranged from 0.064-0.76. It can therefore be concluded that the exposures obtained were below the values observed in humans, which indicates that the effects observed in animals could be clinically relevant.

Interspecies comparison

The *in vivo* PK/TK studies with futibatinib were conducted via oral administration, which is the intended route of administration in humans, in rats and dogs, which were used for toxicology studies.

In all species oral absorption was fast and maximal exposure was reached in plasma after 1 – 2h (rat, dog), whereafter it declined quickly leaving ~10% in plasma at 8 hours after dosing. With increasing doses in rats and dogs, the exposure (C_{max} and AUC_{0-24}) of futibatinib was generally dose proportional as was also found in human. No differences were seen between males or females. Upon multiple dosing for 4 or 13 weeks in the safety studies, no apparent accumulation of futibatinib was found yielding similar C_{max} and AUC_{0-24} values as on day 1. Oral bioavailability was not determined but based on the mass balance study in the rat, it was estimated to be at least 65%. Terminal elimination half-life ($t_{1/2}$) values were not determined but are estimated to be less than 2h.

In plasma, a high protein binding was found (95.7% in rat, 95.3% in human; 91.2% in dog). This means that the unbound futibatinib concentration (F_u) is about 2-fold higher in dog than in human or rat. A similar metabolism was seen in rat, dog and human, such as O-demethylation, mono- or di-oxidation, hydration, and Phase II (cysteine or N-acetylcysteine conjugation) conversion. The excretion of futibatinib was found to be largely (>90%) via the biliary/faecal route, as numerous phase I and/or phase II metabolites. Renal excretion was minor route in rat (4.8%), dog (1.3%) and human (6%).

2.5.4.7. Local Tolerance

Not applicable.

2.5.4.8. Other toxicity studies

Futibatinib is unlikely to have phototoxic potential.

2.5.5. Ecotoxicity/environmental risk assessment

Table 1. Summary of main study results

Substance (INN/Invented Name): Futibatinib			
CAS-number (if available): 1448169-71-8			
PBT screening		Result	**Conclusion**
Bioaccumulation potential- log K_{ow}	OECD107	2.0 (pH 2) 3.3 (pH 4) 3.3 (pH 6) 3.3 (pH 7) 3.4 (pH 8) 3.4 (pH 10) 3.5 (pH 12)	Potential PBT (N)
Phase I			
Calculation	**Value**	**Unit**	**Conclusion**
$PEC_{surface\ water}$, refined (prevalence and literature)	0.0000048	µg/L	> 0.01 threshold (N)
Other concerns (e.g. chemical class)			(N)

The experimentally determined log K_{ow} is below 4.5. The refined PEC_{sw} is 0.0000048 µg/L, which is below the action limit of 0.01 µg/L. A phase II ERA is not deemed necessary. Futibatinib is considered not PBT nor vPvB.

2.5.6. Discussion on non-clinical aspects

Pharmacology

Pharmacology studies showed that the mechanism of action for futibatinib includes inhibition of FGFR1-4 with high affinity (as opposed to other FGFR inhibitors that inhibit FGFR1-3), indicating that futibatinib is a potent inhibitor of FGFRs. This inhibition translated into inhibition of growth of various cancer cell lines harbouring different FGFR genetic alterations, whereas growth of cancer lines without FGFR genetic alterations was not inhibited, indicating that futibatinib is a selective compound, which may be used for treatment of FGFR driven oncogenesis. In addition, specific FGFR2 mutations associated with drug resistance were potently inhibited by futibatinib, whereas other FGFR inhibitors (competing for the ATP-binding site as opposed to futibatinib covalent binding to FGFRs) showed less

potent inhibition, indicating futibatinib's potency against tumours that are resistant to other FGFR inhibitors. Proof of concept was shown using mice and rat studies where human FGFR2 cancer cell lines were implanted as xenografts. The growth of these xenografts was inhibited upon futibatinib administration, indicating that futibatinib is able to inhibit growth of human FGFR2 cancer cell line growth *in vivo*. To present the primary pharmacodynamics of futibatinib in cholangiocarcinoma models, literature was provided showing futibatinibs activity in reducing tumour volume as well as inhibition of downstream FGFR signalling in patient-derived xenografts from ICC patients (Ochiiwa *et al*, 2013, Arai *et al*, 2014 and Goyal *et al*, 2019).

In order to investigate the selectivity testing of futibatinib, 287 human serine/threonine and tyrosine protein kinases were screened. RET kinase (S891A mutation) was inhibited by >70% at 100 nmol/L. This is considered to be of low clinical relevance. It is considered acceptable that only human serine/threonine and tyrosine protein kinases were screened for secondary PD effects and data regarding the selectivity for other classes of receptors was not provided, as the risk for (off-target) safety effects of futibatinib is considered low. Finally, all required safety pharmacology studies were performed and were negative for futibatinib-associated effects with adequate exposure multiples.

Pharmacokinetics

Futibatinib (TAS-120) was investigated in a range of *in vitro* and *in vivo* pharmacokinetic (PK) and toxicokinetic (TK) studies to define the absorption, distribution, metabolism, and excretion (ADME). The *in vivo* PK/TK studies were conducted via oral administration, which is the route of clinical administration, and with Sprague Dawley (SD) rats and Beagle dogs, which were used in the nonclinical toxicology studies.

Liquid chromatography with tandem mass spectrometry (LC-MS/MS) methods were adequately validated to analyse plasma samples from both GLP and non-GLP nonclinical studies in rat and dog. Analytical methods (C-AT120019 and C-AT120020) used in repeat dose toxicity studies in rats and dogs, however, are not GLP compliant. It was, however, sufficiently demonstrated that the analytical methods supporting GLP repeat dose toxicity studies were adequately validated, as these were in compliance with domestic reliability standards. Moreover, performance parameters met the pre-defined acceptance criteria, set out by EMA Guideline on Analytical Methods ICHS3A.

During the procedure, the applicant was requested to discuss the possible nature of the [^{14}C]futibatinib-related label present for prolonged time (T1/2 >200h) in dog as in humans, and the possible relevance for clinical safety of futibatinib. It was indicated that this may be due to the covalent binding characteristics of the acrylamide moiety, displaying to a minor extent, also off-target binding to blood and plasma proteins, such as the formation of albumin- and haemoglobin-adducts, and this phenomenon was also observed in humans. This is considered a reasonable explanation for the slow elimination of the [^{14}C]futibatinib-related label as this was also found with other irreversible tyrosine kinase inhibitors, acting via the same acrylamide active site. It is, therefore, agreed that the risk for related clinical safety in humans is considered low.

The *in vitro* metabolite profile of futibatinib was obtained following incubation with Sprague-Dawley rat, beagle dog, and human liver microsomes and hepatocytes. Futibatinib was found to be moderately metabolized, mainly by CYP3A4/5 enzymes.

In both rat and dog [^{14}C]futibatinib was metabolized by phase I (*O*-demethylation, mono- or di-oxidation, hydration) and/or phase II (cysteine or *N*-acetylcysteine conjugation, sulfation, glucuronidation) biotransformation. Of the metabolites detected at 9% in human plasma, P1 was found as M18 in rat bile and P5 as main metabolite M8 in both rat a dog plasma. P7, a cysteinylglycine conjugate, which was identified as a major circulating metabolite in human plasma accounting for 13.4% of the total radioactivity, however, was not detected in rat or dog plasma and also not present in faeces, bile or urine. It was indicated that the formation of a glutathione conjugate metabolite (F18

or M9) is a primary metabolism pathway, after which the glutathione group is being degraded yielding the cysteinylglycine conjugate (P7) and the cysteine conjugate (P5 or M8), which can be further N-acetylated to form the N-acetylcysteine conjugate (F20 or M24). The major human metabolite P7 (cysteinylglycine) it is likely formed in rats and dogs as an intermediate metabolite, since M8 (cysteine conjugate) was detected as the major metabolite in these species. Furthermore, if the P7 metabolite is deconjugated, the parent compound and the cysteinylglycine moiety is formed. The parent compound has been toxicologically tested and the latter compound, the glutathione degradation product, is not considered a safety risk. Therefore, the toxicological risk of P7 is considered low.

The excretion of [^{14}C]futibatinib was investigated in fasting male SD rats (intact and Bile Duct Cannulated, BDC) and Beagle dogs and was found to be largely (>90%) cleared via the biliary/faecal route and mainly, as numerous phase I and/or phase II metabolites. Renal excretion was minor route in rat (4.8%), dog (1.3%) and human (6%).

Toxicology

Repeat-dose toxicology studies were performed in rats and dogs. In the pivotal 4-week and 13-week toxicology studies, no mortality was observed during the treatment window or in the recovery period. Every other day (QOD) administration was better tolerated than daily administration (QD). Nevertheless, comparable and severe toxicity was still observed with the QOD administration schedule albeit at higher doses.

Overall, the toxicology programme revealed ectopic mineralisation of multiple tissues, particularly arterial walls, and aortic artery, which was the primary driver of severe toxicity in both rats and dogs. Other findings included increased inorganic phosphorus and calcium in plasma and lesions in bone/cartilage. These effects were reversible with the exception of ectopic mineralization. Corneal lesions were only observed in rats. The severely toxic dose was comparable to the clinical exposure. Therefore, all findings in the toxicology studies must be considered as clinically relevant. Futibatinib was not mutagenic in vitro in the bacterial reverse mutation (Ames) assay. It was positive in the in vitro chromosome aberration test in cultured Chinese hamster lung cell (CHL/IU), but negative in the bone marrow micronucleus assay in rat and didn't induce DNA damage in comet assay in rats. Thus, futibatinib is overall non-genotoxic (see SmPC section 5.3).

To explain the broader TAS-120 systemic toxicity, it was justified that FGF plays a crucial role in the regulation of both systemic calcium and phosphate homeostasis with FGFR. In particular, FGF23 (a member of a subfamily of FGFs that acts as hormones/ systemic factors) plays an essential role in absorption of calcium in the gastrointestinal tract, reabsorption of calcium and phosphate in the kidney and osteogenic regulation in the bone (Shimada et al, 2001; Quarles et al., 2008). As extracellular phosphate had been known to be necessary for matrix mineralization, the TAS-120 systemic toxicological findings such as increases in Ca and IP, ectopic mineralization of the heart and abnormal bone metabolism are deemed to be associated by imbalance of calcium and phosphate homeostasis induced by the pharmacological action of TAS-120 through FGFR23 (Xu et al., 2012).

Dedicated fertility studies with futibatinib have not been conducted. In repeat dose toxicity studies, oral administration of futibatinib did not result in any dose-related findings likely to result in impaired fertility in male or female reproductive organs.

Based on the mechanism of action and observed embryo-foetal toxicity in an animal study, futibatinib can cause foetal harm when administered to a pregnant woman. Pregnant women should be advised of the potential risk to the foetus. An effective method of contraception should be used in women of childbearing potential and in men with women partners of childbearing potential during treatment with Lytgobi and for 1 week following completion of therapy, barrier methods should be applied as a second

form of contraception to avoid pregnancy. A pregnancy test should be performed before treatment initiation to exclude pregnancy (see SmPC sections 4.4, 4.5 and 4.6).

Futibatinib is not indicated for paediatric use. There was no assessment of the translatability of toxicity observed in adult animals. Juvenile animal studies were not conducted.

In accordance with ICH S9, carcinogenicity studies are not required for oncology treatments for patients with terminal cancer, the intended target population of futibatinib.

Environmental Risk Assessment

Futibatinib PEC surfacewater value is below the action limit of 0.01 µg/L. and is not a PBT substance as log Kow does not exceed 4.5.

2.5.7. Conclusion on the non-clinical aspects

The non-clinical pharmacodynamics, pharmacokinetics and toxicology aspects of Lytgobi (futibatinib) have been adequately addressed.

2.6. Clinical aspects

2.6.1. Introduction

GCP aspects

The Clinical trials were performed in accordance with GCP as claimed by the applicant.

The applicant has provided a statement to the effect that clinical trials conducted outside the Community were carried out in accordance with the ethical standards of Directive 2001/20/EC.

- **Tabular overview of clinical studies**

Table 2. Futibatinib clinical pharmacology studies supporting registration.

Phase	Study Number	Study Description	Subject Population	Region
Phase 1/2	TAS-120-101	Phase 1 dose escalation/expansion, Phase 2	Patient	Global
Phase 1	10059010	Phase 1 dose escalation/expansion	Patient	Japan
	10059020	Bioavailability between formulations	Healthy adult	Japan
	TAS-120-102	Food effect	Healthy adult	Canada
	TAS-120-103	DDI with strong CYP3A inhibitor and inducer	Healthy adult	US
	TAS-120-104	DDI with a proton pump inhibitor	Healthy adult	US
	TAS-120-105	DDI with a CYP3A substrate	Healthy adult	US
	TAS-120-106	Mass balance	Healthy adult	US
	TAS-120-107	Cardiac safety	Healthy adult	US
	TAS-120-108	Hepatic impairment (ongoing)	Hepatic impairment	US
Modeling and simulation	20DC01	PBPK analysis for DDI with CYP3A inhibitors and inducers	-	-
	20DC09	PBPK analysis for DDI with transporters	-	-
	TONC-PMX-TAS120-1718	PopPK and ER analyses	-	-

Abbreviations: CYP=cytochrome P450; DDI=drug-drug interaction; ER=exposure-response; PBPK=physiologically based pharmacokinetic; PK=pharmacokinetics; PopPK=population PK; -: not applicable
Note: The dataset for Study TONC-PMX-TAS120-1718 included all clinical pharmacology studies except for Study TAS-120-106 and Study TAS-120-108.

2.6.2. Clinical pharmacology

2.6.2.1. Pharmacokinetics

The pharmacokinetics of futibatinib has been characterized in 10 studies (Table 2), 7 studies in healthy volunteers, 2 studies in patients with advanced solid tumours, and 1 study in subjects with hepatic impairment. The healthy volunteer studies addressed the relative bioavailability of the final tablet formulation, food effect, mass balance and metabolite profile and potential for drug-drug interactions with futibatinib and cardiac safety. The PK study in subjects with impaired hepatic function was finalised and the report submitted during the assessment period. The primary efficacy data supporting this submission was based on clinical data from the pivotal Phase 1/2 Study TPU-TAS-120-101. In addition to the 10 clinical studies, 3 reports on population pharmacokinetics and exposure-response analyses, and PBPK to support drug-drug interactions have been submitted.

Further, in vitro studies with human biomaterials included assessments of membrane permeability (20DB01), plasma protein binding, blood-to-plasma concentration ratio (Rb) (16DA16), metabolism (18DB26, 19DB06, and TDM22BRT010P), and potential for drug-drug interactions (DDIs) (16DA10,

18DB18, and XT133007). In vitro activity of primary circulating metabolites in human plasma was also assessed (Study CBS-200034).

The starting dose of futibatinib is 20 mg once daily. The tablets can be taken with or without food, however, dietary restrictions that limit phosphate intake is recommended as part of hyperphosphatemia management.

A single strength (4 mg) was developed for commercialization, as this strength allows the flexibility for dose adjustment from the recommended dose of 20 mg QD for the management of toxicities.

Methods

Bioanalytical methods (reports JCL10391451, 8291169, CA28028-01)

Validated methods were used to analyse futibatinib in human plasma treated with K_2EDTA anticoagulant by using liquid chromatography with tandem mass spectrometric detection (LCMS/MS) by three different testing facilities. Cross-validation between testing facilities was not conducted. Calibration standard, QC sample, and ISR data indicated that the analytical methods performed acceptably during the bioanalytical studies. Samples were analysed within the established long term stability periods.

PopPK analysis (Report TONC-PMX-TAS120-1718)

PopPK analysis was conducted to characterize the population pharmacokinetics of futibatinib and to evaluate exposure-response relationships for efficacy and safety to support dose selection of futibatinib in adult subjects with CCA harbouring FGFR2 rearrangements (including fusions) aberrations

PopPK development and reporting was in line with the recommendations in the guideline on reporting the results of population pharmacokinetic analyses CHMP/EWP/185990/06. The PK of futibatinib following oral administration was described by a two-compartment model combined with sequential zero- and first-order absorption and first-order elimination (Table 3). 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.

- Serum albumin and futibatinib dose ≥36 mg were found to be significant predictors of CL/F.
- Body weight and futibatinib dose ≥36 mg were found to be significant predictors of Vc/F.

The relative oral bioavailability was impacted by the following factors:

- Reduced to 39% in subjects concomitantly on cytochrome P4503A (CYP3A) inducers (rifampin).
- Increased by 30% in subjects concomitantly on CYP3A inhibitors (itraconazole).
- Reduced to 43% in subjects in Study 10059020 in Japanese healthy volunteers (removed in sensitivity analysis Run085s).
- Reduced to 77% in subjects in Study TAS-120-101, TAS-120-102, or TAS-120-107, respectively, compared to subjects in Studies TAS-120-103, 104, 105, or 10059010. Observed differences between studies could not be attributed to subject-specific covariates, such as healthy status, race, formulation or food. A sensitivity analysis Run85s has been conducted without study as factor on relative bioavailability (Table 3).
- The presence of food reduced ka to 17.7% of the ka under the fasted condition.

Table 3. Parameters of the final pop PK model (run085) for futibatinib and sensitivity analysis (Run85s) without study as covariate on F.

Parameter		Final Model (Run085)		Sensitivity Analysis Model (Run085s)		Difference in %[c]
		Estimate (RSE[a] (%))	IIV[b] (CV%) (RSE (%))	Estimate (RSE[a] (%))	IIV[b] (CV%) (RSE (%))	(Estimate/IIV)
	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 Inducers		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 Inhibitors		1.30 (5.62)		1.31 (5.70)		0.769
F relative for study 10059020		0.428 (12.2)		-		-

Parameter		Final Model (Run085)		Sensitivity Analysis Model (Run085s)		Difference in %[c]
		Estimate (RSE[a] (%))	IIV[b] (CV%) (RSE (%))	Estimate (RSE[a] (%))	IIV[b] (CV%) (RSE (%))	(Estimate/IIV)
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

Abbreviations: CL/F = apparent clearance; CV% = percent coefficient of variation; CYP3A4 = cytochrome P450 3A4; D1 = duration of zero-order absorption rate;; F = bioavailability; HV = healthy volunteer; IIV = inter-individual variability; ka = first-order absorption rate constant; PAT = patient; Q/F = apparent inter-compartmental clearance; RSE = relative standard error; SD = standard deviation; SE = standard error; Vc/F = apparent central volume of distribution; Vp/F = apparent peripheral volume of distribution.

a The RSE of parameter estimate is calculated as 100 × (SE/typical value); the RSE of IIV magnitude is calculated as 100 × (SE/variance estimate).

b Estimates for random effects and IIV are presented in CV% and, based on the estimated variances, are calculated as $\sqrt{}$(exp [variance] - 1) × 100.

c Difference between fixed parameter estimates was calculated as follows: (Sensitivity analysis model parameter - final model parameter)/ final model parameter × 100

Source: run085.lst, run085s.lst, Sensitivity analysis.xlsx

PcVPCs suggests an acceptable fit, adequately capturing the central tendency and range of the data, although the median absorption peak was slightly lower for the model predictions.

PBPK modelling studies 20DC01 & 20DC09

In study 20DC01 a PBPK model of futibatinib was developed to predict effects of coadministration of various inhibitors and inducers of CYP3A on the plasma exposure of futibatinib after multiple administrations in cancer patients. In study 20DC09, the inhibitory effect of futibatinib on the transporters P-gp and BCRP was evaluated using a population-based PBPK software Simcyp® version 19 release 1.

A middle out PBPK development was selected using data from studies TAS-120-103, 104 and 106 for model development. The values of ka, lag time, and Kp scalar were updated by parameter estimation using clinical PK data after single administration of futibatinib alone in the Study TAS-120-104. Subsequently, CLint for CYP2C9, CYP2D6, CYP3A4, and additional hepatic clearance were refined based on the sensitivity analysis on fmCYP3A4 and subsequent retrograde model analysis. It was assumed that Pgp was not relevant in the absorption of futibatinib.

The model verification with multiple dose data from patients and healthy subjects (study TAS-120-105), effect of rifampicin (TAS-120-103), and food effect study (TAS-120-102) and sensitivity analyses showed that the PBPK model for futibatinib describes well the pharmacokinetic profile of futibatinib in healthy subjects and in cancer patients from study TAS-120-101. Futibatinib exposures are predicted to be somewhat higher in patients than in healthy subjects.

The model was then applied to predict the effect of various CYP3A inhibitors and inducers on futibatinib PK after multiple administrations in cancer patients.

In study 20DC09, the effect of coadministration of futibatinib on the plasma exposure of digoxin, a P-gp substrate, and rosuvastatin, a BCRP substrate, in healthy subjects was predicted using a population-based PBPK. The model development strategy was the same as described for study 20DC01. In addition, for this analysis, the absorption model was changed from the first-order model to the advanced dissolution, absorption, and metabolism (ADAM) model using available data. Data from futibatinib 80 mg dose from study TAS-120-107 were used for development of the absorption model. The developed model for futibatinib was then verified using PK data from clinical studies (Studies TAS-120-102, TAS-120-106, and TAS-120-107), which were not used for the model development.

Absorption

In vitro solubility and permeability

Solubility of futibatinib is pH dependent and solubility is low at ≥ pH 3. The in vitro permeability of futibatinib in Caco-2 cells (Study 20DB01) was concentration dependent with a lower apparent permeability at low dose 0.3 µM but high permeability at the higher doses of 6 and 60 µM. Futibatinib can be considered a low solubility, high permeability compound.

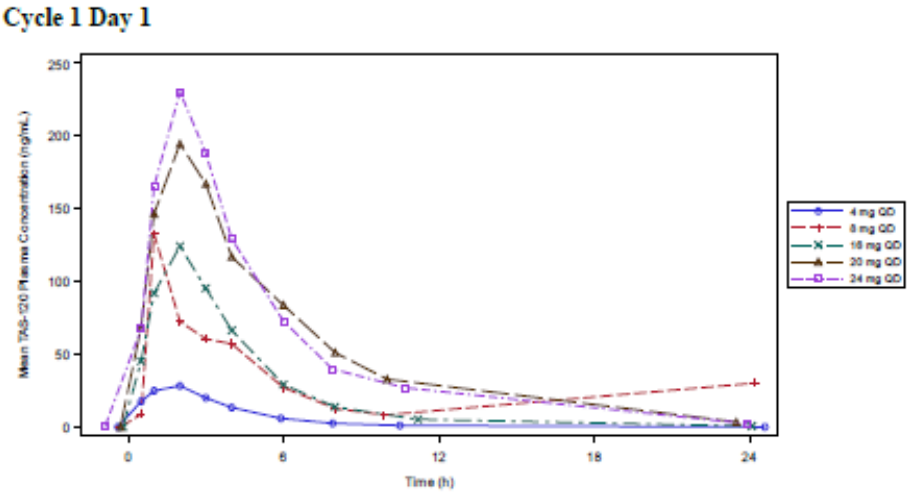
In vivo absorption

Single-dose mean plasma concentrations versus time profiles of futibatinib in cancer patients Study TAS-120-101 are shown in Figure 2. Futibatinib maximal plasma concentrations were reached within 1-3 hours after administration. C_{max} and AUC increased over the dose range of 4 mg to 24 mg. Plasma elimination half-life of futibatinib was 2-3 hours.

Intersubject variability of futibatinib C_{max} and AUC exposure is moderate to high, 19%-52% and 36-68%, respectively, based on the non-compartmental analysis in healthy subjects. Intrasubject

variability was lower 19-36% for C_{max} and between 16-23% for AUC (Table 5).

Figure 2. Mean plasma concentration of futibatinib vs. time for Cycle 1 Day 1 in patients (Study TAS-120-101)



An absolute bioavailability study has not been conducted.

Bioequivalence

Two dosage forms, liquid filled hard capsules and immediate release film-coated tablets were developed for use in clinical studies of futibatinib. Both formulations were available at 4 mg and 20 mg strengths and have been used in the pivotal Phase 1/2 Study TPU-TAS-120-101. Bioequivalence between the capsule and tablet formulation has been demonstrated in study 10059020: the point estimates of the GMRs of C_{max}, AUC_{0-48}, and AUC_{inf} were 0.99 (90% CI 0.83-1.18), 1.05 (90% CI 0.94-1.18), and 1.09 (90% CI 0.97-1.23).

A tablet single strength (4 mg) was developed for commercialization, as this strength provided the required flexibility for dose adjustment to the recommended dose of 20 mg QD. Compared to the tablets used in clinical studies, the commercial tablets had no colorant, which was no longer required to differentiate the strengths in the clinical study. The commercial tablet formulation was used in Phase 1 (QT/QTc study TAS-120-107), and pharmacokinetics of the commercial and clinical tablet formulation were similar in an across study comparison.

Food effect

In Study TAS-120-102, futibatinib PK was assessed in 17 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}, and AUC_{last} of futibatinib with fed:fasted ratio of 0.58 (90% CI 0.47-0.70) and 0.86 (90% CI 0.77-0.96), respectively. T_{max} was delayed by 2.5-3 hours under fed conditions.

Distribution

The mean apparent volume of distribution (Vz/F) (CV%) following single-dose oral administration of futibatinib 20 mg to patients with advanced solid tumours was 73 L (32.9%) (Study TAS-120-101).

Human plasma protein binding was determined by using the equilibrium dialysis method. Protein binding of futibatinib in human plasma is approximately 95% at concentrations of 0.2, 1, and 5 µmol/L and was primarily bound to human serum albumin and α1-acid glycoprotein.

Blood:plasma values of futibatinib varied from 0.589 to 0.664 at concentrations of 0.2, 1 and 5 µmol/L, respectively (study 16DA16). In the mass balance study (TAS-120-106), total radioactivity was preferentially confined to plasma over approximately the first 6 hours post-dose as evidenced by mean blood:plasma ratios of 0.51 – 0.72. From 8 – 48 hours post-dose, total radioactivity distributed to red blood cells as evidenced by mean blood:plasma ratios of 0.85 – 1.70.

Elimination

Following single-dose oral administration of futibatinib 20 mg, the mean oral clearance was 18 L/hr (CV% 44%) and the mean terminal elimination half-life was 2.94 hours (CV% 26.5%) (Study TAS-120-101).

In the mass balance study TAS-120-106, the mean elimination half-life was approximately 2.3 hours for plasma futibatinib, compared to half-lives of approximately 12 and 29 hours for total radioactivity in plasma and whole blood, respectively.

The popPK analyses predicted a geometric mean CL/F (gCV%) in patients of 19.8 L/hr (23%) and an initial half-life of 2.1h (32%) and terminal half-life of 10.5h (3%) (Study TONC-PMX-TAS120-1718).

Excretion

Excretion of futibatinib was evaluated in the mass balance study TAS-120-106 in 6 healthy adult male subjects following a single oral dose of 20 mg [14C]-futibatinib oral solution (~100 µCi) under fasted conditions. Faecal excretion represents the major excretion pathway of futibatinib and its metabolites, and the urinary route is minor. Total recovery of radioactivity ranged from 77% to 85% in 5 of the 6 subjects, but was low at 26% for Subject 6. Of the 70%±25% of the administered radioactivity recovered was 64%±25% as recovered in faeces: only 6%±1% of the administered radioactivity was recovered in urine. Futibatinib excretion into either urine or faeces in unchanged form was negligible.

In patients with advanced solid tumours, urinary excretion of the unchanged form of futibatinib was less than 0.1% of administered dose following single dose administration of futibatinib (Study TAS-120-101 and Study 10059010).

Metabolism

The in vitro metabolite profiling of futibatinib was conducted in liver microsomes, S9 fractions and hepatocytes. The major metabolites in human liver microsomes were an O-demethylated product, mono-oxidized and hydrated products whereas in human hepatocytes the major metabolites of futibatinib were a cystine conjugate and a glutathione conjugate. In vitro assessments with human hepatic hepatocytes suggested that the contribution of CYP enzymes to hepatic metabolism of futibatinib was approximately 40% of which CYP3A is the primary CYP enzyme (estimated 70%) involved in the futibatinib metabolism (Study 19DB06). Futibatinib was stable in human blood; therefore, metabolizing enzymes in erythrocytes and plasma are considered to make little contribution to the futibatinib metabolism.

The metabolism of futibatinib was evaluated in the mass balance study TAS-120-106 following a single oral dose of 20 mg (~100 µCi) [14C]-futibatinib. The main component in plasma was futibatinib parent compound (59.19%). A cysteinylglycine conjugate (TAS-06-22952), cysteine conjugate (TAS-06-22947), and a glucuronide conjugate of mono-oxidized product accounted for 13.37%, 8.68%, and 8.97% of the radioactivity in the plasma sample, respectively. On the other hand, in the faeces samples, O-demethylated metabolites (a di-O-demethylated, mono-oxidized and hydrogenated product, a di-O-demethylated and hydrogenated product, an O-demethylated, hydrated and hydrogenated product, and an O-demethylated and hydrogenated product) existed at the higher level compared to a glutathione conjugate and its derivatives (an N-acetylcysteine conjugate of mono-

oxidized product and an N-acetylcysteine conjugate) (29% vs. 8% of the dose). Futibatinib was negligible in the faeces and urine samples.

The two primary circulating metabolites in human plasma a cysteinylglycine conjugate (TAS-06-22952) and a cysteine conjugate (TAS-06-22947) showed no in vitro activity (Study CBS-200034).

Futibatinib has an asymmetric centre but no racemization is observed.

Dose proportionality and time dependencies

Dose proportionality of pharmacokinetics of futibatinib following single dose and multiple dose administration was evaluated in patients in studies TAS-120-101 and 10059010 following a QD schedule over the dose range 4-24 mg futibatinib (Table 4) or QOD schedule over the dose range 8-200 mg. C_{max} and $AUC_{0\text{-}last}$ increased dose proportional over the dose range 4-24 mg. For the QOD dosing schedule (range 8-200 mg), Cmax increased in a less than dose-proportional manner in the dose range of 8 to 200 mg while AUCs increased dose-proportionally.

Table 4. PK Parameters of futibatinib in plasma for Cycle 1 Day 1 and Day 21, QD Schedule in patients (Study TAS-120-101)

Visit		Cycle 1 Day 1					Cycle 1 Day 21					
Dose Level	Statistic	T_{max} [hr]	$T_{1/2}$ [hr]	C_{max} [ng/mL]	$AUC_{0\text{-}last}$ [ng·hr/mL]	$AUC_{0\text{-}inf}$ [ng·hr/mL]	T_{max} [hr]	$T_{1/2}$ [hr]	C_{max} [ng/mL]	$AUC_{0\text{-}last}$ [ng·hr/mL]	R_{Cmax}	R_{AUC}
4 mg (N=4)	n	4	4	4	4	4	3	3	3	3	3	3
	Mean	0.960 [0.50-2.02]	1.750	33.101	114.076	116.961	1.080 [1.00-3.00]	1.626	52.469	134.170	2.073	2.058
	SD		0.5099	20.3791	85.8877	86.9959		0.7475	38.1259	100.4673	0.3258	0.7241
	CV (%)		29.1	61.6	75.3	74.4		46.0	72.7	74.9	15.7	35.2
8 mg (N=5)	n	5	4	5	5	4	5	5	5	5	5	5
	Mean	2.000 [1.00-25.50]	2.262	168.888	666.067	523.737	2.000 [1.00-3.08]	2.754	98.163	550.414	1.324	1.373
	SD		0.7822	149.7500	504.8350	421.2346		0.5936	56.5178	442.3017	1.5279	1.1210
	CV (%)		34.6	88.7	75.8	80.4		21.6	57.6	80.4	115.4	81.6
16 mg (N=14)	n	14	14	14	14	14	9	9	9	9	9	9
	Mean	2.000 [1.00-3.00]	2.726	148.347	536.161	549.251	2.070 [0.93-3.07]	2.531	171.667	736.726	1.237	1.653
	SD		1.7606	67.0449	283.7782	290.3819		1.1349	72.6475	373.3028	0.6108	0.6701
	CV (%)		64.6	45.2	52.9	52.9		44.8	42.3	50.7	49.4	40.5
20 mg (N=7)	n	7	6	7	7	6	2	2	2	2	2	2
	Mean	1.920 [1.00-3.00]	2.940	256.703	1189.003	1301.454	3.515 [3.05-3.98]	3.436	170.580	1179.475	0.727	1.166
	SD		0.7779	70.0737	647.9791	654.9837		NC	NC	NC	NC	NC
	CV (%)		26.5	27.3	54.5	50.3		NC	NC	NC	NC	NC
24 mg (N=14)	n	14	13	14	14	13	3	2	3	3	3	3
	Mean	1.980 [0.98-3.08]	3.128	245.755	1217.251	1270.288	2.000 [1.98-6.07]	3.115	193.556	1415.655	0.921	1.511
	SD		0.9405	112.7337	656.0345	668.4572		NC	112.3671	903.2421	0.3052	0.8611
	CV (%)		30.1	45.9	53.9	52.6		NC	58.1	63.8	33.2	57.0

Abbreviations: $AUC_{0\text{-}last}$=area under the concentration-time curve up to the last observable concentration; $AUC_{0\text{-}inf}$=area under the concentration-time curve up to infinity; C_{max}=maximum concentration in plasma; CV=coefficient of variation; NC=not calculable; PK=pharmacokinetics; QD=Once daily (continuous) dosing; R_{AUC}=accumulation ratio calculated based on $AUC_{0\text{-}last}$; R_{Cmax}=accumulation ratio calculated based on C_{max}; SD=standard deviation; $T_{1/2}$=terminal half-life time; T_{max}=time to reach maximum concentration in plasma

Notes: T_{max} is represented as the median [minimum-maximum]. PK parameters after repeated doses obtained from patients who had dose interruption or reduction were excluded from the calculation of descriptive statistics.

Source: Table 14.4.2.1.2B

PopPK analysis with 203 patients who received 20 mg QD predicted the accumulation ratio (gCV%) was 1.03 (2.30%) and the steady state exposure was predicted to be reached after the first dose.

Target population

Table 5 summarises plasma futibatinib PK parameters for patients with advanced solid tumours (Study TAS-120-101 and Study 10059010) and healthy adult subjects (Studies 10059020, TAS-120-102, TAS-120-103, TAS-120-104, TAS-120-106, and TAS-120-107) following a single oral dose of futibatinib 20 mg. Considering the large inter-subject variability of Cmax and AUC, it is unlikely that there is a large difference in futibatinib PK between patients with solid tumours and healthy adult subjects.

Table 5. Variability in Cmax, AUClast, and AUCinf values across studies in healthy subjects and patients using non-compartmental analysis and popPK analysis (TONC-PMX-TAS120-1718)

Studies	Statistics	C_{max} (ng/mL)	AUC_{last} (ng·hr/mL)	AUC_{inf} (ng·hr/mL)
Healthy adult subjects				
10059020 (N=24)	Geometric mean[a]	94.4	376[b]	401
	Inter-subject CV (%)	30.5	48.1[b]	44.3
	Intra-subject CV (%)	35.7	22.9[b]	22.8
TAS-120-102 (N=16)	Geometric LSM[c]	156.2	622.7	630.2
	Inter-subject CV (%)	19.2	39.8	38.8
	Intra-subject CV (%)	31.5	17.0	16.0
TAS-120-103 (Part 1) (N=20)	Geometric LSM[c]	167.3	673.9	679.0
	Inter-subject CV (%)	26.24	50.72	50.47
	Intra-subject CV (%)	31.86	26.45	26.52
TAS-120-103 (Part 2) (N=20)	Geometric LSM[c]	222.4	946.7	954.9
	Inter-subject CV (%)	35.12	37.01	36.71
	Intra-subject CV (%)	25.89	30.82	31.13
TAS-120-104 (N=20)	Geometric LSM[c]	216.1	934.0	941.6
	Inter-subject CV (%)	42.72	52.02	51.76
	Intra-subject CV (%)	19.09	18.42	18.22
TAS-120-107 (N = 45)	Geometric Mean	165.2	704.3	713.5
	Geometric CV (%)	52.3	68.7	68.2
Patients with advanced solid tumors				
TAS-120-101 (N=7)	Geometric mean	247.3	1062	1182
	Geometric CV (%)	31.4	53.4	50.1
10059010 (N=7)	Geometric mean	204	760	765
	Geometric CV (%)	89.2	95.4	95.4
TONC-PMX-TAS120-1718 (N=203)	Geometric mean	144[d]	790[e]	NA
	Geometric CV (%)	50.3	44.7	NA

Abbreviations: ANOVA=analysis of variance; AUC_{inf}=area under the plasma concentration-time curve from time 0 to infinity; AUC_{last}=area under the plasma concentration-time curve from time 0 to time of the last quantifiable plasma concentration; AUC_{ss}=area under the plasma concentration-time curve at steady state; C_{max}=maximum plasma concentration; $C_{max,ss}$=maximum plasma concentration at steady state; CV=coefficient of variation; LSM=least square mean; NA=not available

[a] Geometric means of PK parameters of the tablet formulation (AUC_{inf} represents of the mean of 22 subjects).

[b] AUC represents area under the plasma concentration-time curve from 0 to 48 hours.

[c] Geometric LSMs of PK parameters for the reference treatment group estimated from an ANOVA linear mixed effect model (for Study TAS-120-102, AUC_{inf} represents the mean of 15 subjects).

[d] $C_{max,ss}$.

[e] AUC_{ss}.

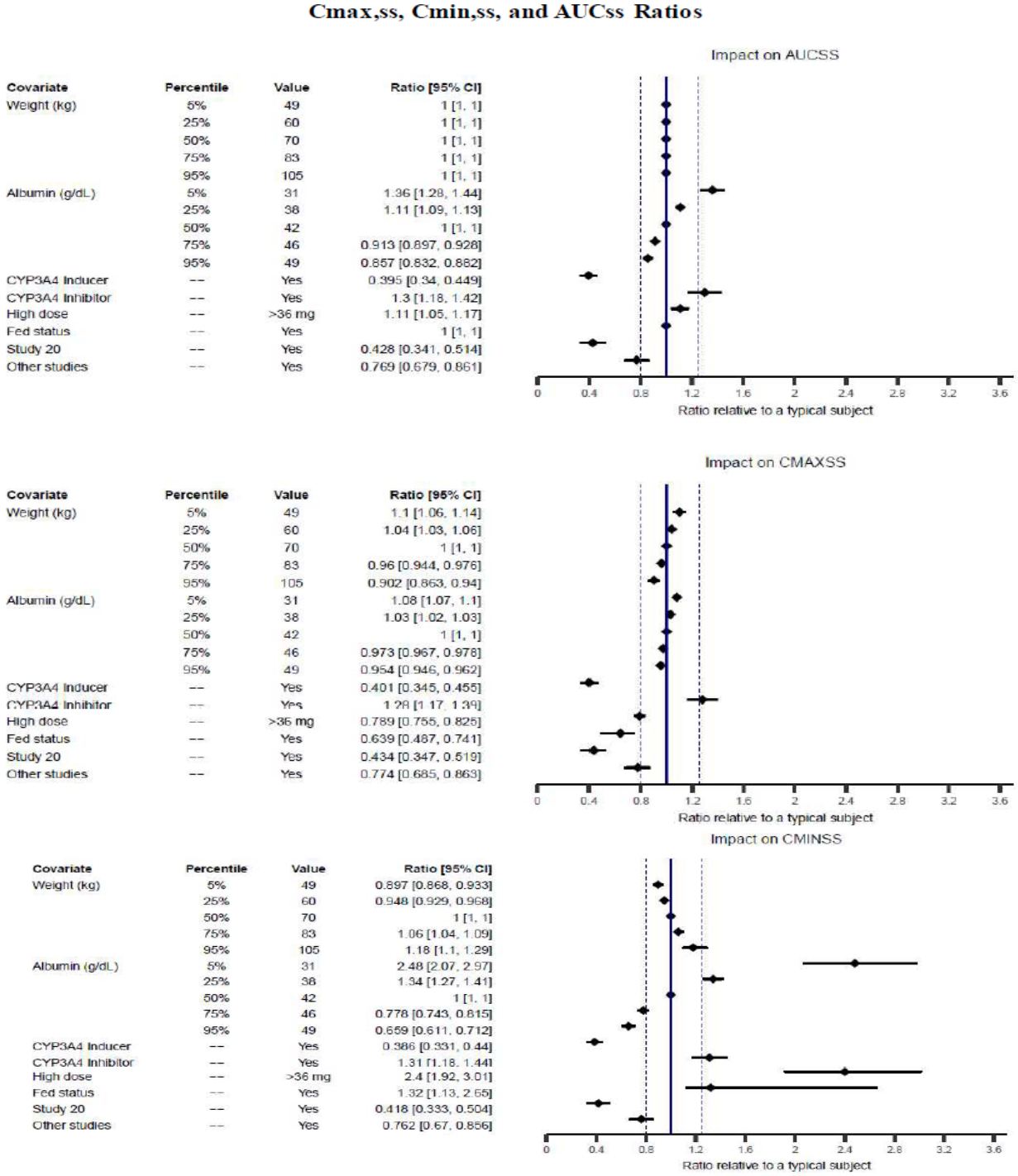
Special populations

Table 6. Age Distribution (Number [Percent] of Patients)

	Age <65 years	**Age 65-74 (Older subjects number /total number)**	**Age 75-84 (Older subjects number /total number)**
PK Trials	396	79	16

Effects of intrinsic and extrinsic factors on futibatinib PK were assessed by the popPK analysis. Serum albumin and futibatinib dose ≥36 mg were found to be significant predictors of CL/F. Body weight and futibatinib dose ≥36 mg were found to be significant predictors of Vc/F. The presence of food has an effect on the absorption rate. CYP3A4 inducers and inhibitors reduced and increased the relative bioavailability. Relative bioavailability was impacted by study. The final popPK model was used to evaluate the influence of covariates on steady-state exposure metrics (area under the concentration-time curve at steady-state [AUC_{ss}], maximum concentration at steady-state [$C_{max,ss}$], and minimum concentration at steady-state [$C_{min,ss}$]) using forest plots (Figure 3). No effects of ALP, formulation, sex, race, renal or hepatic impairment were identified. No effects of mild (N=127) or moderate (N=36) renal impairment on the PK of TAS-120 were found. There were no subjects with severe renal impairment. No effects of mild (N=56) or moderate (N=3) hepatic impairment on the PK of TAS-120 were found. In addition, effect of hepatic function on the pharmacokinetics of futibatinib was evaluated in study TAS-120-108. Similar futibatinib exposures were observed in subjects with mild (Child-Pugh class A), moderate (Child-Pugh class B), or severe (Child-Pugh class C) hepatic impairment compared to subjects with normal hepatic function. The unbound futibatinib concentrations at 2h and 12h also overlapped between healthy subjects and subjects with hepatic impairment.

Figure 3. Forest plot of covariate effects on futibatinib exposure (popPK report TONC-PMX-TAS120-1718)



Abbreviations: AUCSS = area under the concentration-time curve at steady-state; CMAXSS = maximum concentration at steady-state; CMINSS = minimum concentration at steady-state; CYP3A4 = cytochrome P450 3A4; Study 20 = Study 10059020 studies; Other studies = Studies TAS-120-102, TAS-120-107, and TAS-120-101.

Note: Exposures were estimated after a 20 mg QD dose. The first and second dashed vertical lines correspond to ratios of 0.8 and 1.25, respectively. The solid vertical line corresponds to a ratio of 1 and represents the typical subject. Points and whiskers represent the estimates and 90% CIs, respectively. A typical subject is defined as a subject with a body weight of 70.4 kg, serum albumin of 42 g/L, dose <36 mg, receiving no co-administration with a CYP3A4 inducer or inhibitor, administered TAS-120 in fasted state and in Study TAS-120-103, TAS-120-104, TAS-120-105, or 10059010.

Pharmacokinetic interaction studies

Three in vivo drug-drug interaction studies were conducted:

In study TAS-120-104, the effect of elevated gastric pH by multiple-dose lansoprazole on the absorption of futibatinib was investigated.

In study TAS-120-103 the effect of the strong CYP3A4 and Pgp/BCRP inhibitor itraconazole and the strong inducer rifampicin on the pharmacokinetics of futibatinib was investigated.

In study TAS-120-105, the effect of futibatinib as inhibitor of CYP3A4 was investigated on the pharmacokinetics of midazolam.

The results of the effects of lansoprazole, itraconazole, and rifampicin on the pharmacokinetics of futibatinib are summarised in Table 7. Following administration of lansoprazole + futibatinib, the geometric mean values of AUC_{last}, AUC_{inf}, and C_{max} were similar to those following futibatinib alone. Co-administration of futibatinib with itraconazole resulted in approximately 51% and 41% increases in C_{max} and AUC of futibatinib following a single dose in healthy adult subjects. The median T_{max} was approximately 0.5 hours earlier following itraconazole + futibatinib compared to futibatinib alone. The arithmetic mean T1/2 were approximately 3.5 and 2.6 hours following itraconazole + futibatinib and futibatinib alone, respectively. Co-administration of futibatinib with the strong CYP3A and P-gp inducer rifampicin resulted in approximately 53% and 64% decreases in C_{max} and AUCs of futibatinib as shown in Table 7. The median T_{max} was delayed by 0.5 hours following rifampin + futibatinib compared to futibatinib alone. The $T_{1/2}$ arithmetic means were 2.0 and 2.8 hours following rifampicin + futibatinib and futibatinib alone, respectively.

Table 7. Effects of lansoprazole 60 mg QD, itraconazole 200 mg QD and rifampicin 600 mg QD of the pharmacokinetics of futibatinib 20 mg (studies TAS-120-104 and TAS-120-103)

	Lansoprazole + Futibatinib		Futibatinib Alone					
Parameter	Geometric LSMs	n	Geometric LSMs	n	GMR (%)	90% Confidence Interval	Intra-subject CV%	Inter-subject CV%
AUC_{last} (ng·hr/mL)	983.3	20	934.0	20	105.28	95.27 - 116.34	18.42	52.02
AUC_{inf} (ng·hr/mL)	990.7	20	941.6	20	105.22	95.32 - 116.15	18.22	51.76
C_{max} (ng/mL)	234.3	20	216.1	20	108.40	97.74 - 120.21	19.09	42.72

	Itraconazole + Futibatinib		Futibatinib Alone					
Parameter	Geometric LSMs	n	Geometric LSMs	n	GMR (%)	90% Confidence Interval	Intra-subject CV%	Inter-subject CV%
AUC_{last} (ng·hr/mL)	950.7	20	673.9	20	141.07	122.37 - 162.62	26.45	50.72
AUC_{inf} (ng·hr/mL)	956.5	20	679.0	20	140.86	122.15 - 162.45	26.52	50.47
C_{max} (ng/mL)	253.1	20	167.3	20	151.28	127.63 - 179.31	31.86	26.24

	Rifampin + Futibatinib		Futibatinib Alone					
Parameter	Geometric LSMs	n	Geometric LSMs	n	GMR (%)	90% Confidence Interval	Intra-subject CV%	Inter-subject CV%
AUC_{last} (ng·hr/mL)	340.6	20	946.7	20	35.98	30.51 - 42.42	30.82	37.01
AUC_{inf} (ng·hr/mL)	344.4	20	954.9	20	36.06	30.54 - 42.59	31.13	36.71
C_{max} (ng/mL)	105.0	20	222.4	20	47.24	41.10 - 54.30	25.89	35.12

Futibatinib showed time-dependent inhibition of CYP3A4 in vitro. However, in the clinical interaction study with midazolam (TAS-120-105), futibatinib (20 mg QD for 7 consecutive days) did not inhibit

CYP3A4, mean values of AUC_{last}, and C_{max} of midazolam in presence of futibatinib 20 mg QD were similar to those following midazolam alone.

In vitro interactions

Futibatinib is a substrate for CYP3A4, P-gp and to lesser extent also for BCRP.

Futibatinib reversibly inhibited activities of CYP2C8, CYP2C9 and CYP2C19 with IC50 values of 8.14, 23.9, and 26.5 µmol/L, respectively, in vitro (Study 18DB18). These IC50 values are higher than the cut-off values of the basic model indicating that futibatinib 20 mg QD is unlikely to cause clinical DDIs with CYP2C substrates.

Based on the in vitro data, futibatinib could be an inducer of CYP1A2, and could be an inhibitor for Pgp, BCRP and OATP1B1. PBPK modelling was used to further justify the potential of futibatinib to inhibit these transporters in vivo.

PBPK interaction modelling

Since in vivo studies with itraconazole and rifampicin increased and decreased, respectively, the exposure of futibatinib, PBPK modelling (PBPK report 20DC01) was conducted to predict the effect of mild, moderate and strong CYP3A inhibitors and moderate, and strong inducers on futibatinib PK after multiple administrations in cancer patients.

PBPK analyses predicted that strong CYP3A inhibitors (itraconazole and clarithromycin) and moderate CYP3A inhibitors (fluconazole and fluvoxamine) would increase AUCtau of futibatinib 20 mg QD by around 50% and 25% to 40%, respectively. A weak inhibitor, cimetidine would marginally increase futibatinib AUCtau by around 10%.

PBPK analyses predicted that carbamazepine (strong CYP3A inducer), rifampicin (strong CYP3A inducer), and efavirenz (moderate CYP3A inducer) would decrease AUCtau of futibatinib 20 mg QD by approximately 35%, 60%, and 50%, respectively.

Further, in vitro studies indicated that futibatinib is an inhibitor of P-gp and BCRP. The potential to inhibit these transporters was further evaluated by PBPK (PBPK report 20DC09). Under the most conservative assumption made with Ki value by 0.01-fold, futibatinib was predicted to increase C_{max} and AUC of a clinical P-gp substrate, digoxin and a clinical BCRP substrate, rosuvastatin. Additional simulation suggested that a staggered dosing between futibatinib and P-gp/BCRP substrates decreased the elevated exposure of P-gp/BCRP substrates. When using the uncorrected in vitro Ki and 0.1-fold Ki values, futibatinib was predicted to have no clinically relevant impact on exposures of P-gp/BCRP substrates.

2.6.2.2. Pharmacodynamics

The primary efficacy data supporting this submission was based on clinical data from the pivotal Phase 1/2 Study TPU-TAS-120-101. Pharmacodynamics of futibatinib were evaluated by means of serum phosphate and FGF23 levels in patients with solid tumours in the dose escalating part of study TAS-120-101 with dosing schedules QD and QOD evaluated. Exposure-response analyses for efficacy (study TAS-120-101) and safety (study TAS-120-101 and 10059010 in Japanese patients) were submitted as well as a dedicated QTc cardiac safety study in healthy subjects (TAS-120-107).

Mechanism of action

FGFR signalling is deregulated in many human cancers, and FGFR is considered a potential therapeutic target in FGFR-deregulated tumours. Futibatinib is an irreversible inhibitor of FGFR 1–4, with 50% inhibitory concentrations of 1.4 to 3.7 nmol/L. Futibatinib covalently bound the FGFR kinase domain,

inhibiting FGFR phosphorylation and, in turn, downstream signalling in FGFR-deregulated tumour cells. Pathophysiology of FGFR-inhibition is associated hyperphosphatemia. In kidneys, FGFR inhibitors block the catabolism of 1, 25 (OH)2 vitamin D, and sodium-phosphate co-transporters in the proximal renal tubule cell thereby leading to hyperphosphatemia. FGFR inhibitors also block the conversion of cholesterol to bile acid thereby leading to altered bile acid metabolism.

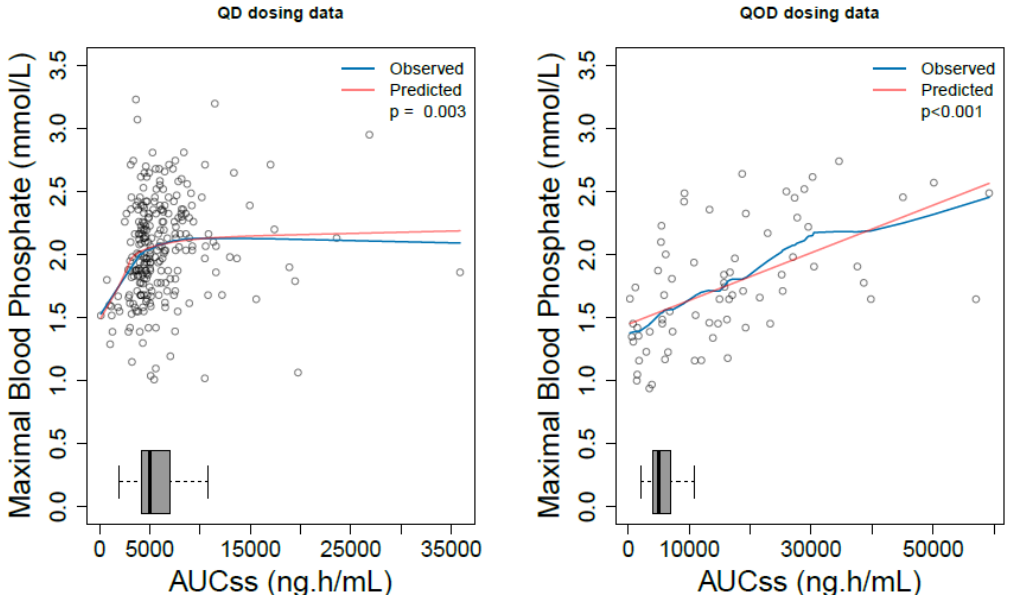
In non-clinical development studies, futibatinib has demonstrated potent and selective inhibition of cancer cell growth of tumour cell lines harbouring various FGFR genomic alterations. In FGFR alteration-driven human tumour xenograft models, futibatinib exhibited statistically significant and dose-dependent antitumor activity with QD administration. Inhibition of FGFR phosphorylation and its downstream signals after a single-dose of futibatinib in AN3 CA Xenografted tumour was demonstrated. (see Non-clinical aspects for more details)

Primary and Secondary pharmacology

In the dose escalating part of study TAS-120-101 in patients with solid tumours, serum phosphate and FGF23 were evaluated for PD analysis as on-target off-tumour effect due to inhibition of FGFR. Futibatinib elevated serum phosphate levels, which were sustained for at least 48h following the first dose. Futibatinib QOD and QD increased FGF23 and phosphate levels, with a tendency towards dose dependency.

Relationships of the $C_{avg\ phosphate}$ with dose or AUC_{inf} of futibatinib are illustrated in Figure 4. The increase in $C_{avg\ serum\ phosphate}$ after repeated doses increased in a dose- or AUC_{inf}-dependent manner in both dosing schedules. As shown by the regression patterns, steeper response in the relationship of C_{avg} with both futibatinib dose and AUC_{inf} was seen in the QD dosing groups compared with the QOD dosing groups.

Figure 4. Relationship between maximal blood phosphate concentration and futibatinib AUC_{ss} (Study TAS-120-101)



Abbreviations: AUCss = area under the concentration-time curve at steady-state; QD = once daily; QOD = once every other day (Monday, Wednesday, and Friday of each week).
Note: The horizontal boxplot below shows the exposure distribution (where the whiskers represent 1.5 × interquartile range) for the 20 mg QD dose group. The p-value is for the slope of the linear fit or the IC50 value of the non-linear model, respectively.
Source: TAS120_ES_analysis_v2-euresp.R, ES_MAXCHB_Pi.pdf

In Study TAS-120-107, the effects of single oral doses of futibatinib on the cardiac QTc interval by assessing the concentration-QT relationship using exposure-response modelling were explored using the clinical dose of 20 mg, but also a supratherapeutic dose of 80 mg futibatinib. Moxifloxacin 400 mg was included as a positive control. Plasma concentration range following single-dose administration of therapeutic dose (20 mg) and supratherapeutic dose (80 mg) covered the highest exposure observed in patients with advanced solid tumours. Futibatinib did not prolong the QTc interval.

Relationship between plasma concentration and effect

The exposure-efficacy analyses included 98 subjects with CCA with FGFR2 rearrangements (including fusions) in the Phase 2 portion of Study TAS-120-101. All subjects in the exposure efficacy analysis data set received 20 mg futibatinib QD.

No statistically significant exposure-efficacy relationships were observed for ORR, disease control rate (DCR), DOR, OS, progression free survival (PFS), or change in tumour size with respect to any of the exposure metrics evaluated (C_{min}, C_{max}, average plasma concentration [C_{avg}], AUC on Cycle 1 Day 1 or at steady state).

The exposure-safety dataset included 318 patients (N=39 from Study 10059010 and N=279 from Study TAS-120-101). For the QD dosing regimen, statistically significant exposure-safety relationships were observed between C_{min}/AUC and hyperphosphatemia, nail disorders, and retinal disorders. No exposure-safety relationships were observed for any grade of hypercalcemia, hepatotoxicity, palmar-plantar erythrodysesthesia syndrome (PPE), rash, and any exposure metric evaluated.

Covariate evaluations of the exposure-response relationships for hyperphosphatemia revealed that baseline serum phosphate and sex are independent predictors of probability of hyperphosphatemia grade ≥ 3, with high baseline phosphate levels and female associated with increased probability of hyperphosphatemia grade ≥3 (Table 8). An increased ECOG score was associated with increased nail disorders, any grade. None of the other covariates tested were significant for retinal disorders, any grade.

Table 8. Model-predicted mean probability of hyperphosphatemia ≥grade 3 by dose group and baseline phosphate and by sex

TAS-120 Dose (mg)	Covariate category	N	Model-Predicted Mean Rate (%) Estimate	Model-Predicted Mean Rate (%) 90% CI
16	Female, baseline phosphate <1.1 mmol/L	56	7.30	3.20, 18.2
20	Female, baseline phosphate <1.1 mmol/L	56	22.4	15.2, 31.5
24	Female, baseline phosphate <1.1 mmol/L	56	49.3	27.6, 69.1
16	Male, baseline phosphate <1.1 mmol/L	61	7.50	3.00, 12.9
20	Male, baseline phosphate <1.1 mmol/L	61	12.8	6.8, 19.8
24	Male, baseline phosphate <1.1 mmol/L	61	25.3	9.90, 47.2
16	Female, baseline phosphate ≥1.1 mmol/L	59	21.1	12.1, 37.2
20	Female, baseline phosphate ≥1.1 mmol/L	59	46.3	37.5, 55.1
24	Female, baseline phosphate ≥1.1 mmol/L	59	74.4	53.6, 87.6
16	Male, baseline phosphate ≥1.1 mmol/L	13	6.60	2.50, 17.1
20	Male, baseline phosphate ≥1.1 mmol/L	13	17.4	10.6, 27.5
24	Male, baseline phosphate ≥1.1 mmol/L	13	37.6	16.7, 63.2

Abbreviations: CI = confidence interval; N = number of patients.
Note: Simulations were based on all patients in the exposure-safety analysis set and used subject-specific exposures. The 90% CI was based on model uncertainty and exposure variability.
Source: TAS120_ES_analysis.R, ES-G3AEPHO-project-multivar-QD.csv

Model-predicted probabilities based on univariate projection of key efficacy and safety endpoint rates were compared for 16, 20, and 24 mg QD regimens in Table 9. Model-based dose projections predicted a steep increase in probability of hyperphosphatemia (45.7%) and hyperphosphatemia ≥3 (40.8%) over the dose range 16 mg to 24 mg QD, whereas a modest increase in objective response (<3%) and nail disorders (4%) over this dose range was projected.

Table 9. Model-predicted probabilities of key efficacy and safety endpoints by dose group

TAS-120 Dose (mg QD)	Model-Predicted Rate (%) Mean 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 (6.10, 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)

Abbreviations: CI = confidence interval; ORR = objective response rate; QD = once daily.
Source: Table 5-14. EE-ORR-projections.csv, ES-ANYAENAI-QD-project-uni.csv, ES-ANYAEPHO-QD-project-uni.csv, ES-G3AEPHO-QD-project-uni.csv

2.6.3. Discussion on clinical pharmacology

Pharmacokinetics

The pharmacokinetics of futibatinib has been characterized in 10 studies in healthy volunteers and in patients with advanced solid tumours. In addition to the 10 clinical studies, 3 reports on population pharmacokinetics and exposure-response analyses, and PBPK analyses to support drug-drug interactions have been submitted.

Methods

All three methods to determine futibatinib in human plasma and urine by LC/MS/MS were sufficiently validated in line with ICH-M10 guideline on bioanalytical method validation. While the methods were sufficiently validated per facility, it appears that cross-validation between the three testing facilities has not been conducted. A sensitivity analysis for testing facility of the popPK model was provided subsequently and showed no difference between CMIC and Covance testing facilities but adding Celerion as testing facility reduced the residual error. Celerion was used to analyse futibatinib in healthy subjects but not in patients. The estimated effects on exposure, though, were limited. Moreover, because the studies in healthy subjects were cross-over studies, the different testing facility has no effect on the covariate analysis tested in healthy subjects such as food effect and drug-drug interactions. In addition, as testing facility has only been used for samples of healthy subjects, this has limited impact on characterisation of futibatinib in patients, covariate analysis and exposure-response analysis.

Bioequivalence

Two dosage forms, liquid filled hard capsules and immediate release film-coated tablets were developed for use in clinical studies of futibatinib. Further, a tablet of 4 mg to be marketed has been developed. Bioequivalence of the 20 mg liquid-filled hard capsule and the 20 mg film-coated tablet clinical trial formulations for futibatinib has been demonstrated (Study 10059020). The composition of the film-coated tablets was not dose proportional, but the difference in composition had no effect on the bioavailability of the 4 mg and 20 mg strengths (study 10059010). Since the difference between the to-be-marketed tablets and the clinical tablets were minor without changing the composition of core tablets, no bioequivalence study between the two formulations was conducted. The formulations were bridged by dissolution profile comparison of the two formulations and across study comparison of the pharmacokinetic parameters.

ADME

Futibatinib was readily absorbed reaching C_{max} values within 1-3 hours after administration. Absorption was dose proportional in the clinical dose range 12-20 mg futibatinib QD. Co-administration with the proton pump inhibitor lansoprazole had no effect on the absorption of futibatinib. Hence, proton pump inhibitors can be co-administered with futibatinib, which has been described adequately in the SmPC. Futibatinib is considered a high permeability compound and no intact futibatinib but many metabolites were recovered in human faeces in the mass balance study (Study TAS-120-106). Additional in vitro stability testing of futibatinib in the gastrointestinal flora showed that the possibility of major metabolites identified in human faeces being generated by intestinal flora from unabsorbed futibatinib is low. Therefore, based on the mass balance data, it is estimated that the absorption of futibatinib is at least 70%.

By consumption of a high-fat, high calorie meal C_{max} and AUC were 42%, and 14% lower, respectively, compared to fasted conditions and T_{max} was 3h delayed. Considering the moderate to high variability of the PK parameters C_{max} and AUC and the lack of dose - ORR response, the food effect is considered not clinically meaningful, and it is agreed that futibatinib can be taken with or without food as is indicated in section 4.2 of SmPC.

The mean apparent volume of distribution following single-dose oral administration of futibatinib 20 mg to patients with advanced solid tumours was 73 L, indicating that futibatinib is moderately distributed

to tissues. In vitro and in vivo data indicate that futibatinib is not distributed to red blood cells as the blood: plasma ratio is ~0.6. However, at later time points, the blood:plasma ratio of ^{14}C -labelled material increased to 0.85-1.7 suggesting that some metabolites are distributed or bound to blood cells. Thus, futibatinib is likely to bind covalently to blood cells via its acrylamide moiety as has been observed for several other TKIs.

The mean elimination half-life of futibatinib of 2-3 hours is much shorter than the elimination half-lives of radioactivity in plasma and blood of 12h and 29h, respectively, in the mass balance study. However, a longer plasma elimination half-life of futibatinib was also observed at high futibatinib doses in the 120-200mg dose range without a more than dose proportional increase in AUC (Studies TAS-120-101, 10059010). The secondary elimination phase is probably slow release of futibatinib from tissues, which is measurable in plasma (concentrations >LLOQ) at higher futibatinib doses.

Futibatinib is eliminated by metabolism since futibatinib excretion into either urine or faeces was negligible. Based on in vitro and in vivo data with itraconazole, it was estimated that 35%-40% of metabolism of futibatinib was mediated by CYP enzymes, predominantly CYP3A4. Additional in vitro metabolism studies showed that glutathione conjugation by both glutathione S-transferase and non-enzymatic formation accounts for the remaining 50%–60% of the futibatinib metabolism. Significant clinical interactions by glutathione S-transferase inhibition are considered unlikely.

However, the interpretation that CYP3A4 is responsible for 30-40% of metabolism is questioned. Itraconazole mostly increased the absorption phase of futibatinib without affecting the elimination phase. This may suggest that it is not the effect of CYP3A4 inhibition but rather P-gp inhibition that is seen. This will be further evaluated post approval in an interaction study with quinidine as P-gp inhibitor (REC).

The pharmacokinetics of the futibatinib metabolites have not been evaluated. The two primary circulating metabolites in human plasma, a cysteinylglycine conjugate (13%) and a cysteine conjugate (9%), were <25% of the exposure to the parent and showed no in vitro activity (Study CBS-200034). It is therefore agreed that further characterisation of the pharmacokinetics of metabolites is not needed, also considering the indication in the scope of ICH S9. Metabolism seems similar in human as in rat and dog with the exception of the major metabolite in human plasma cysteinylglycine conjugate (TAS-06-22952). This metabolite and also the glutathione conjugate were not observed in vitro and in vivo in rat and dog (see Non-clinical aspects).

The applicant did not generate enantioselective/stereoselective data in the nonclinical or clinical program. It is agreed that both enzymatic and non-enzymatic inversion are unlikely for a structure like futibatinib.

PopPK analysis

Based on the non-compartmental analysis, PK parameters are overlapping between patients and healthy volunteers.

PopPK modelling seems to underestimate the absorption rate somewhat as estimated C_{max} in patients (144 ng/mL) is lower as determined by non-compartmental analysis (257 ng/mL). Sparse PK samples were collected (pre-dose and 1h and 3h after dosing in the 2nd cycle) in part B of study TAS-120-101. This could have resulted in apparent lower C_{max} values in patients.

The final model parameter estimates and RSEs were overall reasonable, however, the estimated correlation between CL/F and Vc/F is very low and is associated with high RSE. Rerunning the final model without covariance between CL/F and Vc/F resulted in similar parameter estimates as the final model (data not shown).

A major concern with the popPK analysis is the inclusion of study as co-variate on relative bioavailability. While a study effect on relative bioavailability could improve the covariate analysis, this should only be imputed when there is a solid reason for the between study differences. No scientific rationale was provided for the more than 2-fold lower relative bioavailability for study 10059020 in Japanese healthy volunteers. A true difference between healthy subjects and patients, a true difference between Japanese and White subjects, or a true difference in bioanalytical testing centre could have been missed by introduction of study as covariate on relative bioavailability. It was acknowledged there was no other reason for including the study effect in the model on bioavailability (F) than the noted differences between studies that could not be explained by another common covariate among the grouped studies. A sensitivity analysis with removal of study on F resulted in an increase in apparent Cl/F, Vc/F, Vp/F and Q/F but had no effect on the co-variate analysis. In addition, the exposure estimation in the patient population was comparable with the final popPK model and the sensitivity analysis. On the other hand, when data in healthy subjects were simulated, there was an approximately 20%-difference in exposures predicted between the final model and the sensitivity model. Overall, it is concluded that the performance of the popPK analysis is adequate to describe the pharmacokinetics of futibatinib in the patient population studied in the pivotal study. Since the between study effects remain unexplained, there are unknown factors which influence the pharmacokinetics of futibatinib significantly. Therefore, this popPK model is less suitable for simulations and extrapolation into other populations or settings not described by the data.

Special populations

PopPK analysis was used to estimate intrinsic and extrinsic factors on the pharmacokinetics of futibatinib. Serum albumin was found to be a significant predictor of CL/F, resulting in higher futibatinib exposures at low serum albumin. Patients with low serum albumin < 3.5 g/dL had more (S)AEs, however, this was probably related to worse health status rather than futibatinib exposures. Body weight was found to be significant predictors of Vc/F. However, changes in exposure in patients with 5% and 95% body weight were < 20% and therefore body weight (36 - 152 kg) is unlikely to represent a clinically significant intrinsic variable for futibatinib PK. No effects on CL/F and Vc/F, i.e. <20% difference, of ALP, age (18 - 82 years), sex, or race (Asian/non-Asian) were identified. Negligible amounts of futibatinib are excreted in the urine. Therefore, renal function is not expected to affect the pharmacokinetics of futibatinib and renal function was not a covariate in the popPK model. Subjects with severe renal impairment or in subjects with end-stage renal disease receiving intermittent haemodialysis were not included in the popPK analysis. Hepatic impairment (mild, moderate, and severe) had no impact on the PK of futibatinib. The special populations have been adequately described in sections 4.2 and 5.2 of the SmPC.

The covariate analysis is considered overall acceptable. The following covariates are not considered important predictors for futibatinib PK: race/ethnicity, sex, race, patient vs healthy volunteer.

CYP3A4 inhibitors and inducers were included as categorical covariates on relative F in the final model. From a mechanistic point of view, CYP3A4 may also affect CL. Nevertheless, as the apparent CL (CL/F) was estimated, it could be acknowledged that it may be difficult to separate effects on CL/F or relative F, and thus, including these covariates on relative F is considered acceptable.

Drug-drug interactions

In vitro studies showed that futibatinib is a substrate for CYP3A4 and for P-gp and BCRP. The potential for clinically relevant interaction with BCRP inhibitors though is unlikely. An in vivo interaction study was conducted with itraconazole (a strong CYP3A4 inhibitor and also an inhibitor of P-gp and BCRP) and with rifampicin (a strong inducer of CYP3A4 and P-gp). In presence of itraconazole, C_{max} and AUC were 1.4- to 1.5-fold higher while in presence of rifampicin C_{max} and AUCs of futibatinib were decreased by 53% and 64%, respectively, in healthy adult subjects.

PBPK modelling was conducted to evaluate the effect of other mild-to strong inhibitors and inducers on the exposure of futibatinib. The PBPK model for futibatinib describes reasonably well the pharmacokinetic profile of futibatinib in healthy subjects and in cancer patients from study TAS-120-101.

PBPK analyses predicted that strong CYP3A inhibitors (itraconazole and clarithromycin) and moderate CYP3A inhibitors (fluconazole and fluvoxamine) would increase AUCtau of futibatinib 20 mg QD. Further, PBPK analyses predicted that carbamazepine (strong CYP3A inducer), rifampicin (strong CYP3A inducer), and efavirenz (moderate CYP3A inducer) would decrease AUC_{tau} (PBPK report 20DC01). The presented model is flawed as P-gp is not integrated in it, while futibatinib is both a substrate of CYP3A4 and of P-gp and BCRP. The data from the DDI study with itraconazole and rifampicin suggest an interplay between P-gp and intestinal CYP3A4 since in presence of itraconazole, Tmax was somewhat shorter and the absorption peak sharper, while after induction with rifampicin, Tmax was somewhat later and the absorption peaks broad. It is currently not possible to distinguish whether the net effect of itraconazole and rifampicin is a result of inhibition/induction of CYP3A4, P-gp or both; this implies the model is not fit for simulation. In addition, the PBPK model is considered not sufficiently qualified to predict the effects of inducers, because several enzymes and transporters seem to be involved in the pharmacokinetics of futibatinib, and inducers can affect the activity of many enzymes/transporters differently.

Since the worst-case scenario inhibition/induction of CYP3A4/P-gp is known from the dedicated studies and the effects are modest, any dose adjustments could be based on these results. Along with a discussion on the therapeutic window, the applicant argued the exposure range of the 20 mg represents the upper and lower boundary of the therapeutic window, based on the available efficacy and safety data for 16, 20 and 24 mg QD (and for the QOD regimen). Considering that the difference in dose is quite small between 16, 20 and 24 mg and taking the high variability into account, it would seem appropriate to consider the conservative measures of acceptance of 20 to 25% exposure difference on the mean PK parameters to be the relevant boundaries when determining the need for dose adjustment in special populations or in case of interactions. The applicant will investigate the efficacy of a lower dose of 16 mg (see Specific obligation). Hence the lower boundaries are not yet strongly defined. The concomitant use of strong CYP3A/P-gp inhibitors (e.g. clarithromycin, itraconazole) may increase futibatinib plasma concentration and should be avoided. If this is not possible, a reduction in the futibatinib dose to the next lower dose level based on tolerability observed should be considered. The concomitant use of strong and moderate CYP3A/P-gp inducers (e.g. carbamazepine, phenytoin, phenobarbital, efavirenz, rifampin) may decrease futibatinib plasma concentration and should be avoided. If this is not possible, gradual increase of the futibatinib dose based on careful monitoring of tolerability should be considered.

In vitro studies showed that futibatinib is a potential time-dependent inhibitor toward CYP3A and an inducer of CYP1A2 (Study 18DB18). In the in vivo interaction study TAS-120-105 with midazolam, a sensitive CYP3A4 substrate, futibatinib had no clinically significant impact on C_{max} and AUCs of midazolam showing that futibatinib is not a time-dependent inhibitor of CYP3A4 in vivo. This has been described adequately in the SmPC. However, co-administration of futibatinib with CYP1A2 sensitive substrates (e.g, olanzapine, theophylline) may decrease their exposure and therefore may affect their activity (see section 4.5 of the SmPC).

Potential interaction of futibatinib mediated by transporters was investigated in transporter overexpressing cells. Using EMA's cut-off values (Guideline on the investigation of drug interactions CPMP/EWP/560/95/Rev. 1 Corr. 2*), futibatinib could be an inhibitor for P-gp and BCRP. No in vivo DDI studies were conducted but PBPK modelling was used to further justify the potential of futibatinib to inhibit these transporters in vivo. However, the number of substrates and inhibitors that was used to qualify the PBPK model was not in line with the recommendations provided in Guideline on the

reporting of physiologically based pharmacokinetic (PBPK) modelling and simulation (European Medicine Agency, July 1, 2019, EMA/CHMP/458101/2016), and therefore it cannot be concluded that futibatinib has no clinically relevant impact on exposures of P-gp/BCRP substrates. The applicant is recommended to conduct an in vivo interaction study with digoxin (P-gp substrate) and rosuvastatin (BCRP, OATP1B1 substrate) (REC). Co-administration of futibatinib with P-gp (e.g., digoxin, dabigatran, colchicine) or BCRP (e.g, rosuvastatin) substrates may increase their exposure (see section 4.5 of the SmPC).

It is currently unknown whether futibatinib may reduce the effectiveness of systemically acting hormonal contraceptives. Therefore, women using systemically acting hormonal contraceptives should add a barrier method during Lytgobi treatment and for at least 1 week after the last dose (see section 4.5 of the SmPC). The lack of *in vivo* study with contraceptive steroids is acceptable given that few WOCBP are expected in the target population. Should another indication be studied including a larger proportion of WOCBP, a study investigating this interaction *in vivo* would be required.

Pharmacodynamics

Futibatinib is an irreversible inhibitor of FGFR 1-4. In vitro inhibition IC50 values were 1.4 to 3.7 nM. In vitro studies in cell lines with several FGFR2 mutations indicated that futibatinib is still active against those mutations. In study TAS-120-101, unbound C_{max} values of futibatinib in patients were ~30 nM, high enough for inhibition of FGFR. The mechanism of action has been supported by non-clinical in vitro studies and in vivo studies in xenografts.

In the dose escalating part of study TAS-120-101 in patients with solid tumours, the exposure-response relationship was more pronounced in QD than in the QOD cohorts, which suggests that the turn-over rate of FGFR is rather fast as futibatinib is an irreversible inhibitor.

In Study TAS-120-107, the effects of single oral doses of futibatinib on the cardiac QTc interval by assessing the concentration-QT relationship using exposure-response modelling were explored. Futibatinib did not prolong the QTc interval. This is consistent with non-clinical data.

Several exposure-response analysis (efficacy and safety) were performed by the applicant. Within the current submission, the exposure-response analysis is not viewed as pivotal. The exposure-response is seen as supportive to the proposed dose regimen, including dose reduction recommendations.

Univariate analysis showed no significant correlation between any of the exposure metrics of futibatinib and any of the efficacy measures, indicating that exposure-response for efficacy is rather flat. A study is planned in which 16 mg will be compared with 20 mg dose (SOB). On the other hand, there were steep exposure-response relations for hyperphosphatemia and nail disorders. The performed exposure-response analysis for hyperphosphatemia was primarily conducted for the change from baseline. An additional analysis was conducted based on the absolute, continuous phosphate level (i.e. not baseline-corrected) and the results agree with the exposure-response analyses which were based on the change from baseline phosphate. A phosphate-lowering therapy should be initiated when serum phosphate level is ≥5.5 mg/dL (section 4.2 of the SmPC).

The applicant used serum phosphate as a marker for FGFR inhibition to support the dosing, and together with a tendency of better efficacy response following QD dosing regimen, the QD dosing regimen was selected for the extension study and phase B of study TAS-120-101. Based on the exposure-response analyses, it is not sure whether serum phosphate was the optimal marker to select the dose/ dosing interval since a different exposure response is apparent for efficacy and hyperphosphatemia based on the results of studies TAS-120-101 and study 10059010. A lower dose of 16 mg may be equally efficacious with less hyperphosphatemia grade ≥3 AEs. The applicant will conduct a study in which 16 mg and 20 mg futibatinib will be further evaluated (SOB). Considering that the difference in dose is quite small between 16, 20 and 24 mg and taking into account the high

variability, it is appropriate to consider the conservative measures of acceptance of 20 to 25% exposure difference on the mean PK parameters to be the relevant boundaries when determining the need for dose adjustment in special populations or in case of interactions.

2.6.4. Conclusions on clinical pharmacology

The pharmacology of futibatinib has been sufficiently characterised.

The CHMP considers the following measures necessary to address the issues related to pharmacology: in order to assess the effects of futibatinib on the pharmacokinetics of sensitive substrates of P-gp (digoxin) and BCRP (rosuvastatin), the MAH should submit the results of TAS-120-110, a phase 1, open-label, fixed-sequence study to assess the effect of futibatinib on P-gp and BCRP and the effect of P-gp inhibition by quinidine on the pharmacokinetics of futibatinib in healthy adult subjects.

2.6.5. Clinical efficacy

2.6.5.1. Dose response studies

No formal dose response studies were performed. Study TAS-120-101 is an open-label, non-randomized, dose-escalation and dose-expansion, Phase 1/2 study conducted in 3 parts:

Phase 1 Dose Escalation: to determine the maximum tolerated dose (MTD) and/or recommended phase II dose (RP2D) of futibatinib;

Phase 1 Expansion: to further evaluate the efficacy and safety of the MTD and/or RP2D of futibatinib in patients with tumours harboring specific *FGF*/*FGFR* aberrations; and

Phase 2: to confirm the ORR of futibatinib in iCCA patients with tumours harboring *FGFR2* gene fusions or other *FGFR2* rearrangements.

Starting dose

The futibatinib dosing schedules used in the Dose Escalation portion were selected on the basis of preclinical animal data suggesting that alternate-day dosing prevents continuous upregulation of serum phosphorus.

The starting dose in this study was selected on the basis of preclinical studies in rats and dogs showing that the severely toxic dose in >10% of rats (STD10), and the highest non-severely toxic dose in dogs, both corresponded to approximately 97.2 mg QOD in humans. The starting dose of futibatinib in humans was therefore set at less than one tenth of this (8 mg QOD). Because the STD10 could not be determined for QD dosing, the starting QD dose in this study was based on human clinical experience from the QOD portion; specifically, the starting dose was 4 mg QD, corresponding to an approximately 90% dose reduction compared to Cohort 4 in the QOD arm.

Dose escalation

Dose escalation followed a standard "3 + 3" design. No intra-patient dose escalation was allowed. The MTD was defined as the highest dose level at which less than 33% of the patients experienced a dose limiting toxicity (DLT) during Cycle 1 (21 days). The RP2D was equal to or less than MTD, and the associated dosing schedule was selected based on the safety, PK, pharmacodynamics and preliminary efficacy data observed in Dose Escalation.

Dose Escalation – Overview of Design

Safety was the primary endpoint during the Dose Escalation portion of this study and evaluation of preliminary anti-tumour activity was a secondary endpoint.

The Dose Escalation portion of the study enrolled patients with advanced solid tumours (with or without *FGF*/*FGFR* gene abnormalities) that had progressed on prior standard therapy or for whom standard therapy did not exist. Futibatinib was administered at escalating dose levels either daily (QD) or on Monday, Wednesday, and Friday of each week (QOD).

Rationale for dose selection and Schedules

As of the data cut-off date of 06 March 2017, 73 patients with advanced cancer have been treated with TAS-120 in Study TPU-TAS-120-101; 42 with QOD dosing (range: 8-200 mg), and 31 with QD dosing (range: 4-24 mg). The safety profiles were similar for the QOD and QD schedule. Early signals of clinical activity were observed with both schedules as well. However, with the QD schedule there appears to be a stronger exposure-response relationship with respect to TAS-120 concentrations and serum phosphorus level, which is considered a pharmacodynamic marker of FGFR inhibition. In addition, the QD schedule of administration is expected to be associated with better patient dosing compliance compared to that of QOD administration. Therefore, only the QD regimen will be evaluated during the Phase 1 Expansion and Phase 2 parts of the study.

The Phase 1 Expansion has been initiated with a TAS-120 dose of 16 mg QD, which was determined to be safe in the Phase 1 Dose Escalation. As of Amendment 4, an intermediate dose level of 20 mg QD was also planned to be evaluated for safety (DLTs in Cycle 1) in 6-12 evaluable patients.

The rationale for evaluation of the intermediate dose level is to determine the optimal RP2D. PK analysis showed that dose escalation from 16 mg to 20 mg resulted in a linear increase in drug exposure, suggesting potential for dose optimization.

A total of 86 patients with advanced cancer disease after failure of available standard of care treatment options were enrolled. This included 42 patients receiving futibatinib on a QOD dosing schedule (8-200 mg) and 44 patients receiving futibatinib on a QD dosing schedule (4-24 mg).

PK/PD analysis demonstrated target engagement for futibatinib QOD and QD as measured by increased FGF23 and phosphate serum levels with a trend towards dose dependency. This exposure-response relationship was more pronounced in QD than in the QOD cohorts consistent with a higher incidence of clinical AEs of hyperphosphatemia in QD cohorts compared to QOD cohorts.

MTD

No MTD for QOD dosing was determined in this study as there was only a single DLT reported for a patient receiving futibatinib 8 mg QOD who experienced an asymptomatic and reversible Grade 4 increase in blood creatine phosphokinase.

For QD dosing, no DLT was observed at 4 mg, 8 mg, 16 mg, or 20 mg QD. However, there were 3 DLTs reported for the 9 evaluable patients receiving futibatinib 24 mg QD. DLTs included one patient each with reversible Grade 3 increase of aspartate aminotransferase (AST), alanine aminotransferase (ALT), and bilirubin.

Based on these findings, futibatinib 20 mg QD was identified as the MTD for QD dosing of futibatinib for advanced cancer patients.

2.6.5.2. Main study

TAS-120-101

The main study concerns the phase II part of the multicentre, open-label, single-arm Phase 1/2 study to evaluate the safety, pharmacokinetics, pharmacodynamics, and efficacy of futibatinib in patient with histologically or cytologically confirmed, locally advanced, metastatic, unresectable iCCA harboring FGFR2 gene fusions or other FGFR2 rearrangements (Goyal et al. N Engl J Med. 2023).

Methods

The Phase 2 portion of the study included approximately 100 patients with iCCA harboring confirmed *FGFR2* gene fusions or other *FGFR2* rearrangements. Futibatinib was administered at 20 mg (QD).

- **Study Participants**

Key Inclusion Criteria

For inclusion into the trial, patients were required to fulfill all of the following criteria.

Phase 2

Patient had 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:

Testing by Foundation Medicine as part of study pre-screening; or previously tested by Foundation Medicine (in this case, tumour tissue was to be provided to Foundation Medicine if available).

Local laboratory testing using next generation sequencing [NGS], fluorescence in situ hybridization [FISH], or other assays able to determine FGFR2 gene fusions or other FGFR2 rearrangements on tumour tissues or from circulating tumour DNA (ctDNA). Patients enrolled on this basis were requested to provide tumour tissues to Foundation Medicine, if available from either archival samples or fresh tumour biopsy.

Patient had been treated with at least 1 prior systemic gemcitabine (GEM) / cisplatin (CIS) (GEM/CIS) chemotherapy. A patient with prior adjuvant GEM/CIS chemotherapy was eligible if the patient had recurrence within 6 months of the last dose of the regimen.

Patient had documentation of radiographic disease progression on the most recent prior therapy

Patient had measurable disease as defined by Response Evaluation Criteria in Solid Tumours (RECIST) guidelines (version 1.1, 2009) for advanced solid tumours or Response Assessment in Neuro-Oncology (RANO) criteria (2010) for brain tumours.

Had Eastern Cooperative Oncology Group (ECOG) performance status 0 or 1 on Day 1 of Cycle 1.

Was able to take medications orally (eg, no feeding tube).

Had adequate organ function as defined by the following criteria:

Creatinine clearance (calculated or measured value) ≥ 40 mL/min

Aspartate aminotransferase (AST) and alanine aminotransferase (ALT) ≤ 3.0 ×upper limit of normal (ULN); if liver function abnormalities are due to underlying liver metastasis, AST and ALT ≤ 5 × ULN.

-Total serum bilirubin ≤ 1.5 × ULN.

-International normalized ratio (INR) <1.3 (or < 3.0 on anticoagulants)

Exclusion Criteria

A patient was excluded from this study if any of the following criteria were met:

History and/or current evidence of clinically significant non-tumour-related alteration of calcium-phosphorous homeostasis

History and/or current evidence of clinically significant ectopic mineralization/ calcification

History and/or current evidence of clinically significant retinal disorder confirmed by retinal examination

History or current evidence of serious uncontrolled ventricular arrhythmia

Fridericia's corrected QT interval (QTcF) > 470 msec on ECG conducted during Screening

Treatment with any of the following within the specified time frame prior to the first dose of futibatinib:

Major surgery within the previous 4 weeks

Radiotherapy for extended field within 4 weeks prior to or limited field radiotherapy within 2 weeks prior to the first dose of futibatinib

Patients with locoregional therapy, eg, transarterial chemoembolization (TACE), selective internal radiotherapy (SIRT) or ablation within 4 weeks. Any non-investigational anticancer therapy within 3 weeks prior to futibatinib administration or had not recovered from side effects of such therapy prior to futibatinib administration (mitomycin within prior 5 weeks); targeted therapy or immunotherapy within 3 weeks or within 5 half-lives, whichever is shorter

Any investigational agent received within 5 half-lives of the drug or 4 weeks, whichever is shorter. Concurrent participation in an observational study may have been allowed after review by the Sponsor's Medical Monitor

Patients with prior FGFR-directed therapy

A serious illness or medical condition including, but not limited to, the following:

Known brain metastasis (not including primary brain tumours) unless patient was clinically stable for ≥ 1 month

Removal of Patients from Therapy or Assessment

Patient request at any time irrespective of the reason;

Disease progression of solid tumours according to RECIST, v1.1 or RANO-defined disease progression of brain tumours;

Clinical progression;

Unacceptable adverse events, or change in underlying condition such that the patient could no longer tolerate therapy, as evidenced by: A dose delay >21 days from the scheduled start date of the next cycle;

Need for more than the allowed dose reductions of futibatinib;

Physician's decision including need for other anticancer therapy not specified in the protocol, or surgery or radiotherapy to the only site(s) of disease being evaluated in this protocol

- **Treatments**

Futibatinib was administered either QD or QOD during the dose escalation phase.

Dose reduction

As per Amendment 6 the following dose schedule was used:

Treatment Regimen

The dose for futibatinib is 20 mg (5 x 4 mg or 1 x 20 mg tablet(s) QD). Patients were required to fast for at least 2 hours before and 1 hour after administration of TAS-120. Patients were permitted to drink water during this period. Dietary restrictions that limit phosphate intake may have reduced the risk of hyperphosphatemia.

Futibatinib was to be administered as a daily, continuous, 21-day treatment cycle. Patients received study treatment until disease progression, occurrence of intolerable side effects, discontinued from treatment by the investigator, withdrawal of consent, or other criteria for discontinuation is met. Futibatinib was to be administered as outlined in Study Drug Administration and Dose Reduction/Modification Procedures.

Dose Reduction/Modification Procedures

Dosages will be reduced/modified if AEs are observed according to the criteria described below. In the following sections, AE severity grades are based on the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) grade criteria (version 4.03).

Futibatinib Dose Reductions for Treatment-emergent Toxicities

Dose reductions must be made according to Table 10**Error! Reference source not found.**. A maximum of 2 dose reductions were permitted.

Table 10. Futibatinib Dose Reduction Levels

1st Dose Reduction	**2nd Dose Reduction**
Dose Reduce to 16 mg	Dose Reduce to 12 mg

If dose modification failed to result in achieving minimal criteria to resume treatment, the investigator should have discontinued the patient from study treatment.

Dose Interruption and Modification for Nonhematologic Toxicities

Dosing modifications for nonhematologic toxicities and hyperphosphatemia management are provided in Table 11 and Table 12.

Table 11. Futibatinib Dosing Modification for Nonhematologic Toxicities

Grade[a]	**Dose Interruption/Resumption**	**Dose Adjustment**
Grade 1 or 2	Maintain treatment at the same dose level	None
Grade 3[b,c]	Suspend treatment until return to Baseline or Grade ≤ 1	Reduce by 1 dose levelc from the previous level
Grade 4[d]	Suspend treatment until return to Baseline or Grade ≤ 1	Permanent Discontinuation of futibatinib

a At the discretion of the investigator, patients may continue/discontinue on TAS-120 at the same dose with/without reduction or interruption for AEs (irrespective of grade) considered unlikely to become serious or life-threatening (including, but not limited to, fatigue and dry skin).

b Except for Grade 3 nausea and/or vomiting controlled by aggressive antiemetic therapy or Grade 3 diarrhea responsive to antidiarrheal medication which does not require dose hold or dose reduction.
c See Table 10 for recommended dose level reductions.
d Grade 4 non-hematologic laboratory abnormality: TAS-120 will be permanently discontinued if it is assessed by the Investigator as life threatening.

Table 12. Recommendations for Hyperphosphatemia Management (Protocol TPU-TAS-120-101 Amendment 6)

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	Interrupt TAS-120 dosing and intensify phosphate lowering therapy • If serum phosphorus level resolved to ≤ Grade 1 within 7 days, TAS-120 can be resumed at the same dose level. • If serum phosphorus level resolved to ≤ Grade 1 after 7 days but within 14 days, resume TAS-120 at reduced dose level.[f] • If serum phosphorus level not resolved to ≤ Grade 1 after 14 days, permanent discontinuation of TAS-120.	
P > 10.0 (mg/dL) P > 3.23 (mmol/L)	Grade 4	Permanent discontinuation of TAS-120	

Abbreviations: BID = twice a day; P = Phosphorus; QD = once a day; TID = three times a day; ULN = upper limit of normal
[a] Serum phosphorus will be tested 4 days (± 24 hours) after Day 1 of Cycle 1 to initiate early intervention for hyperphosphatemia.
[b] mmol/L = mg/dL x 0.3229 (conversion factor)
[c] This grading for the range of serum phosphorus levels will be used for the protocol.
[d] Phosphate binder can be used as monotherapy or in combination. Please consult the drug package insert. Sevelamer should be preferably taken in the middle of meals, both tablets and powder, in order to improve gastrointestinal tolerance and compliance. If Sevelamer cannot be used, other Phosphate binders or hyperphosphatemia treatment drugs can be used. Lanthanum carbonate should be taken instead just after meals – tablets of Fosrenol® are quite big, but can be cut if required. No dose adjustments are needed in patients with renal or hepatic impairment.
[e] Titrate the dose every 2-3 weeks until an acceptable serum phosphate level is reached.
[f] Refer to Dose Modification Table 7

- **Objectives**

Phase 2

The Phase 2 portion of the study was designed to evaluate the efficacy in iCCA patients with *FGFR2* gene fusions or other *FGFR2* rearrangements.

Primary objective

To confirm ORR in iCCA patients with *FGFR2* gene fusions or other *FGFR2* rearrangements based on independent central radiology review.

Secondary objectives

To evaluate DOR

To evaluate the safety and tolerability of futibatinib

To evaluate DCR, PFS, and OS

To evaluate Patient-reported Outcomes (PROs)

Exploratory objective

To investigate the PK and to explore the relationship between PK and efficacy or toxicity of futibatinib.

- **Outcomes/endpoints**

Primary endpoint

The primary endpoint of the study was ORR defined as the proportion of patients with objective evidence of confirmed complete response (CR) or partial response (PR) according to RECIST 1.1 per independent central radiographic review.

Secondary endpoints

The secondary endpoints are:

- DOR: defined as the time from first documentation of response to date of objective progression or death

- PFS: defined as the time from the date of first dose to the date of objective disease progression or death due to any cause (whichever occurred first).

DCR, Patient-Reported Outcomes (PROs) and OS (response evaluations based on independent review of images by the Core Imaging Laboratory).

In addition, sensitivity analyses for some key efficacy endpoints (notably ORR and PFS) were planned to be performed based on assessments by the investigator or local radiologist.

- **Sample size**

Approximately 100 iCCA patients with *FGFR2* gene fusions or other *FGFR2* rearrangements were to be treated. Sample size considerations were based on differentiating a historical control ORR of 10% or less with a target ORR of 20%, based on the patient cohort currently being evaluated in the Phase 1 study. Assuming the true ORR is 20%, the study has approximately 81% power to reject the null hypothesis that the true ORR is <=10%, considering a 2-sided alpha of 5%.

In addition, a formal interim analysis of safety and efficacy was to be performed when approximately 70% all treated patients had 6 months of follow-up. Two-sided 95% CI and 99% CIs were to be provided for both interim and primary efficacy analysis of primary efficacy endpoint.

- **Randomisation and Blinding (masking)**

This is a single arm trial; randomisation and blinding is not applicable.

- **Statistical methods**

The primary analysis is to be performed on the Efficacy population, defined as All Intra-hepatic cholangiocarcinoma (iCCA) patients with FGFR2 gene fusions or other FGFR2 rearrangement who received at least 1 dose of TAS-120.

The primary endpoint, 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 Independent Review Committee (IRC) in the Efficacy Population, was to be summarized by a binomial response rate.

95% confidence interval (binomial proportion confidence interval) for ORR were to be constructed with Clopper-Pearson 95% CI. The null hypothesis was to be rejected if the 2-sided 95% CI lower bound is greater than 10%. This translates in observing at least 17 responders out of 100 in the Efficacy Population.

The final analysis for the primary objective was to be performed when majority of patients responding to futibatinib had at least 6 months of follow-up from onset of response.

The secondary endpoint, Duration of Response (DOR) is defined as the time between the date of first response and the subsequent date of objectively documented progression of disease or death. The CR or PR will be derived based on investigators or independent radiologist assessment. The censoring rules for DoR are provided in Table 13.

Table 13. Censoring rules for DoR and PFS

No.	Situation	End Date	Outcome
1	Documented PD between scheduled visits [a]	Date of the first assessment of the series of the tests that determined PD	PFS event
2	Death during the study in absence of PD [a]	Date of death	PFS event
3	Patients still on treatment without PD as of data cut-off [b]	Date of last tumor assessment [c]	Censored
4	Treatment discontinuation for other than PD or death, and no post baseline tumor assessments	Date of first dose	Censored
5	Treatment discontinuation for other than PD or death with post baseline tumor assessments	Date of last tumor assessment	Censored
6	New anticancer treatment started before PD or death	Date of last tumor assessment [c] before start of new treatment	Censored
7	Death or PD after two or more missed tumor assessments [d]	Date of the last tumor assessment [c] before missed assessments	Censored
8	No baseline or unreadable baseline assessment but readable post baseline assessments	Date of first dose	Censored

a. If documented PD and/or death occurs after the last dose, it is counted as a PFS event as long as the PD and/or the death occurs within 21 days since the date of the last dose of study drug and provided that it does not violate other censoring rules (e.g. start of new anticancer therapy before the PD or death). Otherwise the patient will be censored on the date of last tumor assessment before the date of last dose date + 21 days.
b. For PFS analysis, the date of last tumor assessment refers to the date of last adequate tumor assessment of CR, PR, SD, or PD.
c. This refers to patients who were still receiving study treatment at time of data cutoff.
d. Two or more missed tumor assessments is defined as having either one of the following two durations being longer than 2 cycles for the first 6 months of treatment, or thereafter 3:
- Duration between two consecutive tumor assessments
- Duration between the last tumor assessment and death or PD.

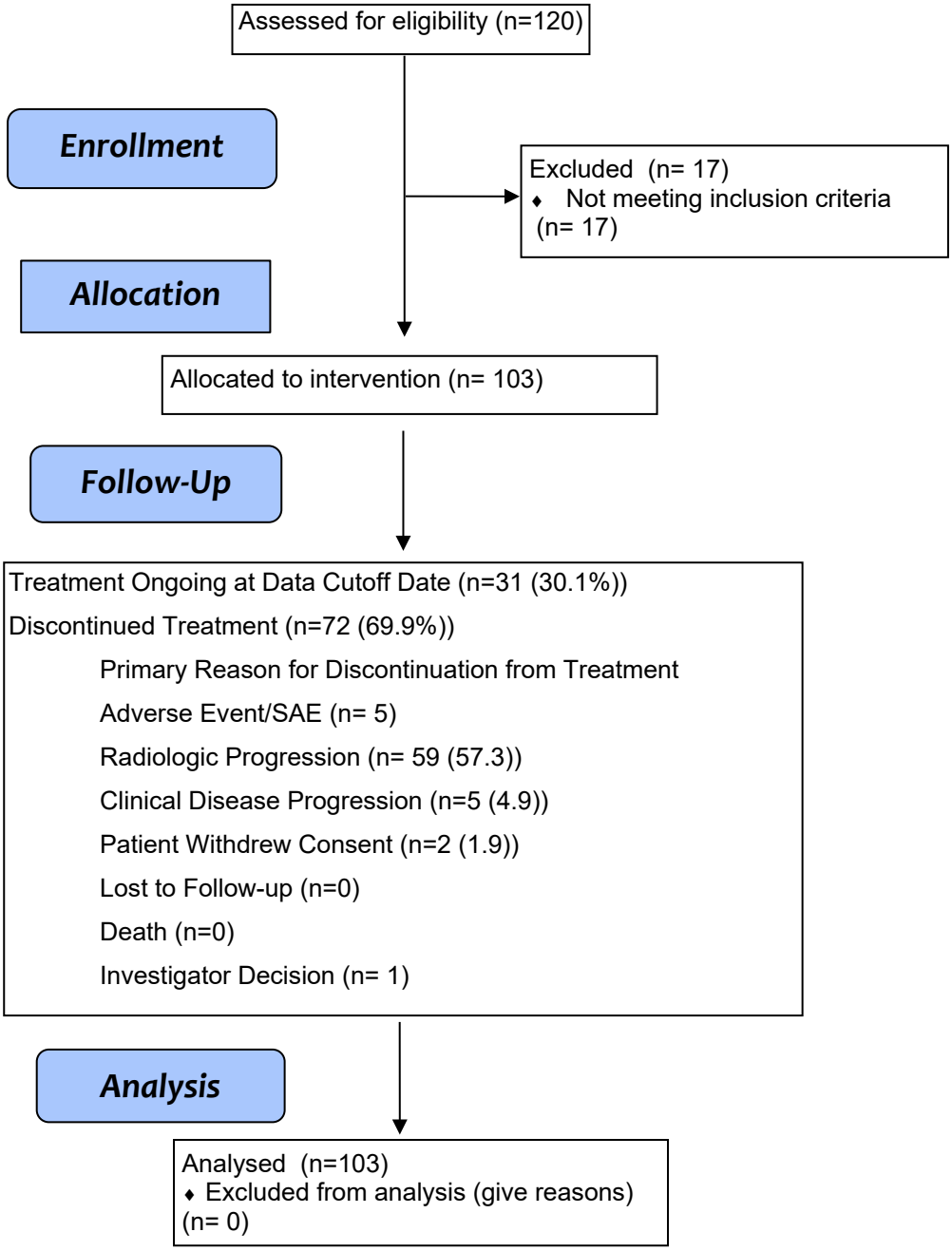
Results

- **Participant flow**

Patients were treated at 48 sites globally, including Australia, Canada, Germany, Spain, France, Great Britain, Hong Kong, Italy, Japan, Korea, the Netherlands, Taiwan, and the United States (US). The highest enrolling sites (>3.0%) were in US (Site 001, 6.7%; Site 002, 3.3%; Site 014, 3.3%; Site 033, 3.3%), Great Britain (Site 151, 3.3%; Site 152, 5.0%), Japan (Site 653, 4.2%), and France (Site 100, 3.3%).

A total of 783 patients were pre-screened for FGFR2 fusions or other re-arrangements. A total of 120 patients signed informed consent in the Phase 2 portion of this study; 17 patients were screen failures and 103 patients received at least 1 dose of futibatinib.

- **Recruitment**



The first patient was treated on 21 July 2014 in study TAS-120-101. The cut-off date for the expansion cohort was 30 June 2019. The cut-off date for phase 2 was 01 October 2020.

- **Conduct of the study**

Amendments

In total there were 9 amendments. A brief summary of the most important changes:

- Amendment 1 (January 2014) and 2 (September 2014): DLT criteria relating to hyperphosphatemia were revised.

- Amendment 3 (February 2016): updated information on assessment of response rate and sample size.

- Amendment 4 (May 2017): added rationale for QD dosing schedule and added intermediate dose level of 20 mg QD to enable a more precise RP2D.

- Amendment 5 (August 2017): updated inclusion criteria to define patients in the expansion and phase II cohort. Updated definitions of populations in statistical methods in expansion and phase II. Revised section on sample size determination.

- Amendment 6 (January 2018): updated inclusion criteria to define patients in the expansion and phase II cohort. Updated determination of sample size information to specify the sample size justification for phase II.

- Amendment 7 (September 2018) phase II expanded eligibility requirements to allow all patient with FGFR2 rearrangements rather than patient with FGFR fusions only.

- Amendment 8 (April 2018): update to manage hyperphosphatemia.

- Amendment 9 (August 2019): requirement of central confirmation of FGFR2 rearrangements prior to enrolment was removed. An interim analysis of efficacy was added. Revised anticipated study completion date to April 2021.

GCP compliance

The FDA conducted inspections did not find significant concerns regarding the management of the clinical trial, GCP compliance, or the data generated.

- **Baseline data**

Phase 2 part study TAS-120-101

Demographics

Demographic characteristics are summarized in Table 14.

All patients had at least 1 prior line of systemic therapy, 30.1% had 2 prior lines of therapy, and 23.3% had 3 or more prior lines of therapy. All patients had received prior platinum-based therapy including 91% with prior gemcitabine/ cisplatin.

Table 14. Summary of Demographics and Baseline Characteristics

	All Treated Patients (N=103) n (%)
Age (years)	
n	103
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)
Region, n (%)	
North America	47 (45.6)
Europe	28 (27.2)
Asia Pacific[a]	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)

Abbreviations: ECOG PS = Eastern Cooperative Oncology Group Performance Status; SD= standard deviation [a] Excluding Japan

The baseline disease characteristics are shown in Table 15. All 103 patients had intra-hepatic cholangiocarcinoma.

Table 15. Summary of Cancer Diagnosis

	All Treated Patients (N = 103)
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)	
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	
n	100
Mean (SD)	2.81 (4.427)
Median (min, max)	1.50 (0.2, 28.3)
Age at most recent progression (years)	
n	87
Mean (SD)	56.5 (11.6)
Median (min, max)	60.0 (22, 78)

Abbreviation: SD = standard deviation

- **Numbers analysed**

103 patients were included for the primary analysis in the single phase I/2 study.

- **Outcomes and estimation**

Primary Efficacy Analysis

Table 16. Tumour Response Rate by Independent Review (Efficacy Population)

	Independent Review (N=103) n (%)
Best overall response, n (%)	
Complete response (CR)	1 (1.0)
Partial response (PR)	42 (40.8)
Stable disease (SD)	42 (40.8)
Progressive disease (PD)	16 (15.5)
Not evaluable	2 (1.9)
Unconfirmed CR or PR	7 (6.8)
Objective response rate (ORR), n (%)	43 (41.7)
95% CI	(32.1, 51.9)
99% CI	(29.4, 54.9)
Disease control rate (DCR), n (%)	85 (82.5)
95% CI	(73.8, 89.3)

Abbreviations: CI = confidence interval
Notes: Objective response rate is based on confirmed PR/CR. Disease control rate is based on confirmed PR/CR/SD. The exact 95% and 99% CIs of tumor response rate are 2-sided and calculated using the Clopper–Pearson method.
Source: Table 14b.2.1.1

The one patient with CR had one remaining nodal lesion which was found to be PET-CT negative. Based on RECIST 1.1 complete disappearance is required for qualifying a response as complete in a non -

target, non - nodal lesion (irrespective of PET scan results). Therefore, all responses observed were partial responses.

One formal interim analysis was conducted after 67 patients with iCCA harboring *FGFR2* rearrangements (including fusions) had been followed for at least 6 months as of 31 January 2020. Results from this analysis were used for early (non-EU) regulatory discussions and were also presented publicly at a scientific conference while follow up of patients for best overall response and duration of response was ongoing (Goyal et al. J Clin Oncol. 2020). As of the cut-off date, 24 patients had confirmed partial responses and 1 had confirmed complete response resulting in an ORR of 37.3 % with a 95% CI of (25.8%, 50.0%).

Secondary Endpoints

Duration of Response

At the time of the data cut-off date, 42 of 43 patients responding to futibatinib had follow-up for at least 6 months following their initial response (median 11.76 months). One patient was followed for less than 6 months since the onset of response. The duration of follow-up for this patient since response was 4.60 months at the data cut-off date, and treatment was ongoing.

At the time of the data cut-off date, the median DOR by Kaplan-Meier analysis for the 43 responders was 9.69 months (95% CI: 7.62, 17.05) (Table 17). The Kaplan-Meier plot of DOR is provided in Figure 5. The majority of responders (31 [72.1%] patients) had DORs of ≥6 months. Fifteen patients had an ongoing response of at least 4 months as of this cut-off date; 10 of these 15 patients had an ongoing response and had not yet reached the median of 9.69 months as of the cutoff date.

The median time to response was 2.50 months (range: 0.7 to 7.4 months) (Table 17).

Table 17. Time to Response and Duration of Response (Responders) - Data cutoff date (Phase 2): 01 October 2020

	Independent Review (N=43) n (%)
Duration of response (months)	
N	43
Mean (SD)	8.35 (4.401)
Median[a] (min, max)	7.56 (2.1, 22.5)
Kaplan-Meier Analysis	
Median (95% CI)	9.69 (7.62, 17.05)
Time to response (months)	
N	43
Mean (SD)	2.63 (1.659)
Median[a] (min, max)	2.50 (0.7, 7.4)
Number of patients with duration of response of at least (%)	
3 Months	42 (97.7)
6 Months	31 (72.1)
12 Months	6 (14.0)
Patients with ongoing response of duration ≥4 months[b]	**15 (34.9)**
Patients with ongoing response of duration ≥6 months[c]	**13 (30.2)**

Abbreviations: CI = confidence interval; SD = standard deviation

Note: Responders are patients with confirmed partial response or complete response.

[a] Median is derived from univariate descriptive statistics.

[c] Subjects with ongoing response consist of responders who had neither progressed nor initiated other anticancer therapy.

Source: Table 14b.2.1.3

Figure 5. Kaplan-Meier Plot of Duration of Response Based on Independent Review (Responders)

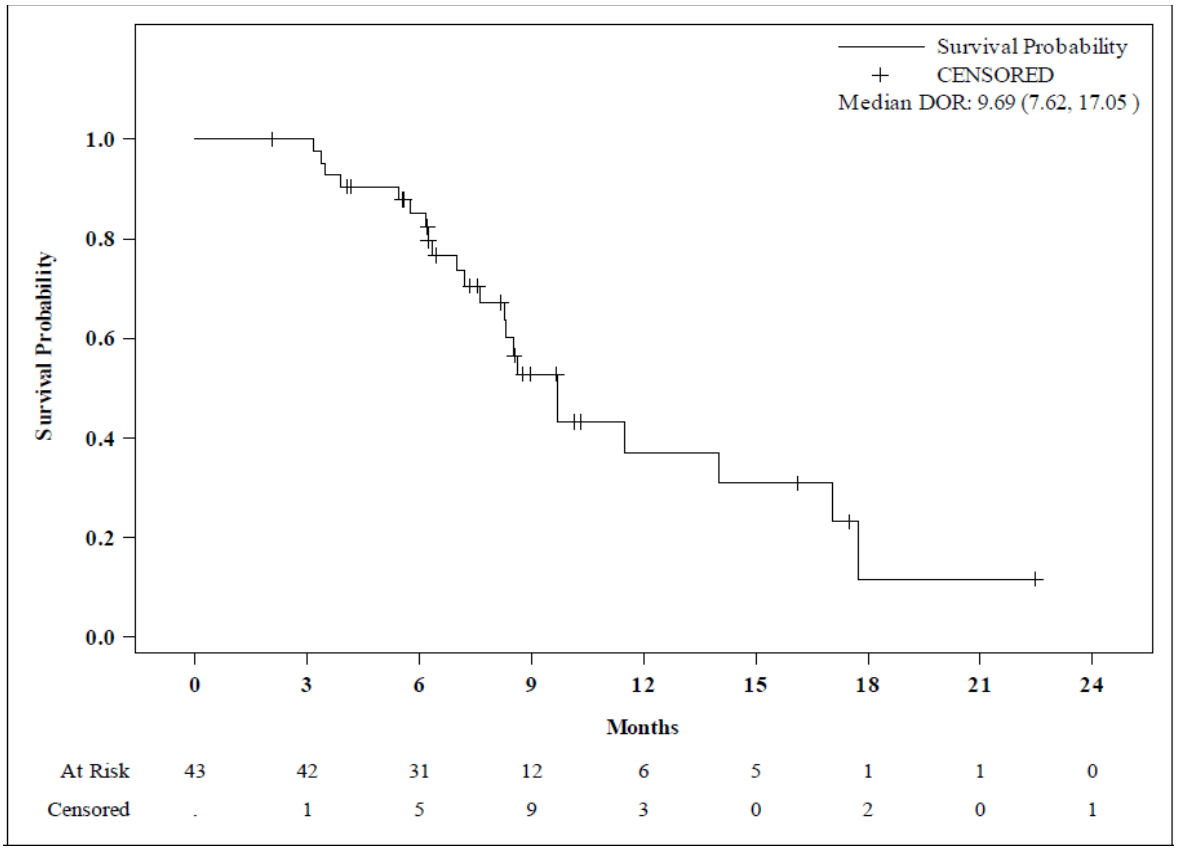


Table 18. Kaplan-Meier estimates of duration of response (95% CI) (DCO 01 October 2020)

	Efficacy Evaluable Population (N = 103)
Kaplan-Meier estimates of duration of response (95 % CI)	
3 months	100 (100, 100)
6 months	85.1 (69.8, 93.1)
9 months	52.8 (34.2, 58.3)
12 months	37.0 (18.4, 55.7)

CI= Confidence Interval
Note: Data are from IRC per RECIST v1.1, and complete and partial responses are confirmed.
In addition to the primary analysis presented here, an interim analysis was conducted without plans to stop the study. Results from both analyses were consistent.

Progression-free Survival

Per independent review, as of the data cut-off (01 October 2020), 64 (62.1%) patients had experienced a PFS event (i.e., disease progression or death) and 39 (37.9%) were censored (20 of the censored patients were ongoing on study treatment at data cut-off. Median PFS was 9.0 months (95% CI: 6.9 months, 13.1 months). At 6 and 12 months, the proportions of patients who were progression free were 66.1% and 40.0%, respectively.

Overall Survival

At the time of the data cut-off (01 October 2020), 40 (38.8%) patients had died and 63 (61.2%) were censored. Of the 63 censored patients, 32 discontinued treatment before the data cutoff date and 31 patients were alive at data cutoff. The median OS was 21.7 months (95% CI: 14.5 months, not

estimable [NE]). The OS rates at 6 and 12 months were 88.1% and 72.2%, respectively. No patients had been lost to follow-up as of the data cut-off date.

- **Ancillary analyses**

Objective Response Rate per Investigator Review

As a sensitivity analysis, the primary endpoint, ORR, was also assessed by the local Investigator or radiologist. The one patient with CR had one remaining nodal lesion which was found to be PET-CT negative. Based on RECIST 1.1 complete disappearance is required for qualifying a response as complete in a non-target, non-nodal lesion (irrespective of PET scan results). Therefore, all responses observed were partial responses.

Table 19. Tumour Response Rate by Investigator Review (Efficacy Population)

	Investigator Review (N=103) n (%)
Best overall response, n (%)	
Complete response (CR)	1 (1.0)
Partial response (PR)	37 (35.9)
Stable disease (SD)	51 (49.5)
Progressive disease (PD)	12 (11.7)
Not evaluable	2 (1.9)
Unconfirmed CR or PR	5 (4.9)
Objective response rate (ORR), n (%)	38 (36.9)
95% CI	(27.6, 47.0)
99% CI	(25.0, 50.0)
Disease control rate (DCR), n (%)	89 (86.4)
95% CI	(78.2, 92.4)

Abbreviations: CI = confidence interval
Notes: Objective response rate is based on confirmed PR/CR. Disease control rate is based on confirmed PR/CR/SD. The exact 95% and 99% CIs of tumor response rate are 2-sided and calculated using the Clopper–Pearson method.
Source: Table 14b.2.1.1

Analysis of Concordance between Independent and Investigator Reviews

To further compare both response assessments, an analysis of concordance between independent and Investigator review of radiographic images has been performed. Twelve (11.7%) patients assessed as having ORR by independent review were not considered ORR by the study Investigator, while 7 (6.8%) patients assessed as having ORR by the study Investigator were not considered ORR by independent assessment. A total of 84 (81.6%) patients had concordant results for response assessment, i.e. 31 (30.1%) patients with both Investigator and independent review of overall response and 53 (51.5%) patients with both Investigator and independent review of no response.

Objective Response Rate for the Per-protocol Analysis Set

As a further pre-specified sensitivity analysis, the primary endpoint, ORR by IRC, was also assessed based on the Per-protocol Analysis Set using a similar analysis method as the primary analysis. The confirmed ORR by IRC per protocol analysis was 43.0% (95% CI: 33.1, 53.3) including 42 patients with PR and 1 patient with CR (Table 20). The one patient with CR had one remaining nodal lesion which was found to be PET-CT negative. Based on RECIST 1.1 complete disappearance is required for qualifying a response as complete in a non-target, non-nodal lesion (irrespective of PET scan results). Therefore, all responses observed were partial responses.

Table 20. Tumour Response Rate (Per-protocol Population)

	Independent Review (N=100) n (%)
Best overall response, n (%)	
Complete response (CR)	1 (1.0)
Partial response (PR)	42 (42.0)
Stable disease (SD)	40 (40.0)
Progressive disease (PD)	15 (15.0)
Not evaluable	2 (2.0)
Unconfirmed CR or PR	7 (7.0)
Objective response rate (ORR), n (%)	43 (43.0)
95% CI	(33.1, 53.3)
99% CI	(30.4, 56.3)
Disease control rate (DCR), n (%)	83 (83.0)
95% CI	(74.2, 89.8)

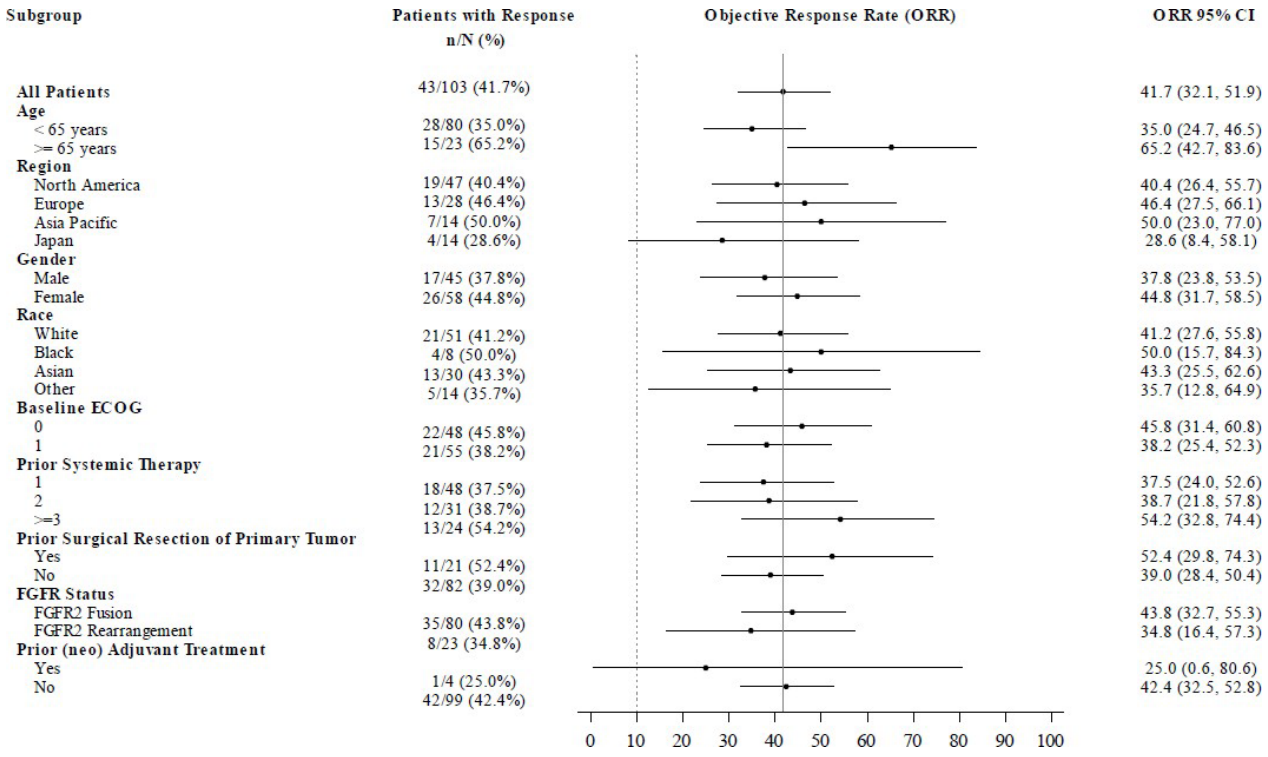
Abbreviations: CI = confidence interval
Notes: Objective response rate is based on confirmed PR/CR. Disease control rate is based on confirmed PR/CR/SD. The exact 95% and 99% CIs of tumor response rate are 2-sided and calculated using the Clopper–Pearson method.
Source: Table 14b.2.1.1.15

Subgroup Analyses for the Primary Endpoint

To assess the consistency of treatment effects across subgroups, analysis of the primary endpoint of confirmed ORR by independent review was performed for the subgroups age, gender, race, baseline ECOG performance score, number of lines of prior systemic therapy, region, prior surgical resection of primary tumour, and prior (neo)adjuvant treatment. The results are provided in a Forest plot (Figure 6).

The treatment effect with respect to confirmed ORR by independent assessment was generally consistent across all subgroups assessed with 95% CIs comprising the primary ORR of 41.7% except for the subgroup of patients at age ≥65 years, with an apparent higher ORR (65.2%; 95% CI: 42.7, 83.6).

Figure 6. Objective Response Rate Subgroup Analysis Based on Independent Review (Efficacy Population)



The confirmed ORR for the 90 patients with any dose modifications (i.e., dose reduction or interruption), as assessed by independent review, was 40.0% (95% CI: 29.8, 50.9)

Objective Response Rate for Patients with *FGFR2* Fusion or Rearrangement

Subgroup analyses were performed on the primary endpoint for patients with FMI results indicating *FGFR2* fusion or *FGFR2* rearrangement by Independent review (Table 21**Error! Reference source not found.**). The ORR was 45.8% (95% CI: 34.0, 58.0) for patients with *FGFR2* fusion and 33.3% (95% CI: 14.6, 57.0) for patients with *FGFR2* rearrangement.

Table 21. Subgroup analysis of tumour response rate by central review, for patients with FGFR2 fusion or rearrangement by Foundation Medicine assay'

	Patients with Results (N=93) n (%)
FGFR2 Fusion (n = 72)	
Best Overall Response, n (%)	
Complete Response (CR)	0
Partial Response (PR)	33 (45.8)
Stable Disease (SD)	26 (36.1)
Progressive Disease (PD)	12 (16.7)
Not Evaluable (NE)	1 (1.4)
Unconfirmed CR or PR	4 (5.6)
Objective Response Rate (ORR), n (%)	33 (45.8)
95% CI	(34.0, 58.0)
Disease Control Rate (DCR), n (%)	59 (81.9)
95% CI	(71.1, 90.0)
FGFR2 Rearrangement (n = 21)	
Best Overall Response, n (%)	
Complete Response (CR)	1 (4.8)
Partial Response (PR)	6 (28.6)
Stable Disease (SD)	10 (47.6)
Progressive Disease (PD)	3 (14.3)
Not Evaluable (NE)	1 (4.8)
Unconfirmed CR or PR	1 (4.8)
Objective Response Rate (ORR), n (%)	7 (33.3)
95% CI	(14.6, 57.0)
Disease Control Rate (DCR), n (%)	17 (81.0)
95% CI	(58.1, 94.6)

Abbreviations: CI = confidence interval; FGFR = fibroblast growth factor receptor; FMI = Foundation Medicine, Inc.
Notes: Objective Response Rate is based on confirmed PR/CR. Disease Control Rate is based on Confirmed PR/CR/SD. The exact 95% CIs of tumor response rate are two-sided and calculated using the Clopper–Pearson method. FMI includes Foundation Medicine local or Foundation Medicine central laboratory results for FGFR2 fusion or FGFR2 rearrangement
Table 14b.2.1.1.10

Duration of response – sensitivity analyses

The primary DOR analysis censored patients for use of anti-cancer therapy, end of treatment due to PD, or death or progressive disease after missing two or more assessments. Pre-specified sensitivity analyses were performed for which these were considered to be events. Results are provided in Table 22.

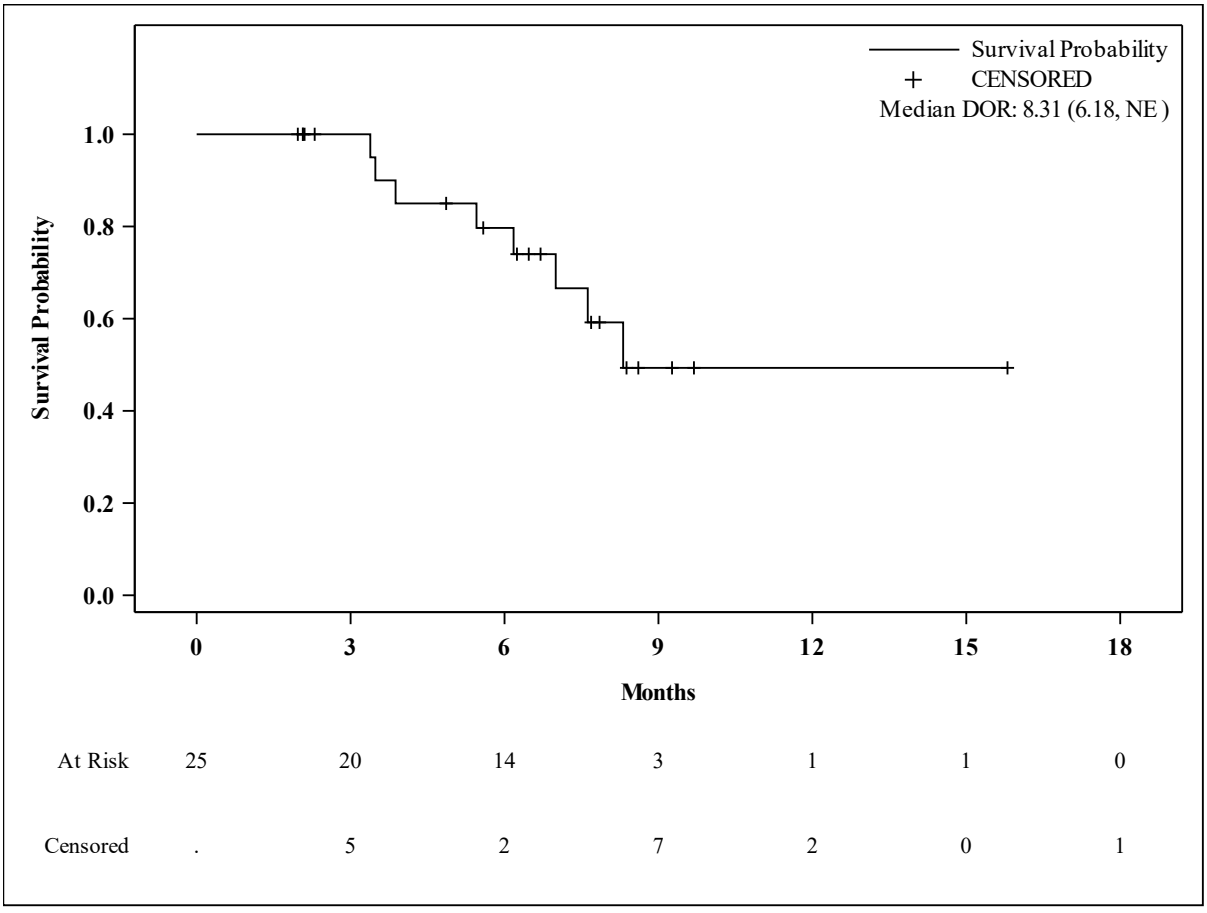
Table 22. Summary of sensitivity/supplementary analyses for duration of response

	Independent Review		Investigator Review	
	Responder	Median (95% CI)	Responder	Median (95% CI)
DOR	43	9.69 (7.62, 17.05)	38	9.69 (7.62, 11.83)
DOR, per-Protocol	43	8.61 (7.62, 11.50)	38	9.69 (7.62, 11.83)
DOR, all PD/Death as events [a]	43	8.61 (7.20, 11.50)	38	9.59 (6.37, 10.64)
DOR, all PD/Death and new-anticancer therapy as events [b]	43	8.61 (7.20, 11.50)	38	9.59 (6.37, 10.64)
DOR, new-anticancer therapy or end of treatment due to PD as events [c]	43	8.51 (6.44, 11.50)	38	9.59 (6.37, 10.64)

Abbreviations: CI = confidence interval; DOR = duration of response; PD = progressive disease
[a] All PD/Death (greater than 21 days after the last dose) are considered as events. Patients who died without post-baseline assessment are considered as events.
[b] In addition to what listed in Footnote a, start of new-anticancer therapy is considered as an event.
[c] Start of new-anticancer therapy or discontinued the treatment due to PD is considered as an event.

The median DOR of the sensitivity analysis taking all PDs and deaths into account based on the interim data is 8.31 months (95% CI: 6.18, NE), see Figure 7.

Figure 7. Kaplan-Meier Plot of Duration of Response Based on Independent Review (all PDs and deaths taken into account based on the interim data)



- **Summary of main efficacy results**

The following table summarises the efficacy results from the main studies supporting the present application. These summaries should be read in conjunction with the discussion on clinical efficacy as well as the benefit risk assessment (see later sections).

Table 23 Summary of efficacy for Study TAS-120-101 (FOENIX-CCA2)

Title: Phase 1/2 Study of TAS-120 in Patients with Advanced Solid Tumours Harboring FGF/FGFR Aberrations			
Study identifier	Protocol Number: TAS-120-101 EudraCT Number: 2013-004810-16		IND Number: 121062 JapicCTI: 18178
Design	The Phase 2 portion of Study TAS-120-101 was a multinational, open-label, non-randomized, single-arm Phase 2 study The Phase 2 portion of TAS-120-101 is the single study of focus and the registration study for this application.		
	Duration of main phase: Duration of Survival Follow-up: Duration of Extension phase:		16 April 2018 – 01 October 2020 (data cut-off date) 01 October 2020 – 29 May 2021 29 May 2021 - Ongoing
Hypothesis	Not applicable (Threshold predetermined by the applicant for a positive outcome which corresponds to a lower limit of the 95% CI for ORR >15%)		
Treatment groups	Futibatinib Treatment Group (N=103)		Treatment: Futibatinib 20 mg QD taken orally continuously on a 21-day treatment cycle Duration of treatment: Until disease progression, unacceptable toxicity, or any other criteria for study treatment discontinuation was met.
Endpoints and definitions	Primary: Objective response rate according to RECIST 1.1 guidelines (Independent Review).	ORR	Objective response rate is defined as the proportion of patients who had best overall response (BOR) of complete response (CR) or partial response (PR) based on independent central radiology review
	Key Secondary: Duration of Response	DOR	Duration of response is defined as the time from the first documented response (CR or PR) to the first documented objective progressive disease (PD) based on independent central radiology review or death due to any cause.
Database lock	30 October 2020 (Primary analysis) / 30 June 2021 (Final analysis)		
Primary Results and Analysis (Data Cut-off Date 01 October 2020)			
Analysis description	**Primary Analysis**		

Analysis population and time point description	Efficacy Population All intra-hepatic cholangiocarcinoma (iCCA) patients with fibroblast growth factor receptor (*FGFR2*) gene fusions or other *FGFR2* rearrangements who received at least 1 dose of futibatinib. The efficacy population is comprised of 103 patients. The pre-specified primary analysis was performed when the majority of patients responding to futibatinib had at least 6 months of follow-up from onset of response.		
Descriptive statistics and estimate variability	Treatment group	Futibatinib	
		Independent Central Review	Investigator Based Assessment
	Number of subjects	103	103
	ORR n (%) [95% CI]	 43 (41.7) [32.1, 51.9]	 38 (36.9) [27.6, 47.0]
	DOR Kaplan-Meier median (95% CI)	 9.69 months (7.62, 17.05)	 9.69 months (7.62, 11.83)
Final Results and Analysis (Data Cut-off Date 29 May 2021)			
Analysis description	**Final analysis**		
Analysis population and time point description	Efficacy Population All intra-hepatic cholangiocarcinoma (iCCA) patients with fibroblast growth factor receptor (*FGFR2*) gene fusions or other *FGFR2* rearrangements who received at least 1 dose of futibatinib. The efficacy population is comprised of 103 patients. The pre-specified final analysis was performed 18 months after the last patient was enrolled in the Phase 2 portion of Study TAS-120-101.		
Descriptive statistics and estimate variability	Treatment group	Futibatinib	
		Independent Review	Investigator Based Assessment
	Number of subjects	103	103
	ORR n (%) [95% CI]	 43 (41.7) [32.1, 51.9]	 39 (37.9) [28.5, 48.0]
	DOR Kaplan-Meier median (95% CI)	 9.46 months (7.62, 10.35)	 9.92 months (6.51, 12.25)

2.6.5.3. Clinical studies in special populations

An overview of all elderly patients included in non-controlled studies by age category is shown in Table 24.

Table 24. Overview of patients included in non-controlled studies by age category

	Age 65-74 (Older subjects number / Total number)	**Age 75-84 (Older subjects number / Total number)**	**Age 85+ (Older subjects number / Total number)**
Non-controlled Trials (patients)	113/469	26/469	0
Non-controlled Trials (healthy volunteer)	0	0	0

2.6.5.4. In vitro biomarker test for patient selection for efficacy

Fibroblast Growth Factor Receptor Aberration Status at Baseline

Out of the 103 subjects enrolled in the Phase 2 trial, 93 were enrolled based on the FGFR2 positivity for rearrangements/fusion as detected by the Foundation Medicine NGS-based F1CDx which is CE-marked. A summary of FGFR status at baseline is summarized in Table 25. The ORR for Patients with FGFR2 Fusion or Rearrangement is provided in Table 21 and Table 25.

Table 25. Summary of FGFR2 Status

	All Treated Patients (N=103) n (%)
Patients with sample for *FGFR2* status (100.0)	**103**
***FGFR2* Status**	
FGFR2 fusion	80 (77.7)
FGFR2 rearrangement	23 (22.3)
Results by local laboratory testing FMI local	
FGFR2 fusion	23 (22.3)
FGFR2 rearrangement	2 (1.9)
Results by FMI central	
FGFR2 fusion	49 (47.6)
FGFR2 rearrangement	19 (18.4)
Source of sample	
Primary tumour site	55 (53.4)
Metastatic tumour site	44 (42.7)
Liquid Sample	4 (3.9)
Not applicable	1 (1.0)

Abbreviations: FGF = fibroblast growth factor; FGFR = fibroblast growth factor receptor; FMI = Foundation Medicine, Inc. **Notes**: One patient had both liquid sample and tissue sample from the primary tumour 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.

Table 26. Summary of responders with FGFR2 Fusion

	All Treated Patients (N=103) n (%)	Responders (N=43) n (%)*
Patients with FGFR2 Fusion	80 (77.7)	35 (43.8)
ARHGAP22	1 (1.0)	1 (100.0)
AXDND1	1 (1.0)	1 (100.0)
AZI1	1 (1.0)	0
BEND3	1 (1.0)	1 (100.0)
BFSP2	1 (1.0)	1 (100.0)
BICC1	24 (23.3)	10 (41.7)
CA10	1 (1.0)	0
CCDC147	1 (1.0)	1 (100.0)
CEP44	1 (1.0)	0
CEP55	1 (1.0)	0
CIT	1 (1.0)	1 (100.0)
CREB5	1 (1.0)	0
CTNNA3	2 (1.9)	1 (50.0)
CUX1	1 (1.0)	1 (100.0)
DDX21	1 (1.0)	1 (100.0)
EVI5	1 (1.0)	0
GPHN	1 (1.0)	1 (100.0)
INA	1 (1.0)	0
KIAA1217	3 (2.9)	2 (66.7)
KIAA1524	1 (1.0)	1 (100.0)
KIAA1598	2 (1.9)	1 (50.0)
LRBA	1 (1.0)	0
MACF1	2 (1.9)	1 (50.0)
MYH9	1 (1.0)	0
NRBF2	1 (1.0)	0
OFD1	1 (1.0)	0
PDE3B	1 (1.0)	1 (100.0)
POC1B	1 (1.0)	0
PUM1	1 (1.0)	0
RBM20	1 (1.0)	1 (100.0)
RXRG	1 (1.0)	1 (100.0)
SEC23IP	1 (1.0)	0
SH3KBP1	1 (1.0)	1 (100.0)
SHROOM3	2 (1.9)	0
SLMAP	1 (1.0)	0
SMARCC1	2 (1.9)	1 (50.0)
SORBS1	1 (1.0)	0
SYNPO2	1 (1.0)	0
TACC1	1 (1.0)	1 (100.0)
TACC2	1 (1.0)	1 (100.0)
TBC1D4	1 (1.0)	0
TRIM8	1 (1.0)	0
TUFT1	1 (1.0)	1 (100.0)
TXLNA	1 (1.0)	0
VCL	2 (1.9)	2 (100.0)
WAC	3 (2.9)	0
Missing	1 (1.0)	0

*Denominator is the number of patients with the same fusion partner

2.6.5.5. Analysis performed across trials (pooled analyses and meta-analysis)

Not applicable.

2.6.5.6. Supportive study(ies)

Not applicable.

2.6.6. Discussion on clinical efficacy

The applicant submitted a conditional marketing authorisation application based on the results of the phase II part of the multicentre, open-label, single-arm Phase 1/2 study to evaluate the safety, pharmacokinetics, pharmacodynamics, and efficacy of futibatinib in patients with histologically or

cytologically confirmed, locally advanced, metastatic, unresectable iCCA harboring FGFR2 gene fusions or other FGFR2 rearrangements.

Design and conduct of clinical studies

There is no established 2L systemic therapy for iCCA following progression after 1L treatment although fluoropyrimidine-based therapy (either in monotherapy or in combination with other cytotoxics) is sometimes used (ESMO Guideline biliary cancer). All patients had to be treated with at least 1 prior systemic GEM/CIS chemotherapy for part II of the TAS-120-101 study. Patients were required to have documentation of radiographic disease progression on the most recent prior therapy.

Despite the low incidence of CCA in Europe, USA and Australasia (0.3–3.5/100 000) compared to other parts of the world (Thailand, China and Korea) almost half of the included patients were Caucasians. The studied population is considered to be of relevance for the EU setting. The majority of the patients had FGFR2 fusions (78%). Twenty two percent of the patients had *FGFR2* rearrangements.

The **inclusion/exclusion criteria** do not fully reflect the **target indication**. One key inclusion criterion was that patients had iCCA. However, the applied indication is for CCA. Given the rarity of extrahepatic cholangiocarcinoma with *FGFR2* rearrangements (including fusions) and the patient inclusion based on the presence of the driver FGFR2 gene rearrangements, homogeneity in effect is expected. The broader CCA target indication is agreed.

The **primary endpoint** of the TAS-120-101 study is ORR. ORR is considered acceptable to investigate antitumor activity of a medicinal product in patients with a defined tumour type.

The applicant stated that the primary analysis is to be performed on the **Efficacy population**, defined as All Intra-hepatic cholangiocarcinoma (iCCA) patients who received at least 1 dose of TAS-120 with FGFR2 gene fusions or other FGFR2 rearrangement. Patients who consented to be part of the study but did not receive at least 1 dose of TAS-120 were screen failures due to not meeting the inclusion or exclusion criteria. Therefore this definition of the efficacy population is considered to be acceptable.

The null hypothesis of no effect was to be rejected if the 2-sided 95% Clopper-Pearson CI lower bound for ORR was greater than 10%.

The **secondary endpoint** was DoR. Rules for how events and censoring are defined for this DoR analysis were provided. The primary DOR analysis censored patients for use of anti-cancer therapy, end of treatment due to PD, and missing two or more assessments (with any known deaths or discontinuations after this point not counted as events). It is considered that these censoring rules are likely to over-estimate the duration of response in the context of a single arm trial. The applicant also pre-planned several sensitivity analyses in which more of the defined situations are considered to be an event rather than censored. This represents a composite estimand strategy, which is relevant to the assessment and informative for the prescribers.

Several **amendments** (9) have been made to the original phase I study protocol and data driven decisions were made in study TAS-120-101.

An interim analysis of efficacy was added while the study was ongoing. Results from this analysis were used for early discussions with (non-EU) regulatory agencies and were presented at a scientific conference while assessments were ongoing for best overall response and duration of response. Results of interim analyses should be kept confidential to prevent the introduction of bias, this is particularly important in single arm trials where there is no possibility of blinding investigators to treatment. While it is acknowledged that interim results are requested by other regulatory agencies as

part of accelerated approval pathways there was no clear need to publicly share this information. In the interest of full transparency this situation is described in the EPAR along with all interim results.

The visit/procedure requirement violations are not expected to affect the B/R assessment. No GCP related critical issues were identified during the GCP inspection.

Efficacy data and additional analyses

The futibatinib dose was 20 mg QD in a continuous 21-day treatment cycle until disease progression or unacceptable toxicity in the phase 2 part of study TAS-120-101. It is uncertain if the optimal dose has been selected. The dose response curve is unknown. The applicant intends to investigate the efficacy of a lower dose 16 mg in the SOB study TAS-120-205.

PK/PD analysis demonstrated target engagement for futibatinib QOD and QD as measured by increased FGF23 and phosphate serum levels with a trend towards dose dependency. However, due to on target hyperphosphatemia, extensive mitigation measures to mitigate hyperphosphatemia were included in the study protocol. The administration of phosphate lowering therapy might have an impact on the interpretation of serum phosphate levels as a potential surrogate for efficacy. Therefore, the serum phosphate level cannot be considered as a surrogate for efficacy.

Efficacy was evaluated in the 103 patients in the Phase 2 portion of study TAS-120-101 with unresectable iCCA harboring **FGFR2 gene fusions** or other **FGFR2 rearrangements**. The majority of the patients had FGFR2 fusions (78%). Twenty two percent of the patients had *FGFR2* rearrangements. Changes were made to the testing requirements for the eligibility of patients based on FGFR rearrangement status, which eventually allowed local or central testing of FGFR status for eligibility via amendment 9. No cross-validation results of the local diagnostic tests for patients' selection with the FMI's FoundationOne clinical trial assay has been reported within the trial due to tissue unavailability. Presence of FGFR2 gene fusions or rearrangements (including gene fusions) should be confirmed by an appropriate diagnostic test prior to initiation of Lytgobi therapy based on the proposed SmPC. All patients with a confirmed PR had some type of FGFR alterations, including FGFR2 rearrangements, FGFR1 mutations (n=2 for both), and FGFR1 amplification (n=1). There were no responses observed in patients without FGF/FGFR alterations (n=3) or patients with no FGF/FGFR test results (n =12) in the Phase 1 dose escalation portion of Study TAS-120-101. The proposed biomarker based selection strategy is considered acceptable as long as there are tests available as used for Phase 2 pivotal trial.

The most common FGFR2 fusion partner was BICC1 (n=24). Ten out of 24 patients with a BICC1 fusion had a response. Given the low number of patients for the other fusion partners no conclusion can be drawn regarding the response rate based on FGFR-fusion partner. Based on the mechanism of action of irreversible inhibition of FGFR 1, 2, 3 and 4, no differences in response rate are expected based on the fusion partner of the driver mutation. At the time of the data cutoff date, with a median follow-up of 11.76 months, the median DOR by Kaplan-Meier analysis for the 43 responders was 9.69 months (95% CI: 7.62, 17.05). Based on the formal interim analysis, of the 67 patients who had been followed for at least 6 months as of 31 January 2020, 24 patients had confirmed partial responses and 1 had confirmed complete response resulting in an ORR of 37.3 % with a 95% CI of (25.8%, 50.0%). The one patient with CR had one remaining nodal lesion which was found to be PET-CT negative. Based on RECIST 1.1 complete disappearance is required for qualifying a response as complete in a non-target, non-nodal lesion (irrespective of PET scan results). Therefore, all responses observed were partial responses.

The median DOR of the sensitivity analysis taking all PDs and deaths into account based on the interim data is 8.31 months (95% CI: 6.18, NE).

The median Independent Review PFS (95% CI) was 8.9 (6.7, 11.0) months. The median OS (95% CI) was 20.0 (16.4, 24.6) months. The prognostic value of FGFR2 gene fusions or other FGFR2 rearrangements is unknown. Due to the SAT design the PFS and OS results are considered of limited value for the B/R assessment.

Due to the SAT design the other secondary endpoints (DCR, PFS, PROs and OS) cannot be used to isolate the drug effect.

One of the inclusion criteria for study TAS-120-101 was the requirement that the patients had documentation of radiographic disease progression on the most recent prior therapy which has been reflected in the wording of the indication in section 4.1 of the SmPC.

Patients with prior FGFR-directed therapy were excluded from the phase II part of study TAS-120-101 which is reflected in section 5.1 of the SmPC.

Additional efficacy data needed in the context of a conditional MA

The applicant will conduct a 'single-arm' Phase 2 Study TAS-120-205 replicating the single-arm efficacy (and safety) data from the pivotal Study TAS-120-101.

The proposed study, TAS-120-205, will provide additional data in a study population similar to the pivotal study population. The efficacy (and safety) data of the 60 patients in the 20 mg Arm A can serve to verify and confirm the benefit-risk balance of futibatinib as observed in the 103 patients in the pivotal Study TAS-120-101. The total (efficacy) dataset will thus be comprised of approximately 160 patients with advanced, unresectable cholangiocarcinoma with a FGFR2 fusion or rearrangement that has progressed after at least one prior line of systemic therapy. In the light of the observed efficacy (ORR and DOR) and safety in the pivotal study, and provided replication of these results is submitted, such a dataset can be considered comprehensive and support a full approval.

Importantly, the efficacy (and safety) data of the 60 patients in the 16 mg Arm B will be regarded as supportive data. The 16 mg data will nevertheless be assessed and may be considered for e.g. inclusion in the SmPC, when scientifically justified and regarded as relevant information for prescribers.

2.6.7. Conclusions on the clinical efficacy

The results of the study TAS-120-101 demonstrated an ORR and DOR indicative of clinical benefit for the target population.

The CHMP considers the following measures necessary to address the missing efficacy data in the context of a conditional MA: results from the 'single-arm' Phase 2 Study TAS-120-205 (SOB) will be provided, which entail replication of the single-arm efficacy (and safety) data from the pivotal Study TAS-120-101 in a new and independent single-arm study cohort.

2.6.8. Clinical safety

2.6.8.1. Patient exposure

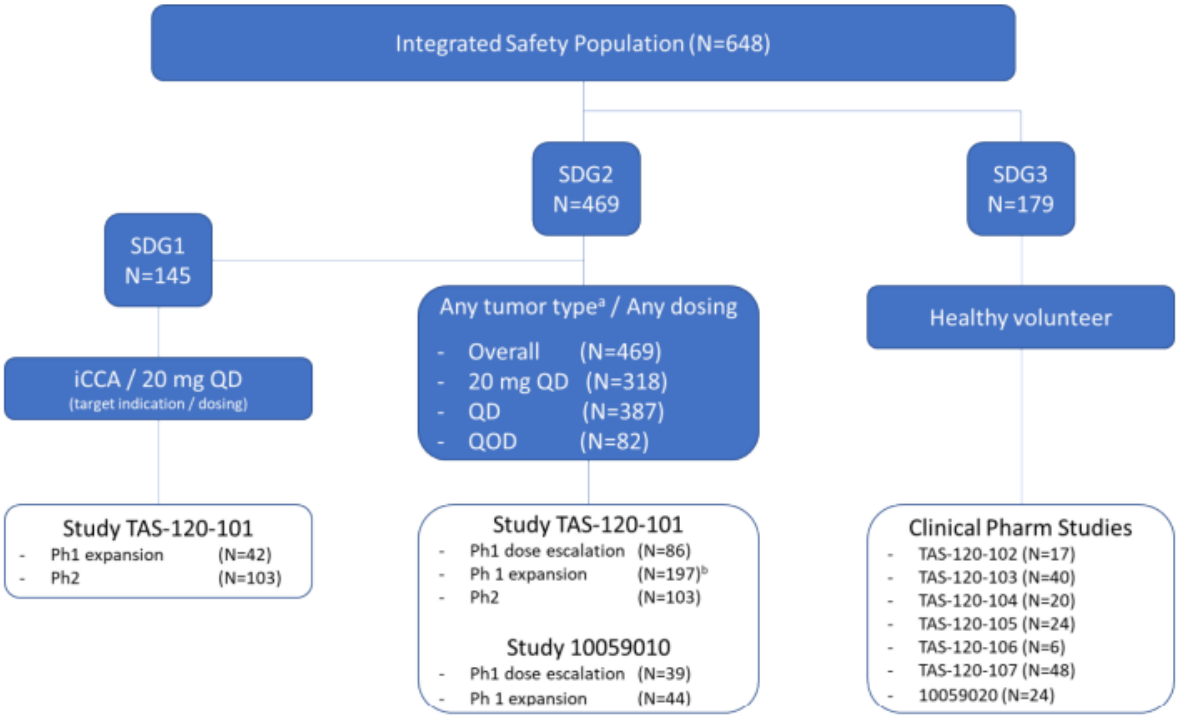
Table 27. Studies included in the safety analysis

Efficacy/ safety	TAS-120-101	5.3.5.2	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.	QOD: 42 QD: 44	Patients aged ≥18 years with advanced solid tumors	Patients may continue until discontinuation criteria were met.	Complete; Full
			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)	16 mg: 27 20 mg: 170	Patients aged ≥18 years with multiple tumor types	Patients may continue until discontinuation criteria were met.	Complete; Full
	FOENIX-CCA2	5.3.5.2	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.	Complete; Full

The primary safety analysis is based on the safety profile of the 42 patients with iCCA included in the phase 1 dose expansion portion of study TAS-120-101 and the 103 patients included in the phase 2 portion of this study (safety data group 1; (SDG)1; n=145), which represents the targeted indication and posology. For the primary safety analysis, the data cut-off date (DCO) was 01 October 2020.

As supportive safety information, safety data on patients with all solid tumours, treated at any dose level in the TAS-120-101 study (phase 1 dose escalation, dose expansion and phase 2) and the Japanese study 10059010 (dose escalation and expansion) is summarized in SDG2 (n=469). Of note, the SDG1 patient population is in full contained within the SDG2 patient population. SDG2 includes 318 patients treated with a starting dose of 20 mg QD futibatinib (Figure 8).

Figure 8. Summary of integrated safety population safety data groups (SDGs)



Abbreviations: iCCA=intrahepatic cholangiocarcinoma; N=number of patients or subjects in group; Ph=Phase; QD=once daily; QOD=every other day; SDG=Safety Data Group

[a] Any tumor type includes patients with iCCA

[b] Includes the 42 patients with iCCA also included in SDG1 population

The median duration of treatment in SDG1 was 8.87 months; the number of treatment cycles ranged from 1 to 46, with a median of 12 cycles and a relative dose intensity of 84.8% (Table 28). Ninety-two patients (63.4%) were treated for a duration ≥6 months, while 34 patients (23.4%) were treated for a duration of ≥12 months. As of DCO, 32 patients (22.1%) were still receiving study treatment, while 113 patients (77.9%) had discontinued study treatment. The primary reason for treatment discontinuation was disease progression (n=97, 66.9%), with 8 patients (5.5%) discontinuing due to an (S)AE, and 4 patients (2.8%) each discontinuing due to withdrawal of consent or investigator decision.

Among the overall population of patients with any tumour type treated at any starting dose (SDG2), the median duration of treatment was 2.76 months. For patients with any tumour type who received a starting dose of 20 mg QD futibatinib (N=318), median duration of treatment was 3.65 months.

Table 28. Study treatment extent of exposure

	Safety Data Group 1 (iCCA)	**Safety Data Group 2 (Any Tumor Type)**	
	20 mg QD (N=145)	**20 mg QD (N=318)**	**Any Dosing (N=469)**
Duration of Treatment (months)			
n	145	318	469
Mean (SD)	8.82 (5.763)	5.91 (5.829)	5.46 (5.943)
Median (Min, Max)	8.87 (0.5, 31.7)	3.65 (0.1, 34.5)	2.76 (0.1, 37.9)
Number of Cycles Treated			
n	145	318	469

	Safety Data Group 1 (iCCA)	Safety Data Group 2 (Any Tumor Type)	
	20 mg QD (N=145)	**20 mg QD (N=318)**	**Any Dosing (N=469)**
Mean (SD)	12.7 (8.14)	8.6 (8.18)	8.0 (8.38)
Median (Min, Max)	12.0 (1, 46)	5.0 (1, 49)	4.0 (1, 54)
Number of Patients with Duration of Treatment, n (%)			
≥6 months	92 (63.4)	116 (36.5)	152 (32.4)
≥12 months	34 (23.4)	41 (12.9)	53 (11.3)
≥18 months	12 (8.3)	17 (5.3)	22 (4.7)
≥24 months	2 (1.4)	5 (1.6)	10 (2.1)
Number of Patients with Dose Modification, n (%)	**132 (91.0)**	**270 (84.9)**	**401 (85.5)**
Dose Reduced			
Yes	77 (53.1)	128 (40.3)	150 (32.0)
Due to AE	74 (51.0)	123 (38.7)	144 (30.7)
Due to Other	8 (5.5)	11 (3.5)	13 (2.8)
Missed Dose	1 (0.7)	1 (0.3)	1 (0.2)
Unknown	N/A[a]	2 (0.6)	2 (0.4)
No	68 (46.9)	190 (59.7)	319 (68.0)
Time to First Dose Reduction due to AE (Days)			
n	74	123	144
Mean (SD)	93.5 (101.06)	81.0 (98.00)	82.1 (103.82)
Median (Min, Max)	46.5 (5, 481)	42.0 (5, 481)	42.0 (5, 610)
Dose Interruption			
Yes	115 (79.3)	227 (71.4)	345 (73.6)
Due to AE	92 (63.4)	194 (61.0)	273 (58.2)
Due to Other	56 (38.6)	82 (25.8)	152 (32.4)
Missed Dose	38 (26.2)	59 (18.6)	62 (13.2)
Unknown	N/A[a]	3 (0.9)	6 (1.3)
No	30 (20.7)	91 (28.6)	124 (26.4)
Time to First Interruption due to AE (Days)			
n	92	194	226
Mean (SD)	65.8 (75.13)	46.8 (59.61)	44.1 (56.75)
Median (Min, Max)	36.0 (4, 325)	22.0 (4, 325)	21.0 (4, 325)
Duration of Interruption (Days)			
n	114	220	258
Mean (SD)	28.8 (35.47)	23.2 (29.24)	21.0 (27.82)
Median (Min, Max)	16.0 (1, 214)	13.0 (1, 214)	10.0 (1, 214)
Relative Dose Intensity (%)			

	Safety Data Group 1 (iCCA)	Safety Data Group 2 (Any Tumor Type)	
	20 mg QD (N=145)	20 mg QD (N=318)	Any Dosing (N=469)
n	145	318	469
Mean (SD)	84.77 (15.383)	84.64 (16.965)	82.59 (18.745)
Median (Min, Max)	88.37 (41.1, 100.0)	90.29 (19.0, 100.0)	88.89 (4.8, 102.9)

Abbreviations: AE=adverse event; iCCA=intrahepatic cholangiocarcinoma; max=maximum; min=minimum; n=number of patients with at least 1 event; N=number of patients in treatment group; N/A=not applicable; QD=once daily; SD=standard deviation

[a] The category "Unknown" is not included in the outputs for SDG1, and is not applicable.

2.6.8.2. Adverse events

An overview of adverse events reported for patients in SDG1 and SDG2 is provided in Table 29.

Table 29. Overview of treatment-emergent and treatment-related adverse events

	Safety Data Group 1 (iCCA)	Safety Data Group 2 (Any Tumor Type)	
	20 mg QD (N=145) n (%)	20 mg QD (N=318) n (%)	Any Dosing (N=469) n (%)
Patients with AEs	**145 (100.0)**	**316 (99.4)**	**467 (99.6)**
Treatment-related	**143 (98.6)**	**309 (97.2)**	**446 (95.1)**
Patients with Serious AEs	59 (40.7)	139 (43.7)	201 (42.9)
Treatment-related	13 (9.0)	23 (7.2)	27 (5.8)
Patients with Grade ≥3 AEs	111 (76.6)	228 (71.7)	313 (66.7)
Treatment-related	79 (54.5)	142 (44.7)	178 (38.0)
Patients with the outcome of death	7 (4.8)	27 (8.5)	38 (8.1)
Treatment-related	0	0	0
Patients with AEs leading to study drug dose adjustment	105 (72.4)	218 (68.6)	305 (65.0)
Treatment-related	87 (60.0)	172 (54.1)	230 (49.0)
Patients with AEs leading to study drug discontinuation	11 (7.6)	29 (9.1)	34 (7.2)
Treatment-related	3 (2.1)	8 (2.5)	9 (1.9)
Patients with AEs leading to study drug dose reduction	73 (50.3)	120 (37.7)	141 (30.1)
Treatment-related	69 (47.6)	114 (35.8)	135 (28.8)
Patients with AEs leading to study drug interruption	89 (61.4)	182 (57.2)	264 (56.3)
Treatment-related	67 (46.2)	135 (42.5)	184 (39.2)

Abbreviations: AE=adverse event; iCCA=intrahepatic cholangiocarcinoma; n=number of patients with at least 1 event; N=number of patients in treatment group; QD=once daily

All patients in SDG1 experienced at least 1 treatment-emergent adverse event (TEAE), and most patients had a treatment-related adverse event (TRAE) (n=143/146, 98.6%). Grade ≥3 TEAEs were reported for 76.6% of patients, most commonly hyperphosphatemia.

Seven patients (4.8%) in SDG1 had AEs with an outcome of death, while 27 patients (8.5%) with any tumour type who received a starting dose of 20 mg QD futibatinib in the integrated population (N=318) experienced an AE with an outcome of death. None of these events were assessed as treatment-related by the investigators.

The percentages of patients who experienced TEAEs (including Grade ≥3) and treatment-emergent SAEs were overall similar between the patients in the TAS-120-101 Phase 2 population (n=103) and patients with iCCA in the integrated population who received 20 mg QD futibatinib (SDG1).

In SDG2, the frequency of TRAEs (97.2%), TEAEs ≥ grade 3 (71.7%; 44.7% treatment-related), SAEs (43.7%; 7.2% treatment-related), and TRAEs leading to dose modifications (interruption 42.5%, reduction 35.8%, discontinuation 2.5%) were comparable to those in SDG1.

Common AEs

The most common TEAEs reported in SDG1 and SDG2, with an incidence of at least 10%, are presented in Table 30.

Table 30. The most common adverse events (≥10% incidence) by Preferred Term

MedDRA Preferred Term	**Safety Data Group 1 (iCCA)**		**Safety Data Group 2 (Any Tumor Type)**			
	20 mg QD (N=145)		**20 mg QD (N=318)**		**Any Dosing (N=469)**	
	Any Grade n (%)	**Grade ≥3 n (%)**	**Any Grade n (%)**	**Grade ≥3 n (%)**	**Any Grade n (%)**	**Grade ≥3 n (%)**
Patients with Any AEs	**145 (100.0)**	**111 (76.6)**	**316 (99.4)**	**228 (71.7)**	**467 (99.6)**	**313 (66.7)**
Hyperphosphataemia	124 (85.5)	39 (26.9)	271 (85.2)	72 (22.6)	376 (80.2)	85 (18.1)
Constipation	54 (37.2)	0	112 (35.2)	2 (0.6)	160 (34.1)	3 (0.6)
Alopecia	51 (35.2)	0	70 (22.0)	0	87 (18.6)	0
Diarrhoea	49 (33.8)	1 (0.7)	106 (33.3)	2 (0.6)	158 (33.7)	3 (0.6)
Dry mouth	45 (31.0)	0	70 (22.0)	0	102 (21.7)	0
Fatigue	45 (31.0)	11 (7.6)	84 (26.4)	17 (5.3)	111 (23.7)	18 (3.8)
Nausea	41 (28.3)	2 (1.4)	86 (27.0)	3 (0.9)	139 (29.6)	5 (1.1)
Dry skin	40 (27.6)	0	57 (17.9)	0	85 (18.1)	0
Aspartate aminotransferase increased	39 (26.9)	13 (9.0)	83 (26.1)	22 (6.9)	108 (23.0)	28 (6.0)
Abdominal pain	36 (24.8)	5 (3.4)	57 (17.9)	8 (2.5)	73 (15.6)	12 (2.6)
Stomatitis	36 (24.8)	9 (6.2)	58 (18.2)	11 (3.5)	89 (19.0)	15 (3.2)
Vomiting	34 (23.4)	1 (0.7)	73 (23.0)	5 (1.6)	105 (22.4)	7 (1.5)
Palmar-plantar erythrodysaesthesia syndrome	33 (22.8)	8 (5.5)	47 (14.8)	11 (3.5)	61 (13.0)	12 (2.6)
Arthralgia	31 (21.4)	0	45 (14.2)	0	58 (12.4)	0

MedDRA Preferred Term	Safety Data Group 1 (iCCA)		Safety Data Group 2 (Any Tumor Type)			
	20 mg QD (N=145)		20 mg QD (N=318)		Any Dosing (N=469)	
	Any Grade n (%)	Grade ≥3 n (%)	Any Grade n (%)	Grade ≥3 n (%)	Any Grade n (%)	Grade ≥3 n (%)
Decreased appetite	29 (20.0)	3 (2.1)	79 (24.8)	8 (2.5)	119 (25.4)	11 (2.3)
Alanine aminotransferase increased	28 (19.3)	9 (6.2)	72 (22.6)	25 (7.9)	96 (20.5)	30 (6.4)
Weight decreased	27 (18.6)	5 (3.4)	44 (13.8)	5 (1.6)	59 (12.6)	7 (1.5)
Dysgeusia	26 (17.9)	0	42 (13.2)	0	52 (11.1)	0
Dry eye	25 (17.2)	1 (0.7)	39 (12.3)	1 (0.3)	48 (10.2)	1 (0.2)
Hypercalcaemia	25 (17.2)	3 (2.1)	39 (12.3)	5 (1.6)	49 (10.4)	9 (1.9)
Anaemia	24 (16.6)	8 (5.5)	53 (16.7)	19 (6.0)	85 (18.1)	31 (6.6)
Back pain	24 (16.6)	3 (2.1)	32 (10.1)	3 (0.9)	48 (10.2)	3 (0.6)
Urinary tract infection	24 (16.6)	3 (2.1)	34 (10.7)	4 (1.3)	48 (10.2)	6 (1.3)
Onycholysis	22 (15.2)	0	29 (9.1)	0	38 (8.1)	0
Hypophosphataemia	21 (14.5)	10 (6.9)	30 (9.4)	15 (4.7)	39 (8.3)	22 (4.7)
Blood creatinine increased	20 (13.8)	0	43 (13.5)	1 (0.3)	63 (13.4)	1 (0.2)
Oedema peripheral	19 (13.1)	0	32 (10.1)	0	41 (8.7)	1 (0.2)
Onychomadesis	19 (13.1)	1 (0.7)	20 (6.3)	1 (0.3)	22 (4.7)	1 (0.2)
Muscle spasms	18 (12.4)	1 (0.7)	29 (9.1)	1 (0.3)	35 (7.5)	1 (0.2)
Myalgia	18 (12.4)	0	22 (6.9)	1 (0.3)	23 (4.9)	1 (0.2)
Nail discolouration	18 (12.4)	0	20 (6.3)	0	26 (5.5)	0
Nail disorder	18 (12.4)	0	28 (8.8)	1 (0.3)	37 (7.9)	1 (0.2)
Hyponatraemia	17 (11.7)	11 (7.6)	30 (9.4)	21 (6.6)	41 (8.7)	30 (6.4)
Pyrexia	17 (11.7)	1 (0.7)	28 (8.8)	3 (0.9)	51 (10.9)	5 (1.1)
Blood alkaline phosphatase increased	16 (11.0)	5 (3.4)	35 (11.0)	7 (2.2)	46 (9.8)	11 (2.3)
Dizziness	16 (11.0)	1 (0.7)	24 (7.5)	2 (0.6)	36 (7.7)	2 (0.4)
Asthenia	8 (5.5)	1 (0.7)	32 (10.1)	7 (2.2)	51 (10.9)	8 (1.7)

Abbreviations: AE=adverse event; iCCA=intrahepatic cholangiocarcinoma; MedDRA=Medical Dictionary for Regulatory Activities; n=number of patients with at least 1 event; N=number of patients in treatment group; N/A=not applicable; QD=once daily

Treatment-related TEAEs and TRAEs of ≥ grade 3

In SDG1, TRAEs were reported for 98.6% of patients, 79 of these patients (54.5%) experienced at least 1 Grade ≥3 TRAE. The most frequently reported TRAEs, reported in at least 20% of patients, included hyperphosphatemia (85.5%), alopecia (34.5%), dry mouth (27.6%), dry skin (26.2%), diarrhea (25.5%), fatigue (22.8%), palmar-plantar erythrodysesthesia syndrome and stomatitis (22.1% each). Grade ≥3 TRAEs reported in ≥5% of patients included hyperphosphatemia (26.9%), stomatitis and AST increased (6.2% each) and palmar-plantar erythrodysesthesia syndrome (5.5%).

In SDG2, these were also the most common TRAEs.

2.6.8.3. Serious adverse event/deaths/other significant events

Deaths

Table 31. Overview of on-study deaths

	Safety Data Group 1 (iCCA)	Safety Data Group 2 (Any Tumor Type)	
	20 mg QD (N=145) n (%)	**20 mg QD (N=318) n (%)**	**Any Dosing (N=469) n (%)**
All Deaths	**71 (49.0)**	**182 (57.2)**	**212 (45.2)**
Time from first dose date to death (month)			
n	71	182	212
Mean (SD)	10.03 (5.901)	8.39 (5.739)	8.58 (6.757)
Median (Min, Max)	9.03 (1.0, 26.4)	6.74 (0.7, 26.4)	6.62 (0.2, 34.0)
The period in which death occurred			
Deaths on-treatment and during 30-day safety follow-up	9 (6.2)	29 (9.1)	41 (8.7)
Deaths >30 days of last dose date	62 (42.8)	153 (48.1)	171 (36.5)
Reasons for all study deaths			
Radiological or clinical disease progression	61 (42.1)	160 (50.3)	184 (39.2)
Adverse event	0	2 (0.6)	2 (0.4)
Unknown[a]	8 (5.5)	17 (5.3)	23 (4.9)
Other	2 (1.4)	3 (0.9)	3 (0.6)
Reasons for deaths on-treatment and during 30 days safety follow-up			
Radiological or clinical disease progression	8 (5.5)	25 (7.9)	33 (7.0)
Adverse event	0	1 (0.3)	1 (0.2)
Unknown[a]	1 (0.7)	3 (0.9)	7 (1.5)
Other	0	0	0

Abbreviations: iCCA=intrahepatic cholangiocarcinoma; max=maximum; min=minimum; n=number of patients with at least 1 event; N=number of patients in treatment group; N/A=not applicable; 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"

In SDG1, no patients died while receiving study treatment. Nine (9) patients (6.2%) died during the 30-day safety follow-up period.

In SDG2, 2 deaths (0.6%) were attributed to AEs. These included 1 patient each with acute pulmonary oedema and acute renal failure. The event of fatal renal failure occurred within the 30-day safety follow-up period, while the acute pulmonary oedema event occurred during the survival follow-up period. Neither of these events were assessed by the investigators as treatment-related. Cause of death for 17 patients (5.3%) was unknown; a majority of these patients died during the survival follow-up period, while 3 patients (0.9%) died from unknown reasons during the 30-day safety follow-

up period. Three patients (0.9%) died due to reasons other than PD or AE. None of these deaths occurred on treatment or during the 30-day safety follow-up period.

Serious adverse events

Table 32. Serious adverse events in ≥1% of patients by SOC and Preferred Term

SOC PT	Safety Data Group 1 (iCCA)		Safety Data Group 2 (Any Tumor Type)			
	20 mg QD (N=145)		20 mg QD (N=318)		Any Dosing (N=469)	
	Any Grade n (%)	Grade ≥3 n (%)	Any Grade n (%)	Grade ≥3 n (%)	Any Grade n (%)	Grade ≥3 n (%)
Patients with at Least One AE	**59 (40.7)**	**52 (35.9)**	**139 (43.7)**	**121 (38.1)**	**201 (42.9)**	**162 (34.5)**
Blood and lymphatic system disorders	**1 (0.7)**	**1 (0.7)**	**3 (0.9)**	**3 (0.9)**	**5 (1.1)**	**5 (1.1)**
Anaemia	1 (0.7)	1 (0.7)	3 (0.9)	3 (0.9)	5 (1.1)	5 (1.1)
Gastrointestinal disorders	**20 (13.8)**	**17 (11.7)**	**42 (13.2)**	**36 (11.3)**	**59 (12.6)**	**48 (10.2)**
Abdominal pain	4 (2.8)	2 (1.4)	6 (1.9)	3 (0.9)	11 (2.3)	6 (1.3)
Ascites	3 (2.1)	3 (2.1)	4 (1.3)	4 (1.3)	4 (0.9)	4 (0.9)
Intestinal obstruction	3 (2.1)	3 (2.1)	7 (2.2)	7 (2.2)	8 (1.7)	8 (1.7)
Nausea	2 (1.4)	1 (0.7)	3 (0.9)	2 (0.6)	6 (1.3)	3 (0.6)
Upper gastrointestinal haemorrhage	4 (2.8)	3 (2.1)	5 (1.6)	4 (1.3)	5 (1.1)	4 (0.9)
Vomiting	2 (1.4)	1 (0.7)	4 (1.3)	3 (0.9)	7 (1.5)	4 (0.9)
General disorders and administration site conditions	**12 (8.3)**	**8 (5.5)**	**29 (9.1)**	**23 (7.2)**	**41 (8.7)**	**32 (6.8)**
Disease progression	6 (4.1)	6 (4.1)	15 (4.7)	15 (4.7)	22 (4.7)	22 (4.7)
Pyrexia	4 (2.8)	0	6 (1.9)	1 (0.3)	11 (2.3)	3 (0.6)
Hepatobiliary disorders	**9 (6.2)**	**8 (5.5)**	**17 (5.3)**	**16 (5.0)**	**22 (4.7)**	**21 (4.5)**
Bile duct obstruction	4 (2.8)	3 (2.1)	6 (1.9)	5 (1.6)	6 (1.3)	5 (1.1)
Cholangitis	2 (1.4)	2 (1.4)	4 (1.3)	4 (1.3)	4 (0.9)	4 (0.9)
Infections and infestations	**18 (12.4)**	**17 (11.7)**	**33 (10.4)**	**32 (10.1)**	**42 (9.0)**	**38 (8.1)**
Biliary tract infection	3 (2.1)	3 (2.1)	3 (0.9)	3 (0.9)	3 (0.6)	3 (0.6)
Pneumonia	1 (0.7)	1 (0.7)	3 (0.9)	3 (0.9)	7 (1.5)	5 (1.1)
Sepsis	4 (2.8)	4 (2.8)	11 (3.5)	11 (3.5)	11 (2.3)	11 (2.3)
Urinary tract infection	2 (1.4)	2 (1.4)	3 (0.9)	3 (0.9)	3 (0.6)	3 (0.6)
Injury, poisoning and procedural complications	**6 (4.1)**	**3 (2.1)**	**7 (2.2)**	**4 (1.3)**	**9 (1.9)**	**5 (1.1)**
Fall	2 (1.4)	1 (0.7)	2 (0.6)	1 (0.3)	2 (0.4)	1 (0.2)
Metabolism and nutrition disorders	**9 (6.2)**	**7 (4.8)**	**15 (4.7)**	**13 (4.1)**	**27 (5.8)**	**18 (3.8)**
Decreased appetite	2 (1.4)	2 (1.4)	4 (1.3)	4 (1.3)	11 (2.3)	5 (1.1)
Dehydration	3 (2.1)	2 (1.4)	6 (1.9)	5 (1.6)	8 (1.7)	6 (1.3)
Hypercalcaemia	2 (1.4)	1 (0.7)	2 (0.6)	1 (0.3)	5 (1.1)	3 (0.6)

SOC PT	Safety Data Group 1 (iCCA)		Safety Data Group 2 (Any Tumor Type)			
	20 mg QD (N=145)		20 mg QD (N=318)		Any Dosing (N=469)	
	Any Grade n (%)	Grade ≥3 n (%)	Any Grade n (%)	Grade ≥3 n (%)	Any Grade n (%)	Grade ≥3 n (%)
Musculoskeletal and connective tissue disorders	**7 (4.8)**	**5 (3.4)**	**9 (2.8)**	**7 (2.2)**	**10 (2.1)**	**7 (1.5)**
Back pain	2 (1.4)	1 (0.7)	2 (0.6)	1 (0.3)	2 (0.4)	1 (0.2)
Pain in extremity	2 (1.4)	2 (1.4)	2 (0.6)	2 (0.6)	3 (0.6)	2 (0.4)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	**7 (4.8)**	**7 (4.8)**	**12 (3.8)**	**12 (3.8)**	**14 (3.0)**	**13 (2.8)**
Tumour pain	2 (1.4)	2 (1.4)	2 (0.6)	2 (0.6)	2 (0.4)	2 (0.4)
Nervous system disorders	**12 (8.3)**	**4 (2.8)**	**23 (7.2)**	**11 (3.5)**	**32 (6.8)**	**16 (3.4)**
Migraine	2 (1.4)	0	2 (0.6)	0	2 (0.4)	0
Transient ischaemic attack	3 (2.1)	0	4 (1.3)	0	6 (1.3)	0
Respiratory, thoracic and mediastinal disorders	**3 (2.1)**	**1 (0.7)**	**10 (3.1)**	**7 (2.2)**	**17 (3.6)**	**10 (2.1)**
Dyspnoea	2 (1.4)	0	3 (0.9)	1 (0.3)	5 (1.1)	3 (0.6)

In SDG1, treatment-emergent SAEs were reported in 59 patients (40.7%) with iCCA who received a starting dose of 20 mg QD futibatinib; of these, 35.9% were ≥ grade 3. 9.0% were considered treatment-related, and none of these were grade 4 or 5 events.

7 SAEs were Grade 5 events (disease progression (n=5, 3.4%), and ascites and hepatic failure (n=1 each, 0.7%).

Of the 13 patients with a treatment-related SAE (9.0%); 9 patients (6.2%) experienced at least 1 treatment-related Grade 3 SAE. There were no treatment-related Grade 4 or Grade 5 SAEs. Treatment-related SAEs reported in >1 patient included intestinal obstruction and migraine (n=2 each, 1.4%); all remaining treatment-related SAEs occurred in a single patient each. The SAEs of intestinal obstruction were both Grade 3 events, while both events of migraine were Grade 2.

In SDG2, a total of 201 patients (42.9%) experienced at least 1 treatment-emergent SAE and 34.5% experienced Grade ≥3 SAEs.

Treatment-related SAEs were reported for a total of 23/318 patients (7.2%), 16 patients (5.0%) had at least 1 treatment-related Grade 3 SAE, and there was a single Grade 4 treatment-related SAE of hyponatremia. There were no Grade 5 treatment-related SAEs. Two patients (0.6%) each experienced SAEs of anemia (grade 3), intestinal obstruction (grade 3), migraine (grade 2), and transient ischemic attack (grade 2).

Adverse events of special interest (AESI)

Based on safety signals during preclinical or clinical trials, or based on class effects of similar drugs, the following AESI for futibatinib were defined: retinal disorders, hyperphosphatemia, hepatotoxicity, nail disorders, Palmar-plantar erythrodysesthesia syndrome (PPES), and rash.

Table 33 summarizes incidence of AESIs observed in the TAS-120-101 Phase 2 population, SDG1 and the 318 patients from SDG2 treated at the proposed dose of 20mg QD.

Table 33. AESIs observed in TAS-120-101, SDG1 and SDG2 (20mg QD dose only)

AESI	TAS-120-101 Phase 2 (iCCA) 20 mg QD (N=103)		Safety Data Group 1 (iCCA) 20 mg QD (N=145)		Safety Data Group 2 (Any Tumor Type) 20 mg QD (N=318)	
	Any Grade n (%)	Grade ≥3 n (%)	Any Grade n (%)	Grade ≥3 n (%)	Any Grade n (%)	Grade ≥3 n (%)
Patients with AESI	**98 (95.1)**	**43 (41.7)**	**136 (93.8%)**	**57 (39.3%)**	**292 (91.8%)**	**109 (34.3%)**
Retinal Disorders	8 (7.8)	0	9 (6.2)	0	27 (8.5)	0
Hyperphosphataemia	94 (91.3)	32 (31.1)	130 (89.7)	40 (27.6)	280 (88.1)	75 (23.6)
Hepatotoxicity	28 (27.2)	13 (12.6)	42 (29.0)	18 (12.4)	94 (29.6)	38 (11.9)
Nail Disorders	48 (46.6)	2 (1.9)	64 (44.1)	2 (1.4)	94 (29.6)	4 (1.3)
Palmar-plantar erythrodysaesthesia syndrome (PPES)	22 (21.4)	5 (4.9)	33 (22.8)	8 (5.5)	48 (15.1)	11 (3.5)
Rash	9 (8.7)	0	13 (9.0)	0	27 (8.5)	0

Source: TAS-120-101 Part 2 CSR Table 14b.3.2.1.1, TAS-120-101 Part 2 CSR Table 14b.3.2.5.2, ISS Table 14.3.2.5.1.1, ISS Table 14.3.2.5.1.2, ISS Table 14.3.2.5.2.1 and ISS Table 14.3.2.5.2.2
Abbreviations: AESI=adverse event of special interest; n=number of patients with at least 1 event; N=number of patients in treatment group; QD=once daily

In SDG1, 136 patients (93.8%) experienced at least 1 AESI, Grade ≥3 AESIs were reported for 57 patients (39.3%), including 1 with an outcome of death (hepatic failure, which was assessed as not treatment-related, see following section on hepatotoxicity).

In SDG2, AESIs were reported for 87.2% of patients (n=409), with 28.8% of patients (n=135) experiencing Grade ≥3 AESIs.

Of the 318 patients with any tumour type who received a starting dose of 20 mg QD futibatinib, 292 patients (91.8%) experienced at least 1 AESI. Grade ≥3 AESIs were reported for 109 patients (34.3%), including 2 patients (0.6%) experiencing hepatic failure with an outcome of death considered to be caused by disease progression.

Retinal disorders

Ophthalmological examination was performed prior to initiation of therapy, 6 weeks thereafter, and urgently at any time for visual symptoms. For serous retinal detachment, the following dose modification guidelines are in place:

Table 34. Dose modifications for serous retinal detachment

Adverse reaction	Futibatinib dose modification
Asymptomatic	• Continue futibatinib at current dose. Monitoring should be performed as described in section 4.4.
Moderate decrease in visual acuity (best corrected visual acuity 20/40 or better or ⩽ 3 lines of decreased vision from baseline); limiting instrumental activities of daily living	• Withhold futibatinib. If improved on subsequent examination, futibatinib should be resumed at the next lower dose level. • If symptoms recur, persist or examination does not improve, permanent discontinuation of futibatinib should be considered based on clinical status.
Marked decrease in visual acuity (best corrected visual acuity worse than 20/40 or >3 lines decreased vision from baseline up to 20/200); limiting activities of daily living	• Withhold futibatinib until resolution. If improved on subsequent examination, futibatinib may be resumed at 2 dose levels lower. • If symptoms recur, persist or examination does not

Adverse reaction	Futibatinib dose modification
	improve, permanent discontinuation of futibatinib should be considered based on clinical status.
Visual acuity worse than 20/200 in affected eye; limiting activities of daily living	• Permanent discontinuation of futibatinib should be considered based on clinical status.

In SDG1, AESIs in the category of retinal disorders were infrequent, with 9 patients (6.2%) experiencing retinal disorders, most frequently subretinal fluid (n=3, 2.1%) and chorioretinopathy (n=2, 1.4%). There were no Grade ≥3 events of retinal disorders.

Median time to onset of retinal disorder was 43 days. In the 3 patients (2.1%) with Grade 2 retinal disorders, all events resolved to Grade <2, after a median of 25 days. There were no SAEs reported, and no AEs led to discontinuation of futibatinib, although 3 patients (2.1%) experienced AEs leading to dose interruption and/or reduction.

In SDG2, retinal disorders occurred in 38 patients (8.1%), most were assessed as treatment-related (7.7%). There were no Grade ≥3 events, six patients (1.9%) had Grade 2 retinal disorders, all of which resolved to Grade <2 after a median of 23 days. Retinal disorders led to dose reduction in 5 patients and interruptions in 4 patients, one patient discontinued futibatinib because of retinal disorders (retinal detachment and cataract).

Hyperphosphatemia

Grading of hyperphosphatemia AEs did not use CTCAE v4.03 (which does not include criteria for grade of hyperphosphatemia), but was conducted based on serum phosphate levels. In this adjusted grading, Grade 3 was defined as serum phosphate level >7 mg/dL irrespective of clinical symptoms. Hyperphosphatemia was the most frequently reported AESI (SDG1/SDG2 89.7/82.1% of patients), and it was always assessed as treatment-related. Grade 3 events were reported for 27.6% and 18.8% of patients, respectively, in SDG1 and SDG2. For the patients from SDG2 treated with a starting dose of 20mg QD, the incidence of grade 3 hyperphosphatemia was 23.6%. There were no grade 4 or 5 events.

In SDG1 and SDG2, respectively, median time to onset was 6 days/5 days (Grade 3: 8.5 days / 9.0 days) and most grade 3 events resolved, with a median time to resolution of 7 days in both groups (range: 2 to 26 days). For 2/75 patients with grade 3 hyperphosphatemia in SDG2, this AESI did not resolve.

Hyperphosphatemia was managed with use of concomitant phosphate lowering medication in 83.4%/76.6% of patients (SDG1/SDG2 20mg QD). In SDG1, hyperphosphatemia led to dose reductions and/or interruptions in 17.9% and 18.6% of patients. In SDG2, these percentages were 12.9% and 21.1%. There were no SAEs, no deaths and no patients discontinued treatment due to hyperphosphatemia.

In an exploratory analysis with hyperphosphatemia defined based on CTCAE v5.0 criteria (including 129 patients in SDG1 and 419 patients in SDG2), there were no ≥grade 3 events in SDG1 or SDG2. In SDG1, the majority of patients (n=102, 79.1%) with normal baseline phosphate results had a maximum post-baseline result of Grade 2, while 21 patients (16.3%) had a maximum result of Grade 1. In SDG2, the majority of the 318 patients who received a starting dose of 20 mg QD futibatinib (n=220, 76.1%) with normal baseline phosphate results had a maximum post-baseline result of Grade 2, while 56 patients (19.4%) had a maximum result of Grade 1.

There were no SAEs, no deaths and no treatment discontinuations due to hyperphosphatemia.

Hepatotoxicity

In SDG1, 42 patients (29%) had an AESI in the category of hepatotoxicity, including 18 patients (12.4%) with Grade ≥3 events (Table 33). The majority was assessed as treatment-related by the investigator (n=30/42 of 145 patients, 20.7%). Hepatotoxicity was most reported as AST increased (n=39; 26.9%) and ALT increased (n=28; 19.3%). Grade 3 results that occurred in ≥5.0% of patients were AST increased (n=15, 10.3%), alkaline phosphatase increased (n=14, 9.7%), and ALT increased (n=8, 5.5%). A Grade 4 result of ALT increased was reported for 1 patient (0.7%). One patient experienced a grade 5 AESI of hepatic failure, due to disease progression, which was assessed as not treatment-related. None of the reported events met Hy's law criteria.

Median time to onset was 57.5 days (Grade ≥3: 71 days). All Grade ≥3 events resolved with a median time to resolution to Grade <3 of 5 days. Nine patients (6.2%) had AESIs resulting in dose reduction and 14 patients (9.7%) had events leading to dose interruption. No patients discontinued study treatment due to hepatotoxicity.

For SDG1, additional analyses regarding corrective treatments and de- and rechallenge information for hepatotoxicity were provided.

Corrective treatments were given for TEAEs included in the definition of the hepatotoxicity AESI, including AEs of ALT increased (n=3 patients, 8 AEs), AST increased (n=4 patients, 11 AEs), and gamma-glutamyl Transferase (GGT) increased (n=1 patient, 1 AE).

Positive de-challenge was reported for TEAEs of ALT increased (n=9 patients, 22 AEs), AST increased (n=9 patients, 22 AEs), and GGT increased (n=2 patients, 4 AEs). Negative de-challenge was reported for TEAEs of ALT increased (n=5 patients, 6 AEs) and AST increased (n=3 patients, 5 AEs). All events reported as negative de-challenge were eventually reported as resolved. Rechallenge information was provided for one patient, and it was positive.

Twenty-two patients who had an AESI of hepatotoxicity died during the 30-day safety follow-up period. Autopsy was performed for 3 patients, the results of which are summarized as follows:

In a patient with Grade 1 ALT increased (recovered) and Grade 1 AST increased (not recovered), autopsy findings described the liver with moderately differentiated cholangiocarcinoma diffusely involving all lobes with metastases to several areas.

In a patient with Grade 1 ALT increased (not recovered) and Grade 1 AST increased (not recovered), the cause of death was acute bronchopneumonia superimposed on metastatic intrahepatic cholangiocarcinoma.

In a patient with Grade 5 hepatic failure (fatal), autopsy findings included intrahepatic cholangiocarcinoma, extensively involving the liver, with metastatic disease.

In SDG2, 126 patients (26.9%) had an AESI in the category of hepatotoxicity, 50 of which were assessed as treatment-related by the investigator (n=50/126 of 469 patients, 10.7%).

For the 318 patients treated with a starting dose of 20mg QD futibatinib, 29.6% had an AESI of hepatotoxicity, most of which (n=74/94 of 318 patients; 23.3%) were assessed as treatment-related. There were 38 patients with a grade ≥3 event (11.9%), including two patients with a grade 5 AESI of hepatic failure, which were both assessed as not treatment-related.

Median time to onset in this group was 15.5 days (Grade ≥3: 25 days). Grade ≥3 events resolved in the majority of cases (34/38; 89.5%) with a median time to resolution to Grade <3 of 7 days. Twenty-one patients (6.6%) had AESIs resulting in dose reduction and 29 patients (9.1%) had events leading to dose interruption. No patients discontinued study treatment due to hepatotoxicity.

Nail disorders

In SDG1, 64 patients (44.1%) had an AESI of nail disorders. Common AEs reported were onycholysis (n=22, 15.2%), onychomadesis (n=19, 13.1%), and nail discoloration and nail disorder (n=18 each, 12.4%). All other AEs occurred in <10% of patients.

Most AEs were Grade 1 or Grade 2; 2 patients experienced Grade 3 AEs (1 event each of onychomadesis and paronychia). Median time to onset was 96.5 days (Grade ≥3: 155.5 days). No AESIs in this category were Grade 4 or 5, serious, or led to treatment discontinuation. Nail disorders were managed with use of concomitant medication(s) (87.5% of patients) and/or futibatinib dose modifications (4.8% reductions/6.9% interruptions).

In SDG2, 127 patients (27.1%) experienced an AESI of nail disorders, most were treatment-related (n=123, 26.2%).

In the group of patients treated with a starting dose of 20 mg QD a total of 94 patients (29.6%) experienced an AESI of nail disorders, also mostly treatment-related (n=91, 28.6%). There were 4 patients (1.3%) with a Grade ≥3 event. No Grade 4 or Grade 5 events were reported.

Median time to onset for AESIs of nail disorders of any grade in this group was 85.0 days, and median time to onset of Grade ≥3 events was 155.5 days. Grade ≥3 AESI of nail disorders resolved to Grade <3 in 2 (0.6%) out of 4 patients, and to Grade <2 in 1 (0.3%) out of 4 patients.

Dose reduction resulting from the AESI of nail disorders was reported for 10 patients (3.1%), dose interruption was performed in 13 patients (4.1%), and one patient (0.3%) discontinued study treatment due to the AESI of nail disorders (onycholysis).

Palmar-plantar erythrodysesthesia syndrome (PPES)

PPES was reported for 33 patients (22.8%) in SDG1, all but one were considered treatment-related. Eight patients (5.5%) had a Grade 3 event. Median time to onset for PPES was 103 days (148 days for grade 3). All grade 3 events resolved to < grade 3, after a median of 7 days.

No AESIs in this category were Grade 4 or 5, serious, or led to treatment discontinuation. PPES was managed with use of concomitant medications in most patients, and/or futibatinib dose modifications (9.7% reductions/9.0% interruptions).

There were no dose discontinuations due to PPES.

In SDG2, 62 patients (13.2%) had an AESI of PPES, all but 2 were considered treatment-related.

In the group of patients treated with a starting dose of 20 mg QD a total of 48 patients (15.1%) experienced an AESI of PPES, also mostly treatment-related (n=47). In this group, there were 11 patients with a grade 3 event (3.5%), no grade 4 or 5 events were reported.

Median time to onset for PPES was 85 days (178 days for grade 3). All grade 3 events resolved to <grade 3, after a median of 8 days, and to <grade 2 after a median of 12 days. Futibatinib dose modifications were rare (5.7% reductions/4.7% interruptions), there were no discontinuations due to PPES.

Rash

The incidence of rash was 9.0% and 8.5% in SDG1 and SDG2, respectively, and it was assessed as treatment-related in 3.4% and 4.3%. Median time to onset of rash was 54 days/43 days in these groups, and there were no Grade ≥3 events, SAEs, or events leading to modification of study treatment.

Other events

Eye disorders

Of note, AEs defined by PTs previously discussed in the section on the AESI of retinal disorders were not included in this analysis.

In SDG1, TEAEs in the SOC of eye disorders were reported for 63 patients (43.4%), Grade ≥3 TEAEs were reported for 3 patients (2.1%). The most frequently reported AEs were dry eye (n=25, 17.2%), vision blurred (n=13, 9.0%), lacrimation increased (n=7, 4.8%), and cataract (n=6, 4.1%).

Treatment-related cataract was reported in 3 patients (2.1%); of these, 2 patients (1.4%) had Grade ≥3 cataract. One patient from SDG2 experienced an SAE of Grade ≥3 cataract assessed as related to treatment that required cataract surgery.

Gastrointestinal disorders

In SDG1, a total of 126 patients (86.9%) experienced TEAEs in the SOC of gastrointestinal disorders. Grade ≥3 TEAEs were present in 31 of these patients (21.4%). The most frequently reported AEs were constipation (n=54, 37.2%), diarrhoea (n=49, 33.8%), dry mouth (n=45, 31.0%), and nausea (n=41, 28.3%).

General disorders and administration site conditions

In SDG1 (n=145) and SDG2 20mg QD dose (n=318) respectively, TEAEs in this SOC were reported for 55.9%/53.1%. Grade ≥3 TEAEs were present for 13.1%/13.2%. Most frequent in both groups were fatigue (31%), peripheral edema (13.1%), pyrexia (11.7%) and asthenia (5.5%) (percentages for SDG1).

Investigations

TEAEs in the SOC of investigations were reported for 88 patients (60.7%) in SDG1, of these, 29 patients (20.0%) experienced Grade ≥3 TEAEs. Weight decreased (n=27, 18.6%), blood creatinine increased (n=20, 13.8%), and blood alkaline phosphatase increased (n=16, 11.0%) were the most frequently reported TEAEs. In SDG2, these were also the most frequently reported TEAEs in this SOC with comparable frequencies.

Metabolism and nutrition disorders

In SDG1, TEAEs in the SOC of metabolism and nutrition disorders were reported for 136 patients (93.8%), 61 of whom (42.1%) experienced Grade ≥3 AEs. The most frequently reported TEAEs included decreased appetite (n=29, 20.0%), hypercalcemia (n=25, 17.2%) and hypophosphatemia (n=21, 14.5%).

Skin and subcutaneous tissue disorders

Of note, AEs defined by PTs previously discussed in the section on the AESIs of nail disorders, PPES and rash were not included in this analysis.

In SDG1, TEAEs in the SOC of skin and subcutaneous tissue disorders were reported for 106 patients (73.1%), 9 of whom (6.2%) experienced Grade ≥3 TEAEs. Alopecia (n=51, 35.2%) and dry skin (n=40, 27.6%) were the most frequently reported AEs.

2.6.8.4. Laboratory findings

Haematology and coagulation

At least 1 shift of ≥2 grades was reported for all haematology and coagulation laboratory tests (with the exception of haemoglobin increased) in both populations.

In both SDG1 and SDG2, the most frequently reported (≥5.0%) Grade 3 results were lymphocyte count decreased (15.2%/15.8%), activated partial thromboplastin time prolonged (6.4%/3.9%) and anemia (5.5%/7.3%). In the patients in SDG2 treated with the 20mg QD dose, the Grade 4 post-baseline results were neutrophil count decreased (0.4%) and lymphocyte count decreased (0.4%) in 1 patient each. The grade 4 post-baseline result of neutrophil count decreased occurred in a patient with a baseline in the normal range (Grade 0).

Clinical chemistry - hyperphosphatemia

Hyperphosphatemia is discussed in the section on AESIs.

Hepatic function

For SDG1, shifts from normal (ie, ≤ ULN) baseline values for ALT increased and AST increased to ≥Grade 3 post-baseline were observed for 5 patients (3.7%) and 4 patients (2.8%), respectively. The single post-baseline Grade 4 result (ALT increased) occurred in a patient with a Grade 2 baseline value.

AST values >3×ULN reported concurrently (within 1 day or within 30 days) with total bilirubin results more than twice the ULN were reported in 3 patients (2.1%); ALT values >3×ULN reported concurrently (within 1 day or within 30 days) with total bilirubin results more than twice the ULN were reported in 1 patient (0.7%). No events met Hy's law criteria.

In SDG2, among the patients who received a starting dose of 20 mg QD futibatinib, Grade 4 results were reported for ALT increased (n=2, 0.6%), and AST increased and blood bilirubin increased (n=1 each, 0.3%). Grade 3 results that occurred in ≥5.0% of patients included alkaline phosphatase increased (n=26, 8.2%), and ALT increased and AST increased (n=25 each, 7.9%).

Shift from baseline to worst post-baseline by CTCAE grade for patients with any tumor type (any dosing or a starting dose of 20 mg QD futibatinib) with at least one relevant post-baseline data point were also evaluated. Among patients who received a starting dose of 20 mg QD futibatinib, a shift from normal (ie, ≤ ULN) baseline values for ALT increased and AST increased to Grade 3 or 4 post-baseline was observed for 15 patients (Grade 3: 14 patients, 4.6%; Grade 4: 1 patient, 0.3%) and 8 patients (Grade 3: 7 patients, 2.2%; Grade 4: 1 patient, 0.3%), respectively.

In this group, AST values >3×ULN reported concurrently (within 1 day or within 30 days) of total bilirubin results more than twice the ULN were reported in 10 patients (3.1%); ALT values >3×ULN reported concurrently (within 1 day or within 30 days) of total bilirubin results more than twice the ULN were reported in 5 patients (1.6%). No events met Hy's law criteria.

Other clinical chemistry results

Among patients in SDG1, the most frequently reported (≥5.0%) Grade 3 results for chemistry laboratory results other than hyperphosphatemia and hepatic function parameters were hypophosphatemia (n=25, 18.1%), and hyponatremia (n=21, 14.5%). Additionally, Grade 4 post-baseline results of hypophosphatemia were reported for 2 patients (1.4%), while 1 patient each experienced Grade 4 results of hypercalcemia (0.7%) and CPK increased (0.7%), and 2 patients experienced hyponatremia (1.4%).

At least 1 shift of ≥2 grades was reported for all clinical chemistry laboratory tests with the exception of hypernatremia. Among patients with normal laboratory results at baseline, incidence rates of patients with Grade ≥3 results at some point during treatment were highest for hypophosphatemia (Grade 3: n=17, 12.5%; Grade 4: n=2, 1.5%), hyponatremia (Grade 3: n=15, 10.3%; Grade 4: n=2, 1.4%), CPK increased (Grade 3: n=4, 3.8%), and hypercalcemia (Grade 3: n=2, 1.6%).

In SDG2, patients treated with a starting dose of 20 mg QD futibatinib, the most frequently reported (≥5.0%) Grade 3 results for chemistry laboratory results other than hyperphosphatemia and hepatic

function parameters were hyponatremia (n=43, 13.6%), and hypophosphatemia (n=39, 13.2%). Grade 4 results were reported for hypophosphatemia (n=1, 0.7%), hyponatremia (n=3, 0.9%), and hypercalcemia (n=1, 0.3%).

In this group, for patients with normal laboratory results at baseline, incidence rates of patients with Grade ≥3 results at some point during treatment were highest for hypophosphatemia (Grade 3: n=30, 10.3%; Grade 4: n=2, 0.7%), hyponatremia (Grade 3: n=30, 9.6%; Grade 4: n=3, 1.0%), CPK increased (Grade 3: n=4, 1.9%; Grade 4: n=1, 0.5%), and hypokalaemia (Grade 3: n=6, 2.0%).

Vital signs

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. Vital signs data were not pooled for analysis in the integrated safety population.

ECGs

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

ECG data were not pooled for analysis in the integrated safety population.

2.6.8.5. In vitro biomarker test for patient selection for safety

Not applicable.

2.6.8.6. Safety in special populations

Several subgroup analyses of adverse events were performed, with subgroups including age (<65, ≥65 years), gender (male, female), and race (Caucasian/White, Black, Asian/Oriental, and Other), geographic region (North America, Europe, Asia Pacific (excluding Japan), and Japan), prior FGFR treatment (yes or no), number of prior systemic therapies (1, 2 or ≥3), and ECOG Performance Status (0 or 1).

Intrinsic factors

Age

Table 35 summarizes AEs (all grades and Grade ≥3) for patients <65 years old and those ≥65 years old in SDG1 and those in SDG2 (any dosing and a starting dose of 20 mg QD).

Table 35. Overview of adverse events by age group

Category	Safety Data Group 1 (iCCA)		Safety Data Group 2 (Any Tumor Type)			
	20 mg QD (N=145)		20 mg QD (N=318)		Any Dosing (N=469)	
	Age <65 n (%)	Age ≥65 n (%)	Age <65 n (%)	Age ≥65 n (%)	Age <65 n (%)	Age ≥65 n (%)
Patients with at Least 1 TEAE	114 (100.0)	31 (100.0)	227 (99.1)	89 (100.0)	328 (99.4)	139 (100.0)
Patients with at Least 1 Grade ≥3 TEAE	88 (77.2)	23 (74.2)	166 (72.5)	62 (69.7)	225 (68.2)	88 (63.3)
Patients with at Least 1 TRAE	113 (99.1)	30 (96.8)	223 (97.4)	86 (96.6)	315 (95.5)	131 (94.2)
Patients with at Least 1 Grade ≥3 TRAE	65 (57.0)	14 (45.2)	114 (49.8)	28 (31.5)	139 (42.1)	39 (28.1)
Patients with at Least 1 SAE	48 (42.1)	11 (35.5)	102 (44.5)	37 (41.6)	139 (42.1)	62 (44.6)
Patients with at Least 1 Grade ≥3 SAE	42 (36.8)	10 (32.3)	86 (37.6)	35 (39.3)	114 (34.5)	48 (34.5)

In SDG1, the median age was 57 years old, with 78.6% of patients aged <65 years. Incidence of TEAEs (100% in both groups), Grade ≥3 TEAEs (77.2 vs 74.2%), and TRAEs regardless of severity (99.1 vs 96.8%) were similar for patients <65 years old and those ≥65 years old. Higher incidence (>5% difference) of SAEs (42.1 vs 35.5%) and Grade ≥3 TRAEs (36.8 vs 32.3%) were reported for patients <65 years old.

The most frequent TEAEs in patients <65 years versus those ≥65 years old included dry mouth and fatigue (29.8% vs 35.5% each), palmarplantar erythrodysaesthesia syndrome (20.2% vs 32.3%), and stomatitis (23.7% vs 29.0%). The most frequently reported Grade ≥3 TEAEs with differences ≥5% in incidence between patients <65 years versus those ≥65 years old included stomatitis (4.4% vs 12.9%), hypophosphatemia (5.3% vs 12.9%) and hyponatremia (4.4% vs 19.4%).

In SDG2, 89/318 patients (28%) treated at the 20mg QD dose were ≥ 65 years of age. The most frequently reported TEAEs in patients <65 years versus those ≥65 years old included decreased appetite (21.0% vs 34.8%), stomatitis (16.6% vs 22.5%), dysgeusia (11.8% vs 16.9%), urinary tract infection (8.7% vs 15.7%) and hyponatremia (6.6% vs 16.9%).

One Grade ≥3 TEAE with ≥5% difference in incidence between patients <65 years versus those ≥65 years old was reported (hyponatremia [4.4% vs 12.4%]).

An overview of safety in patients <65 years of age and >65 years per age cohort is provided in Table 36.

Table 36. Overview of safety per age cohort, SDG1 (N=145)

MedDRA Terms	Age <65 N=114 number (percentage)	Age 65-74 N=25 number (percentage)	Age 75-84 N=6 number (percentage)	Age 85+ N=0 number (percentage)
Total AEs	114 (100.0)	25 (100.0)	6 (100.0)	0
Serious AEs – Total	48 (42.1)	11 (44.0)	0	0
- Fatal	7 (6.1)	0	0	0
- Hospitalization/prolong existing hospitalization	42 (36.8)	11 (44.0)	0	0
- Life-threatening	3 (2.6)	0	0	0
- Disability/incapacity	0	0	0	0

- Other (medically significant)	8 (7.0)	0	0	0
AE leading to drop-out	7 (6.1)	4 (16.0)	0	0
Psychiatric disorders	21 (18.4)	5 (20.0)	0	0
Nervous system disorders	62 (54.4)	15 (60.0)	3 (50.0)	0
Accidents and injuries	13 (11.4)	7 (28.0)	1 (16.7)	0
Cardiac disorders	10 (8.8)	6 (24.0)	1 (16.7)	0
Vascular disorders	16 (14.0)	2 (8.0)	1 (16.7)	0
Cerebrovascular disorders	3 (2.6)	0	0	0
Infections and infestations	60 (52.6)	13 (52.0)	4 (66.7)	0
Anticholinergic syndrome	0	0	0	0
Quality of life decreased	0	0	0	0
Sum of postural hypotension, falls, black outs, syncope, dizziness, ataxia, fractures	10 (8.8)	5 (20.0)	0	0
other AE appearing more frequently in older patients: Eye disorders	46 (40.0)	12 (48.0)	5 (83.3)	0

Gender

There were more female than male patients both in SDG1 (62.8%) and SDG2 (52.9%).

In SDG1, incidence of TEAEs, Grade ≥3 TEAEs, and TRAEs regardless of severity were similar for female and male patients; however, Grade ≥3 TRAEs were reported with greater frequency in female patients (63.7% vs 38.9%), with the largest absolute and relative differences for the preferred term (PT)s of ALT increased (7.7% vs 0%) and PPES (6.6% vs 3.7%). SAEs (any grade 35.2% vs 50.0%; and Grade ≥3 33.0% vs 40.7%) were reported more frequently in male patients.

A comparable distribution was seen in SDG2.

Race

In SDG1, race was classified as Caucasian/White (n=76), Black (n=9), Asian/Oriental (n=36), Other (n=1), and Unknown (n=23). In SDG2, this distribution was comparable. Due to the substantial differences in size of patient populations by race, a detailed presentation of the most frequent AEs is not included. Review of the data did not identify any apparent trends in incidence rates when analysed by race.

Extrinsic factors

Geographic region

Geographic regions included in this subgroup analysis are North America (SDG1, n=75), Europe (SDG1, n=38), Asia Pacific (excluding Japan; SDG1, n=18) and Japan (SDG1, n=14).

In SDG1, the frequency of TEAEs and TRAEs of any grade were comparable for patients in all regions, with all patients experiencing a TEAE and nearly all patients a TRAE. Differences ≥5% were reported between regional groups for Grade ≥3 TEAEs and TRAEs, as well as SAEs of any grade and those of Grade ≥3, with the highest frequency of these events in the subgroup 'Asia Pacific'.

Prior FGFR treatment

A summary of adverse events in SDG1 and SDG2 (starting dose of 20mg QD) by prior treatment with an FGFR-inhibitor is presented in Table 37.

Table 37. Overview of adverse events by prior FGFR Treatment

Category	Safety Data Group 1 (iCCA)		Safety Data Group 2 (Any Tumor Type)			
	20 mg QD (N=145)		20 mg QD (N=318)		Any Dosing (N=469)	
	Received prior FGFR treatment n (%)	No prior FGFR treatment n (%)	Received prior FGFR treatment n (%)	No prior FGFR treatment n (%)	Received prior FGFR treatment n (%)	No prior FGFR treatment n (%)
Patients with at Least 1 TEAE	17 (100.0)	128 (100.0)	33 (100.0)	245 (99.2)	48 (100.0)	336 (99.4)
Patients with at Least 1 Grade ≥3 TEAE	13 (76.5)	98 (76.6)	22 (66.7)	187 (75.7)	32 (66.7)	239 (70.7)
Patients with at Least 1 TRAE	16 (94.1)	127 (99.2)	30 (90.9)	241 (97.6)	44 (91.7)	325 (96.2)
Patients with at Least 1 Grade ≥3 TRAE	7 (41.2)	72 (56.3)	13 (39.4)	123 (49.8)	18 (37.5)	152 (45.0)
Patients with at Least 1 SAE	8 (47.1)	51 (39.8)	14 (42.4)	115 (46.6)	18 (37.5)	153 (45.3)
Patients with at Least 1 Grade ≥3 SAE	8 (47.1)	44 (34.4)	14 (42.4)	98 (39.7)	17 (35.4)	122 (36.1)

Number of prior systemic therapies

The results of this subgroup analysis are summarised in Table 38.

Table 38. Overview of adverse events by number of prior systemic therapies for advanced/metastatic disease

Category	Safety Data Group 1 (iCCA)			Safety Data Group 2 (Any Tumor Type)		
	20 mg QD (N=145)			20 mg QD (N=318)		
	1 Prior Therapy n (%)	2 Prior Therapies n (%)	≥3 Prior Therapies n (%)	1 Prior Therapy n (%)	2 Prior Therapies n (%)	≥3 Prior Therapies n (%)
Patients with at Least 1 TEAE	62 (100.0)	40 (100.0)	38 (100.0)	101 (100.0)	74 (100.0)	84 (97.7)
Patients with at Least 1 Grade ≥3 TEAE	47 (75.8)	33 (82.5)	26 (68.4)	77 (76.2)	56 (75.7)	61 (70.9)
Patients with at Least 1 TRAE	62 (100.0)	40 (100.0)	36 (94.7)	99 (98.0)	74 (100.0)	80 (93.0)

Category	Safety Data Group 1 (iCCA)			Safety Data Group 2 (Any Tumor Type)		
	20 mg QD (N=145)			20 mg QD (N=318)		
	1 Prior Therapy n (%)	2 Prior Therapies n (%)	≥3 Prior Therapies n (%)	1 Prior Therapy n (%)	2 Prior Therapies n (%)	≥3 Prior Therapies n (%)
Patients with at Least 1 Grade ≥3 TRAE	34 (54.8)	24 (60.0)	18 (47.4)	51 (50.5)	36 (48.6)	41 (47.7)
Patients with at Least 1 SAE	24 (38.7)	22 (55.0)	11 (28.9)	46 (45.5)	41 (55.4)	33 (38.4)
Patients with at Least 1 Grade ≥3 SAE	19 (30.6)	20 (50.0)	11 (28.9)	39 (38.6)	33 (44.6)	32 (37.2)

ECOG status

In both SDG1 and SDG2, higher incidence rates of SAEs of any grade, and TEAEs and SAEs of Grade ≥3 were reported for patients with an ECOG score of 1 compared to patients with an ECOG score of 0.

Table 39: Overview of adverse events by ECOG performance status

Category	Safety Data Group 1 (iCCA)		Safety Data Group 2 (Any Tumor Type)	
	20 mg QD (N=145)		20 mg QD (N=318)	
	ECOG=0 n (%)	ECOG=1 n (%)	ECOG=0 n (%)	ECOG=1 n (%)
Patients with at Least 1 TEAE	67 (100.0)	78 (100.0)	130 (100.0)	186 (98.9)
Patients with at Least 1 Grade ≥3 TEAE	44 (65.7)	67 (85.9)	81 (62.3)	147 (78.2)
Patients with at Least 1 TRAE	67 (100.0)	76 (97.4)	129 (99.2)	180 (95.7)
Patients with at Least 1 Grade ≥3 TRAE	35 (52.2)	44 (56.4)	55 (42.3)	87 (46.3)
Patients with at Least 1 SAE	21 (31.3)	38 (48.7)	44 (33.8)	95 (50.5)
Patients with at Least 1 Grade ≥3 SAE	17 (25.4)	35 (44.9)	38 (29.2)	83 (44.1)

2.6.8.7. Immunological events

Not applicable.

2.6.8.8. Safety related to drug-drug interactions and other interactions

Studies examining drug-drug interactions or food effects on the safety and efficacy of futibatinib are discussed in the Clinical Pharmacology section. The results of these studies have shown that moderate to strong inhibitors or inducers of CYP3A have potential clinical drug-drug interactions with futibatinib.

In addition, in vitro studies have shown potential drug-drug interactions may occur with concomitant use of futibatinib and those drugs that are Pgp or BCRP substrates/inhibitors. Based on clinical and in vitro study results, caution is advised if these drugs are given concomitantly:

Moderate and strong CYP3A inducers: The results of Study TAS-120-103 showed a strong CYP3A inducer decreased futibatinib AUC by approximately 64%. A moderate CYP3A inducer was predicted to decrease futibatinib AUC by approximately 48%.

Moderate and strong CYP3A inhibitors: The results of Study TAS-120-103 showed a strong CYP3A inhibitor increased futibatinib AUC by approximately 41%. A moderate CYP3A inhibitor was predicted to increase futibatinib AUC by approximately 20% to 40%.

P-gp and BCRP substrates and inhibitors: Futibatinib is a potential inhibitor of P-gp and BCRP, and substrate of P-gp and BCRP in vitro. Futibatinib may alter the PK and activity of P-gp and BCRP substrates. P-gp and BCRP inhibitors may affect the PK of futibatinib.

A food-effect study demonstrated that consumption of a high-fat, high-calorie meal reduced the relative oral bioavailability and delayed tmax of a single dose of 20 mg futibatinib.

2.6.8.9. Discontinuation due to adverse events

In SDG1, TEAEs leading to study treatment discontinuation were observed for 8/146 patients (5.6%), including 3 patients (2.1%) with treatment-related adverse events (TRAE). TEAEs leading to discontinuation were stomatitis (n=2), anaemia, oesophageal ulcer, oesophagitis, oral dysesthesia, bile duct obstruction, acute cholangitis, back pain, dizziness and pharyngeal inflammation. The cases of stomatitis, oesophagitis, oral dysesthesia and pharyngeal inflammation (in a total of 3 patients) were considered treatment-related.

In SDG2, 20 patients discontinued treatment due to a TEAE (4.3%), and in the group of patients treated with the starting dose of 20mg QD it was 18 patients (5.7%). In this group, there were 8 patients in which the AE was considered treatment-related (2.5%). These treatment-related TEAEs leading to treatment discontinuation were diarrhoea and stomatitis (both n=2), and cataract, retinal detachment, nausea, oesophagitis, oral dysesthesia, vomiting, fatigue, decreased appetite, pharyngeal inflammation, eczema and onycholysis (all n=1).

TEAEs leading to dose interruptions and reductions

In SDG1, 91.0% of patients had at least 1 dose modification.

A total of 115 patients (79.3%) experienced at least 1 dose interruption, a majority of which were due to AEs (n=92, 63.4%). The median time to first dose interruption due to AE was 36 days (range 4-325), and the median total duration of interruption was 16 days (range 1-214). Out of the 92 patients with dose interruptions due to an AE, 41.4% required a second dose interruption due to an AE.

In SDG1, 77 patients (53.1%) experienced a dose reduction, most of which (n=74, 51.0%) were due to AEs. The median time to dose reduction due to AE was 47 days (range 5-481). Out of the 74 patients with dose reductions due to an AE, 22.1% required a second dose reduction due to an AE. TEAEs leading to dose modification (interruption and/or reduction) occurred in 105 patients (72.4%). Hyperphosphatemia (n=39, 26.9%) and palmar-plantar erythrodysaesthesia syndrome (n=17, 11.7%) were the most frequently reported AEs that resulted in dose modification.

Adverse events considered related to study treatment and leading to dose modification were reported for a total of 87 patients (60.0%); also most frequently hyperphosphatemia (n=39, 26.9%), and palmar-plantar erythrodysaesthesia (n=17, 11.7%).

In SDG2, 32% of patients had a dose reduction, mainly due to AEs (30.7%). The median time to dose reduction due to AE was 42 days (range 5-610). Adverse events leading to dose modification (interruption and/or reduction) occurred in 305 patients (65.0%).

In the group of patients treated at a starting dose of 20mg QD, AEs leading to dose modification were reported in 218 patients (68.6%). The most frequently reported AEs resulting in dose modification in this group were hyperphosphatemia (n=83, 26.1%), ALT increased (n=30, 9.4%), and AST increased (n=23, 7.2%). Adverse events considered related to study treatment and leading to dose modification were reported for a total of 172 patients (54.1%); the most frequently reported TRAEs included hyperphosphatemia (n=83, 26.1%), ALT increased (n=27, 8.5%) and palmar-plantar erythrodysaesthesia syndrome (n=21, 6.6%).

2.6.8.10. Post marketing experience

Not applicable.

2.6.9. Discussion on clinical safety

The primary safety assessment is based on a pooled analysis containing data from the 103 patients treated in the pivotal study TAS-120-101 phase 2, and data from 42 patients treated in the phase 1 dose expansion part of this same study. This safety data group 1 (SDG1) represents the target population treated at the target dose. This pooling strategy is adequately justified and safety data for SDG1 is therefore presented in section 4.8 of the SmPC. As supportive safety information, safety data on patients with all solid tumours, treated at any dose level in the TAS-120-101 study (phase 1 dose escalation, dose expansion and phase 2) and the Japanese study 10059010 (dose escalation and expansion) is summarized in SDG2 (n=469). SDG2 includes 318 patients treated with the proposed starting dose of 20 mg QD futibatinib. TAS-120-101 being an uncontrolled study, the assessment of treatment-relatedness of adverse events is hampered. However, some context for the safety profile is made available by data from the other approved FGFR-inhibitor, Pemazyre.

Treatment duration in SDG1 was a median of 8.87 months, but it was only 2.76 months in SDG2. Because of this limited **exposure**, the safety profile of futibatinib is mainly characterised from the data in SDG1. Few patients were treated >12 months (n=53/469 with any tumour type at any starting dose, and n=41/318 at the proposed posology of 20mg QD), limiting the assessment of long-term toxicity as well as rare adverse events. However, considering the limited prognosis of the target population (median OS 21 months) and the fact that some additional safety data is expected from the proposed uncontrolled study TAS-120-205 including two dosing cohorts (20 mg and 16 mg QD), this is acceptable.

Treatment-related AEs were very common, reported for 98.6% of patients in SDG1. 79 of these patients (54.5%) experienced at least 1 Grade ≥3 TRAE. The most frequently reported TRAEs, reported in at least 20% of patients, included hyperphosphatemia, alopecia, dry mouth, dry skin, diarrhoea, fatigue, palmar-plantar erythrodysaesthesia syndrome and stomatitis. AEs of nail disorders were also common, although separate PTs did not occur in >20% of patients. **Grade ≥3 TRAEs** reported in ≥5% of patients included hyperphosphatemia, stomatitis and AST increased and palmar-plantar erythrodysaesthesia syndrome. These most common AEs are compatible with the safety profile as known from other FGFR-inhibitors and the patient population with advanced cancer.

Grade ≥3 TRAEs occurred at a somewhat higher frequency in SDG1 compared to SDG2 (54.5 vs 44.7%), but this can be explained by the longer treatment duration and exposure in SDG1. In SDG2,

the most common TRAEs by PT and SOC were comparable to the most frequent adverse events in SDG1.

There were no on-treatment **deaths** in both SDG1 or SDG2. Most deaths were due to progressive disease.

In SDG2, there were 2 deaths due to **AEs**, including one event of fatal renal failure within the 30-day safety follow-up period. Acute kidney injury is listed as an important potential risk for the other registered FGFR-inhibitor Pemazyre. This death was not treatment related.

Based on safety signals during preclinical or clinical trials, or based on class effects of similar drugs, retinal disorders, hyperphosphatemia, hepatotoxicity, nail disorders, PPES, and rash were defined as **adverse events of special interest (AESI)** for futibatinib.

In SDG1 and SDG2, treatment-related **retinal disorders** were infrequent (6.2 and 7.7%, respectively), most were grade 1 and the six grade 2 events all resolved to <grade 2. Section 4.4 of the SmPC includes recommendations on ophthalmological examinations and retinal disorders are included in the RMP as important identified risk.

Hyperphosphatemia is related to the mechanism of action of FGFR-inhibitors. Of note, grading of hyperphosphatemia AEs did not use CTCAE v4.03 (which does not include criteria for grading of hyperphosphatemia), but was conducted based on serum phosphate levels. In this adjusted grading, Grade 3 was defined as serum phosphate level >7 mg/dL (>2.26 mmol/L) irrespective of clinical symptoms. This explains the higher frequency of hyperphosphatemia Grade ≥3 for futibatinib compared to the frequency as found for Pemazyre.

There were no SAEs, no deaths and no treatment discontinuations due to hyperphosphatemia. In most patients, hyperphosphatemia was managed with use of phosphate lowering medication (83.4%), dose reductions were necessary for 17.9% of patients and interruptions in 18.6%. Complications from hyperphosphatemia have been observed with futibatinib treatment (n=4). In sections 4.2 and 4.4 of the SmPC, information on the risk of soft-tissue mineralization is included and adequate dosing recommendations for hyperphosphatemia are provided.

Hypophosphatemia was reported as a TEAE in 21 patients (14.5%) in SDG1. Based on evaluation of laboratory results the incidence was higher, i.e. 44.2% with 13.7% grade ≥3 events. Hypophosphatemia can be related to the use of phosphate-lowering therapies in case of treatment-induced hyperphosphatemia, which is illustrated by the fact that 17 out of 31 patients in this analysis had a TEAE of hypophosphatemia during the follow-up period (i.e., after futibatinib discontinuation) or while futibatinib treatment was interrupted, including 15 patients receiving phosphate lowering therapy due to previous hyperphosphatemia.

Section 4.2 of the SmPC mentions that phosphate-lowering therapy should be stopped if futibatinib treatment is discontinued. The frequency of grade ≥3 events is not negligible (5.7% investigator reported and 13.7% laboratory derived). Instead of a warning, a description of the symptoms of hypophosphatemia to the recommendation is added in section 4.2 of the SmPC, in line with the description of hypophosphatemia symptoms in the Pemazyre SmPC.

It is acceptable that hyperphosphatemia is not included in the RMP as an important identified risk, in contrast to the RMP of Pemazyre. It is agreed with the applicant that hyperphosphatemia is a well-known risk for which sufficient warnings and recommendations are in place in the SmPC, therefore routine pharmacovigilance activities are considered sufficient.

Hepatotoxicity occurred in 29% of patients in SDG1, including 18 patients (12.4%) with Grade ≥3 events. It is agreed that none of the reported events met Hy's law criteria.

No specific dosing recommendations in case of hepatotoxicity are included in the SmPC, which is acceptable based on relatively low frequency and grade of events.

Nail disorders were frequent but led to treatment modification in a low percentage of patients.

PPES was reported for 33 patients (22.8%) in SDG1, all but one were considered treatment-related. PPES was managed with use of concomitant medications in most patients, and/or futibatinib dose modifications (9.7% reductions/9.0% interruptions); there were no dose discontinuations due to PPES.

Other **eye disorders** were frequently reported with futibatinib (43.4%), but Grade ≥3 TEAEs were reported for only 3 patients (2.1%). The SmPC contains recommendations regarding ophthalmological examinations because of the AESI of retinal disorders, which is considered adequate.

Acute kidney injury is listed as an important potential risk for the other registered FGFR-inhibitor Pemazyre. In the pivotal study on pemigatinib, creatinine increase was reported as a TEAE for 99% of patients. For futibatinib, blood creatinine increased was only reported for 13.8% of patients in SDG1. It was clarified that pemigatinib is a very potent inhibitor for OCT2 while futibatinib has no inhibitory effect on OCT2, which can explain the difference in reported incidence for kidney injury with both treatments.

In in vitro studies, futibatinib acts as an **hERG channel blocker**. However, no cardiovascular effect was found in animal studies and futibatinib did not prolong the QTc interval at therapeutic and supratherapeutic doses in healthy volunteers.

Few patients >65 years of age are included in the clinical studies (89 patients aged >65 years were treated at the 20mg QD dose), limiting the assessment of safety in **elderly patients**. The occurrence of TEAEs, TRAEs and SAEs appears comparable between patients <65 years of age and >65 years of age. However, the pattern is somewhat different with mainly gastro-intestinal side effects (decreased appetite, stomatitis, dysgeusia), urinary tract infection and hyponatremia reported more frequently in the elderly population. No conclusion can be drawn in smaller age cohorts because of the limited numbers. In the subgroup analyses by geographic region and previous treatment, no conclusions could be drawn due to the low number of patients in some subgroups.

No analysis of safety in patients with **hepatic impairment** or **renal impairment** was provided in the dossier. Patients with severe hepatic or renal impairment were excluded from the clinical studies. The applicant has discussed any available safety data in patients with mild or moderate hepatic or renal impairment. The absence of (safety) data in patients with severe hepatic impairment is reflected in the SmPC.

Futibatinib is a substrate for CYP3A. The information in the SmPC regarding co-administration with moderate and strong inducers or inhibitors of CYP3A is considered adequate.

Dose modifications were frequent, with 79.3% of patients experiencing at least 1 dose interruption (mostly due to AEs; n=92, 63.4%) and 53.1% experiencing a dose reduction, most of which (n=74, 51.0%) were also due to AEs. This indicates the limited tolerability of the proposed starting dose of 20mg QD, however, apparently treatment could be successfully continued at a lower dose because the discontinuation rate due to AEs was low (2.1%).

2.6.10. Conclusions on the clinical safety

The safety profile of futibatinib is characterized by a high incidence of low-grade adverse events, which are compatible with the mechanism of action (hyperphosphatemia, PPES, gastro-intestinal symptoms) and a patient population with advanced cancer (fatigue, dry mouth and dry skin).

Dose interruptions and reductions were frequent, indicating the limited tolerability of the proposed starting dose of 20mg QD, however treatment could be successfully continued at a lower dose.

2.7. Risk Management Plan

2.7.1. Safety concerns

Table 40. Summary of safety concerns

Summary of safety concerns	
Important identified risks	Serous retinal detachment
Important potential risks	Embryo-Fetal Toxicity / teratogenicity
Missing information	None

2.7.2. Pharmacovigilance plan

No additional pharmacovigilance activities.

2.7.3. Risk minimisation measures

Table 41. Summary Table of Risk Minimisation Activities by Safety Concern

Safety Concern	**Risk Minimisation Measures**
Serous retinal detachment	**Routine Risk Minimisation Measures:** - SmPC sections 4.2, 4.4, and 4.8 - PL sections 2 and 4 Dose modifications for serous retinal detachment are provided in SmPC section 4.2. Recommendation for routine ophthalmological examination is included in the SmPC section 4.4 and PL section 2. Subject to restricted medical prescription **Additional Risk Minimisation Measures:** None
Embryo-foetal toxicity/teratogenicity	**Routine Risk Minimisation Measures:** - SmPC sections 4.4, 4.6, and 5.3 - PL section 2 Recommendations for pregnancy testing prior treatment initiation is included in the SmPC section 4.4. Recommendation on the use of effective contraception during treatment and for at least 1 week after the last dose is included in the SmPC sections 4.4 and 4.6 and PL section 2. Subject to restricted medical prescription **Additional Risk Minimisation Measures:**

	None

2.7.4. Conclusion

The CHMP and PRAC considered that the risk management plan version 1.2 is acceptable.

2.8. Pharmacovigilance

2.8.1. Pharmacovigilance system

The CHMP considered that the pharmacovigilance system summary submitted by the applicant fulfils the requirements of Article 8(3) of Directive 2001/83/EC.

2.8.2. Periodic Safety Update Reports submission requirements

The requirements for submission of periodic safety update reports for this medicinal product are set out in the Annex II, Section C of the CHMP Opinion. The applicant did request alignment of the PSUR cycle with the international birth date (IBD). The IBD is 30.09.2022. The new EURD list entry will therefore use the IBD to determine the forthcoming Data Lock Points.

2.9. Product information

2.9.1. User consultation

The results of the user consultation with target patient groups on the package leaflet submitted by the applicant show that the package leaflet meets the criteria for readability as set out in the *Guideline on the readability of the label and package leaflet of medicinal products for human use.*

2.9.2. Additional monitoring

Pursuant to Article 23(1) of Regulation No (EU) 726/2004, Lytgobi (futibatinib) is included in the additional monitoring list as

- it contains a new active substance which, on 1 January 2011, was not contained in any medicinal product authorised in the EU
- it is approved under a conditional marketing authorisation [REG Art 14-a]

Therefore the summary of product characteristics and the package leaflet includes a statement that this medicinal product is subject to additional monitoring and that this will allow quick identification of new safety information. The statement is preceded by an inverted equilateral black triangle.

3. Benefit-Risk Balance

3.1. Therapeutic Context

The indication as approved by the CHMP is:

"*Lytgobi monotherapy is indicated for the treatment of adult patients with locally advanced or metastatic cholangiocarcinoma with a fibroblast growth factor receptor 2 (FGFR2) fusion or rearrangement that have progressed after at least one prior line of systemic therapy.*"

3.1.1. Disease or condition

Cholangiocarcinoma is a malignancy originating in the epithelial lining of the biliary tree and it is commonly classified based on anatomical location; extrahepatic cholangiocarcinoma, which includes hilar and distal tumours, accounts for the majority of cases, while intrahepatic cholangiocarcinoma accounts for approximately 5-10% of the cases. The incidence of CCA is overall rare, with 1 to 3 patients per 100,000 in regions like the United States and Europe (Banales 2016; Khan 2019). The prognosis of patients with Stage III or IV CCA is poor, with 5-year survival rates of 10% and 0%, respectively. The natural history of CCA with FGFR alterations and its prognostic role is not fully characterised. *FGFR2* rearrangements (including fusions) occur in about 10% to 16% of patients with iCCA (Krook 2020; Jain 2018).

3.1.2. Available therapies and unmet medical need

The first-line, standard-of-care treatment for patients with unresectable and metastatic disease was gemcitabine and cisplatin at the time of study conduct (ESMO 2016). Recently the ESMO guideline has been updated to recommend cisplatin–gemcitabine–durvalumab for first-line treatment (ESMO 2022; positive CHMP opinion).

Second line treatment

Therapeutic options for patients who progress on first-line therapy are limited. 5-fluorouracil–leucovorin–oxaliplatin (FOLFOX) is recommended in the second-line setting (ESMO 2022). FGFR inhibitors are recommended for the treatment of patients with FGFR2 fusions whose disease has progressed after ≥1 prior line of systemic therapy. Tibsovo monotherapy is indicated for the treatment of adult patients with locally advanced or metastatic cholangiocarcinoma with an IDH1 R132 mutation who were previously treated by at least one prior line of systemic therapy.

On 28 January 2021, the CHMP adopted a positive opinion, recommending the granting of a conditional marketing authorisation for the medicinal product Pemazyre, intended for the second-line treatment of advanced or metastatic cholangiocarcinoma characterized by fusion or rearrangements of FGFR 2 (EPAR Pemazyre EMA/CHMP/105411/2021). On 23 February 2023 the CHMP adopted a positive opinion recommending the granting of a MA for the IDH1-inhibitor Tibsovo (ivosidenib) for the treatment of adult patients with locally advanced or metastatic cholangiocarcinoma with an IDH1 R132 mutation who were previously treated by at least one prior line of systemic therapy.

- **Unmet Medical Need**

Therapeutic options for patients who progress on standard therapy are limited. A systematic review including 761 patients showed a median PFS (3.2 months; 95% CI: 2.7–3.7) and response rates

(7.7%; 95% CI: 4.6–10.9); the mean OS was 7.2 months (95% CI: 6.2–8.2) in the second-line (ESMO Guideline biliary cancer and Lamarca et al. 2014).

Multiple FGFR inhibitors are in development for CCA. The oral FGFR1-3 inhibitor pemigatinib has received a conditional marketing authorisation for the treatment of patients with previously treated CCA harbouring FGFR2 rearrangements/fusions, see above. Tibsovo monotherapy is indicated for the treatment of adult patients with locally advanced or metastatic cholangiocarcinoma with an isocitrate dehydrogenase-1 (IDH1 R132) mutation who were previously treated by at least one prior line of systemic therapy. FGFR2 alterations occur in roughly 10% to 15% of cholangiocarcinoma, however, they rarely co-occur with IDH1 mutations (co-occurrence in approximately 2% to 5%) (Battaglin et al, 2020; Jain et al, 2018; Valle et al, 2017; Saborowski et al, 2020). An unmet medical need however remains.

3.1.3. Main clinical studies

The efficacy data supporting the present application comes from the phase 2 portion of study TAS-120-101 including 103 iCCA patients harbouring FGFR2 gene fusions or other FGFR2 rearrangements of the open label single arm phase 1/2 study of TAS-120 in patients with advanced solid tumours with FGF/FGFR aberrations.

The primary efficacy endpoint of the study was the ORR, defined as the proportion of patients with objective evidence of confirmed complete response (CR) or partial response (PR) according to RECIST 1.1 per independent central radiographic review.

The secondary endpoints are DOR, DCR, PFS, PROs and OS.

The sample size for the phase 2 part of study TAS-120-101 was based on ruling out an ORR of 10% or less. An interim analysis was planned when approximately 70% of all treated patients had 6 months of follow-up. No formal stopping rules were described for this analysis and no adjustment of the Type I error was pre-specified.

3.2. Favourable effects

In the **primary analysis** by independent review, for the 103 patients in the efficacy population, treatment with futibatinib resulted in a **confirmed ORR** of 41.7% (95% confidence interval [CI]: 32.1, 51.9).

At the time of the data cutoff date, with a median follow-up of 11.76 months the median **DOR** by Kaplan-Meier analysis for the 43 responders was 9.69 months (95% CI: 7.62, 17.05).

3.3. Uncertainties and limitations about favourable effects

As the pivotal TAS-120-101 study is a single-arm trial without an active comparator there is a need to further confirm the efficacy. Results from the 'single-arm' Phase 2 Study TAS-120-205 (SOB) will be provided, which entail replication of the single-arm efficacy (and safety) data from the pivotal Study TAS-120-101 in a new and independent single-arm study cohort.

The dose response curve is unknown. It is unknown if the optimal dose has been selected due to the absence of the dose response relationship studies based on the primary endpoint ORR used in part II of the study. The applicant intends to investigate the efficacy of a lower dose 16 mg in the SOB study TAS-120-205.

In the pivotal trial, only patients with intrahepatic CCA were included. Results from the pivotal trial population are extrapolated to the patients with extrahepatic CCA with FGFR2 gene rearrangements as the location of the tumour is not expected to affect the effect of the product.

3.4. Unfavourable effects

The most common (≥20%) adverse reactions were hyperphosphatemia (89.7%), nail disorders (44.1 %), constipation (37.2%), alopecia (35.2%), diarrhoea (33.8%), dry mouth (31.0%), fatigue (31.0%), nausea (28.3%), dry skin (27.6%), increased AST (26.9%), abdominal pain (24.8%), stomatitis (24.8%), vomiting (23.4%), palmar-plantar erythrodysaesthesia syndrome (22.8%), arthralgia (21.4%), and decreased appetite (20.0%). The most common AEs are compatible with the safety profile as known from other FGFR-inhibitors and the patient population with advanced cancer.

54.5% of patients experienced at least 1 Grade ≥3 TRAE, most commonly hyperphosphatemia (26.9%), stomatitis and AST increased (6.2% each) and PPES (5.5%).

SAEs were reported in 40.7% of patients. Of these, 35.9% were ≥ grade 3, most frequently disease progression (n=6, 4.1%) and sepsis (n=4, 2.8%). SAEs were considered treatment-related in 9.0% of patients (n=13), none of these were grade 4 or 5 events. Treatment-related SAEs reported in >1 patient included intestinal obstruction (n=2, grade 3) and migraine (n=2, grade 2).

Seven patients (4.8%) in SDG1 had AEs with an outcome of death, none of these events were assessed as treatment-related. There were no on-treatment deaths in both SDG1 or SDG2. Most deaths were due to progressive disease.

Retinal disorders, hyperphosphatemia, hepatotoxicity, nail disorders, PPES, and rash were defined as AESI for futibatinib. Treatment-related retinal disorders were infrequent (7.7%), most were grade 1 or 2 events and resolved to <grade 2 upon dose modification. The SmPC includes recommendations on ophthalmological examinations and retinal disorders are included in the RMP as important identified risk. There were no SAEs, no deaths and no treatment discontinuations due to hyperphosphatemia. In most patients, hyperphosphatemia was managed with use of phosphate lowering medication (83.4%), dose reductions were necessary for 17.9% of patients and interruptions in 18.6%.

Dose modifications were frequent, with 79.3% of patients experiencing at least 1 dose interruption (mostly due to AEs; n=92, 63.4%) and 53.1% experiencing a dose reduction, most of which (n=74, 51.0%) were also due to AEs. This indicates the limited tolerability of the proposed starting dose of 20mg QD, however, apparently treatment could be successfully continued at a lower dose because the discontinuation rate due to TRAEs was low (2.1%).

3.5. Uncertainties and limitations about unfavourable effects

TAS-120-101 being an uncontrolled study, the causality assessment of adverse events is hampered. However, some context for the safety profile can be obtained with the data from the other FGFR-inhibitor, Pemazyre.

Few patients were treated >12 months (n=53/469 with any tumour type at any starting dose, and n=41/318 at the proposed posology of 20mg QD), limiting the assessment of long-term toxicity as well as rare AEs. Some additional safety data is foreseen from the proposed Study TAS-120-205, but no comparative safety data will become available, as this study does not include a standard-of-care control arm either. No additional pharmacovigilance activities are proposed for long-term toxicity or rare AEs, given the limited prognosis of the target population.

No analysis of safety in patients with hepatic impairment or renal impairment was provided in the dossier. Patients with severe hepatic or renal impairment were excluded from the clinical studies. This is adequately reflected in the SmPC.

3.6. Effects Table

Table 42. Effects Table for Lytgobi as monotherapy for the treatment of adult patients with locally advanced or metastatic cholangiocarcinoma with a fibroblast growth factor receptor 2 (FGFR2) fusion or rearrangement that have progressed after at least one prior line of systemic therapy. Data cut-off: 01 October 2020

Effect	Short Description	Unit	Futibatinib	Control	Uncertainties/ Strength of evidence
Favourable Effects (n=103)					
ORR		N (%) (95%CI)	43 (41.7) [32.1, 51.9]	N/A	Single-arm trial without active comparator Independent Central Review
Median DOR		Months (95% CI)	9.69 months (7.62-17.05)	N/A	Secondary endpoint, no alpha control
Unfavourable Effects, SDG1 (n=145)					
Grade ≥3 TEAEs	Regardless causality	%	76.6	N/A	Uncontrolled study hampers causality assessment
Grade ≥3 TREAEs	Hyperphosphatemia Stomatitis AST increased PPES	%	27.6 6.2 9.0 5.5	N/A	
Serious TEAEs	Regardless causality	%	40.7	N/A	
Treatment-related SAEs	Treatment-related	%	9 (in >1 patient intestinal obstruction (n=2, grade 3) migraine (n=2, grade 2))	N/A	
TEAEs leading to dose reduction	Regardless causality	%	51	N/A	
TEAEs leading to dose interruption	Regardless causality	%	63.4	N/A	
TEAEs leading to dose discontinuation	Regardless causality	%	7.6	N/A	
AEs leading to death	Regardless causality	%	4.8	N/A	

Abbreviations: ORR: objective response rate; DOR: duration of response; TEAE: treatment-emergent adverse event; TREA: treatment related adverse event; AST: aspartate aminotransferase; PPES: Palmar-plantar erythrodysaesthesia syndrome; SAE: serious adverse event; AE: adverse event; N/A:

not applicable; SDG: safety data group.

3.7. Benefit-risk assessment and discussion

3.7.1. Importance of favourable and unfavourable effects

Only one single-arm phase I/II study was submitted to support the efficacy of futibatinib in second line treatment of patients with iCCA with *FGFR2* gene fusions or other *FGFR2* rearrangements and as a consequence, several aspects need explicit consideration. The results show a clinically relevant antitumour activity (ORR 41.7%) with a duration of response (median 9.7 months). Time-to-event secondary endpoints PFS and OS are not interpretable without a comparator arm. In combination with the uncertainty on the impact of FGFR2 genetic alterations on prognosis, the clinical results need confirmation. The applicant, therefore, proposes to conduct Study TAS-120-205 as specific obligation (SOB) in context of the CMA, to provide comprehensive clinical data within an appropriate timeframe to confirm that the benefit-risk balance is positive. For further information, see below section *3.7.3 Additional considerations on the benefit-risk balance*.

Efficacy results need to be weighed against the safety profile, which is mainly characterised by a high frequency of low grade events, which are compatible with the mechanism of action (hyperphosphatemia, PPES, gastro-intestinal symptoms) and the patient population with advanced cancer (fatigue, dry mouth and dry skin). Dose interruptions and reductions due to AEs were frequent, indicating the limited tolerability of the proposed starting dose of 20 mg QD. However, apparently treatment could be successfully continued at a lower dose because the discontinuation rate due to AEs was low. Hyperphosphatemia and retinal disorders are important risks for which adequate recommendations are included in the SmPC. These could generally be managed with supportive therapy or dose modifications, but rarely led to treatment discontinuations.

Exposure was limited and few patients were treated >12 months, hampering the assessment of long-term toxicity as well as the identification of rare adverse events. However, this is acceptable considering the poor disease prognosis. Furthermore, additional safety data is expected from the proposed SOB Study TAS-120-205. This study might also provide more information regarding the safety in elderly patients, which is now limited given that few patients >65 years of age were included in the clinical studies.

3.7.2. Balance of benefits and risks

The reported ORR and DOR are considered clinically relevant in the target population of patients with iCCA with FGFR2 gene rearrangements in second line treatment. Considering the uncertainties due to the single-arm trial design, the clinical results need independent confirmation of the positive benefit-risk balance of futibatinib to be provided as SOB.

The safety profile of futibatinib is characterized by a high incidence of low grade adverse events, which are compatible with the mechanism of action (hyperphosphatemia, PPES, gastro-intestinal symptoms) and a patient population with advanced cancer (fatigue, dry mouth and dry skin). Dose interruptions and reductions were frequent, indicating the limited tolerability of the proposed starting dose of 20 mg QD, however, apparently treatment could be successfully continued at a lower dose because the discontinuation rate due to AEs was low.

The benefit-risk balance is positive.

3.7.3. Additional considerations on the benefit-risk balance

Conditional marketing authorisation

As comprehensive data on the product are not available, a conditional marketing authorisation was requested by the applicant in the initial submission.

The product falls within the scope of Article 14-a of Regulation (EC) No 726/2004 concerning conditional marketing authorisations, as it aims at the treatment of a life-threatening disease. In addition, the product is designated as an orphan medicinal product.

Furthermore, the CHMP considers that the product fulfils the requirements for a conditional marketing authorisation:

- The benefit-risk balance is positive, as discussed.
- It is likely that the applicant will be able to provide comprehensive data.

The applicant will submit the results of Study TAS-120-205, a global, open-label Phase 2 study in patients with advanced, unresectable cholangiocarcinoma with FGFR2 fusions or rearrangements who have received at least one prior systemic therapy. A total of 120 patients will be randomized (1:1) to receive futibatinib at a starting dose of either 20 mg (Arm A) or 16 mg (Arm B) orally QD. The primary endpoint will be ORR according to RECIST 1.1 as determined by blinded independent central review (BICR) with duration of response (DOR) being a key secondary endpoint. The primary analysis will be based on the 20 mg treatment arm.
This study will assess the efficacy and safety of futibatinib in a similar sample size of patients overall to that from the Phase 2 portion of Study TAS-120-101, to provide both replication of evidence on ORR and DoR and a consequent increase in size to the safety dataset.
The applicant considers this second-line study to be feasible for the following reasons:

- Enrolment of 120 patients appears reasonable;
- the second-line treatment setting allows for biomarker testing while the patient is receiving first-line therapy and is thus more aligned with clinical practice; and
- the study design ensures that all patients will receive treatment with futibatinib which is expected to promote enrolment.

The currently proposed study is (also) a post-marketing requirement by the FDA.

Regarding the timelines, it is planned: 1) patient enrolment completed Q2 2026; 2) database lock for primary analysis Q1 2027; and 3) submission of results to CHMP Q4 2027.
This SOB is a replication of the single-arm efficacy (and safety) data in a new and independent single-arm study cohort in order to provide a comprehensive overall data package.
For clarity, the term 'single-arm' also encompasses studies that contain more than one arm, but do not randomise to a control for a formal comparison, i.e. non-randomised trials as well as trials in which only experimental arms are randomised, but without formal comparisons between the arms (text taken from draft reflection paper single-arm trials). With the term 'randomized, controlled trial' ('RCT') is meant here a study that does include a formal comparison to a (standard-of-care) control.
Such independent replication of single-arm data by a separate single-arm cohort has previously been accepted to provide comprehensive data resulting in a full approval.

The proposed study, TAS-120-205, will provide additional data in a study population similar to the pivotal study population. The efficacy (and safety) data of the 60 patients in the 20 mg Arm A can serve to verify and confirm the benefit-risk balance of futibatinib as observed in the 103 patients in the pivotal Study TAS-120-101. The total (efficacy) dataset will thus be comprised of approximately 160

patients with advanced, unresectable cholangiocarcinoma with a FGFR2 fusion or rearrangement that has progressed after at least one prior line of systemic therapy. In the light of the observed efficacy (ORR and DOR) and safety in the pivotal study, and provided replication of these results is submitted, such a dataset can be considered comprehensive and support a full approval.

Importantly, the efficacy (and safety) data of the 60 patients in the 16 mg Arm B will be regarded as supportive data. The 16 mg data will nevertheless be assessed and may be considered for e.g. inclusion in the SmPC, when scientifically justified and regarded as relevant information for prescribers.

The finalised protocol of study TAS-120-205 (Amendment 1: 08 February 2023) has been provided.

- Unmet medical needs will be addressed.

Recent retrospective analyses have shown that the outcomes of post-first-line chemotherapy among the subset of patients with FGFR2 rearrangements/fusions appeared similarly poor as those seen in the overall population, including a response rate <6% for second-line chemotherapy (Javle 2020, ASCO Abstract).

The oral FGFR1-3 inhibitor pemigatinib has received a conditional marketing authorisation for the treatment of patients with previously treated CCA harbouring FGFR2 rearrangements/fusions, based on clinical benefit concluded from ORR and DOR in an uncontrolled phase 2 study. A randomized Phase 3 study as compared to standard of care chemotherapy in first-line advanced CCA patients with FGFR2 rearrangements (including fusions) is ongoing as specific obligation.

Tibsovo (ivosidenib) monotherapy is indicated for the treatment of adult patients with locally advanced or metastatic cholangiocarcinoma with an isocitrate dehydrogenase-1 (IDH1 R132) mutation who were previously treated by at least one prior line of systemic therapy. FGFR2 alterations occur in roughly 10% to 15% of cholangiocarcinoma, however, they rarely co-occur with IDH1 mutations (co-occurrence in approximately 2% to 5%) (Battaglin et al, 2020; Jain et al, 2018; Valle et al, 2017; Saborowski et al, 2020). Therefore, despite these developments an unmet medical need remains for adult patients with previously treated locally advanced or metastatic cholangiocarcinoma with a FGFR2 fusion or rearrangement that have progressed after at least one prior line of systemic therapy.

Importantly, Lytgobi is considered to address the unmet medical need to a similar extent to Pemazyre (that was also conditionally approved), considering that the clinical data packages of both medicinal products are qualitatively (and quantitatively) similar. Results for Lytgobi are comparable to the estimates that formed the basis for the conditional approval of pemigatinib in the same indication Furthermore, as FGFR2 alterations rarely co-occur with IDH1 mutations, Lytgobi can be considered to be of major therapeutic advantage to the large majority of patients with cholangiocarcinoma with a FGFR2 alteration. Their disease will lack a IDH1 R132 mutation and these patients are thus not eligible for treatment with Tibsovo (that has a full marketing authorisation).

- The benefits to public health of the immediate availability outweigh the risks inherent in the fact that additional data are still required.

The benefit-risk balance is positive and, taken the unmet medical need into account, it can be concluded that the benefits to public health of the immediate availability outweigh these risks.

3.8. Conclusions

The overall benefit/risk balance of Lytgobi is positive, subject to the conditions stated in section 'Recommendations'.

Divergent position is appended to this report.

4. Recommendations

Similarity with authorised orphan medicinal products

The CHMP by consensus is of the opinion that Lytgobi is not similar to Pemazyre and Tibsovo within the meaning of Article 3 of Commission Regulation (EC) No. 847/2000.

Outcome

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considers by majority decision that the benefit-risk balance of Lytgobi is favourable in the following indication(s):

Lytgobi monotherapy is indicated for the treatment of adult patients with locally advanced or metastatic cholangiocarcinoma with a fibroblast growth factor receptor 2 (FGFR2) fusion or rearrangement that have progressed after at least one prior line of systemic therapy.

The CHMP therefore recommends the granting of the conditional marketing authorisation subject to the following conditions:

Conditions or restrictions regarding supply and use

Medicinal product subject to restricted medical prescription (see Annex I: Summary of Product Characteristics, section 4.2).

Other conditions and requirements of the marketing authorisation

- **Periodic Safety Update Reports**

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

The marketing authorisation holder shall submit the first periodic safety update report for this product within 6 months following authorisation.

Conditions or restrictions with regard to the safe and effective use of the medicinal product

- **Risk Management Plan (RMP)**

The marketing authorisation holder (MAH) shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the marketing authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

Specific Obligation to complete post-authorisation measures for the conditional marketing authorisation

This being a conditional marketing authorisation and pursuant to Article 14-a of Regulation (EC) No 726/2004, the MAH shall complete, within the stated timeframe, the following measures:

Description	Due date
In order to confirm the efficacy and safety of futibatinib in adult patients with locally advanced or metastatic cholangiocarcinoma with FGFR2 fusions or rearrangements that have progressed after at least one prior line of systemic therapy, the MAH should submit the results of FOENIX-CCA4 (TAS-120-205), a phase 2 study of futibatinib at a starting dose of 20 mg QD (Arm A) and 16 mg QD (Arm B) in such patients.	October 2027

Conditions or restrictions with regard to the safe and effective use of the medicinal product to be implemented by the Member States

Not applicable.

New Active Substance Status

Based on the CHMP review of the available data, the CHMP considers that futibatinib is to be qualified as a new active substance in itself as it is not a constituent of a medicinal product previously authorised within the European Union.

Divergent position(s)

Divergent position to the majority recommendation is appended to this report.

5. Appendix

5.1. Divergent position(s) to the majority recommendation

DIVERGENT POSITION DATED 26 April 2023

Lytgobi EMEA/H/C/005627/0000

The undersigned members of the CHMP did not agree with the CHMP's positive opinion recommending the granting of the marketing authorisation of Lytgobi for the following indication:

Lytgobi monotherapy is indicated for the treatment of adult patients with locally advanced or metastatic cholangiocarcinoma with a fibroblast growth factor receptor 2 (FGFR2) fusion or rearrangement that have progressed after at least one prior line of systemic therapy.

The reason for divergent opinion was the following:

The clinical evidence supporting the conditional marketing authorisation of Lytgobi in the intended population is based on 103 patients treated in the single-arm trial (SAT) No. TAS-120-101, showing ORR of 41.7% (95% CI 32.1, 51.9), with no patient with CR (0%), and a median DOR of 9.7 month (95% CI 7.6, 17.1).

Notable, the level of evidence provided by a SAT is less robust compared to a randomized clinical trial (RCT), and outcomes such as ORR and DOR are subject to bias (e.g. selection bias) and various sources of variability. The SAT setting also impairs the causality assessment of several key unfavourable effects. Last, the results in ORR and DOR in the SAT No. TAS-120-101 study require confirmation that they will translate in a meaningful clinical benefit.

Therefore, replication of single-arm efficacy (and safety) data in a new and independent SAT to provide a comprehensive overall data package is not acceptable. Confirmatory data from a RCT are considered necessary to provide comprehensive data suitable to confirm the positive benefit-risk balance of Lytgobi.

Martina Weise

Armando Genazzani