EU-Risk Management Plan (RMP) for Lytgobi (Futibatinib)

RMP Version to Be Assessed as Part of This Application:

RMP version number:	1.2
Data lock point for this RMP:	01 October 2020
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Rationale for Submitting an Updated RMP:

Not applicable.

Summary of Significant Changes in This RMP:

Not applicable.

Other RMP Versions Under Evaluation:

RMP version number:	Not applicable.
Submitted on:	Not applicable.
Procedure number:	Not applicable.

Details of the Currently Approved RMP:

RMP version number:	Not applicable.
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QPPV Name: Jana Mladá, MD

The content of this RMP has been reviewed and approved by the marketing authorisation applicant's QPPV. The electronic signature is available on file.

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List of Abbreviations

AE	Adverse Event
ALT	Alanine Aminotransferase
AST	Aspartate Aminotransferase
ATC	Anatomical Therapeutic Chemical Classification System
CCA	Cholangiocarcinoma
CTCAE	Common Terminology Criteria for Adverse Events
ECOG	Eastern Cooperative Oncology Group
eCTD	Electronic Common Technical Document
EEA	European Economic Area
EPAR	European Public Assessment Report
EU	European Union
FGF	Fibroblast Growth Factor
FGFR	Fibroblast Growth Factor Receptor
GLP	Good Laboratory Practice
hERG	Human Ether-a-go-go-Related Gene
IC_{50}	Half Maximal Inhibitory Concentration
iCCA	Intrahepatic Cholangiocarcinoma
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
INN	International Non-Proprietary Name
ISS	Integrated Summary of Safety
MAPK	Mitogen-Activated Protein Kinase
max	Maximum
MedDRA	Medical Dictionary for Regulatory Activities
MEK	Mitogen-Activated Protein Kinase
min	Minimum
n	Number of Patients with at least 1 Event
N	Number of Patients in Treatment Group
N/A	Not Applicable
NCI	National Cancer Institute
NOAEL	No-Observable-Adverse-Effect Level
NYHA	New York Heart Association
Ph	Phase
PL	Package Leaflet

PPES	Palmar-Plantar Erythrodysaesthesia Syndrome
PRO	Patient Reported Outcome
PT	Preferred Term
QD	Once Daily
QOD	Every Other Day
QPPV	Qualified Person for Pharmacovigilance
QTcF	Fridericia's Corrected QT Interval
RMP	Risk Management Plan
SAP	Statistical Analysis Plan
SD	Standard Deviation
SDG	Safety Data Group
SmPC	Summary of product characteristics
ULN	Upper Limit of Normal

PART I: Product(s) Overview

Active Substance(s) (INN or Common Name)	Futibatinib
Pharmacotherapeutic Group(s) (ATC code)	L01EN04
Marketing Authorisation Applicant	Taiho Pharma Netherlands BV
Medicinal Product(s) to Which This RMP Refers	1
Invented Name(s) in the European Economic Area (EEA)	LYTGOBI
Marketing Authorisation Procedure	Centralised
Brief Description of the Product	**Chemical Class:** Futibatinib is a small-molecule kinase inhibitor (irreversible fibroblast growth factor [FGF] receptor [FGFR] 1-4 inhibitor).
	Summary of Mode of Action: Futibatinib is a kinase inhibitor that irreversibly inhibits FGFR 1-4 by covalent binding with IC_{50} values of less than 4 nM. Futibatinib inhibits FGFR phosphorylation and signalling and decreases cell viability in cells expressing FGFR genetic alterations, including point mutations, amplifications, and rearrangements/fusions. Futibatinib exhibited in vitro anti-proliferation activity against cancer cell lines harbouring acquired FGFR2 resistance mutations in the kinase domain (N549K/D/H, V564I/L, E565G, K659M). Futibatinib demonstrated anti-tumour activity in mouse and rat xenograft models of human tumours with activating FGFR genetic alterations. FGFR2 rearrangements/fusions are strong oncogenic drivers and are the most common FGFR alteration occurring in 10-16% of intrahepatic cholangiocarcinoma (iCCA).
	Important Information About Its Composition: None
Hyperlink to the Product Information	Module 1.3.1
Indication(s) in the EEA	**Current:** Treatment of adult patients with locally advanced or metastatic cholangiocarcinoma (CCA) with a fibroblast growth factor receptor 2 (FGFR2) fusion or rearrangement that have progressed after at least one prior line of systemic therapy

Dosage in the EEA	**Current:** The recommended starting dose is 20 mg futibatinib taken orally once daily (QD).
Pharmaceutical Form(s) and Strength(s)	**Current:** Film-coated tablet Each film-coated tablet contains 4 mg of futibatinib.
Will the Product Be Subject to Additional Monitoring in the EU?	Yes

Abbreviations: ATC=anatomical therapeutic chemical classification system; EEA=European Economic Area; EU=European Union; IC_{50}=half maximal inhibitory concentration; INN=international non-proprietary name; RMP=Risk Management Plan.

PART II: Safety Specification

PART II: Module SI - Epidemiology of Indication(s) and Target Population(s)

Locally Advanced or Metastatic Cholangiocarcinoma Harbouring Fibroblast Growth Factor Receptor 2 Gene Rearrangements, Including Gene Fusions

CCA is an aggressive malignancy of the biliary system with poor overall prognosis and limited treatment options (Krook, 2020; Rizvi, 2017).

CCAs are diverse epithelial tumours arising from the liver or large bile ducts with features of cholangiocyte differentiation. Anatomically, CCA is classified into extrahepatic and intrahepatic (i.e. iCCA) forms. The extrahepatic form is more common, accounting for 80% to 90% of the CCAs (Blechacz, 2008). Each subtype has distinct risk factors, molecular pathogenesis, therapeutic options, and prognosis (Banales, 2020; Rizvi, 2017).

Symptoms of CCA are not usually apparent until the disease is at an advanced stage, and thus, most patients have incurable disease at diagnosis. Unresectable, locally advanced (stage III) or metastatic (stage IV) disease has a dismal prognosis (Krook, 2020; Rizvi, 2017) with the 5-year overall survival rates for patients with locally advanced and metastatic disease at 10% and 0%, respectively (Lamarca, 2014).

Dysregulation of the FGF/FGFR signalling pathway has been associated with many developmental disorders and cancer, including CCA (Krook, 2020; Rizvi, 2017). The FGFR signalling axis has been well characterised for its role in proliferation, differentiation, migration, and survival, and it is fundamental to embryonic development, regulation of angiogenesis, and wound healing in adults (Turner, 2010). As such, the FGF/FGFR signalling axis play an important role in normal organ, vascular, and skeletal development.

Incidence and Prevalence:

CCAs represent the second most common malignancy of the liver, accounting for approximately 15% of all primary liver cancers and approximately 3% of all gastrointestinal cancers (Banales, 2020).

The epidemiological profile of CCA and its subtypes displays significant geographical variation, reflecting the exposure to different risk factors. Although in most countries CCA is a rare cancer (incidence less than 6 cases per 100,000 people), its incidence is exceptionally high in some countries and regions, including Chile, Bolivia, South Korea, and Northern Thailand (Banales, 2016; Banales, 2020).

For example, the incidence of iCCA varies substantially worldwide with the highest known rates in the Northeast Thailand (more than 80 per 100,000 population). The Western world has lower rates of 1 to 2 per 100,000 population (Bridgewater, 2014; Buettner, 2017). The incidence in European countries is reported to range from less than 1 to 4 cases per 100,000 population (Banales, 2016; Banales, 2020).

The incidence of iCCA has been rising worldwide. By contrast, the incidences of extrahepatic forms seem to be decreasing (Banales, 2016).

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

FGFR2 rearrangements (including fusions) occur in about 10% to 16% of patients with iCCA (Graham, 2014; Jain, 2018).

Demographics of the Population in the Proposed Indication – Age, Gender, Racial and/or Ethnic Origin and Risk Factors for the Disease:

CCA shows a considerable geographic variation in incidence worldwide, reflecting the exposure to different risk factors. Although iCCA represents in most countries a rare type of cancer, its incidence is significantly higher in some countries or regions, including Chile, Bolivia, South Korea, and Northeast Thailand (Banales, 2016; Banales, 2020).

In the Western world, the median age at presentation of CCA is more than 65 years, and it is only rarely diagnosed in patients below 40 years of age (except in patients with pre-existing primary sclerosing cholangitis). There is a slight male predominance for CCA (Blechacz, 2008).

Baseline demographics of CCA patients with *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 (approximately 65 years) and a female preponderance (13% versus 4%) (Graham, 2014).

- **Risk factors:**

  Risk factors for the development of CCA are established (Banales, 2016; Banales, 2020; Bridgewater, 2014; Gupta, 2017; Ross, 2014), despite the fact that the majority of CCAs occur in the absence of an evident chronic liver disease or other risk factors (Banales, 2016; Blechacz, 2008). Known risk factors for CCA are only involved in approximately 20% of cases (Banales, 2020).

  - Infectious diseases (e.g. *Opisthorchis viverrini* and *Clonorchis sinesis* infection [liver flukes], hepatitis B virus and hepatitis C virus-related liver disease).
  - General risk factors (e.g. obesity and diabetes mellitus [i.e. metabolic syndrome], alcohol consumption, tobacco smoking).
  - Inflammatory disease (e.g. primary sclerosing cholangitis, hepatolithiasis, biliary tract stone disease, biliary-enteric anastomosis, and liver cirrhosis).
  - Environmental factors (e.g. nitrosamine-contaminated food, asbestos, dioxins, vinyl chlorides, and thorotrast).
  - Congenital factors (e.g. choledochal cysts, Caroli's disease, and congenital hepatic fibrosis).

  Intrahepatic CCA occurs more frequently than the extrahepatic forms in patients with chronic liver disease and/or cirrhosis (Banales, 2016).

Main Treatment Options:

Surgery with complete tumour resection, including liver transplantation in highly selected cases, is the only curative therapy for CCA (Banales, 2020; Buettner, 2017). When the disease is unresectable, only palliative treatment is currently possible (Banales, 2020).

In patients with unresectable tumours, systemic chemotherapy/targeted therapy can be considered (Banales, 2020).

- **Surgical resection:**

  Approximately 25% up to 45% of the CCA patients have a resectable tumour at the time of diagnosis (Banales, 2020; Goldaracena, 2018). Surgery may improve both survival and quality of life, but comes with a substantial risk of postoperative morbidity and mortality (Buettner, 2017). The survival rates after surgical treatment of intrahepatic as well as extrahepatic CCA have significantly improved, possibly reflecting a more careful patient selection, thereby achieving higher rates of negative margin resection (Blechacz, 2008).

  Survival after resection mainly depends on the presence of tumour-negative margins, absence of vascular invasion and lymph node metastasis, and adequate functional liver remnant. Overall, 5-year survival after resection has been reported in the range from 22% to 44% for iCCA (Banales, 2016).

  Adjuvant chemotherapy with capecitabine is recommended by the international guidelines for 6 months after surgical resection with curative intent in patients with iCCA (Banales, 2020).

- **Systemic therapy (chemotherapy, targeted therapy):**

  In patients presenting with unresectable or metastatic disease, systemic chemotherapy remains the main palliative treatment modality (Banales, 2020).

  The first-line, standard-of-care treatment for patients with unresectable/metastatic disease is gemcitabine and cisplatin. Oxaliplatin may be substituted for cisplatin in the presence of renal function concerns (Valle, 2016).

  FOLFOX combination therapy (folinic acid, 5-fluorouracil, and oxaliplatin) can be recommended as second-line, standard-of-care chemotherapy (Banales, 2020).

  Pemigatinib is a small-molecule tyrosine kinase inhibitor of FGFR1, FGFR2, and FGFR3 conditionally approved in the EU for the second-line treatment of adults with locally advanced or metastatic CCA with a FGFR2 fusion or rearrangement that have progressed after at least one prior line of systemic therapy.

- **Liver transplant:**

  Liver transplantation has been associated with rapid tumour recurrence and low survival (10-25%), and has historically not been recommended as treatment for unresectable CCA (Banales, 2016; Banales, 2020).

  Only two locations of CCA have been identified as to benefit from liver transplant, including perihilar CCA (a subtype of extrahepatic CCA) and ‘very early’ iCCA

(Goldaracena, 2018). In selected patients with an early-stage (I-II) perihilar CCA, the rate of recurrence-free survival after 5 years has been reported in the range from 65% to 68% after liver transplantation, following protocols using neoadjuvant therapy (Banales, 2016; Banales, 2020). Until recently, the presence of iCCA had been considered a contraindication for liver transplantation due to historically very poor results. However, an international multicentre study showed a 5-year survival rate of 65% in patients with 'very early' iCCA (tumour size <2 cm) following liver transplantation compared to 45% in the 'advanced' group (tumour size >2 cm) (Sapisochin, 2016).

- **Locoregional therapy:**

  The role of locoregional therapies, such as trans arterial chemoembolisation and trans arterial radioembolisation, has increasingly been investigated for patients with CCA, showing some evidence of improved survival. Radiofrequency ablation seems to prolong the survival in inoperable CCA (Banales, 2016).

Natural History of the Indicated Condition in the (Untreated) Population, Including Mortality and Morbidity:

CCA is generally asymptomatic in early stages and the initial symptoms are often nonspecific and include abdominal pain, anorexia, and palpable abdominal mass lesions (Ross, 2014). Some patients present with painless jaundice (the most frequent clinical onset in extrahepatic CCA), when the tumour grows towards the biliary confluence (Banales, 2016; Banales, 2020; Buettner, 2017).

As a result, most patients present with an advanced disease, preventing curative treatment options. For the limited number of patients who do present with resectable disease, survival rates remain low mainly due to tumour recurrence (Krook, 2020).

FGFR2 rearrangements (including fusions) occur in about 10% to 16% of patients with iCCA (Jain, 2018; Krook, 2020), and at a much lower incidence in patients with extrahepatic CCA (Arai, 2014; Jain, 2018). Additionally, retrospective studies indicate a longer survival of CCA patients with FGFR2 rearrangements, suggesting the potential utility of *FGFR2* fusion identification as a prognostic marker (Graham, 2014; Jain, 2018). However, the natural history of CCA with *FGFR* alterations and its prognostic role is not yet fully characterised.

The global mortality is estimated at 1-6 per 100,000 inhabitants per year (Banales, 2020). The median survival is less than 6 months for inoperable tumours and only 20% to 40% for patients who undergo surgery and achieve clear margins (Ross, 2014). The overall 5-year survival rate in patients eligible for surgery is reported to range from 30 to 35% (de Jong, 2011). The 5-year overall survival rates for patients with locally advanced and metastatic disease are 10% and 0%, respectively (Lamarca, 2014).

Important Co-Morbidities:

- Liver dysfunction related to disease risk factors (e.g. viral hepatitis, cirrhosis, fatty liver, etc.)

PART II: Module SII - Nonclinical Part of the Safety Specification

The nonclinical development programme for futibatinib included preliminary dose range-finding, repeat-dose toxicity, genotoxicity, reproductive, and phototoxicity studies in mice, rats, and dogs, all using oral administration.

The embryo-foetal toxicity of futibatinib was investigated in rats. Studies in rabbits were not performed as per the International Council for Harmonisation (ICH)-S9 guideline.

Carcinogenicity, peri/postnatal development and juvenile toxicology studies were not conducted in accordance with the ICH-S9 guideline.

The full nonclinical development programme is described in the eCTD Module 2.4 (Nonclinical Overview).

Table 1: Key Safety Findings from the Nonclinical Development Programme for Futibatinib

Study Type	Finding	Relevance to Human Usage
Repeat-dose toxicity	**Hyperphosphatemia and ectopic mineralisation in various organs/tissues** Increased inorganic phosphorus values in plasma and ectopic mineralisation in various organs and bone/cartilage lesions were the main toxicity finding in 3-week oral repeat-dose toxicity studies in rats and dogs (Studies 12CB24 and 12CB22, respectively). Increased inorganic phosphorus and calcium values in plasma and ectopic mineralisation in various organs and tissues, and bone/cartilage lesions were the main toxicity findings in 4-week oral toxicity studies in rats and dogs (Studies B-7416 and B-7417, respectively). Except for the ectopic mineralisation, all these findings resolved during the recovery period in both rats and dogs. Results of the 13-week GLP toxicity study in rats and dogs (Studies B-8203 and B-8204, respectively) showed no new toxicological findings or exacerbation of known toxicities in comparison to the 4-week study.	Hyperphosphatemia is the most common adverse reaction observed in the clinical development programme for futibatinib, where a dose-dependent elevation in serum phosphate was seen. The increased inorganic phosphorus in plasma is likely to be a mechanism-based class effect of FGFR inhibition (Brown, 2005; Gattineni, 2009; Martin, 2012; Wöhrle, 2011) that has been shown to have an effect on mineral homeostasis, including calcium. Hyperphosphatemia is considered as an (non-important) identified risk of futibatinib (refer to PART II: Module SVII. Ectopic mineralisation in various organs is also attributable to FGFR inhibition-mediated mineral imbalance (Hierro, 2015). However, no significant serious adverse events or deaths attributed to the mineralisation of any organs (heart, aorta, kidney, and lungs) were identified and reported from clinical trials.
Reproductive and developmental toxicity	**Embryo-foetal toxicity and teratogenicity** Futibatinib inhibited normal development of the rat embryo-foetus and resulted in embryo-foetal lethality (Study 18CC01). The dose of 10 mg/kg was lethal for embryos/foetuses. Futibatinib revealed teratogenic effects in rat embryo-foetus. The definitive visceral and	Pregnant women were excluded from the clinical development programme for futibatinib and as such, the relevance of these findings to human use is unknown. However, embryotoxicity was reported in association with many tyrosine kinase inhibitors (Abruzzese, 2014). Therefore,

Table 1: Key Safety Findings from the Nonclinical Development Programme for Futibatinib

Study Type	Finding	Relevance to Human Usage
	skeletal abnormalities were observed at the doses of 0.5 and 1.0 mg/kg (Study 18CB09). Therefore, the NOAEL for embryo-foetal development was < 0.5 mg/kg.	embryo-foetal toxicity/teratogenicity represents an important potential risk of futibatinib (refer to PART II: Module SVII).
Genotoxicity	Futibatinib did not show a genotoxic potential in a standard battery of genotoxicity tests, including in vitro reverse mutation test and in vivo tests in the selected *Salmonella typhimurium* and *Escherichia coli* bacterial strains. However, futibatinib showed to have a potential for inducing chromosomal aberrations in vitro; however, a micronucleus test revealed that futibatinib did not show any clastogenic potential in vivo.	The results of an in vitro mutagenicity study (Ames assay) and two in vivo genotoxicity studies (micronucleus test in rats and Comet assay in rats) suggest that the risk of genotoxicity in humans is low.
Safety pharmacology	Futibatinib suppressed the hERG current at concentrations of 10 µmol/L (4,185 ng/mL) or higher in vitro (Study 8215). The IC_{50} value for the hERG current of futibatinib was 7.42 µmol/L (3,105 ng/mL). There was no inhibition on the peak tail currents by futibatinib at a concentration of 1 µmol/L. No cardiovascular effect was noted in an in vivo study using conscious dogs at doses up to the maximum tested dose of 10 mg/kg (Study 8214). Moreover, the IC_{50} value for the hERG current (i.e. 3,105 ng/mL) was more than 5-fold higher than the maximum plasma concentration of futibatinib observed at a severely toxic dose of 10 mg/kg (531 ng/mL) in a 4-week oral repeated dose toxicity study in dogs. Therefore, a risk of potential QT interval prolongation associated with arrhythmia was considered low. There were no effects seen in either the central nervous or respiratory system at up to 30 mg/kg (Studies 8212 and 8213). Therefore, based on these nonclinical studies, no potential risks were identified for these systems.	The incidences of adverse events within the clinical development programme for futibatinib, involving cardiovascular, respiratory, and central nervous systems, were low. No significant risks were identified in cardiovascular (e.g. QT prolongation), respiratory, and central nervous systems.

Abbreviations: FGFR=fibroblast growth factor receptor; GLP=Good Laboratory Practice; hERG=human ether-a-go-go-related gene; IC_{50}=half-maximal inhibitory concentration; NOAEL=no-observable-adverse-effect level.

PART II: Module SIII - Clinical Trial Exposure

The clinical data supporting the marketing authorisation application originated from 9 clinical studies (2 studies in patients with cancer and 7 clinical pharmacology studies in healthy volunteers). The integrated safety population (N=648) includes the following data sets (refer also to Figure 1):

- **Safety Data Group 1 (SDG1; N=145):**
  This group comprises patients with iCCA harbouring *FGFR2* rearrangement and treated at a starting dose of 20 mg QD in Study TAS-120-101 (Phase 1 Expansion Part [N=42] and Phase 2 Part [N=103]).
- **Safety Data Group 2 (SDG2; N=469):**
  This group comprises patients with all solid tumours, at any dose level in Study TAS-120-101 (Phase 1 Dose Escalation Part, Phase 1 Expansion Part, and Phase 2 Part) and Study 10059010 (Dose Escalation Part and Expansion Part).

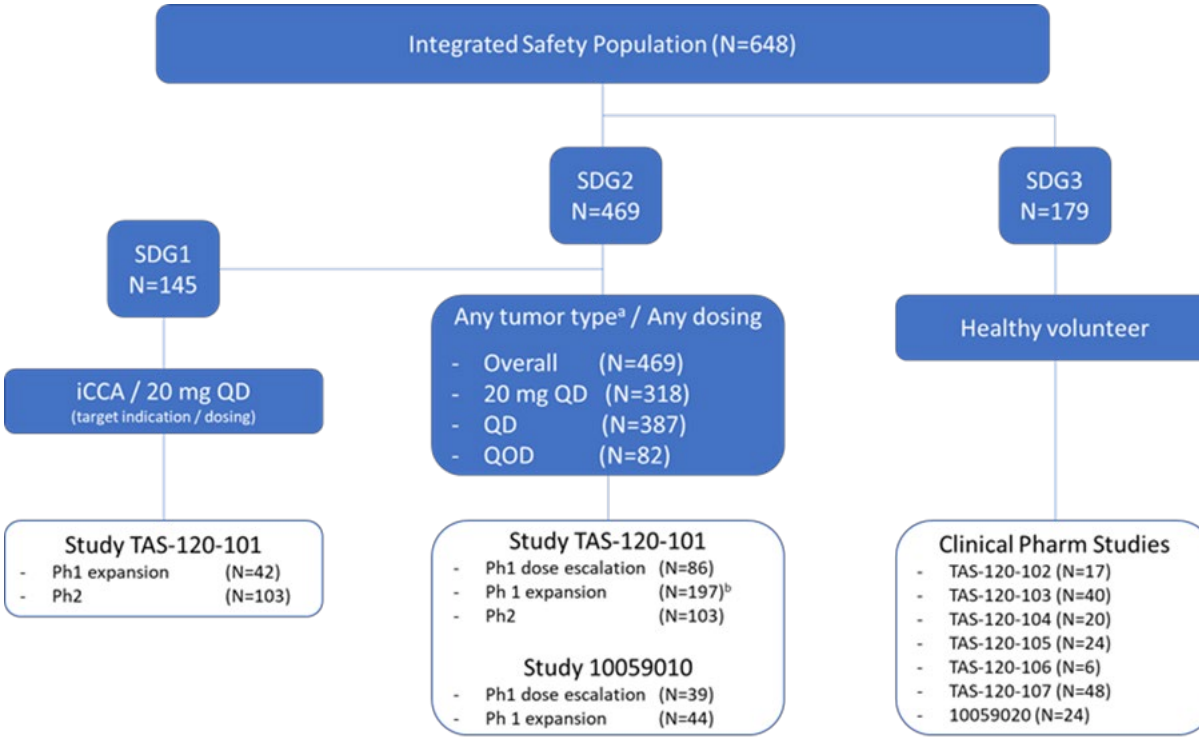
  Additional outputs for SDG2 by dose and dosing regimen are provided for:

  – Futibatinib 20 mg QD population (N=318)
  – Futibatinib QD population (N=387)
  – Futibatinib every other day (QOD) population (N=82)

  The futibatinib 20 mg QD population (N=318) comprises all patients with any tumour type who received a starting dose of 20 mg QD futibatinib and is included as supportive information.
- **Safety Data Group 3 (SDG3; N=179):**
  This group comprises healthy volunteers in clinical pharmacology studies: TAS-120-102, TAS-120-103, TAS-120-104, TAS-120-105, TAS-120-106, TAS-120-107, and 10059020.

The primary safety analysis provided in this summary is based upon SDG1, with supporting information presented from SDG2.

Figure 1 provides a detailed overview of the integrated safety population (N=648).



Source: Module 2.7.4
[a] Any tumour type' includes also patients with iCCA.
[b] Includes 42 patients with iCCA also included in SDG1 population
Abbreviations: iCCA=intrahepatic cholangiocarcinoma; Ph=phase; QD=once daily; QOD=every other day; SDG=Safety Data Group.

Figure 1: Summary of Integrated Safety Population Safety Data Groups

Of note, the entirety of SDG1 is included in the SDG2 population. Therefore, data presented for SDG1 are also represented in the SDG2 dataset. As the SDG3 population consists entirely of healthy volunteers, the safety data reported for this group are not discussed in the RMP.

The extent of patient exposure is provided in Table 2, while the demographic and baseline characteristics of patients are provided in Table 3.

Detailed information on the clinical development programme for futibatinib is provided in the eCTD Module 2.5 (Clinical Overview) and Module 2.7.4 (Summary of Clinical Safety).

Table 2: Study Treatment Extent of Exposure to Futibatinib (Safety Data Group 1 and Safety Data Group 2)

Variable	Safety Data Group 1 (iCCA)	Safety Data Group 2 (Any Tumour 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)
No. of Cycles Treated			
n	145	318	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)
No. 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	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			
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 (%)			
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)

Table 2: Study Treatment Extent of Exposure to Futibatinib (Safety Data Group 1 and Safety Data Group 2)

Variable	Safety Data Group 1 (iCCA)	Safety Data Group 2 (Any Tumour Type)	
	20 mg QD (N=145)	20 mg QD (N=318)	Any Dosing (N=469)

Source: ISS Table 14.3.1.1 and Table 14.3.1.2
[a] The category 'Unknown' is not included in the outputs for SDG1 and is not applicable.
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

Table 3: Demographics and Baseline Characteristics (Safety Data Group 1 and Safety Data Group 2)

Variable	Safety Data Group 1 (iCCA)	Safety Data Group 2 (Any Tumour Type)	
	20 mg QD (N=145)	20 mg QD (N=318)	Any Dosing (N=469)
Age (Years)			
n	145	318	469
Mean (SD)	55.4 (12.30)	56.8 (12.77)	56.9 (12.82)
Median (Min, Max)	57.0 (22, 83)	59.0 (20, 83)	59.0 (18, 83)
Age Groups, n(%)			
<65 years	114 (78.6)	229 (72.0)	330 (70.4)
≥65 and <75 years	25 (17.2)	71 (22.3)	113 (24.1)
≥75 years	6 (4.1)	18 (5.7)	26 (5.5)
Sex, n (%)			
Male	54 (37.2)	151 (47.5)	221 (47.1)
Female	91 (62.8)	167 (52.5)	248 (52.9)
Race, n (%)			
Caucasian/White	76 (52.4)	157 (49.4)	233 (49.7)
Black	9 (6.2)	12 (3.8)	15 (3.2)
Asian/Oriental	36 (24.8)	90 (28.3)	138 (29.4)
Other	1 (0.7)	2 (0.6)	4 (0.9)
Unknown	23 (15.9)	57 (17.9)	79 (16.8)
Region, n (%)			
North America	75 (51.7)	124 (39.0)	167 (35.6)
Europe	38 (26.2)	112 (35.2)	163 (34.8)
Asia Pacific (excluding Japan)	18 (12.4)	30 (9.4)	42 (9.0)
Japan	14 (9.7)	52 (16.4)	97 (20.7)
Ethnicity, n (%)			
Hispanic or Latino	4 (2.8)	5 (1.6)	9 (1.9)
Not Hispanic or Latino	119 (82.1)	252 (79.2)	364 (77.6)
Unknown	22 (15.2)	61 (19.2)	96 (20.5)
ECOG Performance Status, n (%)			
0	67 (46.2)	130 (40.9)	197 (42.0)
1	78 (53.8)	188 (59.1)	272 (58.0)

Source: ISS Table 14.1.5.1 and Table 14.1.5.2
Abbreviations: ECOG=Eastern Cooperative Oncology Group; max=maximum; min=minimum; n=number of patients with at least 1 event; N=number of patients in treatment group; QD=once daily; SD=standard deviation

PART II: Module SIV - Populations Not Studied in Clinical Trials

SIV.1 Exclusion Criteria in Pivotal Clinical Studies Within the Development Programme

The main exclusion criteria discussed below are based on the exclusion/inclusion criteria established for the Phase 1/2 pivotal Study TAS-120-101 in patients with advanced solid tumours harbouring FGF/FGFR aberrations.

Table 4: Important Exclusion Criteria from Pivotal Clinical Trials

Criteria	Reason for Exclusion	Is It Considered to Be Included as Missing Information?
History or current evidence of serious uncontrolled ventricular arrhythmias. Myocardial infarction, severe/unstable angina, symptomatic congestive heart failure (NYHA Class III or IV) within the previous 2 months; if > 2 months, cardiac function must be within normal limits and the patient must be free of cardiac-related symptoms. QTcF > 470 ms on electrocardiogram conducted during Screening. Congenital long QT syndrome, or any known history of torsade de pointes, or family history of unexplained sudden death.	The potential for QT prolongation is a class effect of tyrosine kinase inhibitors but the clinical implications differ between individual agents. Cardiac toxicity is mainly seen with multitarget tyrosine kinase inhibitors (Porta-Sanchez, 2017; Shah, 2015; Shah, 2013). The nonclinical studies of futibatinib showed that a risk of potential QT interval prolongation associated with arrhythmia is considered low (refer to PART II: Module SII). The respective exclusion criteria were established as precautionary measures, limiting the number of at-risk patients who could potentially develop severe cardiovascular events.	No – **Rationale:** The clinical development programme showed low incidence of adverse events involving cardiovascular, respiratory, and central nervous systems. Based on the data collected from the overall development programme, the safety profile of futibatinib in patients excluded from the clinical development programme is not expected to differ from the general safety profile.
AST and ALT ≥ 3.0 × ULN; if liver function abnormalities are due to underlying liver metastases, AST and ALT ≥ 5.0 × ULN Total bilirubin ≥ 1.5 × ULN or ≥ 3.0 × ULN for patients with Gilbert's syndrome	These exclusion criteria were established to minimise the potential confounding factors for evaluation of the efficacy, pharmacokinetics, and safety of futibatinib. Futibatinib is primarily metabolised in the liver.	No – **Rationale:** Study TAS-120-108 included subject with mild, moderate, and severe hepatic impairment. Since the data pertinent to the use of futibatinib in patients with various degree of hepatic impairment has been provided during the initial marketing authorisation procedure, this topic is not considered missing information for the post-authorisation experience.

Table 4: Important Exclusion Criteria from Pivotal Clinical Trials

Criteria	Reason for Exclusion	Is It Considered to Be Included as Missing Information?
Creatinine clearance (calculated or measured value) ≤ 40 mL/min	This exclusion criterion was established to minimise the potential confounding factors for evaluation of the efficacy, pharmacokinetics and safety of futibatinib.	No – **Rationale:** The results of the mass balance study showed that only 6% of the administered single dose of [^{14}C]-futibatinib (Study TAS-120-106) was recovered in urine, indicating it is a minor elimination pathway. Similarly, in patients with advanced solid tumours following a single dose of futibatinib, less than 0.1% of the dose was excreted in urine as an unchanged form (Studies TPU-TAS-120-101 and 10059010). These results indicate that urinary excretion does not represent a significant mechanism of elimination for futibatinib and its metabolites, and therefore alterations in renal function are not expected to have any clinically significant impact on the pharmacokinetics of futibatinib. The safety profile of futibatinib is not expected to differ in patients with renal impairment.
Pregnant or breastfeeding women	These criteria represent standard ethical measures. Furthermore, the nonclinical programme showed embryo-foetal toxicity/teratogenicity of futibatinib in rats (refer to PART II: Module SII).	No – **Rationale:** The effects of futibatinib on pregnancy are part of the important potential risk of embryo-foetal toxicity/teratogenicity and no missing information is applicable. There are no data regarding the secretion of futibatinib or its metabolites in human milk nor on their effects on the breastfed infant or on milk production. Because of the potential for adverse reactions in breastfed infants, breastfeeding should be discontinued during treatment with futibatinib and for 1 week after the last administered dose. Considering the proposed target population, it is expected that futibatinib will not be used during

Table 4: Important Exclusion Criteria from Pivotal Clinical Trials

Criteria	Reason for Exclusion	Is It Considered to Be Included as Missing Information?
		breastfeeding and no data on use in this special population are expected to be collected from the post-marketing setting.

Abbreviations: ALT=alanine aminotransferase; AST=aspartate aminotransferase; NYHA=New York Heart Association; QTcF=Fridericia's corrected QT interval; ULN=upper limit of normal.

SIV.2 Limitations to Detect Adverse Reactions in Clinical Trial Development Programmes

CCA is a rare disease and as such, the clinical development programme for futibatinib is unlikely to detect certain types of adverse reactions such as infrequent adverse reactions. Furthermore, the programme is unlikely to detect adverse reactions with a long latency or those caused by prolonged or cumulative exposure.

SIV.3 Limitations in Respect to Populations Typically Underrepresented in Clinical Trial Development Programmes

Table 5: Exposure To Futibatinib in Special Populations

Type of Special Population	Exposure
Pregnant women	Not included in the clinical development programme.
Breastfeeding women	
Patients with relevant comorbidities: – Patients with hepatic impairment	Patients with severe hepatic impairment were excluded from the pivotal clinical study (TAS-120-101). Pharmacokinetics, safety, and tolerability of single dose futibatinib was investigated in subjects with mild, moderate, and severe hepatic impairment.in the completed Study TAS-120-108.
– Patients with renal impairment	Patients with severe renal impairment were excluded from the clinical development programme. The clinical development programme for futibatinib included 127 subjects with mild and 36 subjects with moderate renal impairment. No patient with severe renal impairment was included (refer to SIV.1).
– Patients with cardiovascular impairment	Not included in the clinical development programme.
Patients with a disease severity different from inclusion criteria in clinical trials	Not included in the clinical development programme.
Population with relevant different ethnic origin	Refer to Table 3 in PART II: Module SIII.
Subpopulations carrying relevant genetic polymorphism	Not applicable.
Other	Not applicable.

PART II: Module SV - Post-Authorisation Experience

Futibatinib has not been approved for marketing in any country at the data lock point of this document.

PART II: Module SVI - Additional EU Requirements for Safety Specification

Potential for Misuse for Illegal Purposes

Considering the mechanism of action of futibatinib, the potential for misuse for illegal purposes is considered to be negligible.

PART II: Module SVII - Identified and Potential Risks

SVII.1 Identification of Safety Concerns in the Initial RMP Submission

SVII.1.1 Risks Not Considered Important for Inclusion in the List of Safety Concerns in the RMP

Reason for not including an identified or potential risk in the list of safety concerns in the RMP:

- **Known risks that require no further characterisation and are followed up via routine pharmacovigilance namely through signal detection and adverse reaction reporting, and for which the risk minimisation messages in the product information are adhered by prescribers (e.g. actions being part of standard clinical practice in each EU Member state where the product is authorised):**

Identified Risk: Hyperphosphataemia

Hyperphosphataemia is a well-known on-target class effect of FGFR inhibitors, presumably linked to FGFR inhibition and its effect on phosphate homeostasis (Hierro, 2015; Wöhrle, 2011; Yanochko, 2013).

The role of FGFRs in the transduction of renal FGF23/Klotho signalling was confirmed in vivo, providing evidence for their involvement in the maintenance of phosphate homeostasis. FGF23 is a bone-derived mediator of phosphate homeostasis and loss of FGF23 function is associated with hyperphosphataemia. FGFR signalling in bone regulates *Fgf23* transcription, ultimately leading to the modulation of systemic FGF23 protein levels (Wöhrle, 2011).

Reversible increased phosphorus in plasma and irreversible ectopic mineralisation in various organs and tissues were the main adverse findings in the nonclinical programme for futibatinib (refer to PART II: Module SII). Hyperphosphatemia was the most common adverse event in the clinical development programme for futibatinib.

In the **SDG1 population** (N=145), 130 patients (89.7%) experienced an event of hyperphosphataemia, of which 40 patients (27.6%) experienced at least one Grade 3 event (defined as serum phosphate > 7 mg/dl irrespective of clinical symptoms) and there were no Grade 4 or Grade 5 events.[1] All reported events were assessed as treatment-related by the investigator. Among all patients in the SDG1 population, 121 patients (83.4%) received treatment with at least one phosphate binder for management of ≥Grade 1 event. Among the 40 patients with a ≥Grade 3 event, 24 patients (16.6%) received treatment with a phosphate binder and 16 patients (11.0%) received treatment with more than one phosphate binder. All

[1] The grading of hyperphosphatemia events did not use the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) v4.03 but was conducted based on serum phosphate levels as specified in the corresponding study protocols and the ISS SAP.
Grade 3 hyperphosphataemia was defined by serum phosphate levels ≥ 7 mg/dl, irrespective of any clinical symptoms.
Additionally, as an exploratory analysis, hyperphosphataemia toxicity grading based on CTCAE v5.0 was derived using the criteria summarized in the ISS SAP. Summaries of maximum post-baseline CTCAE grades using these criteria for hyperphosphatemia laboratory results are presented in ISS Table 14.3.3.8.1 and ISS Table 14.3.3.8.2 for patients in the SDG1 and SDG2 populations, respectively.

events resolved in both groups (i.e. patients treated with a phosphate binder versus patients treated with >1 phosphate binder), with a median time to resolution to <Grade 3 of 7 days. Time to resolution to <Grade 2 was also comparable between both groups (median of 8 days and 9 days, respectively). Time to resolution to <Grade 1 was shorter for patients receiving one phosphate binder (median of 8 days) than for patients receiving >1 phosphate binder (median of 15 days).

In the **SDG2 population** (N=469), 385 patients (82.1%) experienced an event of hyperphosphataemia, including 280 patients (88.1%) who received 20-mg QD futibatinib (N=318). All events in the total SDG2 and 20-mg QD populations were assessed as treatment-related by the investigator. Among patients who received 20-mg QD futibatinib (N=318), 75 patients (23.6%) had a ≥Grade 3 event and no Grade 4 or Grade 5 events were reported. Among these 75 patients with a ≥Grade 3 event, 44 patients (13.8%) received treatment with a phosphate binder and 28 patients (8.8%) received treatment with more than one phosphate binder. Median time to resolution to <Grade 3 was 7 days and median time to resolution to <Grade 2 was 8 days for patients receiving one or >1 phosphate binder.

In the full SDG2 population (N=469), among the 88 patients (18.8%) with a ≥Grade 3 event, 52 patients (11.1%) received treatment with a phosphate binder and 32 patients (6.8%) received treatment with more than one phosphate binder. Median time to resolution to <Grade 3 was 7 days for patients receiving one or >1 phosphate binder. Similarly, median time to resolution to <Grade 2 was 8 days for both patient groups.

Overall incidence rate trends were generally similar between SDG1 and SDG2 populations.

The reported events were non-serious and manageable by standard phosphate lowering therapy, temporary dose interruptions and/or dose reductions. In SDG1 population, dose reduction occurred in 26 patients (17.9%), of whose in 20 patients (13.8%) due to ≥Grade 3 event, and dose interruption in 27 patients (18.6%), of whose in 21 patients (14.5%) due to ≥Grade 3 event. In SDG2 population, dose reduction occurred in 41 patients (12.9%), of whose in 27 patients (8.5%) due to ≥Grade 3 event, and dose interruption in 67 patients (21.1%), of whose in 46 patients (14.5%) due to ≥Grade 3 event. All events in both patient safety populations (i.e. SDG1 and SDG2) resolved and no patient discontinued study treatment due to the event of hyperphosphataemia.

Unlike in animal models, soft tissue mineralisation/calcification was not observed in the clinical studies with futibatinib or pan-FGFR inhibitors (Hierro, 2015). No significant undesirable clinical outcomes associated with hyperphosphatemia were observed in the clinical development programme for futibatinib.

Considering the routine risk minimisation measures in place for this risk (i.e. monitoring of phosphate levels, management with phosphate-lowering therapy, dose modifications in response to phosphate levels), representing a standard clinical practice in the EU for hyperphosphataemia, the well-established nature of hyperphosphataemia associated with FGFR inhibitors (Goyal, 2021) and the lack of clinically significant undesirable outcomes associated with hyperphosphataemia, this risk does not represent an important risk of futibatinib, requiring

additional pharmacovigilance and/or risk minimisation activities, and will continue to be monitored via routine pharmacovigilance.

- **Risks with minimal clinical impact on patients (in relation to the severity of the indication treated):**

Identified Risk: Nail Toxicities

Nail toxicities are considered an off-target adverse events of FGFR inhibition and have been associated with the treatment with FGFR inhibitors, especially with increased duration of treatment. The events observed include onycholysis, paronychia or less frequent nail discoloration, nail disorder, nail dystrophy, nail hypertrophy, nail infection, and onychalgia (Goyal, 2021; Lacouture, 2021).

Mild to moderate nail toxicity was observed in the clinical development programme for futibatinib. None of the reported events was assessed as serious.

In the **SDG1 population** (N=145), 64 patients (44.1%) experienced an event of nail toxicity, all but 1 of which were assessed as treatment-related by the investigator. Only 2 patients (1.4%) experienced Grade 3 event of nail toxicity (onychomadesis and paronychia occurring in 1 patient [0.7%] each). There were no Grade 4 or Grade 5 events.

In the **SDG2 population** (N=469), 127 patients (27.1%) experienced an event of nail toxicity, the majority of which (123 patients; 26.2%) were assessed as treatment-related by the investigator. Among patients who received 20 mg futibatinib in the SDG2 population (N=318), 94 patients (29.6%) experienced an event of nail toxicity. Most of these (91 patients; 28.6%) were assessed as treatment-related by the investigator. There were only 4 patients (1.3%) with a ≥Grade 3 event and no Grade 4 or Grade 5 events were reported.

Overall incidence rate trends in the SDG2 population were generally similar to or lower than those described for the SDG1 population.

Dose reductions and interruptions associated with nail toxicity were infrequent and only one patient (0.3%) discontinued study treatment due to the event of nail toxicity. No patient in the SDG1 population discontinued the treatment due to nail toxicity.

Considering the nature of this risk in the context of the intended target population, this risk is not considered important and will continue to be monitored via routine pharmacovigilance.

Identified Risk: Palmar-Plantar Erythrodysaesthesia Syndrome

Palmar-plantar erythrodysaesthesia syndrome (PPES) often presents as a mild to moderate cutaneous oedema, erythema, and hyperkeratosis with FGFR inhibitors that can impact patients' quality of life and can limit daily functioning and lead to a reduction of the duration and intensity of treatment or its discontinuation. The pathophysiological mechanisms behind these adverse events are not yet fully elucidated (Lacouture, 2021).

In the **SDG1 population** (N=145), 33 patients (22.8%) experienced an event of PPES, all but 1 of which were assessed as treatment-related by the investigator. Eight patients (5.5%) experienced Grade 3 event and there were no Grade 4 or Grade 5 events.

In the **SDG2 population** (N=469), 62 patients (13.2%) experienced an event of PPES, all but 2 of which were assessed as treatment-related by the investigator. Among patients who received 20 mg futibatinib in the SDG2 population (N=318), 48 patients (15.1%) experienced an event of PPES and all but 1 of which were assessed as treatment-related by the investigator. There were 11 patients (3.5%) with a Grade 3 event and no Grade 4 or Grade 5 events were reported.

Overall incidence rate trends in the SDG2 population were slightly lower than those described for the SDG1 population.

Dose reduction occurred in 18 patients (5.7%) in the 20-mg QD futibatinib SDG2 subpopulation (N=318). Of these, 7 patients (2.2%) had a dose reduced due to Grade 3 event. The event of PPES resulted in dose interruption in 15 patients (4.7%). Of these, 7 patients (2.2%) had a dose interruption due to ≥Grade 3 event. No patients discontinued study treatment due to the event of PPES.

Considering the nature of this risk in the context of the intended target population, this risk is not considered important and will continue to be monitored via routine pharmacovigilance.

Potential Risk: Gastrointestinal Toxicity (Diarrhoea, Nausea, Dry Mouth, Stomatitis, and Constipation)

Various gastrointestinal adverse effects have been observed in association with FGFR inhibitors and their frequency depended on the selectivity of FGFR inhibitor (Mahipal, 2020).

In the **SDG1 population** (N=145), 126 patients (86.9%) experienced an event of gastrointestinal disorder and 31 of these patients (21.4%) experienced ≥Grade 3 event. The most frequently occurring events were constipation (37.2%), diarrhoea (33.8%), dry mouth (31.0%), and nausea (28.3%).

Of the reported events, 100 patients (69.0%) experienced event assessed as related to study treatment by the investigator. The most frequently occurring treatment-related events were dry mouth (27.6%), diarrhoea (25.5%), and stomatitis (22.1%). Additional treatment-related events that occurred in >15% of patients included constipation (15.9%) and nausea (15.2%).

The nature and characteristics of the events in 382 patients (81.4%) who experienced an event of gastrointestinal disorder in the **SDG2 population** (N=469) and in 260 patients (81.8%) in the subpopulation who received 20-mg QD (N=318) was generally similar to that observed in the SDG1 population.

Dose modifications and discontinuations were infrequent. Twenty-eight patients (19.3%) in the SDG1 population and 69 patients (14.7%) in the SDG2 population required dose modification in response to gastrointestinal events, including nausea, stomatitis, and vomiting. Three patients (2.1%) in the SDG1 population and 9 patients (1.9%) in the SDG2 population discontinued treatment due to the gastrointestinal event. In the SDG1 population, 2 patients discontinued due to stomatitis and 1 patient each due to oesophageal ulcer, oesophagitis, and oral synaesthesia. In the SDG2 population, 2 patients each discontinued treatment due to diarrhoea, nausea, stomatitis, and vomiting, and 1 patient each due to duodenal obstruction, gastrointestinal haemorrhage, intestinal obstruction, oesophageal ulcer, oesophagitis, and oral synaesthesia.

Considering the nature of this risk in the context of the intended target population, this risk is not considered important and will continue to be monitored via routine pharmacovigilance.

Potential Risk: Hepatotoxicity

Mainly asymptomatic hepatic enzyme elevations were observed in the clinical development programme for futibatinib.

In the **SDG1 population** (N=145), 42 patients (29.0%) experienced an event of hepatotoxicity (Table 6), of which in 30 patients (20.7%) were assessed as treatment-related by the investigator (AST increased reported in 28 patients [19.3%], ALT increased in 22 patients [15.2%], and gamma-glutamyltransferase increased in 1 patient [0.7%]). Eighteen patients (12.4%) experienced at least one ≥Grade 3 event (assessed as treatment-related in 12 patients [8.3%]). One patient (0.7%) experienced a Grade 5 event of hepatic failure due to disease progression. This event was assessed as not related to study treatment by the investigator.

In the **SDG2 population** (N=469), 126 patients (26.9%) experienced the event of hepatoxicity, of which in 93 patients (19.8%) being assessed as treatment-related by the investigator (AST increased in 79 patients [16.8%], ALT increased in 77 patients [16.4%], and gamma-glutamyltransferase increased in 4 patients [0.9%]). Among patients who received 20 mg futibatinib in the SDG2 population (N=318), 94 patients (29.6%) experienced an event of hepatotoxicity (Table 6). Most of these events (74 patients; 23.3%) were assessed as treatment-related by the investigator. There were 38 patients (11.9%) with a ≥Grade 3 event, including two Grade 5 events of hepatic failure (0.6%), both considered not related to study treatment.

Overall incidence rate trends were generally similar between SDG1 and SDG2 populations (Table 6).

Table 6: Treatment-Emergent Adverse Events of Hepatic Disorders (Safety Data Group 1 and Safety Data Group 2)

Adverse Event (in Preferred Term)	Safety Data Group 1 (iCCA)		Safety Data Group 2 (Any Tumour 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 %)
Hepatic Disorders	**42 (29.0)**	**18 (12.4)**	**94 (29.6)**	**38 (11.9)**	**126 (26.9)**	**50 (10.7)**
Alanine aminotransferase increased	28 (19.3)	9 (6.2)	72 (22.6)	25 (7.9)	96 (20.5)	30 (6.4)
Aspartate aminotransferase increased	39 (26.9)	13 (9.0)	83 (26.1)	22 (6.9)	108 (23.0)	28 (6.0)
Bilirubin conjugated increased	1 (0.7)	0	3 (0.9)	0	3 (0.6)	0
Gamma-glutamyltransferase increased	3 (2.1)	2 (1.4)	8 (2.5)	3 (0.9)	11 (2.3)	6 (1.3)
Hepatic failure	1 (0.7)	1 (0.7)	2 (0.6)	2 (0.6)	4 (0.9)	4 (0.9)

Table 6: Treatment-Emergent Adverse Events of Hepatic Disorders (Safety Data Group 1 and Safety Data Group 2)

Adverse Event (in Preferred Term)	Safety Data Group 1 (iCCA)		Safety Data Group 2 (Any Tumour 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 %)
Transaminases increased	N/A	N/A	1 (0.3)	0	1 (0.2)	0

Source: ISS Table 14.3.2.5.2.1 and Table 14.3.2.5.2.2
Abbreviations: iCCA=intrahepatic cholangiocarcinoma; n=number of patients with at least 1 event; N=number of patients in treatment group; N/A=not applicable; QD=once daily

Dose modifications and discontinuations were infrequent. Dose reduction resulting from the event of hepatotoxicity was reported in 9 patients (6.2%) in the SDG1 population (in 7 patients [4.8%] due to ≥Grade 3 event) and 21 patients (6.6%) in the SDG2 population (in 16 patients [5.0%] due to ≥Grade 3 event).

Dose interruption was reported in 14 patients (9.7%) in the SDG1 population (in 12 patients [8.3%] due to ≥Grade 3 event) and 29 patients (9.1%) in the SDG2 population (in 21 patients [6.6%] due to ≥Grade 3 event).

No patient discontinued study treatment due to any hepatic event.

Overall, the majority of hepatic adverse events were Grade 1 and Grade 2 in severity and resolved. No Grade 5 event was assessed as related to futibatinib. Hepatic adverse events in patients treated with futibatinib were reversible and manageable with or without dose interruption and dose reduction. No event led to study treatment discontinuation. No events met the criteria for Hy's law.

Majority of reported events had confounding factors for the hepatic events, including concomitant medications and underlying disease.

Considering the nature of this risk in the context of the intended target population, this risk is not considered important and will continue to be monitored via routine pharmacovigilance.

SVII.1.2 Risks Considered Important for Inclusion in the List of Safety Concerns in the RMP

Important Identified Risk(s):

- **Serous Retinal Detachment**

  Risk-Benefit Impact: Retinal toxicities, including central serous retinopathy and serous retinal detachment, represent class effects of mitogen-activated protein kinase (MEK) inhibitors (Francis, 2017; Urner-Bloch, 2016; Weber, 2016). FGFR acts upstream of the MEK kinase in the FGF-mitogen-activated protein kinase (MAPK) pathway and as such, FGFR inhibition leads to inhibition of the MAPK pathway and development of ocular toxicities (van der Noll, 2013). However, since FGFR inhibition has a much broader range

of molecular downstream signalling pathways affected, the nature of retinal toxicities associated with FGFR inhibitors may differ.

Ocular toxicities were observed in clinical trials with various FGFR inhibitors (Alekseev, 2021; Goyal, 2021; Morales-Barrera, 2020), including the clinical development programme for futibatinib where Grade 1 and Grade 2 events associated with retinal toxicities occurred in 6.2% of iCCA patients, none of which reporting serious event and all but one assessed as related to futibatinib. All events resolved or improved with dose interruptions and dose reductions. Considering the limited information available for this risk and the lack of data on the long-term outcomes, this risk is considered important.

Important Potential Risk(s):

- **Embryo-Foetal Toxicity/Teratogenicity**

  Risk-benefit impact: The FGFR signalling axis is fundamental for embryonic development and the nonclinical studies in rats confirmed the futibatinib's potential for embryofoetal toxicity. In the absence of comprehensive clinical data, the actual impact on pregnancy or foetal development is unknown, however, the impact on the benefit-risk of the product is significant, albeit acceptable in the intended target population.

Missing Information:

- None

SVII.2 New Safety Concerns and Reclassification with a Submission of an Updated RMP

Not applicable.

SVII.3 Details of Important Identified Risks, Important Potential Risks, and Missing Information

SVII.3.1 Presentation of Important Identified Risks and Important Potential Risks

Important Identified Risk 1: Serous Retinal Detachment

Potential Mechanism(s):

FGFR inhibition leads to the blockage of the MAPK pathway and adverse ocular events, including central serous retinopathy, are known class effects of inhibitors of MAPK pathways.

Since FGFR inhibition has a much broader range of molecular downstream signalling pathways affected, clinically meaningful differences between the ocular adverse effects of FGFR inhibitors and MEK inhibitors are expected (Alekseev, 2021).

Evidence Source(s) and Strength of Evidence:

Retinal toxicities, including central serous retinopathy and serous retinal detachment, represent class effects of MEK inhibitors (Francis, 2017; Urner-Bloch, 2016; Weber, 2016). FGFR acts upstream of the MEK kinase in the FGF-MAPK pathway and as such, FGFR inhibition leads to inhibition of the MAPK pathway and development of ocular toxicities (van der Noll, 2013).

Ocular toxicities were observed in clinical trials with various FGFR inhibitors (Alekseev, 2021; Goyal, 2021; Morales-Barrera, 2020), including the clinical development programme for futibatinib where Grade 1 and Grade 2 events associated with retinal toxicities occurred in 6.2% of iCCA patients.

Characterisation of the Risk:

Frequency, Severity and Nature of the Risk (Including Reversibility and Long-Term Outcomes)

During the conduct of the clinical development programme, there was no routine monitoring, to detect asymptomatic serous retinal detachment. Therefore, the incidence of asymptomatic serous retinal detachment with futibatinib is unknown.

- **Safety Data Group 1 (N=145)**

Nine patients (6.2%) experienced the event associated with retinal toxicities[2], all but one assessed as related to treatment by the investigator. All reported events were non-serious.

The most commonly reported events regardless of causality were subretinal fluid (3 patients; 2.1%) and chorioretinopathy (2 patients; 1.4%). The remaining events occurs in a single patient each. An overview of reported events in provided in Table 7.

No ≥Grade 3 event associated with retinal toxicities was reported.

Median time to onset of the event of any grade was 43.0 days. Three patients (2.1%) had ≥Grade 2 events, all of which resolved to <Grade 2 with the median time to resolution to of 25 days. All events resolved or improved with dose interruptions and dose reductions.

Dose reduction occurred in 3 patients (2.1%). Dose interruption occurred in in 3 patients (2.1%). These dose modifications concerned Grade 2 events of chorioretinopathy, detachment of retinal pigment epithelium, and subretinal fluid (reported 1 patient each [0.7%]). No patients discontinued study treatment due to the event of retinal toxicities.

- **Safety Data Group 2 (N=469)**

Thirty-eight patients (8.1%) experienced the event associated with retinal toxicities, most of which (36 patients; 7.7%) were assessed as treatment-related by the investigator. Only 1 patient (0.2%) in the 20 mg group had a serious event of retinal detachment. This Grade 2 event was assessed as related to study treatment by the investigator.

[2] Retinal disorders include the following MedDRA PTs (version 22.0): Retinal detachment, Retinal disorder, Chorioretinopathy, Detachment of retinal pigment epithelium, Detachment of macular retinal pigment epithelium, Maculopathy, Serous retinal detachment, Macular oedema, Retinal oedema, Retinopathy, Retinal thickening, and Subretinal fluid.

Among patients who received 20 mg futibatinib in the SDG2 population (N=318), 27 patients (8.5%) experienced the event of retinal toxicity. Most of these events (25 patients; 7.9%) were assessed as treatment-related by the investigator. No ≥Grade 3 events were reported (Table 7).

Overall incidence rate trends in the SDG2 population were generally similar to those described for the SDG1 population (Table 7).

Median time to onset of the event of any grade among patients who received 20 mg QD futibatinib was 40.0 days. Six patients (1.9%) had ≥Grade 2 events, all of which resolved to <Grade 2 with the median time to resolution to of 23 days. All events resolved or improved with dose interruptions and dose reductions.

Dose reduction occurred in 5 patients (1.6%). Dose interruption occurred in 4 patients (1.3%). Dose modifications concerned Grade 2 events of retinal detachment (3 patients [0.6%]), chorioretinopathy, detachment of retinal pigment epithelium, and subretinal fluid (1 patient each [0.2%]), and a Grade 1 event of retinal detachment (1 patient [0.2%]).

One patient (0.3%) discontinued study treatment due to Grade 2 retinal detachment.

Table 7: Treatment-Emergent Adverse Events of Retinal Disorders (Safety Data Group 1 and Safety Data Group 2)

Adverse Event (in Preferred Term)	Safety Data Group 1 (iCCA)		Safety Data Group 2 (Any Tumour Type)			
	20mg QD (N=145)		20 mg QD (N=318)		Any Dosing (N=469)	
	Total (n %)	≥Grade 3 (n %)	Total (n %)	≥Grade 3 (n %)	Total (n %)	≥Grade 3 (n %)
Retinal Disorders [a]	**9 (6.2)**	**0**	**27 (8.5)**	**0**	**38 (8.1)**	**0**
Chorioretinopathy	2 (1.4)	0	3 (0.9)	0	5 (1.1)	0
Detachment of retinal pigment epithelium	1 (0.7)	0	2 (0.6)	0	3 (0.6)	0
Macular oedema	1 (0.7)	0	3 (0.9)	0	3 (0.6)	0
Maculopathy	1 (0.7)	0	1 (0.3)	0	1 (0.2)	0
Retinal detachment	N/A	N/A	4 (1.3)	0	4 (0.9)	0
Retinopathy	N/A	N/A	1 (0.3)	0	1 (0.2)	0
Serous retinal detachment	1 (0.7)	0	5 (1.6)	0	13 (2.8)	0
Subretinal fluid	3 (2.1)	0	8 (2.5)	0	8 (1.7)	0

Source: ISS Table 14.3.2.5.2.1 and Table 14.3.2.5.2.2

[a] Retinal disorders included the following MedDRA preferred terms (version 22.0): Retinal detachment, Retinal disorder, Chorioretinopathy, Detachment of retinal pigment epithelium, Detachment of macular retinal pigment epithelium, Maculopathy, Serous retinal detachment, Macular oedema, Retinal oedema, Retinopathy, Retinal thickening, and Subretinal fluid.

Abbreviations: 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

The long-term outcomes of retinal toxicities associated with futibatinib have not yet been established.

Impact on Quality of Life

Retinal toxicities such as serous retinal detachment can cause symptoms such as blurred vision, visual floaters, or photopsia that are generally mild (Goyal, 2021). There is not enough experience with FGFR-related retinal toxicities; however, multifocal subretinal fluid in MEK retinopathy is typically transient and non-vision-threatening (Alekseev, 2021).

Despite often being mild and non-serious, ocular adverse effects have an impact on daily life in affected patients.

Risk Factors and Risk Groups:

The specific risk factors and risk groups have not yet been established for futibatinib.

Preventability:

No preventive measures have yet been established for futibatinib. Careful consideration should be taken with patients that have clinically significant medical eye disorders, such as retinal disorders, including but not limited to, central serous retinopathy, macular/retinal degeneration, diabetic retinopathy, and previous retinal detachment.

Ophthalmological examination should be performed prior to initiation of therapy, 6 weeks thereafter, and urgently at any time for visual symptoms. For serous retinal detachment reactions, the following dose modification guidelines should be followed:

- If an asymptomatic serous retinal detachment occurs that is stable on serial examination, futibatinib should be continued at current dose. Monitoring described above should be performed.
- If a moderate decrease in visual acuity occurs (defined as best corrected visual acuity 20/40 or better or ≤ 3 lines of decreased vision from baseline), limiting instrumental activities of daily living, futibatinib should be withheld until resolution. If improved on subsequent examination, futibatinib should be resumed at the next lower dose level. If it recurs, symptoms persist or examination does not improve, permanent discontinuation of futibatinib should be considered based on the clinical status.
- If a marked decrease in visual acuity occurs (defined as best corrected visual acuity worse than 20/40 or > 3 lines decreased vision from baseline up to 20/200), limiting activities of daily living, futibatinib should be withheld until resolution. If improved on subsequent examination, futibatinib may be resumed at 2 dose levels lower. If it recurs, symptoms persist or examination does not improve, permanent discontinuation of futibatinib should be considered, based on clinical status.
- If a visual acuity worse than 20/200 occurs in affected eye, limiting activities of daily living, futibatinib should be withheld until resolution. If improved on subsequent examination, futibatinib may be resumed at 2 dose levels lower. If it recurs, symptoms persist or examination does not improve, permanent discontinuation of futibatinib.

Impact on the Risk-Benefit Balance of the Product:

Ocular toxicities were observed in clinical trials with various FGFR inhibitors (Alekseev, 2021; Goyal, 2021; Morales-Barrera, 2020), including the clinical development programme for futibatinib, where Grade 1 and Grade 2 events associated with retinal toxicities occurred in

6.2% of iCCA patients, none of which reporting serious event and all but one assessed as related to futibatinib. All events resolved or improved with dose interruptions and dose reductions. Considering the limited information available for this risk and the lack of data on the long-term outcomes, this risk is considered important.

Public Health Impact:

Not yet established for futibatinib.

Important Potential Risk 1: Embryo-Foetal Toxicity/Teratogenicity

Potential Mechanism(s):

Teratogenic effects of futibatinib are potentially a consequence of its mechanism of action, causing FGFR inhibition as the FGFR signalling axis is fundamental for embryonic development (Turner, 2010).

Evidence Source(s) and Strength of Evidence:

Teratogenicity may potentially be linked directly to the mechanism of futibatinib action since the FGFR signalling axis is fundamental for embryonic development (Turner, 2010). The nonclinical development programme showed reproductive toxicity associated with futibatinib in the rat, where visceral and skeletal abnormalities were observed (refer to PART II: Module SII).

The clinical relevance of these findings is unclear since there is no experience with the use of futibatinib during pregnancy. However, embryotoxicity/teratogenicity was reported in association with many tyrosine kinase inhibitors (Abruzzese, 2014), including FGFR inhibitors (e.g. erdafitinib).

Characterisation of the Risk:

Frequency, Severity and Nature of the Risk (Including Reversibility and Long-Term Outcomes)

Not yet established for futibatinib.

There were no cases of pregnancy reported from the clinical development programme for futibatinib.

Impact on Quality of Life

In general, teratogenic effects represent a significant complication of pregnancy with marked impact on both the mother and the foetus/child (Abruzzese, 2014).

The experience with tyrosine kinase inhibitors-exposed pregnancies, which completed to term, showed severe malformations in the newborns leading in some cases to premature death (Abruzzese, 2014).

Risk Factors and Risk Groups:

Any women of childbearing potential who receives futibatinib or whose partner receives futibatinib are at risk of embryo-foetal toxicity associated with futibatinib.

Preventability:

Pregnant women should be advised of the potential risk to the foetus. Futibatinib should not be used during pregnancy unless the potential benefit for the women justifies the potential risk to the foetus. A pregnancy test should be performed before treatment initiation to exclude pregnancy.

Women of childbearing potential should be advised to use effective contraception during treatment with futibatinib and for 1 week after the last dose. Since the effect of futibatinib on the metabolism and efficacy of contraceptives has not been investigated, barrier methods should be applied as a second form of contraception, to avoid pregnancy.

Male patients with female partners of childbearing potential should be advised to use effective contraception during treatment with futibatinib and for at least 1 week after the last dose.

Impact on the Risk-Benefit Balance of the Product:

The FGFR signalling axis is fundamental for embryonic development and the nonclinical studies in rats confirmed the futibatinib's potential for embryo-foetal toxicity. In the absence of comprehensive clinical data, the actual impact on pregnancy or foetal development is unknown, however, the impact on the benefit-risk of the product is significant, albeit acceptable in the intended target population.

Public Health Impact:

Not yet established for futibatinib.

SVII.3.2 Presentation of Missing Information

None.

PART II: Module SVIII - Summary of safety concerns

Table 8: Summary of Safety Concerns

Important Identified Risks	Serous retinal detachment
Important Potential Risks	Embryo-foetal toxicity/teratogenicity
Missing Information	None

PART III: Pharmacovigilance Plan (Including Post-Authorisation Safety Studies)

III.1 Routine Pharmacovigilance Activities

The pharmacovigilance plan does not include any routine pharmacovigilance activities beyond signal management and reporting of adverse reactions.

III.2 Additional Pharmacovigilance Activities

The pharmacovigilance plan does not include any additional pharmacovigilance activities.

III.3 Summary Table of Additional Pharmacovigilance Activities

Not applicable.

PART IV: Plans for Post-Authorisation Efficacy Studies

Table 9: Planned and Ongoing Post-Authorisation Efficacy Studies

Study **Status**	**Summary of Objectives**	**Efficacy Uncertainties Addressed**	**Milestones**	**Due Date**
Efficacy Studies Which Are Specific Obligations in the Context of a Conditional Marketing Authorisation or a Marketing Authorisation Under Exceptional Circumstances				
"Phase 2 Study of Futibatinib 20 mg and 16 mg in Patients with Advanced Cholangiocarcinoma with *FGFR2* Fusions or Rearrangements" (TAS-120-205) Planned	Primary: • To assess the efficacy of futibatinib administered at 20 mg and 16 mg QD to verify and describe the clinical benefit Secondary: • To evaluate further efficacy parameters of futibatinib administered at 20 mg and 16 mg QD • To evaluate the safety and tolerability of futibatinib administered at 20 mg and 16 mg QD • To evaluate PROs	To confirm the positive benefit-risk balance of futibatinib at a starting dose of 20 mg QD in adult patients with locally advanced or metastatic cholangiocarcinoma with FGFR2 fusions or rearrangements that has progressed after at least one prior line of systemic therapy	Final clinical study report submission	October 2027

Abbreviations: FGF=Fibroblast Growth Factor; FGFR=Fibroblast Growth Factor Receptor; PK=pharmacokinetic; PRO = Patient Reported Outcome; QD=once daily.

PART V: Risk Minimisation Measures (Including Evaluation of the Effectiveness of Risk Minimisation Activities)

Risk Minimisation Plan

V.1 Routine Risk Minimisation Measures

Table 10: Description of Routine Risk Minimisation Measures by Safety Concern

Safety Concern	Routine Risk Minimisation Activities
Serous retinal detachment	**Routine Risk Communication:** SmPC sections 4.2, 4.4, and 4.8 PL sections 2 and 4 **Routine Risk Minimisation Activities Recommending Specific Clinical Measures to Address the Risk:** 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. **Other Routine Risk Minimisation Measures Beyond the Product Information:** Subject to restricted medical prescription
Embryo-foetal toxicity/teratogenicity	**Routine Risk Communication:** SmPC sections 4.4, 4.6, and 5.3 PL section 2 **Routine Risk Minimisation Activities Recommending Specific Clinical Measures to Address the Risk:** 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. **Other Routine Risk Minimisation Measures Beyond the Product Information:** Subject to restricted medical prescription

Abbreviations: PL=package leaflet; SmPC=summary of product characteristics.

V.2 Additional Risk Minimisation Measures

Routine risk minimisation activities as described in Part V.1 are sufficient to manage the safety concerns of the medicinal product.

V.3 Summary of Risk Minimisation Measures

Table 11: Summary Table of Pharmacovigilance Activities and Risk Minimisation Activities by Safety Concern

Safety Concern	Risk Minimisation Measures	Pharmacovigilance Activities
Serous retinal detachment	**Routine Risk Minimisation Measures:** – SmPC sections 4.2, 4.4, and 4.8	**Routine Pharmacovigilance Activities Beyond Signal Detection and Adverse Reactions Reporting:**

Table 11: Summary Table of Pharmacovigilance Activities and Risk Minimisation Activities by Safety Concern

Safety Concern	Risk Minimisation Measures	Pharmacovigilance Activities
	– 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	None **Additional Pharmacovigilance Activities:** 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	**Routine Pharmacovigilance Activities Beyond Signal Detection and Adverse Reactions Reporting:** None **Additional Pharmacovigilance Activities:** None

Abbreviations: PL=package leaflet; SmPC=summary of product characteristics.

PART VI: Summary of the risk management plan

Summary of risk management plan for Lytgobi (futibatinib)

This is a summary of the risk management plan (RMP) for Lytgobi. The RMP details important risks of Lytgobi, how these risks can be minimised, and how more information will be obtained about Lytgobi's risks and uncertainties (missing information).

Lytgobi's summary of product characteristics (SmPC) and its package leaflet give essential information to healthcare professionals and patients on how Lytgobi should be used.

This summary of the RMP for Lytgobi should be read in the context of all this information including the assessment report of the evaluation and its plain-language summary, all which is part of the European Public Assessment Report (EPAR).

Important new concerns or changes to the current ones will be included in updates of Lytgobi's RMP.

I. The medicine and what it is used for

Lytgobi is authorised for treatment of adult patients with locally advanced or metastatic cholangiocarcinoma (CCA) with a fibroblast growth factor receptor 2 (FGFR2) fusion or rearrangement (see SmPC for the full indication). It contains futibatinib as the active substance and it is given by oral route of administration.

Further information about the evaluation of Lytgobi's benefits can be found in Lytgobi's EPAR, including in its plain-language summary, available on the EMA website, under the medicine's webpage.

II. Risks associated with the medicine and activities to minimise or further characterise the risks

Important risks of Lytgobi, together with measures to minimise such risks and the proposed studies for learning more about Lytogobi's risks, are outlined below.

Measures to minimise the risks identified for medicinal products can be:

- Specific information, such as warnings, precautions, and advice on correct use, in the package leaflet and SmPC addressed to patients and healthcare professionals;
- Important advice on the medicine's packaging;
- The authorised pack size — the amount of medicine in a pack is chosen so to ensure that the medicine is used correctly;
- The medicine's legal status — the way a medicine is supplied to the patient (e.g. with or without prescription) can help to minimise its risks.

Together, these measures constitute *routine risk minimisation* measures.

In addition to these measures, information about adverse reactions is collected continuously and regularly analysed, including PSUR assessment so that immediate action can be taken as necessary. These measures constitute *routine pharmacovigilance* activities.

If important information that may affect the safe use of Lytgobi is not yet available, it is listed under 'missing information' below.

II.A List of important risks and missing information

Important risks of Lytgobi are risks that need special risk management activities to further investigate or minimise the risk, so that the medicinal product can be safely taken. Important risks can be

regarded as identified or potential. Identified risks are concerns for which there is sufficient proof of a link with the use of Lytgobi. Potential risks are concerns for which an association with the use of this medicine is possible based on available data, but this association has not been established yet and needs further evaluation. Missing information refers to information on the safety of the medicinal product that is currently missing and needs to be collected (e.g. on the long-term use of the medicine).

List of important risks and missing information	
Important identified risks	Serous retinal detachment
Important potential risks	Embryo-foetal toxicity/teratogenicity
Missing information	None

II.B Summary of important risks

Identified risk: Serous retinal detachment	
Evidence for linking the risk to the medicine	Retinal toxicities, including central serous retinopathy and serous retinal detachment, represent class effects of MEK inhibitors (Francis, 2017; Urner-Bloch, 2016; Weber, 2016). FGFR acts upstream of the MEK kinase in the FGF-MAPK pathway and as such, FGFR inhibition leads to inhibition of the MAPK pathway and development of ocular toxicities (van der Noll, 2013). Ocular toxicities were observed in clinical trials with various FGFR inhibitors (Alekseev, 2021; Goyal, 2021; Morales-Barrera, 2020), including the clinical development programme for futibatinib where Grade 1 and Grade 2 events of central serous retinopathy associated with retinal toxicities occurred in 6.2% of iCCA patients.
Risk factors and risk groups	The specific risk factors and risk groups have not yet been established for futibatinib.
Risk minimisation measures	**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

References: Alekseev O, Ojuok E, Cousins S. Multifocal serous retinopathy with pemigatinib therapy for metastatic colon adenocarcinoma. Int J Retina Vitreous 2021, 7(1): 34.
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Weber ML, Liang MC, Flaherty KT, Heier JS. Subretinal Fluid Associated With MEK Inhibitor Use in the Treatment of Systemic Cancer. JAMA Ophthalmol 2016, 134(8): 855-62.
Abbreviations: FGF=fibroblast growth factor; FGFR=fibroblast growth factor receptor; iCCA=intrahepatic cholangiocarcinoma; MAPK=mitogen activated protein kinase; MEK=mitogen activated protein kinase; PL=package leaflet; SmPC=summary of product characteristics.

Potential risk: Embryo-foetal toxicity/teratogenicity	
Evidence for linking the risk to the medicine	Teratogenicity seems directly linked to the mechanism of futibatinib action since FGFR signalling axis is fundamental for embryonic development (Turner, 2010). The nonclinical development programme showed reproductive toxicity associated with futibatinib in the rat, where visceral and skeletal abnormalities were observed. The clinical relevance of these findings is unclear since there is no experience with the use of futibatinib during pregnancy. However, embryotoxicity/teratogenicity was reported in association with many tyrosine kinase inhibitors (Abruzzese, 2014), including FGFR inhibitors (e.g. erdafitinib).
Risk factors and risk groups	Any women of childbearing potential who receives futibatinib or whose partner receives futibatinib are at risk of embryo-foetal toxicity associated with futibatinib.
Risk minimisation measures	**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

References: Abruzzese E, Trawinska MM, Perrotti AP, De Fabritiis P. Tyrosine kinase inhibitors and pregnancy. J Cereb Blood Flow Metab 2014, 6(1): e2014028.
Turner N, Grose R. Fibroblast growth factor signalling: from development to cancer. Nat Rev Cancer 2010, 10(2): 116-29.
Abbreviations: FGFR=fibroblast growth factor receptor; PL=package leaflet; SmPC=summary of product characteristics.

II.C Post-authorisation development plan

II.C.1 Studies which are conditions of the marketing authorisation

The following study is specific obligation of Lytgobi:

Study TAS-120-205

Purpose of the study:

- Primary objective:
  - To assess the efficacy of futibatinib administered at 20 mg and 16 mg once daily (QD) to verify and describe the clinical benefit
- Secondary objective(s):

- To evaluate further efficacy parameters of futibatinib administered at 20 mg and 16 mg QD
- To evaluate the safety and tolerability of futibatinib administered at 20 mg and 16 mg QD
- To evaluate Patient Reported Outcomes

II.C.2 Other studies in post-authorisation development plan

There are no studies required for Lytgobi.

PART VII: Annexes

Annex 1 - EudraVigilance Interface

Not applicable.

Annex 2 - Tabulated Summary of Planned, Ongoing, and Completed Pharmacovigilance Study Programme

Not applicable.

Annex 3 - Protocols for Proposed, Ongoing, and Completed Studies in the Pharmacovigilance Plan

Not applicable.

Annex 4 - Specific Adverse Drug Reaction Follow-Up Forms

Not applicable.

Annex 5 - Protocols for Proposed and Ongoing Studies in RMP Part IV

Study TAS-120-205 protocol

Annex 6 - Details of Proposed Additional Risk Minimisation Measures

Not applicable.

Annex 7 - Other Supporting Data (Including Referenced Material)

List of References

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Annex 8 - Summary of Changes to the Risk Management Plan Over Time

Not applicable.