ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

▼This medicinal product is subject to additional monitoring. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse reactions. See section 4.8 for how to report adverse reactions.

1. NAME OF THE MEDICINAL PRODUCT

Lytgobi 4 mg film-coated tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film-coated tablet contains 4 mg of futibatinib.

Excipient with known effect
Each film-coated tablet contains 5.4 mg lactose monohydrate.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Film-coated tablet (tablet).

Round (6 mm), white, film-coated tablet debossed on one side with “4MG” and “FBN” on the reverse.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

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.

4.2 Posology and method of administration

Lytgobi therapy should be initiated by a physician experienced in the diagnosis and treatment of patients with biliary tract cancer.

Presence of FGFR2 gene fusions or rearrangements should be confirmed by an appropriate diagnostic test prior to initiation of Lytgobi therapy.

Posology
The recommended starting dose is 20 mg futibatinib taken orally once daily.

If a dose of futibatinib is missed by more than 12 hours or vomiting occurs after taking a dose, an additional dose should not be taken, and treatment should be resumed with the next scheduled dose.

Treatment should be continued until disease progression or unacceptable toxicity.

In all patients, dietary restrictions that limit phosphate intake are recommended as part of hyperphosphatemia management. A phosphate-lowering therapy should be initiated when serum phosphate level is ≥ 5.5 mg/dL. If the serum phosphate level is > 7 mg/dL, the dose of futibatinib should be modified based on the duration and severity of hyperphosphatemia (see Table 2). Prolonged hyperphosphatemia can cause soft tissue mineralization, including cutaneous calcification, vascular

calcification, and myocardial calcification (see section 4.4).

If Lytgobi treatment is stopped or serum phosphate level falls below normal range, phosphate-lowering therapy and diet should be discontinued. Severe hypophosphatemia may present with confusion, seizures, focal neurologic findings, heart failure, respiratory failure, muscle weakness, rhabdomyolysis, and hemolytic anemia.

Dose adjustment due to drug interaction

Concomitant use of futibatinib with strong CYP3A inhibitors
Co-administration of futibatinib with strong CYP3A4 inhibitors, such as itraconazole, should be avoided (see sections 4.4 and 4.5). If this is not possible, based on careful monitoring of tolerability, a futibatinib dose reduction to the next lower level should be considered.

Concomitant use of futibatinib with strong or moderate CYP3A inducers
Co-administration of futibatinib with strong or moderate CYP3A4 inducers, such as rifampicin, should be avoided (see sections 4.4 and 4.5). If this is not possible, gradually increasing the futibatinib dose based on careful monitoring of tolerability should be considered.

Management of toxicities
Dose modifications or interruption of dosing should be considered for the management of toxicities. The recommended dose reduction levels are provided in Table 1.

Table 1: Recommended futibatinib dose reduction levels

Dose	**Dose reduction levels**	
20 mg taken orally once daily	**First**	**Second**
	16 mg taken orally once daily	12 mg taken orally once daily

Treatment should be permanently discontinued if patient is unable to tolerate 12 mg futibatinib once daily.

Dose modifications for hyperphosphatemia are provided in Table 2.

Table 2: Dose modifications for hyperphosphatemia

Adverse reaction	**Futibatinib dose modification**
Serum phosphate ≥5.5 mg/dL - ≤ 7 mg/dL	• Initiate phosphate lowering therapy and monitor serum phosphate weekly • Futibatinib should be continued at current dose
Serum phosphate >7 mg/dL - ≤ 10 mg/dL	• Initiate/intensify phosphate lowering therapy and monitor serum phosphate weekly AND • Dose reduce futibatinib to next lower dose – If the serum phosphate resolves to ≤7.0 mg/dL within 2 weeks after dose reduction, continue at this reduced dose – If serum phosphate is not ≤ 7.0 mg/dL within 2 weeks, further reduce futibatinib to the next lower dose – If serum phosphate is not ≤ 7.0 mg/dL within 2 weeks after the second dose reduction, withhold futibatinib until serum phosphate is ≤ 7.0 mg/dL and resume at the dose prior to suspending
Serum phosphate >10 mg/dL	• Initiate/intensify phosphate lowering therapy and monitor serum phosphate weekly AND • Suspend futibatinib until phosphate is ≤ 7.0 mg/dL and resume futibatinib at the next lower dose • Permanently discontinue futibatinib if serum phosphate is not ≤ 7.0 mg/dL within 2 weeks following 2 dose reductions

Dose modifications for serous retinal detachment are provided in Table 3.

Table 3: 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 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.

Dose modifications for other adverse reactions are provided in Table 4.

Table 4: Dose modifications for other adverse reactions

Other Adverse Reactions	Grade 3[a]	• Withhold futibatinib until toxicity resolves to Grade 1 or baseline, then resume futibatinib – for hematological toxicities resolving within 1 week, at the dose prior to suspending. – for other adverse reactions, at next lower dose.
	Grade 4[a]	Permanently discontinue futibatinib

[a] Severity as defined by National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE version 4.03).

Special populations

Elderly
No specific dose adjustment is required for elderly patients (≥ 65 years) (see section 5.1).

Renal impairment
Dose adjustment is not required for patients with mild and moderate renal impairment (creatinine clearance [CLcr] 30 to 89 mL/min estimated by Cockcroft-Gault). There are no data in patients with severe renal impairment (CLcr < 30 mL/min) or for patients with end-stage renal disease receiving intermittent haemodialysis and therefore no dosing recommendation can be made (see section 5.2).

Hepatic impairment
No dose adjustment is required when administering futibatinib to patients with mild (Child-Pugh class A), moderate (Child-Pugh class B), or severe (Child-Pugh class C) hepatic impairment. However, there is no safety data in patients with severe hepatic impairment. (see section 5.2).

Paediatric population
The safety and efficacy of futibatinib in children less than 18 years of age have not been established. No data are available.

Method of administration
Lytgobi is for oral use. The tablets should be taken with or without food at about the same time each day. The tablets should be swallowed whole to ensure that the full dose is administered.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

4.4 Special warnings and precautions for use

Hyperphosphatemia
Hyperphosphatemia is a pharmacodynamic effect expected with futibatinib administration (see section 5.1). Prolonged hyperphosphatemia may cause soft tissue mineralization, including cutaneous calcification, vascular calcification, and myocardial calcification, anaemia, hyperparathyroidism, and hypocalcemia that may cause muscle cramps, QT interval prolongation, and arrythmias (see section 4.2).

Recommendations for management of hyperphosphatemia include dietary phosphate restriction, administration of phosphate-lowering therapy, and dose modification when required (see section 4.2). Phosphate-lowering therapy was used by 83.4 % of patients during treatment with futibatinib (see section 4.8).

Serous retinal detachment
Futibatinib can cause serous retinal detachment, which may present with symptoms such as blurred vision, visual floaters, or photopsia (see section 4.8). This can moderately influence the ability to drive and use machines (see section 4.7)

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 dose modification guidelines should be followed (see section 4.2).

During the conduct of the clinical study, there was no routine monitoring, including optical coherence tomography (OCT), to detect asymptomatic serous retinal detachment; therefore, the incidence of asymptomatic serous retinal detachment with futibatinib is unknown.

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.

Dry eye
Futibatinib can cause dry eye (see section 4.8). Patients should use ocular demulcents, in order to prevent or treat dry eye, as needed.

Embryo-foetal toxicity
Based on the mechanism of action and findings in an animal study (see section 5.3), 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 (see section 4.6). A pregnancy test should be performed before treatment initiation to exclude pregnancy.

Combination with strong CYP3A inhibitors
Concomitant use of strong CYP3A inhibitors should be avoided because it may increase futibatinib plasma concentration (see sections 4.2 and 4.5).

Combination with strong or moderate CYP3A inducers
Concomitant use of strong or moderate CYP3A inducers should be avoided because it may decrease futibatinib plasma concentration (see sections 4.2 and 4.5).

Lactose
Lytgobi contains lactose. Patients with rare hereditary problems of galactose intolerance, total lactase deficiency or glucose-galactose malabsorption should not take this medicinal product.

Sodium
Lytgobi contains less than 1 mmol sodium (23 mg) per tablet, that is to say essentially "sodium-free".

4.5 Interaction with other medicinal products and other forms of interaction

Effects of other medicinal products on futibatinib

CYP3A inhibitors
Co-administration of multiple doses of 200 mg itraconazole, a strong CYP3A inhibitor, increased futibatinib C_{max} by 51% and AUC by 41% following a single oral dose of 20 mg futibatinib. Therefore, the concomitant use of strong CYP3A 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 (see sections 4.2 and 4.4).

CYP3A inducers
Co-administration of multiple doses of 600 mg rifampin, a strong CYP3A inducer, decreased futibatinib C_{max} by 53% and AUC by 64% following a single oral dose of 20 mg futibatinib. Therefore, the concomitant use of strong or moderate CYP3A inducers (e.g. carbamazepine, phenytoin, phenobarbital, efavirenz, rifampin) may decrease futibatinib plasma concentration and should be avoided. If this is not possible, gradually increasing the futibatinib dose based on careful monitoring of tolerability should be considered (see sections 4.2 and 4.4).

P-gp inhibitors
Co-administration of multiple doses of 200 mg quinidine, a P-gp inhibitor, increased futibatinib C_{max} by 8% and AUC_{inf} by 17% following a single oral dose of 20 mg futibatinib. Therefore, co-administration of P-gp inhibitors is not likely to have a clinically relevant effect on futibatinib exposure.

Proton pump inhibitors
Futibatinib geometric mean ratios for C_{max} and AUC were 108% and 105%, respectively, when co-administered in healthy subjects with lansoprazole (a proton pump inhibitor) relative to futibatinib alone. Therefore, co-administration of proton pump inhibitors is not likely to have a clinically relevant effect on futibatinib exposure.

Effects of futibatinib on other medicinal products

Effect of futibatinib on CYP3A substrate
Midazolam (a CYP3A sensitive substrate) geometric mean ratios for C_{max} and AUC were 95% and 91%, respectively, when co-administered in healthy subjects with futibatinib relative to midazolam alone. Therefore, co-administration of futibatinib is not likely to have a clinically relevant effect on the exposure of CYP3A substrates.

Effect of futibatinib on P-gp substrates
Digoxin (a sensitive P-gp substrate) geometric mean ratios for C_{max} and AUC_{inf} were 95% and 100%, respectively, when co-administered in healthy subjects with futibatinib relative to digoxin alone. Therefore, co-administration of futibatinib is not likely to have a clinically relevant effect on the exposure of P-gp substrates.

Effect of futibatinib on BCRP substrates
Rosuvastatin (a sensitive BCRP substrate) geometric mean ratios for C_{max} and AUC_{inf} were 110% and 113%, respectively, when co-administered in healthy subjects with futibatinib relative to rosuvastatin alone. Therefore, co-administration of futibatinib is not likely to have a clinically relevant effect on the exposure of BCRP substrates.

Effect of futibatinib on CYP1A2 substrates
In vitro studies indicate that futibatinib has the potential to induce CYP1A2. Co-administration of futibatinib with CYP1A2 sensitive substrates (e.g, olanzapine, theophylline) may decrease their exposure and therefore may affect their activity.

Hormonal contraceptives
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 4.6).

4.6 Fertility, pregnancy and lactation

Women of childbearing potential/Contraception in males and females
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. 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.

Pregnancy
There are no available data from the use of futibatinib in pregnant women. Studies in animals have shown embryo-foetal toxicity (see section 5.3). Lytgobi should not be used during pregnancy unless the potential benefit for the women justifies the potential risk to the foetus.

Breast-feeding
It is unknown whether futibatinib or its metabolites are excreted in human milk. A risk to the breast-fed newborns/infants cannot be excluded. Breast-feeding should be discontinued during treatment with Lytgobi and for 1 week after the last dose.

Fertility
There are no data on the effect of futibatinib on human fertility. Animal fertility studies have not been conducted with futibatinib (see section 5.3). Based on the pharmacology of futibatinib, impairment of male and female fertility cannot be excluded.

4.7 Effects on ability to drive and use machines

Futibatinib has moderate influence on the ability to drive and use machines. Patients should be advised to be cautious when driving or operating machines in case they experience fatigue or visual disturbances during the treatment with Lytgobi (see section 4.4).

4.8 Undesirable effects

Summary of the safety profile
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 serious adverse reactions were intestinal obstruction (1.4%) and migraine (1.4%).

Permanent discontinuation due to adverse reactions was reported in 7.6% of patients; the most common adverse reaction led to dose discontinuation was stomatitis (1.4%),all other adverse reactions were single occurrence.

Tabulated list of adverse reactions

Table 5 summarises the adverse reactions occurring in 145 patients treated in the indicated population of Study TAS-120-101. Median duration of exposure of futibatinib was 8.87 months (min: 0.5, max: 31.7). Adverse reactions are listed according to MedDRA system organ class (SOC). Frequency categories are very common (≥ 1/10) and common (≥ 1/100 to < 1/10). Within each frequency grouping, adverse reactions are presented in order of decreasing seriousness.

Table 5: Adverse reactions observed in the indicated population in TAS-120-101 study (N=145) – frequency reported by incidence of treatment emergent events

System organ class	Frequency	Adverse reactions
Metabolism and nutrition disorders	Very common	Hyperphosphatemia Decreased appetite Hyponatraemia Hypophosphataemia
Nervous system disorders	Very common	Dysgeusia
	Common	Migraine
Eye disorders	Very common	Dry eye
	Common	Serous retinal detachment[a]
Gastrointestinal disorders	Very common	Stomatitis Diarrhoea Nausea Constipation Dry mouth Vomiting Abdominal pain
	Common	Intestinal obstruction
Skin and subcutaneous tissue disorders	Very common	Palmar-plantar erythrodysaesthesia syndrome Nail disorders[b] Dry skin Alopecia
Musculoskeletal and connective tissue disorders	Very common	Myalgia Arthralgia
General disorders and administration site conditions	Very common	Fatigue
Investigations	Very common	Liver transaminases increased

[a] Includes serous retinal detachment, detachment of retinal pigment epithelium, subretinal fluid, chorioretinopathy, macular oedema, and maculopathy. See below "*Serous retinal detachment*".

[b] Includes nail toxicity, nail bed tenderness, nail disorder, nail discolouration, nail dystrophy, nail hypertrophy, nail infection, nail pigmentation, onychalgia, onychoclasis, onycholysis, onychomadesis, onychomycosis and paronychia

Description of selected adverse reactions

Hyperphosphatemia

Hyperphosphatemia was reported in 89.7% of patients treated with futibatinib and 27.6% patients had Grade 3 events, defined as serum phosphate > 7 mg/dL and ≤ 10 mg/dL irrespective of clinical symptoms. The median time to onset of hyperphosphatemia of any grade was 6.0 days (range: 3.0 to 117.0 days).

None of the reactions were Grade 4 or 5 in severity, serious, or led to discontinuation of futibatinib.

Dose interruption occurred in 18.6 % patients and reduction in 17.9 % of patients.
Hyperphosphatemia was manageable with dietary phosphate restriction and/or administration of phosphate lowering therapy and /or dose modification.

Recommendations for management of hyperphosphatemia are provided in sections 4.2 and 4.4.

Serous retinal detachment
Serous retinal detachment occurred in 6.2 % of patients treated with futibatinib. Reactions were all Grade 1 or 2 in severity. Dose interruption occurred in 2.1 % patients and reduction in 2.1 % of patients. None of the reactions led to discontinuation of futibatinib. Serous retinal detachment was generally manageable.

Recommendations for management of serous retinal detachment are provided in sections 4.2 and 4.4.

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system listed in Appendix V.

4.9 Overdose

There is no information on overdose of futibatinib.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: antineoplastic agents, protein kinase inhibitors, ATC code: L01 EN04

Mechanism of action
Constitutive fibroblast growth factor receptor (FGFR) signalling can support the proliferation and survival of malignant cells. Futibatinib is a tyrosine kinase inhibitor that irreversibly inhibits FGFR 1, 2, 3, and 4 by covalent binding. Futibatinib exhibited *in vitro* inhibitory activity against FGFR2 resistance mutations (*N550H, V565I, E566G, K660M*).

Pharmacodynamic effects

Serum phosphate
Futibatinib increased serum phosphate level as a consequence of FGFR inhibition.
Phosphate-lowering therapy and dose modifications are recommended to manage hyperphosphatemia: see sections 4.2, 4.4 and 4.8.

Clinical efficacy and safety
TAS-120-101 a multicentre, open-label, single-arm study evaluated the efficacy and safety of futibatinib in previously treated patients with unresectable locally advanced or metastatic intrahepatic cholangiocarcinoma. Patients with prior FGFR-directed therapy were excluded. The efficacy population consists of 103 patients that had progressed on or after at least 1 prior gemcitabine and platinum-based chemotherapy and had FGFR2 fusion (77.7%) or rearrangement (22.3%), as determined by tests performed at central or local laboratories.

Patients received futibatinib orally once daily at a dose of 20 mg until disease progression or unacceptable toxicity. The primary efficacy outcome measure was objective response rate (ORR) as determined by an independent review committee (IRC) according to RECIST v1.1, with duration of response (DoR) as a key secondary endpoint.

The median age was 58 years (range: 22 to 79 years), 22.3% were ≥65 years, 56.3% were female, 49.5% were Caucasian. All (100 %) patients had a baseline Eastern Cooperative Oncology Group (ECOG) performance status of 0 (46.6 %) or 1 (53.4 %). 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.

Efficacy results are summarized in Table 6. The median time to response was 2.5 months (range 0.7 – 7.4 months).

Table 6: Efficacy results

	Efficacy Evaluable Population (N = 103)
ORR (95 % CI) [a]	42% (32, 52)
Partial response (N)	42% (43)
Median duration of response (months) (95% CI)[b]	9.7 (7.6, 17.1)
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, 68.3)
12 months	37.0 (18.4, 55.7)

ORR = Complete Response + Partial Response
CI= Confidence Interval
Note: Data are from IRC per RECIST v1.1, and complete and partial responses are confirmed.
[a]The 95 % CI was calculated using the Clopper–Pearson method
[b]The 95% CI was constructed based on a log-log transformed CI for the survival function.

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. The primary analysis for DoR included censoring for new anti-cancer treatment, progressive disease or death after two or more missed tumour assessments, or at least 21 days after treatment discontinuation.

Elderly patients
In the clinical study of futibatinib, 22.3% of patients were 65 years and older. No difference in efficacy was detected between these patients and in patients < 65 years of age.

Paediatric population
The European Medicines Agency has waived the obligation to submit the results of studies with Lytgobi in all subsets of the paediatric population in the treatment of cholangiocarcinoma. See section 4.2 for information in paediatric use.

Conditional approval
This medicinal product has been authorised under a so-called ‘conditional approval’ scheme. This means that further evidence on this medicinal product is awaited. The European Medicines Agency will review new information on this medicinal product at least every year and this SmPC will be updated as necessary.

5.2 Pharmacokinetic properties

The pharmacokinetics of futibatinib were evaluated in patients with advanced cancer administered 20 mg once daily unless otherwise specified.

Futibatinib exhibits linear pharmacokinetics over the dose range of 4 to 24 mg. Steady-state was reached after the first dose with a geometric mean accumulation ratio of 1.03. The geometric mean steady-state AUC_{ss} was 790 ng·h/mL (44.7% gCV) and $C_{max,ss}$ was 144 ng/mL (50.3% gCV) at the recommended dosage of 20 mg once daily.

Absorption
Median time to achieve peak plasma concentration (t_{max}) was 2 (range: 1.2 to 22.8) hours.

No clinically meaningful differences in futibatinib pharmacokinetics were observed following administration of a high-fat and high-calorie meal (900 calories to 1000 calories with approximately 50% of total caloric content of the meal from fat) in healthy subjects.

Distribution
Futibatinib is approximately 95% bound to human plasma proteins, predominantly to albumin and α1-acid glycoprotein. The estimated apparent volume of distribution was 66.1 L (17.5%).

Biotransformation
Futibatinib is predominantly metabolised by CYP3A (40-50%) as well as glutathione conjugation (50-60%) *in vitro*. Following oral administration of a single 20 mg radiolabelled futibatinib dose in healthy adult male subjects, the main drug-related moiety in plasma was unchanged futibatinib (59.19% of the total sample radioactivity) in a human [^{14}C] mass balance study in healthy adult male subjects, followed by one inactive metabolite, a cysteinylglycine conjugate TAS-06-22952 (at >10% of dose).

Elimination
The mean elimination half-life ($t_{1/2}$) of futibatinib was 2.94 (26.5% CV) hours and the geometric mean apparent clearance (CL/F) was 19.8 L/h (23.0%).

Excretion
Following a single oral dose of 20 mg radiolabelled futibatinib in healthy adult male subjects, approximately 64% of the dose was recovered in faeces and 6% in urine. Futibatinib excretion in unchanged form was negligible in either urine or faeces.

Drug-drug interactions

Effect of futibatinib on CYP enzymes
In vitro studies indicate that futibatinib does not inhibit CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6 or CYP3A, and does not induce CYP2B6 or CYP3A4 at clinically relevant concentrations.

Effect of futibatinib on drug transporters
In vitro studies indicated that futibatinib didn't inhibit OAT1, OAT3, OCT2, OATP1B1, OATP1B3, MATE1 or MATE2K at clinically relevant concentrations. Futibatinib is a substrate of P-gp and BCRP in vitro. Inhibition of BCRP is not expected to result in clinically relevant changes in the exposure of futibatinib. Inhibition of P-gp did not result in a clinically relevant effect on futibatinib exposure in vivo (see section 4.5).

Special populations
No clinically meaningful differences in the systemic exposure (less than 25% difference in AUC) of futibatinib were observed based on age (18 - 82 years), sex, race/ethnicity, body weight (36 - 152 kg), mild to moderate renal impairment, or hepatic impairment. The effect of severe renal impairment and renal dialysis in end-stage renal disease on futibatinib exposure is unknown (see section 4.2).

Hepatic impairment
Compared to subjects with normal hepatic function, systemic exposure following a single dose of futibatinib was similar in subjects with mild (Child-Pugh class A), moderate (Child-Pugh class B), or severe (Child-Pugh class C) hepatic impairment (see section 4.2).

Exposure-response relationship
Dose-dependent increase in blood phosphate levels was observed following once daily futibatinib 4 mg to 24 mg dose range.

No statistically significant exposure-efficacy relationships observed for ORR within the exposure range produced by futibatinib 20 mg once daily regimen.

5.3 Preclinical safety data

Repeat-dose toxicity
The main toxicological findings following repeat-dose administration of futibatinib in both rats and dogs were related to the pharmacological activity of futibatinib as an irreversible inhibitor of FGFR, including increased inorganic phosphorus and calcium in plasma, ectopic mineralization in various organs and tissues, lesions in bone/cartilage at futibatinib exposures lower than the human exposure at the clinical dose of 20 mg. Corneal lesions were found only in rats. These effects were reversible with the exception of ectopic mineralization.

Genotoxicity
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.

Carcinogenicity
Carcinogenicity studies with futibatinib have not been conducted.

Impairment of fertility
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.

Developmental toxicity
Oral administration of futibatinib to pregnant rats during the period of organogenesis resulted in 100% post-implantation loss at 10 mg/kg per day (approximately 3.15 times the human exposure by AUC at the recommended clinical dose). At 0.5 mg/kg per day (approximately 0.15 times the human exposure by AUC at the recommended clinical dose), reduced mean foetal body weight, an increase in foetal skeletal and visceral malformations including major blood vessel variations were observed.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet core
Mannitol (E421)
Maize starch
Lactose monohydrate
Sodium laurilsulfate
Cellulose, microcrystalline
Crospovidone
Hydroxypropylcellulose (E463)
Magnesium stearate

Film-coating
Hypromellose (E464)
Macrogols
Titanium dioxide (E171)

Lustering agent
Magnesium stearate

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

4 years.

6.4 Special precautions for storage

This medicinal product does not require any special storage conditions.

6.5 Nature and contents of container

PVC/PCTFE laminated blisters with aluminium foil backing with one tablet per cavity. Each blister contains a 7-day supply of film-coated tablets sealed inside a folding cardboard wallet in the following three dose packs:

- 20 mg daily dose: Each wallet contains 35 tablets (5 tablets once daily).
- 16 mg daily dose: Each wallet contains 28 tablets (4 tablets once daily).
- 12 mg daily dose: Each wallet contains 21 tablets (3 tablets once daily).

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

No special requirements for disposal.

7. MARKETING AUTHORISATION HOLDER

Taiho Pharma Netherlands B.V.
Barbara Strozzilaan 201
1083HN Amsterdam
Netherlands

8. MARKETING AUTHORISATION NUMBER(S)

Lytgobi 4 mg tablets
EU/1/23/1741/001
EU/1/23/1741/002
EU/1/23/1741/003

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 04 July 2023
Date of latest renewal: 02 June 2025

10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency http://www.ema.europa.eu.

ANNEX II

A. MANUFACTURER(S) RESPONSIBLE FOR BATCH RELEASE

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

E. SPECIFIC OBLIGATION TO COMPLETE POST-AUTHORISATION MEASURES FOR THE CONDITIONAL MARKETING AUTHORISATION

A. MANUFACTURER RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturer responsible for batch release

PCI Pharma Services (Millmount Healthcare Limited)
Block 7, City North Business Campus
Stamullen, Co. Meath, K32 YD60
Ireland

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

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

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

- **Periodic safety update reports (PSURs)**

The requirements for submission of PSURs 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 PSUR for this product within 6 months following authorisation.

D. 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.

E. 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 has 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

ANNEX III

LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

WALLET CARD FOR BLISTER

1. NAME OF THE MEDICINAL PRODUCT

Lytgobi 4 mg film-coated tablets
futibatinib

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each film-coated tablet contains 4 mg futibatinib.

3. LIST OF EXCIPIENTS

Contains lactose. See leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

21 tablets
28 tablets
35 tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Oral use

12 mg daily dose
16 mg daily dose
20 mg daily dose

Take three tablets once daily
Take four tablets once daily
Take five tablets once daily

Day 1
Day 2
Day 3
Day 4
Day 5
Day 6
Day 7

Push tablet through to the other side.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Taiho Pharma Netherlands B.V.
Barbara Strozzilaan 201
1083HN Amsterdam
Netherlands

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/23/1741/001	21 tablets
EU/1/23/1741/002	28 tablets
EU/1/23/1741/003	35 tablets

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Lytgobi 4 mg

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC
SN
NN

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

BLISTER

1. NAME OF THE MEDICINAL PRODUCT

Lytgobi 4 mg
futibatinib

2. NAME OF THE MARKETING AUTHORISATION HOLDER

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. OTHER

B. PACKAGE LEAFLET

Package leaflet: Information for the patient

Lytgobi 4 mg film-coated tablets
futibatinib

▼This medicine is subject to additional monitoring. This will allow quick identification of new safety information. You can help by reporting any side effects you may get. See the end of section 4 for how to report side effects.

Read all of this leaflet carefully before you start taking this medicine because it contains important information for you.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or pharmacist.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

1. What Lytgobi is and what it is used for

Lytgobi contains the active substance futibatinib, which belongs to a group of cancer medicines called tyrosine kinase inhibitors. It blocks the action of a protein in the cell, called fibroblast growth factor receptor (FGFR), that helps regulate cell growth. Cancer cells may have an abnormal form of this protein. By blocking FGFR, futibatinib can prevent the growth of such cancer cells.

Lytgobi is used on its own (monotherapy)to treat adults with bile duct cancer (also known as cholangiocarcinoma) that has spread or cannot be removed by surgery in patients who have already received previous treatment, and whose tumour has a certain type of abnormal “FGFR”.

2. What you need to know before you take Lytgobi

Do not take Lytgobi if you are allergic to futibatinib or any of the other ingredients of this medicine (listed in section 6).

Warnings and precautions
Talk to your doctor or pharmacist before taking Lytgobi if you have:
- been told you have high levels of phosphate in your blood (a condition known as hyperphosphataemia) based on a blood test result
- vision or eye problems such as problems with the retina (light-sensitive layers of nerve tissue at the back of the eye)

Eye examinations are recommended:
- before starting treatment with Lytgobi
- 6 weeks thereafter or at any time if any visual or eye problems occur.

Lytgobi can cause serous retinal detachment (retina pulls away from its normal position). Symptoms include blurred vision, flashes of light in the field of vision (photopsia) and small dark shapes moving in the field of vision (floaters). Tell your doctor straight away if you get any problems with your vision.

Lytgobi can cause high levels of phosphate in your blood and may lead to a build-up of minerals such as calcium in different tissues in your body. Your doctor may prescribe changes in your diet, phosphate lowering therapy, or change or stop treatment with Lytgobi if needed. Tell your doctor straight away if you develop painful skin lesions, any muscle cramps, numbness or tingling around your mouth, or an abnormal heartbeat.

Lytgobi may harm the unborn baby. If you are a woman of childbearing age or your partner is of childbearing capacity, you must use an effective contraception during treatment and for 1 week after the last dose of Lytgobi. Because it is not known if Lytgobi decreases the effectiveness of birth control medication, barrier methods should be applied in addition to such medication to avoid pregnancy.

Children and adolescents

Lytgobi should not be given to children or adolescents under 18 years. It is not known whether it is safe and effective in this age group.

Other medicines and Lytgobi
Tell your doctor or pharmacist if you are taking, have recently taken, or might take any other medicines.

In particular, you should tell your doctor if you are taking any of the following medicines so that the doctor can decide if your treatment needs to change:
- **itraconazole**: a medicine to treat fungal infections
- **clarithromycin**: medicines to treat certain infections
- **rifampicin**: a medicine to treat tuberculosis or certain other infections
- **carbamazepine**, **phenytoin**, **phenobarbital**: medicines to treat epilepsy
- **efavirenz**: medicine to treat HIV infection
- **theophylline:** a medicine to treat breathing problems
- **olanzapine:** a medicine to manage symptoms of mental health conditions

Pregnancy and breast-feeding
If you are pregnant or breast-feeding, think you may be pregnant, or are planning to have a baby, ask your doctor or pharmacist for advice before taking this medicine.

- **Pregnancy /Contraception -information for women**
  You should not become pregnant during the treatment with Lytgobi because this medicine could harm your baby. A pregnancy test should be performed before initiating treatment, and women who could become pregnant must use effective contraception during treatment and for 1 week after the last dose of Lytgobi. Barrier methods should be applied as a second form of contraception to avoid pregnancy. Talk to your doctor about the most suitable contraception for you.
- **Contraception -information for men**
  You should not conceive a child during treatment with Lytgobi because this medicine may harm the baby. You must use effective contraception during treatment and for 1 week after the last dose of Lytgobi.
- **Breast-feeding**
  Do not breast-feed during treatment with Lytgobi and for 1 week after the last dose. This is because it is not known if Lytgobi can pass into breast milk and could therefore harm your baby.

Driving and using machines
Lytgobi can cause side effects such as fatigue or visual disturbances. Do not drive or operate

machinery if this happens.

Lytgobi contains lactose and sodium
This medicine contains lactose (found in milk or dairy products). If you have been told by your doctor that you have an intolerance to some sugars, contact your doctor before taking this medicine.

This medicine contains less than 1 mmol sodium (23 mg) per tablet, that is to say essentially "sodium-free".

3. How to take Lytgobi

Lytgobi treatment should be started by a doctor who is experienced in the diagnosis and treatment of bile duct cancer. Always take this medicine exactly as your doctor or pharmacist has told you. Check with your doctor or pharmacist if you are not sure.

The recommended dose is
5 tablets of Lytgobi 4 mg (20 mg futibatinib in total) taken orally once daily. Your doctor will adjust the dose or stop treatment if needed.

Method of administration
Swallow the tablet whole with one glass of water at the same time every day. Lytgobi may be taken with food or between meals. The tablets should be swallowed whole to ensure that the full dose is taken.

Duration of treatment
Take Lytgobi for as long as it is prescribed by the doctor.

If you take more Lytgobi than you should
Tell your doctor straight away if you have taken more Lytgobi than you should have.

If you forget to take Lytgobi
- If you miss a dose of Lytgobi by 12 hours or less, take the missed dose as soon as you remember.
- If you miss a dose of Lytgobi by more than 12 hours, skip the missed dose. Take your next dose at the usual time.
- Do not take a double dose of Lytgobi if you experience vomiting. Take the next dose at your scheduled usual time.
- Do not take a double dose to make up for a missed dose.

If you stop taking Lytgobi
Do not stop taking Lytgobi without discussing it with your doctor, as stopping treatment could reduce the success of therapy.

If you have any further questions on the use of this medicine, ask your doctor, pharmacist or nurse.

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them.

If you have any of the serious side effects below, tell your doctor immediately. These side effects listed below are common (may affect up to 1 in 10 people).
- Migraine
- Intestinal obstruction

Other side effects
Talk to your doctor if you get any other side effects. These may occur with the following frequencies:

Very common (may affect more than 1 in 10 people)
- high or low phosphate levels seen in blood tests
- low sodium levels seen in blood tests
- nails separating from the nail bed, poor formation of the nail, change in colour of the nails
- constipation
- diarrhoea
- dry mouth
- vomiting
- abdominal pain
- hair loss (alopecia)
- feeling tired or weak
- dry skin
- high levels of liver enzyme seen in blood tests
- nausea
- inflammation of the lining of the mouth (stomatitis)
- decreased appetite
- dry eye
- redness, swelling, peeling or tenderness, mainly on the hands or feet ('hand-foot' syndrome)
- change in sense of taste
- muscle pain
- joint pain

Common (may affect up to 1 in 10 people)
- Eye problems including inflammation of the eyes or cornea (front part of the eye), blurred vision, sudden appearance of small dark shapes moving in the field of vision (floaters) and flashes of light in the field of vision (photopsia).

Reporting of side effects
If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the national reporting system listed in Appendix V. By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store Lytgobi

Keep this medicine out of the sight and reach of children.

Do not use this medicine after the expiry date which is stated on the carton and blister after EXP. The expiry date refers to the last day of that month.

This medicine does not require any special storage conditions.

Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.

6. Contents of the pack and other information

What Lytgobi contains
- The active substance is futibatinib.
  Each film-coated tablet contains 4 mg futibatinib.

- The other ingredient(s) are:
  Tablet core: maize starch, crospovidone, hydroxypropylcellulose, lactose monohydrate, magnesium stearate, mannitol, cellulose microcrystalline and sodium lauril sulfate (see section 2, "Lytgobi contains lactose and sodium")
  Film coating: hypromellose, macrogols, and titanium dioxide
  Lustering agent: magnesium stearate

What Lytgobi looks like and contents of the pack
Lytgobi 4 mg is supplied as round, white, film-coated tablets, debossed on one side with "4MG" and "FBN" on the other side.

Lytgobi tablets are packaged in a blister card sealed inside a folding wallet containing a 7-day supply as follows:
- 20 mg daily dose: Each wallet contains 35 tablets (5 tablets once daily).
- 16 mg daily dose: Each wallet contains 28 tablets(4 tablets once daily).
- 12 mg daily dose: Each wallet contains 21 tablets (3 tablets once daily).

Marketing Authorisation Holder
Taiho Pharma Netherlands B.V.
Barbara Strozzilaan 201
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Manufacturer
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Block 7, City North Business Campus
Stamullen, Co. Meath, K32 YD60
Ireland

This leaflet was last revised in {MM/YYYY}
This medicine has been given 'conditional approval'.
This means that there is more evidence to come about this medicine.
The European Medicines Agency will review new information on this medicine at least every year and this leaflet will be updated as necessary.

Other sources of information
Detailed information on this medicine is available on the European Medicines Agency website: http://www.ema.europa.eu.

This leaflet is available in all EU/EEA languages on the European Medicines Agency website.