Summary Report of Benefit-Risk Assessment

LYTGOBI FILM-COATED TABLETS 4MG

NEW DRUG APPLICATION

Active Ingredient(s)	Futibatinib
Product Registrant	Taiho Pharma Asia Pacific Pte. Ltd.
Product Registration Number	SIN17316P
Application Route	Abridged evaluation
Date of Approval	25 August 2025

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A INTRODUCTION

Lytgobi monotherapy is indicated for the 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.

Lytgobi contains futibatinib, a tyrosine kinase inhibitor that irreversibly inhibits FGFR 1, 2, 3, and 4 through covalent binding. Inhibition of constitutive FGFR signalling is associated with the regulation of proliferation and survival in malignant cells. Futibatinib has been shown to inhibit FGFR phosphorylation and downstream signalling, and to decrease cell viability in cancer cell lines with FGFR alterations such as FGFR fusions/rearrangements, amplifications, and mutations.

Lytgobi is available as film-coated tablets containing 4 mg of futibatinib. Other ingredients in the tablet core are magnesium stearate, corn starch, crospovidone, hydroxypropyl cellulose, lactose monohydrate, mannitol, microcrystalline cellulose and sodium lauryl sulfate. Ingredients in the film coating include hypromellose, polyethylene glycol and titanium dioxide.

B ASSESSMENT OF PRODUCT QUALITY

The drug substance, futibatinib, is manufactured at Taiho Pharmaceutical Co., Ltd, Saitama, Japan. The drug product, Lytgobi Film-coated Tablets, is manufactured at Penn Pharmaceutical Services, Limited, United Kingdom.

Drug substance:

Adequate controls have been presented for the starting materials, intermediates and reagents. The in-process control tests and acceptance criteria applied during the manufacturing of the drug substance are considered appropriate.

The characterisation of the drug substance and its impurities has been appropriately performed. Potential and actual impurities are adequately controlled in accordance with ICH Q3A and Q3C guidelines.

The drug substance specifications were established in accordance with ICH Q6A guideline and the impurity limits have been appropriately qualified. The analytical methods used were adequately described and non-compendial methods have been validated in accordance with ICH Q2 guidelines, with information on the reference standards used for identity, assay and impurities testing presented.

The stability data presented was adequate to support the storage of the drug substance at 25ºC with a re-test period of 60 months. The packaging is triple low-density polyethylene (LDPE) bags and placed in a high-density polyethylene (HDPE) drum with a secure fitting lid.

Drug product:

The tablets are manufactured using wet granulation approach followed by film-coating, which is considered a standard manufacturing process.

The manufacturing site is compliant with Good Manufacturing Practice (GMP) standard. Proper development and validation studies were conducted. It has been demonstrated that the manufacturing process is reproducible and consistent. Adequate in-process controls are in place.

The specifications have been established in accordance with ICH Q6A guideline and impurity limits were considered adequately qualified. The analytical methods used were adequately described and non-compendial methods have been validated in accordance with ICH Q2 guideline with information on the reference standards used for identity and assay presented.

The stability data submitted was adequate to support the approved shelf-life of 48 months when stored at or below 30ºC. The container closure system is polyvinyl chloride (PVC) and polychlorotrifluoroethylene (PCTFE) -Aluminum blister containing 5 tablets per blister and 7 blisters per carton.

C ASSESSMENT OF CLINICAL EFFICACY

The clinical efficacy of Lytgobi in the treatment of CCA was based on one pivotal study, TAS-120-101. This Phase 1/2, multicentre, open-label, single-arm study was conducted in 3 portions: Phase 1 Dose Escalation, Phase 1 Expansion and a Phase 2 study conducted in patients with unresectable locally advanced or metastatic intrahepatic cholangiocarcinoma harbouring *FGFR2* gene fusions or other *FGFR2* rearrangements, who had progressed on at least one line of prior gemcitabine and platinum-based chemotherapy.

Participants in selected Phase 1 dose-expansion cohorts and Phase 2 received futibatinib 20 mg once daily until disease progression or unacceptable toxicity. Given the absence of a current standard-of-care treatment for this condition, a single-arm study design was considered acceptable for demonstrating efficacy.

The primary endpoint of the study was the objective response rate (ORR), defined as a complete response (CR) or partial response (PR), as determined by an independent review committee (IRC) based on RECIST v1.1. Based on historical ORR data from published literature in CCA patients, the study was predetermined to be considered positive if the lower limit of the 95% CI for ORR exceeded 10%. Duration of response (DoR) was the key secondary endpoint. Other secondary endpoints included progression-free survival (PFS) and overall survival (OS).

The efficacy population consisted of 103 patients enrolled in the Phase 2 portion of the study, all of whom had intrahepatic disease that had progressed after at least one prior therapy and who had *FGFR2* fusion (77.7%) or rearrangement (22.3%) as determined by tests performed at central or local laboratories. The most commonly identified *FGFR2* fusion partner was *BICC1* (23.3%). The majority of patients were female (56.3%) and Caucasian (49.5%), and 29.1% were Asian. The median age was 58 years (range: 22 to 79 years) and 22.3% were aged 65 years or older. All participants had received at least one prior line of systemic therapy, with 30.1% having received two previous lines and 23.3% with three or more lines. All patients

received gemcitabine plus platinum-based therapy, including 91.3% who had previously been treated with gemcitabine/cisplatin.

The primary analysis demonstrated an ORR of 41.7% (95% CI: 32.1, 51.9%) based on IRC-assessed confirmed tumour responses. Among these patients, one achieved CR and 40.8% had PR. Regarding the key secondary endpoint, the median DoR among the responders was 9.69 months (95% CI: 7.62, 17.05) with 14.0% of patients having a DoR of 12 months. The median PFS was 9.0 months (95% CI: 6.9, 13.1) and the median OS was 21.7 months (95% CI: 14.5, NE).

Subgroup analyses of the primary endpoint ORR were generally consistent with the overall population. These included analyses by number of prior lines of systemic therapy (ORRs of 37.5%, 38.7%, and 54.2% in patients with one, two, or at least three prior lines, respectively) and FGFR status (43.8% with *FGFR2* fusion and 34.8% with *FGFR2* rearrangement). However, these results should be interpreted with caution due to small sample sizes.

Summary of efficacy results

Endpoint	**All treated patients (N=103)**
ORR, n (%)	43 (41.7)
95% CI	32.1, 51.9
CR, n (%)	1 (1.0)
PR, n (%)	42 (40.8)
Median DoR (months) (95% CI)	9.69 (7.62, 17.05)
Median PFS (months) (95% CI)	9.0 (6.9, 13.1)
Median OS (months) (95% CI)	21.7 (14.5, NE)

ORR: Objective response rate; CR: Complete response; PR: Partial response; DoR: Duration of response; PFS: Progression-free survival; OS: Overall survival; NE: Not evaluable

Overall, the efficacy of futibatinib based on the primary endpoint ORR was numerically higher than that reported for current chemotherapy in the second-line setting (ORR of 5% and median PFS of 4 months for FOLFOX). The ORR was also comparable to that achieved by the current registered FGFR inhibitor pemigatinib (37%) and is considered clinically meaningful in the context of a rare, life-threatening disease. An ongoing Phase 2, randomised study (TAS-120-205) assessing the efficacy and safety of futibatinib 16 mg and 20 mg in the same patient population is required to be submitted to confirm the clinical benefit of futibatinib.

D ASSESSMENT OF CLINICAL SAFETY

The overall safety population comprised 145 patients enrolled in the Phase 1 Expansion (n=42) and Phase 2 (n=103) portions of Study TAS-120-101 who received futibatinib 20mg once daily. The median duration of exposure was 8.87 months.

Overview of treatment-emergent adverse events (TEAEs) (TAS-120-101)

Category, n (%)	All treated patients (N=145)
TEAE	145 (100.0)
Treatment-related	143 (98.6)
≥ Grade 3 TEAE	111 (76.6)
Treatment-related	79 (54.5)
SAE	59 (40.7)
Treatment-related	13 (9.0)
TEAE leading to treatment discontinuation	11 (7.6)
Treatment-related	3 (2.1)
Deaths	7 (4.8)
Treatment-related	0

The most frequently reported treatment-emergent adverse events (TEAEs) were hyperphosphatemia (85.5%), constipation (37.2%), alopecia (35.2%), diarrhoea (33.8%), dry mouth (31.0%), fatigue (31.0%), nausea (28.3%), dry skin (27.6%), increased aspartate aminotransferase (AST) (26.9%), abdominal pain (24.8%), stomatitis (24.8%), vomiting (23.4%), palmar-plantar erythrodysaesthesia syndrome (PPES) (22.8%), arthralgia (21.4%), and decreased appetite (20.0%). The most commonly reported ≥ Grade 3 TEAEs included hyperphosphataemia (26.9%), increased AST (9.0%), hyponatraemia, fatigue (7.6% each), hypophosphataemia (6.9%), stomatitis and increased alanine aminotransferase (ALT) (6.2% each).

Serious adverse events (SAEs) were reported in 40.7% of patients, which included disease progression (4.1%), and abdominal pain, upper gastrointestinal haemorrhage, pyrexia, bile duct obstruction, and sepsis (n=4 each, 2.8%). TEAEs leading to futibatinib discontinuation occurred in 7.6% of patients. With the exception of stomatitis reported for 2 patients, all TEAEs leading to treatment discontinuation occurred in 1 patient each. Seven patients (4.8%) had fatal TEAEs (disease progression [n=5, 3.4%], ascites, and hepatic failure [n=1 each, 0.7%]; none of these events were considered related to futibatinib by the investigator.

The adverse events of special interest (AESIs) with futibatinib included hyperphosphataemia and retinal disorders. Hyperphosphatemia (grouped term comprising AEs of hyperphosphataemia and blood phosphorus increased) occurred in 89.7% of patients; 27.6% experienced at least 1 event of Grade 3 severity, and none were Grade 4 or Grade 5. Dose interruption occurred in 18.6% of patients and dose reduction in 17.9%, however no patients discontinued study treatment due to hyperphosphatemia. Recommendations for management of hyperphosphatemia include dietary phosphate restriction, administration of phosphate-lowering therapy, and dose modification when required.

Retinal disorder events occurred in 6.2% of patients, which included subretinal fluid (2.1%) and chorioretinopathy (1.4%). These events were Grade 1 or 2 in severity and non-serious. Dose interruption and reduction occurred in 2.1% of patients each and none discontinued treatment due to this AESI. Ophthalmological examination, including optical coherence tomography (OCT), should be performed prior to initiation of therapy, every 2 months for the first 6 months of treatment and every 3 months thereafter. In addition, dose modification recommendations to manage serous retinal detachment have been included in the product labelling.

Overall, the safety profile of futibatinib was consistent with its mechanism of action. The main AESIs included hyperphosphataemia and retinal disorders including serous retinal detachment. These AESIs would require appropriate management through dose reductions or interruptions, with appropriate warnings and dose modification recommendations included in the product labelling to mitigate the known risks.

E ASSESSMENT OF BENEFIT-RISK PROFILE

CCA is a rare and aggressive disease accounting for approximately 15% of all primary liver cancers and approximately 3% of all gastrointestinal cancers. For patients with advanced or unresectable CCA, the median overall survival with standard of care chemotherapy is less than one year. The prognosis is particularly poor in intrahepatic CCA, where only 30–40% of patients present with surgically resectable disease and the majority of cases recur even in apparently resectable disease. The first-line chemotherapy for CCA is based on gemcitabine and cisplatin, with FOLFOX regimen as the second-line treatment. However, success with chemotherapies and targeted therapies in the second-line and above setting in molecularly unselected biliary tract cancers remains limited.

The clinical efficacy of futibatinib was based on one pivotal Phase 2, single-arm, open-label study in CCA patients with *FGFR2* fusion or rearrangement who have been previously treated with at least 1 prior therapy. The ORR achieved by futibatinib was 41.7% with a robust duration of response of 9.69 months. The response rate was numerically higher than that demonstrated by current second-line therapies (ORR of 5% for FOLFOX).

The most common adverse events occurring with futibatinib included hyperphosphataemia (85.5%), 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%), PPES (22.8%), arthralgia (21.4%), and decreased appetite (20.0%). The AESIs included hyperphosphataemia and retinal disorders, which occurred in 89.7% and 6.2% of patients, respectively. These AESIs were consistent with the known safety risks of FGFR inhibitors and the relevant warnings and dose modification recommendations have been included in the product labelling.

Considering the aggressive nature of the disease and the limited availability of second-line therapies, the benefits of futibatinib in the proposed indication outweigh the known safety risks. The registrant is required to submit the final study report of Study TAS-120-205 to further confirm the benefit-risk profile of futibatinib in the treatment of CCA.

F CONCLUSION

Based on the review of quality, safety and efficacy data, the benefit-risk of Lytgobi for the treatment of locally advanced or metastatic CCA with a FGFR2 fusion or rearrangement that has progressed after at least one prior line of systemic therapy was deemed favourable and approval of the product registration was granted on 25 August 2025.

APPROVED PACKAGE INSERT AT REGISTRATION

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/P-gp inhibitors
Co-administration of futibatinib with strong CYP3A4/P-gp 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/P-gp inducers
Co-administration of futibatinib with strong or moderate CYP3A4/P-gp 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).

Perform a comprehensive ophthalmological examination, including optical coherence tomography (OCT) of the macula, prior to initiation of therapy, every 2 months for the first 6 months, and every 3 months thereafter. For onset of visual symptoms, refer patients for ophthalmologic evaluation urgently, with follow-up every 3 weeks until resolution or discontinuation of futibatinib. 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 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/P-gp inhibitors
Concomitant use of strong CYP3A/P-gp inhibitors should be avoided because it may increase futibatinib plasma concentration (see sections 4.2 and 4.5).

Combination with strong or moderate CYP3A/P-gp inducers
Concomitant use of strong or moderate CYP3A/P-gp 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/P-gp inhibitors
Co-administrations of multiple doses of 200 mg itraconazole, a strong CYP3A/P-gp 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/P-gp inhibitors (e.g. clarithromycin, itraconazole) may increase futibatinib plasma concentration and should be avoided. If this is not possible, a reduction in the futibatinib dose to the next lower dose level based on tolerability observed should be considered (see sections 4.2 and 4.4).

CYP3A/P-gp inducers
Co-administrations of multiple doses of 600 mg rifampin, a strong CYP3A/P-gp 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 and moderate CYP3A/P-gp inducers (e.g. carbamazepine, phenytoin, phenobarbital, efavirenz, rifampin) may decrease futibatinib plasma concentration and should be avoided. If this is not possible, gradually increasing the futibatinib dose based on careful monitoring of tolerability should be considered (see sections 4.2 and 4.4).

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. Co-administrations of a proton pump inhibitor (lansoprazole) did not result in a clinically important change in 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. Co-administrations of futibatinib had no clinically significant impact on midazolam exposure.

Effect of futibatinib on P-gp and BCRP substrates
In vitro, futibatinib is an inhibitor of P-gp and BCRP. Co-administration of futibatinib with P-gp (e.g., digoxin, dabigatran, colchicine) or BCRP (e.g, rosuvastatin) substrates may increase their exposure.

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.

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 in-frame FGFR2 fusion (77.7%) or rearrangement (22.3%), as determined by tests performed at central or local laboratories. The most commonly identified FGFR2 fusion partner was BICC1 (n=24, 23%).

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.

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% gCV).

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% gCV).

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 inhibited P-gp and BCRP, but 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.

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)
Corn starch
Lactose monohydrate
Sodium lauryl sulfate
Microcrystalline cellulose
Crospovidone
Hydroxypropyl cellulose (E463)
Magnesium stearate

Film-coating
Hypromellose (E464)
Polyethylene glycol
Titanium dioxide (E171)

Lustering agent
Magnesium stearate

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

4 years.

6.4 Special precautions for storage

Store at or below 30°C.

6.5 Nature and contents of container

Tablets are supplied in PVC/PCTFE blister film with aluminium foil lidding. Each blister strip contains five tablets. Pack size of 35 film-coated tablets.

6.6 Special precautions for disposal

No special requirements for disposal.

7. BATCH RELEASER

Taiho Pharmaceutical Co., Ltd. Kitajima Plant
1-1, Iuchi, Takabo, Kitajima-cho,
Itano-gun, Tokushima, 771-0206, Japan

8. DATE OF REVISION OF THE TEXT

Aug 2025