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Committee for Orphan Medicinal Products

Orphan designation withdrawal assessment report

Lytgobi 1-[(3S)-3-{4-amino-3-[(3,5-dimethoxyphenyl)ethynyl]-1H-pyrazolo[3,4-d]pyrimidin-1-yl}pyrrolidin-1-yl]-2-propen-1-one
Treatment of biliary tract cancer
EU/3/19/2146

Sponsor: Taiho Pharma Netherlands B.V.

Note

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

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1. Product and administrative information

Product	
Designated active substance	1-[(3S)-3-{4-amino-3-[(3,5-dimethoxyphenyl)ethynyl]-1H-pyrazolo[3,4-d]pyrimidin-1-yl}pyrrolidin-1-yl]-2-propen-1-one
Other name	Lytgobi
International Non-Proprietary Name	Futibatinib
Tradename	Lytgobi
Orphan condition	Treatment of biliary tract cancer
Sponsor's details:	Taiho Pharma Netherlands B.V. Barbara Strozzilaan 201 1083 HN Amsterdam Noord-Holland Netherlands
Orphan medicinal product designation procedural history	
Sponsor/applicant	Taiho Pharma Europe Limited
COMP opinion	21 February 2019
EC decision	1 April 2019
EC registration number	EU/3/19/2146
Post-designation procedural history	
Transfer of sponsorship	Transfer from Taiho Pharma Europe Limited to Taiho Oncology Europe B.V.– EC decision of 4 September 2020 Transfer from Taiho Oncology Europe B.V.to Taiho Pharma Netherlands B.V.– EC decision of 4 June 2021
Marketing authorisation procedural history	
Rapporteur / Co-rapporteur	Johannes Lodewijk Hillege / Alexandre Moreau
Applicant	Taiho Pharma Netherlands B.V.
Application submission	29 April 2022
Procedure start	19 May 2022
Procedure number	EMA/H/C/005627/0000
Invented name	Lytgobi
Proposed therapeutic indication	Lytgobi monotherapy is indicated for the treatment of adult patients with locally advanced or metastatic cholangiocarcinoma with a fibroblast growth factor receptor 2 (FGFR2) fusion or rearrangement who have progressed after at least one prior line of systemic therapy. Further information on Lytgobi can be found in the European public assessment report (EPAR) on the Agency's website https://www.ema.europa.eu/en/medicines/human/EPAR/Lytgobi
CHMP opinion	26 April 2023
COMP review of orphan medicinal product designation procedural history	
COMP rapporteurs	Maria Elisabeth Kalland / Elisabeth Johanne Rook

Sponsor's report submission	27 December 2022
COMP discussion and adoption of list of questions	18-20 April 2023
Sponsor's removal request	5 May 2023

2. Grounds for the COMP opinion

The COMP opinion that was the basis for the initial orphan medicinal product in 2019 designation was based on the following grounds:

- "the intention to treat the condition with the medicinal product containing 1-[(3S)-3-{4-amino-3-[(3,5-dimethoxyphenyl)ethynyl]-1H-pyrazolo[3,4-d]pyrimidin-1-yl}pyrrolidin-1-yl]-2-propen-1-onewas considered justified based on preliminary clinical observations in relapsed/refractory patients, who responded to treatment with the product as a monotherapy;
- the condition is life-threatening and chronically debilitating due to the development of liver insufficiency, cholestasis, cholangitis, weight loss and cachexia. Patients with unresectable tumours die between 6- and 12-months following diagnosis. Death usually occurs from liver failure or infectious complications accompanying the progressive biliary obstruction;
- the condition was estimated to be affecting approximately 1.5 in 10,000 persons in the European Union, at the time the application was made.

The sponsor has also established that there exists no satisfactory method of treatment in the European Union for patients affected by the condition".

3. Review of criteria for orphan designation at the time of marketing authorisation

Article 3(1)(a) of Regulation (EC) No 141/2000

Intention to diagnose, prevent or treat a life-threatening or chronically debilitating condition affecting not more than five in 10 thousand people in the Community when the application is made

Condition

Biliary tract cancer (BTC) is a heterogeneous group of invasive carcinomas arising in the bile duct epithelium (cholangiocytes), the gallbladder or the ampulla of Vater. BTC includes gallbladder cancer (GBC), cholangiocarcinoma (CCA) and ampullary carcinoma (AC). CCAs, also known as bile duct cancer, comprises all tumours arising from bile duct epithelium where the majority (over 90%) are adenocarcinomas. The classification of CCAs is further divided anatomically as intrahepatic CCA (iCCA) and extrahepatic CCA (eCCA; perihilar- or distal CCA). GBC is classified as extrahepatic biliary cancer and is the most common malignancy of the biliary tract accounting for 80-95% of BTCs.

BTC is difficult to diagnose owing to its anatomic location and growth patterns. CCA is rarely diagnosed before 40 years of age, except in patients with primary sclerosing cholangitis (Bridgewater et al., 2014; Khan et al., 2012), and GBC is strongly associated with age >65 years (Marcano-Bonilla et al., 2016).

The proposed therapeutic indication is: "*Lytgobi monotherapy is indicated for the treatment of adult patients with locally advanced or metastatic cholangiocarcinoma with a fibroblast growth factor receptor 2 (FGFR2) fusion or rearrangement who have progressed after at least one prior line of systemic therapy*". The therapeutic indication falls within the scope of the designated orphan condition "treatment of biliary tract cancer".

Intention to diagnose, prevent or treat

The medical plausibility is confirmed by the positive benefit/risk assessment of the CHMP, see EPAR.

Chronically debilitating and/or life-threatening nature

The disease is difficult to treat primarily because it is generally diagnosed at an advanced stage (Blechacz et al., 2008; Bridgewater et al., 2014; Valle et al., 2017), a point at which the tumour obstructs the bile ducts or has spread to other organs.

BTC remains a serious life-threatening disease with limited treatment options. Affected patients have a poor prognosis, with an estimated 5-year overall survival (OS) rate across all disease stages of <20% (Lamarca et al., 2021). Patients often present with advanced and incurable disease, with up to 90% of patients being ineligible for potentially curative surgical resection at diagnosis (Nathan et al., 2007; Cidon, 2016). Common presentation includes symptoms related to biliary tract obstruction including cholestasis, cholangitis, jaundice, abdominal pain, weight loss, fever, fatigue, cachexia, and abnormal liver function tests and can swiftly become life-threatening due to development of liver insufficiency and serious infections (Lamarca et al., 2021).

In the advanced, non-resectable or metastatic CCA setting, the disease is incurable and palliative chemotherapy is the primary treatment option. In this setting, the 5-year survival rates associated with CCA are around 10% and even less for patients with distant metastases (ACS 2021).

There has been no change in the severe nature of the condition since the orphan designation was granted in 2019. The COMP considers the condition to be chronically debilitating due to development of hepatic insufficiency, progressive biliary obstruction followed by complications such as infections, and life-threatening with a low overall median survival of less than two year following diagnosis.

Number of people affected or at risk

The sponsor proposed a prevalence estimate for BTC within a range of less than 0.2 to 0.9 per 10,000 persons in the European community.

Most cancer registries or publications do not report the incidence or prevalence for the whole BTC population but rather only for the different sub-entities. The sponsor therefore reviewed literature and registries and approached the issue of prevalence in the EU for BTC as a sum of the patients with CCA and number of patients with GBC.

The European Cancer Information System (ECIS) reports separate incidence data for GBC, but no figures for CCA are reported. The following incidence data were first retrieved as a first step of the estimation and reporting of prevalence.

- GBC: According to the ECIS, there were 7,764 estimated incident cases of GBC in 2020 in the 27 countries in the EU (EU27).
- CCA: According to the ECIS, there were also 60,934 estimated incident cases of liver cancer in 2020 in the EU27, and the sponsor also referred to recent publications reporting that CCA

comprises approximately 10-15% of all primary liver tumours (Banales et al., 2020; Vithayathil et al., 2022). Based on this, an estimate of 9,140 incident cases (60,934*0.15) of CCA in 2022 in the EU27 was estimated.

The sponsor emphasised that although large regional differences in the temporal trend of CCA incidence have been registered in Europe, the age standardised incidence rate for CCA still remains low in Europe (0.3-3.4 cases per 100,000 population; Bragazzi et al., 2012).

The sponsor claimed that an accurate determination of median duration of disease is difficult to establish, and consecutively, direct estimation of prevalence is difficult. In a phase 3 study published in 2010, median OS among patients with treatment-naïve, locally advanced or metastatic BTC ranged from 8.1 months (with gemcitabine treatment) to 11.7 months (with gemcitabine-cisplatin treatment) (Valle et al., 2010). Median OS for patients who receive surgical resection is higher, ranging from 27 to 36 months (Buettner et al., 2017). Accordingly, for the purposes of the calculations described below, the sponsor used the midpoint of these figures (22 months, or approximately 1.83 years) as the estimate for the median duration of the disease.

As shown in Table 1, depending upon the incidence estimate used in the calculation, prevalence of BTC may range from <0.2 to 0.9 per 10,000 people in the EU27.

Table 1. Calculated prevalence of BTC in the EU27 based on ECIS data from 2020

Cancers Reference	Incidence ranges	Calculated prevalence (incidence x 1.83)
Valle et al. 2010	0.2 – 0.5 per 10000[a]	0.4 – 0.9 per 10000
Bridgewater et al. 2016	<0.1 – 0.2 per 10000[b]	<0.2 – 0.4 per 10000

a. Incidence for EU only

b. Incidence for Western population including EU and United States

The proposed prevalence is estimated to be lower than the estimate that was concluded on at the time of the orphan designation and is also lower than those values that have been accepted in recent designations for BTC. The COMP considered that the prevalence is underestimated, and the sponsor should therefore re-calculate it based on the most relevant epidemiological data on the incidences of all the different sub-entities of BTC, including the number of patients with ampullary carcinoma. The revised estimate should also reflect the current ratio of incident iCCA cases among all incident liver cancer cases in Europe as well as the proportion of patients with eCCA among all CCA cases.

Article 3(1)(b) of Regulation (EC) No 141/2000

Existence of no satisfactory methods of diagnosis prevention or treatment of the condition in question, or, if such methods exist, the medicinal product will be of significant benefit to those affected by the condition.

Existing methods

The approved medicinal product Pemazyre (pemigatinib), which is indicated for the treatment of adult patients with locally advanced or metastatic CCA characterized by fusion or rearrangements of FGFR2 after at least one line of systemic therapy, which is indicated for the same patient group as proposed for Lytgobi (futibatinib).

The sponsor referred to the latest European Society for Medical Oncology (ESMO) clinical practice guideline for BTC, which describe existing treatment options that are commonly used by clinicians as first- and second-line treatment, including surgery, systemic chemotherapy, and chemo-radiotherapy (Vogel et al., 2022).

The treatment guideline is as follows:

- Surgery: radical surgery (with lymphadenectomy) is the only curative treatment of BTC. The exact nature and extent of surgery will depend on tumour subtype/location. Adjuvant chemotherapy with capecitabine should be considered for patients with CCA or GBC following resection. Radiotherapy, after completion of adjuvant capecitabine, might be considered in selected patients.
- First line systemic chemotherapy: Cisplatin–gemcitabine is recommended as standard of care (SoC) in the first line setting for patients with good performance status (PS; 0-1); the combination of cisplatin–gemcitabine with durvalumab should be considered in first line BTC; oxaliplatin may substitute cisplatin in cases where there is a concern about renal function, gemcitabine monotherapy may be used for patients with PS 2. Only the cisplatin–gemcitabine–durvalumab regimen is approved as a first-line treatment (Imfinzi; MA extension in 2022).
- Second line: 5-fluorouracil–leucovorin–oxaliplatin (FOLFOX) is recommended as SoC in the second line setting after first-line cisplatin–gemcitabine-based therapy for all-comers; patients should be tested for genomic alterations (e.g., IDH1 mutations, FGFR2 fusions, MSI-H/dMMR) and if positive considered for targeted therapy as early as possible (e.g., ivosidenib, FGFR inhibitors, pembrolizumab). Radiotherapy may be considered in patients with localised disease, after first-line chemotherapy. Radio-embolisation may be considered in patients with inoperable iCCA, usually after first-line chemotherapy.

The sponsor's product Lytgobi (futibatinib) is intended to be used as monotherapy for the treatment of adult patients with locally advanced or metastatic CCA with FGFR2 fusion or rearrangement in the second- and later lines setting. The authorised FGFR-targeting therapy Pemazyre (pemigatinib) is indicated for the same therapeutic indication. The COMP considered that Pemazyre thus qualifies as a satisfactory method of treatment for the purpose of examining the significant benefit of Lytgobi in patients with CCA.

On 23 February 2023, the Committee for Medicinal Products for Human Use (CHMP) adopted a positive opinion, recommending the granting of a marketing authorisation for the medicinal product Tibsovo (ivosidenib), intended for the treatment of adult patients with locally advanced or metastatic CCA. In case the Commission Decision for Tibsovo is published before the adoption of the maintenance report (17th May 2023), Tibsovo would have to be added to the list of approved products for treatment of BTC, and a discussion will be needed on the satisfactoriness for the target population of Lytgobi.

Significant benefit

The sponsor argued that available clinical data have demonstrated that futibatinib is of significant benefit based on a clinically relevant advantage in terms of improved efficacy and a better safety profile, in comparison to pemigatinib in the overall target CCA population with FGFR2 fusions or other rearrangements. In addition, futibatinib has demonstrated a significant benefit in CCA patients with FGFR2 fusions or rearrangements who have progressed on prior treatment with different ATP-competitive FGFR inhibitors, including pemigatinib. Protocol assistance from EMA was sought by the sponsor, but they did not ask for any advice on the approach for collecting the evidence needed to justify significant benefit of futibatinib over existing methods of treatment.

Futibatinib is a tyrosine kinase inhibitor (TKI) that irreversibly inhibits FGFR1-4 by covalent binding, leading to inhibition of FGFR phosphorylation and downstream signalling and decreased cell viability in cancer cells with activating FGFR alterations, including FGFR fusions or rearrangements, amplifications, or mutations. The primary data supporting the efficacy and safety of futibatinib in advanced CCA in the conditional marketing authorisation (MA) application were obtained from the phase 2 part of the multicentre, open-label, single-arm phase 1/2 study TAS-120-101. The study was designed to evaluate the safety, pharmacokinetics, pharmacodynamics, and efficacy of futibatinib in advanced cancer patients. The phase 2 part consisted of previously treated patients with unresectable locally advanced or metastatic iCCA. Patients with prior FGFR-directed therapy were excluded from the study. The efficacy population consists of 103 patients who had progressed on or after at least one 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. The data cut-off (DCO) date for the efficacy and safety analyses provided was 01-Oct-2020.

Patients received futibatinib orally once daily at a dose of 20 mg in a continuous 21-day treatment cycle 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. Additional secondary endpoints in the phase 2 portion of the study included disease control rate (DCR; ORR and stable disease [SD]), progression-free survival (PFS), and OS.

The enrolled CCA patients in the phase 2 part had a median age of 58 years (range: 22 to 79), 22.3% were ≥65 years, 56.3% were female, and 49.5% were Caucasian. All patients had a baseline Eastern Cooperative Oncology Group (ECOG) performance status of 0 (46.6 %) or 1 (53.4 %). All patients had received at least one prior line of systemic therapy, 30.1% had two prior lines of therapy, and 23.3% had three or more prior lines of therapy. All patients had received prior platinum-based therapy including 91% with prior gemcitabine-cisplatin.

Futibatinib showed a confirmed ORR of 41.7% (95% CI: 32.1, 51.9), including 40.8% (42/103) with a best response of partial response (PR) and 1 patient (1.0%) with a complete response (CR). The tumour responses were durable for the 43 responders with a median DOR of 9.7 months (95% CI: 7.6, 17.1). The DCR was reported to be 82.5% (85/103; 95% CI: 73.8, 89.3) at DCO. Futibatinib treatment resulted in a median PFS of 9.0 months (95% CI: 6.9, 13.1) relative to a median PFS of 6.9 months (95% CI: 6.2, 9.6) for pemigatinib in its pivotal study FIGHT-202. The median OS for futibatinib was reported to be 21.7 months (95% CI: 14.5, not estimable [NE]).

The sponsor claimed that futibatinib demonstrated clinical efficacy in the overall target population of CCA patients with FGFR2 fusions or other rearrangements with numerically non-inferior efficacy results as reported for pemigatinib. The ATP-competitive FGFR1-3 inhibitor pemigatinib (Pemazyre) showed in its pivotal multicenter, open-label, single-arm phase 2 study FIGHT-202 with 107 locally advanced or metastatic iCCA patients with FGFR2 fusions or rearrangements an ORR of 35.5% (95% CI: 26.5, 45.4) and a median DOR of 7.5 months (95% CI: 5.7, 14.5) (Abou-Alfa et al., 2020). In total, 46.7% had a SD as the best response maintained for a minimum of 39 days after the first pemigatinib dose, which resulted in a DCR of 82.2% (95% CI: 73.7, 89.0). The median OS was 21.1 months (95% CI: 14.8, NE). The median study follow-up at the DCO of 22-Mar-2019 in FIGHT-202 was 17.8 months (range: 11.6–21.3).

The sponsor also claimed that beside its efficacy in advanced CCA patients with FGFR2 fusions or rearrangements, futibatinib also showed significant benefit in CCA patients with FGFR2 fusions or rearrangements progressing on prior treatment with different ATP-competitive FGFR inhibitors, including pemigatinib. The sponsor considers that the distinct structural features and binding mode of

futibatinib being covalent provides significant benefit to CCA patients who have progressed on pemigatinib due to distinct acquired FGFR2 resistance mutations, which has been supported by preclinical and clinical data.

Treatment with the irreversible pan-FGFR inhibitor futibatinib has been reported to result in confirmed durable responses in CCA patients who have progressed on prior ATP-competitive FGFR inhibitors and developed acquired FGFR kinase domain mutations (Goyal et al., 2019). In a proof-of-concept study, futibatinib provided clinical benefit to patients with resistance to ATP-competitive inhibitors (i.e., BGJ398 or Debio 1347) and overcame several clinically observed acquired FGFR2 kinase domain mutations in iCCA models. In a single patient monitored for secondary FGFR2 kinase mutations by circulating tumour DNA (ctDNA) analysis from blood samples, an acquired FGFR2 resistance mutations (i.e., K660M) was detected at the time of progression to the ATP-competitive inhibitor and suppressed below the level of detection during the 16 months lasting response to futibatinib. In a similar report for iCCA patients with activating FGFR2 extracellular domain in-frame deletions (EIDs) a patient initially responding to the ATP-competitive inhibitor Debio 1374, a secondary FGFR2 kinase domain mutation (L618V) was detected at the time of progression (Cleary et al., 2021). The authors showed *in vitro* that this FGFR2 mutation causes resistance to ATP-competitive inhibitors as compared with FGFR2 wildtype, whereas *in vitro* efficacy of the irreversible inhibitor futibatinib was unaffected. Based on these *in vitro* results, the patient received futibatinib under a single-patient investigational new drug (IND) application and treatment with futibatinib resulted in a PR, with a 61% tumour reduction and a response duration of 17 months.

Similar observations for a clinical benefit of futibatinib have been noted in CCA patients progressing on pemigatinib. In a recent publication, Rengan and Denlinger described a 50-year-old woman with metastatic iCCA tumour harbouring a FGFR2 fusion who showed a robust response to futibatinib for 23.6 months, having previously benefited from pemigatinib (Rengan and Denlinger, 2022). At the time of progression on pemigatinib, ctDNA analysis revealed a new FGFR2 point mutation N549D in the kinase domain, which was shown to confer resistance to ATP-competitive inhibitors (Goyal et al., 2017; Goyal et al., 2019). During the treatment with futibatinib this N549D FGFR2 kinase domain mutation was not detected anymore in ctDNA samples suggesting that futibatinib successfully suppressed this FGFR2 aberrant clone causing resistance to ATP-competitive inhibitors.

The sponsor also presented non-published cases from futibatinib named-patient programs where CCA patients with FGFR2 fusions or rearrangements initially responding to pemigatinib developed resistance and then were switched to futibatinib treatment. In several patients the subsequent treatment with futibatinib resulted in a radiographic response. Patient summaries provided by the treating physicians for 11 cases who received futibatinib via compassionate use/individual patient request were presented.

The COMP agreed with the sponsor's conclusion that based on the results of study TAS-120-101, the observed clinical efficacy in the overall target population of CCA patients with FGFR2 fusions or other rearrangements appeared comparable to that reported for pemigatinib. However, since patients with prior FGFR-directed therapy were excluded from the pivotal study, the claim that futibatinib also showed significant benefit in CCA patients with FGFR2 fusions or rearrangements progressing on prior treatment with pemigatinib should be further substantiated by more details on the 11 cases presented. In addition, only 8 of these cases had received prior treatment with pemigatinib. In these cases, it is not evident whether responses have been achieved in those patients who were treated with futibatinib following prior treatment with pemigatinib.

Furthermore, the sponsor claimed that futibatinib provides a significant benefit in terms of improved safety to CCA patients with FGFR2 fusion or other rearrangements by a more than 50% lower incidence of grade ≥3 hypophosphatemia over pemigatinib while not compromising on efficacy in the

proposed indication, based on indirect comparison of the results from the pivotal study TAS-120-101 for futibatinib versus that for pemigatinib. This could according to the sponsor constitute a clinically relevant advantage of futibatinib since severe hypophosphatemia may present with confusion, seizures, focal neurologic findings, heart failure, respiratory failure, muscle weakness, rhabdomyolysis, and haemolytic anaemia (Sharma et al., 2022). The COMP considered that given the limited experience with futibatinib thus far, the claim of a better safety profile in comparison to pemigatinib cannot be concluded on at present stage and no adequate quantification is possible in the proposed indirect comparison of a specific adverse reaction.

Lastly, the sponsor claimed a significant benefit of futibatinib based on its pharmacological properties and the absent of any clinically significant impact of the co-administration of proton pump inhibitors (PPIs) on futibatinib exposure in contrast to pemigatinib where a significant reduction of the exposure was observed in more than one third of patients given PPIs (Pemazyre SmPC). Futibatinib thus provides a significant benefit in clinical practice by being suitable to be combined with PPIs, which are considered as the most effective and commonly used acid reducing therapy for cancer patients. However, this claim cannot be used to justify the significant benefit of futibatinib versus pemigatinib in the target patient population, since co-administration of PPIs is not a contraindication for the use of Pemazyre, according to the approved SmPC.

Based on the data provided by the sponsor, a conclusion on the significant benefit of futibatinib vis a vis the satisfactory method pemigatinib in BTC cannot be drawn.

4. COMP list of issues

- Prevalence

The sponsor should recalculate the prevalence for the proposed orphan condition based on EU data and the methodologies referred to in the "Points to Consider on the Estimation and Reporting of a Prevalence of a Condition for Orphan Designation".

The most relevant epidemiological data on the incidences of all biliary tract cancer subsets, including the number of patients with ampullary carcinoma, should be included in the indirect calculation of the prevalence. The revised estimate should also reflect the current ratio of the incidence of intrahepatic cholangiocarcinoma cases among all liver cancer cases in the EU and the proportion of patients with extrahepatic cholangiocarcinoma among all cholangiocarcinoma cases.

- Significant benefit

The sponsor argued that a significant benefit has been observed based on patient summaries provided by the treating physicians for 8 cases who have progressed on prior treatment with pemigatinib and were treated with futibatinib. However, it is not clear from the summaries provided whether responses have been achieved in these patients. The sponsor should further elaborate on this. A waterfall plot may be helpful.

On 23 February 2023, the Committee for Medicinal Products for Human Use (CHMP) adopted a positive opinion, recommending the granting of a marketing authorisation for the medicinal product Tibsovo, intended for the treatment of adult patients with locally advanced or metastatic cholangiocarcinoma. In case the Commission Decision for Tibsovo is published before the adoption of the maintenance report (17th May 2023) the maintenance report for Lytgobi should be updated accordingly.