29 April 2025
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Committee for Orphan Medicinal Products

Orphan Maintenance Assessment Report

of an orphan medicinal product submitted for marketing authorisation application

Ziihera (zanidatamab)
Treatment of biliary tract cancer
EU/3/21/2458

Sponsor: Jazz Pharmaceuticals Ireland Limited

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(s)	Zanidatamab
Other name(s)	--
International Non-Proprietary Name	Zanidatamab
Tradename	Ziihera
Orphan condition	Treatment of biliary tract cancer
Sponsor's details:	Jazz Pharmaceuticals Ireland Limited 5th Floor Waterloo Exchange Waterloo Road Dublin 4 D04 E5W7 Ireland
Orphan medicinal product designation procedural history	
Sponsor/applicant	Voisin Consulting
COMP opinion	17 June 2021
EC decision	19 July 2021
EC registration number	EU/3/21/2458
Post-designation procedural history	
Sponsor's name change	Name change from Voisin Consulting to Voisin Consulting Life Sciences – EC letter of 12 October 2021
Transfer of sponsorship	Transfer from Voisin Consulting Life Sciences to Jazz Pharmaceuticals Ireland Limited – EC decision of 5 June 2023
Marketing authorisation procedural history	
Rapporteur / Co-rapporteur	Boje Kvorning Pires Ehmsen / Robert Porszasz
Applicant	Jazz Pharmaceuticals Ireland Limited
Application submission	23 May 2024
Procedure start	20 June 2024
Procedure number	EMA/H/C/006380
Invented name	Ziihera
Approved therapeutic indication	Ziihera as monotherapy is indicated for the treatment of adults with unresectable locally advanced or metastatic HER2-positive (IHC3+) biliary tract cancer (BTC) previously treated with at least one prior line of systemic therapy (for biomarker-based patient selection, see section 4.2). Further information on Ziihera can be found in the European public assessment report (EPAR) on the Agency's website ema.europa.eu/en/medicines/human/EPAR/ziihera
CHMP opinion	25 April 2025

COMP review of orphan medicinal product designation procedural history	
COMP rapporteur(s)	Maria Elisabeth Kalland / Frauke Naumann-Winter
Sponsor's report submission	20 December 2024
COMP discussion and adoption of list of questions	18-20 March 2025
COMP opinion (adoption via written procedure)	29 April 2025

2. Grounds for the COMP opinion

The COMP opinion that was the basis for the initial orphan medicinal product designation in 2021 was based on the following grounds:

Having examined the application, the COMP considered that the sponsor has established the following:

- the intention to treat the condition with the medicinal product containing zanidatamab was considered justified based on early clinical data showing that pre-treated patients with high HER2 expression may achieve durable partial responses;
- the condition is life-threatening and chronically debilitating due to late diagnosis, development of hepatic insufficiency, progressive biliary obstruction followed by complications such as infections, and a low overall median survival of less than one year following diagnosis;
- the condition was estimated to be affecting approximately 1.6 in 10,000 persons in the European Union, at the time the application was made.

Thus, the requirements under Article 3(1)(a) of Regulation (EC) No 141/2000 on orphan medicinal products are fulfilled.

In addition, although satisfactory methods of treatment of the condition exist in the European Union, the sponsor has provided sufficient justification for the assumption that the medicinal product containing zanidatamab will be of significant benefit to those affected by the condition. The sponsor has provided preliminary clinical data that demonstrate that some patients with inoperable, pre-treated biliary tract cancer, with high expression of HER2, achieved durable partial responses. The proposed product targets a different patient population within the proposed orphan condition (patients overexpressing HER2) than the currently authorised product, pemigatinib (patients with FGFR2 mutations). This would offer a treatment option to a new patient population who have no remaining treatment options. The Committee considered that this constitutes a clinically relevant advantage.

Thus, the requirement under Article 3(1)(b) of Regulation (EC) No 141/2000 on orphan medicinal products is fulfilled.

The COMP concludes that the requirements laid down in Article (3)(1) (a) and (b) of Regulation (EC) No 141/2000 on orphan medicinal products are cumulatively fulfilled. The COMP therefore recommends the designation of this medicinal product, containing zanidatamab as an orphan medicinal product for the orphan condition: treatment of biliary tract cancer.

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 originating in the bile duct epithelium (cholangiocytes), the gallbladder and the ampulla of Vater. BTC encompasses gallbladder cancer (GBC), cholangiocarcinoma (CCA), and ampullary Vater carcinoma (AVC). CCAs, also referred to as bile duct cancer, include all tumours arising from the bile duct epithelium, with the majority (over 90%) being adenocarcinomas. CCAs are further classified anatomically into intrahepatic CCA (iCCA) and extrahepatic CCA (eCCA), the latter subdivided into perihilar CCA (pCCA) and distal CCA (dCCA). GBC, classified as an extrahepatic biliary cancer, is the most common malignancy of the biliary tract, accounting for 80-95% of BTC cases. It is also the most aggressive subtype, with the shortest median overall survival (OS).

The prognosis for BTC is generally poor, as most cases are diagnosed at an advanced stage. More than 65% of adult patients with BTC present with unresectable disease at diagnosis. Even among those who undergo potentially curative surgery, relapse rates remain high (Vogel, 2023). The median OS for BTC is less than 12 months, depending on the subtype (Fornaro et al., 2015).

Nearly 40% of patients with BTC harbour genetic alterations that are potential targets for precision medicine (Vogel et al., 2023). As a result, the current European Society for Medical Oncology (ESMO) clinical treatment guideline recommends molecular profiling to identify actionable mutations, particularly for second-line and subsequent therapies (Vogel et al., 2023). Among the targetable genetic alterations in BTC are amplifications of *ERBB2,* the gene encoding human epidermal growth factor receptor-2 (HER2), which is the target of zanidatamab (Ziihera). Other actionable mutations include those involving *BRAF, FGFR2* and *IDH1*. The sponsor noted that these mutations generally do not co-occur with HER2 amplifications in BTC (Jain et al., 2016; Lowery et al., 2018). It is important to highlight that the most common genetic alterations in BTC, such as mutations in *KRAS* and *p53*, are non-targetable prognostic markers (Table 1).

Genetic alterations frequently observed in BTC, including targetable and non-targetable alterations (Adapted from M. Benavides et al., 2015; Lendvai et al., 2020)

	More frequent genetic alterations	**BTC (%)**	**ICC (%)**	**ECC (%)**	**GBC (%)**
Gene	**Mutations**		2.9	4.4	4
K-Ras	Codon 12 mutation	17-54	4-54	10-42	11-25
B-RAF	Mutation (exclusive of K-Ras mutation)		5-22	1-3	1-33
EGFR	Mutation Amplification		2-20 1-27	1-18 19	9-12
HER2	**Amplification**		**0-5**	**5-25**	**11-25**
p53	Mutation (exon 5) Amplification	35-44	24-37	33-45	36
PTEN	Amplification	15	4	5	
PI3K/TOR	Mutation/others[a]		5-9	0-14	4-15
SMAD4	Mutation	16	2.6-13	14-55	
IDH1/2	Mutations	18/5	5-23.6	0-1	0
BAP1		25	9-15	4-10	
ARID1A		12-20	15-20	5-13	13
CDKN2 A/B		5.6-15 17-19	3-88	15-55	19-62
FGFR	Mutations/translocations		11-12.7	0-5	3
MET	Activation		2-4	0	0

[a] Pathway implied in 25% of ICC and 40% ECC but only 6% mutations described.
IDH1/2: isocitrate dehydrogenase 1/2

The approved therapeutic indication "*Ziihera as monotherapy is indicated for the treatment of adults with unresectable locally advanced or metastatic HER2-positive (IHC3+) biliary tract cancer (BTC) previously treated with at least one prior line of systemic therapy (for biomarker-based patient selection, see sections 4.2)*" falls within the scope of the designated orphan condition: Treatment of biliary tract cancer.

Intention to diagnose, prevent or treat

The medical plausibility has been 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), at which point the tumour obstructs the bile ducts or has spread to other organs. 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). The prognosis remains poor, with an estimated 5-year overall survival (OS) rate across all disease stages of <20% (Lamarca et al., 2021). Patients with advanced BTC face a median OS of 6-12 months following diagnosis, and death usually occurs from liver insufficiency or infectious complications accompanying progressive biliary obstruction.

Common clinical presentation includes symptoms related to biliary tract obstruction, such as cholestasis, cholangitis, jaundice, abdominal pain, weight loss, fever, fatigue, cachexia, and abnormal

liver function tests. These symptoms can swiftly escalate to life-threatening complications, including liver insufficiency and serious infections (Lamarca et al., 2021).

Therapeutic options for BTC remain limited, particularly for patients who progress on standard first-line therapy. Second-line regimens, such as FOLFOX (folinic acid, fluorouracil, and oxaliplatin), have demonstrated modest clinical benefit, with a median OS of 6.2 months compared to 5.3 months with active symptom control (ASC) alone (Lamarca, 2019; Vogel, 2023). However, these therapies are associated with significant toxicity burdens. For example, Grade 3–5 adverse events (AEs) such as neutropenia, fatigue, and infection, as well as chemotherapy-related deaths were reported in the phase 3 study ABC-06 evaluating the benefit of second-line FOLFOX (Lamarca, 2021). Other second-line treatment options, including capecitabine-based regimens, gemcitabine-based combinations, and irinotecan-based therapies, show similarly modest objective response rates (ORRs) of approximately 3-15%, with median progression-free survival (PFS) and OS of 3-4 months and 6-7 months, respectively (Brieau, 2015; Lowery, 2019; Fornaro, 2015; Lamarca, 2014; Lamarca, 2021; Yoo, 2021).

The sponsor has not identified any significant changes in the seriousness of BTC since the orphan designation was granted in 2021. The COMP considers the condition to remain both life threatening, with low overall survival rates following diagnosis, and chronically debilitating due to the development of hepatic insufficiency during the disease course, progressive biliary obstruction, and associated complications such as infections.

Number of people affected or at risk

At the time of the orphan designation in June 2021, the COMP agreed on a prevalence estimate for BTC of approximately 1.6 in 10,000 persons in the European Union (EU). The newly proposed prevalence estimate for the purpose of this orphan maintenance procedure remains consistent with this figure.

In preparation for the orphan maintenance procedure, the sponsor conducted a review of available EU cancer registries, national cancer registries, and relevant literature up to August 2024. However, the specific registries and publications utilised for the review have not been disclosed by the sponsor. BTC is sub-classified into CCA (all subtypes considered) and GBC. The sponsor used the following formula for the calculation of BTC prevalence: Prevalence (BTC) = Prevalence (CCA) + Prevalence (GBC).

The prevalence figures for BTC calculated by the sponsor are presented in Table 1 and Table 2 below.

Table 1. Calculated prevalence of BTC based on literature incidence data

$Prevalence_{(CCA)}$	1.27 per 10,000
$Prevalence_{(GBC)}$	0.37 per 10,000
$Prevalence_{(BTC)}$	1.64 per 10,000

Table 2. Calculation of BTC prevalence based on CCA and GBC prevalence calculated from database search

$Prevalence_{(CCA)}$	0.32 per 10,000
$Prevalence_{(GBC)}$	0.17 per 10,000
$Prevalence_{(BTC)} = Prevalence_{(CCA)} + Prevalence_{(GBC)}$	0.49 per 10,000

Based on literature data, the sponsor estimated the prevalence of BTC to be 1.64 per 10,000 people in the European Community. In contrast, the prevalence of BTC derived from the database search is estimated to be 0.49 per 10,000 people. With a prevalence of 1.64 per 10,000 and a projected EU population of 453,476,671 in 2020 (EU27 plus Iceland, Liechtenstein and Norway; Eurostat 2021), it is estimated that approximately 74,370 individuals in the European Community are living with BTC.

The sponsor has not provided citations for the literature incidence data, or the methodology used to derive prevalence from incidence values (1.64 per 10,000; Table 2). Calculating prevalence from incidence requires a multiplication by the expected disease duration (or survival), but this information has not been included. Similarly, for the prevalence estimate based on the database search (0.49 per 10,000; Table 3), the sponsor has not disclosed the specific data sources or calculation methods used. Furthermore, the subset of BTC known as ampullary Vater carcinoma has not been included in the prevalence calculation. According to the latest ESMO clinical practice guideline for BTC from 2023, cancers arising from the ampulla of Vater are sometimes included under the term BTC due to their rarity, despite having a distinct clinical course and management approach. The guideline also notes that ampullary carcinoma is not discussed in detail, which may reflect its ambiguous classification within BTC.

The COMP concluded that further clarification on the proposed prevalence estiamte is required and adopted a question outlining specific points for the sponsor to address.

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

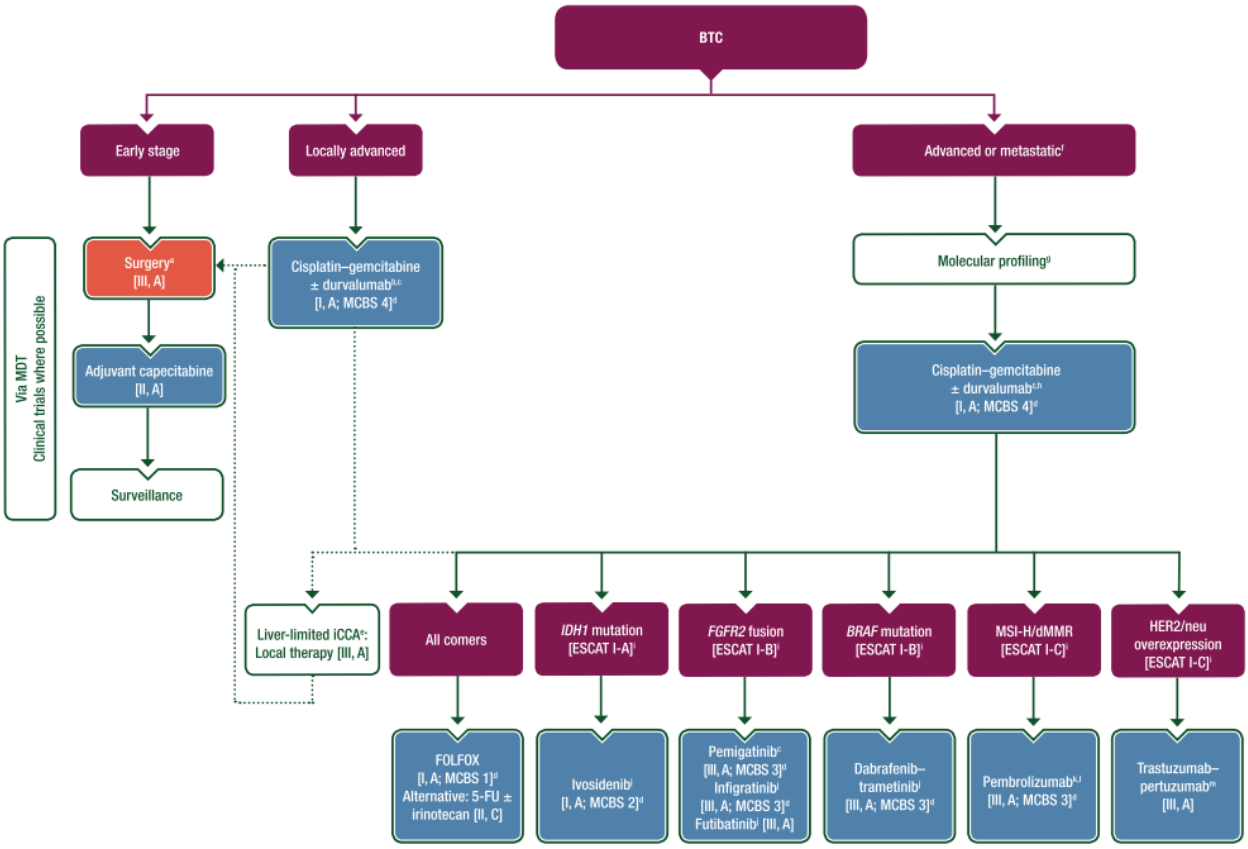
At the time of orphan maintenance review, satisfactory methods are determined by the authorised indication of a medicinal product, as per the summary of product characteristics (SmPC). Ziihera is indicated for the treatment of adults with unresectable locally advanced or metastatic HER2-positive BTC in second- and later-line settings. Notably, only authorized medicinal products indicated for the treatment of the target patient population can be considered satisfactory methods.

The latest ESMO clinical treatment guideline for BTC recommends chemotherapy regimens such as FOLFOX or, alternatively, 5-fluorouracil combined with nano-liposomal irinotecan as second-line treatment options for patients whose BTC does not harbour a targetable genetic alteration (Vogel et al., 2023). While these therapies have demonstrated modest effects on OS, they are not authorized for the treatment of BTC in the EU.

For patients whose BTC harbours targetable genetic alterations (e.g., BRAF, FGFR2, IDH1, or HER2), targeted therapies are recommended in the second-line setting. Specifically, for HER2-positive BTC patients, the guideline suggests targeted therapy with trastuzumab or pertuzumab. However, these products are not authorized for the treatment of BTC in the EU and are therefore not considered satisfactory methods. The treatment algorithm from the ESMO guideline is presented in Figure 1.

For completeness, first-line treatment options for BTC, including HER2-positive patients, consist of the chemotherapy combination cisplatin and gemcitabine, with or without PD-1 or PD-L1 inhibitors such as pembrolizumab (Keytruda) or durvalumab (Imfinzi). These therapies are authorized for use in BTC in the first-line treatment setting.

Figure 1. Treatment algorithm for BTC* according to ESMO guideline (Vogel et al., 2023)



* : BTCs refer to a spectrum of invasive tumours, usually adenocarcinomas, arising from the gallbladder or cystic duct [gallbladder carcinoma (GBC)] or the biliary tree (CCA). Abbreviations: 5-FU, 5-fluorouracil; BTC, biliary tract cancer; ChT, chemotherapy; dCCA, distal cholangiocarcinoma; dMMR, mismatch repair deficiency; EMA, European Medicines Agency; ESCAT, ESMO Scale for Clinical Actionability of Molecular Targets; FDA, Food and Drug Administration; FGFR2, fibroblast growth factor receptor 2; FOLFOX, 5-fluorouracileleucovorineoxaliplatin; GBC, gallbladder carcinoma; HER2, human epidermal growth factor receptor 2; iCCA, intrahepatic cholangiocarcinoma; IDH1, isocitrate dehydrogenase 1; MCBS, ESMO-Magnitude of Clinical Benefit Scale; MDT, multidisciplinary team; MSI-H, microsatellite instability-high; NTRK, neurotrophic tyrosine receptor kinase; pCCA, perihilar cholangiocarcinoma; PD-1, programmed cell death protein 1; PS, performance status.

Approved targeted therapies for BTC in second- and later-line settings are summarized in Table 4. These therapies are specific to subpopulations of BTC patients based on genetic alterations such as FGFR2 fusions or rearrangements, IDH1 R132 mutations, or microsatellite instability high (MSI-H) or mismatch repair deficiency (dMMR). However, none of these therapies are approved for HER2-amplified or HER2-expressing BTC, and three out of four of them are restricted to treatment of only patients with CCA.

Table 3. Summary of approved second- and later-line therapies for BTC patients in the EU

Product (INN)	Therapeutic indication per SmPC
Lytgobi (futibatinib)	Lytgobi monotherapy is indicated for the treatment of adult patients with locally advanced or metastatic CCA with a FGFR2 fusion or rearrangement that have progressed after at least one prior line of systemic therapy.
Pemazyre (pemigatinib)	Pemazyre monotherapy is indicated for the treatment of adults with locally advanced or metastatic CCA with a FGFR2 fusion or rearrangement that have progressed after at least one prior line of systemic therapy.
Tibsovo (ivosidenib)	Tibsovo monotherapy is indicated for the treatment of adult patients with locally advanced or metastatic CCA with an IDH1 R132 mutation who were previously treated by at least one prior line of systemic therapy.
Keytruda (pembrolizumab)	KEYTRUDA as monotherapy is indicated for the treatment of biliary cancer with microsatellite instability high (MSI-H) or mismatch repair deficient (dMMR) who have disease progression on or following at least one prior therapy.

In summary, only one of the targeted therapies is approved for the treatment of patients with GBC, and none are approved for patients with HER2-amplified or HER2-expressing BTC. Additionally, non-targeted second-line chemotherapy options, such as FOLFOX or 5-fluorouracil combined with nano-liposomal irinotecan, are not authorized in the EU for BTC. Genetic alterations commonly described in BTC (e.g., BRAF, FGFR2, IDH1) generally do not co-occur with HER2 amplifications (Jain et al., 2016; Lowery et al., 2018). Therefore, no approved treatment qualifies as a satisfactory method for the purpose of examining the significant benefit compared to zanidatamab (Ziihera) in patients with BTC.

Significant benefit

Zanidatamab (Ziihera) is intended for a patient population for whom no other satisfactory method is available (see the section about Existing methods above). No justification for significant benefit is therefore required.

Overall conclusion by the COMP:

The COMP requested a revision of the sponsor's prevalence calculation as follows:

- Detailed information on the data sources (including citations) and actual data used in both their literature search and their EU and national registry (database) approach should be provided.
- The sponsor is asked to present the full methodology and calculations used to derive prevalence for each approach presented.
- For the prevalence estimate derived from incidence values, the sponsor is asked to provide and discuss disease duration (or survival) data used in their calculation.
- Furthermore, the biliary tract cancer subset of ampullary Vater carcinoma needs to be included in the prevalence calculation, or a justification should be provided if it is excluded.

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 on the prevalence of a condition for the purpose of orphan designation.

Comments on sponsor's response to the COMP list of issues

In the written response to the COMP's request for revision of the prevalence calculation, the sponsor clarified that the literature review conducted for the current orphan maintenance report for zanidatamab (Ziihera) included publications from the Embase.com database (January 2013–July 2023), supplemented by published registry data from sources such as the European Cancer Information System (ECIS), the Surveillance, Epidemiology, and End Results (SEER) programme, the Global Cancer Observatory (GLOBOCAN), Cancer Statistics in Japan (Ganjoho), Cancer Research UK, The Office for National Statistics (UK), and the Orphanet database. The searches were conducted on 26 July 2023 and limited to the past 10 years.

As requested, the sponsor has provided detailed information on the methodology, data sources, and calculations used to derive the updated prevalence estimates for BTC, which now include the CCA subtypes (iCCA and eCCA), GBC, and AVC. The prevalence was calculated using the standard formula: prevalence (P) = incidence (I) × duration of disease (D) for each of the subtypes. This methodology was applied consistently across all subtypes. This resulted in a combined prevalence estimate of 1.9 in 10,000 persons in the European Community based on the literature data presented. The main data sources and calculations are summarised below.

Calculation of CCA prevalence from the literature and database search

The European prevalence rate of CCA, based on the literature data presented, was derived from incidence values ranging from 0.05 to 0.96 per 10,000 inhabitants, with 0.96 per 10,000 being used as the conservative estimate in the final calculation. The variations in incidence reported across European studies reflect differences in methodology, population size, and regional factors (Floreani et al., 2013; Florio et al., 2020; Jepsen et al., 2007; Witjes et al., 2012a; Alvaro et al., 2010; Borie et al., 2009). The lowest reported values include 0.03 per 10,000 for iCCA in the Netherlands and 0.01 per 10,000 for eCCA in Poland from 2008 to 2012 (Florio et al., 2020), while the highest incidence rates were observed in Northeast Italy (Veneto Region), with 0.49 per 10,000 for iCCA and 0.47 per 10,000 for eCCA, as reported by Floreani and colleagues in a retrospective analysis of hospital discharge records conducted from 2005 to 2009 (Floreani et al., 2013).

Based on ECIS data from 2020, the incidence of CCA was indirectly calculated to be 0.32 per 10,000 inhabitants in the EU27. This estimate was derived from the reported liver cancer incidence of 1.28 per 10,000 persons and the assumption that 25% of all liver cancer cases are attributable to CCA.

The median OS for patients with CCA was reported as 15.8 months (1.32 years) (David and Patel 2017). This retrospective study included 242 patients diagnosed with bile duct cancer at the Mayo Clinic in Florida from 1992 to 2010, with a median follow-up duration of 11.6 months. The mean age at diagnosis was 63 years, and 13.8% of patients presented with Stage I disease, while 28% presented with Stage IV. A total of 156 patients underwent surgery, chemotherapy, radiotherapy, or a combination of treatments. The median OS differed between the subtypes: 13.5 months for iCCA, 13.9 months for pCCA, and 22 months for dCCA. It should be noted that the study has certain limitations, including its single-center retrospective design, the study period, which may not reflect advancements in treatment options introduced after 2010, and its focus on a single center in the US, which may limit generalizability to other regions.

Multiplying the highest incidence value reported in the literature by the median OS of 1.32 years resulted in a prevalence estimate of 1.27 per 10,000 inhabitants in the European Community.

Calculation of GBC prevalence from the literature and the database search

The reported incidence for GBC ranged from 0.07 to 0.37 per 10,000 inhabitants. This variation in incidence rates again reflects differences in methodology, population size, and study periods across European studies (Noel et al., 2016; Floreani et al., 2013; Faivre et al., 2012; Witjes et al., 2012b; Alexander et al., 2012; Cziupka et al., 2012; Alvaro et al., 2010). The lowest harmonized incidence rates were reported in the Netherlands, with 0.07 per 10,000 based on retrospective analyses of cancer registration data for both males and females in 2008 (Witjes et al., 2012b; Alexander et al., 2012). In contrast, the highest harmonized incidence rate was observed in Northeast Italy (Veneto Region), with 0.37 per 10,000 (Floreani et al. 2013). Other notable findings include a harmonized incidence rate of 0.3 per 10,000 in Sweden, based on national inpatient and cancer registry data from 2013 (Noel et al., 2016), and 0.11 per 10,000 in Western Pomerania, Germany, derived from chart reviews conducted at a tertiary referral center between 2001 and 2009 (Cziupka et al., 2012). To adopt a conservative approach, the highest incidence figure of 0.37 per 10,000, as reported in Italy (Floreani et al., 2013), was retained.

The incidence of GBC in the EU27 was reported by ECIS to be 0.16 per 10,000 inhabitants in 2020.

As the median OS for GBC patients has been reported to be less than 12 months (Valle et al., 2010; Okusaka et al., 2010; Fornaro et al., 2015; Oh et al., 2022; Kelley et al., 2023), the GBC prevalence was estimated to equal the GBC incidence, in line with the COMP/436/01 final "Points to Consider on the Calculation and Reporting of the Prevalence of a Condition for Orphan Designation". Fornaro and colleagues describe a median OS of less than 12 months depending on the subtype (Fornaro et al., 2015). Furthermore, studies such as ABC-02 (Valle et al., 2010) and BT22 (Okusaka et al., 2010) demonstrated median OS of 11.7 months and 11.2 months, respectively, for gemcitabine-cisplatin treatment. The Valle study is particularly relevant as it established the standard first-line treatment for BTC, namely gemcitabine-cisplatin (CisGem), and thus serves as a foundational reference for subsequent advancements in therapy. More recent studies, including the phase 3 TOPAZ-1 study, showed a modest improvement in median OS to 12.8 months with the addition of durvalumab to gemcitabine-cisplatin (Oh et al., 2022). Similarly, the KEYNOTE-966 phase 3 study demonstrated comparable survival benefits with the addition of pembrolizumab, further supporting the potential role of immune checkpoint inhibitors in this patient population (Kelley et al., 2023). These references substantiate the estimate that the median OS for BTC remains less than 1 year.

Calculation of AVC prevalence from the literature

The reported global incidence for AVC ranged from 0.018 to 0.093 per 10,000 inhabitants (Taturu 2024, Koshiol 2022, Kim 2021, Baria 2022). To take a conservative approach, the highest incidence value of 0.093 per 10,000 was used to estimate the AVC prevalence.

The median OS for patients with AVC was reported as 33.1 months (2.76 years) in a study conducted by Kim and colleagues (Kim et al., 2021). This population-based trend analysis utilized data from US national incidence records (2009–17) and mortality records (2009–2018), encompassing a total population of 103,048 individuals, of whom 2,053 were diagnosed with AVC. While these findings provide valuable insights, it should be noted that the data are based on the US population, which may limit their applicability to the European community. By multiplying the highest incidence value reported in the literature by the disease duration of 2.76 years, the prevalence of AVC was estimated at 0.26 per 10,000 inhabitants in the European Community.

Combined prevalence for BTC

Based on the literature data presented, the prevalence of the entire BTC population, considering the prevalence rates for the CCA subtypes, GBC, and AVC, was estimated to be 1.90 per 10,000 inhabitants in the European Community (1.27 [CCA] + 0.37 [GBC] + 0.26 [AVC] = 1.90 [BTC]).

Based on ECIS data, the prevalence of the BTC subtypes of CCA and GBC, excluding AVC, was estimated to be 0.58 per 10,000 inhabitants in the European Community. For CCA, the prevalence was calculated by multiplying the incidence of 0.32 per 10,000 inhabitants by the median OS of 1.32 years (0.32 × 1.32 = 0.42 [CCA]). The GBC prevalence was estimated to be 0.16 per 10,000 inhabitants, and combining the two subtypes resulted in a total prevalence of 0.58 per 10,000 inhabitants (0.42 [CCA] + 0.16 [GBC] = 0.58 [BTC]).

Discussion and final conclusion by the COMP

The COMP noted that the updated prevalence estimate of 1.9 per 10,000 is slightly higher than those figures accepted in recent designations and in the latest orphan maintenance procedures for BTC, where estimates of approximately 1.5–1.7 per 10,000 persons were deemed acceptable. The sponsor has adopted a conservative approach, using the highest incidence values and survival data available in the literature, while also including the occurrence of AVC in the prevalence calculation. The methods employed are consistent with previously accepted methodologies, although the sources used vary. The variations in incidence values reported across European studies for the BTC subsets highlight the inherent challenges in harmonizing data and deriving prevalence rates through indirect calculations.

In the calculation, the sponsor has referred to the reported global incidence for AVC instead of the values reported in EU27/EEA countries. In the European Community, the reported incidence for AVC ranged from 0.038 per 10,000 inhabitants in Italy to 0.045 per 10,000 inhabitants in Spain during the period 2008–2012 (Baria et al., 2022). Other notable findings include incidence rates of 0.042 per 10,000 in France and Germany, and 0.04 per 10,000 in Poland. Multiplying the highest incidence value in the European Community of 0.045 per 10,000 by the disease duration of 2.76 years results in a prevalence estimate for AVC of 0.12 per 10,000 inhabitants. Use of this estimate in the updated prevalence of the entire BTC population would then give an overall BTC prevalence of 1.76 per 10,000 inhabitants in the European Community.

Based on the epidemiological data sources presented in this application and the assumptions made, the COMP concluded that BTC affects approximately 1.8 per 10,000 persons in the EU. Consequently, BTC remains a rare disease that meets the prevalence threshold for orphan designation in the European Community.

The COMP adopted a positive opinion on the maintenance of orphan designation.

4. COMP position adopted on 29 April 2025

The COMP concluded that:

- the proposed therapeutic indication falls entirely within the scope of the orphan condition of the designated Orphan Medicinal Product;
- the prevalence of biliary tract cancer (hereinafter referred to as "the condition") was estimated to remain below 5 in 10,000 and was concluded to be approximately 1.8 in 10,000 persons in the European Union, at the time of the review of the designation criteria;
- the condition is chronically debilitating due to the development of hepatic insufficiency, progressive biliary obstruction, and associated complications such as infections, and life-threatening with a low overall survival following diagnosis;
- at present no satisfactory method has been authorised in the European Union for the treatment of the entirety of patients covered by the therapeutic indication of Ziihera.

The COMP, having considered the information submitted by the sponsor and on the basis of Article 5(12)(b) of Regulation (EC) No 141/2000, is of the opinion that:

- the criteria for designation as set out in the first paragraph of Article 3(1)(a) are satisfied;
- the criteria for designation as set out in Article 3(1)(b) are satisfied.

The Committee for Orphan Medicinal Products has recommended that Ziihera, zanidatamab for treatment of biliary tract cancer (EU/3/21/2458) is not removed from the Community Register of Orphan Medicinal Products.