EU RISK MANAGEMENT PLAN

ZIIHERA (zanidatamab)

RMP version to be assessed as part of this application:

RMP Version number: 0.5

Data lock point for this RMP	11JUL2024	Version number	0.5
Date of final sign off	12MAY2025		

Rationale for submitting an updated RMP:

Not applicable as this is initial marketing authorisation.

Summary of significant changes in this RMP: Not applicable

Other RMP versions under evaluation: Not applicable

QPPV name: Ilaria Grisoni

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

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PART I PRODUCT(S) OVERVIEW

Table Part I.1: Product Overview

Active substance(s) (INN or common name)	Zanidatamab
Pharmacotherapeutic group(s) (ATC Code)	L01FD07
Marketing Authorisation <Holder> <Applicant>	Jazz Pharmaceuticals Ireland Limited
Medicinal products to which this RMP refers	1
Invented name(s) in the European Economic Area (EEA)	Ziihera
Marketing authorisation procedure	Centralised
Brief description of the product	Chemical class: Monoclonal antibody
	Summary of mode of action: Zanidatamab is a dual HER2-targeted bispecific antibody that simultaneously binds extracellular domains 2 and 4 on separate HER2 monomers (binding in trans). Binding of zanidatamab with HER2 results in internalization leading to a reduction of the receptor on the cell surface. Zanidatamab induces complement-dependent cytotoxicity (CDC), antibody-dependent cellular cytotoxicity (ADCC) and antibody-dependent cellular phagocytosis (ADCP). These mechanisms result in tumour growth inhibition and tumour cell death.
	Important information about its composition: One single-dose vial of powder for concentrate for solution for infusion contains 300 mg of zanidatamab. After reconstitution one vial contains 50 mg/mL of zanidatamab.
Hyperlink to the Product Information	Link to SmPC
Indication(s) in the EEA	Current: Ziihera as monotherapy is indicated for the treatment of adults with unresectable locally advanced or metastatic HER2-positive biliary tract cancer (BTC) previously treated with at least one prior line of systemic therapy.
	Proposed (if applicable): Not applicable

Dosage in the EEA	Current: The recommended dose of Ziihera is 20 mg/kg, administered as an intravenous infusion every 2 weeks (every 14 days) until disease progression or unacceptable toxicity. For duration of infusion, see Table 3 of SmPC.
	Proposed (if applicable): Not applicable
Pharmaceutical form(s) and strengths	Current: 300 mg powder for concentrate for solution for infusion. White lyophylised cake
	Proposed (if applicable): Not applicable
Is/will the product be subject to additional monitoring in the EU?	Yes

PART II SAFETY SPECIFICATION

PART II: MODULE SI EPIDEMIOLOGY OF THE INDICATION(S) AND TARGET POPULATION(S)

Biliary tract cancer

Biliary tract cancer (BTC) is a collective term for a group of gastrointestinal (GI) tract cancers that include gallbladder cancer (GBC), ampulla of Vater cancer (AVC) intrahepatic cholangiocarcinoma (ICC), and extrahepatic cholangiocarcinoma (ECC), with the latter further divided into perihilar extrahepatic cholangiocarcinomas and distal extrahepatic cholangiocarcinomas. Cholangiocarcinoma (CC) categorization as either ICC or ECC is based on anatomic location with respect to the second-order bile ducts. Approximately 5% to 10% of CC are intrahepatic and arise from peripheral bile ducts within the liver parenchyma proximal to the secondary biliary radicals (Kodali, 2021). The majority (60% to 70%) of ECCs are perihilar or "Klatskin" tumours involving the hepatic duct bifurcation; the remaining ECCs involve the distal common bile duct (Kodali, 2021).

In 2017, 210,878 incident cases, 173,974 mortalities, and 3,483,046 disability-adjusted life years were associated with BTC globally, representing a major health burden (Ouyang, 2021). While early-stage BTC can be cured through complete surgical resection, the nonspecific symptomatology of BTC can often delay diagnosis until more advanced stages when surgical resection with curative intent is not possible, and chemotherapy and chemoradiation are instead used to slow the spread (van Keulen, 2023; Zhang, 2023). As a result, BTC is generally viewed as being difficult to treat and is associated with a poor prognosis (Ayasun, 2023).

Human epidermal growth factor receptor-2 (HER2) has been receiving growing attention in the context of BTC research, based on findings that HER2 overexpression (HER2-positive) in BTC patients was associated with shorter disease-free survival and overall survival (OS) compared to HER2-negative cases. HER2-positive BTC is rare, representing a minority within this already rare disease, with approximately 11% to 25% of GBCs expressing HER2 and 0% to 25% of CCs (both intrahepatic and extrahepatic) expressing HER2 (Yan, 2014; Yoshikawa, 2008; Benavides, 2015; Lendvai, 2020).

Incidence

According to the Information Network on Rare Cancers (RARECARENet), the overall incidence of BTC in the European Union (EU) was found to be 2.86 per 100,000 in 2003-2007, with females having a slightly higher incidence than males (2.90 vs 2.81) (RARECARENet, 2023). Eastern Europe was found to be the region with the highest incidence (3.39 per 100,000), while Ireland and the United Kingdom (UK) were found to have the lowest (2.43 per 100,000) (RARECARENet, 2023). The age-standardized incidence rate of BTC across EU-27 countries ranged from 2.06 to 3.59 per 100,000 person-years. Country-specific rates (per 100,000 person-years) were as follows: Bulgaria (2.06), France (2.76), Germany (2.84), Italy (3.59), Poland (2.95) and Spain (2.93) (Baria, 2022). Incidence rates of gender-specific BTC subtypes are provided below in Table Part II: Module SI.1.

Table Part II: Module SI.1: Age-standardized incidence (per 100,000 PY) of BTC subtypes, by country and gender, 2008–2012

[a]Country	ECC		ICC		GBC	
	Male	Female	Male	Female	Male	Female
Bulgaria	0.42	0.24	0.42	0.24	0.69	1.39
France	0.80	0.42	1.32	0.76	0.45	0.64
Germany	0.98	0.56	0.80	0.59	0.48	0.85
Italy	1.06	0.73	0.88	0.59	0.81	1.23
Poland	0.11	0.13	0.47	0.47	0.80	2.17
Spain	0.89	0.49	0.88	0.57	0.66	0.96

[a] Adapted from Baria (2022). BTC: biliary tract cancer; GBC: gallbladder cancer; ECC: extrahepatic cholangiocarcinoma; ICC: intrahepatic cholangiocarcinoma; PY: person-years; Incidence rates were age-adjusted using the 1960 Segi World Standard Population.

According to the European Cancer Information System (ECIS), the 2022 age-standardized incidence of GBC combined with ECC (per ECIS registries definitions) across EU-27 countries was lower among men than among women (1.2 vs 1.9 per 100,000, respectively) (Randi et al., 2023). According to GLOBOCAN data, where CC is explicitly not included in GBC estimates, the incidence of GBC was found to be lowest in Southern Europe, and highest in Central and Eastern Europe (0.62 vs 0.81 per 100,000 respectively) (Global Cancer Observatory, 2023). In males, incidence ranged from 0.36 per 100,000 in Western Europe to 0.58 per 100,000 in Central and Eastern Europe (Global Cancer Observatory, 2023). In females, incidence ranged from 0.58 per 100,000 in Western Europe to 0.96 per 100,000 in Central and Eastern Europe (Global Cancer Observatory, 2023).

Prevalence

Information on prevalence data related to BTC and its subtypes in official sources and published literature is limited. RARECARENet data estimates the overall complete prevalence of BTC in Europe as 6.73 per 100,000 persons, with prevalence being lowest in Ireland and the UK (6.50 per 100,000) and highest in Southern Europe (7.36 per 100,000) (RARECARENet, 2023). A national database analysis of German cancer cases identified GBC and BTC from 2017–2018. The 5-year, 10-year, and 25-year prevalence rates were estimated as 8.6, 13.8, and 23.3 per 100,000 persons, respectively, for women, and 9.3, 13.4, and 20.3 per 100,000 persons, respectively, for men (Statista, 2023).

HER2-positive BTC

The specific prevalence of HER2-positive BTC in Europe has been reported by at least 9 recently published studies (Table Part II: Module SI.2). The reported prevalence of HER2-positive BTC among all BTCs was 2.2% in the UK (Lamarca, 2020), 3.9% in Austria (Taghizadeh, 2023), 4.1% in France (Augustin, 2020), and 11% in Italy (Vivaldi, 2020). The reported prevalence of HER2-positive in GBC reported for 7 studies ranged from 5.4%

(Albrecht, 2020) to 14.6% (Ramalhosa, 2022). One study reported 0%, but only contained a single patient with GBC (Lamarca, 2020). All studies including the prevalence of HER2-positive for both ECC and ICC reported a higher prevalence for ECC than ICC (Albrecht, 2019; Augustin, 2020; Lamarca, 2020; Vivaldi, 2020). The estimates for ECC ranged from 1.8% (Albrecht, 2019) to 14.3% (Vivaldi, 2020), and the estimates for ICC ranged from 0.6% (Albrecht, 2019) to 11.1% (Vivaldi, 2020).

Table Part II: Module SI.2: Prevalence of HER2-positive BTC in Europe in recently published studies

[a]Author & Year	Country	Reported Prevalence			
		Overall	GBC	ECC	ICC
Taghizadeh 2023	Austria	3.9%	NR	NR	NR
de Bitter 2022	the Netherlands	NR	9.4%	NR	NR
Ramalhosa 2022	Portugal	NR	14.6%	NR	NR
Albrecht 2020	Germany	NR	5.4%	NR	NR
Augustin 2020	France	4.1%	11.1%	2.6%	1.4%
Hryciuk 2020	Poland	NR	10.4%	NR	NR
Lamarca 2020	United Kingdom	2.2%	0%	5.0%	1.6%
Vivaldi 2020	Italy	11%	7.7%	14.3%	11.1%
Albrecht 2019	Germany	NR	NR	1.8%	0.6%

[a] BTC: biliary tract cancer; GBC: gallbladder cancer; ECC: extrahepatic cholangiocarcinoma; ICC: intrahepatic cholangiocarcinoma; NR: not reported

Demographics of the indicated population

Age

Data suggest that patients with BTC are older than the general population (Izquierdo-Sanchez, 2022; Jansson, 2023; Lundgren, 2019; Moik, 2019; Zhang, 2023). The median age at first diagnosis of BTC is 62 years (range: 24–81 years) (Zhang, 2023). A Swedish cohort study (2011–2019) of 14,083 BTC patients identified in the Swedish Cancer Register reported that 89.9% of the cohort were 55–84 years of age, while only 10.1% were 20–54 years of age (Rahman, 2022). A large, multicenter, retrospective observational study capturing histologically or cytologically confirmed CC during 2010 - 2019 in the European Network for the Study of Cholangiocarcinoma Patients (ENSCAA), provided demographic characteristics of 2,234 patients across 26 hospitals in 11 European countries (Izquierdo-Sanchez, 2022). Across all CC, the median age at diagnosis was 66 years (Interquartile Range [IQR]: 58–73 years); ICC were associated with a median age of 65 years (IQR: 56–72 years) and ECC had a median age of 68 years (IQR: 59–73 years) for distal CC and 66 years (IQR 59–73 years) for perihilar CC. The

median age of patients receiving resection for ICC in European studies ranged from 61 to 68 years (Jansson, 2023; van Keulen, 2023).

Gender

BTC occurs in both men and women, with the incidence of CC (ICC and ECC) appearing to be higher in males while the incidence of GBC is higher in females (per Table Part II: Module SI.1 above) (IIzquierdo-Sanchez, 2022). Single-center studies from Germany and Austria reported that 47.1% and 52.5% of BTC participants were male, respectively (Zhang, 2023; Moik, 2019), while a national study of Swedish patients with BTC reported that 47.2% were male (Rahman, 2022). Two systematic reviews of ICC patients receiving resection reported that 46–77% of patients were male across European studies (Jansson, 2023; van Keulen, 2023). Meanwhile, a single-center observational study of 249 Swedish patients with incidental GBC reported that only 20.9% of patients were male (Lundgren, 2019). These findings are consistent with International Agency for Research on Cancer (IARC) data presented in Table Part II: Module SI.1 (Baria, 2022).

Racial and ethnic origin

While there are differences in the epidemiology of BTC and its subtypes among countries and geographic areas (described above), current published literature does not indicate an association between BTC frequency and race/ethnicity examined in a given region. A pan-European study of 2,234 patients with CC reported that 96.6% of patients with CC (all types) were White, while 96.6% of patients with ICC and 96.1-97.1% of patients with ECC (including distal and perihilar CC) were White (Izquierdo-Sanchez, 2022). However, these data are insufficient to draw conclusions on the association of BTC with race and ethnicity.

Risk Factors

As described above, the risk of BTC increases with age and overall appears to be higher in men than women. Additional risk factors identified in the published literature included bile duct infections, chronic liver disease, choledocholithiasis, gallstones, and primary sclerosing cholangitis (Hemminki, 2023a).

Risk factors for CC in adults include primary sclerosing cholangitis (PSC) (the most commonly known predisposing condition with 5% to 40% of CC in Western countries), fibropolycystic liver disease, parasitic infection (liver fluke infections especially with *Opisthorcis viverrini* and *Clonorchis sinensis*), and intrahepatic biliary stones (hepatolithiasis) (Blechacz, 2017; Khan, 2005; Marcano-Bonilla, 2016; Razumilava, 2013; Vogel, 2023). Chronic liver disease (cirrhosis and viral hepatitis), obesity, diabetes, and alcohol are also recognized as risk factors, especially for development of ICC (Blechacz, 2017; Bridgewater, 2014, Izquierdo-Sanchez, 2022). A less commonly recognized cause of CC is biliary-enteric drainage, which can cause bile stasis, inflammation, and stone formation (Razumilava, 2013). Risk factors for GBC include gallstone disease, such as cholelithiasis (which is the strongest risk factor for GBC present in 70% to 90% of GBC cases), porcelain gallbladder, gallbladder polyps, and anomalous pancreaticobiliary duct junctions. In addition, a number of other clinical conditions are associated with higher risk of GBC, including inflammatory bowel disease (IBD), PSC, chronic infection (e.g., *Salmonella typhi* and *paratyphi*; and *Helicobacter bilis* and *pylori*), congenital malformations, and obesity

(Bridgewater, 2016; Kanthan, 2015; Marcano-Bonilla, 2016; Zhu, 2010). A global review identified risk factors associated with GBC including body mass index and gallstones (Argyrakopoulou, 2021; Marcano-Bonilla, 2016). Another global meta-analysis identified smoking as a risk factor for GBC, reporting pooled relative risk (RR) values (relative to never smokers) of 1.33 (95% Confidence Interval [CI] 1.17–1.51) and 1.07 (95% CI 0.94–0.12) for current and former smokers (both compared to never smokers), respectively; RR increased to 1.60 (95% CI 1.21–2.11) among those smoking 30 cigarettes per day and to 1.25 (95% CI 0.10–1.56) for smokers of at least 30 years (Lugo, 2020). PSC has also been noted in a global meta-analysis as a significant risk factor for CC and GBC, with a RR of 584.37 (95% CI 269.4–1267.5) pooled across four CC studies and a standardized incidence ratio of 78.3 (95% CI 21.3–200.0) from a single Finnish study of GBC patients (Aune 2021; Barner-Rasmussen, 2020).

Main existing treatment options

Radical surgery, which includes lymphadenectomy, is the only curative treatment for BTC today. First-line systemic chemotherapy is the treatment of choice for adult patients with locally advanced or inoperable disease. Studies have demonstrated an overall survival benefit of gemcitabine and cisplatin combination compared to gemcitabine monotherapy (Valle, 2010, Vogel, 2023), which is therefore currently considered the recommended first-line treatment. Gemcitabine plus cisplatin and durvalumab can be considered for the first-line treatment of advanced BTC. Oxaliplatin may be substituted for cisplatin where there is a concern about renal function, and gemcitabine monotherapy may be considered for patients with a performance status (PS) of 2 (Vogel, 2023). FOLFOX (folinic acid, fluorouracil (5FU), and oxaliplatin) is recommended as the second-line treatment for adult patients after first-line gemcitabine/cisplatin combination therapy.

Natural history of the indicated condition in the untreated population, including mortality and morbidity

Like many cancers, BTC is staged as I-IV based on TNM (tumor, node, metastasis) criteria from the Union for International Cancer Control (UICC) or American Join Committee on Cancer (AJCC) (Lundgren, 2019; Saleh, 2020; Zhang, 2023). The stage-specific criteria will vary depending on the BTC subtype, ranging from small, localized tumors that tend to be targets for surgery (Stage I) to metastatic cancers which have spread to distant parts of the body or into the lymph nodes (Stage IV). Unfortunately, most patients do not receive their initial diagnosis until more advanced stages, due to the nonspecific symptoms and inconsistent clinical manifestations associated with early BTC (Khan, 2019; Saleh, 2020). Early disease stages are often asymptomatic, with general symptoms such as abdominal pain, itching, fever, weight loss, and malaise associated with progression as tumors grow, exhibit vascular invasion, multiply, and metastasize (Zamani & Fatima, 2023).

The age-standardized mortality rate of BTC (adjusted using the 1960 Segi World Standard Population) ranges from 2.21 to 6.04 per 100,000 person-years across EU-27 countries. Country-specific rates per 100,000 person-years are as follows: Bulgaria (2.21), Romania (2.41), Latvia (2.49), Denmark (2.73), Belgium (2.81), Netherlands (2.93), Lithuania (2.95), France (3.23), Portugal (3.49), Cyprus (3,60), Estonia (3.68), Spain (3.71), Ireland (3.93), Germany (4.03),

Poland (4.17), Italy (4.33), Sweden (4.34), Austria (4.51), Malta (4.55), Croatia (5.14), Hungary (5.29), Slovakia (6.04), and the Czech Republic (6.04). Age-standardized mortality rates by gender and BTC subtype are provided in Table Part II: Module SI.3.

Table Part II: Module SI.3: Age-standardized mortality rates (per 100,000 PY) of BTC subtypes, by country and gender, 2006–2016

[a]Country	ECC		ICC		GBC	
	Male	Female	Male	Female	Male	Female
Austria	1.23	0.91	2.95	1.94	0.70	1.27
Belgium	0.20	0.11	2.35	1.77	0.33	0.52
Bulgaria	0.23	0.27	0.35	0.33	0.96	1.32
Croatia	1.15	0.68	1.69	1.13	2.02	3.14
Cyprus	0.38	0.22	2.59	1.52	0.51	0.70
Czech Republic	0.87	0.64	0.97	0.72	2.14	3.75
Denmark	0.28	0.36	1.23	1.20	0.33	0.47
Estonia	0.70	0.32	1.51	0.96	0.40	1.07
France	0.15	0.09	2.87	1.73	0.32	0.49
Germany	1.18	0.89	2.03	1.42	0.74	1.39
Hungary	1.27	0.98	0.72	0.48	1.67	2.92
Ireland	0.83	0.59	1.59	2.17	0.86	0.53
Italy	0.42	0.26	1.65	1.09	0.89	1.43
Latvia	0.67	0.39	1.05	0.87	0.39	0.69
Lithuania	0.53	0.38	1.17	0.95	0.64	1.22
Malta	0.52	0.67	2.50	1.18	0.90	0.63
Netherlands	0.71	0.59	1.58	1.18	0.43	0.77
Poland	0.25	0.22	0.26	0.22	1.31	3.45
Portugal	0.69	0.43	2.47	1.30	0.50	0.64
Romania	0.50	0.37	0.65	0.38	0.99	0.95
Slovakia	0.57	0.66	1.11	0.65	2.17	4.03
Spain	0.15	0.08	2.80	1.70	0.59	0.90
Sweden	1.06	1.19	1.12	1.01	0.72	1.74

[a] Adapted from Baria (2022). BTC: biliary tract cancer; GBC: gallbladder cancer; ECC: extrahepatic cholangiocarcinoma; ICC: intrahepatic cholangiocarcinoma; PY: person-years

A German study of BTC patients demonstrated that 43.1% of the patients presented with Stage IV BTC at initial diagnosis, compared to only 3.0% at Stage I, 18.3% at Stage II, and 26.1% at Stage III (9.2% had unknown staging). The median OS of the overall cohort was 21 months from initial diagnosis (95% CI 17.1–24.9 months) compared to 13 months (95% CI 8.9–17.1 months) for those with unresectable, metastasized disease (Zhang, 2023).

Among Swedish incidental GBC patients, 15.7% presented at Stage I, 29.3% at Stage II, 30.2% at Stage III, and 17.7% at Stage IV, respectively (Lundgren, 2019). Among patients who did not undergo resection, 1-year, 3-year, and 5-year survival rates of 86%, 50%, and 43%, respectively, were reported (median survival 39.3 months), compared to 1-year, 3-year and 5-year survival rates of 90%, 78%, and 64%, respectively among those receiving resection.

ECIS data on GBC mortality suggested that males have a lower mortality than females (0.8 vs 1.2 per 100,000 respectively). Among the examined countries, Luxembourg had the lowest mortality of GBC (0.0 per 100,000) while Croatia had the highest (2.8 per 100,000) (Randi, 2023). Meanwhile, GLOBOCAN data on GBC found that mortality was lowest in Western Europe and highest in Central and Eastern Europe, with estimates of 0.28 vs. 0.60 per 100,000, respectively (Global Cancer Observatory, 2023). For males, mortality was lowest in Western Europe and highest in Central and Eastern Europe, with estimates of 0.21 vs. 0.44 per 100,000, respectively. For females, mortality was lowest in Western Europe and highest in Central and Eastern Europe, with estimates of 0.34 vs. 0.72 per 100,000, respectively.
In CC patients identified across 11 EU countries, 28.4% had metastatic disease at diagnosis, compared to 42.2% with local disease and 29.4% with locally advanced disease. Those receiving resection experienced a median OS of 45.1 months (1-year, 3-year, and 5-year survival of 84.5%, 56.3%, and 43.3%, respectively), compared to 10.6 months for those receiving active palliative therapies (1-year, 3-year, and 5-year survival of 45.2%, 8.4%, and 1.8%, respectively) and 4.0 months for those receiving best supportive care (1-year, 3-year, and 5-year survival of 18.8%, 1.5%, and 0.5%, respectively) (Izquierdo-Sanchez, 2022).

HER2-positive Biliary Tract Cancer

Several studies have examined the association between HER2-positive BTC and clinical outcomes with mixed results. In a study from Italy (Vivaldi, 2020), HER2-positive BTC was associated with decreased duration of disease-free survival (10.6 months versus 20.9 months). In a United States (US) study, patients with HER2-positive CC had significantly shorter time to disease progression on first-line chemotherapy (Hazard ratio [HR] 3.26 [95% CI 1.27-8.35]) (Lowery, 2018). In contrast, several other studies have not shown a statistically significant association between HER2-positive BTC and worse clinical outcomes. In studies from Germany, HER2-positive was not associated with survival time in patients with CC (Albrecht, 2019) or mortality for patients with GBC (Albrecht, 2020). Similarly, in studies from Portugal (Ramalhosa, 2022) and Poland (Hryciuk, 2020), HER2-positive GBC was not associated with survival. Importantly, the number of HER2-positive BTC patients among studies ranged from 5 (Hryciuk, 2020) to 11 (Vivaldi, 2020); thus, all studies' conclusions were limited by small sample sizes.

Important comorbidities

Two large observational studies of Swedish patients with BTC, identified between 1987 and 2018 using the Swedish Inpatient Register and Swedish Cancer Registry, listed 13 comorbidities of particular relevance to patients with ICC, ECC, and GBC (Hemminki, 2023a; Hemminki, 2023b):

- Alcohol-related liver disease
- Autoimmune hepatitis
- Chronic obstructive pulmonary disease
- Diabetes mellitus
- Gallstone disease
- Hepatitis B virus
- Hepatitis C virus
- Hepatitis of other kinds
- Infection of bile ducts
- Non-alcoholic fatty liver disease
- Other autoimmune disease
- Overweight/obesity
- Primary biliary cirrhosis

These comorbidities are consistent with those identified in other studies (Baria, 2022), though a pan-European analysis of patients with CC also identified arterial hypertension, hypertriglyceridemia, low high-density lipoprotein cholesterol, biliary conditions, cirrhosis, alcohol use, and tobacco use as important comorbidities (Izquierdo-Sanchez, 2022). It should also be noted that the presence of comorbidities can increase the risk of developing BTC (Baria, 2022; Hemminki, 2023a, Hemminki, 2023b).

Concomitant medications

Current published literature providing common concomitant medications among EU-27 countries, patients with BTC was not identified. A UK study of 2,934 patients with BTC identified in the Clinical Practice Research Datalink between 1990 and 2017 reported that 9% of patients were aspirin users at baseline, while an additional 12% initiated aspirin use following BTC diagnosis (Jackson, 2019). Meanwhile, a retrospective analysis of 1,140 BTC patients presenting at the University of Michigan between 2010 and 2020 reported that 20.8% were taking angiotensin-converting enzyme inhibitors concurrently, 9.6% were taking angiotensin II receptor blockers, 21.8% were taking statins, and 21.4% were taking aspirin (Gunchick, 2023). Based on the comorbidities listed above, as well as the typically advanced age of the patients, it is reasonable to assume that a substantial percentage of patients diagnosed with BTC is also treated with steroids, other anti-hypertensives, anti-diabetic, anti-viral and anti-inflammatory medications.

PART II: MODULE SII NON-CLINICAL PART OF THE SAFETY SPECIFICATION

Toxicology

A comprehensive series of non-Good Laboratory Practice (GLP) and GLP toxicology studies were conducted to support the zanidatamab clinical programme. These studies included single-dose (slow bolus) and multiple-dose (1-hour) infusions with intravenous (IV) administration of zanidatamab for up to 13 weeks duration with recovery period assessments in cynomolgus monkeys, and a tissue cross-reactivity study in a panel of human tissues. The toxicology programme was performed in cynomolgus monkeys, as it was demonstrated that zanidatamab bound both human and monkey HER2 with similar sub-nanomolar affinity but does not bind to rodent HER2.

All GLP studies were conducted in compliance with US Food and Drug Administration (FDA) GLP regulations (GLP 2018). Development of zanidatamab also followed applicable International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH), Committee for Proprietary Medicinal Products, and FDA guidance documents.

In the GLP cynomolgus monkey study, no adverse effects were observed at doses up through 150 mg/kg administered as weekly IV infusions for up to 13 weeks. In this study, non-adverse effects associated with the administration of zanidatamab at all dose levels included a non-dose dependent increase in the incidence of watery/soft feces. In some animals, this finding correlated with a mild increase in urea nitrogen concentration at all dose levels, which may have been secondary to mild subclinical dehydration associated with watery/soft feces. Based on the lack of adverse effects observed in the GLP study, the no observed adverse effect level (NOAEL), and highest non-severely toxic dose (HNSTD) were considered to be 150 mg/kg.

Repeat-dose GLP Toxicity Study

A GLP toxicology study (ZW25-04-13WTOX) evaluated the potential toxicity, toxicokinetics (TK), and the progression or reversibility of any potential treatment-related effects of zanidatamab when administered under a repeated-dose regimen to cynomolgus monkeys. Zanidatamab or vehicle was administered as a 1-hour IV infusion, once weekly, at doses of 0 (vehicle control), 5, 50, and 150 mg/kg. The study was divided into 2 phases, with the monkeys in phase 1 (8-week dosing cohorts; Groups 1 through 4) receiving 8 weekly treatments, and those in the second phase (13-week dosing cohorts; Groups 5 through 8) receiving 13 weekly treatments. Both 8- or 13-week phases included study animals that were euthanized 7 days after the last dose (main study animals) and recovery animals that were euthanized following an 8-week treatment-free period.

All animals were evaluated through 8 or 13 weeks for changes in clinical signs, body weight, food consumption, ophthalmology parameters, and clinical pathology (clinical chemistry, hematology, coagulation, and urinalysis). In addition, measurement of organ weights, and a full macroscopic and microscopic examination of tissues was performed after euthanasia of each study group. Finally, potential treatment-related effects on safety pharmacology parameters (neurobehavioral function [measured by clinical observations of activity and general behavior], cardiovascular function [measured by electrocardiograms (ECGs) and blood pressure] and

respiratory rate [visual]) were evaluated. Blood samples were collected at various time points throughout the study for TK and anti-drug antibodies (ADA) analysis.

Administration of zanidatamab was generally well tolerated at doses tested in both the 8-week and 13-week dosing cohorts and all animals survived to intended study endpoints. No effects considered related to treatment were noted in food consumption, body weight, respiration rate, blood pressure, hematology, coagulation and urinalysis parameters, ECG parameters, ophthalmic parameters, or postmortem parameters.

No adverse effects were observed at any dose tested up through 150 mg/kg for animals in both the 8-week and 13-week dosing cohorts. TK confirmed systemic exposure in all zanidatamab-treated animals. In summary, based on the lack of adverse effects observed in the GLP study, the NOAEL and HNSTD were considered to be 150 mg/kg.

Genotoxicity

The range and type of genotoxicity studies routinely conducted for small-molecule drug products are generally not applicable to biotechnology-derived products (ICH 2011) and are generally not performed for products intended for use in patients with advanced cancer (ICH 2009). It is not expected that a HER2 dual targeting bispecific antibody, such as zanidatamab that binds to the extracellular domain of HER2, would interact directly with Deoxyribonucleic acid (DNA) or other chromosomal material. Thus, mutagenicity studies were not warranted and not conducted.

Immunotoxicity

The monkeys receiving weekly doses of zanidatamab for 13 weeks in the GLP toxicology study did not exhibit any evidence of immunotoxicity. Specifically, there were no changes in the hematology or histopathology endpoints that raised concern about immunotoxicity. Zanidatamab paratopes do not bind immune cells and thus it is not expected to directly impact the immune system. Therefore, no further assessment of immunotoxicity is planned.

Developmental and Reproductive Toxicity

Reproductive and developmental toxicity studies have not been performed with zanidatamab. While a formal, stand-alone fertility study was not performed, no treatment-related effects were noted in the microscopic examination of male and female reproductive organs through 13-weeks of treatment and the 8-week recovery animals. However, antibodies that bind to HER2 have been observed to cause foetal harm. The use of trastuzumab during pregnancy resulted in cases of oligohydramnios and oligohydramnios sequelae manifesting as pulmonary hypoplasia, skeletal abnormalities, and neonatal death. Pertuzumab administered to pregnant cynomolgus monkeys resulted in oligohydramnios, delayed foetal kidney development, and embryo-foetal deaths at exposures of 2.5 to 20-fold greater than the recommended human dose. Because the potential teratogenic effects of zanidatamab, if any, in laboratory animals are unknown, zanidatamab should not be administered to pregnant women. To avoid pregnancy, appropriate precautions are taken for male and female participants of childbearing potential enrolled in the zanidatamab clinical studies. Precautions are also taken to avoid the theoretical risk of human teratogenicity/foetotoxicity in a female partner of childbearing potential from exposure to seminal fluid of a male study participant.

Table Part II: Module SII.1: Toxicology Study Summary

Study No.	Species/Strain (n per Dose Level, Gender)	ZW25 Dose Level (mg/kg) a	Dose Schedule	ZW25 NOAEL (mg/kg)	Summary of Toxicity Findings
Single-dose exploratory toxicity studies (non-GLP)					
ZW25-01-PKTOL	Cynomolgus Monkeys	10, 30	IV injection, Slow bolus	–	No mortalities and no evidence of treatment-related effects were observed in clinical signs, body weight, hematology, clinical chemistry, ECG or respiratory parameters.
Repeat-dose exploratory toxicity studies (non-GLP)					
ZW25-02-28DTOX	Cynomolgus Monkeys	5, 50, 150	60 minutes IV infusion, 28 days	150	No treatment-related effects were noted in evaluated safety parameters, including clinical observations, body weight, clinical pathology (hematology, clinical chemistry), ECGs, or anatomic pathology (gross pathology, organ weights and histopathology).
Repeat-dose toxicity studies (GLP-compliant)					
ZW25-04-13WTOX	Cynomolgus Monkeys	5, 50, 150	60 minutes IV infusion, 13 weeks	150	No adverse effects were observed at any dose tested. Non-adverse effects associated with the administration of ZW25 at all dose levels included a non-dose dependent increase in the incidence of watery/soft feces. In some animals, this finding correlated with a mild increase in urea nitrogen and/or a minimal to mild decrease in albumin concentration at all dose levels which may have been secondary to mild subclinical dehydration or gastrointestinal loss associated with watery/soft feces. Overall, based on the lack of adverse effects, the NOAEL

Study No.	Species/Strain (n per Dose Level, Gender)	ZW25 Dose Level (mg/kg) a	Dose Schedule	ZW25 NOAEL (mg/kg)	Summary of Toxicity Findings
					was determined to be 150 mg/kg.
Tissue Cross-reactivity (non-GLP)					
ZW25-03-TCR	Human	5, 20 µg/mL	*In Vitro*	–	ZW25-specific staining was generally consistent with the expected expression of HER2 (Press, 1990). Of the positive tissues not identified in the published literature as expressing HER2, all exhibited cytoplasmic staining.
Tissue Cross-reactivity (GLP-compliant)					
ZW25-09-GLP-TCR	Human	1, 10	*In Vitro*	–	The ZW25 staining pattern was generally consistent with expression of HER2 reported in the published literature for human tissues (Liu, 2001), (Press, 1990), with the exception of the following: lung (type II pneumocytes), pituitary pars (intermedia glandular epithelium), spinal cord (ependymal epithelium) and thyroid (follicular epithelium). While the spinal cord exhibited membrane staining, the existence of the blood-spinal cord barrier should limit *in vivo* exposure of these tissues to ZW25 (Rossi, 2013).
Antigenicity (non-GLP)					
ZW25-02-28DTOX	Cynomolgus Monkeys	5, 50, 150	60 minutes IV infusion	–	No anti-ZW25 antibodies were noted at any dose level following 4 weekly infusions.
Antigenicity (GLP-compliant)					
ZW25-04-13WTOX	Cynomolgus Monkeys	5, 50, 150	60 minutes IV infusion	–	Anti-ZW25 antibodies were detected in a single male animal in the 5 mg/kg (Group 2) dose group on Days 29 and 57 which correlated with

Study No.	Species/Strain (n per Dose Level, Gender)	ZW25 Dose Level (mg/kg) a	Dose Schedule	ZW25 NOAEL (mg/kg)	Summary of Toxicity Findings
					ZW25 concentrations below the level of quantification from Day 29 through Day 50.

ECG = electrocardiogram; GLP = Good Laboratory Practice; HER2 = human epidermal growth factor receptor 2; IV = intravenous; NOAEL = no observed adverse effect level; ZW25 = zanidatamab.

a All doses were administered intravenously.

Other nonclinical toxicity-related information or data

Carcinogenicity

No carcinogenicity studies have been conducted with zanidatamab. Based on the mechanism of action of zanidatamab, it is not expected to be carcinogenic. Additionally, zanidatamab is neither a growth factor nor an immunosuppressant. Thus, given the intended patient population and lack of mechanistic concern, carcinogenicity studies are not planned (ICH 2009).

Local Tolerance

No stand-alone local tolerance studies have been performed as consistent with ICH S9 (ICH 2009); however, consistent with ICH S6 (ICH 2011), evaluation of local tolerance of zanidatamab (clinical observations, macro- and microscopic examination of tissue samples from the injection site) was performed as part of the GLP repeat-dose toxicity study. No evidence of treatment-related effects at injection sites were observed in any animal.

Tissue Cross-Reactivity

A GLP tissue cross-reactivity study was conducted to evaluate the binding of zanidatamab to cryosections of normal human tissues obtained from 3 individuals. Most of the tissues that exhibited zanidatamab staining are known to express HER2 from the published literature (Press, 1990), (Liu, 2001). Of the tissues not identified in the published literature as expressing HER2, only the spinal cord exhibited membrane staining. The existence of the blood-spinal cord barrier should limit in vivo exposure of these tissues to zanidatamab (Rossi, 2013).

Immunogenicity

General immunogenicity testing was not conducted for zanidatamab as outlined in ICH S9 guidance on nonclinical testing for anticancer pharmaceuticals (ICH 2009). However, the GLP toxicology study included an assessment of ADA following repeat dosing with zanidatamab. In this study, a total of 292 samples from all dosing cohorts were screened for ADA. One animal had evidence of ADA on Days 29 and 57.

Photosafety Testing

Since ICH S9 is not specific for monoclonal antibodies (ICH 2009), such as zanidatamab, ICH S10 (ICH 2013) was used to guide photosafety evaluation. ICH S10 states photosensitivity

generally applies to small molecules and does not generally apply to peptides and proteins. Therefore, no further assessment of photosafety is planned.

Systemic Exposure

Toxicokinetics of zanidatamab in the GLP repeat-dose toxicology study demonstrated a long t1/2 ranging from 74.3 hours through 215 hours following administration of doses of 5 mg/kg through 150 mg/kg (3 days through 9 days). These data are consistent with other monoclonal antibodies (Dirks, 2010) and demonstrate confirmed systemic exposure in all zanidatamab-treated animals. Based on the lack of adverse effects observed in the GLP study, the NOAEL and HNSTD were considered to be 150 mg/kg.

Safety Pharmacology Studies

Dedicated general safety pharmacology studies with zanidatamab were not conducted, in accordance with ICH S9 (ICH 2009). Safety pharmacology assessments, including assessments of the effect of zanidatamab on cardiovascular, respiratory, renal, and central nervous systems, were included as part of the general toxicology studies. No effects on safety pharmacology parameters were observed in these studies.

Table Part II: Module SII.2: Key safety finding from nonclinical data

Key Safety Findings (from Nonclinical Studies)	Relevance to Human Usage
Developmental and Reproductive Toxicity	
Reproductive and developmental toxicity studies have not been performed with zanidatamab. However, antibodies that bind to HER2 have been observed to cause foetal harm. Use of trastuzumab during pregnancy resulted in cases of oligohydramnios and oligohydramnios sequelae manifesting as pulmonary hypoplasia, skeletal abnormalities, and neonatal death. Pertuzumab administered to pregnant cynomolgus monkeys resulted in oligohydramnios, delayed foetal kidney development, and embryo-foetal deaths at exposures of 2.5 to 20-fold greater than the recommended human dose.	Because the potential for teratogenic effects of zanidatamab in laboratory animals are unknown, zanidatamab should not be administered to pregnant women. To avoid pregnancy, appropriate precautions (highly effective methods of contraception) will be taken for female participants of childbearing potential enrolled in the zanidatamab clinical studies). Similarly, precautions will also be taken to avoid the theoretical risk of teratogenicity/foetotoxicity in a female partner of childbearing potential following exposure to seminal fluid of a male study participant.

Table Part II: Module SII.3: Conclusions on non-clinical data

Summary of Safety Concerns	
Important identified risks	None
Important potential risks	Embryo-foetal toxicity
Missing information	None

See Section SVII.1.1 for additional information and rationale.

PART II: MODULE SIII CLINICAL TRIAL EXPOSURE

As of the data cut off (DCO) date in each study (11 July 2024 for Study 203 and 14 January 2022 for Study 101), a total of 279 participants from Studies 203 and 101 received zanidatamab monotherapy.

Table Part II: Module SIII.1: Duration of Exposure

Safety Analysis Set	Statistic	Studies ZW25-101 Part 2 BTC and ZW25-203 (N=109)	Studies ZW25-203 +ZW25-101 (Parts 1 & 2) all dose levels & all indications (N=279)
Duration of ZW25 treatment (months)	**n**	**109**	**279**
	Mean (StD)	7.93 (8.497)	6.85 (7.588)
	Median	5.03	4.07

Safety Analysis Set	Statistic	Studies ZW25-101 Part 2 BTC and ZW25-203 (N=109)	Studies ZW25-203 +ZW25-101 (Parts 1 & 2) all dose levels & all indications (N=279)
	25th, 75th Percentiles	1.87, 9.72	1.87, 7.92
	Min, Max	0.2, 35.4	0.2, 44.6
Number of ZW25 cycles - initiated	**n**	**109**	**279**
	Mean (StD)	8.6 (8.89)	7.5 (8.13)
	Median	6.0	4.0
	25th, 75th Percentiles	2.0, 11.0	2.0, 9.0
	Min, Max	1, 35	1, 47
	1	10 (9.2)	25 (9.0)
	2	24 (22.0)	65 (23.3)
	3	7 (6.4)	17 (6.1)
	4	11 (10.1)	34 (12.2)
	5	2 (1.8)	9 (3.2)
	6	10 (9.2)	26 (9.3)
	7	4 (3.7)	11 (3.9)
	8	8 (7.3)	20 (7.2)
	9	3 (2.8)	8 (2.9)
	>=10	30 (27.5)	64 (22.9)

Table Part II: Module SIII.2: Age Group and Gender

Age group	Studies ZW25-101 Part 2 BTC and ZW25-203 Patients (N=109)	Studies ZW25-203 +ZW25-101 (Parts 1 & 2) all dose levels & all indications Patients (N=279)
< 65 years	59	170
Elderly people		
65-74 years	45	93
≥ 75 years	5	16
Total	**109**	**279**

Age group	Studies ZW25-101 Part 2 BTC and ZW25-203 Patients (N=109)	Studies ZW25-203 +ZW25-101 (Parts 1 & 2) all dose levels & all indications Patients (N=279)
Gender		
Female	61	150
Male	48	129
Total	**109**	**279**

Table Part II: Module SIII.3: Dose

Dose of exposure	Studies ZW25-101 Part 2 BTC and ZW25-203 Patients (N=109)	Studies ZW25-203 +ZW25-101 (Parts 1 & 2) all dose levels & all indications Patients (N=279)
5 mg/kg QW	0	3
10 mg/kg QW	0	13
15 mg/kg QW	0	7
20 mg/kg Q2W	109	233
25 mg/kg Q2W	0	6
30 mg/kg Q2W	0	6
30 mg/kg Q3W	0	11
Total	**109**	**279**

Table Part II: Module SIII.4: Racial and Ethnic Origin

Racial Origin[ab]	Studies ZW25-101 Part 2 BTC and ZW25-203 Patients (N=109)	Studies ZW25-203 +ZW25-101 (Parts 1 & 2) all dose levels & all indications Patients (N=279)
American Indian or Alaska Native	1	2
Asian	72	125
Black or African American	1	7
Native Hawaiian or Other Pacific Islander	0	2
White	30	133
Not reportable [a]	2	2

Unknown	3	8
Other [b]	0	2
Total	**109**	**279**
Ethnic origin		
Hispanic or Latino	6	20
Not Hispanic or Latino	100	252
Not reported	2	6
Unknown	1	1
Total	**109**	**279**

a: Not Reportable: Collection and/or reporting of this information is prohibited by local and/or regional laws or regulations
b: Other: A person for whom the above categories do not apply.

PART II: MODULE SIV POPULATIONS NOT STUDIED IN CLINICAL TRIALS

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

The following were key exclusion criteria from Study ZWI-ZW25-203:

Criterion

Received systemic anti-cancer therapy within 3 weeks of the first dose of zanidatamab. Received radiotherapy within 2 weeks of the first dose of zanidatamab.

Reason for exclusion: To allow for patients to recover from adverse events from prior therapy and to allow residual drug to be metabolized and excreted.

Is it considered to be included as missing information? No

Rationale: This exclusion was not due to a specific safety concern with the use of zanidatamab or radiotherapy but to aid in the evaluation of the efficacy and safety profile of zanidatamab.

Criterion

Had major surgery within 4 weeks of the first dose of zanidatamab.

Reason for exclusion: To ensure adequate wound healing and no post-surgical infections to ensure patient safety.

Is it considered to be included as missing information? No

Rationale: No specific warning or exclusion is included in the EU Summary of Product Characteristics (SmPC) for Ziihera since assessment of a patient's fitness to receive treatment is

considered part of routine oncology practice for a physician experienced in the treatment of patients with biliary tract cancer.

Criterion

Prior treatment with HER2-targeted agents.

Reason for exclusion: To test activity in patients without prior exposure to HER2 targeting agents.

Is it considered to be included as missing information? No

Rationale: This exclusion was not due to a specific safety concern but to aid in the evaluation of the efficacy and safety profile for zanidatamab.

Criterion

Untreated central nervous system (CNS) metastases, symptomatic CNS metastases, or radiation treatment for CNS metastases within 4 weeks of start of study treatment. Stable, treated brain metastases are allowed (defined as participants who are off steroids and anticonvulsants and are neurologically stable with no evidence of radiographic progression for at least 4 weeks at the time of screening).

Reason for exclusion: The molecule is not expected to penetrate the blood brain barrier, so these patients are excluded to maintain clinical equipoise.

Is it considered to be included as missing information? No

Rationale: These patients were excluded to avoid factors that may confound understanding of the zanidatamab safety profile and efficacy and to ensure appropriate interpretation of the safety data. No specific warning or exclusion is included in the EU SmPC for Ziihera since assessment of a patient's fitness for treatment is part of routine oncology practice for a physician experienced in the treatment of patients with biliary tract cancer.

Criterion

Known leptomeningeal disease (LMD). If LMD has been reported radiographically on baseline magnetic resonance imaging, but is not suspected clinically by the investigator, the participant must be free of neurological symptoms of LMD.

Reason for exclusion: The molecule is not expected to penetrate the blood brain barrier, so these patients are excluded to maintain clinical equipoise.

Is it considered to be included as missing information? No

Rationale: These patients were excluded to avoid factors that may confound understanding of the zanidatamab safety profile and efficacy and to ensure appropriate interpretation of the safety data. No specific warning or exclusion is included in the EU SmPC for Ziihera since assessment of a patient's fitness for treatment is part of routine oncology practice for a physician experienced in the treatment of patients with biliary tract cancer.

Criterion

Concurrent uncontrolled or active hepatobiliary disorders or untreated or ongoing complications after laparoscopic procedures or stent placement, including but not limited

to active cholangitis, unresolved biliary obstruction, infected biloma or abscess. Any complications must be resolved more than 2 weeks prior to the first dose of zanidatamab.

Reason for exclusion: To enable study of drug in appropriately functioning hepatic elimination.

Is it considered to be included as missing information? No

Rationale: These patients were excluded to avoid factors that may confound understanding of the zanidatamab safety profile and efficacy and to ensure appropriate interpretation of the safety data. No specific warning or exclusion is included in the proposed EU SmPC for Ziihera since assessment of a patient's fitness for treatment is part of routine oncology practice for a physician experienced in the treatment of patients with biliary tract cancer. Guidance on administration in patients with hepatic impairment is included in Section 4.2 of the proposed zanidatamab EU SmPC.

Criterion

Prior or concurrent malignancy whose natural history or treatment has, in the opinion of the investigator or medical monitor, the potential to interfere with the safety or efficacy assessment of the investigational regimen.

Reason for exclusion: To exclude patients who may have recurrence or progression of non-biliary tract cancers thereby protecting patients' safety and allowing for accurate activity assessments.

Is it considered to be included as missing information? No

Rationale: No specific warning or exclusion is included in the EU SmPC for Ziihera since such patients should still benefit from treatment with Ziihera. Assessment of a patient's fitness and need for treatment is part of routine oncology practice for a physician experienced in the treatment of patients with biliary tract cancer.

Criterion

Significant acute infection or chronic infections that have not stabilized with treatment.

Reason for exclusion: To protect patient safety.

Is it considered to be included as missing information? No

Rationale: These patients were excluded to avoid factors that may confound understanding of the zanidatamab safety profile and to ensure appropriate interpretation of the safety data. No specific warning or exclusion is included in the EU SmPC for Ziihera since assessment of a patient's fitness for treatment is part of routine oncology practice for a physician experienced in the treatment of patients with biliary tract cancer.

Criterion

Active hepatitis, including the following:

- **Acute or chronic hepatitis B virus (HBV) infection (Exception: participants who are hepatitis B surface antigen positive are eligible if they have HBV DNA less than 500 IU/mL)**

- **Infection with hepatitis C virus (Exception [i] participants who have no history of curative viral treatment and are documented to be viral load negative are eligible; [ii] participants who have completed curative viral therapy ≥ 12 weeks prior to enrollment, and viral load is negative are eligible)**

Reason for exclusion: To protect patient safety and to avoid potential confounders interfering with the assessment of safety for zanidatamab.

Is it considered to be included as missing information? No

Rationale: These patients were excluded to avoid factors that may confound understanding of the zanidatamab safety profile and to ensure appropriate interpretation of the safety data. No specific warning or exclusion is included in the EU SmPC for Ziihera since assessment for treatment is part of routine oncology practice for a physician experienced in the treatment of patients with biliary tract cancer.

Criterion

Infection with human immunodeficiency virus (HIV)-1 or HIV-2 (Exception: participants with well-controlled HIV [e.g., CD4 > 350/mm3 and undetectable viral load] are eligible).

Reason for exclusion: To protect patient safety to avoid potential confounders interfering with the assessment of safety for zanidatamab.

Is it considered to be included as missing information? No

Rationale: No specific warning or exclusion included in the EU SmPC for Ziihera since assessment of a patient's fitness for treatment is part of routine oncology practice for a physician experienced in the treatment of patients with biliary tract cancer.

Criterion

Females who are breastfeeding or pregnant, and females and males planning a pregnancy.

Reason for exclusion: As is usual in clinical trials, women known to be pregnant, or lactating were excluded from the studies.

Is it considered to be included as missing information? No

Rationale: No clinical data are available for zanidatamab in pregnancy. No embryo-foetal development toxicity studies in animals have been conducted. Information available for other HER2-targeted antibodies indicates that HER2-targeted antibodies can cause foetal harm. Both male patients with partners of childbearing potential and female patients should use effective contraception during treatment with zanidatamab and for 4 months following the last dose of zanidatamab. It is not known whether zanidatamab is excreted in human breast milk. Women of child-bearing age are advised to avoid becoming pregnant and to avoid breast-feeding during and for 4 months after completion of zanidatamab treatment, see Section SVII.3.

Criterion

History of life-threatening hypersensitivity to monoclonal antibodies or to recombinant proteins or excipients in the drug formulation of zanidatamab.

Reason for exclusion: To protect patient safety and to avoid potential confounders interfering with the assessment of safety for zanidatamab.

Is it considered to be included as missing information? No

Rationale: Dose modifications for Infusion related reactions, including life-threatening events are described in the EU SmPC, see Section 4.2: Posology and method of administration. Adverse reactions of Infusion related reactions are described in Section 4.4: Precautions and warnings of the EU SmPC. In addition, information on hypersensitivity reactions is included in Section 4.8.

Criterion

Treatment with anthracyclines within 90 days before first dose of zanidatamab and/or total lifetime load exceeding 360 mg/m2 Adriamycin® or equivalent.

Reason for exclusion: To protect patient safety due to potential impacts from both anthracycline and HER2 blockade on cardiac function and to avoid potential confounders interfering with the assessment of safety for zanidatamab.

Is it considered to be included as missing information? No

Rationale: No specific warning or exclusion is included in the EU SmPC for Ziihera since assessment of a patient's fitness for treatment is part of routine oncology practice for a physician experienced in the treatment of patients with biliary tract cancer.

Criterion

Use of corticosteroids administered at doses equivalent to > 15 mg per day of prednisone within 2 weeks of first zanidatamab dosing unless otherwise approved by the medical monitor. Topical, ocular, intra-articular, intranasal, and/or inhalational corticosteroids are permitted.

Reason for exclusion: To protect patient safety and to allow for a proper efficacy assessment.

Is it considered to be included as missing information? No

Rationale: No specific warning or exclusion is included in the EU SmPC for Ziihera since assessment of a patient's fitness for treatment is part of routine oncology practice for a physician experienced in the treatment of patients with biliary tract cancer.

Criterion

Ongoing, clinically significant toxicity (Grade 2 or higher) associated with prior cancer therapies, with the following exceptions:

- **Alopecia**
- **Congestive heart failure (CHF), which must have been ≤ Grade 1 at the time of occurrence and which must have completely resolved**
- **Grade 2 peripheral sensory neuropathy**

Reason for exclusion: To protect patient safety and to allow for accurate capture of treatment emergent adverse events.

Is it considered to be included as missing information? No

Rationale: No specific warning or exclusion included in the EU SmPC for Ziihera since assessment of a patient's fitness for treatment is part of routine oncology practice for a physician experienced in the treatment of patients with biliary tract cancer.

Criterion

QTc Fridericia (QTcF) > 470 ms.

Reason for exclusion: To protect patient safety and to avoid potential confounders interfering with the assessment of safety for zanidatamab.

Is it considered to be included as missing information? No

Rationale: No specific warning or exclusion is included in the EU SmPC for Ziihera since assessment of a patient's fitness for treatment is part of routine oncology practice for a physician experienced in the treatment of patients with biliary tract cancer. Additionally, the relationship between time-matched zanidatamab serum concentrations and ΔQTcF measurements was evaluated using linear regression based on data obtained during treatment with zanidatamab from participants in Study 101. There was no statistically significant relationship between the ΔQTcF and zanidatamab serum concentration. The upper bound of the 2-sided 90% CI (or upper bound of the 1-sided 95% CI) for the effect on the QTcF interval did not exceed 10 milliseconds (ms), which is the threshold level of regulatory concern.

Criterion

History of myocardial infarction or unstable angina within 6 months prior to enrollment, troponin levels consistent with myocardial infarction, or clinically significant cardiac disease, such as ventricular arrhythmia requiring therapy, uncontrolled hypertension, or any history of symptomatic CHF.

Reason for exclusion: To protect patient safety and to avoid potential confounders interfering with the assessment of safety for zanidatamab.

Is it considered to be included as missing information? No

Rationale: No specific warning or exclusion is included in the EU SmPC for Ziihera since assessment of a patient's fitness for treatment is part of routine oncology practice for a physician experienced in the treatment of patients with biliary tract cancer.

Criterion

Acute or chronic uncontrolled pancreatitis or Child-Pugh Class C liver disease.

Reason for exclusion: To protect safety and to avoid potential confounders interfering with the assessment of safety for zanidatamab.

Is it considered to be included as missing information? No

Rationale: No specific warning or exclusion is included in the EU SmPC for Ziihera since assessment of a patient's fitness for treatment is part of routine oncology practice for a physician experienced in the treatment of patients with biliary tract cancer.

Criterion

Interactions with Other Medicinal Products and Other Forms of Interactions

Reason for exclusion: No formal drug-drug interaction studies have been conducted with zanidatamab.

Is it considered to be included as missing information? No

Rationale: No dedicated clinical studies evaluating the drug interaction potential of zanidatamab have been conducted. Zanidatamab is an antibody that is not expected to impact the cytochrome P450 enzymes. Also, zanidatamab is not known to target mechanisms related to proinflammatory cytokines or any mechanism related to proinflammatory cytokines that may impact the PK of concomitant medicines.

Criterion

Carcinogenesis and Mutagenesis

Reason for exclusion: Long-term studies in animals to evaluate carcinogenic potential or studies to evaluate mutagenic potential have not been conducted with zanidatamab.

Is it considered to be included as missing information? No

Rationale: It is not expected that a therapeutic antibody targeting HER2 would have carcinogenic or mutagenic potential.

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

The clinical development programme is unlikely to detect certain types of adverse reactions such as rare adverse reactions, adverse reactions with a long latency, or those caused by prolonged or cumulative exposure.

SIV.3 Limitations in Respect to Populations Typically Under-Represented in Clinical Trial Development Programmes

This section aims to present the size of the safety database in each of the populations that are under-represented.

Table Part II: Module SIV.1: Exposure of Special Populations Included or Not in Clinical Trial Development Programmes

Type of Special Population	Exposure
Pregnant women and/or breastfeeding women	Not included in the clinical development programme

Type of Special Population	Exposure
Patients with relevant comorbidities: Patients with cardiovascular impairment	Not included in the clinical development programme: History of myocardial infarction or unstable angina within 6 months prior to enrolment, troponin levels consistent with myocardial infarction, or clinically significant cardiac disease, such as ventricular arrhythmia requiring therapy, uncontrolled hypertension, or any history of symptomatic CHF. In the ZW25-203 and ZW25-101 studies (Parts 1 and 2) (N=279), baseline left ventricular ejection fraction (LVEF) ≥ 50%: 279 (100 %) <50%: 0
Patients with hepatic impairment	Participants with acute or chronic uncontrolled liver disease (with exception of participants with Gilbert's Syndrome, asymptomatic gall stones, liver metastases, or stable chronic liver disease) were not included in the clinical development programme. In the ZW25-203 and ZW25-101 studies (Parts 1 and 2) (N=279), baseline hepatic impairment were as follows: None: 172 (61.6%) Mild: 104 (37.3%) Moderate: 3 (1.1%) Severe: 0 Baseline hepatic impairment was determined per the National Cancer Institute Organ dysfunction working group.

Type of Special Population	Exposure
Patients with renal impairment	Participants with acute or chronic uncontrolled renal disease were not included in the clinical development programme. In the ZW25-203 and ZW25-101 studies (Parts 1 and 2) (N=279), baseline renal impairment was as follows: Normal: 117 (41.9%) Mild to Moderate: 162 (58.1%) Baseline renal impairment was determined per the Cockcroft-Gault formula for estimating creatinine clearance and FDA guidance titled: Pharmacokinetics in Patients with Impaired Renal Function - Study Design, Data Analysis, and Impact on Dosing and Labelling, September 2020.
Patients with a disease severity different from inclusion criteria in clinical trials	Not applicable
Population with relevant different ethnic origin	Patients with various ethnic origins and race were included in Clinical Trials, see Table Part II: Module SIII.4: Racial and Ethnic Origin
Subpopulations carrying relevant genetic polymorphisms	Not applicable
Children	Not included in the clinical development programme
Elderly	Patients ≥65 years of age were included in the clinical development programme. In the ZW25-203 and ZW25-101 studies (Parts 1 and 2) (N=279), 109 patients were ≥65 years (39.1%).

PART II: MODULE SV POST-AUTHORISATION EXPERIENCE

SV.1 Post-Authorisation Exposure

Not applicable

PART II: MODULE SVI ADDITIONAL EU REQUIREMENTS FOR THE SAFETY SPECIFICATION

Potential for misuse for illegal purposes

Based on the pharmacological properties of zanidatamab and the fact that the product is available as a prescription only medicine and is administered under medical supervision, there is no potential misuse for an illegal purpose.

PART II: MODULE SVII IDENTIFIED AND POTENTIAL RISKS

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

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

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

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

- Decreased appetite
- Fatigue
- Rash
- Nausea

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

Known risks that do not impact the risk-benefit profile:

- Anaemia
- Diarrhoea
- Vomiting
- Abdominal pain
- Infusion-related reactions
- Ejection fraction decreased
- Alanine aminotransferase increased
- Aspartate aminotransferase increased
- Pneumonitis

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

Important Identified Risk:

There are no important identified risks for zanidatamab.

Important Potential Risk 1: Embryo-foetal Toxicity

Risk-benefit impact:

HER2 inhibitors have been associated with teratogenicity and foetal death. Potential embryo-foetal toxicity AESIs were identified using the 'Pregnancy and neonatal topics (SMQ)'. Cumulatively, as of the DCO, no events of embryo-foetal toxicity were identified among participants treated with zanidatamab in studies ZW25-203 and ZW25-101 (Parts 1 and 2) across all dose levels and indications.

Zanidatamab is not intended to be administered to pregnant or lactating women. No pregnancies have been reported in clinical trial participants enrolled in zanidatamab studies to date. The sponsor continues to monitor the incidence and severity of embryo-foetal toxicity through routine pharmacovigilance activities.

Missing information:

There is no missing information for zanidatamab.

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

Not applicable.

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

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

There are no important identified risks for zanidatamab.

Table Part II: Module SVII.3.1: Important Potential Risk: Embryo-foetal Toxicity

Potential Risk: Embryo-foetal Toxicity	
Potential mechanisms	HER2 inhibitors have been associated with teratogenicity and foetal death. HER2 is expressed broadly in epithelial tissues in the developing foetus, including in the respiratory tract, digestive tract, reproductive system, and skin (Press, 1990), as well as the brain, heart (Quirke, 1989), and placenta (Fock, 2015). Studies of embryonic development in mice homozygous for deletion or mutation in the kinase domain of the ERBB2 gene (coding for the HER2 protein) reveal that these changes produce embryonic lethality at Day 9.5 due to heart and brain malformations (Lee, 1995; Erickson, 1997; Chan, 2002).
Evidence source	The publicly available literature strongly supports a potential class effect of HER2 function blocking antibodies during foetal development, and the Sponsor considers embryo-foetal toxicity to be associated with this class of drug.

Potential Risk: Embryo-foetal Toxicity	
Characterisation of the risk	There have been no reports of pregnancy or embryo-foetal toxicity in zanidatamab studies ZW25-101 (Part 1 and 2) and ZW25-203 across all dosing levels and indications.
Risk groups or risk factors	Females who are breastfeeding or pregnant, and females planning a pregnancy.
Preventability	Routine risk communication: Preventative measures in the reference safety information include Section 4.4 of the EU SmPC Special warnings and precautions for use: Embryo-foetal toxicity Based on the mechanism of action, Ziihera may cause foetal harm when administered to a pregnant woman. In post-marketing reports of other HER2-directed antibodies, use during pregnancy resulted in cases of oligohydramnios manifesting as pulmonary hypoplasia, skeletal abnormalities, and neonatal death. Contraception and pregnancy Patients should be advised to avoid becoming pregnant while receiving Ziihera. A pregnancy test should be performed before initiating treatment with Ziihera to exclude pregnancy. Female patients of childbearing potential should use an effective method of contraception while receiving Ziihera and for 4 months following the last dose. Routine risk minimisation activities recommending specific clinical measures to address the risk: Sections 4.6 of the EU SmPC: Fertility, pregnancy and lactation Women of childbearing potential/Contraception in females: To exclude pregnancy, women of childbearing potential should undergo pregnancy testing before initiation of Ziihera. Based on the mechanism of action, zanidatamab may cause embryo-foetal harm when administered during pregnancy. Female patients should use effective contraception during treatment with Ziihera and for 4 months following the last dose. *Pregnancy* Based on the mechanism of action, zanidatamab may cause foetal harm when administered to a pregnant woman. There are no human or animal data on the use of zanidatamab in pregnancy. In post-marketing reports of other HER2-directed antibodies, use during pregnancy resulted in cases of oligohydramnios manifesting as pulmonary hypoplasia, skeletal abnormalities, and neonatal death. Ziihera is not recommended for use during pregnancy and in women of childbearing potential not using contraception. Patients should be advised of potential risks to the foetus. Women who received Ziihera during pregnancy or within 4 months prior to conception should be monitored for oligohydramnios. If oligohydramnios occurs, foetal testing that is appropriate for

Potential Risk: Embryo-foetal Toxicity	
	gestational age and consistent with local standard of care should be performed. *Breastfeeding* It is not known whether zanidatamab is excreted in human milk, or what effect it has on a breastfed child or milk production. A decision should be made whether to discontinue breast-feeding or to discontinue treatment, taking into account the benefit of breast-feeding for the child and the benefit of Ziihera therapy for the woman. This consideration should also take into account the washout period of 4 months. *Fertility* Fertility studies have not been performed with zanidatamab. Additional risk minimisation measures: None.
Impact on the risk-benefit balance of the product	The impact on the risk- benefit profile is low as "Embryo-Foetal Toxicity", "Contraception and Pregnancy" are described in Section 4.4 of the SmPC: Special warning and precautions for use and Section 4.6 of the SmPC: "Fertility, pregnancy and lactation".
Public health impact	The public health impact is low as Embryo-Foetal Toxicity, Contraception and Pregnancy are described in Section 4.4 of the SmPC: Special warning and precautions for use and Section 4.6 of the SmPC Fertility, pregnancy and lactation.
MedDRA search criteria	Modified Pregnancy and neonatal topics SMQ, which excludes the sub SMQ Lactation related topics including neonatal exposure through breast milk SMQ.

SVII.3.2 Presentation of the Missing Information

Missing information:

There is no missing information for zanidatamab.

PART II: MODULE SVIII SUMMARY OF THE SAFETY CONCERNS

Table Part II: Module SVIII.1: Summary of Safety Concerns

Summary of safety concerns	
Important identified risks	None
Important potential risks	Embryo-foetal Toxicity
Missing information	None

PART III PHARMACOVIGILENCE PLAN (INCLUDING POST-AUTHORISATION SAFETY STUDIES)

III.1 Routine Pharmacovigilance Activities

Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:

Specific adverse reaction follow-up questionnaires: None proposed

Other forms of routine pharmacovigilance activities: None proposed

III.2 Additional Pharmacovigilance Activities

None proposed

PART IV PLANS FOR POST-AUTHORISATION EFFICACY STUDIES

Study short name and title:

JZP598-302 An open-label randomized trial of the efficacy and safety of zanidatamab with standard-of-care therapy against standard-of-care therapy alone for advanced HER2-positive biliary tract cancer.

Rationale and study objectives:

Primary:

Compare the efficacy of zanidatamab plus CisGem with or without a PD-1/L1 inhibitor versus CisGem with or without a PD-1/L1 inhibitor in participants with advanced or metastatic HER2-positive BTC.

Secondary:

Further compare the efficacy of zanidatamab plus CisGem with or without a PD-1/L1 inhibitor versus CisGem with or without a PD-1/L1 inhibitor.

Evaluate the safety of zanidatamab plus CisGem with or without a PD-1/L1 inhibitor versus CisGem with or without a PD-1/L1 inhibitor.

Evaluate the PK of zanidatamab in combination with CisGem with or without a PD-1/L1 inhibitor.

Evaluate the immunogenicity of zanidatamab in combination with CisGem with or without a PD-1/L1 inhibitor.

Evaluate the effect of zanidatamab plus CisGem with or without a PD-1/L1 inhibitor versus CisGem with or without a PD-1/L1 inhibitor on physical functioning and patient-reported symptoms.

Study design:

An open-label randomized trial of zanidatamab for advanced HER2-positive biliary tract cancer.

Study population: patients with locally advanced or metastatic HER2-positive biliary tract cancer who have not received systemic therapy in the locally advanced or metastatic setting.

Milestones:

Protocol submission (03/06/2024)

Final report (3Quarter (Q) 2029)

Table Part IV.1: Summary Table of Post Authorisation Efficacy Studies

Study Status	Summary of Objectives	Efficacy uncertainties addressed	Milestones	Due Dates (DD/MM/YYYY)
Efficacy studies which are conditions of the marketing authorisation				
JZP598-302: An open-label randomized trial of zanidatamab for advanced HER2-positive biliary tract cancer On-going	Primary: Compare the efficacy of zanidatamab plus CisGem with or without a PD-1/L1 inhibitor versus CisGem with or without a PD-1/L1 inhibitor in participants with advanced or metastatic HER2-positive BTC. Secondary: Further compare the efficacy of zanidatamab plus CisGem with or without a PD-1/L1 inhibitor versus CisGem with or without a PD-1/L1 inhibitor Evaluate the safety of zanidatamab plus CisGem with or without a PD-1/L1 inhibitor versus CisGem with or without a PD-1/L1 inhibitor. Evaluate the PK of zanidatamab in combination with CisGem with or without a PD-1/L1 inhibitor. Evaluate the immunogenicity of zanidatamab in combination with CisGem with or without a PD-1/L1 inhibitor. Evaluate the effect of zanidatamab plus CisGem with or without a PD-1/L1 inhibitor	Confirm the efficacy and safety of zanidatamab as monotherapy for the treatment of adults with unresectable locally advanced or metastatic HER2-positive (IHC 3+) biliary tract cancer (BTC) previously treated with at least one prior line of systemic therapy.	Protocol submission Final report	03/06/2024 3Q 2029

Study Status	Summary of Objectives	Efficacy uncertainties addressed	Milestones	Due Dates (DD/MM/YYYY)
	versus CisGem with or without a PD-1/L1 inhibitor on physical functioning and patient-reported symptoms			
Efficacy studies which are Specific Obligations in the context of a conditional marketing authorisation or a marketing authorisation under exceptional circumstances: Not applicable				

PART V RISK MINIMISATION MEASURES (INCLUDING EVALUATION OF THE EFFECTIVENESS OF RISK MINIMISATION ACTIVITIES)

Risk Minimisation Plan

The safety information in the proposed product information is aligned to the reference safety information of the medicinal product.

V.1 Routine Risk Minimisation Measures

Table Part V.1: Description of Routine Risk Minimisation Measures by Safety Concern

Safety concern	Routine risk minimisation activities
Embryo-foetal Toxicity	Routine risk communication: PL Section 2 Routine risk minimisation activities recommending specific clinical measures to address the risk: Section 4.4 of the EU SmPC Special warnings and precautions for use includes Embryo-foetal toxicity and Contraception and pregnancy. Section 4.6 of the EU SmPC addresses Fertility, pregnancy and lactation. Other routine risk minimisation measures beyond the Product Information: Legal status: restricted medical prescription

V.2 Additional Risk Minimisation Measures

Routine risk minimisation activities as described in Part V.1 are sufficient to manage the safety concerns of the medicinal product. No additional risk minimization measures for the safety concerns are proposed.

V.3 Summary of Risk Minimisation Measures

Table Part V.3: Summary Table of Pharmacovigilance Activities and Risk Minimization Activities by Safety Concern

Safety concern	Risk minimisation measures	Pharmacovigilance activities
Embryo-foetal Toxicity	Routine risk minimisation measures: SmPC Section 4.4 where advice is given on Embryo-Foetal Toxicity, Contraception and Pregnancy. SmPC Section 4.6 where advice is given on Fertility, pregnancy, and lactation.	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None proposed.

PART VI SUMMARY OF THE RISK MANAGEMENT PLAN

SUMMARY OF RISK MANAGEMENT PLAN FOR ZIIHERA (ZANIDATAMAB)

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

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

I THE MEDICINE AND WHAT IT IS USED FOR

Ziihera is authorised as monotherapy for the treatment of adults with unresectable locally advanced or metastatic HER2-positive biliary tract cancer (BTC) previously treated with at least one prior line of systemic therapy. It contains zanidatamab as the active substance and it is administered as an intravenous infusion.

Further information about the evaluation of Ziihera's benefits can be found in Ziihera's European public assessment reports (EPAR), including in its plain-language summary, available on the EMA website, under the medicine's webpage <link to the EPAR summary landing page>.

II RISKS ASSOCIATED WITH THE MEDICINE AND ACTIVITIES TO MINIMISE OR FURTHER CHARACTERIZE THE RISKS

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

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

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

Together, these measures constitute routine risk minimisation measures.

II.A List of Important Risks and Missing Information

Important risks of Ziihera are risks that need special risk management activities to further investigate or minimise the risk, so that the medicinal product can be safely administered. Important risks can be regarded as identified or potential. Identified risks are concerns for which

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

Table II.1: Lists of Important Risks and Missing Information

List of Important Risks and Missing Information	
Important identified risks	None
Important potential risks	Embryo-foetal Toxicity
Missing information	None

II.B Summary of Important Risks

Table II.2: Summary of Important Risks

Important Potential Risk: Embryo-foetal Toxicity	
Evidence for linking the risk to the medicine	The publicly available literature strongly supports a potential class effect of HER2 function blocking antibodies during foetal development, and the Sponsor considers embryo-foetal toxicity to be associated with this class of drug.
Risk factors and risk groups	Females who are breastfeeding or pregnant, and females planning a pregnancy
Risk minimisation measures	SmPC Section 4.4 where advice is given on Embryo-Foetal Toxicity, Contraception and Pregnancy. SmPC Section 4.6 where advice is given on Fertility, pregnancy, and lactation.
Additional pharmacovigilance activities	Additional pharmacovigilance activities: None proposed See section II.C of this summary for an overview of the post-authorisation development plan.

II.C Post-Authorisation Development Plan

II.C.1 Studies Which Are Conditions of the Marketing Authorization

The following study is a condition of the marketing authorisation:

Study short name: JZP598-302: An open-label randomized trial of zanidatamab for advanced HER2-positive biliary tract cancer.

Purpose of the study: To compare the efficacy of zanidatamab plus CisGem with or without a PD-1/L1 inhibitor versus CisGem with or without a PD-1/L1 inhibitor in participants with advanced or metastatic HER2-positive BTC.

II.C.2 Other Studies in Post-Authorisation Development Plan

There are no studies required for zanidatamab.

PART VII ANNEXES

LIST OF ANNEXES

ANNEX 4 SPECIFIC ADVERSE DRUG REACTION FOLLOW-UP FORMS

Not applicable

ANNEX 6 DETAILS OF PROPOSED ADDITIONAL RISK MINIMISATION ACTIVITIES (IF APPLICABLE)

Not applicable

ANNEX 7 OTHER SUPPORTING DATA (INCLUDING REFERENCED MATERIAL)

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