National Institute for Health and Care Excellence

Health Technology Evaluation
Zanidatamab for treating HER2-positive advanced biliary tract cancer after 1 or more systemic treatments [ID6388]

Response to stakeholder organisation comments on the draft remit and draft scope

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Comment 1: the draft remit and proposed process

Section	Stakeholder	Comments [sic]	Action
Appropriateness of an evaluation and proposed evaluation route	Jazz Pharmaceuticals	Human epidermal growth factor receptor 2-positive (HER2+) biliary tract cancer (BTC) is a very rare cancer – as such, Jazz Pharmaceuticals believe that this topic is appropriate for a Highly Specialised Technology (HST) evaluation, as stated by the company in the updated HST application submitted as part of this scoping consultation (dated 1 April 2025). A diagnosis of advanced BTC is devastating for patients, their families, and caregivers due to the poor prognosis, burden of symptoms, and current chemotherapy treatment regimens. HER2+ BTC is a rare and aggressive cancer, with most patients diagnosed once the disease is metastatic (1, 2), Survival rates for BTC are among the worst for any cancer (3) and only 1 in 4 patients survive for >1 year after a BTC diagnosis (4). Systemic therapy with cisplatin and gemcitabine (CisGem) with durvalumab is first-line (1L) treatment for patients with unresectable locally advanced or metastatic BTC without contraindications. Second-line (2L) treatment options in the UK are very limited and there are currently no approved HER2 targeted therapies for BTC. Systemic chemotherapy regimens, such as folinic acid, fluorouracil, and oxaliplatin (FOLFOX), may be used 2L; however, treatment with FOLFOX is often	Thank you for your comment. Topic routing was discussed at the NICE Prioritisation Board in May 2025. The Board concluded that the topic was suitable for a Technology Appraisal. Please see project documents for further details.

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		challenging and/or contraindicated as it is associated with a low disease response, poor tolerability, and toxicity (5). In England, only 28.4% of patients with advanced BTC who initiated 1L treatment received subsequent lines of therapy (4). Zanidatamab is an innovative HER2-targeted therapy and as a chemotherapy-free treatment, represents a step change in the 2L treatment of locally advanced or metastatic BTC. If approved, zanidatamab will be the first HER2-targeted therapy for this patient population, whose treatment options are currently limited to systemic chemotherapy with its associated tolerability burden.  Furthermore, the European Medicines Agency (EMA) granted orphan drug designation to zanidatamab on 19th July 2021 (EU/3/21/2458), confirming the rare nature of the patient population as defined by the EMA criteria: 1.The medicine must be intended for the treatment, prevention or diagnosis of a disease that is life-threatening or chronically debilitating 2.The prevalence of the condition in the European Union must not be more than 5 in 10,000 or it must be unlikely that marketing of the medicine would generate sufficient returns to justify the investment needed for its development	

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		3.No satisfactory method of diagnosis, prevention or treatment of the condition concerned can be authorised, or, if such a method exists, the medicine must be of significant benefit to those affected by the condition. **References**: 1. National Comprehensive Cancer Network (NCCN). NCCN Clinical Practice Guidelines in Oncology: Biliary Tract Cancers v6.2024. 2025. Available from: https://www.nccn.org/professionals/physician_gls/pdf/btc.pdf. Accessed on: 18 February 2025. 2. Vogel A, Bridgewater J, Edeline J, Kelley R, Klümpen H, Malka D, et al. Biliary tract cancer: ESMO Clinical Practice Guideline for diagnosis, treatment and follow-up☆. Annals of Oncology. 2023;34(2):127-40. 3. AMMF: The cholangiocarcinoma charity. Introduction to cholangiocarcinoma: An educational resource for patient organisations. 2023. 4. Tataru D, Khan SA, Hill R, Morement H, Wong K, Paley L, et al. Cholangiocarcinoma across England: Temporal changes in incidence, survival and routes to diagnosis by region and level of socioeconomic deprivation. JHEP Rep. 2024;6(3):100983. 5. Lamarca A, Palmer DH, Wasan HS, Ross PJ, Ma YT, Arora A, et al. Second-line FOLFOX chemotherapy versus active symptom control for advanced biliary tract cancer (ABC-06): a phase 3, open-label, randomised, controlled trial. The Lancet Oncology. 2021;22(5):690-701.	
	Cholangiocarcinoma UK, an affiliate of the British Association for	A single technology appraisal is appropriate	Thank you for your comment. Topic routing was discussed at the NICE Prioritisation Board in May 2025. The Board concluded that

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	Study of Liver Disease (BASL)		the topic was suitable for a Technology Appraisal. Please see project documents for further details.
Wording	Jazz Pharmaceuticals	The EMA marketing authorisation for zanidatamab is expected to be: [redacted] Jazz Pharmaceuticals suggest that the wording of the remit is updated to reflect the anticipated marketing authorisation for zanidatamab, as follows: 'To appraise the clinical and cost effectiveness of zanidatamab within its marketing authorisation for treating [redacted].' **References**: 6. Jazz Pharmaceuticals. Data on file. Zanidatamab SmPC (DRAFT). 2025.	Thank you for your comment. As the anticipated marketing authorisation wording is still confidential, the remit of the scope has not been updated. No action required.
	Cholangiocarcinoma UK, an affiliate of the British Association for Study of Liver Disease (BASL)	Yes	Thank you for your comment. No action required.

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Timing issues	Jazz Pharmaceuticals	Jazz Pharmaceuticals consider this appraisal to be important due to the high unmet need for patients with advanced or metastatic HER2+ BTC after systemic therapy. As noted above, a diagnosis of advanced BTC is devastating to patients and their families/caregivers (3) and this aggressive disease impacts on all aspects of their lives. Highly burdensome symptoms, including fatigue, abdominal pain, insomnia and gastrointestinal signs/symptoms, negatively impact health-related quality of life (HRQoL), impairing physical and cognitive functioning, work participation, and emotional wellbeing (3, 7-9). The HRQoL impact is worsened by the poor prognosis of advanced BTC and the very limited treatment options available. There are currently no targeted treatment options for HER2+ BTC and patients whose disease has progressed after 1L therapies have very poor survival outcomes. Current 2L systemic chemotherapy regimens, such as FOLFOX, offer minimal improvements in survival when compared with palliative care with active symptom control (ASC). The ABC-06 clinical trial showed a median overall survival (OS) improvement of only 0.9 months with FOLFOX+ASC versus ASC alone (6.2 months [95% CI 5.4, 7.6] vs 5.3 months [95% CI 4.1, 5.8], respectively) (5). The small survival improvement with FOLFOX versus ASC is often at the expense of debilitating side effects due to the non-targeted action of systemic chemotherapies that attack both malignant and non-malignant cells. These side effects can be extremely detrimental to HRQoL (10) and many patients are unsuitable for 2L chemotherapy with FOLFOX due to considerable toxicity and tolerability (11). Therefore, patients with [redacted] urgently need effective 2L targeted therapies that offer a demonstrated survival benefit over conservative management or standard chemotherapies, a more manageable tolerability profile versus FOLFOX, and preservation of their HRQoL. Zanidatamab is an innovative HER2-targeted therapy and represents a step change in the [redacted],	Thank you for your comment. This topic has been scheduled into NICE's work programme. For further details, please see the NICE website: https://www.nice.org.uk/guidance/indevelopment/gid-ta11468

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		offering patients improved survival and a more manageable side effect profile versus the current treatment options. [redacted] In summary, given the substantial unmet need in [redacted] and the benefits offered by zanidatamab, Jazz Pharmaceuticals consider rapid and equitable access to zanidatamab to be a priority topic. **References:** 3. AMMF: The cholangiocarcinoma charity. Introduction to cholangiocarcinoma: An educational resource for patient organisations. 2023. 7. Bibeau K, Bachini M, Lindley A, Barkey NM, Lindsey S. Exploring the diagnostic journey and life impact of patients with cholangiocarcinoma (CCA): Results from a large patient survey in the United States. American Society of Clinical Oncology; 2021. 8. Bibeau K, Jackson TD, Bachini M, Lindley A, Blanco F, LaFiura C, et al. Diagnostic journey and life impact of cholangiocarcinoma: results from surveys of patient and caregiver experiences. Future Oncology. 2024;20(15):997-1012. 9. Patel N, Lie X, Gwaltney C, Rokutanda N, Barzi A, Melisi D, et al. Understanding patient experience in biliary tract cancer: a qualitative patient interview study. Oncology and Therapy. 2021;9:557-73. 10. National Institute for Health and Care Excellence (NICE). Pemigatinib for treating relapsed or refractory advanced cholangiocarcinoma with FGFR2 fusion or rearrangement. 2021. Available from: https://www.nice.org.uk/guidance/ta722. Accessed on: 6th February 2025.	

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		11.Bridgewater J, Sah J, Szende A, Paskow M, Messina P, Baur B, et al. Real-world treatment patterns and challenges of patients with biliary tract cancer: retrospective chart review survey in Europe (GARNET-2). ESMO Real World Data and Digital Oncology. 2024;5:100060.	
	AMMF – The Cholangiocarcinoma Charity	The survival rates for cholangiocarcinoma are among the worst for cancers. The cohort of patients who would be eligible for zanidatamab are those with unresectable cancer, meaning they are unable to have potentially curative surgery. Their five-year survival rate is as low as 2%. Due to the extremely low five-year survival rate for this cohort of patients, there is an urgent need for access to new therapies which could extend life. Delays in the evaluation of this therapy will result in time lost with families and loved-ones for those affected by the disease.	Thank you for your comment. This topic has been scheduled into NICE's work programme. For further details, please see the NICE website: https://www.nice.org.uk/guidance/indevelopment/gid-ta11468
	Cholangiocarcinoma UK, an affiliate of the British Association for Study of Liver Disease (BASL)	Biliary tract cancer is a cancer with poor outcomes and significant unmet need. Potentially beneficial treatment should be expedited.	Thank you for your comment. This topic has been scheduled into NICE's work programme. For further details, please see the NICE website: https://www.nice.org.uk/guidance/indevelopment/gid-ta11468

Comment 2: the draft scope

Section	Consultee/ Commentator	Comments [sic]	Action
Background information	Jazz Pharmaceuticals	The first paragraph of the background section includes reference to peri-hilar and distal cholangiocarcinoma (CCA). In general, CCA is categorised as 'intrahepatic' or 'extrahepatic'. Extrahepatic CCA is further subdivided into peri-hilar and distal CCA. It is suggested to define extrahepatic CCA prior to defining peri-hilar and distal CCA. Jazz Pharmaceuticals also suggest including patient survival information in the background section as this is a major consideration in advanced BTC. Specifically, in patients receiving 2L FOLFOX+ASC, median OS is 6.2 months (95% CI 5.4, 7.6) and only 0.9 months longer than with ASC alone (5.3 months [95% CI 4.1, 5.8]) (5). **References:** 5. Lamarca A, Palmer DH, Wasan HS, Ross PJ, Ma YT, Arora A, et al. Second-line FOLFOX chemotherapy versus active symptom control for advanced biliary tract cancer (ABC-06): a phase 3, open-label, randomised, controlled trial. The Lancet Oncology. 2021;22(5):690-701.	Thank you for your comment. The background section of the scope is intended to give a brief overview of the condition and treatment options. The scope has been updated to include a definition of extrahepatic CCA.
	AMMF – The Cholangiocarcinoma Charity	The background information states, *"Currently, there are no UK wide statistics available for bile duct cancer and gallbladder cancer survival by stage"*. Whilst there are no UK wide statistics currently, there are some staging statistics for England: https://doi.org/10.4251/wjgo.v15.i12.2077 • Only 55% of CCA patients had records with complete staging. • Only 21% of staged patients were diagnosed at stage 1 or 2. • 79% of staged patients were diagnosed at stage 3 or 4.	Thank you for your comment. The scope has been updated to add that most people are diagnosed at stages 3 or 4 and that diagnosis at a later stage is associated with poorer survival outcomes.

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		In addition, there are data indicating that diagnosis at later stages is associated with poorer survival. https://doi.org/10.1016/j.eclinm.2023.101969 • Patients with more advanced stages of CCA were less likely to receive curative treatments (liver surgery, transplant or ablation). • Patients with advanced stages of CCA were less likely to survive over a longer period.	
Population	Jazz Pharmaceuticals	As noted above, the EMA marketing authorisation for zanidatamab is expected to be: [redacted] Jazz Pharmaceuticals suggest that the population definition is reworded to align with the anticipated marketing authorisation (6) as follows: 'Adults with [redacted]' **References**: 6. Jazz Pharmaceuticals. Data on file. Zanidatamab SmPC (DRAFT). 2025.	Thank you for your comment. The population in the scope has been updated.
	AMMF – The Cholangiocarcinoma Charity	Yes	Thank you for your comment. No action required.

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	Cholangiocarcinoma UK, an affiliate of the British Association for Study of Liver Disease (BASL)	Yes, there are no reliable data to suggest a worse outcome for HER amplified BTC therefore it would be appropriate to use the comparators defined in the ABC-06 study[5,6] **References**: 5. Crolley VE, Guest R, Beggs AD, et al. Investigating alterations in cancer driver genes and other potentially targetable mutations in patients with intrahepatic cholangiocarcinoma (iCCA) treated on the randomised phase III multicentre BILCAP clinical trial. *Journal of Clinical Oncology* 2023; **41**(16_suppl): 4019-. 6. Lamarca A, Palmer DH, Wasan HS, et al. Second-line FOLFOX chemotherapy versus active symptom control for advanced biliary tract cancer (ABC-06): a phase 3, open-label, randomised, controlled trial. *The Lancet Oncology* 2021; **22**(5): 690-701.	Thank you for your comment. No action required.
Subgroups	Jazz Pharmaceuticals	With regard to subgroups, the draft scope states 'If evidence allows, results by type of biliary tract cancer.' Jazz Pharmaceuticals recommend that this wording is amended to 'No relevant subgroups'. The level of unmet need in 2L HER2+ BTC is very high and restricting zanidatamab to a BTC subtype risks denying some patients an effective treatment option. Currently, the only 2L treatment for people with HER2+ BTC is FOLFOX, which is associated with a low disease response, poor survival, toxicity, and poor tolerability (5). The lack of effective and tolerable treatment options is a major emotional and mental burden for people with BTC and their families/caregivers (7, 9, 12, 13). Furthermore, initial analyses of HERIZON-BTC-01 (the key trial of zanidatamab) indicate no difference in efficacy between BTC subtypes. While the number of patients with gallbladder cancer/extrahepatic CCA/intrahepatic CCA in HERIZON-BTC-01 is too low for meaningful analysis by BTC subtype (due to the rarity of the disease), there is no evidence to suggest that one	Thank you for your comment. The subgroups have been kept inclusive to allow committee to consider any subgroups it considers relevant. No action required.

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		subpopulation would benefit more from zanidatamab than another. This applies not only to BTC subtype but also to other subgroups, including sex, geographical region, and number of prior regimens (14). Jazz Pharmaceuticals therefore suggest that no subgroups of the [redacted] population are considered. **References**: 5. Lamarca A, Palmer DH, Wasan HS, Ross PJ, Ma YT, Arora A, et al. Second-line FOLFOX chemotherapy versus active symptom control for advanced biliary tract cancer (ABC-06): a phase 3, open-label, randomised, controlled trial. The Lancet Oncology. 2021;22(5):690-701. 7. Bibeau K, Bachini M, Lindley A, Barkey NM, Lindsey S. Exploring the diagnostic journey and life impact of patients with cholangiocarcinoma (CCA): Results from a large patient survey in the United States. American Society of Clinical Oncology; 2021. 9. Patel N, Lie X, Gwaltney C, Rokutanda N, Barzi A, Melisi D, et al. Understanding patient experience in biliary tract cancer: a qualitative patient interview study. Oncology and Therapy. 2021;9:557-73. 12. Sangruangake M, Summart U, Songthamwat M, Sangchart B. The relationship between unmet need, physical symptoms, psychological well-being and health-related quality of life in cholangiocarcinoma survivors. Asian Pacific Journal of Cancer Prevention: APJCP. 2022;23(8):2821. 13. Elberg Dengsø K, Hillingsø J, Marcussen AM, Thomsen T. Health-related quality of life and anxiety and depression in patients diagnosed with cholangiocarcinoma: a prospective cohort study. Acta Oncologica. 2017;56(2):198-204. 14. Jazz Pharmaceuticals. Data on File. HERIZON-BTC-01 IHC3+ Cohort 1 Subgroup Analysis - Tables, Listings, and Figures. DCO 28th July 2024. . 2025.	

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	AMMF – The Cholangiocarcinoma Charity	1-year and 3-year survival estimates for cholangiocarcinoma (CCA) are worse than for gallbladder cancer (GBC) and ampullary cancer (AoV). https://doi.org/10.1016/j.jhepr.2023.100983 1-year overall survival estimates: • CCA – 25.1% • GBC – 27.6% • AoV – 58.3% 3-year overall survival estimates: • CCA – 7.7% • GBC – 12.9% • AoV – 32.3% This may potentially mean that the technology is more cost effective for CCA patients.	Thank you for your comment. Differences in survival benefits for CCA patients may be captured in the current subgroups. No action required.
	Cholangiocarcinoma UK, an affiliate of the British Association for Study of Liver Disease (BASL)	Patients with HER2 3+ amplification on IHC should be considered. [3] The data support limited benefit in HER2 2+ fISH positive patients and although there is some concordance between HER2 copy number defined by DNA profiling and IHC, the concordance is modest. **References**: 3.Harding JJ, Fan J, Oh D-Y, et al. Zanidatamab for HER2 amplified, unresectable, locally advanced or metastatic biliary tract cancer (HERIZON-BTC-01): a multicentre, single-arm, phase 2b study. *The Lancet Oncology* 2023; **24**(7): 772-82.	Thank you for your comment. The committee will consider the clinical evidence presented to it and make recommendations based on the available evidence. No action required.
Comparators	Jazz Pharmaceuticals	FOLFOX and best supportive care (BSC) are both appropriate comparators. Jazz Pharmaceuticals intend to use the active symptom control (ASC) only arm from ABC-06 (FOLFOX trial) as the 'BSC' comparison. This approach	Thank you for your comment. The scope

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		aligns with the NICE appraisal of pemigatinib (TA722) (10). In ABC-06, ASC included but was not limited to: biliary drainage, antibiotics, analgesia, steroids, anti-emetics, other palliative treatment for symptom control, palliative radiotherapy (e.g. for painful bone metastases), and blood transfusions (5). Therefore, Jazz Pharmaceuticals suggest that the comparator wording is updated as follows: 'Established clinical management without zanidatamab, which may include: • Folinic acid, fluorouracil and oxaliplatin (FOLFOX) • Best supportive care (**active symptom control**)' **References**: 5. Lamarca A, Palmer DH, Wasan HS, Ross PJ, Ma YT, Arora A, et al. Second-line FOLFOX chemotherapy versus active symptom control for advanced biliary tract cancer (ABC-06): a phase 3, open-label, randomised, controlled trial. The Lancet Oncology. 2021;22(5):690-701. 10. National Institute for Health and Care Excellence (NICE). Pemigatinib for treating relapsed or refractory advanced cholangiocarcinoma with FGFR2 fusion or rearrangement. 2021. Available from: https://www.nice.org.uk/guidance/ta722. Accessed on: 6th February 2025.	has been updated to include active symptom control as part of best supportive care.
	AMMF – The Cholangiocarcinoma Charity	The list of comparators is appropriate.	Thank you for your comment. No action required.
	Cholangiocarcinoma UK, an affiliate of the British	It would be appropriate to use the comparators of BSC and FOLFOX defined in the ABC-06 study. [5] [6] **References**:	Thank you for your comment. No action required.

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	Association for Study of Liver Disease (BASL)	5.Crolley VE, Guest R, Beggs AD, et al. Investigating alterations in cancer driver genes and other potentially targetable mutations in patients with intrahepatic cholangiocarcinoma (iCCA) treated on the randomised phase III multicentre BILCAP clinical trial. *Journal of Clinical Oncology* 2023; **41**(16_suppl): 4019-. 6. Lamarca A, Palmer DH, Wasan HS, et al. Second-line FOLFOX chemotherapy versus active symptom control for advanced biliary tract cancer (ABC-06): a phase 3, open-label, randomised, controlled trial. *The Lancet Oncology* 2021; **22**(5): 690-701.	
Outcomes	Jazz Pharmaceuticals	The outcomes listed in the scope are appropriate.	Thank you for your comment. No action required.
	AMMF – The Cholangiocarcinoma Charity	The list of outcome measures is appropriate.	Thank you for your comment. No action required.
	Cholangiocarcinoma UK, an affiliate of the British Association for Study of Liver Disease (BASL)	Yes the outcomes are appropriate.	Thank you for your comment. No action required.
Equality	Jazz Pharmaceuticals	No edits to the scope are needed to meet NICE's equality aims and no equality issues associated with the use of zanidatamab are foreseen. However, increased access to targeted therapies, including zanidatamab if recommended, has the potential to reduce health inequalities in the UK; real-world evidence from patients with BTC in England showed a higher incidence	Thank you for your comment. This will be incorporated and considered in the equalities impact

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		of BTC and poorer treatment outcomes in socio-economically deprived populations compared with other areas of England (4). **References**: 4. Tataru D, Khan SA, Hill R, Morement H, Wong K, Paley L, et al. Cholangiocarcinoma across England: Temporal changes in incidence, survival and routes to diagnosis by region and level of socioeconomic deprivation. JHEP Rep. 2024;6(3):100983.	assessment form and will be considered by the committee during the appraisal
	AMMF – The Cholangiocarcinoma Charity	I am not aware of any potential equality considerations within the scope of this appraisal.	Thank you for your comment. No action required.
	Cholangiocarcinoma UK, an affiliate of the British Association for Study of Liver Disease (BASL)	I do not see any issues of inequality.	Thank you for your comment. No action required.
Other considerations	Cholangiocarcinoma UK, an affiliate of the British Association for Study of Liver Disease (BASL)	Although HER2 IHC and appropriate targeted therapy has been recommended in the BSG and ESMO guidelines, HER2 testing is not standard for BTC. There should be consultation with the Royal College of Pathologists and GMSA/Cellular Pathology genomics Centres in order to establish HER2 IHC as standard in BTC.	Thank you for your comment. The economic analysis section of the PICO table has been expanded to add information on inclusion of HER2 testing costs.

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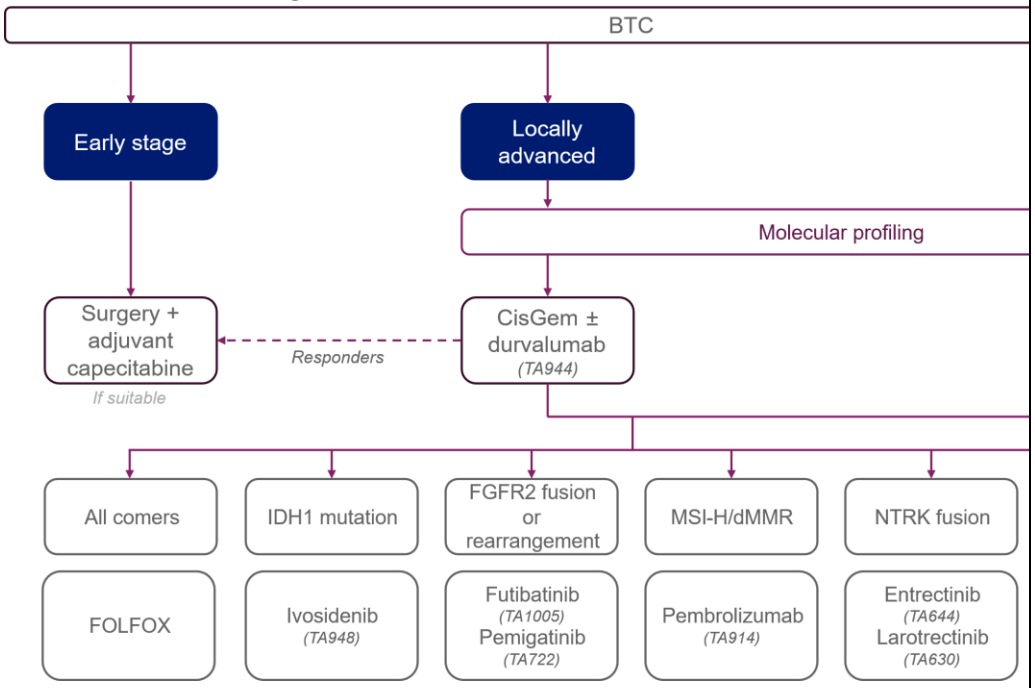
Questions for consultation	Jazz Pharmaceuticals	**1. Where do you consider zanidatamab will fit into the existing care pathway for HER2-positive advanced biliary tract cancer?** If approved, zanidatamab will be indicated for the [redacted] (6). Zanidatamab will be the first HER2-targeted treatment for BTC, providing a chemotherapy-free regimen with a demonstrated improved survival benefit over standard systemic 2L therapy (5, 15). Zanidatamab is recommended by European Society for Medical Oncology (ESMO) as a 2L treatment for patients with HER2+ BTC (16) and it is anticipated that this will be the positioning of zanidatamab in the existing BTC care pathway in the UK; Figure 1 shows the proposed positioning of zanidatamab within the current UK treatment pathway for BTC. If approved, zanidatamab would provide an additional treatment option for patients with [redacted], as an alternative to systemic chemotherapy with FOLFOX. Zanidatamab would also provide a disease-modifying treatment for patients who are ineligible for or cannot tolerate treatment with FOLFOX and currently only receive ASC.	Thank you for your comments. No action required.

Figure 1: Current treatment algorithm in BTC and zanidatamab's proposed positioning



Abbreviations: BTC, biliary tract cancer; CisGem, cisplatin and gemcitabine; dMMR, mismatch repair deficient; FGFR2, fibroblast growth factor receptor 2; FOLFOX, folinic acid, fluorouracil and oxaliplatin; HER2, human epidermal growth factor receptor 2; IDH1, isocitrate dehydrogenase 1; NICE, National Institute for Health and Care Excellence; MSI-H, microsatellite instability-high; NTRK, neurotrophic tyrosine receptor kinase; TA, technology appraisal.
Sources: Vogel et al (2025), relevant NICE TAs (10, 16-22).

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		1L treatment for advanced BTC usually consists of CisGem with durvalumab (unless contraindicated) (16, 19, 23). Patients who experience disease progression or unsuitable toxicity after 1L therapies can be offered 2L treatment (2, 16, 23). Currently, 2L treatment of advanced BTC in the UK comprises standard chemotherapy combined with ASC for eligible patients (23, 24). ASC in this patient population includes palliative surgical intervention to unblock or bypass blockages in the bile duct or small intestine and radiotherapy (25). Current standard systemic chemotherapies used to treat 2L BTC include FOLFOX (11). Targeted treatments may be offered instead of FOLFOX if tumours have an actionable molecular target (approximately 40% of BTC tumours) (16, 26). Currently approved targeted treatments in the UK for BTC include pemigatinib (TA722; advanced CCA with *FGFR2* fusion/rearrangement (10)), ivosidenib (TA948; advanced CCA with *IDH1 R132* mutation (20)), and futibatinib (TA1005; advanced CCA with *FGFR2* fusion/rearrangement (21)). No targeted 2L treatments are currently recommended by NICE for patients with HER2+ BTC. Importantly, co-occurring alterations in BTC are not expected; patients with BTC do not generally harbour (1) an actionable mutation targeted by one of the currently approved treatments and (2) HER2 amplification or overexpression (15) (see Question 4 for further details). This creates a high level of unmet need in patients with HER2+ BTC after 1L systemic therapy. **2. Have all relevant subgroups been included?** Please refer to the table above. **3. Have all relevant comparators been included?** Yes, please refer to the table above. **4. Would futibatinib and ivosidenib be considered relevant comparators? Is it possible that people with FGFR fusion or**	

		rearrangement or people with a IDH1 R132 mutation would also be HER2 positive? Futibatinib, pemigatinib, and ivosidenib are not considered relevant comparators to zanidatamab, as none of these targeted therapies are indicated for patients with advanced [redacted], since they are indicated for other targets (*FGFR2* fusion/rearrangements [futibatinib, pemigatinib] or *IDH1* R132 mutations [ivosidenib]). BTCs arise from distinct anatomical locations in the biliary tree and have different driver mutations (e.g. *FGFR2, IDH1*) (1-3, 23, 27, 28). There are no identified studies exploring patterns of co-mutations associated with HER2 amplification or overexpression and other genetic alterations in BTC. Patients with BTC generally do not harbour both 1) an actionable mutation targeted by approved precision medicines and 2) HER2 amplification or overexpression (15). In the unlikely situation of co-occurring mutations, the decision on choice of therapy by local multidisciplinary teams or molecular tumour boards can be aided using guidelines such as the ESMO Scale of Clinical Actionability of molecular Targets framework (29); therapies would not be used concurrently. **5. Please select from the following, will zanidatamab be:** • Prescribed in secondary care with routine follow-up in secondary care **6. For comparators and subsequent treatments, please detail if the setting for prescribing and routine follow-up differs from the intervention.** There are some differences in the prescribing and routine follow-up setting for patients treated with comparators and subsequent treatments versus zanidatamab. Both treatments are delivered in secondary care outpatient settings; however, there is reduced healthcare resource and patient burden with the administration of zanidatamab compared with FOLFOX. Zanidatamab is administered every 2 weeks as monotherapy via intravenous infusion using a canula. FOLFOX is a combination chemotherapy of folinic acid and oxaliplatin that is administered every 2 weeks and delivered intravenously via a central line (peripherally inserted central catheter),	

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		followed by a 46-hour infusion pump of fluorouracil (5-FU); this requires additional follow-up care (either in hospital or in the community). **7. Would zanidatamab be a candidate for managed access?** Zanidatamab will not be a candidate for managed access as the key trial (HERIZON-BTC-01) has been completed. **8. Do you consider that the use of zanidatamab can result in any potential substantial health-related benefits that are unlikely to be included in the QALY calculation?** **a. Please identify the nature of the data which you understand to be available to enable the committee to take account of these benefits.** The lack of effective and tolerable treatment options has a devastating impact on the lives of people with locally advanced or metastatic HER2+ BTC and their families/caregivers (7, 9, 12, 13). Depression, emotional distress, exhaustion, and overwhelming feelings are prevalent among caregivers for people with BTC (8). As described above, if approved, zanidatamab will be the first HER2-targeted treatment for BTC, providing a chemotherapy-free regimen with a demonstrated improved survival benefit over standard systemic 2L therapy (5, 15). Zanidatamab would also provide a disease-modifying treatment for patients who are ineligible for or cannot tolerate treatment with FOLFOX and currently only receive ASC. The availability of an innovative and targeted medicine like zanidatamab would give hope to patients and their families, potentially offering more quality time together versus currently available treatments (due to the improved survival and side effect profile with zanidatamab versus FOLFOX). Although this family/caregiver impact will not be quantified in the utility data, these additional elements of value identified by ISPOR, such as 'value of hope',	

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		'real option value' and 'equity' for patients, families and caregivers should not be underestimated (30). The caregiver burden will not be included in the economic model and therefore the benefits of zanidatamab may be underestimated. In HERIZON-BTC-01, HRQoL was assessed using the EQ-5D 5 Levels (EQ-5D-5L) and EQ-5D visual analogue scale (VAS). Overall, the baseline utility values obtained in the trial were higher than expected for a disease like BTC with such a substantial unmet need. For example, the mean (standard deviation, StD) baseline EQ-5D VAS score was [redacted]. However, this aligns with other recent BTC studies, including the FOENIX-CCA2 study of futibatinib in which the mean (StD) baseline EQ-5D VAS score was 71.7 (20.3) (31). The high baseline utilities may also reflect the 'value of hope' that patients with a poor prognosis and few treatment options may experience when enrolling in a clinical trial (30, 32). **References** 2. Vogel A, Bridgewater J, Edeline J, Kelley R, Klümpen H, Malka D, et al. Biliary tract cancer: ESMO Clinical Practice Guideline for diagnosis, treatment and follow-up. Annals of Oncology. 2023;34(2):127-40. 3. AMMF: The cholangiocarcinoma charity. Introduction to cholangiocarcinoma: An educational resource for patient organisations. 2023. 5. Lamarca A, Palmer DH, Wasan HS, Ross PJ, Ma YT, Arora A, et al. Second-line FOLFOX chemotherapy versus active symptom control for advanced biliary tract cancer (ABC-06): a phase 3, open-label, randomised, controlled trial. The Lancet Oncology. 2021;22(5):690-701. 6. Jazz Pharmaceuticals. Data on file. Zanidatamab SmPC (DRAFT). 2025. 7. Bibeau K, Bachini M, Lindley A, Barkey NM, Lindsey S. Exploring the diagnostic journey and life impact of patients with cholangiocarcinoma	

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		(CCA): Results from a large patient survey in the United States. American Society of Clinical Oncology; 2021. 8. Bibeau K, Jackson TD, Bachini M, Lindley A, Blanco F, LaFiura C, et al. Diagnostic journey and life impact of cholangiocarcinoma: results from surveys of patient and caregiver experiences. Future Oncology. 2024;20(15):997-1012. 9. Patel N, Lie X, Gwaltney C, Rokutanda N, Barzi A, Melisi D, et al. Understanding patient experience in biliary tract cancer: a qualitative patient interview study. Oncology and Therapy. 2021;9:557-73. 10. National Institute for Health and Care Excellence (NICE). Pemigatinib for treating relapsed or refractory advanced cholangiocarcinoma with FGFR2 fusion or rearrangement. 2021. Available from: https://www.nice.org.uk/guidance/ta722. Accessed on: 6th February 2025. 11. Bridgewater J, Sah J, Szende A, Paskow M, Messina P, Baur B, et al. Real-world treatment patterns and challenges of patients with biliary tract cancer: retrospective chart review survey in Europe (GARNET-2). ESMO Real World Data and Digital Oncology. 2024;5:100060. 12. Sangruangake M, Summart U, Songthamwat M, Sangchart B. The relationship between unmet need, physical symptoms, psychological well-being and health-related quality of life in cholangiocarcinoma survivors. Asian Pacific Journal of Cancer Prevention: APJCP. 2022;23(8):2821. 13. Elberg Dengsø K, Hillingsø J, Marcussen AM, Thomsen T. Health-related quality of life and anxiety and depression in patients diagnosed with cholangiocarcinoma: a prospective cohort study. Acta Oncologica. 2017;56(2):198-204. 15. Harding JJ, Fan J, Oh DY, Choi HJ, Kim JW, Chang HM, et al. Zanidatamab for HER2-amplified, unresectable, locally advanced or metastatic biliary tract cancer (HERIZON-BTC-01): a multicentre, single-arm, phase 2b study. Lancet Oncol. 2023;24(7):772-82.	

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		16. Vogel A, Ducreux M, Committee EG. ESMO Clinical Practice Guideline interim update on the management of biliary tract cancer. ESMO open. 2025:104003. 17. National Institute for Health and Care Excellence (NICE). Entrectinib for treating NTRK fusion-positive solid tumours (TA644). 2020. Available from: https://www.nice.org.uk/guidance/ta644. Accessed on: 11th March 2025 18. National Institute for Health and Care Excellence (NICE). Larotrectinib for treating NTRK fusion-positive solid tumours (TA630). 2020. Available from: https://www.nice.org.uk/guidance/ta630. Accessed on: 11th March 2025 19. National Institute for Health and Care Excellence (NICE). Durvalumab with gemcitabine and cisplatin for treating unresectable or advanced biliary tract cancer. 2024. Available from: https://www.nice.org.uk/guidance/ta944. Accessed on: 25th February 2025. 20. National Institute for Health and Care Excellence (NICE). Ivosidenib for treating advanced cholangiocarcinoma with an IDH1 R132 mutation after 1 or more systemic treatments. 2024. Available from: https://www.nice.org.uk/guidance/ta948. Accessed on: 6th February 2025. 21. National Institute for Health and Care Excellence (NICE). Futibatinib for previously treated advanced cholangiocarcinoma with FGFR2 fusion or rearrangement. 2024. Available from: https://www.nice.org.uk/guidance/ta1005. Accessed on: 6th February 2025. 22. National Institute for Health and Care Excellence (NICE). Pembrolizumab for previously treated endometrial, biliary, colorectal, gastric or small intestine cancer with high microsatellite instability or mismatch repair deficiency. 2023. Available from: https://www.nice.org.uk/guidance/ta914. Accessed on: 11th March 2025	

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		23.Rushbrook SM, Kendall TJ, Zen Y, Albazaz R, Manoharan P, Pereira SP, et al. British Society of Gastroenterology guidelines for the diagnosis and management of cholangiocarcinoma. Gut. 2024;73(1):16-46. 24.NHS East Genomics. Integrating genomic testing into Biliary Tract Cancer management (BTC) pathway. 2024. Available from: https://www.eastgenomics.nhs.uk/about-us/genomic-medicine-service-alliance/Transformation_Projects/biliary_tract_cancer_management_pathway/. Accessed on: 21 February 2025. 25. NHS. Treatment for bile duct cancer (cholangiocarcinoma). 2023. Available from: https://www.nhs.uk/conditions/bile-duct-cancer/treatment/. Accessed on: 21 February 2025. 26. Valery M, Vasseur D, Fachinetti F, Boilève A, Smolenschi C, Tarabay A, et al. Targetable molecular alterations in the treatment of biliary tract cancers: an overview of the available treatments. Cancers. 2023;15(18):4446. 27.Moeini A, Haber PK, Sia D. Cell of origin in biliary tract cancers and clinical implications. JHEP Reports. 2021;3(2):100226. 28.Bridgewater J, Imber C. New advances in the management of biliary tract cancer. HPB. 2007;9(2):104-11. 29.ESMO. A framework to rank genomic alterations as targets for cancer precision medicine. 2025. Available from: https://www.esmo.org/scales-and-tools/esmo-scale-for-clinical-actionability-of-molecular-targets-escat. Accessed on: 11th March 2025 30.Lakdawalla DN, Doshi JA, Garrison LP, Phelps CE, Basu A, Danzon PM. Defining Elements of Value in Health Care—A Health Economics Approach: An ISPOR Special Task Force Report [3]. Value in Health. 2018;21(2):131-9. 31.Goyal L, Meric-Bernstam F, Hollebecque A, Valle JW, Morizane C, Karasic TB, et al. Futibatinib for FGFR2-Rearranged Intrahepatic Cholangiocarcinoma. N Engl J Med. 2023;388(3):228-39.	

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		32.Lakdawalla DN, Romley JA, Sanchez Y, Maclean JR, Penrod JR, Philipson T. How Cancer Patients Value Hope And The Implications For Cost-Effectiveness Assessments Of High-Cost Cancer Therapies. Health Affairs. 2012;31(4):676-82.	
	Cholangiocarcinoma UK, an affiliate of the British Association for Study of Liver Disease (BASL)	Where do you consider zanidatamab will fit into the existing care pathway for HER2-positive advanced biliary tract cancer? Zanidatumab should be considered following failure of 1st and subsequent line treatment for advanced disease. Have all relevant subgroups been included? Yes Have all relevant comparators been included? Yes Would futibatinib and ivosidenib be considered relevant comparators? Is it possible that people with FGFR fusion or rearrangement or people with a IDH1 R132 mutation would also be HER2 positive? Co-occurrence of HER2 amplification and other alterations is very uncommon. [1] In the context of co-occurrence, the ESMO ESCAT scale should be used to determine the sequence of therapies. [2] Zanidatamab be prescribed in secondary care with routine follow-up in secondary care. Would zanidatamab be a candidate for managed access? Yes Do you consider that the use of zanidatamab can result in any potential substantial health-related benefits that are unlikely to be included in the QALY calculation? Yes Please identify the nature of the data which you understand to be available to enable the committee to take account of these benefits. [3] [4]	Thank you for your comments. No action required.

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		References: 1.Lowery MA, Ptashkin R, Jordan E, et al. Comprehensive Molecular Profiling of Intrahepatic and Extrahepatic Cholangiocarcinomas: Potential Targets for Intervention. *Clin Cancer Res* 2018; **24**(17): 4154-61. 2.Mosele MF, Westphalen CB, Stenzinger A, et al. Recommendations for the use of next-generation sequencing (NGS) for patients with advanced cancer in 2024: a report from the ESMO Precision Medicine Working Group. *Annals of Oncology* 2024; **35**(7): 588-606. 3.Harding JJ, Fan J, Oh D-Y, et al. Zanidatamab for HER2 amplified, unresectable, locally advanced or metastatic biliary tract cancer (HERIZON-BTC-01): a multicentre, single-arm, phase 2b study. *The Lancet Oncology* 2023; **24**(7): 772-82. 4.Crespo MJ, M and Bridgewater, J. Unveiling the secrets of real-world use of Zanidatamab in an English biliary tract cancer cohort. Precision BTC Annual Meeting; 2025; Mallorca; 2025. 5.Crolley VE, Guest R, Beggs AD, et al. Investigating alterations in cancer driver genes and other potentially targetable mutations in patients with intrahepatic cholangiocarcinoma (iCCA) treated on the randomised phase III multicentre BILCAP clinical trial. *Journal of Clinical Oncology* 2023; **41**(16_suppl): 4019-. 6.Lamarca A, Palmer DH, Wasan HS, et al. Second-line FOLFOX chemotherapy versus active symptom control for advanced biliary tract cancer (ABC-06): a phase 3, open-label, randomised, controlled trial. *The Lancet Oncology* 2021; **22**(5): 690-701.	
Additional comments on the draft scope	Jazz Pharmaceuticals	Regarding the inclusion of TA944 (durvalumab with gemcitabine and cisplatin for treating unresectable or advanced BTC) in the related technology appraisals, Jazz Pharmaceuticals would like to note that durvalumab is used as 1L treatment for BTC. Only patients who experience disease progression or unsuitable toxicity with 1L treatment would require 2L therapy. The	Thank you for your comment. The background section of the scope intends to provide an overview of

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		proposed positioning of zanidatamab is as 2L treatment and therefore durvalumab is of limited relevance to this appraisal.	the treatment pathway and information given about previous NICE recommendations in the relevant disease area. No action required.
Comments on the stakeholder list	Jazz Pharmaceuticals	In addition to the stakeholders on the provisional list, Jazz Pharmaceuticals suggest that the following patient groups and research organisations could be invited to participate in this evaluation: • StandUpToCancer • The Christie Charity • The Cholangiocarcinoma Foundation • Conquer Cancer Foundation • National Cancer Research Institute Upper Gastrointestinal clinical studies group • National Institute for Health Research Manchester Clinical Research Facility • OPA Cancer Charity • The Christie NHS Foundation Trust Systemic Therapy Research group	Thank you for your comment. Stand Up To Cancer is a fundraising campaign part of Cancer Research UK – this organisation is already on the stakeholder list. Please note that only UK based patient groups and research organisations are included as part of the stakeholder list.
	Cholangiocarcinoma UK, an affiliate of the British Association for	This should include the Royal College of Pathologists and Genomic medicine service alliance (GMSA)/Cellular Pathology genomics Centres.	Thank you for your comment. The Royal College of Pathologists is already listed on the stakeholder list.

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	Study of Liver Disease (BASL)		The NHS Genomic Medicine Service has been added to the stakeholder list.

The following stakeholders indicated that they had no comments on the draft remit and/or the draft scope

AMMF (patient 2)