National Institute for Health and Care Excellence

Health Technology Evaluation

Futibatinib for previously treated advanced cholangiocarcinoma with FGFR2 fusion or rearrangement ID6302

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

Please note: Comments received in the course of consultations carried out by NICE are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the submissions that NICE has received, and are not endorsed by NICE, its officers or advisory committees.

Comment 1: the draft remit and proposed process

Section	Stakeholder	Comments [sic]	Action
Appropriateness of an evaluation and proposed evaluation route	Taiho Pharma Europe, Limited	The Company would like to propose futibatinib for the cost-comparison process versus pemigatinib. Pemigatinib is the only targeted treatment currently recommended by NICE in the target patient population for futibatinib.[1] UK clinical experts in cholangiocarcinoma (CCA) confirmed that in UK clinical practice, pemigatinib is the only treatment used in the target population and therefore represents the only relevant comparator for futibatinib.[2] In the absence of head-to-head evidence, the comparative effectiveness of futibatinib versus pemigatinib was assessed via a matching adjusted indirect	Comment noted. NICE has determined that cost comparison is not an appropriate route for this topic, so it will proceed as an STA. The comparators listed in the scope aim to be inclusive. A strong and clear rationale should be provided for excluding any comparators from the evidence submission,

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		comparison (MAIC) between the FOENIX-CCA2 and FIGHT-202 trials. Before and after matching, the results showed that futibatinib and pemigatinib are associated with equal efficacy with respect to progression-free survival (PFS) and overall survival (OS), with no statistically significant differences detected between the two treatments in any of the analyses considered. Based on these results and their broader clinical experience, feedback received from UK clinical experts indicated that they would expect futibatinib to be associated with at least equal efficacy, to that of pemigatinib in clinical practice, with potential for reduced treatment-resistance mutations for patients treated with futibatinib.[2] Furthermore, UK clinical experts in CCA noted that the safety profile for futibatinib was in line with clinical expectations for an FGFR inhibitor in UK clinical and that in particular, the safety profiles of futibatinib and pemigatinib were extremely similar. Based on the above evidence, the clinical experts concluded that futibatinib and pemigatinib were expected to have equal impacts on patient quality of life and therefore that an assumption of equal efficacy, safety and quality of life benefits between futibatinib and pemigatinib was suitable.[2] The Company acknowledges that, as data supporting the comparable efficacy of futibatinib versus pemigatinib are informed by a MAIC, the results are associated with some uncertainty. To address this, the Company proposes that the results of a cost-utility analysis, where the relative efficacies of futibatinib and pemigatinib are informed by the MAIC, will also be presented as a scenario analysis in the Company submission for completeness.	which can be considered by the committee. No action needed.

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	Incyte Biosciences UK Ltd	Agree	No action needed.
Wording	Taiho Pharma Europe, Limited	Futibatinib is indicated as a monotherapy for the treatment of adult patients with fibroblast growth factor receptor 2 (FGFR2) fusions or rearrangements, as opposed to CCA more broadly. The draft remit/evaluation objective should therefore be updated to state: "To appraise the clinical and cost effectiveness of futibatinib monotherapy within its marketing authorisation for treating adult patients with previously treated cholangiocarcinoma with FGFR2 fusion or rearrangements."	The draft remit specifies that futibatinib will be appraised 'within its marketing authorisation' (which is specific to people with FGFR2 fusion or rearrangements). Further detail on the population can be found later in the document. No action required.
	Incyte Biosciences UK Ltd	Agree	No action required.
Timing	Taiho Pharma Europe, Limited	Futibatinib received marketing authorisation from the MHRA for the indication of interest to this submission in August 2023.[3] As such, to prevent delays in access, futibatinib should be prioritised for evaluation.	Comment noted. No action required.

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	Incyte Biosciences UK Ltd	No urgency as current treatments address patient need	Comment noted. No action required.
Additional comments on the draft remit	Taiho Pharma Europe, Limited	N/A – no additional comments.	Comment noted. No action required.

Comment 2: the draft scope

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Background information	Taiho Pharma Europe, Limited	Overall, the presented background information is correct, however, a couple of clarifications are noted below. **Background** A wide range of varying estimates for the proportion of intrahepatic cholangiocarcinoma (iCCA) cases among all cholangiocarcinomas (CCAs) have been reported in recent epidemiology studies in the published literature. However, feedback received from UK clinical experts in CCA at an advisory board for this submission noted that ~20% of CCA cases in the UK represent iCCA.[2] It is therefore politely requested that the phrasing in the background section is updated to; *"Approximately **20%** of these cases are iCCA, and ~10–15% of those will have fusions or rearrangements for FGFRs".*	Comments noted. The background section has been updated to reflect the broad range of estimates for the proportion of cholangiocarcinomas (CCAs) which are intrahepatic

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		Additionally, please note that the 2023 guidelines of the British Society of Gastroenterology (BSG) have recently become available.[4] **Technology** Futibatinib is indicated as a monotherapy for the treatment of adult patients with locally advanced or metastatic CCA with a FGFR2 fusion or rearrangement that have progressed after at least one prior line of systemic therapy.[3] Furthermore the manufacturer of futibatinib is "Taiho Pharma Europe, Limited". It is therefore politely requested that the technology phrasing is updated to state: *"Futibatinib **monotherapy (Lytgobi, Taiho Pharma Europe, Limited)** is indicated for the treatment of **adult patients with** locally advanced or metastatic CCA with a FGFR2 fusion or rearrangement that have progressed after at least one prior line of systemic therapy."*	cholangiocarcinoma (iCCA). The 2023 guidelines of the British Society of Gastroenterology (BSG) have also been added to the draft scope. The company name and indication have been updated.
	Incyte Biosciences UK Ltd	We note overall annual incidence of cholangiocarcinoma is cited as 2,800 people and that approximately 10% of these cancers are intrahepatic CCA (iCCA). We believe this is incorrect. Data cited in the recently published BSG Guidelines comment that the National Cancer Registration Dataset found 74% of CCAs were iCCA, a higher proportion compared to historical studies and data cited elsewhere. (Rushbrook SM et al. Gut. 2023;0:1–31. doi:10.1136/gutjnl-2023-330029)	Comment noted. The background section has been updated to reflect the broad range of estimates for the proportion of cholangiocarcinomas (CCAs) which are intrahepatic

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			cholangiocarcinoma (iCCA). The 2023 BSG guidelines (Rushbrook SM et al. Gut. 2023) have also been referenced in the draft scope.
Population	Taiho Pharma Europe, Limited	The draft scope is accurate, no amendments are required.	No action required.
	Incyte Biosciences UK Ltd	Agree	No action required.
Subgroups	Taiho Pharma Europe, Limited	No subgroups are expected to be relevant for separate consideration in this appraisal.	No action required.
Comparators	Taiho Pharma Europe, Limited	The list of relevant comparators included in the draft scope is inaccurate - pemigatinib represents the sole standard of care in UK clinical practice for patients with CCA with FGFR2-fusions or other rearrangements and is also the only treatment licensed in this indication. As such, pemigatinib represents the only relevant comparator to futibatinib in this indication.	Comment noted. The comparators listed in the scope aim to be inclusive. A strong and clear rationale

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		As part of an Advisory Board, UK clinical experts noted that owing to the significant survival benefits associated with treating patients with recognisable oncogenic mutations with targeted treatments, in UK clinical practice patients with FGFR2 fusions or rearrangements solely receive targeted treatment with pemigatinib (an FGFR2 inhibitor).[2] The experts noted that the response rate in patients with CCA with FGFR2 fusions or rearrangements receiving chemotherapy is ~5%, while for pemigatinib it is ~40%.[2,5] This is in line with the 2023 British Society of Gastroenterology (BSG) guidelines on treating CCA, which state that patients should have molecular profiling at the earliest opportunity and targeted treatments should be considered.[4] The current European Society of Medical Oncology (ESMO) guidelines confirm that FGFR inhibitors are recommended for the treatment of patients with FGFR2 fusions, whose disease has progressed after ≥1 prior line of systemic therapy.[6] As such, non-FGFR targeted treatments, including the modified FOLFOX regimen (folinic acid, fluorouracil and oxaliplatin) and best supportive care (BSC) do not form part of routine standard of care in UK clinical practice for patients with FGFR2 fusions or rearrangements, and are therefore not relevant comparators for futibatinib in this indication.	should be provided for excluding any comparators from the evidence submission, which can be considered by the committee. No action needed.
	Incyte Biosciences UK Ltd	Agree	No action needed.

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Outcomes	Taiho Pharma Europe, Limited	The draft scope is accurate, no amendments are required.	No action needed.
	Incyte Biosciences UK Ltd	Agree	No action needed.
Equality	Taiho Pharma Europe, Limited	No equality issues were identified.	No action needed.
	Incyte Biosciences UK Ltd	Agree	No action needed.
Other considerations	Taiho Pharma Europe, Limited	No comments.	No action needed.
Questions for consultation	Taiho Pharma Europe, Limited	**Where do you consider futibatinib will fit into the existing care pathway for advanced cholangiocarcinoma?** Pemigatinib is the only targeted treatment recommended by NICE in this indication. Futibatinib will fit alongside pemigatinib in the existing care pathway; as an alternative second line treatment option for patients with advanced or metastatic CCA with FGFR2 fusions or rearrangements. This	Comment noted. No action needed.

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		positioning within the existing care pathway was validated by UK clinical experts in CCA at an Advisory Board.[2] **Which treatments are considered to be established clinical practice in the NHS for locally advanced or metastatic cholangiocarcinoma with FGFR2 fusion or rearrangement that has progressed after at least 1 prior systemic therapy?** As noted above, pemigatinib represents the only treatment option that has been recommended by NICE in adult patients with CCA with FGFR fusions or rearrangements that have progressed after at least one prior line of systematic therapy, and therefore represents the sole standard of care for this patient population.[1] UK clinical experts consulted as part of an UK Advisory Board noted that owing to the significant survival benefits associated with treating patients with recognisable oncogenic mutations with targeted treatments, in UK clinical practice, patients with FGFR2 fusions or rearrangements solely receive targeted treatment with pemigatinib (FGFR2 inhibitor).[2] **Should best supportive care be included as a comparator? If so, what does best supportive care consist of and, is mFOLFOX a relevant comparator? Would any other chemotherapy regimens be used?** As noted in the comparator box above, owing to the significant survival benefits offered by targeted treatments to patients with FGFR2 fusions or rearrangements, pemigatinib represents the sole standard of care for this patient population in UK clinical practice. Therefore, neither BSC nor mFOLFOX are considered relevant comparators. This aligns with the 2023	Comment noted. The comparators listed in the scope aim to be inclusive. A strong and clear rationale should be provided for excluding any comparators from the evidence submission, which can be considered by the committee. No action needed. Comment noted. As above, no action required.

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		BSG guidelines and 2022 ESMO guidelines and was confirmed by UK clinical experts.[2,4,6] **Is genetic testing for FGFR2 fusion or rearrangement routinely done in NHS clinical practice?** In line with 2023 BSG guidelines, genetic testing for FGFR2 fusions or rearrangements is included in standard NHS clinical practice for patients with CCA.[7] This has been confirmed by UK clinical experts in CCA.[2,4] **Would futibatinib be a candidate for managed access?** The FOENIX-CCA2 trial (the principal trial informing the relative efficacy and safety for futibatinib in this indication) is complete, and no further data-cuts are planned.[8] Therefore, it is anticipated that the efficacy data presented in this submission are suitably robust to allow futibatinib to be considered for routine commissioning, and futibatinib is not anticipated to be a candidate for managed access. **Do you consider that the use of futibatinib can result in any potential substantial health-related benefits that are unlikely to be included in the QALY calculation?** Treatment-resistant mutations can arise over the course of treatment with FGFR2 inhibitors, including futibatinib and pemigatinib.[9] Importantly, the covalent/irreversible binding nature of futibatinib to FGFR2 has been shown to lead to significantly fewer resistance mutations than pemigatinib and other reversibly binding FGFR2-inhibitors.[10,11] This has been supported by	Comment noted. No action required. Comment noted. No action required. Comment noted. No action required.

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		preclinical experiments in murine cells, as shown in Figure 1 in Goyal et al. (2023).[12] UK clinical experts in CCA noted that this difference can be clinically significant for some patients, since resistance to pemigatinib is most commonly caused by N550 mutations, which futibatinib can overcome. The experts highlighted that, although this difference is not likely to be reflected in the survival results from the clinical trial, for individual patients this distinction may be important.[2] In addition, clinical experts explained that resistance mutations emerge during treatment and cannot be measured in advance; since futibatinib results in fewer resistance mutations, they would prefer to use it instead of pemigatinib in clinical practice.[2] Consequently, based on this feedback from clinical experts, it is plausible that futibatinib may be associated with additional health benefits versus pemigatinib that are not reflected in QALY calculations. **Please provide comments on the appropriateness of appraising this topic through the cost-comparison process** The efficacy of futibatinib is expected to be at least equal to pemigatinib, based on the results of the matching-adjusted indirect comparison (MAIC) presented within this submission and UK expert opinion[2]. The safety profiles of futibatinib and pemigatinib are also expected to be similar, which was confirmed by clinical experts.[2] Therefore, it is expected that this submission is suitable for the cost-comparison route.	Comment noted. NICE has determined that cost comparison is not an appropriate route for this topic, so it will proceed as an STA.

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		As pemigatinib is the only targeted treatment in the patient population of interest, it is anticipated that futibatinib will fit alongside pemigatinib in the treatment pathway; this positioning was validated by UK clinical experts in CCA at an Advisory Board.[2] Since both FIGHT-202 and FOENIX-CCA2 trials were single-arm trials, relative efficacy estimates had to be obtained via an MAIC. The results of the MAIC found no statistically significant differences between futibatinib and pemigatinib with respect to PFS and OS in any of the analyses considered, before and after weighting, and therefore an assumption of equal efficacy was considered appropriate. This assumption was supported by UK clinicians and health economics experts at a UK Advisory Board.[2] Additionally, clinical experts noted that the safety profiles of futibatinib and pemigatinib are expected to be very similar, and that comparable efficacy is expected to translate to comparable health-related quality of life (HRQoL).[2] Futibatinib and pemigatinib are both orally administered FGFR2 inhibitors, and therefore anticipated to be associated with same resource use. As such, it is considered that futibatinib is suitable for the cost-comparison route as it is anticipated to deliver similar clinical benefits at similar or reduced costs compared with pemigatinib. The Company however acknowledges that, as data supporting the comparable efficacy of futibatinib versus pemigatinib are informed by a MAIC, the results are associated with some uncertainty. To address this uncertainty, the submission will present a cost-comparison approach in the base case economic analysis, where the efficacy of futibatinib and pemigatinib are assumed to be equal. For completeness,	

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		scenario analyses will be explored where the relative efficacy of futibatinib and pemigatinib are informed by the results of the MAIC.	
	Incyte Biosciences UK Ltd	**Is genetic testing for FGFR2 fusion or rearrangement routinely done in NHS clinical practice?** Currently genetic testing for FGFR2 fusion or rearrangement is available on the NHS though more could be done to support timely delivery of test results within the service. Anecdotally HCPs have reported that test turnaround time could take up to two months. This has a great impact on patients and their outcomes especially with CCA being an aggressive cancer with patients potentially progressing quite quickly. **Would it be appropriate to use the cost-comparison methodology for this topic?** Due to the lack of direct comparative evidence for futibatinib in relation to the comparators delineated in the draft scope, it is likely that the company will undertake indirect treatment comparisons concerning the outcomes encompassing overall survival, progression-free survival, tumour response and adverse events. However, it is worth highlighting that the clinical evidence of futibatinib derives from single-arm trial characterised by a relatively small sample size. The absence of a comparator group precluded accurate quantification of the treatment effect within an indirect treatment comparison, consequently introducing a degree of uncertainty into the	Comment noted. No action required. Comment noted. NICE has determined that cost comparison is not an appropriate route for this topic, so it will proceed as an STA. standard technology appraisal.

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		evaluation of the clinical efficacy of futibatinib relative to other comparators that forms the basis of cost comparison evaluation process.	
Additional comments on the draft scope	Taiho Pharma Europe, Limited	N/A	No action required.

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

- AMMF – The Cholangiocarcinoma Charity
- Royal College of Pathologists