National Institute for Health and Care Excellence

Single Technology Appraisal (STA)

Cabozantinib for previously treated advanced hepatocellular carcinoma [ID3917] (review of TA582)

Response to consultee and commentator comments on the draft remit and draft scope (pre-referral)

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

Section	Consultee/ Commentator	Comments [sic]	Action
Wording	British Association for the Study of the Liver (BASL) / HCC-UK	Wording is appropriate	Thank you for your comment. No action required.
	British Society of Gastroenterology (BSG)	Wording is appropriate	Thank you for your comment. No action required.
	Bayer plc	No comments	No action required.
	Ipsen Limited	The wording of the remit is appropriate.	Thank you for your comment. No action required.

Section	Consultee/ Commentator	Comments [sic]	Action
Timing Issues	British Association for the Study of the Liver (BASL) / HCC-UK	There is some urgency as there is only one other approved treatment for this group of patients – regorafenib. Regorafenib is not suitable for patients who did not tolerate prior sorafenib and hence there is a group of patients for whom there is no current available therapeutic option	Comment noted. NICE has scheduled this topic into its work programme. For further details, see the NICE website: https://www.nice.org.uk/guidance/indevelopment/gid-ta10805. No action required.
	British Society of Gastroenterology (BSG)	There is some urgency as there is only one other approved treatment for this group of patients – regorafenib. Regorafenib is not suitable for patients who did not tolerate prior sorafenib and hence there is a group of patients for whom there is no current available therapeutic option	Comment noted. NICE has scheduled this topic into its work programme. For further details, see the NICE website: https://www.nice.org.uk/guidance/indevelopment/gid-ta10805. No action required.
	Bayer plc	No comments	No action required.
	Ipsen Limited	The timing for NICE appraisal is relevant as there are limited treatment options in this disease area which still holds a poor prognosis and has a history of very few drugs having been successfully developed for it, indicating a clear unmet need for this group of people.	Comment noted. NICE has scheduled this topic into its work programme. For further details, see the NICE website:

Section	Consultee/ Commentator	Comments [sic]	Action
			https://www.nice.org.uk/guidance/indevelopment/gid-ta10805. No action required.
Additional comments on the draft remit	British Association for the Study of the Liver (BASL) / HCC-UK	No further comments	No action required.
	British Society of Gastroenterology (BSG)	No further comments	No action required.
	Bayer plc	No comments	No action required.
	Ipsen Limited	No	No action required.

Comment 2: the draft scope

Section	Consultee/ Commentator	Comments [sic]	Action
Background information	British Association for the Study of the Liver (BASL) / HCC-UK	Accurate and complete	Thank you for your comment. No action required.

Section	Consultee/ Commentator	Comments [sic]	Action
	British Society of Gastroenterology (BSG)	Accurate and complete	Thank you for your comment. No action required.
	NCRI Hepatobiliary Working Group	The statement that patients with advanced disease are treated with chemoembolization and systemic therapy is reserved for those who do not respond or have metastatic disease is not correct. The combination of atezolizumab and bevacizumab are now approved by NICE as first line options for systemic therapy in addition to sorafenib and lenvatinib. I would rephrase: For patients with advanced disease and those progressing or not suitable for locoregional therapy, first-line systemic therapy with atezolizumab and bevacizumab, or sorafenib or lenvatinib are approved treatment options. If patients progress on or do not tolerate atezolizumab and bevacizumab, sorafenib or lenvatinib may be given second-line. For patients with disease progression on sorafenib, regorafenib is an approved option.	Thank you for your comment. The scope has been updated to include atezolizumab plus bevacizumab as a treatment option.
	Bayer plc	No comments	No action required.
	Ipsen Limited	Ipsen agrees with the background information describing the epidemiology and treatment pathway. This highlights that there is only one treatment option following sorafenib. The introduction of cabozantinib into the treatment pathway will provide a treatment that has shown efficacy in a broader prior sorafenib population (i.e. beyond second-line of therapy and sorafenib intolerant patients) (Abou-Alfa et al, 2018). Abou-Alfa GK, Meyer T, Cheng AL et al. Cabozantinib in Patients with Advanced and Progressing Hepatocellular Carcinoma. N Engl J Med 2018;379(1):54-63	Thank you for your comment. The scope has been updated to include atezolizumab plus bevacizumab as a treatment option.

Section	Consultee/ Commentator	Comments [sic]	Action
		The background section is missing the recent guidance issued by NICE (TA666) which recommends atezolizumab plus bevacizumab as an option for treating advanced or unresectable HCC in adults who have not had previous systemic treatment.	
The technology/ intervention	British Association for the Study of the Liver (BASL) / HCC-UK	Yes, accurate description	Thank you for your comment. No action required.
	British Society of Gastroenterology (BSG)	Yes, accurate description	Thank you for your comment. No action required.
	NCRI Hepatobiliary Working Group	Yes [the descriptions of the technology or technologies is accurate]	Thank you for your comment. No action required.
	Bayer plc	No comments	No action required.
	Ipsen Limited	The description of the technology could be more clearly described in more detail as: Cabozantinib (Cabometyx, Ipsen) is a small molecule tyrosine kinase inhibitor. In addition to the VEGFR (vascular endothelial growth factor receptor), cabozantinib targets both MET (hepatocyte growth factor [HGF] receptor) and AXL (receptor for the vitamin K-dependent protein growth-arrest-specific gene 6). This inhibits multiple receptor tyrosine kinases implicated in tumour growth and angiogenesis, pathologic bone remodelling and metastatic progression of cancer. Both MET and AXL receptors play an	Thank you for your comment. This section is intended to provide a brief overview of the technology. No change to scope.

Section	Consultee/ Commentator	Comments [sic]	Action
		important role in the emergence of resistance mechanisms to anti-VEGFR inhibitor. It is administered orally.	
Population	British Association for the Study of the Liver (BASL) / HCC-UK	The title of the draft remit is '**Cabozantinib for previously treated advanced hepatocellular carcinoma**' It would be appropriate for the STA to consider patients who have been previously treated with lenvatinib as first-line systemic therapy. This is a separate group from patients who have previously received sorafenib. There is also the potential to use cabozantinib after atezolizumab/bevacizumab as an alternative 2nd-line therapy to sorafenib/lenvatinib	Thank you for your comment. NICE will appraise cabozantinib within its marketing authorisation for treating hepatocellular carcinoma in adults who have previously been treated with sorafenib.
	British Society of Gastroenterology (BSG)	The title of the draft remit is '**Cabozantinib for previously treated advanced hepatocellular carcinoma**' It would be appropriate for the STA to consider patients who have been previously treated with lenvatinib as first-line systemic therapy. This is a separate group from patients who have previously received sorafenib. There is also the potential to use cabozantinib after atezolizumab/bevacizumab as an alternative 2nd-line therapy to sorafenib/lenvatinib	Thank you for your comment. NICE will appraise cabozantinib within its marketing authorisation for treating hepatocellular carcinoma in adults who have previously been treated with sorafenib.
	NCRI Hepatobiliary Working Group	Yes [the population is defined appropriately]	Thank you for your comment. No action required.
	Bayer plc	No comments	No action required.
	Ipsen Limited	Yes, Ipsen agrees with the description of the population as defined as	Thank you for your

Section	Consultee/ Commentator	Comments [sic]	Action
		'adults with advanced hepatocellular carcinoma (HCC) who have had sorafenib'. This is the target population for cabozantinib which will reflect eligible patients in NHS practice. Furthermore, this is the population reflected in the primary clinical evidence (i.e. CELESTIAL randomised control trial) supporting the marketing authorisation. There are no groups (sub-groups) that should be considered separately.	comment. No action required.
Comparators	British Association for the Study of the Liver (BASL) / HCC-UK	The comparator for most patients who have previously received sorafenib is regorafenib, but in addition some patients will not be suitable for regorafenib due to poor tolerance of sorafenib and hence for these patients the comparator would be best supportive care (BSC). In addition for patients who received lenvatinib first-line the comparator would be BSC (as regorafenib is not approved for these patients). If cabozanitinb was used as second-line therapy after atezolizumab/bevacizumab then the comparator would be sorafenib or lenvatinib.	Thank you for your comment. The scope has been updated to include best supportive care as a comparator.
	British Society of Gastroenterology (BSG)	The comparator for most patients who have previously received sorafenib is regorafenib, but in addition some patients will not be suitable for regorafenib due to poor tolerance of sorafenib and hence for these patients the comparator would be best supportive care (BSC). In addition for patients who received lenvatinib first-line the comparator would be BSC (as regorafenib is not approved for these patients). If cabozanitinb was used as second-line therapy after atezolizumab/bevacizumab then the comparator would be sorafenib or lenvatinib.	Thank you for your comment. The scope has been updated to include best supportive care as a comparator.
	NCRI Hepatobiliary Working Group	Yes [these are the standard treatments currently used in the NHS with which the technology should be compared]	Thank you for your comment. No action required.

Section	Consultee/ Commentator	Comments [sic]	Action
	Bayer plc	No comments	No action required.
	Ipsen Limited	The comparators are accurate for this population. People with advanced hepatocellular carcinoma have few treatment options. Regorafenib is currently the only other licensed treatment option for patients with advanced hepatocellular carcinoma who have had prior sorafenib. The clinical evidence for regorafenib is from the RESORCE trial which reflects a pure second-line population of patients that were tolerable to sorafenib. (Bruix et al, 2017) In contrast the clinical evidence demonstrated by the CELESTIAL trial (Abou-Alfa et al, 2018) for cabozantinib also includes beyond second-line treatment and sorafenib intolerant patients. Therefore, Ipsen believe there exists a limitation for the comparison with regorafenib in the target population. Abou-Alfa GK, Meyer T, Cheng AL et al. Cabozantinib in Patients with Advanced and Progressing Hepatocellular Carcinoma. N Engl J Med 2018;379(1):54-63 Bruix J, Qin S, Merle P. Regorafenib for patients with hepatocellular carcinoma who progressed on sorafenib treatment (RESORCE): a randomised, double-blind, placebo-controlled, phase 3 trial. Lancet 2017;389(10064):56-66	Thank you for your comment. No action required.
Outcomes	British Association for the Study of the Liver (BASL) / HCC-UK	Outcomes are appropriate	Thank you for your comment. No action required.
	British Society of Gastroenterology (BSG)	Outcomes are appropriate	Thank you for your comment. No action required.

Section	Consultee/ Commentator	Comments [sic]	Action
	NCRI Hepatobiliary Working Group	Worth adding dose reduction as well as discontinuation. Also disease control rate in addition to response rate.	Thank you for your comment. Outcomes in the scope are generally kept broad.
	Bayer plc	No comments	No action required.
	Ipsen Limited	The outcome measures to be considered are appropriate. It should be noted that the clinical evidence for regorafenib does not allow a comparison in terms of time to treatment discontinuation as this data is not available in the public domain.	Thank you for your comment. No action required.
Economic analysis	British Association for the Study of the Liver (BASL) / HCC-UK	No further comments	No action required.
	British Society of Gastroenterology (BSG)	No further comments	No action required.
	NCRI Hepatobiliary Working Group	The median survival for patients treated second-line with cabozantinib is around 10 months. This may help define time horizon.	Thank you for your comment. No action required.
	Bayer plc	No comments	No action required.
	Ipsen Limited	The economic analysis is appropriate and consistent with NICE reference case. The analysis will include an appropriate time horizon to capture all the	Thank you for your comment. No action

Section	Consultee/ Commentator	Comments [sic]	Action
		relevant costs and QALYs.	required.
Equality and Diversity	British Association for the Study of the Liver (BASL) / HCC-UK	I have no concerns regarding equality or discrimination.	Thank you for your comment. No action required.
	British Society of Gastroenterology (BSG)	I have no concerns regarding equality or discrimination.	Thank you for your comment. No action required.
	NCRI Hepatobiliary Working Group	No issues	Thank you for your comment. No action required.
	Bayer plc	No comments	No action required.
	Ipsen Limited	There are no equality issues to raise at this stage.	Thank you for your comment. No action required.
Other considerations	British Association for the Study of the Liver (BASL) / HCC-UK	As mentioned above I would recommend considering cabozantinib in patients who previously received lenvatinib, or who had previously received atezolizumab/bevacizumab.	Thank you for your comment. NICE will appraise cabozantinib within its marketing authorisation for treating of hepatocellular carcinoma in adults who have previously been

Section	Consultee/ Commentator	Comments [sic]	Action
			treated with sorafenib.
	British Society of Gastroenterology (BSG)	As mentioned above I would recommend considering cabozantinib in patients who previously received lenvatinib, or who had previously received atezolizumab/bevacizumab.	Thank you for your comment. NICE will appraise cabozantinib within its marketing authorisation for treating of hepatocellular carcinoma in adults who have previously been treated with sorafenib.
	NCRI Hepatobiliary Working Group	Given that the preferred first line option is atezolizumab and bevacizumab, sorafenib may be given second line and cabozantinib third line. Selective internal radiotherapy may also be given.	Thank you for your comment. No action required.
	Bayer plc	No comments	No action required.
	Ipsen Limited	Cabozantinib has previously received a MHRA PIM designation in renal cell carcinoma (RCC) highlighting its ability to address unmet needs.	Thank you for your comment. No action required.
Innovation	British Association for the Study of the Liver (BASL) / HCC-UK	Yes, the technology is innovative. It is a multi-kinase inhibitor with action against the MET pathway which other multi-kinase inhibitors used in HCC do not. I wouldn't expect any benefits not accounted for in the QALY calculation.	Thank you for your comment. During the development of the appraisal, the committee will consider the degree to which cabozantinib is an innovative technology

Section	Consultee/ Commentator	Comments [sic]	Action
			when making its recommendations. No action required.
	British Society of Gastroenterology (BSG)	Yes, the technology is innovative. It is a multi-kinase inhibitor with action against the MET pathway which other multi-kinase inhibitors used in HCC do not. I wouldn't expect any benefits not accounted for in the QALY calculation.	Thank you for your comment. During the development of the appraisal, the committee will consider the degree to which cabozantinib is an innovative technology when making its recommendations. No action required.
	NCRI Hepatobiliary Working Group	The majority of patients with advanced HCC will not tolerate, or progress after sorafenib, and there remains a need for effective sequential therapy. Regorafenib has only been demonstrated to be tolerable and effective as second-line therapy in those that had had tolerated sorafenib first-line. By contrast, the CELESTIAL trial allowed cabozantinib to be given second or third line and did not require sorafenib tolerance. Despite this more flexible inclusion criteria, the benefit of cabozantinib was similar to that of regorafenib. Additionally, cabozantinib targets cMET which is thought to represent an adaptive resistance pathway for sorafenib. Therefore, cabozantinib represents a more attractive option for patients progressing on, or intolerant to sorafenib.	Thank you for your comment. No action required.
	Bayer plc	No comments	No action required.

Section	Consultee/ Commentator	Comments [sic]	Action
	Ipsen Limited	Cabozantinib is an innovative therapy in a disease area of high unmet medical need. It offers an alternative treatment option to a patient population with poor prognosis where there is only one other treatment option currently recommended by NICE after failure of sorafenib first line therapy. Cabozantinib is a tyrosine kinase inhibitor (TKI), targeting multiple receptors. It is the only approved TKI that, in addition to the VEGFR (vascular endothelial growth factor receptor), targets both MET (hepatocyte growth factor [HGF] receptor) and AXL (receptor for the vitamin K-dependent protein growth-arrest-specific gene 6) receptors which play an important role in the emergence of resistance mechanisms to anti-VEGFR inhibitors (Qu et al, 2016; .Xie et al, 2016, Zhou et al, 2016), such as sorafenib, this leads to poor patient outcomes (Reichl, et al, 2015), thereby differentiating cabozantinib from other VEGF-targeting agents. Reichl P, Dengler M, van Zijl F, et al. Axl activates autocrine transforming growth factor-β signaling in hepatocellular carcinoma. Hepatology 2015;61:930-941 Qu L, Ding J, Chen C, et al. Exosome-Transmitted lncARSR Promotes Sunitinib Resistance in Renal Cancer by Acting as a Competing Endogenous RNA. Cancer cell. 2016;29(5):653-668 Xie Z, Lee YH, Boeke M, et al. MET Inhibition in Clear Cell Renal Cell Carcinoma. J Cancer. 2016;7(10):1205-1214 Zhou L, Liu XD, Sun M, et al. Targeting MET and AXL overcomes resistance to sunitinib therapy in renal cell carcinoma. Oncogene. 2016;35(21):2687-2697	Thank you for your comment. During the development of the appraisal, the committee will consider the degree to which cabozantinib is an innovative technology when making its recommendations. No action required.
Questions for consultation	British Association for the Study of the Liver (BASL) /	***Have all relevant comparators for cabozantinib been included in the scope?*** Please see comment above about comparing to BSC for patients who have previously received lenvatinib.	Thank you for your comment. Best supportive care has been added to the

Section	Consultee/ Commentator	Comments [sic]	Action
	HCC-UK	***Which treatments are considered to be established clinical practice in the NHS for previously treated hepatocellular carcinoma?*** *Since the approval of atezolizumab/bevacizumab as first-line therapy, patients treated with this combination may receive sorafenib or lenvatinib as subsequent therapy*. Established treatments after sorafenib are regorafenib, SIRT (in patients with liver only disease), and BSC ***Are the outcomes listed appropriate?*** Yes ***Are there any subgroups of people in whom cabozantinib is expected to be more clinically effective and cost effective or other groups that should be examined separately?*** No ***Where do you consider cabozantinib will fit into the existing NICE pathway, Liver cancers? Appendix B*** ***Draft scope for the appraisal of cabozantinib for previously treated advanced hepatocellular carcinoma (review of TA582) Issue Date: March 2021 Page 4 of 5 © National Institute for Health and Care Excellence 2021. All rights reserved.*** Cabozanitinib will fit into the existing pathway after sorafenib (and potentially after lenvatinib). It is possible that lenvatinib could also be used after atezolizumab/bevacizumab as an alternative 2nd-line therapy to sorafenib/lenvatinib ***To help NICE prioritise topics for additional adoption support, do you consider that there will be any barriers to adoption of this technology into practice? If yes, please describe briefly.*** No barriers	scope as a comparator.

Section	Consultee/ Commentator	Comments [sic]	Action
		NICE intends to appraise this technology through its Single Technology Appraisal (STA) Process. ***We welcome comments on the appropriateness of appraising this topic through this process.*** Appropriate • ***Would it be appropriate to use the cost comparison methodology for this topic?*** Unable to comment • ***Is the new technology likely to be similar in its clinical efficacy and resource use to any of the comparators?*** Yes. • ***Is the primary outcome that was measured in the trial or used to drive the model for the comparator(s) still clinically relevant?*** Yes • ***Is there any substantial new evidence for the comparator technology/ies that has not been considered? Are there any important ongoing trials reporting in the next year?*** There are other trials of first-line systemic therapy that may lead to alternative first-line therapy choices (eg LEAP-002, Cosmic-312, CheckMate 9DW	
	British Society of Gastroenterology (BSG)	***Have all relevant comparators for cabozantinib been included in the scope?*** Please see comment above about comparing to BSC for patients who have previously received lenvatinib. ***Which treatments are considered to be established clinical practice in the NHS for previously treated hepatocellular carcinoma?*** *Since the*	Thank you for your comment. Best supportive care has been added to the scope as a comparator.

Section	Consultee/ Commentator	Comments [sic]	Action
		approval of atezolizumab/bevacizumab as first-line therapy, patients treated with this combination may receive sorafenib or lenvatinib as subsequent therapy. Established treatments after sorafenib are regorafenib, SIRT (in patients with liver only disease), and BSC ***Are the outcomes listed appropriate?*** Yes ***Are there any subgroups of people in whom cabozantinib is expected to be more clinically effective and cost effective or other groups that should be examined separately?*** No ***Where do you consider cabozantinib will fit into the existing NICE pathway, Liver cancers? Appendix B*** ***Draft scope for the appraisal of cabozantinib for previously treated advanced hepatocellular carcinoma (review of TA582) Issue Date: March 2021 Page 4 of 5 © National Institute for Health and Care Excellence 2021. All rights reserved.*** Cabozanitinib will fit into the existing pathway after sorafenib (and potentially after lenvatinib). It is possible that lenvatinib could also be used after atezolizumab/bevacizumab as an alternative 2nd-line therapy to sorafenib/lenvatinib ***To help NICE prioritise topics for additional adoption support, do you consider that there will be any barriers to adoption of this technology into practice? If yes, please describe briefly.*** No barriers ***NICE intends to appraise this technology through its Single Technology Appraisal (STA) Process.*** ***We welcome comments on the appropriateness of appraising this topic through this process.*** Appropriate • ***Would it be appropriate to use the cost comparison methodology for this topic?*** Unable to comment • ***Is the new technology likely to be similar in its clinical efficacy***	

Section	Consultee/ Commentator	Comments [sic]	Action
		and resource use to any of the comparators? Yes. • ***Is the primary outcome that was measured in the trial or used to drive the model for the comparator(s) still clinically relevant?*** Yes • ***Is there any substantial new evidence for the comparator technology/ies that has not been considered? Are there any important ongoing trials reporting in the next year?*** There are other trials of first-line systemic therapy that may lead to alternative first-line therapy choices (eg LEAP-002, Cosmic-312, CheckMate 9DW	
	NCRI Hepatobiliary Working Group	1. The main comparator for cabozantinib is regorafenib which is in use in the UK. 2. Outcomes have been addressed above 3. Regorafenib has not been demonstrated to be safe or effective in those that did not tolerate first-line sorafenib. In these patients, the evidence favours cabozantinib. 4. Cabozantinib should be considered as a second line therapy for those treated with first-line sorafenib or a third-line therapy in those treated with Atezolizumab and bevacizumab first-line, followed by sorafenib second-line 5. No equality issues that I can think of. 6. I do not consider that there will be barriers to adoption of cabozantinib for HCC providing patients are managed in specialised clinics. 7. Cost comparison methodology seems appropriate 8. Clinical efficacy and resource use will be similar to regorafenib 9. Overall survival was the primary endpoint of the trial remains the most clinically meaningful endpoint	Thank you for your comment. No action required.

Section	Consultee/ Commentator	Comments [sic]	Action
		10. There are likely to be advances in first-line treatment options with combinations of immunotherapy agents and tyrosine kinase inhibitors. But I am not aware of second line agents likely to be approved.	
	Bayer plc	Are there any subgroups of people in whom cabozantinib is expected to be more clinically effective and cost effective or other groups that should be examined separately? *The key evidence comes from the CELESTIAL trial in which cabozantinib has been studied in patients with Child–Pugh class A liver function and an ECOG status of 0 or 1 (a single patient had ECOG 2 in the trial). Therefore, it would be appropriate to consider how these subgroups fit in the appraisal and whether there is sufficient evidence to inform the clinical and cost effectiveness of cabozantinib beyond these subgroups.*	Thank you for your comment. NICE will consider the evidence provided by the company.
	Ipsen Limited	Have all relevant comparators for cabozantinib been included in the scope? *Yes.* Which treatments are considered to be established clinical practice in the NHS for previously treated hepatocellular carcinoma? *Regorafenib is currently the only NICE recommended option (TA555) for treating advanced unresectable hepatocellular carcinoma (HCC) in adults who have had sorafenib. Sorafenib (TA474) is recommended by NICE as an option for treating advanced hepatocellular carcinoma (it does not distinguish the line of therapy). The current treatment algorithm for previously treated HCC incorporates the above NICE recommendations but also as described in the Cancer Fund Drugs list the ability to use sorafenib or lenvatinib after first line use of atezolizumab plus bevacizumab (TA666).*	Thank you for your comment. The scope has been updated to include atezolizumab plus bevacizumab as a treatment option.

Section	Consultee/ Commentator	Comments [sic]	Action
		NICE recommend lenvatinib (TA551) only for untreated, advanced, unresectable hepatocellular carcinoma, not previously treated HCC. Patients with advanced HCC have poor prognosis therefore there is a need to have flexibility and a range of options within the lines of treatment to optimise outcomes. *The NICE recommendation for regorafenib post-sorafenib means it could be prescribed second or third line in the treatment algorithm despite the regorafenib evidence being for only for sorafenib tolerant patients. There are currently no treatment options post-lenvatinib. This need for choice and range of second/third line treatment options was recognised by clinical experts in Canada and led to cabozantinib receiving a positive recommendation following pan-Canadian Oncology Drug Review (pCODR) assessment for use in both post sorafenib and post lenvatinib patients.* Are the outcomes listed appropriate? *Yes. Ipsen consider the listed outcomes appropriate. It should be noted that the clinical evidence for regorafenib does not allow a comparison in terms of time to treatment discontinuation as this data is not available in the public domain.* Are there any subgroups of people in whom cabozantinib is expected to be more clinically effective and cost effective or other groups that should be examined separately? *No.* Where do you consider cabozantinib will fit into the existing NICE pathway, Liver cancers?	

Section	Consultee/ Commentator	Comments [sic]	Action
		Cabozantinib is indicated as monotherapy for the treatment of hepatocellular carcinoma (HCC) in adults who have previously been treated with sorafenib. It is therefore likely to be positioned as a treatment option after sorafenib treatment failure or intolerance. *As described above in this section of the scoping response, regarding the treatments considered to be established clinical practice in the NHS for previously treated hepatocellular carcinoma, there is a need flexibility to provide patients with the greatest treatment choice considering their poor prognosis.* Do you consider cabozantinib to be innovative in its potential to make a significant and substantial impact on health-related benefits and how it might improve the way that current need is met (is this a 'step-change' in the management of the condition)? *Current need is not met with regorafenib as the RESORCE trial did not include sorafenib intolerant patients nor third line patients which CELESTIAL trial did. Cabozantinib targets VEGFR, MET and AXL receptors whereas regorafenib does not MET and AXL receptors which have been associated with sorafenib intolerance.* Do you consider that the use of cabozantinib can result in any potential significant and substantial health-related benefits that are unlikely to be included in the QALY calculation? *No.* To help NICE prioritise topics for additional adoption support, do you	

Section	Consultee/ Commentator	Comments [sic]	Action
		consider that there will be any barriers to adoption of this technology into practice? If yes, please describe briefly. *Cabozantinib is an oral therapy taken as one tablet once daily and is likely to have even less barriers to adoption compared to the established comparator where the recommended dose of regorafenib is more complicated as it is 160 mg (4 tablets of 40 mg) taken once daily for 3 weeks followed by 1 week off therapy.* NICE intends to appraise this technology through its Single Technology Appraisal (STA) Process. We welcome comments on the appropriateness of appraising this topic through this process. (Information on the Institute's Technology Appraisal processes is available at http://www.nice.org.uk/article/pmg19/chapter/1-Introduction). NICE has published an addendum to its guide to the methods of technology appraisal (available at https://www.nice.org.uk/Media/Default/About/what-wedo/NICE-guidance/NICE-technology-appraisals/methods-guide-addendumcost-comparison.pdf), which states the methods to be used where a cost comparison case is made. Would it be appropriate to use the cost comparison methodology for this topic? *No.* Is the new technology likely to be similar in its clinical efficacy and resource use to any of the comparators? *Yes.*	

Section	Consultee/ Commentator	Comments [sic]	Action
		There are no direct head-to-head data for cabozantinib vs. regorafenib. [redacted]*. Clinical experts consulted by Ipsen believe that the clinical efficacy, safety and resource use of cabozantinib vs. regorafenib is likely to be similar* [redacted]. *Cabozantinib has a simple one tablet, once daily regimen whilst the recommended dose of regorafenib is 160 mg (4 tablets of 40 mg) taken once daily for 3 weeks followed by 1 week off therapy. The simplicity of the cabozantinib regimen thus could facilitate patient adherence*. Is the primary outcome that was measured in the trial or used to drive the model for the comparator(s) still clinically relevant? *Yes. Overall survival was the primary endpoint in the CELESTIAL pivotal trial underpinning the marketing authorisation and is still clinically relevant.* Is there any substantial new evidence for the comparator technology/ies that has not been considered? Are there any important ongoing trials reporting in the next year? *No.*	

Section	Consultee/ Commentator	Comments [sic]	Action
Additional comments on the draft scope	British Association for the Study of the Liver (BASL) / HCC-UK	None	No action required.
	British Society of Gastroenterology (BSG)	None	No action required.
	Bayer plc	No comments	No action required.

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

Children's Liver Disease Foundation