Single Technology Appraisal

Cabozantinib for treating advanced neuroendocrine tumours that have progressed after systemic treatment [ID6474]

Committee Papers

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

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Cabozantinib for treating advanced neuroendocrine tumours that have progressed after systemic treatment [ID6474]

Contents:

The following documents are made available to stakeholders:

1. **Comments on the Draft Guidance from Ipsen**

2. **Consultee and commentator comments on the Draft Guidance** from:
   a. Neuroendocrine Cancer UK, written by Patient Expert Nikie Jervis

3. **External Assessment Group critique of company comments on the Draft Guidance**
   a. EAG critique of company response
   b. EAG addendum – crossover method

Any information supplied to NICE which has been marked as confidential, has been redacted. All personal information has also been redacted.

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Cabozantinib for treating advanced neuroendocrine tumours that have progressed after systemic treatment [ID6474]

Draft guidance comments form

Consultation on the draft guidance document – deadline for comments 5pm on Wednesday 22 October 2025. Please submit via NICE Docs.

	Please read the checklist for submitting comments at the end of this form. We cannot accept forms that are not filled in correctly. The Appraisal Committee is interested in receiving comments on the following: • has all of the relevant evidence been taken into account? • are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence? • are the provisional recommendations sound and a suitable basis for guidance to the NHS? NICE is committed to promoting equality of opportunity, eliminating unlawful discrimination and fostering good relations between people with particular protected characteristics and others. Please let us know if you think that the preliminary recommendations may need changing in order to meet these aims. In particular, please tell us if the preliminary recommendations: • could have a different impact on people protected by the equality legislation than on the wider population, for example by making it more difficult in practice for a specific group to access the technology; • could have any adverse impact on people with a particular disability or disabilities. Please provide any relevant information or data you have regarding such impacts and how they could be avoided or reduced.
Organisation name – Stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank):	Ipsen Ltd.

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Disclosure Please disclose any funding received from the company bringing the treatment to NICE for evaluation or from any of the comparator treatment companies in the last 12 months. [Relevant companies are listed in the appraisal stakeholder list.] Please state: • the name of the company • the amount • the purpose of funding including whether it related to a product mentioned in the stakeholder list • whether it is ongoing or has ceased.	N/A
Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	N/A
Name of commentator person completing form:	xxxxxxxxxxxxxxxx

Comment number	Comments Insert each comment in a new row. Do not paste other tables into this table, because your comments could get lost – type directly into this table.
Executive summary	Ipsen appreciate the opportunity to participate in this guidance. Detailed responses have been presented to address the committee's key areas of uncertainty surrounding the company submission, as well as a revised economic base case and supporting scenario analyses. Neuroendocrine tumours (NETs) have a substantial impact on patients' survival and quality of life, and the committee recognised the unmet need for more effective, widely available treatments for patients with NETs who have progressed on prior systemic treatments. The patient expert testimony in the Draft Guidance highlights the debilitating and life-changing nature of the condition, including the high and heterogeneous symptom burden, the burden of treatment and disease management, the resulting impact on daily life, as well as the wider impact on family and carers.[1] The unmet need for new treatments is multifaceted, with

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	patients facing a poor prognosis and limited treatment options. The clinical experts explained that for extrapancreatic (epNETs), particularly lung NETs, there are limited treatment options after progression on prior systemic treatments. Clinical and patient experts explained that having different treatment options is particularly important, as currently available treatments are not suitable for everyone and often have unpleasant side effects. The committee recognised that cabozantinib is an effective treatment option to extend progression-free survival (PFS), with patients in the CABINET trial treated with cabozantinib experiencing a 77% and 62% lower risk of disease progression or death than those treated with placebo in the pNET and epNET cohorts, respectively. There is a strong and established surrogacy relationship between PFS and overall survival (OS), which has been extensively validated in the literature and by clinical experts consulted as part of this response. A robust pre-submission structured expert elicitation (SEE) exercise and feedback obtained by clinicians as part of this response unanimously supports an OS benefit for cabozantinib versus best supportive care (BSC) in the long-term, and thus cabozantinib is expected to also provide an effective option to improve survival in NET patients.[2] Cabozantinib also offers a convenient mode of administration and a broad licence that does not restrict patient eligibility, and thus has the potential to addresses the significant unmet need in this disease area. NETs are rare, with a prevalence of 34.9 per 100,000 people in England.[3] The presentation of NETs is also highly heterogenous, with symptoms and prognosis dependent on many factors, including tumour location, stage, histology (such as somatostatin receptor expression, mitotic count and Ki-67 index) and functional status. The heterogenous nature of the condition necessitates highly individualised treatment pathways and influences rates of progression and survival.[4-7] The rare and heterogenous nature of NETs means that evidence generation for novel technologies is particularly challenging. The NICE manual notes that in such circumstances the committee may be able to make recommendations accepting a higher degree of uncertainty.[8] It is critical that the committee's conclusions surrounding the uncertainty in the evidence presented in this appraisal, including further evidence presented by the company within this response, should carefully consider the patient and clinical expert testimony, the significant unmet need and the rarity of the condition. Ipsen has provided detailed responses to address the committee's key areas of uncertainty surrounding the company's submission. The company urge the committee to consider the following key points: 1. Applying an OS hazard ratio (HR) of 1 between cabozantinib and best supportive care (BSC) lacks clinical validity and is inappropriate for decision-making 2. Inverse Probability of Censoring Weights (IPCW) is the most robust method to adjust for crossover in the CABINET trial 3. The committee's preferences for OS curve selection for cabozantinib in pancreatic NETs (pNETs) and epNETs lack justification and are misaligned

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	with clinical expert expectations. The company's selected curves offer good visual and statistical fit and are the most clinically robust 4. Subsequent treatments should be included to ensure balance of modelled costs and benefits derived from the CABINET trial 5. The company have revised the modelling of concomitant treatment based on further feedback from UK clinical experts 6. Patients with lung NETs face higher unmet need and a fragmented UK care pathway which ultimately leads to poorer prognosis. Therefore, if a positive recommendation in the overall epNET group is not possible, the committee should consider an optimised recommendation in the lung population to address unmet need 7. Cabozantinib offers meaningful additional benefits that are not captured by the quality-adjusted life year (QALY) calculation 8. The comparator of relevance for the appraisal is BSC, but the committee's description of the target population as "later-line" is overly simplistic 9. A severity modifier of 1.2 is appropriate for all analyses in the epNETs population **Revised company base case** In line with feedback from the committee, the company has presented a revised base case. The company have aligned with the following committee preferences: • BSC as the only relevant comparator • pNETs and epNETs modelled as the main subgroups • Modelled OS informed by the August 2024 data cut-off (DCO) • Weibull curves to extrapolate PFS for both cabozantinib and BSC The revised base case incorporates the following, which are justified based on the additional evidence presented as part of this response, and represent the only areas of outstanding misalignment between the committee and company preferences: • An OS HR for cabozantinib versus BSC of 1 is clinically invalid, due to the statistically significant and clinically meaningful PFS benefit shown by cabozantinib, the established surrogacy relationship between PFS and OS, and clinical expert estimates of survival derived from a robust elicitation exercise. OS HRs from the IPCW analysis to adjust for crossover in CABINET have been used to derive OS for BSC in the pNETs and epNETs subgroups • Loglogistic curves have been used to extrapolate OS for cabozantinib in pNET and epNETs subgroups • The proportion of patients receiving concomitant SSAs has been based on clinical expert feedback.[2] Somatostatin analogues (SSAs) can be

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	continued until death, but a constant discontinuation rate has been applied to reflect discontinuation due to adverse events or loss of effect • Subsequent treatments have been modelled to ensure a balance of costs and benefits Full details of the company base case are presented in Appendix 1. The results of the scenario analyses conducted by the company as part of this response are provided in Appendix 2. Additional details have been provided to support the committee's decision making, namely diagnostic plots and tables for the IPCW analysis for the updated DCO (Appendix 3), an IPCW sensitivity analysis adjusting for crossover and all subsequent systemic treatments (Appendix 4) and the requested full details of the utility analysis (Appendix 5). The revised base case results demonstrate that cabozantinib (at PAS price) is cost-effective in the epNETs population (with an incremental cost-effectiveness ration [ICER] versus BSC of £9,013). Across all scenarios explored in the epNETs subgroup, the ICER remained close to or below the lower end of NICE's cost-effectiveness threshold (£20,000) including the scenario exploring lung NETs only (with an ICER of £20,554). The base case ICER for cabozantinib versus BSC in the pNETs group is £144,912, but the company maintain that assuming a HR of 1 between cabozantinib and BSC in this group is pessimistic. Notably, in contrast to the base case analysis, the ICER for the scenario excluding subsequent treatment costs and where OS for BSC was derived by applying the ICPW-adjusted HRs from IPCW analysis adjusting for all subsequent anticancer therapy was £23,341, demonstrating potential for cabozantinib to represent a cost-effective last-line therapy in patients with pNETs. Therefore, company urges the committee to reconsider their recommendation on the basis of the additional evidence presented to ensure cabozantinib can be made available to patients with NETs with a severe unmet need (reflected in cabozantinib qualifying for the x 1.2 modifier in the epNETs subgroup) facing no effective treatment options at the end of their terminal illness.
1	**An OS benefit associated with the use of cabozantinib is expected in UK clinical practice. Modelling an OS hazard ratio of 1 versus BSC lacks clinical plausibility and is inappropriate for decision making** ***Landmark survival estimates were estimated by clinical experts on the basis of the CABINET trial as part of a clinical expert elicitation exercise, and clearly indicate an OS benefit for cabozantinib*** The company conducted a robust SEE exercise to inform the approach taken to model OS in the cost-effectiveness model. The methods and results of this exercise were presented comprehensively in the company submission. It is disappointing that there was limited discussion in the External Assessment Group (EAG) report, the first Appraisal Committee Meeting (ACM), and limited reporting in the Draft Guidance. It should be noted that the EAG and committee preferences for the modelling of OS directly contradict the feedback from the clinical experts.

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	NICE Decision Support Unit (DSU) Technical Support Document (TSD) 26 highlights that decision-makers must rely on alternative sources of evidence to fill knowledge gaps, typically using expert knowledge, in cases where robust evidence generation is challenging, such as rare diseases.[9] Given the rare and heterogeneous nature of NETs, challenges demonstrating a clear OS benefit in clinical trials is not unexpected, and interpretation of OS data from the CABINET trial is further complicated by the crossover design and its immaturity at the time of clinical trial termination. Expert judgement should therefore play a key role in decision-making within this appraisal. Five UK clinical experts in NETs were included in the SEE exercise during submission development, hereafter referred to as the pre-submission SEE exercise. Experts were provided with pre-read materials and subsequent discussions were held via individual teleconferences. Full details of this process can be found in Section 3.3.2 and Section 13.4.1 of the company submission as well as the associated reference pack. During the teleconference, clinicians were asked to provide a most plausible estimate of OS, as well as upper and lower limits (representing where clinicians judged it to be extremely unlikely that the true value of OS could be higher or lower than these limits, respectively), at 5, 10 and 15 years for BSC and cabozantinib. The approach to the elicitation exercise was guided by published elicitation protocols (albeit conducted under high time-pressure and thus necessitating modification, such as the omission of a facilitated group discussion), and is in line with several of the recommendations outlined in TSD26.[9] These included: • Five clinicians, all who were consultant oncologists and experts in the treatment of patients with NETs were consulted, spanning different NHS sites across the UK (one in Wales, one in Scotland, and three in England [one practicing in each of the North, North East and Midlands]; TSD26 recommends no fewer than three experts, with no restriction to exclude those with knowledge of the trial data[9] • All clinicians, given their expertise in the treatment of NETs, were already familiar with the CABINET trial and published data. Nevertheless, relevant clinical evidence was provided to inform clinician's estimates as per the recommendations for an "evidence dossier", including the baseline characteristics of the CABINET trial and available landmark OS data derived from CABINET Kaplan–Meier (KM) data for cabozantinib and BSC (adjusted for crossover) • Parametric survival models (fitted to CABINET data) were not shared with the clinical experts to avoid anchoring effects • Upper and lower plausible limits (akin to 95% CIs) were elicited to characterise uncertainty around the value of the survivor function for a given time point, rather than just a single value It should be noted that TSD26 was not published at the time this elicitation exercise was conducted (February 2025), so differences between this exercise and the procedures outlined in TSD26 are not unexpected, and reflect differences

in recommendations between published elicitation protocols.[9] For example, guidance based on the Medical Research Council (MRC) protocol notes that elicitation of long-term survival parameters may require estimates at multiple timepoints to explore how hazards change over time, whereas TSD26 recommends elicitation at a single timepoint with qualitative discussion around changes to the hazard over the extrapolation period.[9, 10] The methods used in this pre-submission SEE exercise are consistent with prior appraisals using structured elicitation methods to inform survival modelling, as summarised in Section 5.2 of TSD26.[9]

These elicited landmark survival estimates were linearly pooled, and subsequently used to inform selection of parametric curves that were clinically plausible (i.e. those that did not predict survival above or below the upper and lower values elicited from the experts, respectively). There was broad consistency between the individual assessments provided by the experts, albeit with greater variation for the survival predictions for epNETs (likely driven by the more heterogenous nature of this cohort of patients). The elicited estimates are presented in Table 1 and graphically in Figure 1 and Figure 2.

Table 1: Clinician landmark estimates for OS for cabozantinib and BSC (pNETs and epNETs)

Category	Curve	OS %		
		5	10	15
pNETs				
Cabozantinib	Lower plausible limit	24.1%	13.4%	6.8%
	Most likely	36.0%	19.2%	10.8%
	Upper plausible limit	44.0%	23.6%	15.0%
BSC	Lower plausible limit	11.0%	2.8%	0.5%
	Most likely	20.0%	6.0%	2.0%
	Upper plausible limit	27.8%	9.8%	2.8%
epNETs				
Cabozantinib	Lower plausible limit	12.3%	6.0%	1.0%
	Most likely	21.1%	10.5%	3.5%
	Upper plausible limit	24.0%	13.8%	4.7%
BSC	Lower plausible limit	5.8%	2.0%	0.5%
	Most likely	10.8%	3.8%	1.5%
	Upper plausible limit	15.5%	6.8%	2.3%

Abbreviations: BSC: best supportive care; epNET: extrapancreatic neuroendocrine tumour; OS: overall survival; pNET: pancreatic neuroendocrine tumour.

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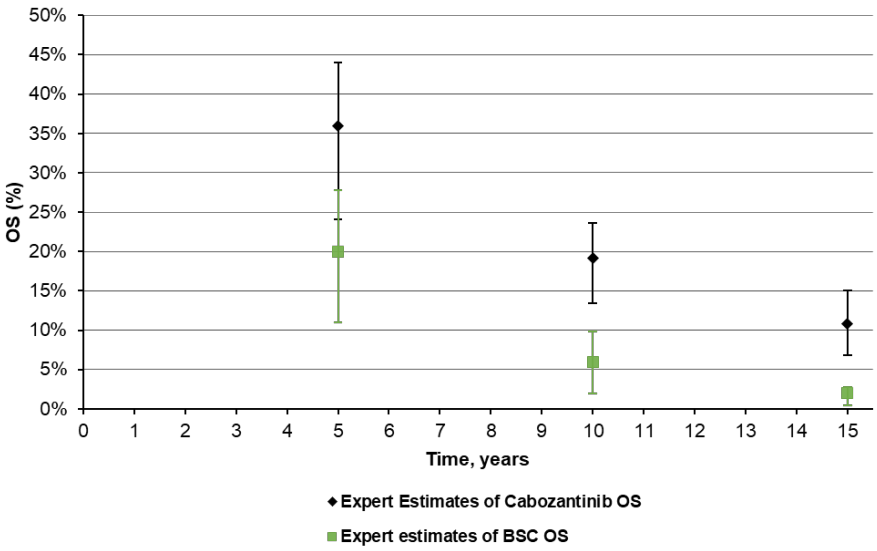
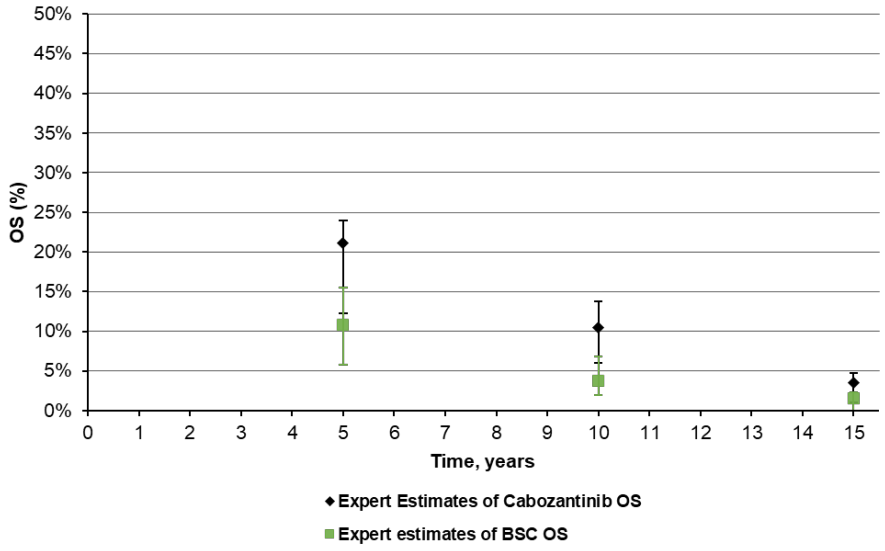
Figure 1: Clinician landmark estimates for OS for cabozantinib and BSC (pNETs)



Note, the y axis has been adjusted to improve readability.
Abbreviations: BSC: best supportive care; OS: overall survival; pNETs: pancreatic neuroendocrine tumours.

Figure 2: Clinician landmark estimates for OS for cabozantinib and BSC (epNETs)



Note, the y axis has been adjusted to improve readability.
Abbreviations: BSC: best supportive care; OS: overall survival; epNETs: extrapancreatic neuroendocrine tumours.

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	Given the rare and heterogeneous nature of NETs and the resulting challenges generating robust OS data from clinical trials, SEE provides the most robust evidence on which to base decisions around the modelling of long-term survival for cabozantinib and BSC in the economic model. It is disappointing that the EAG and committee's preferred assumption contradicts the unanimous expectations of clinical experts in NETs. ***Challenges demonstrating an OS benefit are common in clinical trials in NETs*** Given the complexity and individualised nature of the disease pathway, clinical trials in NETs are typically designed to permit crossover and there can be variation in subsequent treatments following progression, both of which confound the detection of a treatment-related OS benefit. The RADIANT-3, A6181111 and NETTER-1 trials permitted crossover from the control arm to intervention after progression.[11, 12] Furthermore, indolent cancers, including NETs, are typically characterised by long OS times of 5–10 years, making it generally infeasible to power trials to provide definitive OS effects of an intervention within a reasonable time-frame. This is particularly challenging in rare indications due to restricted sample sizes which limit statistical power.[13] Finally, challenges are exacerbated where it is necessary to consider subgroups separately, as with the stratification by pNETs and epNETs in CABINET. Clinical expert testimony at the first ACM explained that conflicting PFS and OS data from CABINET might be explained by small sample sizes for the relevant populations, high percentage of people crossing over to cabozantinib, treatment sequences used and short trial follow-up. Additionally, four clinical experts in NETs consulted as part of this response unanimously acknowledged the inherent difficulty in demonstrating OS in clinical trials in NETs.[2] Demonstrating an OS benefit in CABINET was noted as particularly difficult given crossover, heterogeneity in prior treatments and high levels of subsequent therapies.[2] Consequently, pivotal trials in these disease areas frequently rely on intermediate clinical endpoints such as PFS.[14] ***PFS is a widely validated and accepted surrogate for OS in NETs*** Delaying disease progression is a key treatment goal in unresectable or metastatic NETs. PFS indicates better control of tumour-associated clinical symptoms and tumour growth, and delaying disease progression is associated with overall life extension. PFS is accepted as a surrogate endpoint for OS in NETs, and this surrogacy relationship has been validated in multiple studies. In observational cohorts of patients with metastatic NETs treated with single-agent SSAs or everolimus, PFS showed a significant correlation with OS, with a Kendall's tau of 0.31 and 0.44 respectively ($p<0.001$).[15] Landmark analyses confirmed that progression status at multiple timepoints ranging from 6 to 24 months was associated with OS.[15] Additionally, a literature review of 22 trials in NETs demonstrated a significant association between median time to disease progression and median OS (coefficient: 0.595; $p=0.022$), also supporting PFS as a viable alternative endpoint.[16] Furthermore, in neuroendocrine neoplasms (NENs)

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	a systematic review of 20 Phase II and III trials found a statistically significant correlation between PFS and OS (r_s: 0.587; 95% confidence interval [CI]: 0.249, 0.925).[17] Accordingly, PFS was selected as the primary endpoint in the CABINET trial and has been validated and accepted as an endpoint for other treatments in patients with progressive NETs.[18-20] PFS is the National Cancer Institute (NCI)-recommended endpoint for Phase III studies for well-differentiated NETs.[20] The NET Task Force of the NCI GI Steering Committee also recommend PFS as a feasible and relevant primary endpoint for Phase III studies in NETs where there is likely to be a delay in progression.[19, 20] PFS is primary endpoint of multiple key clinical trials in advanced NETs, irrespective of NET location.[15, 21-23] Clinical experts consulted at the first ACM for this appraisal stated that even if trials are unable to demonstrate an OS benefit, this does not mean the treatment lacks clinical benefit. As such, they determined PFS as the most clinically relevant endpoint. Similarly, four clinical experts consulted as part of this response endorsed PFS as a clinically relevant endpoint and a biologically plausible surrogate for OS.[2] The clinicians commented that PFS represents the most sensitive endpoint available.[2] ***Cabozantinib demonstrates a statistically significant and clinically relevant improvement in PFS. Based on this PFS improvement, clinicians expect an OS benefit associated with cabozantinib*** In the CABINET trial, cabozantinib demonstrated a statistically significant and clinically meaningful improvements in PFS; patients treated with cabozantinib had a 77% and 62% lower risk of disease progression or death than those treated with placebo in the pNET and epNET cohorts, respectively.[18] Given the accepted surrogacy between PFS and OS, an improvement in the former is expected to translate into a survival benefit. As described above, OS estimates elicited from five clinical experts in the pre-submission SEE exercise unanimously indicate an OS benefit in NET patients treated with cabozantinib in UK clinical practice, with one expert explicitly commenting that a long-term benefit of cabozantinib was plausible.[24] Accordingly, all four clinical experts consulted as part of this response considered that without the above complexities in NETs and in the CABINET trial design, they would anticipate there to be an OS benefit for cabozantinib. Two clinicians commented that if they were able to fully observe a treatment effect, then they would expect to see a treatment benefit comparable with the treatment effect estimated in the IPCW analyses (i.e. a HR between 0.70–0.75).[2] Assuming an OS HR of 1 between cabozantinib and BSC therefore lacks clinical plausibility and does not reflect the expected clinical benefit of cabozantinib. ***There is precedence from prior appraisals in NETs to recognise OS benefit despite a failure to demonstrate statistical significance in clinical trials*** Prior appraisals in NETs have recognised OS benefits for systematic therapies despite a failure to demonstrate statistical significance in clinical trials, and these

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	OS benefits have informed cost-effectiveness analyses underpinning NICE recommendations for these therapies. The company acknowledge that there was no statistically significant benefit in OS between cabozantinib and BSC in either pNETs or epNETs for either data cut (except in lung NETs alone), as noted by the committee. However, as outlined earlier in this section, additional feedback collected by the company from clinical experts as part of this response suggests this is likely to be due to heterogeneity in prior treatments and high levels of subsequent treatments, rather than improvements in PFS failing to translate into improvements in OS. Similarly, in TA449, OS results were confounded by high levels of crossover in the comparator arms of both trials (73% in RADIANT-3 and 69% in A6181111), and neither sunitinib nor everolimus demonstrated statistically significant OS improvements versus placebo in pNETs.[12] Confidence intervals [CIs] for crossover-adjusted HRs spanned one in both cases: an adjusted HR of 0.60 (95% CI: 0.09–3.95) was reported for everolimus versus placebo from RADIANT-3, and 0.34 (95% CI 0.14–1.28) for sunitinib versus placebo from A6181111.[11, 12] However, despite these non-significant OS results and high levels of crossover, the committee deemed that both everolimus and sunitinib are clinically effective for treating pNETs. Furthermore, the committee concluded that they would consider the clinical benefit of everolimus and sunitinib to be similar, with this decision based on the PFS data from the trials and expert feedback.[12] Similarly, no statistically significant OS improvement was observed in the RADIANT-4 trial for everolimus vs BSC in epNETs (HR: 0.73; 95% CI 0.48–1.11), yet the committee concluded that everolimus is a clinically effective treatment for these patients.[25] For both everolimus and sunitinib, the assessment group modelled an OS benefit via independent extrapolation of the intervention and placebo arms; in the assessment group base case, incremental life years for everolimus and sunitinib versus BSC ranged from 1.23–2.93.[12] For comparison, the revised company base case provided incremental life years for cabozantinib versus BSC of 0.79 for epNETs and 0.00 for pNETs. The committee concluded that the assessment group's economic model was the most appropriate for decision-making. Importantly, it should also be noted that this approach was accepted despite high levels of uncertainty in the crossover adjusted HRs, where the proportion of patients crossing over was significantly higher than those observed in CABINET (73% in RADIANT-3 and 69% in A6181111 in comparison to [redacted]% and [redacted]% in the updated data cut in CABINET for epNETs and pNETs, respectively). Consequently, the adjusted HRs had extremely wide 95% CIs (0.09 to 3.95 for everolimus in RADIANT-3 and 0.14 to 1.28 for sunitinib in A6181111) comparison to those from CABINET at [redacted] to [redacted] for pNETs and [redacted] to [redacted] for epNETs. Although the company acknowledge that there is uncertainty in the OS HRs derived from CABINET, this level of uncertainty is not any greater than that observed in the prior appraisals where it was deemed appropriate to model an OS benefit. The committee's preference to assume equal OS for cabozantinib and BSC in the model due to high levels of uncertainty in the OS extrapolation is therefore not consistent with conclusions from appraisals of other systemic treatments in NETs, which were based on similarly uncertain evidence.

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	Furthermore, longer-term survival data of sunitinib from OPALINE, a real-world study of targeted treatment (sunitinib and everolimus) use in pNETs, reported a median OS of 176.5 months in those who had received at least one of these treatments in comparison to 128.4 months in patients who did not receive a targeted treatment.[26] This supports clinical opinion from the first ACM, as well as from the four clinicians consulted by the company as part of this response, that a real-world long-term OS benefit for targeted treatments in NETs is expected, even if a statistically significant improvement in OS was not observed during a trial period or in initial data cuts. **Conclusion** Given the accepted surrogacy between PFS and OS in NETs, which has been extensively validated in the literature and by clinical experts consulted as part of this response, the strong PFS results from CABINET indicate that a long-term OS benefit with cabozantinib will be realised in UK clinical practice. A lack of statistical significance in OS benefit was not unexpected, given this is common in rare diseases and indolent cancers, and is consistent with clinical trials for targeted treatments (everolimus and sunitinib) in NETs. Given clinical trials for systemic therapies face similar limitations, there is a clear precedence to model an OS benefit for cabozantinib, in line with accepted approaches in prior appraisals. This is supported by feedback obtained from a robust pre-submission SEE exercise and additional feedback obtained by clinicians as part of this response, which unanimously supports an OS benefit for cabozantinib versus BSC in the long-term. Modelling an OS hazard ratio of 1 lacks clinical plausibility and is not appropriate for decision making.
2	**The IPCW approach is the most appropriate method to adjust for crossover in the CABINET trial and to inform OS for the base case economic analysis** ***The key IPCW assumptions are satisfied, with no breakdown in positivity and a comprehensive identification and inclusion of all relevant confounders*** The key assumption made by the IPCW method is the "no unmeasured confounders" assumption – that is, data must be available on all baseline and time-dependent prognostic factors for mortality that independently predict informative censoring (switching).[27] The IPCW method also relies on the "positivity assumption" – that there are no combinations of covariate levels which *ensure* treatment switching will occur (i.e., where the probability equals 1).[27] An inspection of the distribution of confounding variables included in the model by treatment arm and switch status demonstrated that no confounder perfectly predicted switching for any population, indicating that the positivity assumption was met (Appendix 3). Furthermore, the choice of covariates was based on extensive clinician input regarding relevant prognostic factors predicting switching and survival (see Appendix L.4 of the company submission), suggesting that no important confounders were missing from the model. While the EAG alleged that there was insufficient evidence of no unmeasured confounders, no evidence or justification has been provided that suggests the analysis was impacted by any unmeasured confounders. Namely, the identification of potential confounders based on clinical

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input was robust and it is appropriate to assume no unmeasured confounders based on clinical considerations alone as this assumption is not empirically testable. Therefore, the key assumptions of the IPCW approach of positivity and no unmeasured confounders were reasonable. Furthermore, the coefficients in the weight estimation models (Table 13, Appendix 3) and the distribution of estimated weights were sensible, suggesting that the re-weighting successfully accounted for the artificial censoring of switchers.

IPCW weights were highly stable across cohorts and data cuts, and the EAG's assertion that IPCW weights were unstable because of small patient numbers and a high percentage of people crossing over is factually inaccurate

Crucially, the EAG suggested that the IPCW weights may be unstable due to small patient numbers and a high percentage of patients switching treatments in the placebo arms. However, the assertion that weights were unstable is factually inaccurate. The stabilised weight estimation procedure produced IPCW weights with no extreme values across data cuts (and so can be considered stable). This is illustrated clearly in the histograms of IPCW weights in Figure 9 and Figure 10 of Appendix 3. Further evidence of stability comes from the similarity in the results with and without truncation of weights for the most extreme percentile, suggesting that extreme weights were not influencing the analysis. The IPCW-adjusted stratified HRs for cabozantinib versus placebo based on the updated DCO were [redacted] (95% CI: [redacted]) and [redacted] (95% CI: [redacted]) with and without truncation, respectively, in the epNETs cohort, and were [redacted] (95% CI: [redacted]) and [redacted] (95% CI: [redacted]) with and without truncation, respectively, in the pNETs cohort.

Although sample sizes were relatively small given the rarity of NETs, simulation studies by Latimer et al. (2014, 2018) demonstrate that IPCW and other adjustment methods (rank preserving structural failure time model [RPSFTM], iterative parameter estimation [IPE] and two-stage adjustment) provide reliable estimates of the true treatment effect when sample sizes are moderate (approximately 300–500 patients) and the proportion of patients switching is moderate (<60% of control group patients who become eligible to switch).[28,29] Bias only became extreme when almost all control-group patients switched (~90%).[28,29] Latimer *et al.* (2018) also concluded that, although there was an increase in bias associated with all adjustment methods when the sample size was smaller, this was only marginal.[29] Nevertheless, as stated in Section 6.2.34 of the NICE reference case, the committee should be mindful of difficulties faced in evidence generation for rare diseases like NETs on their willingness to accept a higher degree of uncertainty, even if anticipated to only have a marginal effect in the CABINET IPCW analyses.

In CABINET, the proportion of switchers was moderate in both pNET and epNET cohorts ([redacted]% and [redacted]% of all patients in the placebo arms of the pNET and epNET cohorts, respectively, Table 2). PFS data are not available from the latest DCO, so switchers as a proportion of at-risk patients (those who survived to progression) is not known, but it is expected that both the number of switchers and the number of at-risk patients increased with longer follow-up. At the original DCO, [redacted]% and [redacted]%

of at-risk patients had switched. TSD16 notes that the IPCW method is unlikely to produce reliable results when almost all patients switch, and/or very few events are observed in patients who do not switch, which is not the case in this analysis.[30]

There is no evidence that the IPCW analysis of CABINET is associated with greater uncertainty or risk of bias than other approaches, such as RPSFTM, nor is there evidence for the direction of any potential bias. Smaller sample sizes are an inherent limitation of clinical trials for rare diseases such as NETs, and the NICE manual notes that in such circumstances the committee may be able to make recommendations accepting a higher degree of uncertainty.[8]

Table 2: Proportion of switchers at the updated DCO

Population	Arm	N	Crossover, n (%)
epNET	Cabozantinib	134	N/A
	Placebo	69	[redacted]
pNET	Cabozantinib	64	N/A
	Placebo	31	[redacted]

Abbreviations: DCO: data cut-off; epNET: extra pancreatic neuroendocrine tumour; pNET: pancreatic neuroendocrine tumour.

Research suggests that when key assumptions are met and weights are stable, IPCW performs well regardless of sample sizes or proportions of switchers

Latimer *et al.* (2020) confirm the finding of a substantial body of research into IPCW that the method generally performs well if weights are not extreme (provided the key assumptions hold), and demonstrate that this is even true in the presence of serious time-dependent confounding.[28, 29, 31-33] In particular, the study suggests that IPCW is associated with a low risk of bias when there is no breakdown in positivity and the maximum weight as a proportion of the group being weighted was less than 6%. With no concerns regarding positivity and maximum weights of 1.22 for the pNET cohort and 1.64 for epNET cohort, the proportions relative to the group being weighted for CABINET at the updated DCO were [redacted]% and [redacted]%, respectively, indicating that there were would be no concerns of substantial bias in the IPCW estimates despite the relatively small sample size.[28] Conclusions surrounding the robustness of the IPCW analysis should be based on relevant performance metrics, which demonstrate the analysis performs adequately.

IPCW results were clinically plausible in contrast to RPSFTM results which generally lacked clinical plausibility

OS HRs derived from the ITT, IPCW and RPSFTM analyses for updated DCO are presented in Table 3 (with further details in Appendix 3), alongside the results from the corresponding analyses for the primary DCO.

The results from the IPCW are consistent with feedback from four clinical experts consulted as part of this response, who stated that without the complexities in

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NETs and in the CABINET trial design, they would anticipate there to be an OS benefit for cabozantinib. Two of the clinicians commented that if they were able to fully observe a treatment effect, then they would expect to see a treatment benefit comparable with the treatment effect estimated in the IPCW analyses (i.e. a HR between 0.70–0.75).[2] An implausible result was observed for the IPCW-adjusted stratified HR for OS at the updated DCO for the pNETs cohort, but this is likely to be due to the influence of subsequent treatment beyond crossover to cabozantinib; more plausible estimates were observed with adjustment for further subsequent systemic treatments beyond crossover cabozantinib as shown in Section 4 and Appendix 4 (HR: [redacted] [95% CI: [redacted]]). Notably, these results are closely aligned with the results observed for the IPCW analysis conducted for the primary analysis of the CABINET trial as per Table 3 (HR 0.74 [95% CI: 0.36–1.52]).

In contrast, RPSFTM results suffered from a lack of clinical plausibility for the analyses based on the updated DCO, where HRs were similar to the intention-to-treat (ITT) analysis. In the epNET group, the point estimate of the HR moved even further in favour of placebo after adjustment, implying that patients in the placebo arm would have had improved survival had they not crossed over – this is clinically implausible and is a direct result of the assumptions underlying the RPSFTM approach as outlined below. There were also inconsistencies in the direction of the HRs for the RPSFTM analyses between the primary and updated DCOs.

Table 3: OS hazard ratios derived from ITT and analyses adjusting for crossover (cabozantinib vs BSC)

Population	ITT (Unstratified) (95% CI)	ITT (Stratified)[a] (95% CI)	IPCW (Stratified)[a] (95% CI)	RPSFTM (Stratified)[a,b] (95% CI)
Primary DCO				
pNET	0.88 (0.42, 1.83)	0.95 (0.45, 2.00)	0.74 (0.36, 1.52)	[redacted]
epNET	0.86 (0.57, 1.29)	0.86 (0.56, 1.31)	0.65 (0.39, 1.07)	[redacted]
Updated DCO				
pNET	[redacted]	[redacted]	[redacted]	[redacted]
epNET	[redacted]	[redacted]	[redacted]	[redacted]

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[a] Stratified HRs were based on the relevant stratification factors for each population (pNET: concomitant SSA use and prior sunitinib use; epNET: concomitant SSA use and primary site [midgut/unknown vs non-midgut GI/lung/other]). [b] 95% CI for RPSFTM are based on adjusted standard errors obtained by dividing the point estimate by the square root of the Chi-square statistic of the ITT analysis, this was done in order to reflect the uncertainty associated with estimating the RPSFTM counterfactual dataset.
Abbreviations: BSC: best supportive care; DCO: data cut-off; epNET: extra pancreatic neuroendocrine tumour; HR: hazard ratio; IPCW: inverse probability coefficient weighting; ITT: intention-to-treat; OS: overall survival; pNET: pancreatic neuroendocrine tumour; RPSFTM: rank-preserving structural failure time model.

The EAG have provided insufficient justification that the RPSFTM method is more appropriate than the IPCW and failed to adequately reflect the substantial limitations of RPSFTM, especially when ITT HRs are close to or greater than 1. In particular, the EAG provided insufficient evidence for the common treatment effect assumption

The EAG did not provide a clear justification that the RPSFTM is more appropriate than IPCW. The EAG asserted that, although the number of people crossing over was small, the proportion of the at-risk population (those surviving to progression) crossing over was large. As described above, the proportion of switchers was moderate (<60%). Furthermore, whilst the IPCW can be associated with greater uncertainty for smaller sample sizes and higher proportions of switchers, this is true for all adjustment methods. The EAG considered the limited difference in RPSFTM-adjusted HRs when applying different multiplicative factors *k* to psi as evidence that the common treatment assumption was met. However, this might equally suggest that it was not meaningful to estimate a single value of psi and assume that the actual treatment effect received by the treatment groups is a multiplicative factor of it. Rather, it appears likely that there are differences in prognosis between switchers and non-switchers that are not reflected in this approach, leading to a violation of the common treatment effect assumption and implausible results.

Latimer *et al.* (2024) show that the number of switchers is not the only aspect that informs the robustness of crossover adjustment approaches. For example, even in cases with low to moderate proportions of switchers, adjustment methods can be prone to error if there are differences in prognosis between switchers and non-switchers.[34] In particular, the RPSFTM approach is likely to inadequately adjust survival in situations where ITT HRs are close to 1. This is because the RPSFTM method evaluates treatment exposure and survival times in each randomised group, and estimates a treatment effect that would balance average survival times across arms reflecting a counterfactual scenario where no patients crossed over to the active treatment. If there is very little observed difference in survival between arms, only a very small treatment effect will be attributed to the additional exposure to active treatment in the control arm.[34] While the EAG claimed that this limitation of RPSFTM may not be generalisable as it was highlighted in the context of a case study of a single randomised controlled trial (RCT), the authors provided a clear account why, from a theoretical point of view, the RPSFTM approach would rely on an appreciable difference in survival between both arms.

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In the case of the updated DCO, the point estimates of the unstratified ITT OS HRs (which inform the RPSFTM acceleration factors) were extremely close to 1 in the pNET group and in favour of placebo in the epNET subgroup (Table 3). Therefore, in the pNET group, no meaningful treatment effect is attributed to the additional exposure to cabozantinib in the control arm. In the epNET group, the RPSFTM attributes some of the observed worse survival to the exposure to cabozantinib, estimating longer survival times for the treated patients if they had not received cabozantinib, which lacks clinical validity given the strong PFS benefit observed for cabozantinib from the CABINET trial. Accordingly, the point estimates of the HRs are unchanged in the pNET group and move further in favour of placebo after adjustment in the epNET subgroup. With HRs close to 1 at the primary DCO and extremely close to or even greater than 1 at the updated OS DCO, the RPSFTM was therefore unable to adequately adjust for crossover at the primary DCO and completely unable to adjust for crossover at the updated OS DCO. The results of the RPSFTM analysis are not suitable for decision-making.

The two-stage estimation method is not feasible

The two-stage estimation (TSE) method involves modelling post-progression survival for patients eligible for treatment switching, with disease progression used as a 'secondary baseline' as patients were only permitted to switch after disease progression. Feasibility depends on a sufficiently large crossover cohort and adequate OS event counts to estimate the switching process and to obtain stable, covariate-adjusted outcome estimates. As noted in the Draft Guidance, the feasibility of the two-stage method was explored by the company.

Unlike the RPSFTM and IPCW method, the two-stage approach separately models post-progression survival in patients eligible to switch (i.e., patients in the placebo arm who progressed). For the analyses explored as part of the original company submission (presented in Appendix L), the number of patients eligible for crossover and OS events among these were few (<10 events in patients that switched in both pNET and epNET groups) (Table 4). It was therefore not possible to robustly adjust for a sufficient number of prognostic factors to balance differences between patients who did and did not switch within the model estimating the 'acceleration factor' associated with switching. Given this, the two-stage method was not feasible.

The datasets for the ad-hoc OS sweep (updated DCO) do not contain data on disease progression, and thus it is not feasible to conduct TSE as there are no data on progression to use as the secondary baseline.

Table 4. Summary of the number of patients eligible to switch

Population	Number of patients eligible to switch	Number of OS events in patients eligible to switch	Number of OS events in patients that switched
pNET[a]	[redacted]	[redacted]	[redacted]
epNET[b]	[redacted]	[redacted]	[redacted]

Footnote: [a] Includes patients with non-pancreas tumour site that were initially misclassified to the pNET cohort; [b] Includes patients with pancreas primary tumour site that were initially misclassified to the epNET cohort, and are in the unknown/other subgroup.

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	Abbreviations: epNET: extrapancreatic neuroendocrine tumours; OS, overall survival; pNET, pancreatic neuroendocrine tumours. ***Subsequent treatments other than crossover cabozantinib might have confounded estimated treatment effects substantially at the updated DCO, which can be addressed through IPCW*** A considerable proportion of patients in both the cabozantinib and placebo arms of the CABINET trial received subsequent systemic treatments (beyond crossover to cabozantinib from the placebo arm). In addition to the greater methodological robustness and clinical plausibility of estimates for IPCW versus RPSFTM, the former additionally allows for the adjustment for the exposure of other subsequent treatments. The committee's preferred assumption is to exclude all subsequent systemic treatments from the economic model, given the positioning of cabozantinib as an alternative to BSC. In any scenario where subsequent systemic treatments are excluded, the confounding impact of these treatments on the treatment effect for OS must also be adjusted for. Therefore, an exploratory IPCW analysis was conducted adjusting for all subsequent anticancer therapies in the CABINET trial (with the exception of SSAs), as presented in Appendix 4. It should be noted that, whilst this analysis is limited by a high proportion of switchers, the distribution of weights appears reasonable, and the HRs are more favourable for cabozantinib than the analyses only adjusting for crossover. A scenario has been explored in the model in line with the committee's preferences, excluding subsequent treatment costs and adjusting for the confounding impact of subsequent treatment on the treatment effect for OS (see Section 4).
3	**The committee's preference for the selection of the Weibull curve to model OS for cabozantinib for both pNETs and epNETs lacks justification, and is misaligned with survival estimates derived from the structured expert elicitation exercise** The committee concluded that they would prefer to see Weibull curves for both treatment arms for both pNETs and epNETs but presented limited justification. The EAG suggested that loglogistic curves were not compatible with fixed HRs because they indicate time-varying hazards. However, it should be acknowledged that the use of fixed HRs in combination with models that imply time-varying hazards is also commonplace in oncology modelling, on the assumption that the resulting curves are clinically plausible. The purpose of not limiting the choice of parametric extrapolations to proportional hazard models (PH) was to maximise the choice from a range of potentially clinically valid extrapolations. Combining HRs with survival probabilities estimated from an accelerated failure time (AFT) model is technically mixing assumptions on how treatment effects would (theoretically) be applied in the survival model (acting on the time scale for an AFT model) and how they are modelled in the comparative analysis (acting on the hazard scale). However, there is no reason to artificially constrain the comparator curve to the same form. If the estimated curve for the comparators are clinically valid, the conflating of technical assumptions is immaterial.

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	The application of the HR to derive BSC OS is necessary, given the limitations of the IPCW analysis in generating true counterfactual KM data. The EAG agreed that the PH assumption for OS holds, as neither the residual plots nor the Schoenfeld tests showed any evidence of non-proportional hazards for treatment arms in the pNET and epNET cohorts, with all p-values higher than 0.1 (Figure 15 and Figure 16 in the company response to clarification). As such, it was deemed appropriate to model the relative treatment effect based on the IPCW-adjusted OS HR. Models should not be excluded solely on the basis of the model and HR mixing technical assumptions. Decisions should be made on balance, considering the long-term predictions of the models across treatment arms. The EAG's preference for the Weibull model is based on statistical fit, however this in isolation is not sufficient justification given similarity in Akaike information criterion (AIC) and Bayesian information criterion (BIC) values across models. There were no substantial differences between the AIC and BIC values for the fitted OS curves, with the majority of extrapolations showing a difference of <5 points, suggesting a similar goodness of fit to the KM data for all curves. Additionally, all extrapolations appeared to provide a similar fit to the observed KM data in the assessment of visual fit. As such, the selection of the base case curves was largely driven by expert clinical opinion from structured expert elicitation, as described above.[9] Given OS for BSC was derived by applying the IPCW-adjusted HRs from the CABINET trial to the cabozantinib OS curve, base case curve selection for cabozantinib was informed by clinical plausibility across cabozantinib and BSC simultaneously, as described in Section 3.3.4 of the company submission. The committee preferences are considerably misaligned with the clinician landmark estimates for cabozantinib, as shown in Figure 3 and Figure 5 for the epNET and pNET populations, respectively, falling below the lowest plausible estimates across all timepoints. Therefore, there is no clinical justification for the committee's choice of the Weibull curve. **The loglogistic model is the most appropriate selection to inform OS for cabozantinib, given good statistical and visual fit to the KM data and long-term OS predictions consistent with clinical expert expectations, and thus has been retained for the revised company base case** The company have aligned with the committee's preference to use the most mature data to inform OS in the economic model (August 2024 DCO). The loglogistic model for cabozantinib provides the best fit to the clinician estimates across both cabozantinib, is associated with a reasonable statistical fit and acceptable visual fit to the KM curve. Furthermore, when incorporating the company's preferred approach to use the IPCW-adjusted HR to derive OS for BSC, the resulting survival predictions are in line with the clinician estimates at all timepoints in the epNETs subgroup (Figure 4). The company maintain that a HR of 1 in the pNETs group is overly pessimistic, and the implausible result observed for the IPCW-adjusted HR at the updated DCO for the pNETs cohort is likely to be due to the confounding influence of subsequent treatment beyond crossover to cabozantinib. Accordingly, there is a poor fit for the BSC to the clinician estimates, as shown in Figure 6.

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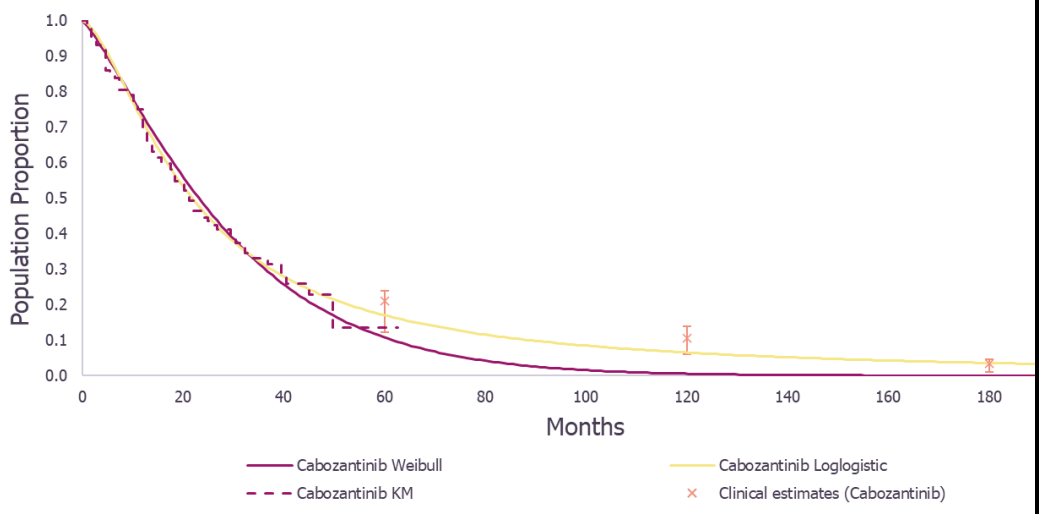
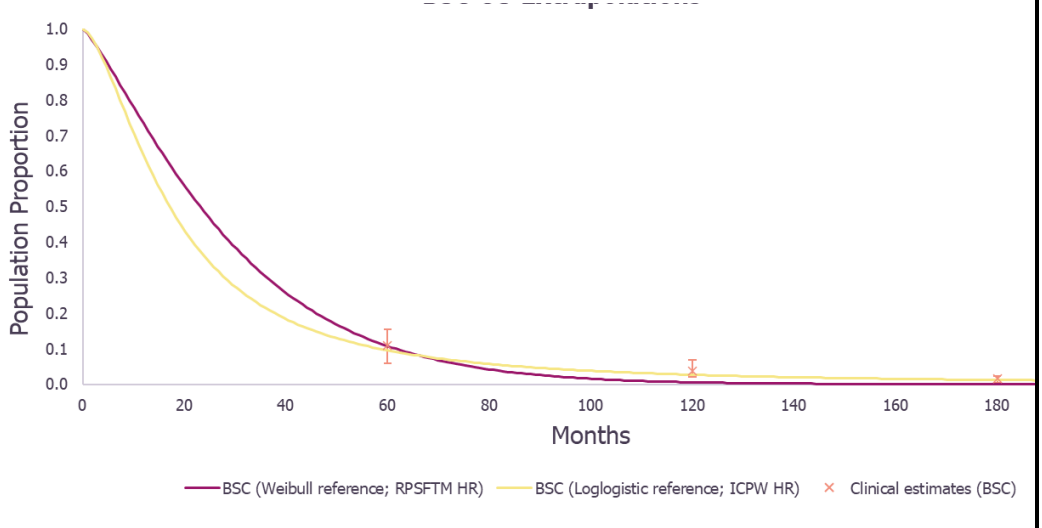
The company maintain the loglogistic model is the most appropriate model to inform OS for cabozantinib in both pNET and epNET populations. The AIC and BIC values for the models for the most recent DCO are presented in Appendix 1. The exponential model has been explored in a scenario analysis in both pNET and epNET populations, representing a mid-way point between the company and committee-preferred extrapolations (Appendix 2).

Figure 3: Company versus committee-preferred OS extrapolations and clinician landmark estimates – cabozantinib (epNETs)



Abbreviations: epNETs: extrapancreatic neuroendocrine tumours; KM: Kaplan–Meier; OS: overall survival.

Figure 4: Company versus committee-preferred OS extrapolations and clinician landmark estimates – BSC (epNETs)



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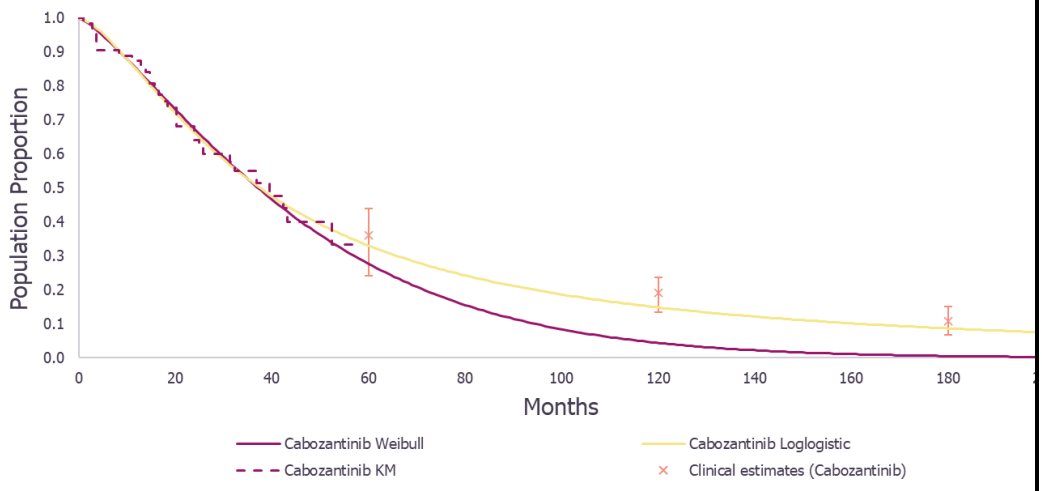
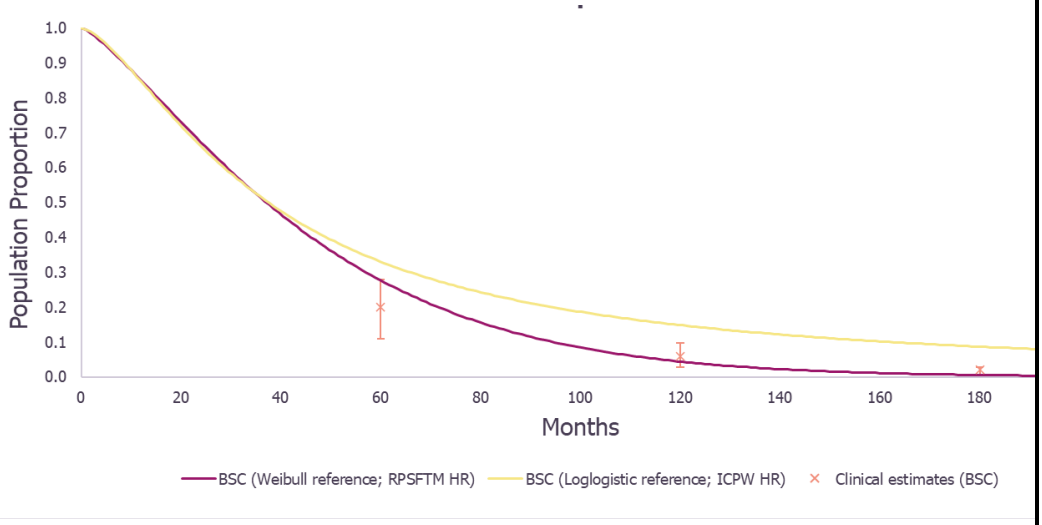
Abbreviations: BSC: best supportive care; epNETs: extrapancreatic neuroendocrine tumours; HR: hazard ratio; IPCW: inverse probability of censoring weights; KM: Kaplan–Meier; OS: overall survival; RPSFTM: rank-preserving structural failure time model.

Figure 5: Company versus committee-preferred OS extrapolations and clinician landmark estimates – cabozantinib (pNETs)



Abbreviations: pNETs: pancreatic neuroendocrine tumours; KM: Kaplan–Meier; OS: overall survival.

Figure 6: Company versus committee-preferred OS extrapolations and clinician landmark estimates – BSC (pNETs)



Abbreviations: BSC: best supportive care; HR: hazard ratio; IPCW: inverse probability of censoring weights; KM: Kaplan–Meier; OS: overall survival; pNETs: pancreatic neuroendocrine tumours; RPSFTM: rank-preserving structural failure time model.

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4	**Subsequent treatment costs should be retained in the economic model in line with the CABINET trial to ensure a balanced comparison of costs and the confounding impact of post-progression subsequent treatments on the treatment effect for OS. Despite the positioning of cabozantinib as an alternative to BSC, subsequent treatments may be used, although they are off-label and not standardised** Subsequent treatments were received by patients in the CABINET trial, and thus the impact of these subsequent treatments is implicitly captured within the OS data informing cabozantinib and BSC in the model. Therefore, the costs of these subsequent treatments should be modelled to ensure a balanced comparison of costs and clinical effects. Whilst the company acknowledge the positioning of cabozantinib as an alternative to BSC, four clinicians consulted as part of this response have stated that, even at later lines, subsequent treatments may be considered in UK clinical practice and there would be declining use post-progression.[2] They noted that subsequent treatments are not standardised, reflecting the heterogeneous nature of NETs and the treatment pathway, and that treatment can include rechallenging patients with prior therapies and off-label chemotherapy, which do not represent standard, approved treatment options. The company base case (summarised in Appendix 1) includes a one-off cost for subsequent treatments. Subsequent treatment costs are estimated in line with the EAG's preference to apply the subsequent treatment cost to patients leaving the progression-free health state, rather than patients entering the progressed disease health state, with the proportions of patients receiving subsequent treatment calculated as proportions of the whole patient population. **In any scenario where subsequent treatments are excluded from the economic model, the confounding impact of these treatments on the treatment effect for OS must also be adjusted for** A scenario analysis has been conducted in line with the committee preference to remove subsequent treatment costs (other than SSAs). Accordingly, in line with recommendations in TSD24, an IPCW analysis was conducted to adjust for subsequent anticancer therapies received in the CABINET (other than SSAs), and is presented in Appendix 4.[35] The results of the exploratory IPCW analysis adjusting for all subsequent anticancer therapy (other than SSAs) were favourable for cabozantinib with HRs of [redacted] (95% CI; [redacted]) and [redacted] (95% CI: [redacted]) for cabozantinib versus BSC in pNETs and epNETs, respectively. In line with the IPCW analysis adjusting for crossover alone, an inspection of the distribution of confounding variables included in the model by treatment arm and switch status demonstrated that no confounder perfectly predicted switching for any population, satisfying the positivity assumption. The coefficients in the weight estimation models and the distribution of estimated weights were sensible, suggesting that the re-weighting successfully accounted for the artificial censoring of switchers. However, this analysis is limited by a high proportion of switchers, and thus may be at higher risk of bias than the analysis adjusting for crossover alone.

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	A scenario was explored where subsequent treatment costs (other than SSAs) were excluded, and where OS for BSC was derived by applying the ICPW-adjusted HRs from the exploratory IPCW analysis adjusting for all subsequent anticancer therapy (other than SSAs) (Appendix 2). Since standard KM curves are non-parametric, there are challenges in producing a weighted KM curve for OS that fully reflects IPCW adjustment with stabilised weights. While it is possible to supply the stabilised weights to produce KM curves, these KMs would not account for the fact that treatment effects using stabilised weights are conditional on the baseline prognostic factors and would not reflect the comparative estimate obtained by IPCW. Therefore, no adjustment was made to cabozantinib OS KM data or corresponding extrapolations in the economic model as a simplifying assumption. The ICER for cabozantinib versus BSC was £15,958 in the epNETs subgroup, demonstrating that the cost-effectiveness of cabozantinib remains robust to assumptions around subsequent treatments. Notably, in contrast to the base case analysis, the ICER for the comparison in the pNETs subgroup was £23,341, demonstrating potential for cabozantinib to represent a cost-effective last-line therapy in patients with pNETs.
5	**Concomitant SSAs are primarily indicated for functional disease. Not all patients continue treatment with concomitant SSA until death, with some patients discontinuing due lack of disease control or toxicity** The company consulted four clinical experts as part of this response to address the uncertainty in the modelling of concomitant SSAs in the economic model. Clinicians generally agreed that SSAs are primarily indicated for functional disease, but their use and the degree to which patients discontinue SSA treatment in UK practice varies widely. Three out of four clinicians indicated that SSAs would be indicated for some or all functional patients; one clinician suggested the vast majority would remain on treatment until death, whereas two suggested that use would decline after progression (e.g. unless there was need for hormonal control). All clinicians agreed there would be low concomitant use and higher discontinuation in non-functional disease, but all clinicians acknowledged centre-level variability. One clinician suggested that the majority of patients do not receive SSA in their practice (regardless of functional status). The main reasons for concomitant SSA discontinuation were cited as lack of disease control, frequent visits to the hospital and toxicity, but the reasons can be highly individualised.[2] The company acknowledge the feedback from the clinical experts at the first ACM, which noted that concomitant SSAs do not stop with discontinuation of systemic therapy, and note the committee's preference to model concomitant SSAs from baseline until death. Whilst concomitant SSAs were modelled alongside subsequent treatments in the original company base case (i.e. concomitant SSA use was still modelled post-progression for some patients), the company accept that assuming all patients discontinue initial concomitant SSAs on discontinuation of cabozantinib or placebo in CABINET is unlikely to reflect UK clinical practice. However, all four clinicians consulted as part of this response noted that SSA use is not lifelong and some discontinuation is anticipated. The EAG's assumption that

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	SSAs are continued indefinitely from baseline to death is therefore an overestimate of concomitant SSA use in practice. The company has therefore revised the base case approach as follows: • The proportion of patients receiving concomitant SSAs at baseline in the model has been informed by individual estimates for functional and non-functional patients provided by four clinical experts consulted as part of this response; the overall proportion has been calculated by weighting these estimates according to the pooled proportion of patients with functional disease in the CABINET trial (41.0% in the epNETs subgroup and 36.5% in the pNETs subgroup)[2] • The same approach was taken to derive estimates for the mean proportion of patients who discontinue concomitant SSAs prior to death (52.7% in the epNETs subgroup and 56.2% in the pNETs subgroup). These values were used to derive discontinuation rates for concomitant SSAs, which remained constant across the model time horizon as a simplifying assumption (1.7% for cabozantinib and 2.4% for BSC in the epNETs population, and 1.1% for cabozantinib and BSC in the pNETs subgroup). The derived discontinuation rates ensure that upon reaching the mean OS timepoint (for cabozantinib or BSC), the proportion of patients who have discontinued concomitant SSAs (of those who receive concomitant SSAs as baseline) matched the mean estimates derived from the clinical experts above. Time on treatment for concomitant SSAs in the cabozantinib and BSC arms are presented in Figure 7 and Figure 8 below for epNETs and pNETs, respectively; given longer survival for cabozantinib in the company base case for the epNETs group, time on SSAs is longer in the cabozantinib arm. Given an OS HR of 1 is modelled for the pNETs group, time on SSAs is equal in the cabozantinib and BSC arms of the model.

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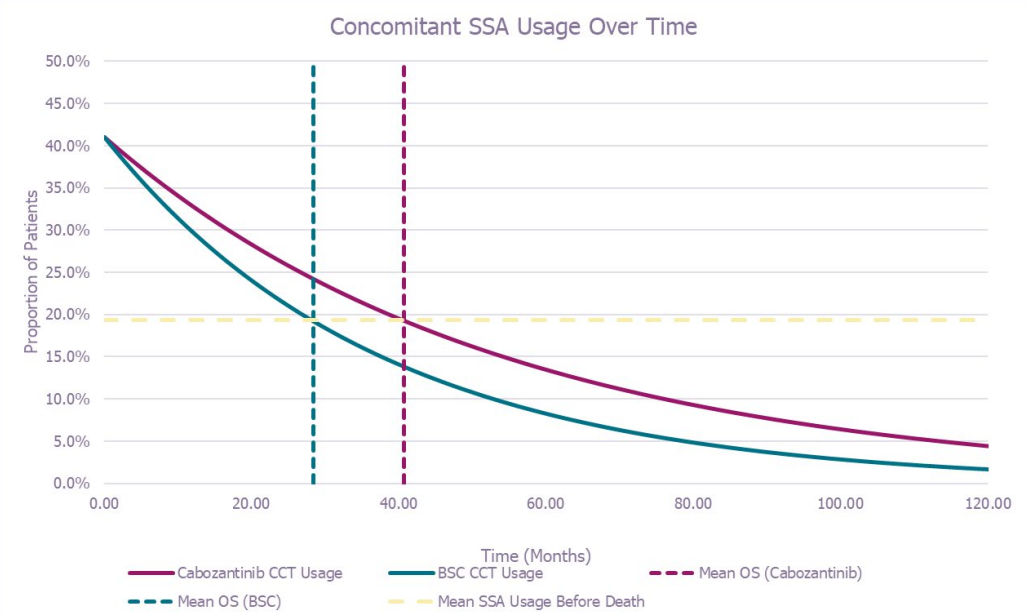
Figure 7: Concomitant SSA discontinuation over time for cabozantinib and BSC (epNETs)



Footnote: The yellow line indicates the proportion of patients on concomitant SSAs at the mean OS timepoint (19.39%), derived by multiplying the proportion with baseline SSA use (41.0%) by the inverse of the mean proportion of patients who discontinue concomitant SSAs prior to death (100 – 52.7%).
Abbreviations: BSC: best supportive care; CCT: concomitant treatment; epNETs: extrapancreatic neuroendocrine tumours; OS: overall survival; SSA: somatostatin analogue.

Figure 8: Concomitant SSA discontinuation over time for cabozantinib and BSC (pNETs)

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	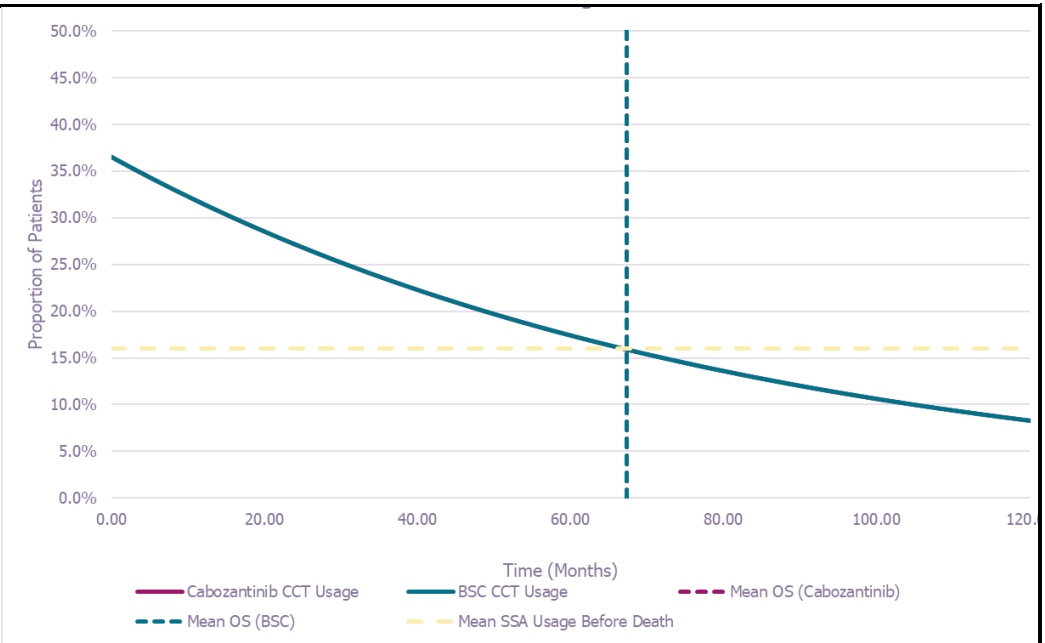 **Footnotes:** Given cabozantinib and BSC OS are set equal in the pNETs subgroup, concomitant SSA discontinuation is equivalent (and thus the cabozantinib curve is hidden by the BSC curves).The yellow line indicates the proportion of patients on concomitant SSAs at the mean OS timepoint (15.99%), derived by multiplying the proportion with baseline SSA use (36.5%) by the inverse of the mean proportion of patients who discontinue concomitant SSAs prior to death (100 – 56.2%). **Abbreviations**: BSC: best supportive care; CCT: concomitant treatment; OS: overall survival; pNETs: pancreatic neuroendocrine tumours; SSA: somatostatin analogue. The revised base case results incorporating these assumptions is presented in Appendix 1. A scenario analysis was also explored where the proportion of patients receiving concomitant SSAs at baseline was aligned with SSA use at baseline in the CABINET trial, as per the original company base case, with the same discontinuation rate applied as per clinical expert feedback above (Appendix 2).
6	**For epNET patients, the company agree that overall the epNETs group is the most relevant for decision-making and are seeking a positive recommendation in this population. Clinical expert opinion is split on the biological distinctiveness of disease for the lung population versus epNETs patients; however, lung NETs patients face higher unmet need and a fragmented UK care pathway which ultimately leads to poorer prognosis. Therefore, if a positive recommendation in the overall epNET group is not possible, the committee should consider an optimised recommendation in the lung population to address unmet need** The company welcome the committee's conclusion that the epNETs subgroup as a whole represents the most robust comparison for decision-making, given this is the most clinically valid and robust approach where the evidence is strongest. The

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company agree that post-hoc subgroup analyses by primary tumour site should be interpreted with caution. The post-hoc subgroups are limited by very small sample sizes and are likely to be subject to bias due to a lack of stratification at randomisation, resulting in imbalances in patient characteristics across treatment arms and associated confounding.

The clinical experts in the committee meeting discussed the current lack of available clinical justification or biological reasoning for separating and analysing lung NETs independently of the broader epNETs subgroup. We also note the committee was in agreement in the Draft Guidance. To address this, the company sought further clinical expert feedback on the suitability of considering the lung population separately from epNET population. Clinical experts provided the following reasons why lung patients may be considered distinct in the UK:

- Both the clinical experts at the committee meeting and four clinical experts consulted as part of this response, acknowledged a significant unmet need in lung NETs given the limited systemic treatment options available for these patients.[2] Everolimus is the only treatment recommended by NICE for these patients, and is restricted to those with non-functional disease. As such, the prognosis faced by patients with lung NETs is typically poor.
- Clinical experts consulted as part of this response highlighted the fragmented UK care pathway for patients with lung NETs, in part due to management by lung cancer multi-disciplinary teams rather than NET specialists. Compounded by diagnostic challenges, patients with lung NET often present with liver metastases and face limited access to peptide receptor radionuclide therapy (PRRT).[2]
- The opinions of the clinical experts diverged on the biological distinctiveness of lung NETs, but there was some consensus that lung NETs may be more aggressive than other NET subtypes.[2]

There was consensus from all four clinicians that separate consideration for lung NETs would be justified for reimbursement decisions.[2]

Therefore, the company have conducted a scenario analysis in lung NETs, reflecting the poorer prognosis for this patient group, but without relying on relative treatment effects derived from uncertain post-hoc analyses (Appendix 2). In line with the approach taken in the company response to EAG clarification questions B2, the PFS and OS curves for cabozantinib have been derived specifically from patients with lung NETs (n=49). BSC curves have been derived by applying the company-preferred IPCW-adjusted HRs for the overall epNETs cohort, which represents the most robust estimate of the relative treatment effect of cabozantinib versus BSC in all epNETs patients. It should be acknowledged that this likely represents a conservative estimate of the cost-effectiveness for cabozantinib in this subgroup, given the OS HR derived from the lung subgroup (HR: [redacted]; 95% CI: [redacted]) indicates a greater relative treatment effect than in the epNETs subgroup as a whole.

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	The company agree that the overall epNETs cohort should be the focus for decision-making. The analysis in the lung subgroup may also be useful for the committee's consideration, demonstrating that cabozantinib remains a cost-effective option in this patient group facing the highest unmet need for novel treatment options.
7	**Cabozantinib offers meaningful additional benefits that are not captured by the QALY calculation** ***Cabozantinib offers a novel treatment option for a rare and heterogenous cancer with high unmet need, with many patients facing limited treatment options other than BSC*** NETs are rare, heterogeneous malignancies which typically present asymptomatically, leading to substantial diagnostic delays and advanced-stage disease at diagnosis. The current treatment pathway is highly individualised, with treatments often being restricted to specific populations or on the basis of distinct disease characteristics such as functional status and somatostatin receptor (SSTR) positivity. Therefore, therapeutic options remain limited across many subtypes and evidence is fragmented due to small trial populations. This combination of rarity and clinical complexity creates a clear unmet need and inequities in access to effective therapies. It should also be acknowledged that the heterogeneity and rarity of NETs (34.9 per 100,000 people in England) hinders the generation of robust evidence, with clinical trials inevitably limited by sample size and therefore statistical power.[3, 36] The high unmet need in NETs and its rarity should be taken into account when contextualising uncertainty in committee decision-making regarding the appropriate cost-effectiveness threshold. It should also be noted that in clinical practice, cabozantinib could simplify the treatment pathway for certain patients by providing an oral, systemic option that does not depend on tumour functionality or SSTR status, allowing access to effective therapy for populations currently underserved by available treatments. ***Cabozantinib offers an effective treatment option that may alleviate health-related quality of life (HRQoL) burden on caregivers/family members*** The committee acknowledged that two-thirds of patients with NETs report having a caregiver (a close family member or friend to help them manage day-to-day NET-associated activities), and caregiver burden is likely to be increased for patients with progressive disease.[37] The significant economic burden and financial problems caregivers experience due to loss of income and out-of-pocket costs has also been shown to lead to distress and reduced quality of life.[37] The economic model does not capture any HRQoL decrement borne by caregivers nor the financial burden experienced, and thus does not capture any corresponding beneficial impact of effective treatment with cabozantinib. ***Cabozantinib offers an effective treatment option that may alleviate elements of patient HRQoL burden that are not explicitly captured by the utility data informing the economic model***

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	There are also multiple aspects of patients' lives that are impacted by living with NETs that are not necessarily captured by the utility data included in the model. These include (as also noted by the committee's patient experts during the first committee meeting): • Frequent testing, lifelong medical appointments, invasive tests and complex treatment regimens • Difficulty in predicting day-to-day symptoms impacting health and overall wellbeing • Inability to work or loss of income • Required dietary changes (particularly due to functional gastrointestinal (GI) tumours or hypoglycaemia associated with pancreatic tumours) Cabozantinib has the potential to provide a much-needed additional, effective treatment option across NET patients, addressing a key unmet need, particularly in lung NETs and functional GI NETs that often face limited treatment options once they have progressed through prior lines of therapy.
8	**The company welcomes the committee's conclusion that the comparator of relevance for the appraisal is BSC. However, the committee's description of the target population as "later-line" is overly simplistic; in line with the CABINET trial, many patients with NETs face BSC as their only treatment option at earlier treatment lines, particularly those with lung NETs** The company welcomes the committee's conclusion that the only comparator of relevance for cabozantinib in this appraisal is BSC. It is anticipated that cabozantinib would be used in UK clinical practice as a treatment option after other targeted systemic treatments and in line with the CABINET trial (primarily in heavily pre-treated patients). This is supported by the EAG's clinical experts who highlighted that they would prescribe cabozantinib in-line with the pivotal CABINET trial, which informed the marketing authorisation for cabozantinib in this indication, given no evidence is available for treatment effectiveness outside of this setting. The number and type of prior treatments will differ greatly according to individual patient characteristics due to the heterogeneity of NETs, particularly for those where there are limited systemic treatment options such as lung and functional GI NETs. The Draft Guidance notes the "*clinical experts explained that for epNETs, particularly functional lung NETs, there are limited treatment options after progression on 1 or 2 systemic treatments."* Therefore, there are considerable proportion of patients who face BSC as their only treatment option at earlier treatment lines. The description of the company positioning of cabozantinib as a "later-line treatment" is therefore overly simplistic. Similarly, the Draft Guidance also notes that *"no evidence was provided for using cabozantinib as an earlier-line treatment"*, but this conclusion does not appreciate the heterogeneity in the population facing BSC as their only treatment option in clinical practice.

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9

A severity modifier of 1.2 is appropriate for all analyses in the epNETs population

The QALY shortfall analysis was conducted in line with the methods outlined in Section 3.6 of the main company submission. The results of the QALY shortfall analysis are summarised in Table 5. For the epNETs population, the proportional QALY shortfall compared to the population receiving treatment with BSC was above the threshold of 0.85, therefore, a severity modifier of 1.2 should be considered for base case results for this comparison. All scenario analyses conducted in epNETs (presented in Table 10) qualify for a severity modifier of 1.2.

Table 5: Summary of QALY shortfall analysis

Population	Expected total QALYs for the general population	Total QALYs that people living with a condition would be expected to have with current treatment (BSC)	Absolute QALY shortfall	Proportional shortfall	Severity weighting
pNETs	12.61	[redacted]	[redacted]	[redacted]	1.00
epNETs	11.61	[redacted]	[redacted]	[redacted]	1.20

Abbreviations: BSC: best supportive care; epNET: extrapancreatic neuroendocrine tumour; pNET: pancreatic neuroendocrine tumour; QALY: quality-adjusted life year.

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- Complete the disclosure about funding from the company and links with, or funding from, the tobacco industry.
- Combine all comments from your organisation into one response. We cannot accept more than one set of comments from each organisation.
- Do not paste other tables into this table – type directly into the table.
- In line with the NICE Health Technology Evaluation Manual (sections 5.4.4 to 5.4.21), if a comment contains confidential information, it is the responsibility of the responder to provide two versions, one complete and one with the confidential information removed (to be published on NICE's website), together with a checklist of the confidential information. Please underline all confidential information, and separately highlight information that is submitted as 'confidential [CON]' in turquoise, and all information submitted as 'depersonalised data [DPD]' in pink. If confidential information is submitted, please submit a second version of

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your comments form with that information replaced with asterixis and highlighted in black.

- Do not include medical information about yourself or another person from which you or the person could be identified.
- Do not use abbreviations.
- Do not include attachments such as research articles, letters or leaflets. For copyright reasons, we will have to return comments forms that have attachments without reading them. You can resubmit your comments form without attachments, it must send it by the deadline.
- If you have received agreement from NICE to submit additional evidence with your comments on the draft guidance document, please submit these separately.

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Appendices

Appendix 1. Revised company base case

In line with feedback from the committee, the company has presented a revised base case. The company have aligned with the following committee preferences:

- BSC as the relevant comparator
- pNETs and epNETs modelled as the main subgroups
- Modelled OS informed by the August 2024 DCO
- Weibull curves to extrapolate PFS for both cabozantinib and BSC

The revised base case incorporates the following, which are justified based on the additional evidence presented as part of this response:

- **OS assumptions:**
    - An OS HR for cabozantinib versus BSC of 1 is clinically invalid, due to the statistically significant and clinically meaningful PFS benefit shown by cabozantinib, the established surrogacy relationship between PFS and OS, and clinical expert estimates of survival derived from a robust elicitation exercise. OS HRs from the IPCW analysis to adjust for crossover in CABINET have been used to derive OS for BSC in the pNETs and epNETs subgroups
    - Loglogistic curves have been used to extrapolate OS for cabozantinib in pNET and epNETs subgroups (as per the company preference in the original submission)
- **Modelling of concomitant SSAs:** The proportion of patients receiving concomitant SSAs has been based on feedback from clinical experts consulted as part of this response.[2] SSAs can be continued until death, but a constant discontinuation rate has been applied to reflect discontinuation due to adverse events or loss of effect. Discontinuation rates are also informed by feedback from clinical experts consulted as part of this response.[2]
- **Subsequent treatments:**
    - Subsequent treatments have been modelled to ensure a balance of costs and benefits
    - Subsequent treatment costs were applied upon leaving the progression-free (PF) state, as per EAG preference. To account for patients moving to the death state instead of the progressed disease state from the PF state, the proportions of patients receiving subsequent treatment were taken as proportions of the whole patient population, rather than the proportions of patients surviving to progression, in line with EAG preferences.
- **Utility values:**

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- The details for the full utility analysis of CABINET have been provided in Appendix 5, including the justification for the use of a linear mixed model repeated measures (MMRM) structure (based on the largely continuous distribution of utility values), the results of the secondary analyses exploring treatment-specific utility values and all relevant prognostic factors (informed by robust clinical expert feedback), including the fitted coefficients for all models. It should be noted that the secondary analyses were consistent with the primary analysis.
- However, given the remaining uncertainty in the utility values derived from the CABINET trial (optional eligibility into the sub-study and limited observations for the progressed disease [PD] state), the revised base case is aligned with the EAG preferences (epNETs: RADIANT-4 for PF and PD; pNETs: Swinburn Vignettes [PF and PD relative decrement]).

- **Dose holds:**
  - Dose holds are included. Dose holds were reported in a proportion of patients in the CABINET trial, reflecting treatment interruptions to manage toxicity. Temporary treatment interruptions to manage adverse drug reactions are recommended in the cabozantinib marketing authorisation, and are expected to occur in UK clinical practice.[24]
  - Given relative dose intensity is not appropriate for orally administered and flat-priced treatments, dose holds are the most accurate way to model the overall anticipated impact on acquisition and administration costs associated of missed doses across the entire eligible population of cabozantinib in NETs. Across a national NETs population, it is expected that assuming a consistent time per cycle in which treatment is not received approximates the reduction in costs expected across the patient cohort due to treatment interruptions. The Company's included dose hold duration was deemed to be reflective of UK clinical practice during UK clinical validation.[24]
- **Other model assumptions:**
  - Adverse events (AEs) were applied as per-cycle probabilities, as per original company base case.
  - Resource use was based on Casciano *et al.* (2013), as per original company base case, given these estimates were deemed to be reflective of UK clinical practice during UK clinical validation.[38]

Revised base case assumptions are otherwise aligned with EAG preferences in all other respects.

Revised deterministic base case results presented in Table 6 and Table 7 for the epNET and pNET subgroups, respectively. The revised base case results demonstrate that cabozantinib (at PAS price) is cost-effective in the epNETs population (with an ICER versus BSC of £9,013). The ICER for cabozantinib versus BSC in the pNETs group is £144,912, but the company maintain that assuming a HR of 1 between cabozantinib and BSC in this group is pessimistic.

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Table 6: Revised company base case results at (cabozantinib PAS price, epNETs)

Intervention	Total costs (£)	Total LYG	Total QALYs	Inc. costs (£)	Inc. LYG	Inc. QALYs	ICER (£/QALY)	Incr. NHB at £30k
Cabozantinib	[redacted]	2.93	[redacted]					
BSC	[redacted]	2.14	1.57	[redacted]	0.79	[redacted]	£9,013	0.49

Abbreviations: BSC: best supportive care; epNET: extra-pancreatic neuroendocrine tumour; ICER: incremental cost-effectiveness ratio; LYG: life years gained; NHB: net health benefit; PAS: Patient Access Scheme; QALY: quality-adjusted life year.

Table 7: Revised company base case results at (cabozantinib PAS price, pNETs)

Intervention	Total costs (£)	Total LYG	Total QALYs	Inc. costs (£)	Inc. LYG	Inc. QALYs	ICER (£/QALY)	Incr. NHB at £30k
Cabozantinib	[redacted]	4.60	[redacted]					
BSC	[redacted]	4.60	2.81	[redacted]	[redacted]	[redacted]	£144,912	-0.51

Abbreviations: BSC: best supportive care; ICER: incremental cost-effectiveness ratio; LYG: life years gained; NHB: net health benefit; PAS: Patient Access Scheme; pNET: pancreatic neuroendocrine tumour; QALY: quality-adjusted life year.

The disaggregated QALYs and LYs per health state for the revised base case are presented in Table 8 and Table 9, respectively.

Table 8: Disaggregated QALYs per health state

Health state	Progression-free	Progressed disease	Death
pNETs			
Cabozantinib	[redacted]	[redacted]	0.00
BSC	[redacted]	[redacted]	0.00
epNETs			
Cabozantinib	[redacted]	[redacted]	0.00
BSC	[redacted]	[redacted]	0.00

Abbreviations: BSC: best supportive care; epNETL: extrapancreatic neuroendocrine tumour; pNET: pancreatic neuroendocrine tumour; QALY: quality adjusted life year.

Table 9: Disaggregated LYs per health state

Health state	Progression-free	Progressed disease	Death
pNETs			
Cabozantinib	[redacted]	[redacted]	0.00
BSC	[redacted]	[redacted]	0.00
epNETs			

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Cabozantinib	[redacted]	[redacted]	0.00
BSC	[redacted]	[redacted]	0.00

Abbreviations: BSC: best supportive care; epNETL: extrapancreatic neuroendocrine tumour; pNET: pancreatic neuroendocrine tumour; QALY: quality adjusted life year.

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Appendix 2. Scenario analyses

As noted throughout this response, a number of scenarios have been explored to test the sensitivity of the revised company base case, as follows:

- The exponential model was explored to inform cabozantinib OS extrapolations in both epNET and pNET populations, representing a mid-way point between the company and committee-preferred extrapolations
- Subsequent treatment costs (other than SSAs) were excluded, and OS for BSC was derived by applying the ICPW-adjusted HRs from the exploratory IPCW analysis adjusting for all subsequent anticancer therapy (other than SSAs), as reported in Appendix 4
- The proportion of patients receiving concomitant SSAs at baseline was aligned with SSA use at baseline in the CABINET trial, as per the original company base case, with the same discontinuation rate applied as per clinical expert feedback above
- Subgroup analyses have been explored for epNETs (lung) and epNETs (no lung):
    - epNETs (lung): the lognormal and Gompertz curves were selected for the cabozantinib PFS and OS extrapolations, as per the selection in the response to the EAG clarification questions (note, the OS curve selection for the updated DCO is presented in the addendum to the response to EAG clarification questions). Cabozantinib time-to-treatment discontinuation (TTD) was informed on the KM data for the lung subgroup. HRs from the overall epNET subgroup were applied to cabozantinib OS, PFS and TTD curves to generate the corresponding curves for BSC.
    - epNETs (no lung): the lognormal and loglogistic curves were selected for the cabozantinib PFS and OS extrapolations, as per the selection in the response to the EAG clarification questions (note, the OS curve selection for the updated DCO is presented in the addendum to the response to EAG clarification questions). Cabozantinib time-to-treatment discontinuation (TTD) was informed on the KM data for the lung subgroup. HRs from the overall epNET subgroup were applied to cabozantinib OS, PFS and TTD curves to generate the corresponding curves for BSC.
- Other scenarios:
    - Resource use estimates informed by Mujica-Mota *et al.* (2018), as per EAG preference[39]
    - AEs are applied in first model cycle, as per EAG preference
    - Dose holds excluded, as per EAG preference
    - The disutility for hypertension and embolism was aligned with EAG preference

Results from these exploratory analyses are presented in Table 10 for epNETs and Table 11 for pNETs. Across all scenarios explored in the epNETs subgroup, the ICER remained below the lower end of NICE's cost-effectiveness threshold and all qualified for a 1.2x severity modifier. In the pNETs subgroup, most scenarios had only a limited impact on the ICER. Notably, in contrast to the base case analysis, the ICER for the comparison in the pNETs subgroup when all subsequent treatment costs and effects were excluded was £23,341, demonstrating potential for cabozantinib to represent a cost-effective last-line therapy in patients with pNETs.

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Table 10: Deterministic updated company base case and scenario analysis results for cabozantinib versus BSC, epNETs (all scenarios qualify for a 1.2x severity modifier)

Scenario		Cabozantinib versus BSC		
		Incr. costs, £	Incr. QALYs	ICER (£/QALY)
Base case				
	Cost-effectiveness analysis	[redacted]	[redacted]	£9,013
Scenarios				
1	Alternative OS extrapolation for cabozantinib: Exponential	[redacted]	[redacted]	£10,726
2	Proportion of CCT usage at baseline based on CABINET data, with discontinuation over time based on clinician estimates	[redacted]	[redacted]	£10,817
3	Resource use source: Mujica-Mota *et al.* (2018)	[redacted]	[redacted]	£11,257
4	Apply AEs in the first model cycle	[redacted]	[redacted]	£9,130
5	Exclude dose holds	[redacted]	[redacted]	£10,913
6	Disutility for hypertension and embolism based on EAG preference	[redacted]	[redacted]	£9,016
7	Subgroup: epNET no lung	[redacted]	[redacted]	£9,919
8	Subgroup: epNET lung only	[redacted]	[redacted]	£20,554
9	Subsequent treatment costs (other than SSAs) excluded; OS for BSC derived by applying the ICPW-adjusted HRs from IPCW analysis adjusting for all subsequent anticancer therapy (other than SSAs)	[redacted]	[redacted]	£15,958

Abbreviations: AE: adverse event; BSC: best supportive care; CCT: concomitant therapy; EAG: External Assessment Group; epNET: extrapancreatic neuroendocrine tumours; HR: hazard ratio; ICER: incremental cost-effectiveness ratio; IPCW: inverse probability of censoring weights; OS: overall survival; QALY: quality-adjusted life year; SSA: somatostatin analogue.

Table 11: Deterministic updated company base case and scenario analysis results for cabozantinib versus BSC, pNETs

Scenario		Cabozantinib versus BSC		
		Incr. costs, £	Incr. QALYs	ICER (£/QALY)
Base case				
	Cost-effectiveness analysis	[redacted]	[redacted]	£144,912
Scenarios				
1	Alternative OS extrapolation for cabozantinib: Exponential	[redacted]	[redacted]	£144,912
2	Proportion of CCT usage at baseline based on CABINET data, with discontinuation over time based on clinician estimates	[redacted]	[redacted]	£144,555
3	Resource use source: Mujica-Mota *et al.* (2018)	[redacted]	[redacted]	£123,422
4	Apply AEs in the first model cycle	[redacted]	[redacted]	£146,548
5	Exclude dose holds	[redacted]	[redacted]	£155,566
6	Disutility for hypertension and embolism based on EAG preference	[redacted]	[redacted]	£144,974
7	Subsequent treatment costs (other than SSAs) excluded; OS for BSC derived by applying the ICPW-adjusted HRs from IPCW analysis adjusting for all subsequent anticancer therapy (other than SSAs)	[redacted]	[redacted]	£23,341

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Abbreviations: AE: adverse event; BSC: best supportive care; CCT: concomitant therapy; EAG: External Assessment Group; epNET: pancreatic neuroendocrine tumours; HR: hazard ratio; ICER: incremental cost-effectiveness ratio; IPCW: inverse probability of censoring weights; OS: overall survival; pNET: pancreatic neuroendocrine tumour; QALY: quality-adjusted life year; SSA: somatostatin analogue.

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Appendix 3. IPCW (updated DCO): Diagnostic plots and tables

Table 12: Patient baseline characteristics by treatment arm and switch status (with / without weighting by mean untruncated IPCW weight, updated DCO)

Population	Arm	Switch Status	Weights	Deaths	Age	ECOG Status at Baseline			Tumour Grade			Functional Status		Number of Prior Therapies			Stratification Factors		
				Deaths (%)	Age (years)	0 (%)	1 (%)	2 (%)	Grade 1 (%)	Grade 2 (%)	Grade 3 (%)	NF (%)	F (%)	1 (%)	2 (%)	3 or more (%)	SSA Usage (%)	Midgut/un-known (%)	Prior sunitinib (%)
pNET	CAB (N=63)	-	-	[redacted]															
	PBO (N=31)	non-switch	-	[redacted]															
			IPCW	[redacted]															
		switch	-	[redacted]															
			IPCW	[redacted]															
epNET	CAB (N=134)	-	-	[redacted]															
	PBO (N=69)	non-switch	-	[redacted]															
			IPCW	[redacted]															
		switch	-	[redacted]															
			IPCW	[redacted]															

Footnotes: An average weight was computed for each patient as the mean of their time-dependent, untruncated IPCW weights. This was used to weight the baseline characteristics.
Abbreviations: CAB: cabozantinib; ECOG: Eastern Cooperative Oncology Group; epNET: extrapancreatic neuroendocrine tumour; F: functional; IPCW: inverse probability of censoring weights; NF: non-functional; PBO: placebo; pNET: pancreatic neuroendocrine tumour; SSA: somatostatin analogue.

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Table 13: Coefficients of IPCW weighting models (estimated HRs with 95% CI, updated DCO)

	pNET		epNET	
	Numerator	Denominator	Numerator	Denominator
Prior SSA use	[redacted]	[redacted]	[redacted]	[redacted]
Age	[redacted]	[redacted]	[redacted]	[redacted]
Primary site: Lung	[redacted]	[redacted]	[redacted]	[redacted]
Primary site: Unknown/other	[redacted]	[redacted]	[redacted]	[redacted]
Tumour grade: Grade 2	[redacted]	[redacted]	[redacted]	[redacted]
Tumour grade: Grade 3	[redacted]	[redacted]	[redacted]	[redacted]
Functional status: Functional	[redacted]	[redacted]	[redacted]	[redacted]
Functional status: Unknown	[redacted]	[redacted]	[redacted]	[redacted]
Number of prior therapies: 2	[redacted]	[redacted]	[redacted]	[redacted]
Number of prior therapies: ≥3	[redacted]	[redacted]	[redacted]	[redacted]
Tumour size (time-dependent)	[redacted]	[redacted]	[redacted]	[redacted]
ECOG status (time-dependent)	[redacted]	[redacted]	[redacted]	[redacted]

Footnotes: The IPCW weight estimation approach as implemented in the *ipcwswitch* package fits two models predicting switching to produce stabilised weights, one with and one without time-dependent covariates. An individual's estimated constant risk of switching based on the model with baseline covariates only (numerator) is divided by their estimated time-dependent risk of switching obtained from the model also including time-dependent confounders (denominator) to obtain a stabilised estimate of their time-dependent inverse probability of censoring, which is then used to reweight the outcome dataset.
Abbreviations: CI: confidence interval; DCO: data cut-off; ECOG: Eastern Cooperative Oncology Group; epNET: extrapancreatic neuroendocrine tumour; HR: hazard ratio; IPCW: inverse probability of censoring weights; pNET: pancreatic neuroendocrine tumour; SSA: somatostatin analogue.

Figure 9: Histogram of stabilised IPCW weights in the placebo arm (not truncated): pNET cohort (updated DCO)

Abbreviations: DCO: data cut-off; IPCW: inverse probability of censoring weights; pNET: pancreatic neuroendocrine tumour.

Figure 10: Histogram of stabilised IPCW weights in the placebo arm (not truncated): epNET cohort (updated DCO)

Abbreviations: DCO: data cut-off; epNET: extrapancreatic neuroendocrine tumour; IPCW: inverse probability of censoring weights; SSA: somatostatin analogue.

Table 14: IPCW-adjusted OS in the pNET cohort: unstratified and stratified HRs

Analysis	Stratified HR (95% CI) Cabozantinib vs Placebo	Unstratified HR (95% CI) Cabozantinib vs Placebo
ITT	[redacted]	[redacted]
IPCW (untruncated weights)	[redacted]	[redacted]
IPCW (truncated weights)	[redacted]	[redacted]

Footnotes: IPCW HRs are adjusted HRs from a Cox model which includes all baseline prognostic factors used as part of the weight estimation procedure as covariates. Cut-off for weight truncation was the most extreme percentile of observations ($p<0.01$).
Abbreviations: CI: confidence interval; HR: hazard ratio; IPCW: inverse probability of censoring weights; ITT: intention to treat; OS: overall survival; pNET: pancreatic neuroendocrine tumour.

Table 15: IPCW-adjusted OS in the epNET cohort: unstratified and stratified HRs

Analysis	Stratified HR (95% CI) Cabozantinib vs Placebo	Unstratified HR (95% CI) Cabozantinib vs Placebo
ITT	[redacted]	[redacted]
IPCW (untruncated weights)	[redacted]	[redacted]
IPCW (truncated weights)	[redacted]	[redacted]

Footnotes: IPCW HRs are adjusted HRs from a Cox model which includes all baseline prognostic factors used as part of the weight estimation procedure as covariates. Cut-off for weight truncation was the most extreme percentile of observations ($p<0.01$).
Abbreviations: CI: confidence interval; epNET: extra-pancreatic neuroendocrine tumour; HR: hazard ratio; IPCW: inverse probability of censoring weights; ITT: intention to treat; OS: overall survival.

Appendix 4. IPCW analysis adjusting for crossover and subsequent systemic treatment

An analysis was explored to adjust for all subsequent systemic treatments received in the cabozantinib and BSC arms of the CABINET trial (excluding subsequent SSAs). The methods for the analysis were consistent with those reported in Appendix L of the main submission. The RPSFTM method is not feasible for switches to non-trial therapies, and thus only TSE and IPCW were considered. For the IPCW method, separate models were fitted to cabozantinib and placebo arms, but switches to all subsequent treatments were considered within the same model.

Feasibility of Two-Stage Estimation (TSE)

In principle, TSE could be used to adjust for switches to other subsequent treatment. However, as the datasets for the ad-hoc OS sweep (updated DCO) do not contain data on disease progression, it is not feasible to conduct TSE as there are no data on progression to use as the secondary baseline. Furthermore, as patients switch onto various subsequent systemic treatment regimens, which may have different efficacy, using an approach that estimates and adjusts for the additional efficacy of receiving subsequent treatments (such as TSE) is likely to be less robust than IPCW, which censors observations upon switching and only uses data prior to switching to estimate survival of all patients.

4.1. Results

The proportion of patients receiving subsequent treatment at the updated DCO is presented in Table 16 below.

Table 16: Proportion of patients receiving subsequent treatment at the updated DCO

Population	Arm	N	Any subsequent treatment (other than SSAs),[a] n (%)
epNET	Cabozantinib	134	[redacted]
	Placebo	69	[redacted]
pNET	Cabozantinib	64	[redacted]
	Placebo	31	[redacted]

Footnote: [a]Any concomitant or subsequent anti-cancer therapy started on or after the date of randomisation excluding SSAs but including crossover cabozantinib.
Abbreviations: BSC: best supportive care; DCO: data cut-off; epNET: extra pancreatic neuroendocrine tumour; HROS: overall survival; pNET: pancreatic neuroendocrine tumour; SSA; somatostatin anaologue.

Using the IPCW method to account for crossover to cabozantinib in the placebo arms, HRs were generated for OS in the different cohorts of interest. Hazard ratios were estimated based on a Cox marginal structural model which accounted for the same confounding baseline covariates as the weight estimation model.

In line with the IPCW analysis adjusting for crossover alone, an inspection of the distribution of confounding variables included in the model by treatment arm and switch status demonstrated that no confounder perfectly predicted switching for any population. The choice of covariates remained based on extensive clinician input regarding relevant prognostic factors predicting switching and survival, suggesting that no important confounders were missing from the model. The coefficients in the weight estimation models (Table 17) and the distribution of estimated weights (Figure 11 and Figure 12) were sensible, suggesting that the re-weighting successfully accounted for the artificial censoring of switchers.

Table 17: Coefficients of IPCW weighting models (estimated HRs with 95% CI)

	pNET				epNET			
	Cabozantinib		Placebo		Cabozantinib		Placebo	
	Numerator	Denominator	Numerator	Denominator	Numerator	Denominator	Numerator	Denominator
Concomitant SSA at baseline								
Age								
Primary site: Lung								
Primary site: pNET								
Primary site: Unknown/other								
Tumour grade: Grade 2								
Tumour grade: Grade 3								
Functional status: Functional								
Functional status: Unknown								
Number of prior therapies: 2								
Number of prior therapies: ≥3								

Footnotes: The IPCW weight estimation approach as implemented in the *ipcwswitch* package fits two models predicting switching to produce stabilised weights, one with and one without time-dependent covariates. An individual's estimated constant risk of switching based on the model with baseline covariates only (numerator) is divided by their estimated time-dependent risk of switching obtained from the model also including time-dependent confounders (denominator) to obtain a stabilised estimate of their time-dependent inverse probability of censoring, which is then used to reweight the outcome dataset. Separate models were fitted for cabozantinib and placebo arms; however, all switches to subsequent treatments (including crossover cabozantinib) were included in the same model.
Abbreviations: CI: confidence interval; epNET: extrapancreatic neuroendocrine tumour; HR: hazard ratio; IPCW: inverse probability of censoring weights; pNET: pancreatic neuroendocrine tumour; SSA: somatostatin analogue.

Figure 11: Histogram of stabilised IPCW weights in both arms (not truncated): epNET cohort

Footnotes: Adjusting for subsequent treatment involves censoring and weight estimation for both arms.
Abbreviations: epNET: extra pancreatic neuroendocrine tumour; IPCW: inverse probability of censoring weights.

Figure 12: Histogram of stabilised IPCW weights in both arms (not truncated): pNET cohort

Footnotes: Adjusting for subsequent treatment involves censoring and weight estimation for both arms.
Abbreviations: pNET: pancreatic neuroendocrine tumour; IPCW: inverse probability of censoring weights.

4.1.1. pNET IPCW Results

The IPCW-adjusted HRs of OS for cabozantinib versus placebo are presented in Table 18.

Table 18. IPCW-adjusted OS in the pNET cohort: unstratified and stratified HRs

Analysis	Stratified HR (95% CI) Cabozantinib vs Placebo	Unstratified HR (95% CI) Cabozantinib vs Placebo
ITT	[redacted]	[redacted]
IPCW (untruncated weights)	[redacted]	[redacted]
IPCW (truncated weights)	[redacted]	[redacted]

Footnotes: IPCW HRs are adjusted HRs from a Cox model which includes all baseline prognostic factors used as part of the weight estimation procedure as covariates. Cut-off for weight truncation was the most extreme percentile of observations (p<0.01).
Abbreviations: CI: confidence interval; HR: hazard ratio; IPCW: inverse probability of censoring weights; ITT: intention to treat; pNET: pancreatic neuroendocrine tumour.

4.1.2. epNET IPCW Results

The IPCW-adjusted HRs of OS for cabozantinib versus placebo are presented in Table 19.

Table 19: IPCW-adjusted OS in the epNET cohort: unstratified and stratified HRs

Analysis	Stratified HR (95% CI) Cabozantinib vs Placebo	Unstratified HR (95% CI) Cabozantinib vs Placebo
ITT	[redacted]	[redacted]
IPCW (untruncated weights)	[redacted]	[redacted]
IPCW (truncated weights)	[redacted]	[redacted]

Footnotes: IPCW HRs are adjusted HRs from a Cox model which includes all baseline prognostic factors used as part of the weight estimation procedure as covariates. Cut-off for weight truncation was the most extreme percentile of observations (p<0.01).
Abbreviations: CI: confidence interval; epNET: extra-pancreatic neuroendocrine tumour; HR: hazard ratio; IPCW: inverse probability of censoring weights; ITT: intention to treat.

Appendix 5. Full details of the utility analysis

5.1.1. Analysis Methodology

5.1.1.1. Analysis of EQ-5D-3L Utility Values

The primary analysis was a regression model to derive the utility values for the PF and PD health states in the cost-effectiveness model (CEM), adjusted for baseline utility and stratified by cohort. Secondary analyses investigated the impact of adjusting for relevant covariates, including prognostic factors and treatment, in the model. Exploratory analyses suggested that there were convergence issues when including both a random slope for time and a random intercept by individual; as such, models fitted only included a random intercept by individual. Whilst models were fitted for both health states, limited data availability meant it was not feasible to robustly assess the PD health state.

Utility values for each health state were reported as estimated marginal means, which adjust the estimated mean utility to account for each of the variables included in the model. For example, in the primary analysis, the average utility for each health state is calculated accounting for the average baseline utility value.

5.1.1.2. Preliminary Data Exploration

Distributions of the utility values were investigated for all participants at baseline and post-baseline using histograms. This was done separately by PF and PD health states for each of the pNET and epNET cohorts

5.1.1.3. Descriptive Statistics

Descriptive analyses were conducted to summarise the EuroQol-5D (EQ-5D)-based utility values. Summary statistics, including number of observations, mean, median, range, and standard deviation, were reported for each health state, by treatment status, and by cohort (pNET and epNET). These were generated at baseline and for all post-baseline values (pooling multiple visits together so there was only one post-baseline set of summary statistics for each health state). Particular consideration was given to the availability of data for PD health state.

5.1.1.4. Primary Analysis

The model formula for the primary analysis is shown below:

$$utility\ value \sim health\ state + baseline\ utility\ value + 1|patient\ ID$$

This regression model derived the relationship between utility value and health state, whilst adjusting for baseline utility. Additionally, a random effect was included to account for the correlation in individual participant's repeated measurements. No random intercept for time was included due to convergence issues.

5.1.1.5. Secondary Analyses

Treatment-Specific

A secondary analysis was conducted to adjust for treatment in the pNET and epNET cohorts, as shown in the model below:

$$utility\ value \sim health\ state + baseline\ utility\ value + treatment + 1|patient\ ID$$

This only included a random intercept by individual as inclusion of both a random slope for time and a random intercept by individual caused convergence issues.

Prognostic Factors

A further secondary analysis was conducted to adjust for prognostic factors, by including these as further covariates in the model as shown below:

$$utility\ value \sim health\ state + baseline\ utility\ value + prognostic\ factor\ 1 + prognostic\ factor\ 2 + \cdots + 1|patient\ ID$$

This only included a random intercept by individual as inclusion of both a random slope for time and a random intercept by individual caused convergence issues.

Relevant prognostic factors for consideration for inclusion in this model were identified through a brief review of relevant literature and Ipsen medical input; these, alongside their relative priority, were then confirmed by clinician input during an advisory board.[40] This is summarised in Table 20.

Table 20. Summary of potential prognostic factors

Characteristic	Advisor Perspective	Notes from Literature Searches[41-47] and CABINET Trial	Adjust for in Analysis	Data Format
Primary tumour site	Highlighted by clinicians as important (related to Ki-67 status, see below)	Potential prognostic factor	**Yes** in epNET overall cohort No in pNETs	Categorised as: lung/thymus, GI tract (reference), unknown/other
Tumour grade	Highlighted by clinicians as important (related to Ki-67 status, see below)	Tumour grade was identified as one of the most important prognostic factors from a brief literature review	**Yes**	Categorised as: Grade 1 (reference), 2, 3 and unknown (if feasible)
Disease differentiation	Highlighted by clinicians, but patients should already be well differentiated. There are no poorly differentiated patients in CABINET	Potential prognostic factor	No, as few patients not well differentiated	-
Disease stage	Highlighted by clinicians as prognostic, but all epNET and most pNET (>94%) patients in CABINET had metastatic disease. Presence of specific metastasises is important, such as liver, peritoneal, bone and lung	Extent of disease is a potential prognostic factor. It was inconsistent as to whether this referred to simply presence, number or specific location	No, as very few patients locally advanced	-
Disease duration	Duration of metastatic disease was mentioned by clinicians as important, at least more so than duration since first therapy/diagnosis	Only information on duration since diagnosis in CABINET, not duration since onset of metastatic disease	No, as not defined from onset of metastatic disease	-
Absolute Ki-67 status	Highlighted as the most important factor by one of the clinicians as it incorporates other characteristics (e.g. tumour grade, tumour site)	No available data from CABINET on this characteristic	No, as not available in CABINET	-
Hormone syndrome/functional status	Highlighted by clinicians as important	Potential prognostic factor	**Yes**	Categorised as: Functional, non-functional (reference)

				and unknown (if feasible)
Prior therapy	Highlighted during the ad-board as important	Lack of prior surgical intervention was a potential further prognostic factor	**Yes**	Categorised as: Number of prior lines of therapy: 1 (reference), 2 or ≥3
ECOG Performance Status	To be discussed in the second ad-board	Potential prognostic factor	**Yes**	Categorised as: 0 (reference) and ≥1
Comorbidities	Of lower importance		No	-
Age	Highlighted during ad-board as potentially important, but not as relevant as other characteristics	Highlighted in the literature as prognostic	**Yes**	As a continuous variable
Sex	Of lower importance		No	-
Race	Of lower importance		No	-

Footnote: Characteristics in **bold blue** are considered to be of primary importance.
Abbreviations: ECOG: Eastern Cooperative Oncology Group; epNET: extrapancreatic neuroendocrine tumours; pNET: pancreatic neuroendocrine tumours.

5.1.1.6. Model Specification

On completion of the initial data exploration investigating the distributions of utility values (Section 5.1.1.2), potentially appropriate classes of models for analyses were selected from those proposed by Hernández Alava *et al.* to be fitted to the model formulae in Sections 5.1.1.4 and 5.1.1.5. These included linear MMRMs, Tobit MMRMs and adjusted limited dependent variable mixture and non-mixture models.[48] Each model was considered to account for unique features of EQ-5D-based utility values. In particular, MMRMs account for correlation in repeated measurements for patients. Tobit models account for the bounded nature of utility values; adjusted limited dependent variable mixture and non-mixture models account for the discontinuities and multi-modality observed in EQ-5D-based utility values.[48]

5.1.1.7. Software Implementation

All data preparation and analyses were performed using the statistical software R (version 4.4.1 or later).[49] Regression models used in the utility analysis will be fitted using the *lme4* R package (version 1.1-35.5 or later).[50] Utility values for each health state were estimated as marginal means over the predictor variables using the *emmeans* R package (version 1.10.3 or later).[51]

5.1.1.8. Model Selection

For both the response mapping generated, and ordinary least squares (OLS) generated utility values, model fit was assessed using the AIC, with lower values indicating a better fit, in addition to other appropriate metrics. Residuals were examined to confirm that model assumptions were not violated; ideally plots should show a random pattern. R^2 was generated; the marginal R^2 is the variance explained by the fixed effects, and the conditional R^2 represents the variance explained by both the fixed and random effects. Mean error (ME), mean squared error (MSE), and root mean squared error (RMSE) were also compared between models. Model selection was based on a combination of statistical metrics and clinical considerations, including interpretability.

5.1.1.9. Missing Data

EQ-5D-3L values were only mapped and analysed for patients that completed the European Organisation for Research and Treatment of Cancer (EORTC) Quality of Life Question-C30 (QLQ-C30) questionnaire at baseline and follow-up. All available data, with the exception of where more than one response was reported for a given planned timepoint, were included in the primary and secondary analyses.

5.2. Results

EORTC QLQ-C30 data collected in CABINET were mapped to EQ-5D-based utility values using the response mapping algorithm, and additionally the OLS regression mapping algorithm as a sensitivity analysis.

Descriptive statistics were used to summarise the EQ-5D-based utility values (Section 5.2.1).

Regression models were then fitted to derive the relationship between utility value and health state in each of the five cohorts, and model fit was assessed (Section 5.2.2). Results are presented for the primary analysis (Section 5.2.2.1) and the secondary analyses, adjusting for relevant prognostic factors and treatment (Section 5.2.2.2).

In general, results were similar when using response mapped and OLS regression mapped values. As such, only results using response mapped utility values are presented here.

5.2.1. Descriptive Statistics

Descriptive statistics were reported for each health state in the pNET and epNET cohorts at baseline and post-baseline (Table 21). Data were also summarised by treatment arm, which showed a similar pattern with only marginal differences across treatments.

The number of participants reporting data at PD compared with PF during follow-up was limited (18 compared with 54 in the pNET and 21 compared 113 in the epNET cohorts). Generally, mean utility was similar across timepoints and health states.

Table 21. Descriptive statistics of utility values

Cohort	Health state	Timepoint	Number of observations	Number of participants	Mean Utility (SD)	Median Utility (range)
pNET[a]	PF	Baseline	[redacted]	[redacted]	[redacted]	[redacted]
		Post-baseline	[redacted]	[redacted]	[redacted]	[redacted]
	PD	Post-baseline	[redacted]	[redacted]	[redacted]	[redacted]
epNET[b]	PF	Baseline	[redacted]	[redacted]	[redacted]	[redacted]
		Post-baseline	[redacted]	[redacted]	[redacted]	[redacted]
	PD	Post-baseline	[redacted]	[redacted]	[redacted]	[redacted]

Footnotes: [a] Includes patients with non-pancreas tumour site that were initially misclassified to the pNET cohort; [b] Includes patients with pancreas primary tumour site that were initially misclassified to the epNET cohort, and are in the unknown/other subgroup.
Abbreviations: epNET: extrapancreatic neuroendocrine tumours; pNET: pancreatic neuroendocrine tumours; PD: progressive disease; PF: progression-free; SD: standard deviation.

5.2.2. Regression Models

Based on initial data exploration of the distribution of EQ-5D-3L-based utility values (which suggested a largely continuous distribution despite the bounded nature of utility values), linear MMRMs were deemed appropriate for the analyses. Only models with random intercepts by individual converged; models with random intercepts and slopes for time, by individual, failed to converge.

Figure 13: Histogram of utility values for the pNET population

Abbreviations: pNET: pancreatic neuroendocrine tumours; PD: progressive disease; PF: progression-free.

Figure 14: Histogram of utility values for the epNET population

Abbreviations: epNET: extrapancreatic neuroendocrine tumours; PD: progressive disease; PF: progression-free.

5.2.2.1. Primary Analysis

The primary analysis models were fitted in each of the populations of interest.

The estimated utility across the PF and PD health states within the pNET and epNET cohorts were similar with differences of less than 0.05 (Table 22; [redacted] compared with [redacted] and [redacted] compared with [redacted] for pNETs and epNETs respectively).

Table 22: Summary of utility values: primary analysis

Model	Health State	Utility Value	SE
pNET[a]	PF	[redacted]	[redacted]
	PD	[redacted]	[redacted]
epNET[b]	PF	[redacted]	[redacted]
	PD	[redacted]	[redacted]

Footnotes: [a] Includes patients with non-pancreas tumour site that were initially misclassified to the pNET cohort; [b] Includes patients with pancreas primary tumour site that were initially misclassified to the epNET cohort, and are in the unknown/other subgroup.
Abbreviations: epNET: extrapancreatic neuroendocrine tumours; pNET: pancreatic neuroendocrine tumours; PD: progressive disease; PF: progression-free; SE: standard error.

The coefficient for baseline utility suggests that an increase of [redacted] unit in baseline utility (i.e. from QoL at death, to perfect health) is expected to increase utility at follow-up by [redacted] in pNETs and [redacted] in epNETs (Table 23).

Table 23: Summary of model regression coefficients: primary analysis

Model	Output	Intercept	PF State Indicator	Baseline Utility	Random Effect SD	
					Subject	Residual
pNET[a]	Estimate (95% CI)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	SE	[redacted]	[redacted]	[redacted]	NA	NA
epNET[b]	Estimate (95% CI)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	SE	[redacted]	[redacted]	[redacted]	NA	NA

Footnotes: [a] Includes patients with non-pancreas tumour site that were initially misclassified to the pNET cohort; [b] Includes patients with pancreas primary tumour site that were initially misclassified to the epNET cohort, and are in the unknown/other subgroup.
Abbreviations: CI: confidence interval; epNET: extrapancreatic neuroendocrine tumours; pNET: pancreatic neuroendocrine tumours; NA: not applicable; PF: progression-free; SD: standard deviation; SE: standard error.

5.2.2.2. Secondary Analyses

Treatment-Specific

The secondary analysis adjusting for treatment was fitted in the full pNET and epNET cohorts.

The estimated utility of PD was similar to PF in both cohorts, with no notable differences in utility across treatments in either population (Table 24). As such, these results were consistent with the primary analysis.

Table 24. Summary of utility values: secondary analysis including treatment

Model	Treatment	Health State	Utility Value	SE
pNET[a]	Cabozantinib	PF	[redacted]	[redacted]
		PD	[redacted]	[redacted]
	Placebo	PF	[redacted]	[redacted]
		PD	[redacted]	[redacted]
epNET[b]	Cabozantinib	PF	[redacted]	[redacted]
		PD	[redacted]	[redacted]
	Placebo	PF	[redacted]	[redacted]
		PD	[redacted]	[redacted]

Footnotes: [a] Includes patients with non-pancreas tumour site that were initially misclassified to the pNET cohort; [b] Includes patients with pancreas primary tumour site that were initially misclassified to the epNET cohort, and are in the unknown/other subgroup.
Abbreviations: epNET: extrapancreatic neuroendocrine tumours; pNET: pancreatic neuroendocrine tumours; PD: progressed disease; PF: progression-free; SE: standard error.

The coefficients indicate that there is minimal impact on expected utility value when receiving cabozantinib compared with placebo across both pNETs and epNETs (Table 25; coefficient: [redacted] and [redacted] respectively, with the 95% confidence interval including zero in both cases).

Table 25: Summary of model regression coefficients: secondary analysis including treatment

Model	Output	Intercept	PF State Indicator	Baseline Utility	Treatment: Cabozantinib	Random Effect SD	
						Subject	Residual
pNET[a]	Estimate (95% CI)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	SE	[redacted]	[redacted]	[redacted]	[redacted]	NA	NA
epNET[b]	Estimate (95% CI)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	SE	[redacted]	[redacted]	[redacted]	[redacted]	NA	NA

Footnotes: [a] Includes patients with non-pancreas tumour site that were initially misclassified to the pNET cohort; [b] Includes patients with pancreas primary tumour site that were initially misclassified to the epNET cohort, and are in the unknown/other subgroup.
Abbreviations: CI: confidence interval; epNET: extrapancreatic neuroendocrine tumours; pNET: pancreatic neuroendocrine tumours; NA: not applicable; PF: progression-free; SD: standard deviation; SE: standard error.

Prognostic Factors

The secondary analysis adjusting for all relevant prognostic factors was fitted in each of the populations.

When adjusting for prognostic factors, the estimated utilities were similar across PF and PD health states. These results were consistent with the primary analysis (within 0.05).

Table 26: Summary of utility values: secondary analysis including prognostic factors

Model	Health State	Utility Value	SE
pNET[a]	PF	[redacted]	[redacted]
	PD	[redacted]	[redacted]
epNET[b]	PF	[redacted]	[redacted]
	PD	[redacted]	[redacted]
	PD	[redacted]	[redacted]

Footnotes: [a] Includes patients with non-pancreas tumour site that were initially misclassified to the pNET cohort; [b] Includes patients with pancreas primary tumour site that were initially misclassified to the epNET cohort, and are in the unknown/other subgroup; [c] Includes patients with thymus primary tumour site.
Abbreviations: epNET: extrapancreatic neuroendocrine tumours; pNET: pancreatic neuroendocrine tumours; PD: progressed disease; PF: progression-free; SE: standard error.

In all populations, the coefficient for each of the prognostic factors were close to zero with the 95% confidence intervals including zero (Table 27). The coefficient for the health state indicator suggested similar utility across the two health states across most populations.

Table 27. Summary of model regression coefficients: secondary analysis including prognostic factors

Model	Output	Intercept	PF State Indicator	Baseline Utility	Tumour Grade		Previous treatments		ECOG	Age	Hormonal Status		Subgroups		RE SD	
					2	3	≥3	2	≥1		Functional	Unknown	Lung	Unknown/ Other	Subject	Residual
pNET[a]	Estimate (95% CI)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	NA	NA	[redacted]	[redacted]
	SE	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	NA	NA	NA	NA
epNET[b]	Estimate (95% CI)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	SE	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	NA	NA

Footnotes: [a] Includes patients with non-pancreas tumour site that were initially misclassified to the pNET cohort; [b] Includes patients with pancreas primary tumour site that were initially misclassified to the epNET cohort, and are in the unknown/other subgroup; [c] Includes patients with thymus primary tumour site.
Abbreviations: CI: confidence interval; ECOG: Eastern Cooperative Oncology Group ; epNET: extrapancreatic neuroendocrine tumours; NA: not applicable; pNET: pancreatic neuroendocrine tumours; PF: progression-free; RE: random effect; SD: standard deviation; SE: standard error.

5.3. Summary

As per the CABINET protocol, PD data were not collected; as a result there were limited, and likely biased, data available for the PD health state. Summary statistics, namely the number of observations and participants in each cohort highlighted this, and the arithmetic mean utility suggested that patients in the PD health state had a similar utility value to those in the PF health state.

The primary analysis fitted a regression model to derive the utility values for each health state in the CEM, adjusted for baseline utility. Each model was fitted separately for each cohort. Secondary analyses investigated both the impact of adjusting for planned treatment and of adjusting for relevant prognostic factors. Model fit was similar across primary and secondary analyses, with adjustment for treatment or prognostic factors not resulting in an improved model fit, as assessed by AIC, ME, MSE and RMSE. However, marginal R^2 showed some improvement for epNETs when adjusting for prognostic factors, suggesting these may explain some variation in utility; this was not the case for pNETs.

The estimated treatment-specific health state utilities suggested minimal differences between cabozantinib and placebo in terms of utility. The analysis including prognostic factors estimated similar health state utilities across all populations. As such, it is reasonable to conclude that neither the adjustment for treatment nor relevant prognostic factors impacted utility notably.

Baseline utility was found to be a significant predictor of utility values at follow-up across all populations. The estimated PF utility values were higher for pNET than for epNET. PD utility values were estimated, however produced counter-intuitive results due to the limited and therefore biased data available; this was investigated further.

Similarity of PF and PD Utility Values

Given the lack of difference between estimated PF and PD utility values, differences between patients who progressed that reported an EORTC QLQ-30 questionnaire response whilst in the PD health state (N=37) and those that did not (N=102) were investigated. A side-by-side comparison of baseline characteristics for these two groups of patients suggested the participants that progressed and reported a response in the PD health state were, on average, healthier than those who progressed and did not report a response whilst in the PD health state. Notably, those with PD data available had a higher average utility at baseline (0.81 compared with 0.76 respectively) and a greater proportion of participants with an ECOG (Eastern Cooperative Oncology Group) performance status of Grade 0 at baseline (57% compared with 36%). As noted previously, baseline utility was consistently a significant predictor of expected utility across all analyses. Additionally, the secondary analysis adjusting for prognostic factors suggested that having an ECOG performance status of Grade ≥1 reduced expected utility, even if this was not a statistically significant decrease (Table 27).

Given the extent of information available for PF, estimates of PF utility are expected to be reliable; however, given missing data on PD patients (since PD patients are less likely to be able to complete the required questionnaires), estimates of PD utility are likely to be biased upwards.

Single Technology Appraisal

Cabozantinib for treating advanced neuroendocrine tumours that have progressed after systemic treatment [ID6474]

Consultee comments on the draft guidance

Name	[redacted]
Organisation	[redacted]
Conflict	N/A
Comments on the DG:	

a. Has all of the relevant evidence been taken into account?
No - see below answer c

b. Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?
Based on the day's incomplete discussion - yes

c. Are the recommendations sound and a suitable basis for guidance to the NHS?
No
As commented on by the Chairperson during the meeting – "this is a very complex group of cancers": and it is a group rather than one diagnosis.

As with more common cancers there are significant variations, as well as similarities, dependent on site and sub-types. For example, adenocarcinomas are addressed by site then sub-types – not as a whole tissue/cell type.

My concern is that the variations in neuroendocrine tumours (NETs) were not clarified as well as they could have been – and therefore a fuller discussion about where the proposed medication may have most benefit was incomplete. My fear is that a negative across-the-board outcome will disadvantage those who have very limited / no alternative treatment options and therefore be an unequitable/unfair conclusion: specifically, those with non-pancreatic and /or functional NETs.

I strongly feet there were several points that required more discussion to assist clarification and decision-making:

• Primary site restrictions on licensed use of alternative options eg what may be licensed for pancreas may not be for lung or other sites
• Grading: some therapies are only licensed for Grade 1-2: those with Grade 3 are excluded.
• Functionality – where hormone excess syndrome may be the more life-limiting factor than tumour mass presence / growth rate alone; i.e., the

benefit a therapy may have on both cell growth and hormone control. This group may not have the same alternative options as others as some treatments are only licensed for non-functioning NETs.
• Somatostatin-receptor status: those with negative status – or are positive but the primary is not within the GI tract or pancreas - are currently precluded from radioligand therapy (Lutetium177) outside of a clinical trial.
• Those with DPYD-deficiency will be precluded from Cap-Tem: as the dihydropyrimidine dehydrogenase (DPD) enzyme, is crucial for breaking down fluoropyrimidine chemotherapy drugs like 5-FU and capecitabine.

a) Everolimus and sunitinib for treating unresectable or metastatic neuroendocrine tumours in people with progressive disease Technology appraisal guidance Reference number:TA449 Published: 28/6/2017
b) Lutetium (177Lu) oxodotreotide for treating unresectable or metastatic neuroendocrine tumours
Technology appraisal guidance Reference number:TA539 Published: 29/8/2018

By site

Non-functioning Pancreatic NETs (those without an associated hormone excess syndrome): options include somatostatin analogues, radioligand therapy (Lutetium 177) – IF receptor positive and Grade 1-2, Everolimus and/or Sunitinib (Grade 1-2), Cap-Tem +/- chemotherapy and/or clinical trial (pending grade and eligibility)
Functioning Pancreatic NETs (eg insulinomas, gastrinomas, glucagonomas, VIPomas, etc): options include somatostatin analogues, radioligand therapy (Lutetium 177) – IF receptor positive and Grade 1-2, Everolimus and/or Sunitinib (Grade 1-2), Cap-Tem +/- chemotherapy and/or clinical trial (pending grade and eligibility)

Non-functioning Lung NETs: options include somatostatin analogues, Everolimus (Grade 1-2) Cap-Tem +/- chemotherapy (if high grade) and/or clinical trial (pending grade and eligibility)
Functioning Lung NETs (1 in 5 may have Carcinoid Syndrome): options include somatostatin analogues, Cap-Tem +/- chemotherapy (if high-grade) and/or clinical trial (pending grade and eligibility)

Non-functioning small bowel NETs: rare especially once metastatic: options include somatostatin analogues, radioligand therapy (Lutetium 177) – IF receptor positive and Grade 1-2, Everolimus, (Grade 1-2), Cap-Tem +/- chemotherapy (rarely used and only if high-grade) and/or clinical trial (pending grade and eligibility)
Functioning small bowel NETs: options include somatostatin analogues, radioligand therapy (Lutetium 177) – IF receptor positive and Grade 1-2, chemotherapy (rarely used and only if high-grade) and/or clinical trial (pending grade and eligibility)

Less common non-functioning NETs: eg phaeochromocytomas, paragangliomas, head & neck, gynaecological and/or genitourinary

primaries: options include somatostatin analogues, Cap-Tem +/- chemotherapy (if high-grade) and/or clinical trial (pending grade and eligibility)
Less common functioning NETs: eg phaeochromocytomas, paragangliomas, head & neck, gynaecological and/or genitourinary primaries: options include somatostatin analogues, Cap-Tem +/- chemotherapy (if high-grade) and/or clinical trial (pending grade and eligibility).

Patient reported impact from trial and in other indications show tolerability: improvement beyond alternatives such as Everolimus, etc . . . prooting self-care and reducing healthcare reliance.
Little comment - as in other NET appraisals, on Best Support Care costings - which often includes somatostatin analogues, especially in functional disease - or an assessment of health costs of not treating.

d. Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of age, disability, gender reassignment, pregnancy and maternity, race, religion or belief, sex or sexual orientation?
No

Cabozantinib for treating advanced neuroendocrine tumours that have progressed after systemic treatment [ID6474]

EAG response to draft guidance

October 2025

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1 Introduction

Following the first appraisal committee meeting (ACM1) for cabozantinib, the committee highlighted a preference for analyses based on the company's positioning with best supportive care as the relevant comparator, with the pNET and epNET cohorts as the main subgroups. The committee also highlighted key areas of uncertainty in the economic model, particularly relating to overall survival (OS) results and the methods used to assess the effects of crossover from the placebo to the cabozantinib arm in CABINET.

In order to determine the most plausible ICER, the committee requested further evidence on the following:

- Results from the August 2024 data cut-off (DCO), using rank-preserving structure failure time models (RPSFTM) to adjust for crossover;
- Results from the 2-stage estimate to adjust for crossover;
- Weibull curves to extrapolate progression-free survival for both cabozantinib and best supportive care;
- Weibull curves to extrapolate overall survival for both treatment arms with a hazard of 1 for cabozantinib, and further data to support a surrogacy assumption;
- Further information on utility values;
- Modelling of concomitant SSAs continued from baseline until death; and
- No subsequent treatments modelled.

Section 2 of this report provides the Evidence Assessment Group's (EAG's) response to the nine points raised by the company in response to the committee's requests highlighted in the draft guidance. In addition, the EAG provides cost-effectiveness results of additional scenario analysis conducted by the EAG and updated EAG base case results in Section 3.

2 EAG response

The company presented a response to the draft guidance which included nine key points. Each of these points are discussed by the EAG in the sections below.

2.1 The use of a HR of 1 to model OS

The company's response noted concern that the preference of the EAG and the committee for modelling OS appeared to contradict both the expectations of the clinical experts who took part in the company's structured elicitation exercise (SEE) and existing evidence regarding the association between PFS and OS in neuroendocrine tumours (NETs). The EAG acknowledges the use of SEEs in cases, such as those highlighted by the company, where there is limited evidence and it may be difficult to generate robust evidence to demonstrate an OS benefit. This method is in accordance with the guidance provided in NICE DSU TSD 26 and as such, the EAG's decisions regarding the modelling of OS did not overlook the information provided by the company but instead considered this alongside the evidence provided from the CABINET trial.[1]

The company highlighted how their clinical experts considered that the differences in PFS and OS data from the CABINET trial (particularly the observed PFS benefit and the lack of an OS benefit for cabozantinib against BSC in the updated DCO) may be due to a range of issues including small sample size, a high percentage of patients in the placebo arm crossing over to cabozantinib, treatment sequences and short trial follow-up. This was used as support for trials for NETs relying on surrogate endpoints, such as PFS, when considering the potential effects of treatment on OS. Further evidence was provided of previous studies which the company reported to have demonstrated significant associations between PFS and OS in NETs, supporting the use of PFS as a surrogate for OS. The EAG considered each of these studies, as discussed below:

- Imaoka *et al.* (2017): A literature review which demonstrated a modest correlation between PFS and OS in studies of advanced neuroendocrine neoplasms (NENs), 75% of which included pNETs (r_2 0.587; 95% CIs 0.249 to 0.925, p=0.001). While this study indicates an association between PFS and OS, the authors noted that it lacked statistical power and was considered an exploratory analysis. No subgroup analysis was provided specifically for the pNET group and results are therefore based on the wider NEN population.[2]
- Singh *et al.* (2014): A systematic review which demonstrated a significant association between median time to disease progression and OS in patients with NETs, most of whom

had gastroenteopancreatic NETs. However, when only RCTs were considered, the association between the two measures was not statistically significant (numerical results not reported), which the authors attributed to small sample sizes.[3]

- Ter-Minassian *et al.* (2017): A retrospective analysis of patients with NETs in a single centre in the USA, which reported non-statistically significant associations between PFS and OS. Associations were highest for patients with pNETs, although these were non-statistically significant by 24 months (12 months adjusted HR of 2.20, 95% CI 1.05 to 4.61, *p*=0.04; 24 months adjusted HR 1.68, 95% CI 0.62 to 4.58, *p*=0.31).[4]

While each study indicated that there is some degree of association between PFS and OS in patients with NETs, each was associated with limitations, as is the case for any surrogacy studies, and so the EAG considers that uncertainty remains about the magnitude of the association between PFS and OS in this population. The EAG acknowledges that PFS has been used as a surrogate endpoint for OS in other trials for NETs and notes the range of factors presented in the company response which can limit the ability of NET trials to demonstrate an OS benefit, including small sample sizes, crossover trial design, the variation in subsequent treatments and the longevity of the disease. As such, the EAG agrees about the potential for PFS benefits to reflect an overall OS benefit in this population but remains of the opinion that there is considerable uncertainty in the magnitude of this correlation.

One of the company's key concerns in relation to the EAG and committee's preferences was the assumption of an OS HR of 1 between cabozantinib and BSC, which the company considers lacks clinical plausibility and does not reflect the potential clinical benefits of cabozantinib. However, the EAG notes that the decision to use a HR of 1 in the economic analysis was based on the HRs from the updated DCO in the CABINET trial numerically favouring BSC. The HR of 1 was therefore selected in order to increase the clinical plausibility of the trial results and assume that cabozantinib would not result in worse OS than BSC. The EAG does not disagree with the plausibility of a survival benefit with cabozantinib vs BSC in light of the observed PFS benefit but notes that the data available from the updated DCO CABINET are not sufficiently robust to determine the magnitude of a potential OS benefit. Importantly, the EAG notes that despite the company's concerns with assuming a HR of 1 in the analysis, the company made the same assumption in their base case for pNETs as, regardless of the crossover adjustment method applied, the OS HRs show a numerical disadvantage with cabozantinib vs BSC.

Finally, the company highlighted how prior NICE TA appraisals have accepted an OS benefit despite a lack of statistical significance in OS in clinical trials. While the EAG recognises that some of the evidence from previous appraisals demonstrated a non-statistically significant OS benefit, it notes the crucial difference between a non-statistically significant numerical OS advantage and a non-statistically significant numerical OS disadvantage (Table 1). While RADIANT-3 and A6181111 demonstrated non-statistically significant OS benefits, the effect estimates were numerically more favourable for everolimus and sunitinib in comparison to BSC.[3, 5] In contrast, the CABINET results show [redacted] with the RPSFTM method. As such, the EAG does not consider comparisons with previous TAs sufficient evidence with which to conclude that cabozantinib is likely to demonstrate an OS benefit in comparison to BSC.

Table 1. OS effect estimates from CABINET and studies in prior NICE TA appraisals

Study	HR (95% CIs)
CABINET updated DCO (pNET)	-
IPCW	[redacted]
RPSFTM	[redacted]
CABINET updated DCO (epNET)	[redacted]
IPCW	[redacted]
RPSFTM	[redacted]
Other NICE TAs for NETS	[redacted]
RADIANT-3 (TA449 - everolimus)[6]	HR 0.60 (0.09 to 3.95)
A6181111 (TA449 – sunitinib)[5]	HR 0.34 (0.14 to 1.28)
NETTER-1 (TA539 – PRRT)[7]	HR 0.49 (0.308 to 0.804)

Abbreviations: CI, confidence interval; epNET, extra-pancreatic neuroendocrine tumour; HR, hazard ratio; IPCW, Inverse Probability of Censoring Weighting; NICE, National Institute for Health and Care Excellence; pNET, pancreatic neuroendocrine tumour; PRRT, Peptide Receptor Radionuclide Therapy; RPSFTM, Rank-preserving structural failure time model; TA, Technology Appraisal

2.2 Adjustment method for crossover in the CABINET OS data

The committee considered the RPSFTM to be the most appropriate method to adjust for crossover in the placebo arm of CABINET and requested the results of the economic analyses for the updated DCO using RPSFTM-adjusted methods. The company did not provide these results (however, did provide the RPSFTM OS HRs for the updated DCO), instead providing further explanation for their

decision that the IPCW is the most appropriate method of adjustment. The company considered the following points in their justification for IPCW:

- The key IPCW assumptions were satisfied;
- The IPCW weights were stable across cohorts and data cuts and the EAG's conclusion that IPCW weights were unstable because of small patient numbers and a high percentage of crossover is factually inaccurate;
- IPCW performs well regardless of sample size or proportion of switchers when key assumptions are met and weights are stable;
- IPCW results were clinically plausible while results of RPSFTM lacked clinical plausibility;
- The EAG did not provide sufficient justification of the benefits of RPSFTM over IPCW, particularly regarding the common treatment effect assumption, and limitations when HRs are close to or greater than 1;
- Subsequent treatments may have confounded treatment effects in the August 2024 DCO, which can be addressed using IPCW.

Due to time constraints, the EAG could not investigate all the issues raised by the company in detail in time for the conclusion of this report. Instead, the EAG produced an addendum to this document containing a more detailed discussion around the appropriateness of the IPCW and the RPSFTM methods.

Importantly, the EAG notes that there is considerable uncertainty in the results from both methods given the small numbers of patients who crossed over in CABINET, who also represented a high proportion of crossover out of the patients eligible for crossover (Table 2). Moreover, the EAG notes that the choice of adjustment for crossover method has very limited impact in the pNET population, where both the RPSFTM and the IPCW methods produce results [redacted] The only comparison where the method of crossover adjustment has an important impact on the effect estimate is for the epNET cohort in the updated DCO, which numerically favoured cabozantinib with the use of IPCW [redacted], and numerically favoured placebo with RPSFTM [redacted], albeit with a lack of statistical significance in both results. While the effect estimates differed with the choice of crossover method, there was considerable overlap in the 95% CIs, further highlighting the uncertainty in the choice of crossover method.

As a result, the EAG provides the results of the EAG analysis using the RPSFTM (which resulted in the use a HR of 1 as discussed in Section 2.1) and the IPCW methods in the epNET cohort for the consideration of the committee. Further discussion on the appropriateness of each method is provided in the addendum.

Table 2. Proportion of switchers in the updated DCO (Reproduced from Table 2 of the company's response)

Population	Arm	N	Crossover, n (%)
epNET	Cabozantinib	134	[redacted]
	Placebo	69	[redacted]
pNET	Cabozantinib	64	[redacted]
	Placebo	31	[redacted]

Abbreviations: DCO, data cutoff; epNET, extra-pancreatic neuroendocrine tumours; N/A, not applicable; pNET, pancreatic neuroendocrine tumours

2.3 OS curve selection preference

In draft guidance, the committee concluded that it would prefer to see Weibull curves for both treatment arms for modelling OS, in line with the EAG's preferred assumption[8]. The company has maintained that the loglogistic curves would be more appropriate for modelling OS in both pNET and epNET. The company's reasons were based on a good statistical and visual fit of the loglogistic to the KM data and the long-term OS predictions being consistent with clinical expert expectations derived from the structured expert exercise conducted by the company.

In their original report, the EAG critiqued the use of loglogistic curves as these are not compatible with the fixed Cox proportional hazard ratios (HRs) the company applied to the OS loglogistic curves, which imply time varying hazards. The company acknowledged the EAG's point but noted its approach is common practice in oncology modelling.

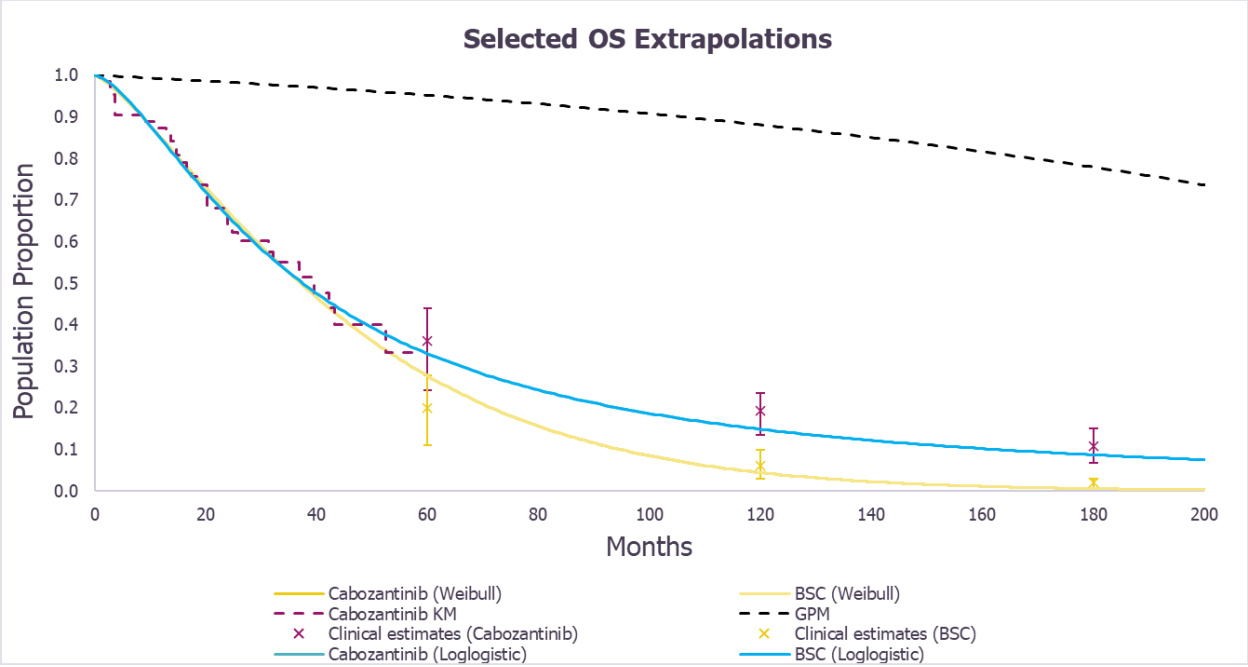
The company also pointed out that using any of the parametric models provided by the company involves mixing assumptions. The company is correct given that all of the survival curves they presented are based on AFT (accelerated failure time) models and are not compatible with the Cox proportional HRs (hazard ratios) they have used. This issue was identified in the EAG report, since HRs should be derived from the same parametric models used to estimate the respective survival curves, to maintain internal validity.

Survival curves from AFT models (such as the company's base case lognormal) are based on treatment effects acting on the time scale (stretching or shrinking time to event), whereas Cox proportional hazard ratios assume treatment effects act on the hazard scale (multiplying the instantaneous risk by a constant). Because these effects operate on fundamentally different scales, applying a Cox HR to AFT-based survival curves is mathematically inconsistent and can produce biased survival estimates. This issue was identified in the original report. However, a Weibull curve can be expressed in AFT or PH (proportional hazards) form if adjusted, which mitigates some of the mathematical issues raised by the EAG with the company's approach. Furthermore, recognising one modelling limitation does not justify introducing an additional, incompatible assumption; doing so compounds rather than resolves the underlying uncertainty.

Crucially, the EAG and the company acknowledge minimal difference in statistical fit according to AIC and BIC between the loglogistic and the Weibull curves. As a result, the company's primary argument in favour of the loglogistic curve selection over Weibull is that it aligns with clinical expert opinion across timepoints. The EAG has produced matching figures comparing the loglogistic and Weibull OS curves for pNET (shown in Figure 1) and epNET (shown in Figure 2).

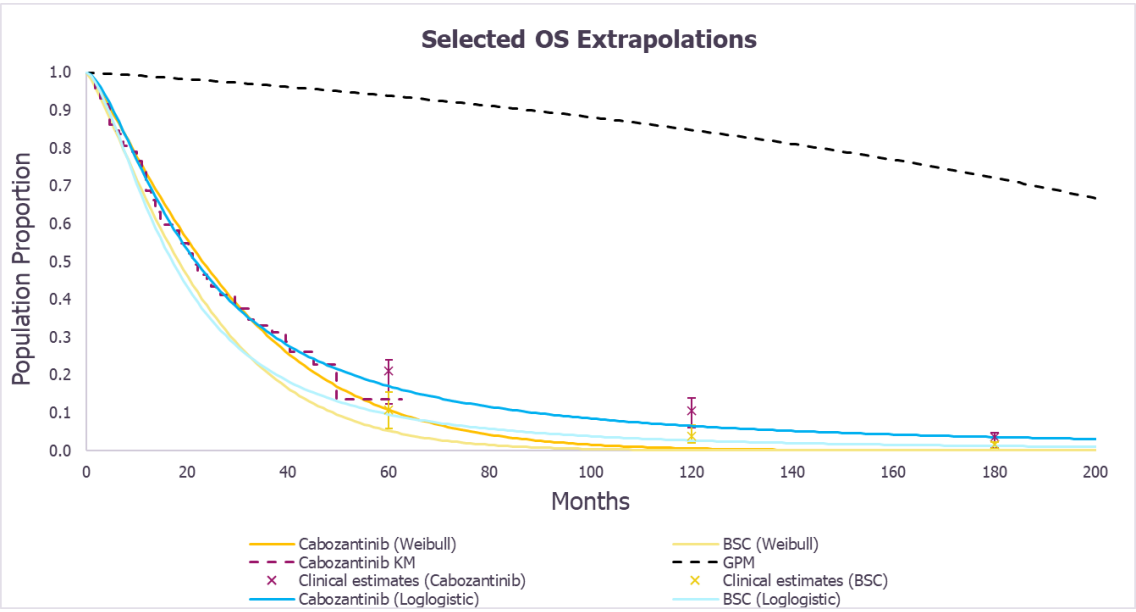
The EAG notes that in Figure 1 the BSC and the cabozantinib curves are overlapped in both the company's and the EAG's preferred use of curves (due to the use of a HR of 1 in both cases as discussed in Section 2.1), whereas for epNETs only the committee and EAG- preferred Weibull cabozantinib curve would overlap with the BSC curve (when a HR of 1 is assumed). This is not the case for the company's preferred IPCW HR and loglogistic curve, which translates a survival benefit with cabozantinib. Therefore, Figure 2 shows the IPCW loglogistic and IPCW Weibull BSC curves, compared with the loglogistic and Weibull cabozantinib curves, with the latter also representing the EAG's-preferred BSC curve.

Figure 1. Company versus committee-preferred OS extrapolations and clinician landmark estimates from the company – cabozantinib and BSC (pNETs)



*HR between BSC and cabozantinib in the pNET population in both the company and EAG base case is assumed to be 1
Abbreviations: BSC, best supportive care; KM, Kaplan-Meir; OS, overall survival.

Figure 2. Company versus committee-preferred OS extrapolations and clinician landmark estimates from the company– cabozantinib and BSC (epNETs) IPCW



*HR between BSC and cabozantinib in the epNET population in the EAG base case is assumed to be 1 using RPSFTM
Abbreviations: BSC, best supportive care; KM, Kaplan-Meir; OS, overall survival.

In Figure 1 it appears the committee/EAG preferred extrapolation aligns best with company's clinician predictions for the BSC arm, whilst the company assumptions align best with the clinical expert prediction for the cabozantinib curve. Given the BSC and the cabozantinib curves are overlapped in both the company's and the EAG's preferred use of curves (due to the use of a HR of 1

in both cases as discussed in Section 2.1), the choice of curve has no impact on the survival benefit estimated, but only on the absolute OS predicted, and thus has no impact on the ICER for pNETs. The committee's and EAG's preference align with the company's clinical expert expectations for the natural course of patients receiving BSC, where clinicians have substantial real-world experience.

For epNETs (Figure 2), the committee and EAG preference for RPSFTM over IPCW leads to using a HR of 1 (as discussed in Section 2.1), which means the EAG/committee preference would be for the BSC curve to be equivalent to cabozantinib (Weibull) for epNET. This is not the case for the company's preferred IPCW HR and loglogistic curve, which translates a survival benefit with cabozantinib. Therefore, for epNETs, the choice of curve has no impact on the survival benefit estimated for the EAG's preferred RPSFTM method, but does affect the survival benefit modelled by the company with the IPCW HR, depending on a Weibull or a loglogistic being used (Table 3).

Table 3. Clinician and committee/company preferred parametric landmark survival estimates for OS in cabozantinib and BSC (epNETs)

Treatment	Category	Curve	OS%		
			5	10	15
Cabozantinib	Clinician estimate	Lower plausible limit	12.3%	6.0%	1.0%
		Most likely	21.1%	10.5%	3.5%
		Upper plausible limit	24.0%	13.8%	4.7%
	Extrapolation	Weibull	10.4%	0.5%	0.0%
		Loglogistic	16.8%	6.5%	3.5%
BSC	Clinician estimate	Lower plausible limit	5.8%	2.0%	0.5%
		Most likely	10.8%	3.8%	1.5%
		Upper plausible limit	15.5%	6.8%	2.3%
	Extrapolation	Weibull (RPSFTM)	10.4%	0.5%	0.0%
		Loglogistic (IPCW)	9.4%	2.6%	1.2%

Abbreviations: BSC, best supportive care; epNET, extra-pancreatic neuroendocrine tumours; N/A, not applicable; pNET, pancreatic neuroendocrine tumours

The EAG notes that the expert elicitation process involved prompting clinicians with landmark survival estimates at six-month intervals from 6 to 24 months, based on crossover-adjusted BSC arm data. As highlighted previously, both the data cut-off and the choice of crossover adjustment method have substantial uncertainty. The EAG is concerned that the experts were not shown the more updated DCO and therefore that the evidence on which they made their recommendations is not that preferred by the committee or used in the company's and the EAG's base case analysis

Given the paramount uncertainty in the magnitude of the survival benefit associated with cabozantinib, the EAG preference is to use the Weibull curve for epNETs, where both the absolute survival and the survival benefit (estimated in the company's IPCW approach) is more conservative than using the loglogistic curve.

2.4 Subsequent treatments

The company has accepted the EAG preferences for using the CABINET subsequent treatments in the model. The EAG agrees with the company that maintaining subsequent treatment costs in line with the trial maintains consistency with the efficacy data.

The EAG notes that in its original report it supported the modelling of subsequent treatments from CABINET for the comparison of cabozantinib with BSC but did not include subsequent treatments in its exploratory analysis comparing cabozantinib with other treatments.

2.5 Concomitant treatment approach

The committee noted that the use of concomitant SSAs in clinical practice is uncertain but that the clinical experts broadly agreed that concomitant SSAs do not stop with treatment discontinuation for cabozantinib, as assumed in the company's original base case. The committee concluded that the EAG's approach of modelling concomitant SSAs from baseline until death was more appropriate.

The company accepted that assuming all patients discontinue initial concomitant SSAs on discontinuation of cabozantinib or BSC is unlikely to reflect UK clinical practice. However, noted that its clinical experts reported that SSA use is not always lifelong and some discontinuation is anticipated.

The company used clinical expert estimates of concomitant SSA use separately for functional and non-functional patients and then weighted these by the proportion of functional disease in CABINET (41.0% in epNETs; 36.5% in pNETs) to derive pooled estimates of baseline SSA use. The same weighting approach was applied to expert estimates of the proportion of baseline SSA users who discontinue SSAs before death, resulting in pooled discontinuation proportions of 52.7% for epNETs and 56.2% for pNETs. These pooled proportions were then used to back-calculate constant monthly SSA discontinuation rates such that the cumulative proportion discontinuing by the mean OS time

matched the expert estimates. This resulted in assumed discontinuation rates of 1.7% (cabozantinib) and 2.4% (BSC) per month in epNETs, and 1.1% per month in both treatment arms for pNETs.

The results of the company elicitation exercise are shown for pNET in Table 4 and for epNET in Table 5. As can be seen in these tables the clinician estimates have huge variation, likely reflecting clinically meaningful heterogeneity, both in absolute terms (i.e. the functional % of patients receiving concomitant SSAs varies from 10%-100%) and in relative terms (ratio of functional:non-functional patients receiving concomitant treatment varies from 2:1 to 1:1). The EAG notes that clinicians C and D did not provide discontinuation rates for SSA prior to death, with expert C stating that the numbers were too low to make an inference, and no reasons provided for D. Despite not providing a rate, clinician D did suggest that usage declines after progression and discontinuation is higher in non-functional patients.

Table 4. Clinical expert estimates of the proportion of pNET patients receiving concomitant SSA and the proportion of these patients who discontinue concomitant SSA (adapted from Table 1 from company validation document)

Clinician	Proportion of patients receiving concomitant SSA		Proportion of patients who discontinue concomitant SSA before death	
	Functional vs non-functional	Weighted average	Functional vs non-functional	Weighted average
A	Functional: 10% Non-functional: 5%	5.8%	Functional: 70% Non-functional: 70%	70.0%
B	Functional: 100% Non-functional: 50%	58.4%	Functional: 5% Non-functional: 50%	42.4%
C	Functional: 25% Non-functional: 25%	25%	-	-
D	Functional: 90% Non-functional: 50%	56.7%	-	-
Pooled total	-	36.5%	-	56.2%

*Weighted averages calculated assuming 32.5% functional patients as per CABINET trial

Abbreviations: SSA, somatostatin analogue

Table 5. Clinical expert estimates of the proportion of epNET patients receiving concomitant SSA and the proportion of these patients who discontinue concomitant SSA (adapted from Table 1 from company validation document)

Clinician	Proportion of patients receiving concomitant SSA		Proportion of patients who discontinue concomitant SSA before death	
	Functional vs non-functional	Weighted average	Functional vs non-functional	Weighted average
A	Functional: 20% Non-functional: 5%	9.9%	Functional: 70% Non-functional: 70%	70.0%

B	Functional: 100% Non-functional: 50%	66.3%	Functional: 5% Non-functional: 50%	35.4%
C	Functional: 25% Non-functional: 25%	25%	-	-
D	Functional: 90% Non-functional: 50%	63.0%	-	-
Pooled total	-	41.0%	-	52.7%

*Weighted averages calculated assuming 32.5% functional patients as per CABINET trial
Abbreviations: SSA, somatostatin analogue

In the EAG's view, the clinical validation exercise demonstrated substantial heterogeneity in expert opinions, making the pooled weighted averages uncertain. The EAG acknowledges that assuming SSA use continues until death is an oversimplification, as experts consistently noted that some patients discontinue therapy. Accordingly, the EAG has revised the base-case approach to incorporate the company's suggested discontinuation rate. The EAG notes that there is substantial uncertainty in the value used, however, there is no alternative source to estimate a rate of discontinuation. Given the uncertainty in the clinical experts' estimates for the proportion of patients receiving concomitant SSAs, the EAG prefers the use of CABINET data for the proportion of patients receiving concomitant SSAs in the model.

2.6 Consideration of the epNET population as a whole

The committee noted the low number of people with lung NETs and that the clinical experts explained that there is no clinical justification or biological reasoning for separating and analysing lung NETs independently. It concluded that the grouping of lung NETs with other epNETs was appropriate, unless stronger justification was provided for analysing lung NETs separately.

The company proposed that, if a general recommendation for the entire epNET population is not possible, the committee should instead consider a recommendation specifically for lung NET patients. The EAG supports the company's statements about the lack of treatment options for patients with lung NETs in comparison to other epNET patients, and notes that a positive recommendation would help to address the unmet need in this population.

The EAG acknowledges that the committee's preference was to consider the epNET population as a whole but emphasises the difference in effect estimates between the lung NET subgroup and other epNET patients. The latter suggest that the benefit associated with cabozantinib is numerically larger for PFS in lung NETs and that a statistically significant benefit is observed for OS with cabozantinib

whereas there is a non-statistically significant disadvantage for OS for cabozantinib in other types of epNETs. This is discussed in detail in the EAG's original report and presented in the company's subgroup analysis of PFS and OS (Table 6).

Table 6. Post-hoc analysis of PFS in the CABINET trial for the epNET cohort (Reproduced from Table 11 of the CS appendix and Table 15 of the clarification response)

Primary site (per OPEN enrolment form)	PFS HR (95% CI)	OS HR (95% CI)
epNET	[redacted]	[redacted]
GI	[redacted]	[redacted]
Lung/thymus	[redacted]	[redacted]
Unknown/other	[redacted]	[redacted]

Abbreviations: CI, confidence interval; epNET, extra-pancreatic neuroendocrine tumours; GI, gastrointestinal; HR, hazard ratio

2.7 Cabozantinib offers benefits that are not captured by the quality-adjusted life year (QALY) calculation

This is a point for the committee's consideration and so the EAG have no additional comment on this point.

2.8 The company takes issue with the description of the target population as "later-line"

The committee was aware that the trial population in CABINET had people who were at a later stage of the treatment pathway. The committee clarified that it could only make a decision based on the evidence presented to it. It noted that no evidence was provided for using cabozantinib as an earlier-line of treatment, thus concluded that the company's positioning of cabozantinib as a later-line treatment and its choice of comparator (that is, best supportive care) was appropriate.

The company accepted the committee's decision that the appropriate treatment for comparison with cabozantinib is BSC. However, they considered the committee's description of cabozantinib as a "later line" treatment to be overly simplistic, highlighting heterogeneity in the number of prior treatments before a patient becomes eligible for cabozantinib.

The EAG agrees with the committee's view on the positioning of cabozantinib and acknowledges the company's comments about the variation in number of prior treatments before a patient would

become eligible for cabozantinib. The EAG reiterates its original view that the population where BSC is the appropriate comparator is that of patients "who are heavily pretreated and reflect NHS patients who may receive cabozantinib as a fourth (or further) line of systemic treatment for pNETs (excluding prior SSAs); or epNET patients who may receive cabozantinib as a third (or further) line of systemic treatment, excluding prior SSAs". This is reflective of the average number of prior treatments received in CABINET for pNET and epNET patients.

2.9 Severity modifier in the epNET population

Results of the severity modifier calculations and consequent weighting for the company's updated analysis and the EAG updated analysis are shown below in Table 7.

The EAG agrees with the company that a severity modifier of 1.2 is appropriate to use in their base case epNET analysis.

Table 7. Summary features of QALY shortfall analysis: EAG and company base case

Population	Expected total QALE for the general population	Current treatment	Total QALE that people living with NETs would be expected to have with current treatment	Absolute QALE shortfall	Proportional shortfall	Severity weighting
Company base case						
pNETs	12.61	BSC	2.81	9.80	0.78	1.00
epNETs	11.61	BSC	1.57	10.04	0.86	1.20
EAG base case						
pNETs	12.61	BSC	2.32	10.29	0.82	1.00
epNETs (RPSFTM)	11.61	BSC	1.53	10.08	0.87	1.20
epNETs (IPCW)	11.61	BSC	1.24	10.37	0.89	1.20

Abbreviations: EAG, External Assessment Group; epNETs, extra-pancreatic neuroendocrine tumours; pNETs, pancreatic neuroendocrine tumours; NETs, neuroendocrine tumours, QALE, quality-adjusted life expectancy.

2.10 Summary of remaining key uncertainties

The EAG notes a number of key uncertainties relating to the company's response, which have been highlighted throughout its critique. The remaining uncertainties in the evidence provided by the company are included in this section.

2.10.1 Adverse events

The company provided no additional information or argument around their modelling of adverse events (AEs) but maintained their base case approach of applying AEs per cycle. As explained in the EAG original report, the company's approach, as applied in the model, underestimates AEs. As a result, the EAG maintains its preference that AEs are applied in the first cycle.

2.10.2 Health state utility values

The EAG noted in its original report that there was insufficient information about the EQ-5D data from the trial, rendering the use of HRQoL data from CABINET too uncertain. After DG, the company provided further details about the utility analysis. Given the committee's usual preference for the use of utilities from the pivotal trial, the EAG has assessed each of the original requests made in the EAG report against the new evidence provided by the company in Table 8.

Table 8. Issues from EAG report resolved by appendix 5 of company response

Request	Resolved?
Details for the rationale for drop-out and missing data from the HRQoL sub-study;	Partially resolved. Missing data section describes data inclusion criteria, not the rationale for or pattern of missingness in the HRQoL sub-study. Summary section describes that progressed disease (PD) data were not collected by protocol, meaning there was systematic missingness in that health state.
Updated regression analyses (simplified and full models) including terms for treatment and/or AEs;	Mostly resolved. Regression analysis has been provided (both simplified and full models) alongside fitted coefficients and confidence intervals. AEs were not included in the analysis. A term for treatment-specific HSUV produced a minimal none statistically significant difference. Goodness of fit statistics (AIC, ME, MSE, RMSE and R^2) have been referenced as part of company decision making but not provided. Diagnostic plots have not been provided.
Fitted coefficients, estimated p-values, goodness-of-fit statistics, and diagnostic plots for the updated regression analyses;	
Full justification for selection of covariates in the full regression model;	Resolved. This has been provided in a summary table.
Justification for use of a linear MMRM rather than a generalised linear model.	Not resolved.

Abbreviations: AE, adverse events; HR, hazard ratio; HRQoL, health related quality of life; HSUV, health state utility values; MMRM, mixed model for repeated measures; PD, progressed disease.

Whilst some issues remain unresolved the EAG believes sufficient information has been provided to justify using the HRQoL study to inform the progression-free health state utility. In the pNET population this approach involves using the PFS utility value from the CABINET data, with Swinburn

et al decrements applied to estimate the progressed disease (PD) utility; and in the epNET population the CABINET PFS utility value data, with a utility decrement from RADIANT-4 applied to generate the PD utility.

2.10.3 AE disutilities (hypertension, embolism)

The company provided no additional information or argument around the assumptions made for the disutilities of hypertension and embolism events but maintained their base case disutility for hypertension and embolism. As explained in the EAG original report, the EAG believes these values are inappropriate. As a result, the EAG maintains its preference for the base case disutilities used in the EAG original report.

2.10.4 Resource use

The company maintained their base case resource use from Casciano *et al*. (2013) as the clinical validation undertaken by the company confirmed it to match clinical practice. The EAG maintains that this is not an appropriate source for the reasons laid out in the EAG original report. The EAG maintains its preference for aligning with TA449 and TA539[9, 10] using Mujica-Mota *et al*. 2018[11] in their base case.

2.10.5 Dose holds

The EAG accepts the company's case for dose holds and has adopted it into the EAG's base case.

3 Updated cost-effectiveness results and additional scenarios

3.1 Company's cost effectiveness results

The company's updated cost-effectiveness results are shown in Table 9 for pNETs and

Interventions	Total Costs (£)	Total LY	Total QALYs	Incremental costs (£)	Incremental LYs	Incremental QALYs	ICER (£/QALY)
Deterministic results							
Cabozantinib	[redacted]	4.60	[redacted]	-	-	-	-
BSC	[redacted]	4.60	[redacted]	[redacted]	0.00	[redacted]	£144,912
Probabilistic results							
Cabozantinib	[redacted]	4.61	[redacted]	-	-	-	-
BSC	[redacted]	4.49	[redacted]	[redacted]	0.12	[redacted]	£91,420

Abbreviations: BSC, best supportive care; ICER, incremental cost-effectiveness ratio; LY, life year; QALY, quality-adjusted life-year

Table 10 for epNETs. The EAG notes that the company's pNETs analysis uses a HR of 1 for OS between cabozantinib and BSC, which is the main driver of the ICER.

Table 9. Company's base case results (pNET)

Interventions	Total Costs (£)	Total LY	Total QALYs	Incremental costs (£)	Incremental LYs	Incremental QALYs	ICER (£/QALY)
Deterministic results							
Cabozantinib	[redacted]	4.60	[redacted]	-	-	-	-
BSC	[redacted]	4.60	[redacted]	[redacted]	0.00	[redacted]	£144,912
Probabilistic results							
Cabozantinib	[redacted]	4.61	[redacted]	-	-	-	-
BSC	[redacted]	4.49	[redacted]	[redacted]	0.12	[redacted]	£91,420

Abbreviations: BSC, best supportive care; ICER, incremental cost-effectiveness ratio; LY, life year; QALY, quality-adjusted life-year

Table 10. Company's base case results (epNET)

Interventions	Total Costs (£)	Total LY	Total QALYs	Incremental costs (£)	Incremental LYs	Incremental QALYs	ICER (£/QALY)
Deterministic results							
Cabozantinib	[redacted]	2.93	[redacted]	-	-	-	-

BSC	[redacted]	2.14	[redacted]	[redacted]	0.79	[redacted]	£9,013
Probabilistic results							
Cabozantinib	[redacted]	2.95	[redacted]	-	-	-	-
BSC	[redacted]	2.15	[redacted]	[redacted]	0.80	[redacted]	£8,870

Abbreviations: BSC, best supportive care; ICER, incremental cost-effectiveness ratio; LY, life year; QALY, quality-adjusted life-year

3.2 EAG preferred assumptions

The EAG's cumulative preferred modelling assumption results are shown in Table 11 for pNETs and Table 12 for epNETs, respectively. The final EAG base case values are shown in Table 13 and Table 14 for pNETs and epNETs, respectively. Table 14 also shows the results with the EAG's base case assumptions and the IPCW HR applied, for the committee's consideration.

For pNETs, the EAG's deterministic ICER is broadly similar to the company's deterministic ICER (£116,802 vs £144,912, respectively). The EAG notes that the EAG's probabilistic ICER amounts to £83,629 per QALY gained, which reflects a paramount level of uncertainty in the pNET results. This variation is due to a small incremental QALY difference leading to a bigger impact from variations in inputs.

For epNETs, the EAG's deterministic ICER amounts to £90,297, compared to the company's deterministic ICER of £9,013. The main driver of these results is the adjustment method used to account for crossover. When the EAG uses the IPCW HR (instead of the base case RPSFTM HR), the EAG deterministic ICER amounts to £18,637. The difference in these ICERs is attributable to the assumption of a survival benefit with cabozantinib (IPCW) or an assumption of no survival benefit (RPSFTM). The EAG reiterates its concern around the uncertainty of using either the RPSFTM or the IPCW in light of the small sample sizes in CABINET.

Table 11. EAG's cumulative preferred model assumptions pNET (deterministic results)

Scenario number	Preferred assumption	Cumulative INHB	Cumulative INMB (£)	Cumulative ICER vs BSC (£)
0	Company base case	-0.51	-£15,194	£144,912
1	EAG choice of OS curves (Weibull and RPSFTM* HR)	-0.51	-£15,194	£144,912

2	Patients receiving CCT treatment based on CABINET	-0.51	-£15,156	£144,624
3	AEs applied 1st cycle	-0.50	-£15,128	£146,255
4	CABINET HSUV for PFS	-0.50	-£14,876	£137,378
5	Alternate AE disutilities	-0.50	-£14,873	£137,300
6	EAG alternate disease management costs	-0.40	-£12,032	£116,802

*RPSFTM does not impact results as the HRs for the IPCW and RPSFTM are limited to a HR of 1

Abbreviation: AE, adverse event; BSC, best supportive care; CCT, concomitant; EAG, economic assessment group; HSUV, health state utility value; ICER, incremental cost effectiveness ratio; INHB, incremental net health benefit; INMB, incremental net monetary benefit; OS, overall survival; PF, progression free; RPSFTM, Rank Preserving Structural Failure Time Model.

Table 12. EAG's cumulative preferred model assumptions epNET (deterministic results)

Scenario number	Preferred assumption	Cumulative INHB	Cumulative INMB (£)	Cumulative ICER vs BSC (£)
0	Company base case	0.49	£14,808	£9,013
1	RPSFTM crossover method	-0.08	-£2,345	£96,289
2	EAG choice of OS curves (Weibull)	-0.07	-£2,133	£80,240
3	Patients receiving CCT treatment based on CABINET	-0.07	-£1,979	£76,607
4	AEs applied 1st cycle	-0.07	-£2,075	£79,624
5	CABINET HSUV for PFS	-0.07	-£2,075	£79,624
6	Alternate AE disutilities	-0.07	-£2,091	£80,697
7	EAG alternate disease management costs	-0.08	-£2,488	£90,297

Abbreviation: AE, adverse event; BSC, best supportive care; CCT, concomitant; EAG, economic assessment group; HSUV, health state utility value; ICER, incremental cost effectiveness ratio; INHB, incremental net health benefit; INMB, incremental net monetary benefit; OS, overall survival; PF, progression free; RPSFTM, Rank Preserving Structural Failure Time Model.

Table 13. EAG's base case results (pNET)

Interventions	Total Costs (£)	Total LY	Total QALYs	Incremental costs (£)	Incremental LYs	Incremental QALYs	ICER (£/QALY)
Deterministic results							
Cabozantinib	[redacted]	3.50	[redacted]	-	-	-	-
BSC	[redacted]	3.50	[redacted]	[redacted]	0.00	[redacted]	£116,802
Probabilistic results							
Cabozantinib	[redacted]	3.54	[redacted]	-	-	-	-
BSC	[redacted]	3.45	[redacted]	[redacted]	0.09	[redacted]	£83,604

Abbreviations: BSC, best supportive care; ICER, incremental cost-effectiveness ratio; LY, life year; QALY, quality-adjusted life-year

Table 14. EAG's base case results (epNET)

Interventions	Total Costs (£)	Total LY	Total QALYs	Incremental costs (£)	Incremental LYs	Incremental QALYs	ICER (£/QALY)
RPSFTM							
Deterministic results							
Cabozantinib	[redacted]	2.31	[redacted]	-	-	-	-
BSC	[redacted]	2.31	[redacted]	[redacted]	0.00	[redacted]	£90,297
Probabilistic results							
Cabozantinib	[redacted]	2.32	[redacted]	-	-	-	-
BSC	[redacted]	2.31	[redacted]	[redacted]	0.00	[redacted]	£80,857
Scenario analysis - IPCW							
Deterministic results							
Cabozantinib	[redacted]	2.31	[redacted]	-	-	-	-
BSC	[redacted]	1.86	[redacted]	[redacted]	0.45	[redacted]	£18,637
Probabilistic results							
Cabozantinib	[redacted]	2.32	[redacted]	-	-	-	-
BSC	[redacted]	1.84	[redacted]	[redacted]	0.48	[redacted]	£17,704

Abbreviations: BSC, best supportive care; ICER, incremental cost-effectiveness ratio; LY, life year; QALY, quality-adjusted life-year

4 References

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Cabozantinib for treating advanced neuroendocrine tumours that have progressed after systemic treatment [ID6474]

Addendum to EAG response to draft guidance

November 2025

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1 EAG response to company crossover argument

In the EAG report the preferred method for adjusting for placebo arm patients who crossed over was Rank Preserving Structural Failure Time Model (RPSFTM) whilst the company preference is for Inverse Probability of Censoring Weighting (IPCW). The company has submitted arguments against the EAG position which are addressed in this document.

The EAG's position is summarised as follows:

- The EAG considers that no established approach to crossover analysis is ideal, due to the small sample sizes and limited OS events in the CABINET trial; to the EAG's knowledge there has been very limited validation of these methods for such small sample sizes. However, using trial OS data directly without adjusting for crossover would *a priori* place cabozantinib at an unfair disadvantage, so crossover analysis should nonetheless be attempted.
- The EAG considers that the RPSFTM methodology is a reasonable approach that should be considered, especially as it gives a more conservative result than IPCW. Although it is associated with some weaknesses (discussed in Section 1.4 below), the EAG considers that these are no more concerning than the weaknesses associated with the IPCW method (see Section 1.3 below in particular).
- Overall, the EAG notes that the results for both the RPSFTM and IPCW methods are associated with uncertainty, and there is considerable overlap between the 95% confidence intervals: With IPCWs HR being [redacted] and RPSFTMs HR being [redacted]
- While it is plausible that cabozantinib results in improved OS compared to best supportive care (BSC), given the benefits in progression-free survival, the magnitude of this benefit cannot be determined with confidence, given the uncertainty resulting from crossover analyses. Therefore, the EAG's preference is to model a hazard ratio of 1 for OS.

The EAG has responded to each of the company's arguments in more detail in the following sections.

1.1 The key IPCW assumptions were satisfied

The company made the case that the key assumptions of positivity and no unmeasured confounders were met. Positivity means that every patient, for any combination of confounders, has a nonzero probability of both switching and not switching treatment. The company states this is met as no

covariate perfectly predicted switching/not switching. The EAG accepts that the positivity assumption has likely been met.

The company suggest there is no evidence of unmeasured confounders with covariates derived through clinician input resulting in a model that included all major prognostic factor. The EAG considers that this is a reasonable but untestable claim.

1.2 The IPCW weights were stable across cohorts and data cuts

The company provided a box plot showing log-transformed stabilised untruncated weights for IPCW remained stable over time, as shown in Figure 1. The median log(weight) remained close to zero, with narrow interquartile ranges and no extreme outliers, demonstrating that most weights were centred around 1 and that reweighting was modest. The slight tendency for weights to fall below 1 (log(weight) < 0) simply reflects that most patients who remained uncensored had a lower model-predicted probability of switching. The absence of large or erratic weights confirms that the positivity assumption was upheld.

Figure 1. Boxplot of stabilised IPCW weights in the placebo arm (not truncated): epNET cohort (updated DCO) (copy of figure 10 from company response to draft guidance)

The EAG accepts the additional evidence provided as showing the stability of weights over time.

1.3 IPCW performs well regardless of sample size or proportion of switchers

While the company cites Latimer *et al*. 2020[1] to support that IPCW performs reliably when weights are stable and the positivity assumption holds, this evidence is based on simulation studies with substantially larger effective sample sizes and event counts than observed in CABINET. In the pNET and epNET cohorts, only [redacted] patients respectively crossed over, despite the inclusion of 12 covariates in the censoring model. This results in a very low number of switching events per variable, increasing the risk of model overfitting and unstable estimation of switching probabilities, even if the observed weight distribution appears well behaved. The reported maximum weights ([redacted]) and proportions relative to the weighted group ([redacted]) are reassuring indicators of numerical stability but do not address the underlying limitation of sparse data informing the weight model. Therefore, while diagnostic data for the IPCW implementation are not concerning, the small number of switchers relative to model complexity means the analysis is subject to considerable statistical uncertainty, and the results should be interpreted with caution despite the absence of extreme weights.

1.4 IPCW results were clinically plausible while results of RPSFTM lacked clinical plausibility

The issue of clinical plausibility is discussed in greater detail in the primary EAG response. As noted there, IPCW still results in what the company considers "clinically implausible" results in the pNET population (i.e., a hazard ratio greater than 1, suggesting greater OS benefit for the placebo arm than the cabozantinib arm); therefore, the company's argument that the RPSFTM methodology should be rejected on the grounds of clinical implausibility is at odds with the pNET data which shows no benefit regardless of crossover adjustment used. In addition, the EAG considers that the results of the company's expert elicitation exercise appear to be insufficient to support the company's argument, since prior to eliciting long-term survival estimates, experts were presented with landmark survival data at six month increments from six to 24 months from the CABINET trial, already adjusted for crossover for BSC. Therefore, the results of the expert elicitation are not reflective of the latest data cut from CABINET and may be inherently biased in favour of long-term values reflective of the IPCW approach depending on the crossover analysis shown.

1.5 The EAG did not provide sufficient justification of the benefits of RPSFTM over IPCW

The company stated that the EAG did not provide sufficient justification for preferring RPSFTM. In particular, the company stated that Latimer *et al.* 2024[2] made the case that RPSFTM becomes less reliable when the ITT hazard ratio is close to 1 because there is little observed difference in survival between treatment arms, leaving the model with too little information to identify the acceleration factor that represents the treatment effect. As a result, the method may estimate an acceleration factor of 0 and produce unstable hazard ratios, or potentially clinically implausible results (e.g., hazard ratios favouring placebo overactive treatment) regardless of any true underlying benefit.

This is true; however, model-based methods such as IPCW can yield spurious differences because the population being reweighted consists only of patients who remained on their assigned treatment and were therefore not fully representative of all randomised participants. As a result, any apparent effects should be interpreted cautiously and in the context of their statistical significance. Furthermore, the EAG notes that the company has accepted OS hazard ratios greater than 1 in the pNETs population based on IPCW analyses rather than rejecting this approach on the grounds of clinical plausibility.

1.6 The two-stage estimation method is not feasible

In the draft guidance document, the committee requested to see the results of two-stage estimation (TSE) as the company had stated that this analysis had been performed. The company stated in response that this method is unfeasible as the TSE method models post-progression survival using progression as a secondary baseline, requiring sufficient numbers of switchers and post-progression deaths to estimate stable, covariate-adjusted effects. In CABINET, [redacted] OS events occurred among switchers in both the pNET and epNET cohorts, making it impossible to fit a reliable model. Moreover, the updated dataset lacked progression information. The EAG accepts this explanation for why the TSE would not produce credible results.

1.7 Subsequent treatments may have confounded treatment effects in the August 2024 DCO, which can be addressed using IPCW

In order to address the potential exclusion of subsequent treatments the company extended the IPCW analysis to both trial arms, modelling the probability of remaining untreated with any subsequent systemic therapy (including crossover in the placebo arm and post-cabozantinib

therapies in the cabozantinib arm). This created a weighted population representing outcomes if no patient in either arm had received further systemic treatment, producing more favourable hazard ratios for cabozantinib in both the pNET and epNET populations. As stated previously the EAG preference is to include subsequent treatments in the economic analysis, so it is not appropriate to use this adjusted data. This method is significantly more uncertain than applying subsequent treatment costs. In addition, as treatment switching is more common in the placebo arm the non-switching group being reweighted are imbalanced which may be a source of bias for results.

2 Conclusion

The company presented a coherent case for IPCW as the preferred crossover-adjustment method, highlighting stable weights, the absence of clear positivity violations, and clinically plausible results. However, despite technically well-behaved weights, the IPCW model remains highly assumption-dependent and based on sparse switching data, leaving considerable uncertainty around the estimated treatment effect. The resulting hazard ratios for OS are not statistically significant and remain compatible with the EAG's preferred approach of modelling an OS hazard ratio of 1 between cabozantinib and BSC.

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