Cabozantinib for previously treated advanced hepatocellular carcinoma (review of TA582). A Technology Appraisal

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Declared competing interests of the authors

None of the authors have any conflicts of interest to declare.

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Rider on responsibility for report

The views expressed in this report are those of the authors and not necessarily those of the NIHR Evidence Synthesis Programme. Any errors are the responsibility of the authors.

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Contributions of authors

Ruth Wong critiqued the company's search strategy. Katy Cooper summarised and critiqued the clinical effectiveness data reported within the company's submission. Rebecca Harvey critiqued the statistical aspects of the submission. Paul Tappenden critiqued the company's health economic analyses. All authors were involved in drafting and commenting on the final report.

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CONTENTS

List of Tables

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List of Figures

List of Boxes

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Abbreviations

AE	Adverse event
AFP	Alpha-fetoprotein
AIC	Akaike Information Criterion
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
AUC	Area under the curve
BCLC	Barcelona Clinic Liver Cancer
BIC	Bayesian Information Criterion
BNF	British National Formulary
BSC	Best supportive care
CDF	Cancer Drugs Fund
CI	Confidence interval
cPAS	Comparator Patient Access Scheme
CR	Complete response
CRUK	Cancer Research UK
CS	Company's submission
CSR	Clinical Study Report
ECOG	Eastern Cooperative Oncology Group
EMA	European Medicines Agency
EPAR	European Public Assessment Report
EQ-5D	Euroqol 5-Dimensions
EQ-5D-5L	Euroqol 5-Dimensions 5-Level
ERG	Evidence Review Group
ESS	Effective sample size
FTA	Fast-Track Appraisal
HCC	Hepatocellular carcinoma
HR	Hazard ratio
HRQoL	Health-related quality of life
ICER	Incremental cost-effectiveness ratio
IPD	Individual patient data
ITC	Indirect treatment comparisons
ITT	Intention-to-treat
LOR	Log odds ratio
MAIC	Matching-adjusted indirect comparison
mg	Milligram
mRECIST	Modified Response Evaluation Criteria In Solid Tumours
N	Number
NA	Not applicable
NASH	Non-alcoholic steatohepatitis
NHS	National Health Service
NHSE	NHS England
NICE	National Institute for Health and Care Excellence
NR	Not reported
OR	Odds ratio
ORR	Objective response rate
OS	Overall survival
PAS	Patient Access Scheme
PD	Progressive disease
PFS	Progression-free survival
PH	Proportional hazards
PPES	Palmar-plantar erythrodysaesthesia syndrome
PR	Partial response
PS	Performance status

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PSSRU	Personal Social Services Research Unit
QALY	Quality-adjusted life year
RCT	Randomised controlled trial
RDI	Relative dose intensity
RECIST	Response Evaluation Criteria In Solid Tumours
SA	Sensitivity analysis
SAE	Serious adverse event
SmPC	Summary of Product Characteristics
TA	Technology Appraisal
TACE	Transarterial chemoembolisation
TKI	Tyrosine kinase inhibitor
ToT	Time on treatment
TTD	Time to treatment discontinuation
TTP	Time to progression
VAS	Visual analogue scale

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1. SUMMARY OF THE ERG'S VIEW OF THE COMPANY'S FTA CASE

The company is seeking a positive NICE recommendation for cabozantinib in the same indication as the existing NICE recommendation for regorafenib (in TA555), that is, for the treatment of advanced unresectable hepatocellular carcinoma (HCC) in adults who have had sorafenib, only if they have Child–Pugh grade A liver impairment and an Eastern Cooperative Oncology Group (ECOG) performance status (PS) of 0 or 1. This intended positioning means that the target population for cabozantinib is narrower than the patient population defined in the final scope issued by the National Institute for Health and Care Excellence (NICE) and the full marketing authorisation for cabozantinib. The company's submission (CS) presents clinical evidence for cabozantinib and a single comparator – regorafenib; no comparison has been made against best supportive care (BSC) or any other active therapy. Cabozantinib and regorafenib are both orally administered tyrosine kinase inhibitors (TKIs); whilst these drugs are part of the same class, there are some differences in their molecular targeting profiles (further details are provided in Sections 2.4 and 2.5). The ERG's clinical advisors believe that regorafenib is the most appropriate comparator for cabozantinib. The clinical advisors also commented that the target population is small and that whilst the trial of regorafenib (RESORCE) was undertaken in a second-line population, the positive NICE recommendation for atezolizumab plus bevacizumab in the first-line setting means that regorafenib is now mostly used at third-line in people who are able to receive atezolizumab plus bevacizumab, although some patients will receive regorafenib as second-line therapy.

The CS includes a series of indirect treatment comparisons (ITCs) of cabozantinib versus regorafenib using the Bucher methodology and anchored and unanchored matching-adjusted indirect comparison (MAIC) approaches, informed by data from the pivotal trials of cabozantinib and regorafenib for HCC (CELESTIAL and RESORCE). The ITCs for progression-free survival (PFS) or overall survival (OS) indicate statistically non-significant differences in clinical outcomes between the regimens. The ITCs of safety endpoints indicate statistically non-significant differences between the regimens for individual adverse events (AEs), except for the odds of diarrhoea which was statistically significantly higher for the cabozantinib group, based on an unanchored MAIC. The CS also includes a cost-comparison analysis which suggests that, if clinical equivalence is assumed, the cost of cabozantinib (including a confidential Patient Access Scheme [PAS] discount) is less than the cost of regorafenib (excluding its comparator PAS discount).

The ERG believes that the company's case for considering cabozantinib as a Fast Track Appraisal (FTA) may not be appropriate for the following reasons:

- There is uncertainty around the treatment effect between cabozantinib and regorafenib, including the assumption of equivalence of the two regimens:

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- In CELESTIAL, the OS benefit of cabozantinib over placebo was statistically significant in the second-line subgroup but not in the third-line subgroup. It was not possible to conduct ITCs in the third-line subgroup because the RESORCE trial was restricted to second-line, but regorafenib is now used in clinical practice in both second- and third-line.
- Whilst the company's ITCs consistently indicate statistically non-significant differences in PFS, OS and AEs between the regimens, the Bucher ITCs and the anchored MAICs produce point estimates of relative treatment effects which favour cabozantinib for PFS, but which favour regorafenib for OS. Both the company and the ERG prefer the anchored MAICs; however, there remain some concerns regarding the comparability of the placebo plus BSC arms of CELESTIAL and RESORCE, which means that there is uncertainty around the reliability of the results of this analysis.
- Although the ITCs for AEs indicate no statistically significant differences in individual AEs except for diarrhoea, the ERG's clinical advisors commented that cabozantinib is more toxic than regorafenib. This view is also suggested in the European Public Assessment Report (EPAR) for cabozantinib issued by the European Medicines Agency (EMA) and is likely reflected in the available Euroqol 5-Dimensions 5-Level (EQ-5D-5L) data from CELESTIAL and in the higher frequency of dose reductions in the intervention arm of CELESTIAL compared to RESORCE.

- As part of their clarification response, the company developed a partitioned survival model using PFS, OS and EQ-5D data from CELESTIAL and relative treatment effect estimates from the company's anchored and unanchored MAICs. The model was used to estimate incremental quality-adjusted life years (QALYs) for cabozantinib versus regorafenib in the second-line setting. The analyses which use relative treatment effects on PFS and OS from the anchored MAICs indicate that, excluding any toxicity-related disutilities, cabozantinib is expected to generate fewer QALYs compared with regorafenib. The company's clarification response argues that given the distribution of incremental QALY losses, there is *"no meaningful"* difference between the groups. However, the ERG notes that decisions should be made on the basis of the expectation of the mean and that the expected ICER for cabozantinib versus regorafenib would lie in the North-West or South-West quadrant, depending on the discounted prices of the products. The ERG is unsure whether the magnitude of the company's predicted incremental QALY losses are sufficient to preclude the appraisal from proceeding under the FTA route.
- The expected difference in costs for cabozantinib and regorafenib is dependent on the inclusion of PAS discounts for each product; the results of the company's cost comparison analyses including both relevant discounts cannot be reported here. These are provided in a separate confidential appendix to this report.

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2. ERG'S CRITIQUE OF THE COMPANY'S DECISION PROBLEM

2.1 Introduction

The company's submission[1] (CS) presents evidence relating to the clinical effectiveness and cost of cabozantinib for adult patients with previously treated advanced unresectable hepatocellular carcinoma (HCC). The company has proposed that cabozantinib should be appraised by the National Institute for Health and Care Excellence (NICE) under its Fast Track Appraisal (FTA) process.

2.2 Health condition

The CS[1] provides a short but accurate description of the underlying health condition. HCC is the most common form of primary liver cancer which occurs predominantly in patients with underlying chronic liver disease and cirrhosis, and is typically associated with viral hepatitis, excessive alcohol consumption, non-alcoholic steatohepatitis and haemochromatosis.[2] Based on data for the UK from 2016-2018 reported by Cancer Research UK (CRUK), there are over 6,200 new cases of liver cancer each year and around 5,600 deaths are caused by liver cancer.[3, 4] The prognosis of advanced HCC is poor with age-standardised net survival rates at 1 year and 5 years of 38.1%, and 12.7%, respectively.[4]

2.3 Current pathway for HCC and proposed positioning of cabozantinib

The company's view of the current pathway for advanced HCC and the proposed positioning of cabozantinib is shown in Figure 1. Existing NICE recommendations for treatments for advanced HCC are summarised in Table 1. The company is seeking a positive recommendation for cabozantinib in the same indication as regorafenib, which was previously appraised in NICE Technology Appraisal (TA) Number 514 (TA514) and later in TA555. In 2019, NICE recommended regorafenib as an option for treating advanced unresectable HCC in adults who have had sorafenib, only if they have Child–Pugh grade A liver impairment and an Eastern Cooperative Oncology Group (ECOG) performance status (PS) of 0 or 1, and if the company provides it according to the agreed commercial arrangement.[5] The final NICE scope lists the population for the appraisal as *"Adults with advanced hepatocellular carcinoma who have had sorafenib."* If the company's target population is restricted to the same population as the NICE recommendation for regorafenib, this will be narrower than the populations defined in both the NICE scope and the marketing authorisation for cabozantinib. The company's clarification response[6] (question A1) indicates that the company would support a recommendation without restriction by Child-Pugh grade. However, the company acknowledges that only one patient in CELESTIAL[7] had Child-Pugh grade B disease and the ERG notes that the company's clinical and cost comparisons are restricted to a population in whom regorafenib is used. No comparison has been made against best supportive care (BSC) or any other active treatment (see Section 2.4).

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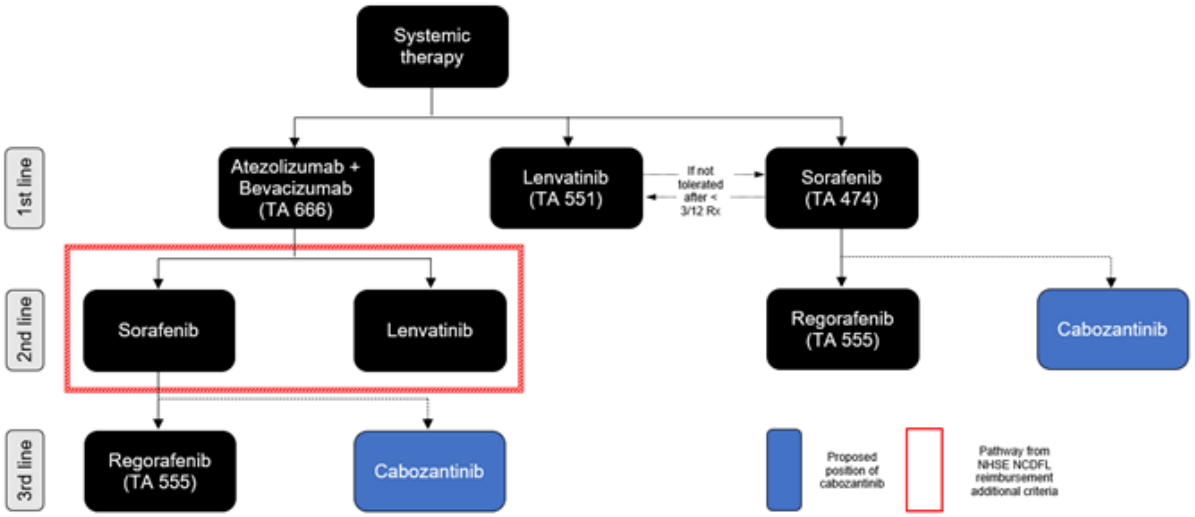
The ERG's clinical advisors agreed that the company's view of the pathway reflects current practice. The clinical advisors commented that it is appropriate to consider cabozantinib in the same indication as that for regorafenib, as this reflects the population of patents in whom the drug would be used in practice and because it reflects the population of the CELESTIAL trial.[7] They further commented that atezolizumab plus bevacizumab has become the preferred first-line treatment for patients who are able to receive it, with sorafenib and lenvatinib now more commonly being used as second-line treatments. As regorafenib is only licensed for use after sorafenib, this treatment option is now mostly used at third-line in people who are able to receive atezolizumab plus bevacizumab, although some patients will receive regorafenib as second-line therapy. The ERG's clinical advisors commented that because atezolizumab plus bevacizumab is the preferred treatment of choice, and survival prospects in advanced HCC are poor, few patients reach third-line treatment. As such, the overall target population for cabozantinib is small. Both clinical advisors commented that they do not frequently use regorafenib.

Figure 1: Current systemic therapy treatment pathway in UK clinical practice as per NICE and Cancer Drugs Fund recommendations (reproduced from CS, Figure 2)



NCDFL - National Cancer Drug Fund List; NHSE - National Health Service England; NICE - National Institute for Health and Care Excellence; Rx – prescription

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Table 1: Previous NICE recommendations for treatments for HCC

Technology	Year	Recommendation
Atezolizumab plus bevacizumab (TA666)[8]	2020	Recommended as an option for treating advanced or unresectable HCC in adults who have not had previous systemic treatment, only if: • they have Child-Pugh grade A liver impairment and an ECOG PS of 0 or 1 and • the company provides it according to the commercial arrangement.
Lenvatinib (TA551)[9]	2018	Recommended as an option for untreated, advanced, unresectable HCC in adults, only if: • they have Child–Pugh grade A liver impairment and an ECOG PS of 0 or 1 and • the company provides it according to the commercial arrangement
Sorafenib (TA474)[10]	2017	Recommended as an option for treating advanced HCC only for people with Child-Pugh grade A liver impairment, only if the company provides sorafenib within the agreed commercial access arrangement
Regorafenib (TA555)[5]	2019	Recommended as an option for treating advanced unresectable HCC in adults who have had sorafenib, only if: • they have Child–Pugh grade A liver impairment and an ECOG PS of 0 or 1 and • the company provides it according to the commercial arrangement.

TA - Technology Appraisal; HCC - hepatocellular carcinoma; ECOG - Eastern Cooperative Oncology Group; PS - performance status

2.4 Intervention

The intervention considered in the CS[1] is cabozantinib given as monotherapy. Cabozantinib is a multi-targeted inhibitor of receptor tyrosine kinases (RTKs) that potently inhibits several RTKs known to influence tumour growth, metastasis and angiogenesis, including MET, VEGFR2 and AXL.[11] Cabozantinib is available as tablets which are taken orally. The recommended daily dose of cabozantinib is 60mg per day. The marketing authorisation issued by the European Medicines Agency (EMA) is for cabozantinib as monotherapy for the treatment of HCC in adults who have previously been treated with sorafenib. The Summary of Product Characteristics (SmPC) for cabozantinib states that *"treatment should continue until the patient is no longer clinically benefiting from therapy or until unacceptable toxicity occurs."*[11] Cabozantinib is available in packs of 30 tablets at doses of 20mg, 40mg or 60mg (30 days' supply). The NHS indicative price for each pack of cabozantinib is £5,143, irrespective of the dose.[12] A Patient Access Scheme (PAS) discount is available for cabozantinib, resulting in a discounted cost per pack of [redacted] ([redacted] discount from the list price).

2.5 Comparator

The CS[1] includes a single comparator – regorafenib given as monotherapy. Regorafenib is a tumour deactivation agent that potently blocks multiple protein kinases, including kinases involved in tumour angiogenesis (VEGFR1, -2, -3, TIE2), oncogenesis (KIT, RET, RAF-1, BRAF, BRAFV600E), metastasis (VEGFR3, PDGFR, FGFR) and tumour immunity (CSF1R).[13] Regorafenib is available as tablets which are taken orally. The recommended daily dose of regorafenib is 160mg (4 x 40mg tablets)

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with treatment taken for 3 weeks followed by 1 week off treatment. The EMA marketing authorisation for regorafenib is as monotherapy for the treatment of adult patients with HCC who have been previously treated with sorafenib. As with cabozantinib, the SmPC for regorafenib[13] states that treatment should continue as long as benefit is observed or until unacceptable toxicity occurs. Regorafenib is available in packs of 84 tablets at a dose of 40mg (28 days' supply). The NHS indicative price for each pack is £3,744.[12] A comparator Patient Access Scheme (cPAS) discount is available; details of this discount can be found in a separate confidential appendix to this ERG report.

The final NICE scope[14] includes a second comparator – BSC. However, BSC is not considered within the CS as it has not been recommended by NICE. The ERG agrees that BSC is not a relevant comparator for the population in whom regorafenib would otherwise be used.

2.6 Outcomes

The final NICE scope[14] lists six outcomes:

- Overall survival (OS)
- Progression-free survival (PFS)
- Response rates
- Time to treatment discontinuation (TTD)
- Adverse effects of treatment
- Health-related quality of life (HRQoL).

The pivotal study of cabozantinib for HCC is the CELESTIAL trial.[7] The pivotal study of regorafenib for HCC is the RESORCE trial.[15] The CS[1] reports data from CELESTIAL on PFS, OS, objective response rate (ORR), time on treatment and adverse events (AEs). The CS does not report data on TTD or HRQoL from CELESTIAL. The CS reports indirect treatment comparisons (ITCs) using data from the CELESTIAL and RESORCE studies[7, 15] for PFS, OS and AEs; these analyses are summarised and critiqued in Section 3 of this report. The company's cost comparison, which is underpinned by an assumption of equivalence between cabozantinib and regorafenib for all efficacy endpoints, is summarised and critiqued in Section 4 of this report.

2.7 Equality considerations

The CS[1] states that no equality issues related to the use of cabozantinib have been identified.

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3. ERG'S CRITIQUE OF THE CLINICAL EFFECTIVENESS EVIDENCE SUBMITTED

3.1 Company's systematic review methods

The company conducted three searches across a wide range of sources to identify randomised controlled trials (RCTs) of cabozantinib or regorafenib in adults with advanced HCC who have received prior sorafenib (CS Appendices,[16] Section D.1.1):

1. Initial search (inception until March 2018) for cabozantinib, regorafenib, pembrolizumab, lenvatinib, nivolumab, sorafenib sunitinib, pazopanib and ramucirumab.
2. Update search (March 2018 to February 2021) for cabozantinib and regorafenib only.
3. Pragmatic search (February 2021 until January 2022) by applying high specificity RCT filters.

Two RCTs met the inclusion criteria: the CELESTIAL trial of cabozantinib[7] and the RESORCE trial of regorafenib.[15] Despite the differences between the three searches, the ERG is not aware of any relevant RCTs for cabozantinib and regorafenib that have been missed. Both trials are summarised side-by-side in the following sections.

3.2 Summary and critique of CELESTIAL and RESORCE trials

3.2.1 Overview of trials

The CS[1] focusses on a comparison between two trials: the CELESTIAL trial of cabozantinib plus BSC versus placebo plus BSC,[7] and the RESORCE trial of regorafenib plus BSC versus placebo plus BSC.[15] The two trials are summarised in Table 2, based on data presented in the CS on CELESTIAL (CS, Section B.3), RESORCE (CS Appendices,[16] Section D.1.1.9) and both trials (CS, Table 22). Patients in both trials had received prior sorafenib. CELESTIAL included both second- and third-line patients, whereas RESORCE included only second-line patients. RESORCE only included patients who had tolerated sorafenib, whereas CELESTIAL included patients irrespective of tolerance of sorafenib.

3.2.2 Study quality of CELESTIAL and RESORCE trials

The CS[1] presents a quality assessment of CELESTIAL[7] and RESORCE[15] using the standard NICE criteria for RCTs (CS, Section B.3.5 and CS Appendices, Section D.1.3). Both trials were considered to be of good methodological quality on all criteria. The ERG agrees with this assessment.

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Table 2: Summary of design of CELESTIAL and RESORCE trials

Trial name	CELESTIAL	RESORCE
Intervention (N)	Cabozantinib (60mg/day) plus BSC (N=470)	Regorafenib (160mg/day, weeks 1-3 per 4-week cycle) plus BSC (N=379)
Comparator (N)	Placebo plus BSC (N=237)	Placebo plus BSC (N=194)
Analysis sets: - **ITT (all randomised)** - **Safety (≥1 dose)**	ITT: Cabozantinib 470, Placebo 237 Safety: Cabozantinib 467, Placebo 237	ITT: Regorafenib 379, Placebo 194 Safety: Regorafenib 374, Placebo 193
Patient population; key inclusion criteria (ITT)	- Second and third-line patients - Received prior sorafenib - Sorafenib tolerant and intolerant - Progression following ≥1 prior systemic treatment - ECOG PS 0 or 1 - Child-Pugh status A (further inclusion criteria: CS, Table 9)	- Second-line patients only - Failure on prior sorafenib - Sorafenib tolerant only - ECOG PS 0 or 1 - Child-Pugh status A (further inclusion criteria: CS Appendix D.1.1.9, Table 12)
Methodology	Phase III, double-blind	Phase III, double-blind
Stratification factors	- Aetiology of disease (hepatitis B, hepatitis C, other) - Geographic region (Asia, other) - Extrahepatic disease and/or macrovascular invasion (yes, no)	- Geographical region (Asia, other) - Extrahepatic disease (yes, no) - Macrovascular invasion (yes, no) - α-fetoprotein (<400 or ≥400 ng/mL) - ECOG PS (0, 1)
Study initiation and completion (years)	September 2013 – June 2017 (data cut-off date)	May 2013 – Feb 2016 (primary completion date)
Study centres	- Multicentre (Europe, North America, Australia, New Zealand, Asia) - UK: [redacted]	- Multicentre (Europe, North America, Australia, South America, Asia) - UK: 5 study sites, 20 participants
Treatment stopping rule	Continued as long as patient had clinical benefit (as judged by investigator) or until unacceptable toxicity[7, 17]	Continued until disease progression as defined by mRECIST, clinical progression (defined as an ECOG PS ≥3 or symptomatic deterioration, including increased liver function tests), death, unacceptable toxicity, withdrawal of consent by the patient, or decision by the treating physician that discontinuation would be in the patient's best interest.[15]
Median follow-up	22.9 months (2017 data-cut)	7.0 months (2016 data-cut)
% censored for OS	32%	37%
Outcomes	- OS - PFS: via RECIST 1.1 - TTD - ORR: complete or partial response - HRQoL: EQ-5D-5L until 8 weeks after progression or discontinuation - Safety and tolerability	- OS - PFS: via RECIST 1.1 and mRECIST - TTP - ORR: complete or partial response - HRQoL: EQ-5D - Safety and tolerability

BSC - best supportive care; ECOG - Eastern Cooperative Oncology Group; PS - performance status; HRQoL - health-related quality of life; ITT - intention-to-treat; N - number of participants; ORR - overall response rate; OS - overall survival; PFS - progression-free survival; RECIST - Response Evaluation Criteria in Solid Tumours; TTD - time to treatment discontinuation; TTP - time to progression

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3.2.3 Baseline characteristics: CELESTIAL and RESORCE

The baseline characteristics of CELESTIAL[7] and RESORCE[15] are shown in Table 3. This table is based on data presented in CS,[1] Table 10 (CELESTIAL), CS Appendix D,[16] Table 13 (RESORCE) and CS, Table 23 (both trials).

Comparison of baseline characteristics between trials: The CELESTIAL and RESORCE trials[7, 15] were similar in terms of age, sex, Child-Pugh grade, baseline disease spread, aetiology (hepatitis B and C or alcohol-related) and alpha-fetoprotein. Key differences were as follows. CELESTIAL patients were 72% second-line and 28% third-line, whereas RESORCE patients were entirely second-line. CELESTIAL included patients irrespective of whether they had tolerated sorafenib, whereas RESORCE included only patients who had tolerated sorafenib. The European Public Assessment Report (EPAR) for cabozantinib[11] states that 96% of patients in CELESTIAL had progressed on prior sorafenib and *"therefore, it seems unlikely that many sorafenib-intolerant patients were recruited"*. Patients in CELESTIAL had a shorter duration of prior sorafenib treatment (mean of 8 versus 12 months). CELESTIAL had fewer Asian patients than RESORCE (34% versus 41%), more white patients (56% versus 36%), and fewer patients from the Asian geographic region (25% versus 38%). ECOG PS was slightly worse in CELESTIAL (53% ECOG PS 0, 47% ECOG PS 1) than RESORCE (66% ECOG PS 0, 34% ECOG PS 1). In terms of prognosis, the EPAR for cabozantinib[11] states that *"there are no important differences between the two trial populations that may have impacted efficacy."* The ERG's clinical advisors stated that patients in RESORCE may have had a better prognosis as they were all second-line. Conversely however, the ERG's advisors also suggested that line of treatment may make little difference since other prognostic factors were similar between the trials, and one advisor further commented that patients reaching third-line treatment would have a better disease biology than those at second-line, by virtue of reaching this line of therapy. The clinical advisors considered that the restriction to sorafenib-tolerant patients in RESORCE was unlikely to substantially affect prognosis.

Relevance of trials to UK HCC population: The ERG's clinical advisors stated that the CELESTIAL trial population did not reflect the full UK population of advanced HCC post-sorafenib patients as it restricted the population to those with ECOG PS 0-1 and Child-Pugh grade A. However, the clinical advisors considered that the trial reflected the population of patients who are likely to receive cabozantinib in clinical practice, as patients would need to be relatively fit in order to tolerate it. The CS[1] reports a comparison of the CELESTIAL trial population versus a retrospective UK audit of 448 advanced HCC patients from 15 hospitals having received first-line sorafenib[18] (CS, Table 11). Patient characteristics were broadly similar, though more patients in CELESTIAL (versus those in the UK audit) had ECOG PS 0 and Child-Pugh grade A, and more patients in CELESTIAL had extrahepatic spread or hepatitis B or C.

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Table 3: Baseline characteristics in CELESTIAL and RESORCE

	CELESTIAL		RESORCE	
Treatment (N)	**Cabozantinib (N = 470)**	**Placebo (N=237)**	**Regorafenib (N = 379)**	**Placebo (N=194)**
Age, years: median (range)	64 (22-86)	64 (24-86)	64 (54-71)	62 (55-68)
Male (%)	81	85	88	88
Race (%)				
White	56	55	36	35
Asian	34	35	41	40
Other	10	10	23	25
Geographic region				
Europe	49	46	NR	NR
Asia	25	25	38	38
USA/Canada	23	25	NR	NR
Australia/New Zealand	3	5	NR	NR
ECOG PS (%)				
0	52	55	65	67
1	48	45	35	33
Child-Pugh status (%)				
A	98	99	98	97
B	1	0.8	1	3
Baseline disease (%)				
Extrahepatic spread	79	77	70	76
Macrovascular invasion	27	34	29	28
Aetiology at baseline (%)				
Hepatitis B	38	38	38	38
Hepatitis C	24	23	21	21
Alcohol-related	24	16	24	28
NASH	9	10	7	7
Other/unknown	21	27	24	21
Alpha-fetoprotein ≥400 ng/mL (%)	41	43	43	45
Line of treatment (systemic):				
Second	71	73	100	100
Third	28	26	0	0
Duration prior sorafenib, months				
Mean	8	NR	12	NR
Median	5.3	4.8	NR	NR
Range	0.3 to 70.0	0.2 to 76.8	NR	NR
Time from progression on sorafenib (as most recent systemic agent), months, median	1.61	1.66	NR	NR
Prior local therapy (inc. TACE) (%)	44	48	NR	NR
Prior TACE (%)	43	47	NR	NR

AFP - alpha-fetoprotein; ECOG - Eastern Cooperative Oncology Group; ITT - intention to treat; NASH - non-alcoholic steatohepatitis; TACE - transarterial chemoembolisation

3.2.4 Clinical effectiveness: OS and PFS (CELESTIAL and RESORCE)

Results for OS and PFS for CELESTIAL[7] and RESORCE[15] are summarised in Table 4, which presents medians, hazard ratios (HRs) and 95% confidence intervals (CIs) for intention-to-treat (ITT) analyses

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and subgroups by line of therapy. These results are based on data presented in CS,[1] Section B.3.6 (CELESTIAL), CS Appendix E[16] (CELESTIAL subgroups) and CS Appendix D.1.1.9 (RESORCE).

OS: The Kaplan-Meier plot for OS in CELESTIAL[7] is shown in Figure 2. In CELESTIAL, there was a statistically significant difference in OS between cabozantinib and placebo in the ITT population at the 2017 data cut-off (HR 0.76, 95% CI 0.63 to 0.92) and in the second-line subgroup (HR 0.74, 95% CI 0.59 to 0.92), but not in the third-line subgroup (HR 0.90, 95% CI 0.63 to 1.29). The company's clarification response[19] (question A10) highlights the lower patient numbers in the third-line subgroup (28% of trial patients) and notes that regorafenib is currently being used as third-line treatment in NHS practice, despite the lack of trial evidence. In RESORCE,[15] there was a statistically significant difference in OS between regorafenib and placebo in the second-line ITT population, both at the 2016 data cut-off (HR 0.63, 95% CI 0.50 to 0.79) and at later cut-offs (see Table 4).

The CS[1] notes that some patients in CELESTIAL[7] and RESORCE[15] continued to receive their assigned treatment beyond disease progression. The company's clarification response[19] (questions A11 and B2) states that this was more pronounced for regorafenib and that this may bias OS in favour of regorafenib. The clarification response (question B2) also states that subsequent systemic anticancer therapies were received by 25% of the cabozantinib arm in CELESTIAL and 23.2% of the regorafenib arm in RESORCE. The company states that since the numbers were relatively small and similar across trials, the effect of subsequent treatment on OS is expected to be limited.

PFS: The Kaplan-Meier plot for PFS in CELESTIAL[7] is shown in Figure 3. In CELESTIAL, there was a statistically significant difference in PFS between cabozantinib and placebo in the ITT population at the 2017 data cut-off (HR 0.44, 95% CI 0.36 to 0.52) and in the second-line subgroup (HR 0.43, 95% CI 0.35 to 0.52), while in the third-line subgroup, results were less favourable though still statistically significant (HR 0.58, 95% CI 0.41 to 0.83). In RESORCE,[15] PFS was statistically significant in the second-line ITT population at the 2016 data cut-off, both when using RECIST 1.1 (HR 0.43, 95% CI 0.35 to 0.52) and modified RECIST (mRECIST) (HR 0.46, 95% CI 0.37 to 0.56).

OS and PFS data used in ITC: Table 4 also indicates which data were used in the company's indirect treatment comparisons (ITCs), which include Bucher ITCs and matching-adjusted indirect comparisons (MAICs). The company ITCs are detailed further in Section 3.3 of this report.

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Table 4: OS and PFS: CELESTIAL and RESORCE

Line of treatment	Criteria	CELESTIAL					RESORCE				
		Data-cut (FU)	Cabozantinib: median	Placebo: median	HR (95% CI)	Used in analysis	Data-cut (FU)	Regorafenib: median	Placebo: median	HR (95% CI)	Used in analysis
OS											
Second 72% Third 28%		2017 (22.9mo) **(ITT)**	10.2 months	8.0 months	0.76 (0.63 to 0.92)	Bucher ITT					
Second		2017 (22.6mo)	11.4 months	7.7 months	0.74 (0.59 to 0.92)	Bucher 2L MAIC	2016 (7.0mo)	10.6 months	7.8 months	0.63 (0.50 to 0.79)	Bucher ITT MAIC
							2017 (NR)	10.7 months	7.9 months	0.61 (0.50 to 0.75)	
							2018 (NR)	10.7 months	7.9 months	0.62 (0.51 to 0.75)	Bucher 2L
Third		2017 (NR)	8.6 months	8.6 months	0.90 (0.63 to 1.29)						
PFS											
Second 72% Third 28%	RECIST 1.1	2017 (22.9mo) **(ITT)**	5.2 months	1.9 months	0.44 (0.36 to 0.52)	Bucher ITT					
Second	RECIST 1.1	2017 (22.6mo)	5.5 months	1.9 months	0.43 (0.35 to 0.52)	Bucher 2L MAIC	2016 (7.0mo)	3.4 months	1.5 months	0.43 (0.35 to 0.52)	Bucher 2L
	mRECIST						2016 (7.0mo)	3.1 months	1.5 months	0.46 (0.37 to 0.56)	Bucher ITT MAIC
Third	RECIST 1.1	2017 (NR)	3.7 months	1.9 months	0.58 (0.41 to 0.83)						

Bucher ITT = CELESTIAL 2nd/3rd-line vs. RESORCE 2nd-line (presented in CS); Bucher 2L = all 2nd-line (presented in company's clarification response,[19] question A13).
CI - confidence interval; FU- follow-up; HR - hazard ratio; ITT - intention-to-treat; MAIC - matching-adjusted indirect comparison; mo - months; NR - not reported; OS - overall survival; PFS - progression-free survival; RECIST - Response Evaluation Criteria in Solid Tumours
Source: CS,[1] Tables 16 and 17 (CELESTIAL), CS Appendix E,[16] Table 22 (CELESTIAL subgroups) and CS Appendix D, Table 14 (RESORCE)

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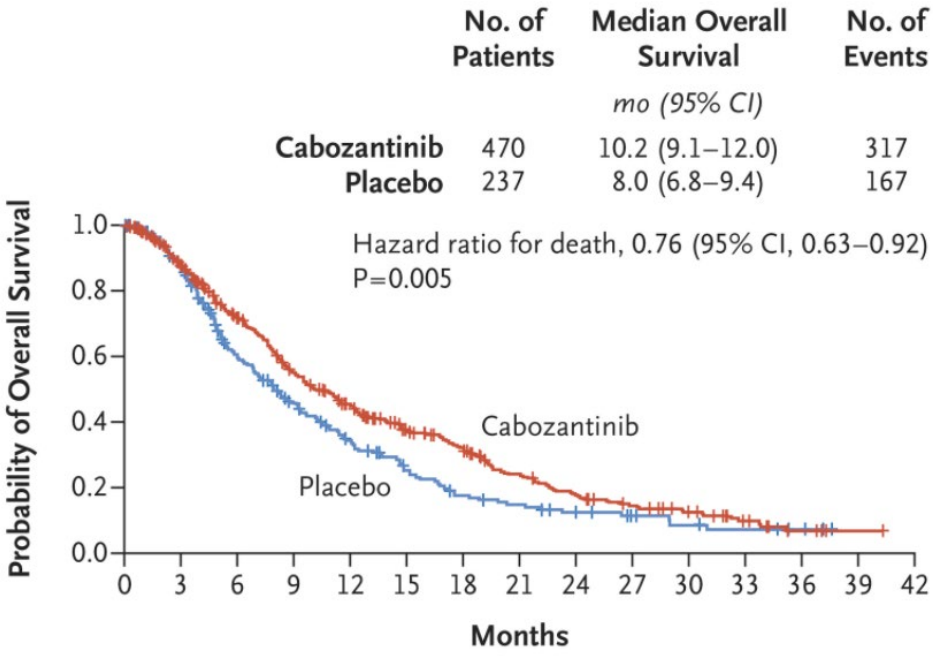
Figure 2: Kaplan-Meier plot for OS, CELESTIAL (ITT, 2017 data cut-off)

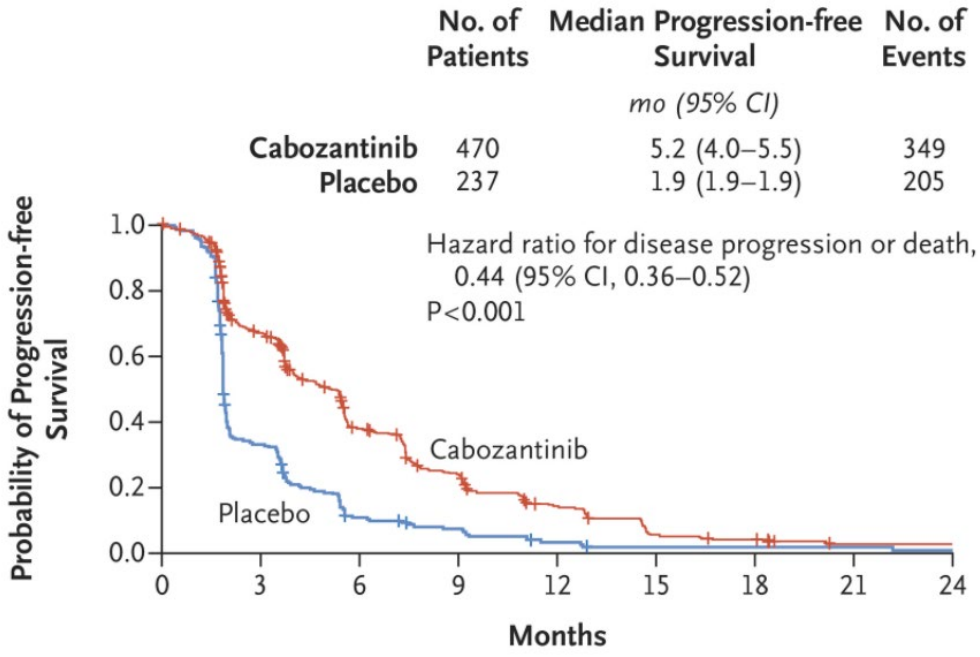


No. at Risk

Cabozantinib	470	328	281	206	159	116	93	63	44	31	22	12	4	1	0
Placebo	237	190	117	82	57	37	25	20	15	10	7	5	3	0	0

Source: Abou-Alfa et al., 2018 [17].

Figure 3: Kaplan-Meier plot for PFS, CELESTIAL (ITT, 2017 data cut-off)



No. at Risk

Cabozantinib	470	266	131	80	39	15	10	3	3
Placebo	237	70	21	13	5	2	2	2	1

Source: Abou-Alfa et al., 2018 [17].

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3.2.5 Subgroup analyses for OS and PFS (CELESTIAL and RESORCE)

The subgroup analyses for OS and PFS in CELESTIAL[7] and RESORCE[15] are provided in CS Appendix E, Figure 6 and CS Appendix D, Figure 3.[16] In CELESTIAL, the HRs for PFS and OS for cabozantinib were less favourable for third-line than second-line patients. In addition, the HR for OS in CELESTIAL was close to 1.0 (indicating little effect of cabozantinib) in patients from Asia, patients without extrahepatic disease, and patients with hepatitis C virus. The company's clarification response[19] (question A9) states that clinical experts who attended an advisory board held by the company considered these findings to be related to small sample sizes as there was no clear clinical explanation. In RESORCE, the HR for OS was close to 1.0 (indicating little effect of regorafenib) in patients without extrahepatic disease and patients with a history of alcohol use.

3.2.6 Clinical effectiveness: Overall response rate (CELESTIAL and RESORCE)

The overall response rates (ORRs) for CELESTIAL[7] and RESORCE[15] are shown in Table 5 (data from CS,[1] Table 19 and CS Appendix,[16] Table 14). Using RECIST 1.1, the ORR in CELESTIAL was 4% for cabozantinib and 0.4% for placebo, whilst the ORR in RESORCE was 7% for regorafenib and 3% for placebo. All were partial responses (PR); there were no complete responses (CR) in either trial when using RECIST 1,1.

Table 5: Overall response rate in CELESTIAL and RESORCE

Response: n (%)	CELESTIAL (RECIST 1.1)		RESORCE (RECIST 1.1)		RESORCE (mRECIST)	
	Cabozantinib (N = 470)	Placebo (N=237)	Regorafenib (N = 379)	Placebo (N=194)	Regorafenib (N = 379)	Placebo (N=194)
ORR [CR+PR]	18 (4%)	1 (0.4%)	25 (7%)	5 (3%)	40 (11%)	8 (4%)
CR	0	0	0	0	2 (0.5%)	0
PR	18 (4%)	1 (0.4%)	25 (7%)	5 (3%)	38 (10%)	8 (4%)

Source: CELESTIAL: CS,[1] Table 19; RESORCE: CS Appendix,[16] Table 14 and Bruix et al., 2017[15]
CR - complete response; ORR - overall response rate; PR - partial response; RECIST - Response Evaluation Criteria in Solid Tumours

3.2.7 HRQoL (CELESTIAL and RESORCE)

HRQoL in CELESTIAL: HRQoL data for CELESTIAL[7] are not presented in the CS or its appendices.[1, 16]

[redacted]

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[redacted] The ERG's clinical advisors stated that HRQoL is a very important factor in this population and that there is a need to consider the balance between positive gains of treatment in PFS and OS and negative effects on HRQoL.

Table 6: CELESTIAL: EQ-VAS and EQ-Index Scores: Change from baseline, repeated-measures analysis (EQ-5D Index: ITT population for countries in which index is validated; EQ-VAS: ITT population)

	Cabozantinib (N = 470) LS means (SE) [n]	Placebo (N = 237) LS means (SE) [n]	Difference in mean change[a]	Pooled SD	*p*-value[a]	Effect size[b]
EQ-5D index	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
EQ-VAS	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

[redacted]

HRQoL in RESORCE: The NICE TA555 guidance for regorafenib[5] states that HRQoL scores were generally similar across treatment arms with different measures, including the EQ-5D. Scores were slightly worse for regorafenib than for BSC but these differences did not pass the 'minimally important difference' threshold established in the literature. The TA555 guidance also states that the EQ-5D utility values from RESORCE[15] appear high for patients who have progressed on sorafenib, and that most patients tend to have side effects from treatment with a serious impact on their HRQoL, which did not appear to be reflected in the utility values. The EQ-5D decrement for progression (–0.048) in RESORCE appeared low for an advanced HCC population with progressed disease. It was also noted that the EQ-5D questionnaire was completed on the first day of each treatment cycle, when a patient had not had treatment for a week.

3.2.8 Safety (CELESTIAL and RESORCE)

Adverse event (AE) data are provided for CELESTIAL[7] in the CS,[1] Section B.3.8 (Tables 20 and 21) and CS Appendix F,[16] and for RESORCE[15] in the CS Appendix D.1.1.9 (Table 16). During the clarification stage, the company provided summary data on AEs for both CELESTIAL and RESORCE. These data are provided in Table 7 and Table 8.

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Safety overview for CELESTIAL: In CELESTIAL,[7] AEs occurred as follows for cabozantinib vs. placebo (Table 7): Grade 3 or 4 AEs (68% vs. 36%); serious adverse events (SAEs) (50% vs. 37%); treatment-related SAEs (18% vs. 6%); AEs leading to dose modification (89% vs. 40%) and AEs leading to discontinuation (21% vs. 4%).

Comparison with RESORCE: An overview of AEs for RESORCE[15] is also shown in Table 7. The percentages of Grade 3 or 4 AEs appeared similar in CELESTIAL and RESORCE, while SAEs and treatment-related SAES appeared slightly higher in CELESTIAL than in RESORCE. AEs leading to dose modification also appeared somewhat higher in CELESTIAL, while AEs leading to discontinuation appeared similar in the two active treatment arms, though the difference from placebo was more marked in CELESTIAL.

Table 7: Summary of safety data in CELESTIAL and RESORCE

AEs	Cabozantinib (n=467), n (%)	Placebo (n=237), n (%)	Regorafenib (N=374), n (%)	Placebo (N=193), n (%)
Any AE (all grades)	460 (99)	219 (92)	374 (100)	179 (93)
Treatment-related AEs	439 (94)	148 (62)	346 (93)	100 (52)
Grade 3 or 4 AEs	316 (68)	86 (36)	248 (66)	75 (38)
SAEs	232 (50)	87 (37)	166 (44)	90 (47)
Treatment-related SAEs	82 (18)	14 (5.9)	36 (10)	5 (3)
Treatment-related Grade 5 AEs (deaths)	6 (1.3)	1 (0.4)	7(2)	2 (1)
Deaths (at any time, excluding PD)	314 (67)	167 (70)	50 (13)	38 (20)
AE leading to dose modification	416 (89)	94 (40)	255 (68)	60 (31)
AE leading to discontinuation of study drug	96 (21)	10 (4.2)	93 (25)	37 (19)

AEs - adverse events; PD - progressive disease; SAEs - serious adverse events
Source: CS,[1] Table 20 (CELESTIAL), CS Appendices,[16] Section D.1.1.9 (RESORCE) and company's clarification response[6] (question A7)

Individual AEs for CELESTIAL: In CELESTIAL,[7] the most common AEs (see Table 8) were as follows (for cabozantinib vs. placebo): diarrhoea (54% vs. 44%); decreased appetite (48% vs. 18%); palmar-plantar erythrodysaesthesia syndrome (PPES or hand-foot syndrome) (46% vs. 5%); fatigue (45% vs. 30%); nausea (31% vs. 18%); hypertension (29% vs. 6%); vomiting (26% vs. 12%); increased aspartate aminotransferase (AST) (22% vs. 11%) and asthenia (22% vs. 8%). The most common Grade 3 or 4 AEs were: PPES (17%, vs. 0%); hypertension (16% vs. 2%); increased AST (12% vs. 7%); fatigue (10% vs. 4%) and diarrhoea (10% vs. 2%). Treatment-related deaths occurred in 6 patients in the cabozantinib arm (hepatic failure, tracheoesophageal fistula, portal-vein thrombosis, upper gastrointestinal haemorrhage, pulmonary embolism, hepatorenal syndrome) and in 1 patient in the placebo arm (hepatic failure). The CS[1] states that AEs with cabozantinib were typical of those with TKI therapies.

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Comparison with RESORCE: AE data from RESORCE[15] for regorafenib versus placebo are also presented in Table 8. Section B.3.10 of the CS[1] presents the results of ITCs between cabozantinib and regorafenib for selected AEs. The company ITCs are discussed further in Section 3.3 of this report.

The EPAR for cabozantinib[11] (page 106) states that, based on reported safety data for both drugs, *"cabozantinib appears to be more toxic than regorafenib."* The ERG's clinical advisors were asked about their views on comparative toxicity of cabozantinib and regorafenib. One advisor stated that, based on their clinical experience and the trial results, they considered cabozantinib to have a more severe and less predictable AE profile than regorafenib, with many patients on cabozantinib requiring dose reductions or discontinuation due to AEs (key AEs impacting on patients, based on their experience, included diarrhoea, severe fatigue and mouth ulcers). The other clinical advisor did not have experience of using cabozantinib, but noted that trial results suggested higher levels of AE-related dose modifications with cabozantinib than regorafenib. One of the clinical advisors commented that the inclusion of sorafenib-intolerant patients may have contributed to the higher numbers of AEs in CELESTIAL[7] than RESORCE.[15] However, as noted in Section 3.2.3, the EPAR for cabozantinib[11] states that 96% of patients in CELESTIAL had progressed on previous sorafenib and *"therefore, it seems unlikely that many sorafenib-intolerant patients were recruited."* The ERG's clinical advisor with experience of using the drug considered that the higher number of AEs for cabozantinib was likely to be attributable to its different mechanism of action.

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Table 8: AEs (any grade) reported in ≥10% of patients in either treatment group for CELESTIAL and RESORCE

AEs	Cabozantinib (n=467) n (%)			Placebo (n=237) n (%)			Regorafenib (N=374) n (%)			Placebo (N=193) n (%)		
	Any Grade	Grade 3	Grade 4	Any Grade	Grade 3	Grade 4	Any Grade	Grade 3	Grade 4	Any Grade	Grade 3	Grade 4
Any AE	460 (99)	270 (58)	46 (10)	219 (92)	80 (34)	6 (3)	374 (100)	208 (56)	40 (11)	179 (93)	61 (32)	14 (7)
Diarrhoea	251 (54)	45 (10)	1 (<1)	44 (19)	4 (2)	0	155 (41)	12 (3)	0	29 (15)	0	0
Decreased appetite	225 (48)	27 (6)	0	43 (18)	1 (<1)	0	NR	NR	NR	NR	NR	NR
PPES	217 (46)	79 (17)	0	12 (5)	0	0	198 (53)	47 (13)	NA	15 (8)	1 (1)	NA
Fatigue	212 (45)	49 (10)	0	70 (30)	10 (4)	0	151 (40)	34 (9)	NA	61 (32)	9 (5)	NA
Nausea	147 (31)	10 (2)	0	42 (18)	4 (2)	0	64 (17)	2 (1)	NA	26 (13)	0	NA
Hypertension	137 (29)	73 (16)	1 (<1)	14 (6)	4 (2)	0	116 (31)	56 (15)	1 (<1)	12 (6)	9 (5)	0
Vomiting	121 (26)	2 (<1)	0	28 (12)	6 (3)	0	47 (13)	3 (1)	0	13 (7)	1 (1)	0
Increase in AST level	105 (22)	51 (11)	4 (1)	27 (11)	15 (6)	1 (<1)	92 (25)	37 (10)	4 (1)	38 (20)	19 (10)	3 (2)
Asthenia	102 (22)	31 (7)	1 (<1)	18 (8)	4 (2)	0	NR	NR	NR	NR	NR	NR
Dysphonia	90 (19)	3 (1)	0	5 (2)	0	0	NR	NR	NR	NR	NR	NR
Constipation	87 (19)	2 (<1)	0	45 (19)	0	0	65 (17)	1 (<1)	0	22 (11)	1 (1)	0
Abdominal pain	83 (18)	7 (1)	1 (<1)	60 (25)	10 (4)	0	105 (28)	13 (3)	NA	43 (22)	8 (4)	NA
Weight loss	81 (17)	5 (1)	0	14 (6)	0	0	51 (14)	7 (2)	NA	9 (5)	0	NA
Increase in ALT level	80 (17)	23 (5)	0	13 (5)	5 (2)	0	55 (15)	10 (3)	2 (1)	22 (11)	5 (3)	0
Mucosal inflammation†	65 (14)	8 (2)	0	5 (2)	1 (<1)	0	47 (13)	4 (1)	0	6 (3)	1 (1)	0
Pyrexia	64 (14)	0	0	24 (10)	1 (<1)	0	72 (9)	0	0	14 (7)	0	0
Upper abdominal pain	63 (13)	3 (1)	0	31 (13)	0	0	NR	NR	NR	NR	NR	NR
Cough	63 (13)	1 (<1)	0	26 (11)	0	0	40 (11)	1 (<1)	NA	14 (7)	0	NA
Peripheral oedema**	63 (13)	4 (1)	0	32 (14)	2 (1)	0	60 (16)	2 (1)	NA	24 (12)	0	NA
Stomatitis	63 (13)	8 (2)	0	5 (2)	0	0	NR	NR	NR	NR	NR	NR
Dyspnoea	58 (12)	15 (3)	0	24 (10)	1 (<1)	0	NR	NR	NR	NR	NR	NR
Rash	58 (12)	2 (<1)	0	14 (6)	1 (<1)	0	NR	NR	NR	NR	NR	NR
Ascites	57 (12)	17 (4)	1 (<1)	30 (13)	11 (5)	0	58 (16)	16 (4)	0	31 (16)	11 (6)	0
Dysgeusia	56 (12)	0	0	5 (2)	0	0	NR	NR	NR	NR	NR	NR
Hypoalbuminemia	55 (12)	2 (<1)	0	12 (5)	0	0	57 (15)	6 (2)	0	16 (8)	1 (1)	0
Headache	52 (11)	1 (<1)	0	16 (7)	1 (<1)	0	NR	NR	NR	NR	NR	NR
Insomnia	49 (10)	1 (<1)	0	17 (7)	0	0	NR	NR	NR	NR	NR	NR

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AEs	Cabozantinib (n=467) n (%)			Placebo (n=237) n (%)			Regorafenib (N=374) n (%)			Placebo (N=193) n (%)		
	Any Grade	Grade 3	Grade 4	Any Grade	Grade 3	Grade 4	Any Grade	Grade 3	Grade 4	Any Grade	Grade 3	Grade 4
Dizziness	48 (10)	2 (<1)	0	15 (6)	0	0	NR	NR	NR	NR	NR	NR
Dyspepsia	47 (10)	0	0	7 (3)	0	0	NR	NR	NR	NR	NR	NR
Anaemia	46 (10)	18 (4)	1 (<1)	19 (8)	12 (5)	0	58 (16)	16 (4)	2 (1)	22 (11)	0	NA
Back pain	46 (10)	5 (1)	0	24 (10)	1 (<1)	0	42 (11)	6 (2)	1 (<1)	17 (9)	2 (1)	0
Increase in serum bilirubin level	45 (10)	10 (2)	4 (1)	17 (7)	2 (1)	2 (1)	108 (29)	37 (10)	2 (1)	34 (19)	15 (8)	6 (3)
Decrease in platelet count	45 (10)	13 (3)	4 (1)	7 (3)	2 (1)	0	29 (10)	13 (3)	1 (<1)	5 (3)	0	0

† Mucosal inflammation reported in CELESTIAL, whereas in RESORCE oral mucositis reported
*** Peripheral oedema reported in CELESTIAL, whereas in RESORCE limb oedema recorded.*
AE - adverse event; ALT - alanine aminotransferase; AST - aspartate aminotransferase; NA - not applicable; NR - not reported; PPES - palmar-plantar erythrodysaesthesia syndrome.
Source: CS,[1] Table 21 (CELESTIAL), CS Appendices,[16] Section D.1.1.9 Table 16 (RESORCE) and company's clarification response[19] (question A7, Table 3)

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3.2.9 Ongoing studies of cabozantinib and regorafenib

The CS[1] states that no relevant studies of cabozantinib for advanced HCC are expected to report in the next 12 months. The company's clarification response[19] (question A8) states that there are no ongoing or planned studies of cabozantinib or regorafenib in the post-sorafenib setting.

3.2.10 Summary of ERG's critique of clinical effectiveness evidence

The main points highlighted by the ERG relating to the clinical effectiveness evidence are as follows:

- Population: The CS[1] focusses on patients with advanced HCC who have had prior sorafenib and have Child–Pugh grade A liver impairment and an ECOG PS of 0 or 1. The ERG's clinical advisors considered this appropriate as it is consistent with the populations of the relevant trials[7, 15] and reflects the population who would be treated in clinical practice.
- Clinical trials: The CS focusses on a comparison between the CELESTIAL trial of cabozantinib and the RESORCE trial of regorafenib. Patients in both trials had received prior sorafenib. Almost all trial patients had Child-Pugh grade A and ECOG PS 0-1. CELESTIAL included both second- and third-line patients while RESORCE included only second-line patients. RESORCE included sorafenib-tolerant patients only, while CELESTIAL included patients irrespective of sorafenib tolerance. The ERG's clinical advisors were uncertain to what extent these differences would affect PFS, OS and AEs.
- OS: CELESTIAL showed a statistically significant effect of cabozantinib on OS in the ITT population and in the second-line subgroup, but not in the third-line subgroup. In RESORCE, there was a statistically significant effect of regorafenib on OS in the second-line ITT population, whilst there is no RCT evidence in third-line patients.
- PFS: CELESTIAL showed a statistically significant effect of cabozantinib on PFS in the ITT population and in the second-line and third-line subgroups, though results were less favourable in the third-line subgroup. In RESORCE, the treatment effect on PFS was statistically significant in the second-line ITT population.
- HRQoL: The mean difference in change from baseline EQ-5D for regorafenib versus placebo in RESORCE was reported to be small and non-significant. [redacted].
- Safety: In CELESTIAL, AEs occurred as follows for cabozantinib vs. placebo: Grade 3 or 4 AEs (68% vs. 36%); SAEs (50% vs. 37%), treatment-related SAEs (18% vs. 6%); AEs leading to dose modification (89% vs. 40%) and AEs leading to discontinuation (21% vs. 4%). The most common AEs were: diarrhoea; decreased appetite; PPES; fatigue; nausea; hypertension; vomiting; increased AST and asthenia. The ERG's clinical advisors considered cabozantinib to have a more severe AE profile than regorafenib. One of the ERG's clinical advisors believed

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that it is not clear to what extent the trial AE results were affected by the inclusion of sorafenib-intolerant patients in CELESTIAL. One of the ERG's clinical advisors commented that the reason for not including sorafenib-intolerant patients in RESORCE was because regorafenib is essentially the same molecule as sorafenib, but that cabozantinib is different. As noted in Section 3.2.2, the EPAR for cabozantinib suggests that it is unlikely that many sorafenib-intolerant patients were recruited into CELESTIAL.

3.3 Summary and critique of company's indirect treatment comparisons

3.3.1 Summary of ITCs presented

As discussed in Section 2.3, the company is seeking a positive NICE recommendation for cabozantinib which is the same as that for regorafenib. Owing to the absence of direct evidence comparing cabozantinib against regorafenib, the CS[1] (Section B.3.10) presents the results of a series of ITCs of these treatments. These ITCs utilise data from the CELESTIAL and RESORCE trials.[7, 15] The ERG agrees that ITC methods are required to provide estimates of relative treatment effects.

ITC analyses are presented in the CS[1] and the company's clarification response[19] for OS, PFS and a number of individual safety endpoints (Grade 3/4 AEs which occurred in ≥5% of patients in either arm), including: increased AST; elevated bilirubin; fatigue; hypertension; diarrhoea and PPES. The ITC analyses submitted by the company comprise:

- ITCs using the Bucher approach,[20] comparing cabozantinib against regorafenib, anchoring on placebo plus BSC (which is used as the common comparator arm) using aggregate level data from both the CELESTIAL and RESORCE trials.[7, 15]
- Anchored MAICs comparing cabozantinib against regorafenib (using placebo plus BSC as a common comparator arm), using individual patient data (IPD) from the CELESTIAL trial. This analysis relies upon the assumption of proportional hazards (PH), and uses a Cox PH model to estimate a constant HR.
- Anchored MAICs comparing cabozantinib and regorafenib (using placebo plus BSC as a common comparator arm), using IPD from the CELESTIAL trial. This analysis does not rely upon the PH assumption, and instead involved fitting a series of independent parametric models to both arms of the weighted CELESTIAL and RESORCE trials to estimate a time-varying HR.
- Unanchored MAICs comparing cabozantinib against regorafenib by comparing absolute treatment effects by fitting independent parametric models to the weighted cabozantinib arm from CELESTIAL and the regorafenib arm from RESORCE.

A summary of the ITC analyses conducted by the company is presented in Table 9.

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Table 9: Summary of company's ITC analyses

ITC method	Study	Population	Arms utilised in comparison	Type of comparison	Attempts to adjust for imbalances in trial populations	Outcomes assessed
Bucher indirect comparison	CELESTIAL	ITT: second- and third-line HCC patients	Cabozantinib; placebo plus BSC	Anchored	No	Efficacy: OS; PFS Safety: Hypertension; elevated AST; fatigue
	RESORCE	ITT: second-line HCC patients	Regorafenib; placebo plus BSC			
Bucher indirect comparison*	CELESTIAL	Subpopulation: second-line HCC patients	Cabozantinib; placebo plus BSC	Anchored	No	Efficacy: OS; PFS
	RESORCE	ITT: second-line HCC patients	Regorafenib; placebo plus BSC			
MAIC using constant HR (Cox PH model for OS/PFS) or OR (safety outcomes)	CELESTIAL	Subpopulation: second-line HCC patients	Cabozantinib; placebo plus BSC	Anchored	Yes	Efficacy: OS; PFS Safety: Increased AST, elevated bilirubin; fatigue; hypertension
	RESORCE	ITT: second-line HCC patients	Regorafenib; placebo plus BSC			
MAIC using time-varying HRs (log-logistic model presented in CS)	CELESTIAL	Subpopulation: second-line HCC patients	Cabozantinib; placebo plus BSC	Anchored	Yes	Efficacy: OS; PFS Safety: N/a
	RESORCE	ITT: second-line HCC patients	Regorafenib; placebo plus BSC			
MAIC using independent parametric models (log-logistic or generalised gamma model presented in CS)[a] or OR (safety outcomes)	CELESTIAL	Subpopulation: second-line HCC patients	Cabozantinib	Unanchored	Yes	Efficacy: OS; PFS Safety: Diarrhoea; PPES
	RESORCE	ITT: second-line HCC patients	Regorafenib			

BSC - best supportive care; HCC - hepatocellular carcinoma; HR - hazard ratio; ITC - indirect treatment comparison; ITT, intention-to-treat; MAIC - matching-adjusted indirect comparison; OR - odds ratio; OS - overall survival; PFS - progression-free survival; PH - proportional hazards; AST - aspartate aminotransferase; PPES - palmar-plantar erythrodysaesthesia syndrome; CS - company's submission; N/a - not applicable

Notes: a – the company's clarification response (question A15) highlights that this model was incorrectly labelled as the generalised gamma model for OS in the CS

** Additional analysis presented as part of company's clarification response (question A13)*

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3.3.2 Methods of company's ITC analyses

3.3.2.1 Bucher approach

The first ITC approach presented by the company includes a series of Bucher indirect comparisons. This form of comparison used aggregate-level data from the CELESTIAL and RESORCE trials,[15, 17] with placebo plus BSC as the common comparator arm. The relative treatment effect of cabozantinib versus regorafenib was estimated for efficacy outcomes including: OS, PFS, and three safety outcomes: hypertension, increased AST and fatigue. The CS[1] reports results from Bucher ITCs which utilised the ITT population from both CELESTIAL and RESORCE, where the CELESTIAL ITT population was broader than the RESORCE trial population as it included both second- and third-line patients.

The results of the Bucher ITCs are presented in Section B.3.10.2 of the CS.[1] The comparison for PFS was based on RECIST 1.1 criteria from the CELESTIAL trial[7] and modified RECIST (mRECIST) criteria from the RESORCE trial,[15] and the comparison for OS was based on a 2016 data-cut for the RESORCE trial. As part of their clarification response[19] (questions A13, A25 and A26), the company provided results from Bucher ITCs for both PFS and OS using the second-line subpopulation from CELESTIAL in order to more closely align with the RESORCE ITT population. Of note, this comparison using the second-line population of the CELESTIAL trial was based on RECIST 1.1 criteria for PFS for both trials, as well as the latest data-cut (2018) of the RESORCE trial for OS. Results from all Bucher ITCs are summarised in Section 3.3.3 of this report (see Table 11).

3.3.2.2 MAIC approach

The company also conducted a series of MAICs comparing cabozantinib versus regorafenib, citing differences in baseline characteristics between the CELESTIAL and RESORCE trials[7, 15] as a rationale for performing this type of ITC. These differences included the proportion of patients with ECOG PS 0, ethnicity and geographical regions (CS,[1] Section B.3.10.3). IPD were available for the CELESTIAL trial. In the MAIC analyses, the company used a subpopulation of the CELESTIAL trial, specifically second-line HCC patients who had prior treatment with sorafenib (i.e., "pure" second-line patients) to better align the population with that of the RESORCE trial (which only evaluated second-line patients). The company's clarification response[19] (question A14) provides details of the sample size of the second-line population with complete baseline characteristics (i.e., after exclusion of subjects with missing covariate data): a total of 484 patients were included in the MAIC analysis (out of a total of 707 patients included in the ITT trial population). The ERG notes that no attempt was made by the company to impute missing covariate data in the CELESTIAL trial.

Aggregate-level baseline characteristics and outcome data were extracted for the RESORCE trial;[15] Kaplan-Meier curves for PFS and OS were digitised and pseudo IPD were reconstructed using the algorithm reported by Guyot *et al.* (2012).[21] The proportion of patients experiencing individual AEs

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was also extracted, including: increased AST; elevated bilirubin; fatigue; hypertension; diarrhoea and PPES. During the clarification stage, the ERG asked the company to present results from a MAIC evaluating all Grade 3/4 AEs combined, rather than individually (see clarification response,[19] question A19). However, the company did not undertake this analysis as they stated that the incidence of Grade 3/4 AEs was almost identical between the two treatment arms. However, without quantifying the results for this analysis, there remains uncertainty around the treatment effect for this outcome.

The CS[1] (Section 3.10.3) states that the baseline characteristics which were used to inform the weighting process were selected from the preliminary set based on their potential influence on key efficacy outcomes (PFS and OS) and AEs. Baseline characteristics for the company's base case analyses (denoted Scenario "S1") were justified for inclusion in the MAIC based on feedback received by clinical experts from a UK advisory board meeting and were further confirmed at a second advisory board meeting. The potential effect modifiers included: age; race; geographical region; ECOG PS; Child-Pugh grade; duration of prior sorafenib treatment; extrahepatic disease; macrovascular invasion; aetiology of HCC (Hepatitis B, alcohol use and Hepatitis C) and alpha fetoprotein level (AFP) level. The company also explored a second scenario (denoted Scenario "S2") which included only effect modifiers for OS (primary survival outcome), identified using a stepwise regression approach. The subset of factors included: gender; ECOG PS; extrahepatic disease; macrovascular invasion and AFP level; however, the CS states that following clinical feedback received from the advisory board, gender was not included in the matching. In response to a request for clarification from the ERG[19] (question A18), the company provided further information around the selection of these factors, and clarified that the classification of each factor was determined by how the data were reported in the RESORCE trial;[15] all factors included in the matching (apart from duration of prior sorafenib and aetiology of disease) were reported as dichotomous variables. Duration of sorafenib was retained as a continuous variable and aetiology of disease was split into multiple categories. A summary of the effect modifiers and their respective classification is presented in Table 10.

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Table 10: Summary of effect modifiers included in company's matching (adapted from clarification response, question A18)

Factor included in matching	Classification of factor	Factor included in Scenario 1 (S1)	Factor included in Scenario 2 (S2)	Rationale for classification
Age	< 65 years ≥ 65 years	✓		To reflect average age in RESORCE. This was categorised to minimise impact on ESS
Race	Female Male	✓		Binary variable
Geographical region	Asia Other	✓		To reflect reporting of RESORCE trial region baseline characteristic
ECOG performance status	ECOG 0 ECOG 1 or 2	✓	✓	Binary variable. ECOG 1 and ECOG 2 combined due to low ECOG 2 numbers
Child Pugh grade	A, B or unknown	✓		Binary variable
Duration of prior sorafenib	Continuous variable	✓		-
Extrahepatic disease	Present Absent	✓	✓	Binary variable
Macrovascular invasion	Present Absent Unknown	✓	✓	Binary variable
Aetiology of HCC (Hepatitis B)	Present Absent Unknown	✓		Binary variable
Aetiology of HCC (Alcohol use)	Present Absent Unknown	✓		Binary variable
Aetiology of HCC (Hepatitis C)	Present Absent Unknown	✓		Binary variable
AFP level	≥ 400 ng/ml < 400 ng/ml	✓	✓	To reflect reporting of RESORCE trial AFP level baseline characteristic. This is a diagnostic threshold for HCC

ESS - effective sample size; AFP - alpha fetoprotein level; ECOG - Eastern Cooperative Oncology Group; HCC - hepatocellular carcinoma

The ERG's clinical advisors considered that Scenario S1 included the key prognostic variables and treatment effect modifiers; however, they also suggested that the number of prior local regional therapies and Barcelona Clinic Liver Cancer (BCLC) staging were additional important prognostic factors. The ERG notes that there is a potential for the presence of strong correlation between BCLC stage and Child Pugh grade and ECOG PS if these variables are considered to measure similar aspects of health, which may result in overmatched data and an unnecessary reduction in the effective sample

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size (ESS) if included in the matching process. Further, BCLC staging was not captured in the CELESTIAL trial[7] and could not be matched on. The ERG's clinical advisors suggested that Child Pugh grade, extrahepatic disease and ECOG PS were considered as being particularly important potential prognostic factors and/or treatment effect modifiers.

In response to a request for clarification from the ERG[19] (question A23), the company provided histograms which display the distribution of estimated weights obtained for Scenarios S1 and S2. These are provided in Figures 14 and 15 of the company's clarification response. The histograms indicate that some individuals were assigned large weights in S1, with a maximum rescaled weight of 9.21. In S2, no extreme weights were observed, with a maximum rescaled weight of 1.61. However, the company acknowledges that S2 does not include matching on some baseline characteristics which were identified as being important effect modifiers. In their response to clarification question A21, the company confirmed that the weights from S1 were used in the company's anchored and unanchored MAICs conducted for OS and PFS; no results were presented for these outcomes using weights from S2.

In S1, the ESS for the cabozantinib arm was reported by the company to be 187.27 (57.4% of the original sample size [N=326]). A small ESS indicates that weights are highly variable due to a lack of population overlap and that the resulting estimates may be unstable.[22] Whilst the ESS was notably higher for S2 (ESS=303.24), this has been at the expense of matching on fewer effect modifiers in an attempt to balance trial populations. The ERG notes that there may be residual confounding if all effect modifiers are not accounted for in the matching process.[22]

Three types of population-adjusted analyses were performed for PFS and OS using the weights from Scenario S1, including:

- Anchored comparisons which apply the PH assumption, and which utilise a constant HR estimated from a Cox regression model using weighted CELESTIAL data and RESORCE data to provide a comparison for cabozantinib versus regorafenib.
- Anchored comparisons which do not assume PH, and which explore if there is any difference in the treatment effect emerging between cabozantinib and regorafenib over time by generating time-varying HRs from hazard profiles of fitted parametric models to the weighted CELESTIAL data and RESORCE data.
- Unanchored comparisons, which evaluate absolute effects through fitting parametric models to weighted cabozantinib data and regorafenib data.

One form of anchored MAIC conducted by the company was based on the estimation of a constant HR to represent the treatment effect between cabozantinib and regorafenib. The company also provided

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results from a time-varying anchored MAIC analysis, fitting parametric models to the weighted cabozantinib and regorafenib arms of their respective trials;[7, 15] the company stated that that a log-logistic model was considered to provide the best fit for both OS and PFS based on an assessment of Akaike Information Criterion (AIC) and Bayesian Information Criterion (BIC) statistics (CS,[1] Section B.3.10.3). At the clarification stage, further details were requested from the company regarding the time-varying approach, including the methodology adopted to estimate the time-varying HR after fitting parametric curves to the data, and further, how the weights from the matching were incorporated into the ITC (see clarification response,[19] question A20). The company's response states that independent parametric models of the same distribution were fitted to both arms of the weighted CELESTIAL data and both arms of the RESORCE trial to generate a hazard function for each treatment arm. The time-varying HR between cabozantinib versus placebo from the CELESTIAL trial was generated by dividing the hazard for the cabozantinib parametric model by the hazard for the placebo parametric model at each timepoint. The time-varying HR for regorafenib versus placebo from the RESORCE trial was generated in a similar way. The time-varying HR for cabozantinib versus regorafenib was then estimated by calculating the ratio of the cabozantinib versus placebo HR versus the regorafenib versus placebo HR. Weights from the population-adjustment process were incorporated into the analysis by fitting weighted parametric survival models.

An unanchored MAIC analysis was also performed by the company, which was undertaken by fitting a series of independent parametric models to the weighted cabozantinib and regorafenib arms of the respective trials.[7, 15] The CS[1] states that a generalised gamma distribution was considered to provide the best fit to the data based on an assessment of AIC and BIC statistics. However, the company's clarification response[19] (question A15) includes a correction which states that the best fitting model for OS should have been labelled as the log-logistic model.

Results from all MAIC analyses are presented in Section B.3.10.3 of the CS.[1] The results for comparisons of efficacy and safety are summarised in Table 11 and Table 12, respectively (see Section 3.3.3).

3.3.3 Results of company's ITC analyses

The results of the ITCs presented in the CS[1] are summarised in Table 11 (efficacy outcomes, including OS and PFS) and Table 12 (safety outcomes, including hypertension, elevated AST, fatigue, elevated bilirubin, diarrhoea and PPES).

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Table 11: Summary of company's ITC analyses conducted for efficacy outcomes

Line of treatment	Analysis	Description	Efficacy outcomes, HR (95% CI)		
			Comparison	OS	PFS
Second 72%, third 28%	Bucher	ITC anchored on placebo plus BSC, without adjustment for cross-trial differences	Cabozantinib vs. regorafenib	1.21 (0.90, 1.62)	0.96 (0.73, 1.26)
Second	Bucher	ITC anchored on placebo plus BSC, without adjustment for cross-trial differences		1.13[a,c] (0.83, 1.53)	0.93[a,b] (0.69, 1.25)
	Anchored MAIC (Constant HR)[d,e]	Weighted Cox PH regression model (where weights are estimated from matching on trial baseline characteristics)		1.15 (0.79, 1.69)	0.79 (0.56, 1.11)
	Anchored MAIC (Time-varying HR)	The company selected a log-logistic model as the best fitting model to estimate a time-varying HR for both OS and PFS		Time-varying HR>1.0, suggesting a trend of improved OS for regorafenib over cabozantinib. Results across the models show that over time, the HR is not statistically different from 1.0 (95% CI interval includes a time-varying HR of 1.0)	Time-varying HR<1.0, suggesting a trend of improved PFS for cabozantinib over regorafenib. Results across the models show that over time, the HR is not statistically different from 1.0 (95% CI interval includes a time-varying HR of 1.0)
	Unanchored MAIC	The company selected a log-logistic model[d] (OS) and generalised gamma model (PFS) fitted to weighted cabozantinib and regorafenib arms		Large amount of overlap until year 1 when cabozantinib begins to show a relatively small benefit over regorafenib. Cabozantinib has a larger point estimate for mean OS (24.65 vs. 21.17 months) and a higher median OS (11.40 versus 10.29 months).	Statistically significant benefit for cabozantinib until approximately 1 year when the PFS curves show minimal difference for the rest of the time horizon. Cabozantinib has a larger point estimate for mean PFS than regorafenib (7.17 vs. 6.04 months) and higher median PFS (5.49 vs. 3.39).

ITC - indirect treatment comparison; BSC - best supportive care; CI - confidence interval; HR - hazard ratio; MAIC - matching-adjusted indirect comparison; OR - odds ratio; OS - overall survival; PFS - progression-free survival; PH - proportional hazards

Notes: HR<1.0 favours cabozantinib over regorafenib, a - analysis conducted in response to clarification question A13, using second-line subgroup data from CELESTIAL trial; b - analysis conducted in response to clarification question A26, using RECIST 1.1 PFS data for both CELESTIAL and RESORCE trials (instead of using RECIST 1.1 in CELESTIAL and mRECIST in RESORCE); c - analysis conducted in response to clarification question A25, using data cut from the RESORCE trial from 2018 (instead of using data cut from the RESORCE trial from 2016); d - a correction has been made by the company which stated that the best fitting model for OS in the unanchored comparison was the log-logistic model instead of the generalised gamma model; e - Weibull model with a constant HR was also explored by the company as part of a response to clarification question B6

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Table 12: Summary of company's ITC analyses conducted for safety outcomes

Line of treatment	Analysis	Description	Safety outcomes, OR (95% CI)						
			Comparison	**Hypertension**	**Elevated aspartate aminotransferase**	**Fatigue**	**Elevated bilirubin**	**Diarrhoea**	**PPES**
Second 72%, third 28%	Bucher	ITC anchored on placebo plus BSC, without adjustment for observed cross-trial differences	Regorafenib vs. cabozantinib[a]	0.2 (0.0-1.2)	0.6 (0.2-1.6)	1.2 (0.3-5.6)	-	-	-
Second	Anchored MAIC	Weighted OR (where weights are estimated from matching on trial baseline characteristics)[b]	Cabozantinib vs. regorafenib	8.17[c] (0.90, 73.70)	2.20[c] (0.63, 7.84)	1.09[c] (0.17, 6.96)	0.78[c] (0.07, 9.30)	-	-
	Unanchored MAIC		Cabozantinib vs. regorafenib	-	-	-	-	**5.70[c] (2.72, 11.94)**	1.05[c] (0.67, 1.65)

ITC - indirect treatment comparison; BSC - best supportive care; CI - confidence interval; HR - hazard ratio; MAIC - matching-adjusted indirect comparison; OR - odds ratio; OS - overall survival; PFS - progression-free survival; PPES - palmar-plantar erythrodysaesthesia syndrome

Notes: Bucher: OR>1 favours cabozantinib over regorafenib; MAIC: OR<1 favour cabozantinib over regorafenib; bold denotes statistically significant comparison at 5% level; a - the ERG believes this comparison to be incorrectly labelled as cabozantinib versus regorafenib in both the CS and the response to clarification question A16; b - results based on weights obtained from Scenario S1; c - results transformed by the ERG from logOR to OR using the exponential function

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3.3.3.1 Bucher approach

A summary of the results from the Bucher ITCs for OS and PFS are presented in the CS[1] (Table 24) and are also summarised in Table 11. The CS states that the results from the Bucher ITCs showed HR estimates which favoured cabozantinib over regorafenib for PFS (HR<1.0) and which favoured regorafenib over cabozantinib for OS (HR>1.0), but the results were statistically non-significant, which the company suggests reflects similar efficacy in terms of OS and PFS for both treatments. For the Bucher ITC analysis using the second-line subpopulation from CELESTIAL[7] (presented in response to clarification question A13[19]), the company also suggested that there was no statistically significant difference between the two treatments in this subgroup of patients and therefore, the conclusions remain unchanged.

A summary of the results from the Bucher ITCs for safety outcomes are presented for cabozantinib versus regorafenib in Table 26 of the CS;[1] these are also summarised in Table 12. The CS states that a Bucher ITC was only feasible when there were events in all arms of the CELESTIAL and RESORCE trials.[7, 15] Therefore, only three AEs were compared: hypertension, elevated AST and fatigue. The CS states that the results show no statistically significant differences between the AE OR estimates for cabozantinib and regorafenib. Further, the CS (Section B.3.10.4) states that the ITC results suggest that cabozantinib has *"similar tolerability compared to regorafenib.*" However, the OR point estimates from the Bucher ITCs conducted for hypertension and elevated AST differ from 1.0. The company's response to clarification question A24[19] regarding the assumption of similar tolerability between cabozantinib and regorafenib suggests that since the *p*-value for hypertension and AST is not significant, and the clinical experts advising the company agreed that the safety profiles of cabozantinib and regorafenib are similar, this may indicate that the tolerability of both regimens is considered to be the same. However, the company's clarification response (question A16) suggests that the Bucher comparisons presented for safety outcomes (hypertension, elevated AST and fatigue) are incorrectly labelled. Upon clarification, the ERG believes the company has also mislabelled the treatment effect in Table 7 of the clarification question response document for both CELESTIAL and RESORCE, which in fact, represent the treatment effect between placebo versus cabozantinib and placebo versus regorafenib, respectively. The ERG has re-labelled the OR estimates from a Bucher ITC for three safety outcomes as a comparison between regorafenib versus cabozantinib (instead of cabozantinib versus regorafenib); these results are presented in Table 12.

The ERG believes that the Bucher ITC approach adopted by the company does not provide robust estimates of comparative efficacy and safety due to the presence of observed cross-trial differences. In addition, the results from the ITCs presented in Table 24 of the CS[1] are further limited by the fact that CELESTIAL data[7] reflect the ITT population and do not utilise data from the second-line subpopulation from the trial. The company's clarification response[19] (question A13) provides estimates of the Bucher

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ITCs for PFS and OS using the second-line population from the CELESTIAL trial. Whilst the conclusions of this analysis remain unchanged from those presented for the CELESTIAL ITT population, the results of this analysis may not be reliable due to the remaining cross-trial differences between the CELESTIAL and RESORCE trial populations.

3.3.3.2 MAIC approach

Anchored comparisons

The CS[1] provides the results of MAIC analyses utilising a subpopulation from the CELESTIAL ITT population,[7] specifically second-line HCC patients who had prior treatment with sorafenib (i.e., pure second-line patients). The ERG agrees that this initial equalisation of study populations is an appropriate step prior to conducting an ITC. The results of the anchored comparison for efficacy outcomes (OS and PFS) between cabozantinib and regorafenib using a constant HR estimated from a Cox regression model are shown in Table 31 of the CS; these are also summarised in Table 11. The point estimate of the HR for cabozantinib versus regorafenib favours PFS cabozantinib, whilst the point estimate of the HR for OS favours regorafenib. Both of these results are statistically non-significant (95% CIs include an HR estimate of 1.0), from which the company concludes that there is no evidence of a difference between the treatments. The ERG believes that the MAIC analysis using a constant HR have been performed appropriately.

During the clarification stage, the ERG asked the company to provide the unweighted and weighted Kaplan-Meier curves for the cabozantinib arm from CELESTIAL[7] (see clarification response,[19] question A15). These are reproduced in Figure 4 and Figure 5 for PFS and OS, respectively, using weights from both Scenarios S1 and S2. The Kaplan-Meier curves show the PFS and OS data prior to-(unweighted) and post-adjustment (weighted), using the weights obtained from the matching process. The company concludes that Scenarios S1 and S2 yield similar results. However, relative to the unweighted curve, the use of weights from Scenario S1 results in a greater shift in the Kaplan-Meier curve compared to the weights from S2, and this trend is observed for both PFS and OS. This is an expected result given the greater reduction in ESS when using weights from Scenario S1 compared to S2.

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Figure 4: Unadjusted and weighted Kaplan-Meier curves for PFS, cabozantinib arm of CELESTIAL, (reproduced from clarification response, question A15)

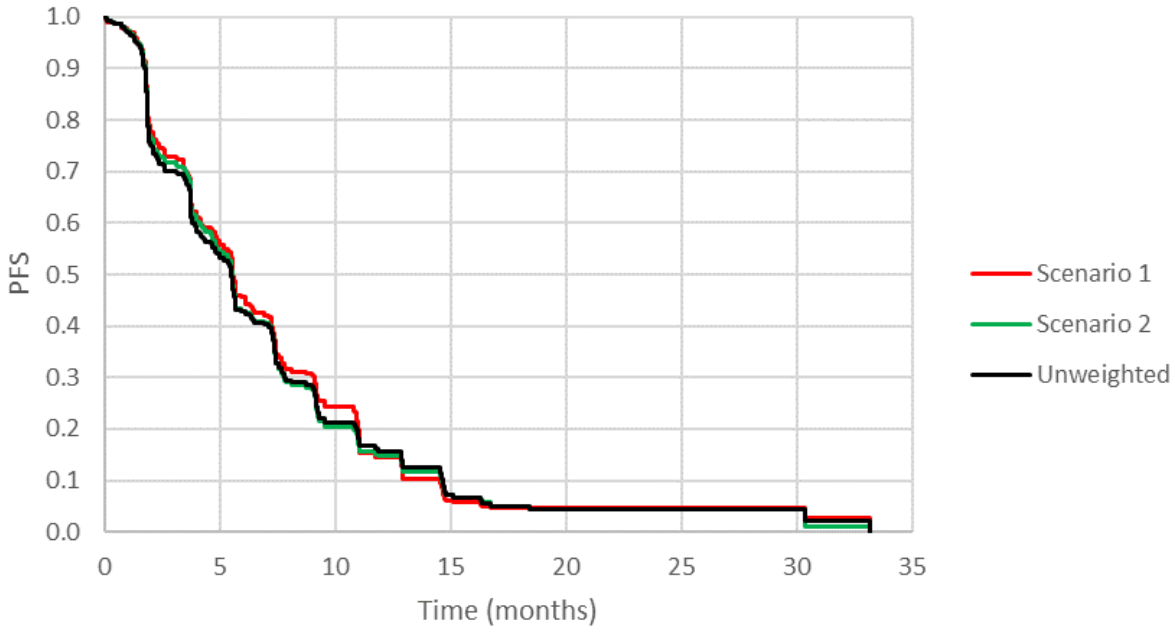
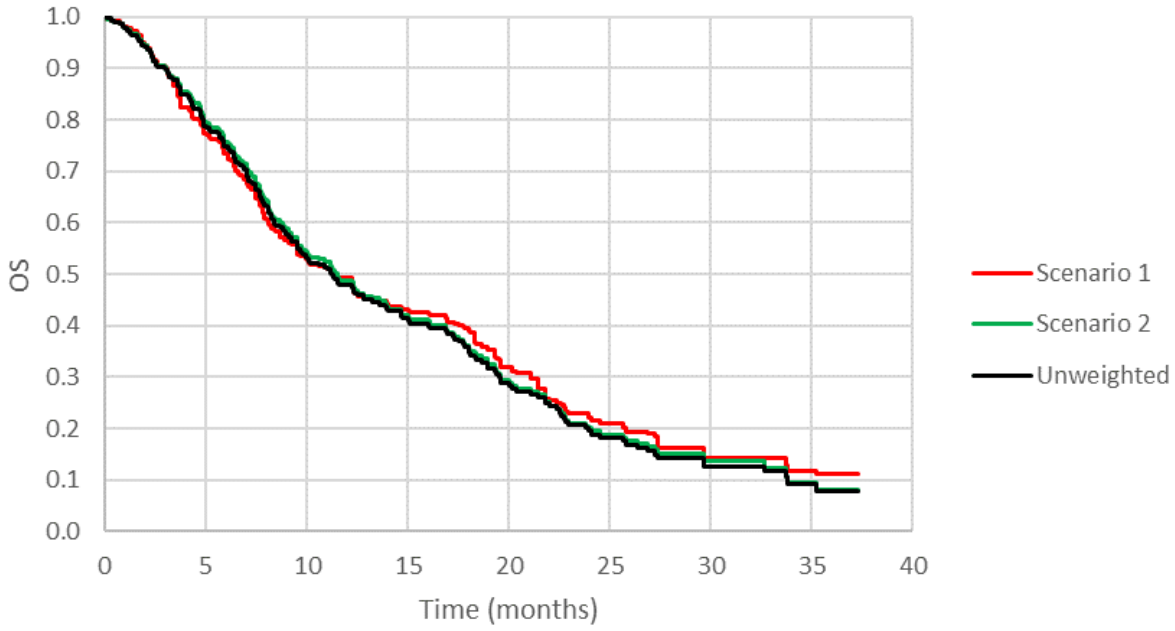


Figure 5: Unadjusted and weighted Kaplan-Meier curves for OS, cabozantinib arm of CELESTIAL, (reproduced from clarification response, question A15)



The company also used the MAIC methodology to evaluate six AE outcomes. An anchored approach was adopted for the analysis of four AEs: increased AST; elevated bilirubin; fatigue and hypertension. An unanchored approach was adopted for the analysis of diarrhoea and PPES due to zero event rates in the placebo arms of the RESORCE and CELESTIAL trials,[7, 15] respectively. The treatment effect for each AE was represented by a log odds ratio (LOR) and associated 95% CI. Results are presented in Table 30 of the CS;[1] these results are also summarised Table 12. The incidence of AEs was generally

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higher for cabozantinib than regorafenib; however, a statistically significant difference was only observed for diarrhoea, and this was based on an unanchored comparison approach.

For the analysis of PFS and OS, the company explored the PH assumption using weighted second-line cabozantinib data from Scenario S1[7] and regorafenib data from the RESORCE trial.[15] The CS[1] states that the PH assumption was not satisfied for PFS or OS based on an assessment of the log cumulative hazard plots, Schoenfeld residuals and the Grambsch-Therneau test. The CS states that due to the uncertainty around the PH assumption, an alternative time-varying HR analysis was performed. The company conducted an anchored analysis, based on the assumption that the PH assumption did not hold, to explore any differences in the treatment effect emerging between cabozantinib and regorafenib over time. The CS states that a log-logistic model was selected for the time-varying approach as it was the best fitting model according to the AIC and BIC statistics. The results of the anchored analysis using time-varying HRs generated from the log-logistic model are presented in the CS (Section 3.10.3, Figures 17-18) for PFS and OS; the key findings are summarised in Table 11. The CS states that other parametric models were tested using a time-varying approach, including Weibull, Gompertz, log-normal and generalised gamma distributions; these are presented in CS Appendix I. The company's clarification response[19] (question A20) provides further information regarding the approach adopted to estimate a time-varying HR. The ERG believes that the time-varying approach adopted by the company has been undertaken appropriately.

Unanchored comparisons

The results of the unanchored analysis for PFS and OS are shown in CS[1] Figures 19 and 20; these are also summarised in Table 11. The company's clarification response[19] (question A15) provides the AIC and BIC statistics for each of the models fitted in the unanchored comparison, which the company used to support the selection of the log-logistic model (this model provided the lowest AIC and BIC values for the weighted cabozantinib arm). However, results for other parametric models (i.e. those explored as part of the anchored comparisons) were not presented by the company.

The unanchored approach using a generalised gamma model for PFS showed a statistically significant benefit for cabozantinib until approximately 1 year; beyond this timepoint the PFS curves show little difference for the remainder of the time horizon. Cabozantinib had a larger point estimate for mean PFS than regorafenib and a higher median PFS. The OS curves based on the log-logistic model showed a large amount of overlap until year 1 when cabozantinib begins to show a relatively small benefit over regorafenib. Cabozantinib had a larger point estimate for mean OS and a higher median OS. The company concluded that the results across the models show that over time, the HR is not statistically different from 1.0, suggesting no difference in treatment effect. Furthermore, the HR is generally seen to be constant and near 1.0 as the treatment effect is extrapolated, which suggested equivalence in

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treatment effect over time. The ERG has concerns that the direction of the treatment effect for OS is not consistent across the different ITC analyses presented by the company - both the Bucher ITC and anchored MAICs (constant HR and time-varying HR) yield HRs which are greater than 1.0 for cabozantinib versus regorafenib (favouring regorafenib), whereas the results from the unanchored MAIC suggests an OS benefit for cabozantinib over regorafenib.

The company's clarification response[19] (question A15) provides other fitted parametric models overlaid on the cabozantinib Kaplan-Meier curves, as shown in Figure 6 (PFS) and Figure 7 (OS). For OS, the log-logistic model does not appear to provide a good fit to the tail of the data and provides the most optimistic estimates of long-term survival (along with the log-normal model).

Figure 6: Parametric curves overlaid on top of the weighted cabozantinib Kaplan-Meier curve for PFS (reproduced from clarification response, question A15)

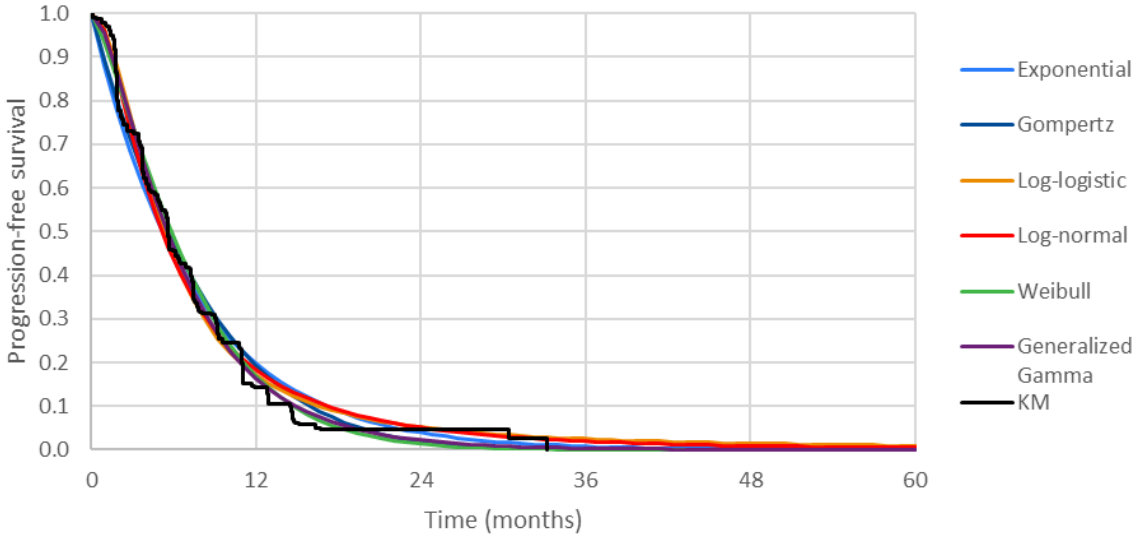
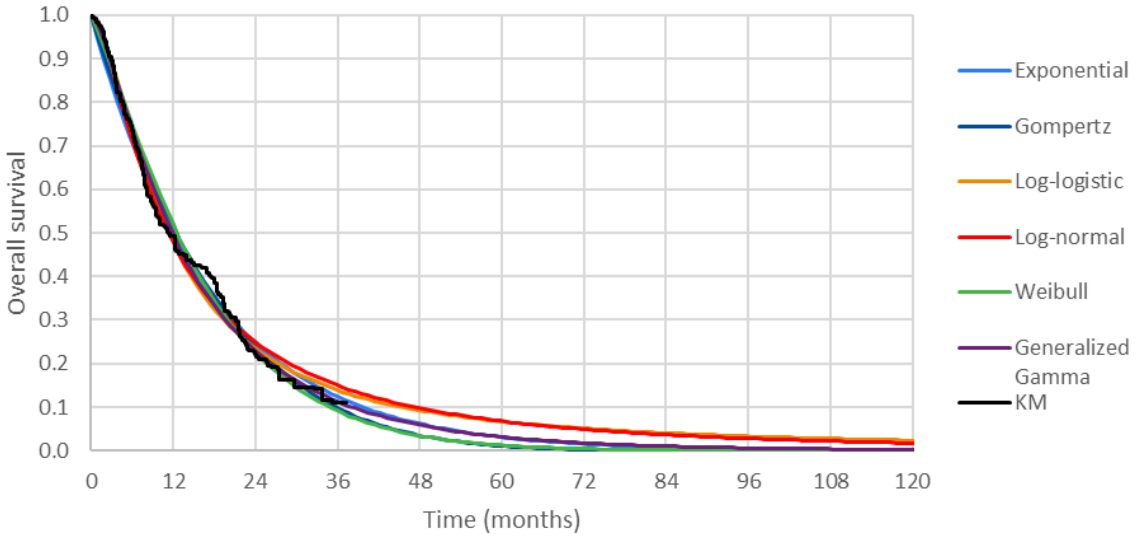


Figure 7: Parametric curves overlaid on top of the weighted cabozantinib Kaplan-Meier curve for OS (reproduced from clarification response, question A15)



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During the clarification process, the ERG asked the company to provide the empirical and smoothed hazard functions (see clarification response,[19] question A15). The company's response provided this for the cabozantinib arm of the CELESTIAL trial[7] and the regorafenib arm of the RESORCE trial[15] in Figures 8 and 9 for OS and Figures 12 and 13 for PFS of the clarification response document, along with the hazard function of the log-logistic and generalised gamma models overlaid (best fitting models for OS and PFS, respectively). The shape of the smoothed hazard function does not follow the same shape as the hazard function of the log-logistic model (selected for OS), which suggests that this may not be the most appropriate model selection. However, for PFS, the smoothed hazard function follows a similar shape to the hazard function of the generalised gamma model, which suggests that this may be an appropriate model selection.

The ERG believes that the unanchored comparisons presented by the company may not be reliable; this form of comparison relies upon strong assumptions which are rarely satisfied, for example, matching on all prognostic factors and treatment effect modifiers, and relies on a comparison of absolute effects, which does not preserve trial randomisation. However, the ERG also recognises that the placebo plus BSC arm of both CELESTIAL and RESORCE trials[7, 15] may differ: the company has shown that the HR between the two placebo plus BSC arms is not equal to 1.0, which suggests that the anchor arm may not be entirely comparable between the two trials. This is a notable limitation of the anchored comparisons, which rely on the assumption of transitivity (i.e. the anchor arm is comparable between the two trials).

The company's clarification response[19] (questions A12 and B6) confirms that the anchored MAIC analysis using a constant HR from the Weibull model is considered to be their base case. This ITC is also denoted as the company's base case scenario in their analysis of incremental quality-adjusted life years (QALYs) gained for cabozantinib versus regorafenib (see Section 4.5.1).

3.3.4 Key limitations of company's ITC analyses

The ERG believes that the company's ITC analyses are subject to a number of uncertainties. Whilst preserving trial randomisation, the use of the Bucher ITC approach is limited by the lack of adjustment for cross-trial differences which are present in the data. One of the key assumptions underpinning the Bucher approach is that there is no difference between trials regarding the distribution of effect modifiers. The company acknowledges that there are considerable observed differences in trial populations (CS,[1] Section 3.10.3, page 61), a consequence being that this assumption is unlikely to be satisfied. Further, the full ITT population from the CELESTIAL trial[7] was used in the Bucher comparison presented in the CS,[1] meaning that second- and third-line patients were compared against second-line patients from the RESORCE trial.[15] Therefore, results from this form of comparison are unlikely to be sufficiently robust to draw inferences. Despite the company also presenting results using

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the second-line population from the CELESTIAL trial, the ERG believes that this form of comparison may lack robustness due to the remaining cross-trial differences between the studies.

The company has conducted a series of population-adjusted ITCs in attempt to overcome cross-trial differences between the CELESTIAL and RESORCE trials.[7, 15] Despite the company utilising the subpopulation of second-line HCC patients who had prior treatment with sorafenib patients from the CELESTIAL trial to align more closely with the population from the RESORCE trial, the ERG has concerns that there may remain differences between the two trials which have not been accounted for in the ITC analyses. Further, whilst anchored comparisons are a recommended approach for ITCs, as they provide a way of comparing two interventions with fewer assumptions required than unanchored comparisons, it is important that the anchor arm (in this case, placebo plus BSC) is consistent across both trials. There are concerns with regard to the comparability of the placebo plus BSC arms across both CELESTIAL and RESORCE trials. Specifically, the company evaluated the treatment effect between the placebo arms of both trials and found that the HR for OS was different from 1.0, although this result was statistically non-significant (HR=0.87; 95% CI [0.67-1.15]; *p*=0.326). For PFS, there was a greater difference between the two trials (HR=0.69; 95% CI [0.55-0.87]; *p*=0.002). A similar result was found for both OS and PFS in Scenario S2. The assumption of transitivity which underpins anchored ITCs may be violated if there are systematic differences in the anchor arm of each trial. The company acknowledges that this finding suggests that there may remain important cross-trial differences which have not been addressed in the MAIC, raising concerns on the robustness of the anchored ITC analyses conducted.

Identification of the baseline characteristics included in the matching process was based on clinical input; however, in Scenario S2, the factors were selected using stepwise regression methods; an empirical approach informed by the data. The ESS estimate for the cabozantinib arm in Scenario S1 is approximately 54% of the original sample size after weighting, showing a substantial reduction in the number of patients informing the analysis. The ESS estimate for the cabozantinib arm was higher in S2, being approximately 93% of the original sample size; however, fewer factors were included in the matching process meaning that important effect modifiers may not have been accounted for and therefore, residual confounding may be present.[22]

The company has also performed an unanchored comparison, comparing cabozantinib versus regorafenib without utilising data from the placebo plus BSC arm from either trial. Unanchored comparisons do not preserve trial randomisation and are limited by the comparison of absolute effects only. Further, unanchored comparisons rely on strong assumptions - that all prognostic factors and treatment effect modifiers are accounted for in the matching process. This condition is rarely met.[22] Therefore, the company's unanchored comparisons may not be robust if there are other factors

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considered influential on outcomes or which may alter the treatment effect between cabozantinib and regorafenib. Remaining differences between study populations may result in the presence of residual confounding, meaning that the unanchored MAIC results are limited. Further, the findings from the unanchored comparison conducted for OS (which uses a log-logistic model fitted to both treatment arms) are inconsistent with those obtained from the Bucher and anchored MAIC analyses, where cabozantinib was found to be superior to regorafenib (higher mean and median OS), despite the HR estimates from the anchored comparisons being greater than 1.0. This inconsistent finding may suggest uncertainty around the treatment effect, but it may be an artefact of comparing absolute effects and breaking trial randomisation. Therefore, the results from the unanchored comparison may not be reliable.

The results of the ITC analyses presented by the company were used to justify an assumption of equivalent clinical effectiveness between cabozantinib and regorafenib; this assumption underpins the company's cost-comparison analysis (see Section 4). However, whilst a statistically non-significant difference has been found between cabozantinib and regorafenib, this does not infer equivalence of the two regimens. The ERG believes that the Bucher ITCs performed by the company are limited because they do not account for cross-trial differences which have been identified. The unanchored ITC is also limited by lack of preservation of trial randomisation and the potential problem of residual confounding. The ERG considers the anchored MAIC analyses to provide the most robust estimates of relative treatment effects between cabozantinib and regorafenib; however, like the company, the ERG also has concerns regarding the comparability of the anchor arm (placebo plus BSC) across the two trials. The analysis conducted by relaxing the PH assumption by allowing the HR to vary with time may be the most appropriate approach in light of violation of the PH assumption for PFS and after assessment of the time-varying HR plots, which show that the HR is not constant for a number of parametric models.

3.3.5 Conclusions on the company's ITCs

The company has explored a number of statistical ITC approaches, all of which show a statistically non-significant difference between cabozantinib and regorafenib. The ERG believes that there are limitations associated with all ITC analyses conducted; however, an anchored approach would be the preferred form of ITC to estimate comparative efficacy and safety in the absence of direct head-to-head data. Due to the limitations and concerns outlined, the ERG believes that there remains uncertainty around the treatment effect between cabozantinib and regorafenib, including the assumption of equivalence of the two regimens and therefore, the results of the ITCs conducted should be interpreted with caution.

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4. ERG'S CRITIQUE OF THE COMPANY'S COST COMPARISON ANALYSIS

4.1 Model summary, assumptions and evidence sources

As part of the CS,[1] the company submitted an executable cost comparison model of cabozantinib versus regorafenib for patients with previously treated advanced HCC. The company's base case analysis estimates the cost savings for cabozantinib versus regorafenib based on the number of whole packs of cabozantinib or regorafenib required to treat patients until progression and the cost per pack of each drug, assuming the same treatment duration for both groups. The model applies a 15 year time horizon to estimate maximum treatment duration based on PFS data from the CELESTIAL trial ITT population[7] as a proxy. Discounting is not included. All analyses presented in the CS use point estimates of parameters; probabilistic analysis has not been undertaken. The company's analyses include the Patient Access Scheme (PAS) discount for cabozantinib and the list price for regorafenib. The results of the company's analyses including both the PAS price for cabozantinib and the comparator Patient Access Scheme (cPAS) price for regorafenib are provided in a separate confidential appendix to this ERG report.

The company's base case analysis makes the following assumptions:

(i) *Equivalent clinical outcomes*. Cabozantinib and regorafenib are assumed to be clinically equivalent in terms of PFS, OS, time on treatment (ToT) and AEs. As such, the incremental QALY gain for cabozantinib versus regorafenib is assumed to be zero.

(ii) *Treatment is given until disease progression.* Whilst the RESORCE and CELESTIAL trials[7, 15] permitted some patients to continue treatment beyond disease progression, the cost comparison model assumes that both drugs are given until disease progression in all patients. PFS duration is estimated using a log-normal model fitted to IPD from the cabozantinib arm of the CELESTIAL trial.[7] The executable model does not include the cumulative probabilities of PFS over time; rather, all calculations are undertaken using the 15-year restricted mean (i.e., the area under the curve [AUC] up to 15 years after starting treatment). The impact of an arbitrary increase/decrease in mean treatment duration for both groups (+/-20%) is tested in sensitivity analysis.

(iii) *No difference in costs except for drug acquisition.* The only difference in costs between the treatment groups in the base case analysis relates to the costs of drug acquisition. The model assumes that there is no difference in the costs of disease management (e.g., clinic visits and monitoring), subsequent anticancer therapies given after disease progression or AEs between the treatment groups. Both drugs are given orally; hence, administration costs are not relevant. The impact of applying treatment-specific AEs on costs is tested in sensitivity analysis.

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(iv) *Perfect relative dose intensity.* The drug acquisition cost calculations assume 100% relative dose intensity (RDI) in both groups (i.e., patients receive the full recommended dose on every day that they receive either drug, irrespective of whether their dose has been reduced). This assumption is tested in sensitivity analysis.

(v) *Wastage costs included.* Both cabozantinib and regorafenib are subject to additional costs associated with wastage; these are captured by estimating the number of full packs of treatment required to treat patients up to the mean PFS duration. The effect of removing this assumption (by splitting packs) is tested in sensitivity analysis.

The company's base case and sensitivity analyses are summarised in Table 13. The evidence sources used to inform the company's model are summarised in Table 14. The frequencies of AEs and associated management costs, as applied in the sensitivity analysis, are summarised in Table 15.

Table 13: Summary of cost comparison analyses presented in the CS

Analysis	Description of analysis
Base case	Assumes equivalence in PFS, OS, ToT and AEs. Includes wastage costs (number of full packs required). Excludes AE costs. Assumes perfect RDI.
SA1 - Time on treatment – 20% ([redacted] months)	Same as base case analysis, but assumes ToT for both drugs is 80% of the mean value
SA2 - Time on treatment + 20% ([redacted] months)	Same as base case analysis, but assumes ToT for both drugs is 120% of the mean value
SA3 - Include drug-specific AE costs	Same as base case analysis, but includes AE frequencies for cabozantinib and regorafenib using RESORCE[15] and the company's MAICs to estimate cost differences
SA4 - Include RDI	Same as base case analysis, but uses mean daily dose received in RESORCE[15] and CELESTIAL[7] to estimate number of packs required
SA5 - Exclude wastage costs	Same as base case analysis, but assumes that packs can be split

SA - sensitivity analysis; PFS - progression-free survival; OS - overall survival; ToT - time on treatment; AE - adverse event; RDI - relative dose intensity; MAIC - matching-adjusted indirect comparison

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Table 14: Evidence sources used to inform the company's cost comparison model

Parameter	Value	Source	ERG comments
Mean time on treatment – both treatment groups	[redacted] months	Log-normal model fitted to PFS data from CELESTIAL[7]	The model estimates that [redacted] packs of cabozantinib and regorafenib are required to treat to progression
Cost per pack – cabozantinib	List price: £5,143.00 PAS price: [redacted]	BNF[12]	Pack size is 30 x 60mg tablets (30 days' supply)
Cost per pack – regorafenib	List price: £3,744 cPAS price: see confidential appendix	BNF[12]	Pack size is 84 x 40mg tablets (28 days' supply)
RDI – cabozantinib (SA only)	0.61	CELESTIAL[7]	Calculated from mean vs. planned dose in trial. Base case analysis assumes RDI=100%
RDI – regorafenib (SA only)	0.90	RESORCE[15]	Calculated from mean vs. planned dose in trial. Base case analysis assumes RDI=100%
AE frequency – cabozantinib (SA only)	See Table 15	MAIC using data from RESORCE and CELESTIAL[1]	Calculated from ORs presented in CS[1] Table 35
AE frequency – regorafenib (SA only)		RESORCE[15]	Data for regorafenib presented in CS[1] Table 25
AE unit costs (SA only)		NHS Reference Costs 2019/20,[6] PSSRU[23] and assumptions	-

ERG - Evidence Review Group; PFS - progression-free survival; PAS - Patient Access Scheme; cPAS - comparator PAS; mg - milligram; RDI - relative dose intensity; SA - sensitivity analysis; BNF - British National Formulary; AE - adverse event; MAIC - matching-adjusted indirect comparison; OR - odds ratio; CS - company's submission

Table 15: Grade 3/4 AE frequency and unit costs (applied in sensitivity analysis 3 only)

AE	Unit cost	Frequency - cabozantinib†	Frequency - regorafenib*
PPES	£420.66	0.13	0.13
Hypertension	£638.81	0.55	0.13
Elevated aspartate aminotransferase	£0.00	0.11	0.05
Fatigue	£63.45	0.07	0.06
Diarrhoea	£629.69	0.12	0.02
Elevated bilirubin	£0.00	0.05	0.07
Expected cost per patient	-	£490.04	£155.86

AE - adverse event; PPES - palmar-plantar erythrodysaesthesia syndrome
** Calculated as the sum of Grade 3 and 4 treatment-emergent drug-related AEs in Bruix et al[15]*
† Calculated by applying the ORs from the company's MAICs to the regorafenib arm AE frequencies as baseline

4.2 Company's model results

The results of the company's base case analysis and sensitivity analyses are presented in Table 16. The company's base case analysis suggests that compared to regorafenib, cabozantinib is estimated to generate cost savings of [redacted] per patient. The estimated cost savings for cabozantinib are reduced slightly if patients spend less time on treatment and/or if the costs of managing AEs are included in the

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analysis. The estimated cost savings are greater if patients spend longer on treatment, if RDI is included and/or if wastage costs are excluded from the model. The ERG notes that as these analyses do not include the cPAS discount for regorafenib, the results are not meaningful. The results of the company's model including the PAS discounted prices for cabozantinib and regorafenib are presented in a separate confidential appendix to this report.

Table 16: Results of company's cost comparison

Scenario	Cabozantinib	Regorafenib	Incremental
Base case	[redacted]	[redacted]	[redacted]
SA1 - Time on treatment – 20% ([redacted] months)	[redacted]	[redacted]	[redacted]
SA2 - Time on treatment + 20% ([redacted] months)	[redacted]	[redacted]	[redacted]
SA3 - Include arm-specific AE costs	[redacted]	[redacted]	[redacted]
SA4 - Include RDI	[redacted]	[redacted]	[redacted]
SA5 - Exclude wastage costs	[redacted]	[redacted]	[redacted]

SA - sensitivity analysis; AE - adverse event; RDI - relative dose intensity
** Regorafenib costs are unchanged from the base case due to patients spending 1-week off treatment at the end of each regorafenib treatment cycle (see clarification response,[19] question B5)*

4.3 ERG critique of the company's cost comparison model

4.3.1 Critical appraisal methods

The ERG adopted a number of approaches to explore, interrogate and critically appraise the company's submitted cost comparison analysis. These included:

- Assessing whether the company's analysis is in line with NICE's guidance on undertaking cost comparison FTAs[24]
- Verifying the calculations used in the model, including double-programming the base case model and sensitivity analyses to check for errors
- Scrutinising the assumptions underpinning the cost comparison model and discussing these with clinical experts
- Checking the correspondence between the description of the model reported in the CS[1] and the company's executable model
- Where possible, checking of key parameter values used in the company's model against their original data sources.

As the company intends cabozantinib to be considered under NICE's FTA process, the focus of the ERG's critical appraisal was on the appropriateness of the cost comparison model and its underlying assumptions. The ERG's concerns around the submitted analysis are summarised briefly in Section 4.3.2. As discussed in Section 3.3, there is uncertainty around whether it is reasonable to assume clinical equivalence between cabozantinib versus regorafenib for PFS, OS and AEs. As such, the ERG's critique also includes some consideration of the likely direction of incremental costs and health outcomes if the assumption of equivalence does not hold.

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4.3.2 ERG critical appraisal - results

The main items identified from the ERG's critique are summarised in Box 1.

Box 1: Summary of key items considered in the ERG's critical appraisal

(1) Adherence to NICE guidance on cost comparison FTAs
(2) Model verification
(3) Appropriateness of evidence sources
(4) Appropriateness of base case assumptions

(1) Adherence to NICE guidance on cost comparison FTAs

The company's cost comparison model includes a single comparator – regorafenib – which was appraised by NICE in TA514 and TA555.[5, 25] As discussed in Section B.1.1 of the CS,[1] the company's proposed positioning for cabozantinib is exactly the same as the current recommendation for regorafenib, that is, as an option for treating advanced unresectable HCC in adults who have had sorafenib, only if they have Child–Pugh grade A liver impairment and an ECOG PS of 0 or 1.[5] This is narrower than the wording of the marketing authorisation for cabozantinib for treating HCC,[11] although the ERG notes that all patients in CELESTIAL[7] had an ECOG PS <2 and only 1 patient had Child Pugh grade B disease. Given the company's intended positioning of cabozantinib, the ERG and its clinical advisors believe that the company's choice of comparator for the cost comparison is appropriate.

The final NICE scope[14] also includes BSC as a comparator. The CS[1] (Section B.1.1) comments that BSC *"is not a relevant comparator for a NICE FTA cost comparison for cabozantinib, as the comparator can only be technologies already recommended in published technology appraisal guidance and/or treatment guidelines for the same indication."*[1] The ERG agrees that BSC is not a relevant comparator for this appraisal and that a positive NICE recommendation for cabozantinib would only displace regorafenib.

The other aspects of the company's cost comparison analysis, including the time horizon adopted and the omission of discounting, are in line with NICE's guidance for companies submitting cost comparisons through the FTA process.[24]

(2) Model verification

The ERG double-programmed the company's cost comparison model. This included replicating the base case scenario and each of the five sensitivity analyses presented in Table 16. The ERG was able to generate the same results as those presented in the CS.[1] The ERG believes that the company's analyses are free from programming errors.

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(3) Appropriateness of evidence sources used to inform model parameters

The ERG believes that the evidence sources used to inform the company's base case model (Table 14) are appropriate and that the values applied in the executable model are consistent with their original sources. The ERG also believes that the sources used to obtain these parameter values are appropriate. The ERG was unable to check whether the company's parametric survival modelling for PFS was implemented correctly as the underlying IPD were not provided.

The ERG notes that unit costs associated with managing AEs have been drawn from NHS Reference Costs 2019/20[6] and from the Personal Social Services Research Unit (PSSRU).[23] The most noticeable differences in AE frequencies between the drugs relate to hypertension and diarrhoea; other AE frequencies are similar between the groups (see Table 15). The unit cost for managing hypertension in the company's model is broadly similar to the value used in TA555[5] (cost comparison model unit cost = £629.69; TA555 model unit cost = £729.87), whilst diarrhoea was not included as an AE in the TA555 model. The ERG notes however that the general approach to modelling AEs differs between the appraisals – the cost comparison model assumes that AEs result in a once-only cost, whereas the TA555 model assumed an ongoing AE probability in every cycle at a lower overall rate.[26] As such, the approaches are therefore not fully comparable. However, neither the company's sensitivity analysis including differential AE costs (Table 16) nor the deterministic sensitivity analyses undertaken by the company in TA555 (see Stevenson *et al.*,[26] Figure 14) indicate that AE costs are a key model driver.

(4) Appropriateness of base case model assumptions

The ERG has some concerns regarding some of the base case model assumptions, in particular:

(a) The assumption of equivalent PFS and OS
(b) The assumption of equivalent AEs
(c) The assumption of equivalent resource use whilst on treatment
(d) The assumption of perfect (100%) RDI for both drugs.

These issues are discussed below.

(a) The assumption of equivalent PFS and OS

As discussed in Section 3.3, the company has undertaken a range of indirect comparisons using the Bucher approach and anchored and unanchored MAICs. All of these analyses suggest a statistically non-significant difference between cabozantinib and regorafenib for PFS and OS. The anchored MAICs, which reflect the preferred analyses of both the company and the ERG, indicate that the point estimate of the HR for PFS favours cabozantinib, whilst the point estimate of the HR for OS favours regorafenib. The ERG believes that there remains uncertainty around the relative treatment effect between cabozantinib and regorafenib, including the assumption of equivalence of the two regimens

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and therefore, the results of the ITCs and the appropriateness of a cost comparison approach should be interpreted with caution.

(b) The assumption of equivalent AEs

The company's base case analysis excludes the costs of AEs. Given the use of a cost comparison approach, the analysis also assumes that there is no differential impact of toxicity on HRQoL between the treatment options. One of the ERG's clinical advisors commented that whilst the toxicity profile for regorafenib is both predictable and manageable, this is not the case for cabozantinib, which by comparison is considered to be less predictable and more toxic. This is likely to lead to increased costs and greater health losses for patients receiving cabozantinib compared with regorafenib. Differences in toxicity between the regimens are also apparent from the results of the company's MAICs, whereby the total sum of probabilities of the individual grade 3/4 AEs is 1.03 for cabozantinib and 0.46 for regorafenib, see Table 15). Whilst the company's sensitivity analyses include group-specific AE costs, the use of a cost comparison model precludes any consideration of associated health losses. Based on clinical advice received from clinical experts and the company's ITCs, the ERG believes that cabozantinib may result in QALY losses due to AEs, even if PFS and OS are broadly equivalent between the options. These effects cannot be fully captured in the company's cost comparison model.

The ERG also notes that the negative effects of toxicity may be reflected in the EQ-5D data from the CELESTIAL and RESORCE trials.[7, 15] The mean difference in change from baseline EQ-5D for regorafenib versus placebo in RESORCE was reported to be small and non-significant (mean difference in index score = -0.01; 95% CI -0.03 to 0.02, p=0.4695).[26] [redacted] Table 6 [redacted] Similarly, the ERG's clinical advisors highlighted the value that patients with advanced HCC place on maintaining HRQoL. One of the ERG's clinical advisors further commented that these toxicity effects are also evident from the data on dose reductions and Grade 3/4 AEs in the cabozantinib arm of CELESTIAL and the high proportion of Grade 3/4 AEs (62% of patients experienced a dose reduction and 68% of patients experienced Grade 3/4 AEs).

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(c) The assumption of equivalent resource use whilst on treatment

The company's base case model assumes that all other resource use is equivalent for cabozantinib and regorafenib. The ERG's clinical advisors commented that owing to its comparatively worse toxicity profile, cabozantinib is expected to lead to additional costs of monthly face-to-face visits whilst patients are still on treatment, which would otherwise have been managed remotely and less frequently (2-monthly) for patients receiving regorafenib. These additional costs are not included in the company's base case or sensitivity analyses.

(d) The assumption of perfect RDI for both drugs

The company's base case analysis includes the costs of full pack dosing, based on the assumption that there are no efficiencies in minimising drug wastage in clinical practice (i.e., dose reductions, even if planned, do not lead to lower drug costs to the NHS). The CS[1] states that this approach reflects a conservative assumption and states that this assumption was used in TA555.[5] The ERG disagrees that this assumption was preferred in final guidance for TA555; the TA555 guidance document states that the company's analyses which assumed full pack dosing were *"unlikely to reflect clinical practice, because the dose reductions in the trial were planned, so it was more likely that wastage would be minimised in clinical practice"* (TA555 guidance, Section 3.15). As part of TA555, the company submitted evidence from pharmacists from two large tertiary centres in the UK supporting the use of pack-splitting to minimise wastage of sorafenib and other TKIs. The NICE Appraisal Committee concluded that *"although wastage could be minimised, the pharmacists' evidence provided by the company suggested that it could not be eliminated entirely"* Overall, the ERG believes that it may be more appropriate to include RDI, together with an assumed level of wastage which is consistent with previous appraisals in HCC.[10, 25]

4.5 Additional analyses undertaken by the company and the ERG

4.5.1 Additional analyses presented in the company's clarification response

During the clarification process, the ERG asked the company to fit parametric survival models to the OS data for the time-varying and constant HR anchored MAICs in the second-line HCC population and, if possible, to estimate incremental QALYs using these survival models together with the EQ-5D data from CELESTIAL[7] (see clarification response,[19] questions A22, B4 and B6). In their response, the company presented additional survival modelling, utility estimates based on CELESTIAL and a partitioned survival model which combines information on PFS, OS and utilities to estimate incremental QALYs for cabozantinib versus regorafenib. Incremental QALYs were presented across four scenarios:

1. Anchored MAIC, constant HR (Weibull HR). This model involved fitting parametric models for PFS and OS to data for each trial including treatment group as a covariate and applying the HR for regorafenib versus placebo to the weighted placebo arm of CELESTIAL. PFS and OS

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were modelled using Weibull distributions. The company's clarification response indicates that this model reflects their base case scenario.

2. Anchored MAIC, constant HR (Cox PH). This model is the same as the company's base case, except that the HR from the Cox model used in the anchored MAIC was applied to the PFS and OS models for the cabozantinib group to estimate outcomes for the regorafenib group.
3. Anchored MAIC time-varying HR. This model applies time-varying HRs from the anchored MAICs. PFS and OS are both modelled using log-logistic models.
4. Unanchored MAIC. This model uses the unanchored MAIC, as described in Section B.3.10.3 of the CS.

For each of these four models, the company applied utility values for the progression-free and progressed disease states, based on a Tobit regression model fitted to the EQ-5D-5L data from CELESTIAL.[7] The same utility values were applied to each treatment group (utility value progression-free = [redacted]; utility value progressed disease = [redacted]). It should be noted that this approach implicitly assumes that cabozantinib is not associated with any further QALY losses due to toxicity compared to regorafenib. Incremental QALY estimates were presented using both the deterministic and probabilistic versions of the model.

The results of the company's partitioned survival models are summarised in Table 17. As expected, the company's anchored MAIC analyses, including their preferred base case, consistently indicate that cabozantinib is expected to result in an incremental QALY loss compared to regorafenib. In contrast, the unanchored MAIC indicates the reverse situation whereby cabozantinib results in an incremental QALY gain. The company's clarification response presents distributions of incremental QALYs from the probabilistic model and suggest that many probabilistic samples are close to zero, *"demonstrating no meaningful difference in QALYs between cabozantinib and regorafenib in a pure second line HCC population previously treated with sorafenib irrespective of tolerability."*[19] The ERG believes that the company's additional analyses are useful and that a good range of scenarios have been presented using appropriate methods. The ERG also agrees that the estimates of incremental QALYs are uncertain, but notes that if a full cost-utility model had been developed, the expected incremental QALYs would be negative and the resulting ICER would be in the North-West or South-West quadrants of the cost-effectiveness plane (depending on the discounted price of cabozantinib).

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Table 17: Results of company's partitioned survival analysis

Scenario	Incremental QALYs gained - cabozantinib versus regorafenib	
	Deterministic model	Probabilistic model
1. Anchored MAIC, constant HR (Weibull HR base case)	[redacted]	[redacted]
2. Anchored MAIC, constant HR (Cox PH base case)	[redacted]	[redacted]
3. Anchored MAIC, time-varying HR	[redacted]	[redacted]
4. Unanchored MAIC	[redacted]	[redacted]

QALY - quality-adjusted life year; MAIC - matching-adjusted indirect comparison; HR - hazard ratio

4.5.2 Additional exploratory analysis undertaken by the ERG

In order to address some of the concerns raised in Section 4.4, the ERG undertook an additional exploratory analysis using the company's cost comparison model. This analysis is the same as the company's base case cost comparison, with the following amendments:

- RDI estimates are included, based on mean estimates reported from RESORCE and CELESTIAL[7, 15]
- AE management costs are included for both drugs
- Wastage costs are included based on two assumptions: (i) packs can be split to avoid inefficiencies in prescribing; (ii) on average, each patient will incur wastage associated with one quarter-pack of a pack of each drug (based on the earlier sorafenib HCC appraisal[10]).
- Monitoring costs are included for both drugs. For regorafenib, the analysis assumes that patients require one consultant-led non-face-to-face clinic visit every two months, whereas for cabozantinib, patients require one consultant-led face-to-face clinic visit every month. Unit costs were based on NHS Reference Costs 2019/20 (Consultant-led Medical Oncology, Service Code 370). The unit costs for non-face-to-face and face-to-face visits are £136.36 and £200.20, respectively.[6]

The results of the ERG's additional analysis are presented in Table 18. This analysis suggests slightly greater cost savings for cabozantinib, which are driven largely by the inclusion of RDI estimates in the analysis. In the absence of a full cost-utility model, the ERG is unable to undertake exploratory analyses under the assumption the cabozantinib and regorafenib are not equivalent in terms of PFS and OS. The ERG was also unable to undertake further analyses using the company's partitioned survival model described in the clarification response[19] (see Section 4.5.1) as the executable model was not provided.

Table 18: ERG's exploratory analyses using the company's cost comparison model

Scenario	Cabozantinib	Regorafenib	Incremental
Company's base case	[redacted]	[redacted]	[redacted]
ERG's preferred analysis under assumption of equivalence	[redacted]	[redacted]	[redacted]

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4.6 ERG's view regarding whether outcomes and costs are likely to be similar for cabozantinib and regorafenib

Table 19 summarises the ERG's view regarding the direction of incremental health outcomes and costs, had a full cost-utility model been developed as part of a usual STA. Overall, the ERG believes that irrespective of whether it is reasonable to assume clinical equivalence in terms of PFS and OS, cabozantinib would likely be associated with fewer QALYs than regorafenib due to its comparatively worse toxicity. If relative treatment effects on clinical endpoints were based on the anchored MAICs, it is expected that cabozantinib would lead to a PFS gain and an OS loss; it is likely that the overall incremental health impact would be negative, as OS tends to have a greater impact on QALYs than PFS. If PFS is greater for cabozantinib than regorafenib, this would also likely lead to higher net drug acquisition costs, although this also depends on differences between the discounted prices of the two drugs. In the absence of a full cost-utility model, the magnitude of these expected QALY losses and cost differences remains unclear.

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Table 19: Summary of ERG's view of the expected direction of incremental health outcomes and costs for cabozantinib versus regorafenib

Endpoint	ERG summary of evidence and comments
PFS	The company's Bucher ITCs and MAICs indicate non-significant differences in PFS. Point estimates of the HR are consistently in favour of cabozantinib. The ERG's clinical advisors commented that both drugs are likely to be similar in terms of PFS, but noted that the wide 95% CIs around the HRs means that there is uncertainty around the assumption of equivalence.
OS	The company's Bucher ITCs and MAICs indicate non-significant differences in OS. Point estimates of the HR are consistently in favour of regorafenib, except for the unanchored MAIC. As noted in the company's clarification response[19] (question B2), the proportions of patients receiving subsequent anticancer therapy in each trial was similar and is unlikely to confound OS results. The ERG's clinical advisors believe that both drugs are likely to be similar in terms of OS, but noted that the wide 95% CIs around the HRs means that there is uncertainty around the assumption of equivalence.
AE frequency	The company's MAICs indicate a greater overall incidence of Grade 3/4 AEs for cabozantinib than regorafenib (see Table 15). The ERG's clinical advisors commented that toxicity is worse for cabozantinib than regorafenib. One clinical advisor commented that this view reflects both the trial data and their own clinical experience with both drugs.
HRQoL	[redacted] Available EQ-5D data from RESORCE do not indicate a significant difference between regorafenib and placebo, which might suggest worse HRQoL for cabozantinib than regorafenib, although the EQ-5D questionnaire in RESORCE was completed on the first day of each treatment cycle, when a patient had not had treatment for a week, which may have affected patient responses. The ERG's clinical advisors commented that toxicity is worse for cabozantinib which likely means comparatively lower HRQoL.
Incremental QALYs	If a full cost-utility model had been developed using estimates of relative treatment effects from the anchored MAICs, regardless of toxicity effects, incremental QALYs for cabozantinib versus regorafenib would likely be negative, as OS tends to drive QALYs more than PFS. This can be seen in the company's partitioned survival analyses provided in their clarification response[19] (see Table 17). If PFS and OS were assumed to be equivalent, incremental QALYs for cabozantinib may still be negative due to toxicity effects. It is unclear whether the magnitude of these expected QALY losses would be sufficiently large to preclude cabozantinib from being considered under the FTA process.
Drug acquisition	In contrast to CELESTIAL and RESORCE, the ERG's clinical advisors commented that both cabozantinib and regorafenib would be given until disease progression. One advisor further commented that they would discontinue treatment if only if the patient had definite evidence of progression and if the patient was no longer benefiting from treatment. Time to treatment discontinuation (TTD) from either trial is therefore not a good proxy for ToT in clinical practice and the use of PFS is more appropriate. Differences in drug acquisition costs are dependent on the comparison of drug acquisition costs (including discounts) per period of time on treatment (see confidential appendix to this ERG report).
Drug administration	Not applicable - both drugs are administered orally.
Monitoring and health state costs	The company's cost comparison assumes no difference in costs of monitoring or visits. The ERG's clinical advisors commented that more frequent and less predictable AEs on cabozantinib would require patients to attend clinic in person, leading to increased costs.
AE costs	The ERG's clinical advisors believed that cabozantinib is more toxic than regorafenib. The costs of managing AEs are excluded from the company's base case analysis, but are included in sensitivity analysis. These costs are higher for cabozantinib than regorafenib and should be included in the analysis.
Incremental costs	Without a full cost-utility model, the incremental costs for cabozantinib versus regorafenib are not fully clear. If both drugs had the same acquisition cost per period of time on treatment, incremental costs for cabozantinib versus regorafenib would likely be slightly higher due to greater requirement to monitor and manage toxicity.

PFS - progression-free survival; OS - overall survival; AE - adverse event; HRQoL - health-related quality of life; QALY - quality-adjusted life year; HR - hazard ratio; ITC - indirect treatment comparison; MAIC - matching-adjusted indirect

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comparison; ERG - Evidence Review Group; CSR - Clinical Study Report; TTD - time to treatment discontinuation; ToT - time on treatment

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5 REFERENCES

1. Ipsen. Cabozantinib for previously treated advanced hepatocellular carcinoma [ID3917]. Fast track appraisal: cost-comparison case. Company's submission Slough, UK; 2022.
2. Blachier M, Leleu H, Peck-Radosavljevic M, Valla DC, Roudot-Thoraval F. The burden of liver disease in Europe: a review of available epidemiological data. *Journal of Hepatology* 2013;58:593-608.
3. Cancer Research UK. Liver cancer incidence statistics. Available from: https://www.cancerresearchuk.org/health-professional/cancer-statistics/statistics-by-cancer-type/liver-cancer/incidence#heading-Zero; 2022.
4. Cancer Research UK. Liver cancer mortality statistics. https://www.cancerresearchuk.org/health-professional/cancer-statistics/statistics-by-cancer-type/liver-cancer/mortality#heading-Zero; 2022.
5. National Institute for Health and Care Excellence. Technology Appraisal Guidance 555 - Regorafenib for previously treated advanced hepatocellular carcinoma. London, UK; 2019.
6. National Health Service. NHS Reference Costs 2019/20. 2021.
7. Exelixis Inc. A Phase 3, randomized, double-blind, controlled study of cabozantinib (XL184) vs placebo in subjects with hepatocellular carcinoma who have received prior sorafenib (CELESTIAL Clinical Study Report). California, US; 2018.
8. National institute for Health and Care Excellence. Technology Appraisal Guidance 666 - Atezolizumab with bevacizumab for treating advanced or unresectable hepatocellular carcinoma. London, UK; 2020.
9. National institute for Health and Care Excellence. Technology Appraisal Guidance 551 - Lenvatinib for untreated advanced hepatocellular carcinoma London, UK; 2018.
10. National institute for Health and Care Excellence. Technology Appraisal Guidance 474 - Sorafenib for treating advanced hepatocellular carcinoma. London, UK; 2017.
11. European Medicines Agency. Cabometyx (cabozantinib) - Summary of Product Characteristics. London, UK; 2021.
12. Joint Formulary Committee. British National Formulary London, UK; 2022.
13. European Medicines Agency. Stivarga (regorafenib) - Summary of Product Characteristics London, UK; 2021.
14. National institute for Health and Care Excellence. Cabozantinib for previously treated advanced hepatocellular carcinoma (review of TA582). Final scope. London, UK; 2022.
15. Bruix J, Qin S, Merle P, Granito A, Huang YH, Bodoky G, *et al.* Regorafenib for patients with hepatocellular carcinoma who progressed on sorafenib treatment (RESORCE): a randomised, double-blind, placebo-controlled, phase 3 trial. *Lancet* 2017;389:56-66.
16. Ipsen. Cabozantinib for previously treated advanced hepatocellular carcinoma [ID3917]. Fast track appraisal: cost-comparison case. Company's submission appendices. Slough, UK; 2022.
17. Abou-Alfa GK, Meyer T, Cheng AL, El-Khoueiry AB, Rimassa L, Ryoo BY, *et al.* Cabozantinib in Patients with Advanced and Progressing Hepatocellular Carcinoma. *N Engl J Med* 2018;379:54-63.
18. King J, Palmer DH, Johnson P, Ross P, Hubner RA, Sumpter K, *et al.* Sorafenib for the treatment of advanced hepatocellular cancer - a UK audit. *Clinical Oncology* 2017;29:256-62.
19. Ipsen. Cabozantinib for previously treated advanced hepatocellular carcinoma [ID3917]. Company's response to clarification questions from the ERG. London, UK; 2022.

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20. Bucher HC, Guyatt GH, Griffith LE, Walter SD. The results of direct and indirect treatment comparisons in meta-analysis of randomized controlled trials. *Journal of Clinical Epidemiology* 1997;50:683-91.

21. Guyot P, Ades AE, Ouwens MJ, Welton NJ. Enhanced secondary analysis of survival data: reconstructing the data from published Kaplan-Meier survival curves. *BMC Medical Research Methodology* 2012;12.

22. Philippo DM, Ades AE, Dias S, Palmer S, Abrams KR, Welton NJ. NICE DSU Technical Support Document 18: Methods for population-adjusted indirect comparisons in submissions to NICE. Sheffield, UK; 2016.

23. Jones K, Burns A. Unit costs of health and social care. Kent, UK; 2021.

24. National institute for Health and Care Excellence. User guide for the cost comparison company evidence subnmission template. London, UK; 2017.

25. National Institute for Health and Care Excellence. NICE Technology Appraisal Guidance 514 - Regorafenib for previously treated advanced hepatocellular carcinoma. London, UK; 2017.

26. Stevenson M, Tappenden P, Carroll C, Ren S, Rawdin A, Wong R*, et al.* Regorafenib for previously treated unresectable hepatocellular carcinoma: A Single Technology Appraisal Sheffield, UK; 2017.

27. Ipsen. Ipsen Advanced Hepatocellular Carcinoma (HCC) Health Technology Assessment (HTA) Advisory Board. 28th June 2018. Meeting minutes. London, UK; 2018.

28. Ipsen. Ipsen NICE submission advisory board meeting. Hepatocellular carcinoma - cabometyx. London, UK; 2021.

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