IQWiG Reports – Commission No. A18-85

Cabozantinib (hepatocellular carcinoma) –

Benefit assessment according to §35a Social Code Book V[1]

Extract

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[2] Table numbers start with “2” as numbering follows that of the full dossier assessment.

List of abbreviations

Abbreviation	Meaning
ACT	appropriate comparator therapy
AE	adverse event
BSC	best supportive care
CI	confidence interval
CTCAE	Common Terminology Criteria for Adverse Events
ECOG PS	Eastern Cooperative Oncology Group Performance Status
EQ-5D	European Quality of Life-5 Dimensions
G-BA	Gemeinsamer Bundesausschuss (Federal Joint Committee)
HBV	hepatitis B virus
HCC	hepatocellular carcinoma
HCV	hepatitis C virus
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (Institute for Quality and Efficiency in Health Care)
PT	Preferred Term
RCT	randomized controlled trial
SAE	serious adverse event
SGB	Sozialgesetzbuch (Social Code Book)
SOC	System Organ Class
SPC	Summary of Product Characteristics
VAS	visual analogue scale

2 Benefit assessment

2.1 Executive summary of the benefit assessment

Background

In accordance with §35a Social Code Book (SGB) V, the Federal Joint Committee (G-BA) commissioned the Institute for Quality and Efficiency in Health Care (IQWiG) to assess the benefit of the drug cabozantinib. The assessment was based on a dossier compiled by the pharmaceutical company (hereinafter referred to as "the company"). The dossier was sent to IQWiG on 11 December 2018.

Research question

The aim of the present report was to assess the added benefit of cabozantinib in comparison with best supportive care (BSC) as appropriate comparator therapy (ACT) in patients with hepatocellular carcinoma (HCC) who have previously been treated with sorafenib. Table 2 shows the research question of the benefit assessment.

Table 2: Research question of the benefit assessment of cabozantinib

Therapeutic indication	**ACT[a]**
Adult patients with hepatocellular carcinoma (HCC) who have previously been treated with sorafenib	Best supportive care (BSC)[b]
a: Presentation of the ACT specified by the G-BA. b: BSC refers to the therapy that provides the patient with the best possible individually optimized supportive treatment to alleviate symptoms and improve quality of life. ACT: appropriate comparator therapy; BSC: best supportive care; G-BA: Federal Joint Committee; HCC: hepatocellular carcinoma	

The company followed the G-BA's specification on the ACT.

The assessment was conducted by means of patient-relevant outcomes on the basis of the data provided by the company in the dossier. Randomized controlled trials (RCTs) were used for the derivation of the added benefit.

Results

Study pool and study characteristics

One relevant study (CELESTIAL) was available for the benefit assessment. The CELESTIAL study is a randomized, placebo-controlled, double-blind, multicentre study. It included adult patients with histologically or cytologically confirmed HCC who had received prior sorafenib therapy. A curative treatment approach (e.g. liver transplantation, surgical resection, radio-frequency ablation) was no longer an option for these patients. The patients had to have an Eastern Cooperative Oncology Group Performance Status (ECOG PS) of 0 or 1. In addition, only patients with mild liver impairment, corresponding to Child-Pugh class A, were included.

The study included a total of 773 patients, randomized in a 2:1 ratio either to treatment with cabozantinib + BSC (N = 512) or placebo + BSC (N = 261).

Treatment of the patients was in compliance with the specifications of the Summary of Product Characteristics (SPC). According to the study protocol, the investigators had been instructed to provide the patients with individual supportive therapies to alleviate symptoms and complications in the sense of BSC.

Overall survival was the primary outcome of the study. Patient-relevant secondary outcomes were health status and adverse events (AEs).

Risk of bias

The risk of bias at study level and for the results on the outcomes "overall survival" and "discontinuation due to AEs" was rated as low. There was a high risk of bias for the results for all other outcomes on side effects, as well as for the outcome "health status", operationalized using the European Quality of Life-5 Dimensions (EQ-5D) visual analogue scale (VAS).

Mortality

Overall survival

A statistically significant difference in favour of cabozantinib + BSC in comparison with placebo + BSC was shown between the treatment groups for the outcome "overall survival". This resulted in an indication of an added benefit of cabozantinib in comparison with BSC for the outcome "overall survival".

Morbidity

Health status (EQ-5D VAS)

A statistically significant difference to the disadvantage of cabozantinib + BSC in comparison with placebo + BSC was shown between the treatment groups for the outcome "health status" measured with the EQ-5D VAS. However, the 95% confidence interval (CI) of the standardized mean difference was not fully outside the irrelevance range of −0.2 to 0.2. It can therefore not be inferred that the effect is relevant. Hence, there was no hint of an added benefit of cabozantinib in comparison with BSC; an added benefit is therefore not proven.

Health-related quality of life

Outcomes in this category were not recorded in the CELESTIAL study.

Side effects

Serious adverse events (SAEs) and severe AEs (Common Terminology Criteria for Adverse Events [CTCAE] grade ≥ 3)

A statistically significant difference to the disadvantage of cabozantinib + BSC in comparison with placebo + BSC was shown between the treatment groups for the outcomes "SAEs" and

"severe AEs (CTCAE grade ≥ 3)". In each case, this resulted in a hint of greater harm from cabozantinib in comparison with BSC.

Discontinuation due to adverse events

A statistically significant difference to the disadvantage of cabozantinib + BSC in comparison with placebo + BSC was shown between the treatment groups for the outcome "discontinuation due to AEs". This resulted in an indication of greater harm from cabozantinib in comparison with BSC.

Specific adverse events

- Severe AEs (CTCAE grade ≥ 3): nervous system disorders (System Organ Class [SOC]), decreased appetite (Preferred Term [PT]), diarrhoea (PT), fatigue (PT), hypertension (PT), and palmar-plantar erythrodysaesthesia syndrome (PT):

  A statistically significant difference to the disadvantage of cabozantinib + BSC in comparison with placebo + BSC was shown between the treatment groups for the following outcomes: nervous system disorders (SOC), decreased appetite (PT), diarrhoea (PT), fatigue (PT), hypertension (PT), and palmar-plantar erythrodysaesthesia syndrome (PT) (in each case severe AEs [CTCAE grade ≥ 3]). In each case, this resulted in a hint of greater harm from cabozantinib in comparison with BSC.

- AEs: mucosal inflammation (PT) and stomatitis (PT):

  A statistically significant difference to the disadvantage of cabozantinib + BSC in comparison with placebo + BSC was shown between the treatment groups for the outcomes "mucosal inflammation (PT)" and "stomatitis (PT)" (in each case AEs). In each case, this resulted in a hint of greater harm from cabozantinib in comparison with BSC.

Probability and extent of added benefit, patient groups with therapeutically important added benefit[3]

On the basis of the results presented, the probability and extent of the added benefit of the drug cabozantinib compared with the ACT is assessed as follows:

The overall assessment showed one positive and several negative effects of cabozantinib in comparison with BSC. There was a positive effect for the outcome "overall survival". This was accompanied by several negative effects, mainly in the category of serious/severe side effects, mostly with the extent "major". There were no data for the outcome category "health-related

[3] On the basis of the scientific data analysed, IQWiG draws conclusions on the (added) benefit or harm of an intervention for each patient-relevant outcome. Depending on the number of studies analysed, the certainty of their results, and the direction and statistical significance of treatment effects, conclusions on the probability of (added) benefit or harm are graded into 4 categories: (1) "proof", (2) "indication", (3) "hint", or (4) none of the first 3 categories applies (i.e., no data available or conclusions 1 to 3 cannot be drawn from the available data). The extent of added benefit or harm is graded into 3 categories: (1) major, (2) considerable, (3) minor (in addition, 3 further categories may apply: non-quantifiable extent of added benefit, added benefit not proven, or less benefit). For further details see [1,2].

quality of life". The negative effects and the missing data on health-related quality of life did not completely outweigh the advantage in overall survival, but resulted in a downgrading of the extent of the added benefit.

In summary, there is an indication of a minor added benefit of cabozantinib in comparison with the ACT BSC for patients with HCC who have previously been treated with sorafenib.

Table 3 presents a summary of the probability and extent of the added benefit of cabozantinib.

Table 3: Cabozantinib – probability and extent of added benefit

Therapeutic indication	**ACT[a]**	**Probability and extent of added benefit**
Adult patients with hepatocellular carcinoma (HCC) who have previously been treated with sorafenib[b]	Best supportive care (BSC)[c]	Indication of minor added benefit
a: Presentation of the ACT specified by the G-BA. b: The relevant study included patients with Child-Pugh class A and an ECOG PS of 0 or 1. It remains unclear whether the observed effects can be transferred to patients with Child-Pugh class B and/or an ECOG PS of > 1. c: BSC refers to the therapy that provides the patient with the best possible, individually optimized, supportive treatment to alleviate symptoms and improve the quality of life. ACT: appropriate comparator therapy; BSC: best supportive care; ECOG PS: Eastern Cooperative Oncology Group Performance Status; G-BA: Federal Joint Committee; HCC: hepatocellular carcinoma		

The approach for deriving an overall conclusion on the added benefit is a proposal by IQWiG. The G-BA decides on the added benefit.

2.2 Research question

The aim of the present report was to assess the added benefit of cabozantinib in comparison with BSC as ACT in patients with HCC who have previously been treated with sorafenib. Table 4 shows the research question of the benefit assessment.

Table 4: Research question of the benefit assessment of cabozantinib

Therapeutic indication	**ACT[a]**
Adult patients with hepatocellular carcinoma (HCC) who have previously been treated with sorafenib	Best supportive care (BSC)[b]
a: Presentation of the ACT specified by the G-BA. b: BSC refers to the therapy that provides the patient with the best possible, individually optimized, supportive treatment to alleviate symptoms and improve quality of life. ACT: appropriate comparator therapy; BSC: best supportive care; G-BA: Federal Joint Committee; HCC: hepatocellular carcinoma	

The company followed the G-BA's specification on the ACT.

The assessment was conducted by means of patient-relevant outcomes on the basis of the data provided by the company in the dossier. RCTs were used for the derivation of the added benefit. This concurred with the company's inclusion criteria.

2.3 Information retrieval and study pool

The study pool of the assessment was compiled on the basis of the following information:

Sources of the company in the dossier:

- study list on cabozantinib (status: 26 September 2018)
- bibliographical literature search on cabozantinib (last search on 26 September 2018)
- search in trial registries for studies on cabozantinib (last search on 26 September 2018)

To check the completeness of the study pool:

- search in trial registries for studies on cabozantinib (last search on 18 December 2018)

The check identified no additional relevant study.

2.3.1 Studies included

The study listed in the following Table 5 was included in the benefit assessment.

Table 5: Study pool – RCT, direct comparison: cabozantinib vs. BSC

Study	Study category		
	Study for approval of the drug to be assessed (yes/no)	Sponsored study[a] (yes/no)	Third-party study (yes/no)
XL184-309 (CELESTIAL[b])	Yes	Yes	No
a: Exelixis sponsors the study and has transferred the approval and marketing rights for Europe to the company Ipsen Pharma responsible for the dossier. b: In the following tables, the study is referred to with this abbreviated form. BSC: best supportive care; RCT: randomized controlled trial; vs.: versus			

Section 2.6 contains a reference list for the study included.

2.3.2 Study characteristics

Table 6 and Table 7 describe the study used for the benefit assessment.

Table 6: Characteristics of the study included – RCT, direct comparison: cabozantinib + BSC vs. placebo + BSC

Study	Study design	Population	Interventions (number of randomized patients)	Study duration	Location and period of study	Primary outcome; secondary outcomes[a]
CELESTIAL	RCT, double-blind, parallel	Adults with ▪ histologically or cytologically confirmed HCC[b] who are not eligible for a curative treatment approach ▪ prior therapy with sorafenib ▪ Child-Pugh class A ▪ ECOG-PS 0 or 1	Cabozantinib + BSC (N = 512) placebo + BSC (N = 261)	Screening: ≤ 28 days[c] Treatment: until there was no longer clinical benefit following the physician's decision, unacceptable side effects, patient's decision, need for another systemic or local anticancer therapy Observation[d]: outcome-specific, at most until death, withdrawal of consent, termination of study by sponsor	94 centres in 19 countries: Australia, Belgium, Canada, France, Germany, Hong Kong, Ireland, Italy, Netherlands, New Zealand, Poland, Romania, Singapore, South Korea, Spain, Taiwan, Turkey, United Kingdom, USA 9/2013–ongoing[e] Data cut-offs: ▪ 15 June 2016[f] ▪ 1 June 2017[f] ▪ 1 December 2017[g]	Primary: overall survival Secondary: health status, AEs

a: Primary outcomes include information without consideration of the relevance for this benefit assessment. Secondary outcomes exclusively include information on relevant available outcomes for this benefit assessment.
b: Patients with fibrolamellar carcinoma or mixed hepatocellular cholangiocarcinoma were excluded from the study.
c: Patients' consents could be obtained and biopsies for the confirmation of the HCC diagnosis could be conducted ≥ 28 days before randomization.
d: Outcome-specific information is provided in Table 8.
e: Inclusion of the last patient: September 2017.
f: Planned interim analyses after about 311 or 466 deaths; a final analysis was planned after about 621 deaths.
g: Last data cut-off before initiation of a planned open-label phase with the option to cross over from the placebo to the cabozantinib arm (according to the study protocol, this is possible after reaching statistical significance in overall survival at one of both planned interim analyses, and following the sponsor's decision and in consultation with the regulatory authorities).

AE: adverse event; BSC: best supportive care; ECOG PS: Eastern Cooperative Oncology Group Performance Status; HCC: hepatocellular carcinoma; N: number of randomized patients; RCT: randomized controlled trial; vs.: versus

Table 7: Characteristics of the interventions – RCT, direct comparison: cabozantinib + BSC vs. placebo + BSC

Study	Intervention	Comparison
CELESTIAL	Cabozantinib, 60 mg, once daily, orally + BSC	Cabozantinib placebo, once daily, orally + BSC
	The patients were advised not to eat anything for at least 2 hours before and 1 hour after administration.	
	Dose reduction and interruption in case of unacceptable toxicity: ▪ first dose reduction: from 60 mg to 40 mg, second dose reduction: from 40 mg to 20 mg ▪ treatment discontinuation if the minimum dose of 20 mg was not tolerated or in case of dose interruptions of > 6 weeks[a] ▪ dose reescalation was possible under certain conditions	
	Permitted pretreatment ▪ ≤ 2 prior systemic anticancer treatment regimens (with progression following at least 1 of the prior systemic treatments); additional systemic treatments only in the form of adjuvant or local therapy ▪ radiation therapy ≥ 4 weeks (≥ 2 weeks for bone metastases) before randomization; radionuclide treatment ≥ 6 weeks before randomization ▪ major surgery ≥ 2 months before randomization **Permitted concomitant treatment** ▪ BSC as clinically appropriate for the treatment of all symptoms and complications ▪ supportive treatment, e.g. with antiemetics, antidiarrhoeal drugs (both also as prevention), analgesics (no nonsteroidal anti-inflammatory drugs), antibiotics, G-CSF, transfusions, hormone replacement therapy, systemic steroids (short-term), heparin, drugs for the treatment of depression and anxiety ▪ antiviral therapy for active HBV infection ▪ palliative radiation therapy for bone or skin/subcutaneous metastases to a restricted extent (if medically necessary) **Non-permitted concomitant treatment** ▪ other systemic or local anticancer therapies ▪ strong CYP3A4 inducers or inhibitors should be avoided ▪ erythropoiesis-stimulating drugs ▪ oral anticoagulants in therapeutic dosages (e.g. warfarin, clopidogrel)	

a: Resumed treatment possible following the sponsor's authorization.

BSC: best supportive care; CYP3A4: cytochrome P450 3A4; G-CSF: granulocyte colony-stimulating factor; HBV: hepatitis B virus; RCT: randomized controlled trial; vs.: versus

The CELESTIAL study is a randomized, placebo-controlled, double-blind, multicentre study. It included adult patients with histologically or cytologically confirmed HCC who had received prior sorafenib therapy. A curative treatment approach (e.g. liver transplantation, surgical resection, radiofrequency ablation) was no longer an option for these patients. The patients had to have an ECOG PS of 0 or 1. In addition, only patients with mild liver impairment, corresponding to Child-Pugh class A, were included.

The approval of cabozantinib in the present therapeutic indication comprises patients with HCC who have previously been treated with sorafenib. According to the SPC, there is a restriction for patients with Child-Pugh C, in whom use of cabozantinib is not recommended [3]. There is

no restriction for patients with Child-Pugh B. Hence, the study population does not completely cover the therapeutic indication with regard to the disease stage. It remains unclear whether the observed effects can be transferred to patients with Child-Pugh class B.

The study included a total of 773 patients, randomized in a 2:1 ratio either to treatment with cabozantinib + BSC (N = 512) or placebo + BSC (N = 261). Randomization was stratified by aetiology of disease at baseline (hepatitis B virus [HBV] with or without hepatitis C virus [HCV], HCV [without HBV], other), geographical region (Asia, other), and by presence of extrahepatic spread of disease and/or macrovascular invasion (yes, no).

Treatment of the patients was conducted in accordance with the regimen described in Table 7 and was in compliance with the recommendations of the SPC [3]. According to the SPC, the dose of the study medication was to be reduced in case of unacceptable toxicity. Dose reduction due to AEs was necessary in 326 (64%) of the patients in the cabozantinib + BSC arm and in 34 (13%) of the patients in the placebo + BSC arm. According to the study protocol, the investigators had been instructed to provide the patients with individual supportive therapies to alleviate symptoms and complications in the sense of BSC. These were to comprise particularly pain therapy and measures in the event of hepatic decompensation, for the treatment of infections, to provide nutrition and psychological support and for the treatment of anaemia.

Treatment with the study medication could be conducted beyond progression, until there was no longer any clinical benefit following the physician's decision, or if any of the further criteria for treatment discontinuation applied: unacceptable side effects, patient's decision, need for another systemic or local anticancer therapy.

Other subsequent systemic or local therapies could be conducted without restrictions after discontinuation of the study medication. 28% of the patients in the cabozantinib + BSC arm and 33% in the placebo + BSC arm received systemic non-radiation anticancer therapy. 3.7% of the patients in the cabozantinib + BSC arm and 5.4% in the placebo + BSC arm received local liver-targeted non-radiation anticancer therapy.

Overall survival was the primary outcome of the study. Patient-relevant secondary outcomes were health status and AEs.

Data cut-offs

The company presented a total of 3 data cut-offs in the available dossier:

- first data cut-off: 15 June 2016 (first interim analysis)
- second data cut-off: 1 June 2017 (second interim analysis)
- third data cut-off: 1 December 2017 (additional analysis)

The CELESTIAL study is currently ongoing. According to the study protocol, 2 interim analyses for the primary outcome "overall survival" were planned after about 311 and

466 deaths, and a final analysis after 621 deaths. The planned interim analyses correspond to the first and second data cut-offs. The study protocol specified the additional option of an open-label phase with the possibility to switch treatments from the placebo + BSC arm to the cabozantinib + BSC arm (crossover). This option was only available after reaching statistical significance in overall survival at one of both planned interim analyses, and following the sponsor's decision and in consultation with the regulatory authorities. Statistical significance in overall survival in favour of cabozantinib was reached with the second data cut-off from 1 June 2017. After 1 December 2017, the study was unblinded and the patients in the placebo arm received the possibility to cross over. Hence, the third data cut-off presented by the company was the last data cut-off before initiation of the open-label phase described above, which offered the possibility to cross over from the placebo + BSC arm to the cabozantinib + BSC arm. Randomization had not yet been completed at the time point of the second data cut-off; the planned sample size of the study was only reached in September 2017. This is why there were an additional 66 patients at the third data cut-off.

The data cut-off from 1 December 2017 was used for the present benefit assessment. Analyses for all outcomes included were available for this data cut-off. This deviates from the approach of the company insofar as the company used the second and the third data cut-offs together. The company presented results on the first data cut-off as sensitivity analysis for the outcome "overall survival".

Planned duration of follow-up observation

Table 8 shows the planned duration of follow-up observation of the patients for the individual outcomes.

Table 8: Planned duration of follow-up observation – RCT, direct comparison: cabozantinib + BSC vs. placebo + BSC

Study **Outcome category** **Outcome**	**Planned follow-up observation**
CELESTIAL	
Mortality	
Overall survival	Every 8 weeks until death, withdrawal of consent, or termination of study by sponsor
Morbidity	
Health status (EQ-5D VAS)	Until week 8 after disease progression or until treatment discontinuation
Health-related quality of life	Not recorded
Side effects	
All outcomes in the category "side effects"	Until 30 days after treatment discontinuation
BSC: best supportive care; EQ-5D: European Quality of Life-5 Dimensions; RCT: randomized controlled trial; VAS: visual analogue scale; vs.: versus	

Only the outcome "overall survival" was to be recorded until the end of study participation in the CELESTIAL study. The observation periods for the outcomes on morbidity and side effects were systematically shortened. Health status, recorded with the EQ-5D VAS, was to be recorded only until week 8 after disease progression or until treatment discontinuation. Outcomes on side effects were to be recorded only for the period of treatment with the study medication (plus 30 days). To be able to draw a reliable conclusion on the total study period or the time until death of the patients, it would be necessary, however, to record these outcomes over the total period of time, as was the case for survival.

Patient characteristics

Table 9 shows the characteristics of the patients in the study included.

Table 9: Characteristics of the study population – RCT, direct comparison: cabozantinib + BSC vs. placebo + BSC

Study Characteristics Category	**Cabozantinib + BSC**	**Placebo + BSC**
CELESTIAL	N[a] = 512	N[a] = 261
Age [years], median [min; max]	64 [22; 86]	64 [24; 86]
Sex [F/M], %	19/81	17/83
Ethnic origin, n (%)		
White	286 (56)	141 (54)
Black or African American	9 (2)	11 (4)
Asian	169 (33)	90 (34)
Native Americans or Native Alaskans	0 (0)	1 (0)
Native Hawaiians or other Pacific Islanders	4 (1)	0 (0)
Several	0 (0)	1 (0)
Other	6 (1)	1 (0)
Not reported	38 (7)	16 (6)
Geographical region, n (%)		
Australia/New Zealand	18 (4)	13 (5)
Asia	124 (24)	66 (25)
Europe	255 (50)	119 (46)
North America (Canada/USA)	115 (22)	63 (24)
ECOG PS, n (%)		
0	267 (52)	146 (56)
1	244 (48)	115 (44)
2	1[b] (0)	0 (0)

(continued)

Table 9: Characteristics of the study population – RCT, direct comparison: cabozantinib + BSC vs. placebo + BSC (continued)

Study **Characteristics** **Category**	**Cabozantinib + BSC**	**Placebo + BSC**
CELESTIAL	N[a] = 512	N[a] = 261
Disease duration: time between first diagnosis and randomization [months], median [min; max]	16.9 [0.2; 263.0]	16.3 [0.4; 208.8]
Child-Pugh class, n (%)		
A (score 5–6)	502 (98)	258 (99)
B (score 7–9)	9 (2)	3 (1)
Missing	1 (0)	0 (0)
Spread of the disease at baseline[c], n (%)		
Portal vein invasion	108 (21)	69 (26)
Bile duct invasion	10 (2)	15 (6)
Macrovascular invasion	143 (28)	85 (33)
Extrahepatic spread	396 (77)	197 (75)
Other	5 (1)	2 (1)
Number of prior systemic non-radiation anticancer treatment regimens for advanced HCC, n (%)		
0	3[d] (1)	0 (0)
1	357 (70)	191 (73)
2	147 (29)	69 (26)
≥ 3[e]	2 (0)	1 (0)
Aetiology of disease[c], n (%)		
Hepatitis B (without hepatitis C)	177 (35)	95 (36)
Hepatitis C (without hepatitis B)	118 (23)	57 (22)
Hepatitis B and C	9 (2)	4 (2)
Alcoholism	121 (24)	42 (16)
Nonalcoholic steatohepatitis (NASH)	54 (11)	26 (10)
Other	107 (21)	66 (25)
Treatment discontinuation, n (%)	464 (91)[f]	248 (95)[f]
Study discontinuation, n (%)	383 (75)[g]	202 (77)[g]

a: Number of randomized patients. Values that are based on other patient numbers are marked in the corresponding line if the deviation is relevant.
b: Patient had an ECOG PS of 1 at the time point of screening.
c: Consideration in more than one category possible.
d: These 3 patients received systemic treatment only as adjuvant therapy.
e: These patients received several anticancer treatment regimens with sorafenib and/or sorafenib in combination with other drugs.
f: The most common reason for treatment discontinuation in both study arms was disease progression (cabozantinib arm 49%, comparator arm 69%).
g: The most common reason for study discontinuation in both study arms was death of the patients (cabozantinib arm 74%, comparator arm 75%).

BSC: best supportive care; ECOG PS: Eastern Cooperative Oncology Group Performance Status; F: female; HCC: hepatocellular carcinoma; M: male; max: maximum; min: minimum; n: number of patients in the category; N: number of randomized patients; RCT: randomized controlled trial; vs.: versus

The demographic and clinical characteristics of the patients in both treatment arms were largely comparable. The median age of the participants was 64 years; slightly more than 80% were male. Slightly more than half of the patients (about 53%) had an ECOG PS of 0 at baseline; patients with an ECOG PS of > 1 were excluded from the study. Concurring with the inclusion criteria, more than 98% of the participants had Child-Pugh class A. The majority of the patients (about 77%) had extrahepatic spread of disease at baseline. The majority of the participants (about 71%) had received 1, and about 28% had received 2 systemic non-radiation anticancer treatment regimens for advanced HCC; all patients had previously been treated with sorafenib.

The number of treatment discontinuations (about 92%) and study discontinuations (about 76%) between both study arms was comparable. Most treatment discontinuations were due to disease progression, whereas the most common reason for study discontinuation was death of the patient.

Treatment duration and observation period

Table 10 shows the mean and median treatment durations of the patients and the observation periods for individual outcomes.

Table 10: Information on the course of the study – RCT, direct comparison: cabozantinib + BSC vs. placebo + BSC

Study **Duration of the study phase** **Outcome category**	**Cabozantinib + BSC**	**Placebo + BSC**
CELESTIAL	N = 509	N = 261
Treatment duration [months]		
Median [min; max]	3.94 [0.3; 43.3]	2.20 [0.4; 27.7]
Mean (SD)	6.19 (6.19)	3.76 (3.61)
Observation period [months]		
Overall survival	ND	ND
Health status (EQ-5D VAS)	ND	ND
Health-related quality of life	Outcome not recorded	
Side effects	ND	ND

BSC: best supportive care; EQ-5D: European Quality of Life-5 Dimensions; max: maximum; min: minimum; N: number of analysed patients; ND: no data; RCT: randomized controlled trial; SD: standard deviation; VAS: visual analogue scale; vs.: versus

The median treatment duration was almost twice as long in the cabozantinib + BSC arm (3.94 months) as in the placebo + BSC arm (2.20 months). There was no information on the observation period for any of the outcomes. Health status (EQ-5D VAS) was to be recorded only until week 8 after disease progression or until the end of treatment, however, and side effects only until 30 days after the end of treatment. It can be inferred from this that the

observation periods for the outcome “health status” and for the outcomes on side effects were notably longer in the cabozantinib + BSC arm than in the placebo + BSC arm.

Risk of bias across outcomes (study level)

Table 11 shows the risk of bias across outcomes (risk of bias at study level).

Table 11: Risk of bias across outcomes (study level) – RCT, direct comparison: cabozantinib + BSC vs. placebo + BSC

Study	Adequate random sequence generation	Allocation concealment	Blinding		Reporting independent of the results	No additional aspects	Risk of bias at study level
			Patients	Treating staff			
CELESTIAL	Yes	Yes	Yes	Yes	Yes	Yes	Low
BSC: best supportive care; RCT: randomized controlled trial; vs.: versus							

The risk of bias across outcomes was rated as low for the CELESTIAL study. This concurs with the company’s assessment.

2.4 Results on added benefit

2.4.1 Outcomes included

The following patient-relevant outcomes were to be included in the assessment (for reasons, see Section 2.7.4.3.2 of the full dossier assessment):

- Mortality
  - overall survival
- Morbidity
  - health status (EQ-5D VAS)
- Health-related quality of life
- Side effects
  - SAEs
  - severe AEs (CTCAE grade ≥ 3)
  - discontinuation due to AEs
  - specific AEs

The choice of patient-relevant outcomes deviated from that of the company, which used further morbidity outcomes in the dossier (Module 4 C) and did not consider specific AEs (see Section 2.7.4.3.2 of the full dossier assessment).

The present benefit assessment was based on the third data cut-off for all outcomes, whereas the company considered the second and third data cut-offs together for all outcomes (see Section 2.3.2).

Table 12 shows for which outcomes data were available in the study included.

Table 12: Matrix of outcomes – RCT, direct comparison: cabozantinib + BSC versus placebo + BSC

Study	Outcomes						
	Overall survival	**Health status (EQ-5D VAS)**	**Health-related quality of life**	**SAEs[a]**	**Discontinuation due to AEs[a]**	**Severe AEs (CTCAE grade ≥ 3)[a]**	**Specific AEs[b]**
CELESTIAL	Yes	Yes	No[c]	Yes	Yes	Yes	Yes

a: Without progression of the underlying condition (see Section 2.7.4.3.2 of the full dossier assessment).
b: The following events (MedDRA coding) are considered: nervous system disorders (SOC, CTCAE grade ≥ 3), decreased appetite (PT, CTCAE grade ≥ 3), diarrhoea (PT, CTCAE grade ≥ 3), fatigue (PT, CTCAE grade ≥ 3), hypertension (PT, CTCAE grade ≥ 3) palmar-plantar erythrodysaesthesia syndrome (PT, CTCAE grade ≥ 3), mucosal inflammation (PT, AEs), and stomatitis (PT, AEs).
c: Outcome not recorded.

AE: adverse event; BSC: best supportive care; CTCAE: Common Terminology Criteria for Adverse Events; EQ-5D: European Quality of Life-5 Dimensions; MedDRA: Medical Dictionary for Regulatory Activities; PT: Preferred Term; RCT: randomized controlled trial; SAE: serious adverse event; SOC: System Organ Class; VAS: visual analogue scale; vs.: versus

2.4.2 Risk of bias

Table 13 describes the risk of bias for the results of the relevant outcomes.

Table 13: Risk of bias across outcomes and outcome-specific risk of bias – RCT, direct comparison: cabozantinib + BSC vs. placebo + BSC

Study	Study level	Outcomes						
		Overall survival	Health status (EQ-5D VAS)	Health-related quality of life	SAEs[a]	Discontinuation due to AEs[a]	Severe AEs (CTCAE grade ≥ 3)[a]	Specific AEs[b]
CELESTIAL	L	L	H[c]	–[d]	H[e]	L	H[e]	H[e]

a: Without progression of the underlying condition (see Section 2.7.4.3.2 of the full dossier assessment).
b: The following events (MedDRA coding) are considered: nervous system disorders (SOC, CTCAE grade ≥ 3), decreased appetite (PT, CTCAE grade ≥ 3), diarrhoea (PT, CTCAE grade ≥ 3), fatigue (PT, CTCAE grade ≥ 3), hypertension (PT, CTCAE grade ≥ 3) palmar-plantar erythrodysaesthesia syndrome (PT, CTCAE grade ≥ 3), mucosal inflammation (PT, AEs), and stomatitis (PT, AEs).
c: Large proportion of patients (> 10%) not considered in the analysis; sharp decline in the number of responses to questionnaires over the course of the study, which differs between the treatment arms.
d: Outcome not recorded.
e: Large proportion of potentially informative censoring.
AE: adverse event; BSC: best supportive care; CTCAE: Common Terminology Criteria for Adverse Events; EQ-5D: European Quality of Life-5 Dimensions 5 Levels; H: high; L: low; MedDRA: Medical Dictionary for Regulatory Activities; PT: Preferred Term; RCT: randomized controlled trial; SAE: serious adverse event; SOC: System Organ Class; VAS: visual analogue scale; vs.: versus

The risk of bias for the result on the outcome "overall survival" was rated as low. This concurs with the company's assessment.

Deviating from the company, the risk of bias was rated as high for the results on the outcome "health status", recorded using the EQ-5D VAS. This was due to the fact that a relevant proportion of patients (>10%) was not included in the analysis and to a sharp decline in the number of responses to questionnaires over the course of the study, which differed between both treatment arms (see Section 2.7.4.2 of the full dossier assessment).

The risk of bias was rated as high for the results on the outcomes in the category of side effects except for the outcome "discontinuation due to AEs". This was due to potentially informative censoring (see Section 2.7.4.2 of the full dossier assessment). The company rated the overall risk of bias for the results on AEs as low without considering the individual outcomes separately.

2.4.3 Results

Table 14 and Table 15 summarize the results from the comparison of cabozantinib + BSC with placebo + BSC in patients with HCC who have previously been treated with sorafenib. Where necessary, calculations conducted by the Institute are provided in addition to the data from the company's dossier. Kaplan-Meier curves on the outcomes included are presented in

Appendix A of the full dossier assessment. Common AEs, SAEs, severe AEs, and discontinuation due to AEs are listed in Appendix B of the full dossier assessment.

Table 14: Results (mortality and side effects) – RCT, direct comparison: cabozantinib + BSC vs. placebo + BSC

Study Outcome category	Cabozantinib + BSC		Placebo + BSC		Cabozantinib + BSC vs. placebo + BSC
Outcome	**N**	**Median time to event in months [95% CI] Patients with event n (%)**	**N**	**Median time to event in months [95% CI] Patients with event n (%)**	**HR [95% CI]; p-value[a]**
CELESTIAL					
Mortality					
Overall survival	512	10.3 [9.1; 11.6] 381 (74.4[b])	261	8.2 [6.9; 9.6] 197 (75.5[b])	0.78 [0.66; 0.93]; 0.006
Side effects					
AEs[c] (additional information)	509	ND	261	ND	–
SAEs[c]	509	10.8 [6.9; 13.3] 230 (45.2[b])	261	10.5 [6.9; 27.9] 86 (33.0[b])	1.31 [1.02; 1.69]; 0.035
Severe AEs[c] (CTCAE grade ≥ 3)	509	1.0 [1.0; 1.1] 428 (84.1[b])	261	4.1 [3.7; 5.6] 132 (50.6[b])	2.60 [2.13; 3.18]; < 0.001
Discontinuation due to AEs[c]	509	19.7 [13.5; NC] 176 (34.6[b])	261	NA [12.6; NC] 46 (17.6[b])	1.64 [1.18; 2.28]; 0.003
Nervous system disorders (SOC, CTCAE grade ≥ 3)	509	NA 46 (9.0)	261	NA 5 (1.9)	4.10 [1.62; 10.37]; 0.001
Decreased appetite (PT, CTCAE grade ≥ 3)	509	NA 29 (5.7)	261	NA 2 (0.8)	5.75 [1.36; 24.27]; 0.007
Diarrhoea (PT, CTCAE grade ≥ 3)	509	NA 49 (9.6)	261	NA [15.4; NC] 4 (1.5)	5.34 [1.92; 14.86]; < 0.001
Fatigue (PT, CTCAE grade ≥ 3)	509	NA 56 (11.0[b])	261	NA 10 (3.8)	2.66 [1.35; 5.24]; 0.003
Hypertension (PT, CTCAE grade ≥ 3)	509	NA [21.9; NC] 81 (15.9[b])	261	NA 5 (1.9)	8.31 [3.36; 20.54]; < 0.001
Palmar-plantar erythrodysaesthesia syndrome (PT, CTCAE grade ≥ 3)	509	NA 85 (16.7[b])	261	NA 0 (0)	NC; < 0.001
Mucosal inflammation (PT, AEs)	509	NA 70 (13.8[b])	261	NA 5 (1.9)	7.40 [2.98; 18.35]; < 0.001
Stomatitis (PT, AEs)	509	NA 70 (13.8[b])	261	NA 5 (1.9)	7.34 [2.96; 18.21]; < 0.001

(continued)

Table 14: Results (mortality and side effects) – RCT, direct comparison: cabozantinib + BSC vs. placebo + BSC (continued)

a: HR, CI: stratified Cox regression model; p-value: stratified log-rank test; stratification factors: aetiology of disease (HBV [with or without HCV], HCV [without HBV], other), geographical region (Asia, other), and presence of extrahepatic spread of disease and/or macrovascular invasion (yes, no).
b: Institute's calculation.
c: Without progression of the underlying condition (see Section 2.7.4.3.2 of the full dossier assessment).
AE: adverse event; BSC: best supportive care; CI: confidence interval; CTCAE: Common Terminology Criteria for Adverse Events; HBV: hepatitis B virus; HCV: hepatitis C virus; HR: hazard ratio; n: number of patients with event; N: number of analysed patients; NA: not achieved; NC: not calculable; ND: no data; PT: Preferred Term; RCT: randomized controlled trial; SAE: serious adverse event; SOC: System Organ Class; vs.: versus

Table 15: Results (morbidity) – RCT, direct comparison: cabozantinib + BSC vs. placebo + BSC

Study **Outcome category**	**Cabozantinib + BSC**			**Placebo + BSC**			**Cabozantinib + BSC vs. placebo + BSC**
Outcome	**N[a]**	**Values at baseline mean (SD)**	**Change at end of study mean (SE)[b]**	**N[a]**	**Values at baseline mean (SD)**	**Change at end of study mean (SE)[b]**	**MD [95% CI]; p-value[b]**
CELESTIAL							
Morbidity							
Health status (EQ-5D VAS)[c]	447	ND[d]	−7.35 (1.37)	242	ND[d]	−2.77 (1.52)	−4.59 [ND]; < 0.001 Hedges' g[e]: −0.26 [−0.41; −0.10]
Health-related quality of life	Outcome not recorded						

a: Number of patients considered in the analysis for the calculation of the effect estimation.
b: MMRM stratified by the following factors: aetiology of disease (HBV [with or without HCV], HCV [without HBV], other), geographical region (Asia, other), and presence of extrahepatic spread of disease and/or macrovascular invasion (yes, no) (see Section 2.7.4.3.1 of the full dossier assessment).
c: Negative values indicate deterioration of health status.
d: The following baseline values were available at the time point of the second data cut-off from 1 June 2017 for the patients randomized at this time point: 73.53 (18.9) in the cabozantinib arm and 76.15 (16.22) in the comparator arm.
e: Effect estimation of Hedges' g: ratio of the mean difference and the pooled standard deviation based on the baseline values of both treatment arms (see Section 2.7.4.3.1 of the full dossier assessment).
CI: confidence interval; BSC: best supportive care; EQ-5D: European Quality of Life-5 Dimensions; HBV: hepatitis B virus; HCV: hepatitis C virus; MD: mean difference; MMRM: mixed-effects model repeated measures; N: number of analysed patients; ND: no data; RCT: randomized controlled trial; SD: standard deviation; SE: standard error; VAS: visual analogue scale; vs.: versus

Based on the available data, at most indications, e.g. of an added benefit, can be derived for the outcomes "overall survival" and "discontinuation due to AEs". Due to the high risk of bias, at

most hints, e.g. of an added benefit, can be determined for all other outcomes on side effects as well as for the outcome “health status (EQ-5D VAS)”.

Mortality

Overall survival

A statistically significant difference in favour of cabozantinib + BSC in comparison with placebo + BSC was shown between the treatment groups for the outcome “overall survival”. This resulted in an indication of an added benefit of cabozantinib in comparison with BSC for the outcome “overall survival”.

This concurs with the company’s assessment.

Morbidity

Health status (EQ-5D VAS)

A statistically significant difference to the disadvantage of cabozantinib + BSC in comparison with placebo + BSC was shown between the treatment groups for the outcome “health status” measured with the EQ-5D VAS. However, the 95% CI of the standardized mean difference was not fully outside the irrelevance range of −0.2 to 0.2. It can therefore not be inferred that the effect is relevant. Hence, there was no hint of an added benefit of cabozantinib in comparison with BSC; an added benefit is therefore not proven.

This concurs with the company’s assessment.

Health-related quality of life

Outcomes in this category were not recorded in the CELESTIAL study.

Side effects

Serious adverse events

A statistically significant difference to the disadvantage of cabozantinib + BSC in comparison with placebo + BSC was shown between the treatment groups for SAEs. This resulted in a hint of greater harm from cabozantinib in comparison with BSC.

This deviates from the assessment of the company insofar as the company derived an indication of lesser benefit.

Severe adverse events (CTCAE grade ≥ 3)

A statistically significant difference to the disadvantage of cabozantinib + BSC in comparison with placebo + BSC was shown between the treatment groups for severe AEs (CTCAE grade ≥ 3). This resulted in a hint of greater harm from cabozantinib in comparison with BSC.

This deviates from the assessment of the company insofar as the company derived an indication of lesser benefit.

Discontinuation due to adverse events

A statistically significant difference to the disadvantage of cabozantinib + BSC in comparison with placebo + BSC was shown between the treatment groups for discontinuation due to AEs. This resulted in an indication of greater harm from cabozantinib in comparison with BSC.

This concurs with the company's assessment.

Specific adverse events

Severe AEs (CTCAE grade ≥ 3): nervous system disorders (SOC), decreased appetite (PT), diarrhoea (PT), fatigue (PT), hypertension (PT), and palmar-plantar erythrodysaesthesia syndrome (PT):

A statistically significant difference to the disadvantage of cabozantinib + BSC in comparison with placebo + BSC was shown between the treatment groups for the following outcomes: nervous system disorders (SOC), decreased appetite (PT), diarrhoea (PT), fatigue (PT), hypertension (PT), and palmar-plantar erythrodysaesthesia syndrome (PT) (in each case severe AEs [CTCAE grade ≥ 3]). In each case, this resulted in a hint of greater harm from cabozantinib in comparison with BSC.

AEs: mucosal inflammation (PT) and stomatitis (PT):

A statistically significant difference to the disadvantage of cabozantinib + BSC in comparison with placebo + BSC was shown between the treatment groups for the outcomes "mucosal inflammation (PT)" and "stomatitis (PT)" (in each case AEs). In each case, this resulted in a hint of greater harm from cabozantinib in comparison with BSC.

This deviates from the approach of the company, which did not use specific AEs for the assessment.

2.4.4 Subgroups and other effect modifiers

The following potential effect modifiers were considered in the present benefit assessment:

- age (< 65 years; 65 to < 75 years; 75 to < 85 years; ≥ 85 years)
- sex (male, female)
- geographical region (Asia [without Japan]; Europe/Australia/New Zealand; North America [Canada/USA]; other)
- extrahepatic spread of disease and/or macrovascular invasion at baseline (yes; no)

The characteristics mentioned above were predefined for the outcome "overall survival".

Subgroup analyses were available for all outcomes except for the outcome "health status (EQ-5D VAS)" and the outcomes on specific AEs.

Only the results with an effect modification with a statistically significant interaction between treatment and subgroup characteristic (p-value < 0.05) are presented. In addition, subgroup results are only presented if there is a statistically significant and relevant effect in at least one subgroup.

No effect modifications for the outcomes “overall survival”, “SAEs”, “severe AEs” and “discontinuation due to AEs” resulted from the available subgroup analyses.

2.5 Probability and extent of added benefit

The derivation of probability and extent of the added benefit is presented below at outcome level, taking into account the different outcome categories and effect sizes. The methods used for this purpose are explained in the *General Methods* of IQWiG [1].

The approach for deriving an overall conclusion on added benefit based on the aggregation of conclusions derived at outcome level is a proposal by IQWiG. The G-BA decides on the added benefit.

2.5.1 Assessment of the added benefit at outcome level

The extent of the respective added benefit at outcome level was estimated from the results presented in Section 2.4 (see Table 16).

Determination of the outcome category for the outcomes on side effects

It could not be inferred from the dossier for all outcomes considered in the present benefit assessment whether they were serious/severe or non-serious/non-severe. The classification of these outcomes is justified below.

Since most events for the outcome “discontinuation due to AEs” were severe AEs (CTCAE grade ≥ 3), the outcome was allocated to the category of serious/severe side effects.

Regarding the AEs “mucosal inflammation” and “stomatitis”, most AEs were non-serious/non-severe, which is why these specific AEs were allocated to the outcome category of non-serious/non-severe side effects.

Table 16: Extent of added benefit at outcome level: cabozantinib vs. BSC

Outcome category **Outcome**	**Cabozantinib vs. BSC** **Median time to event (months) or mean value of the change from baseline to end of study** **Effect estimation [95% CI]** **p-value** **Probability**[a]	**Derivation of extent**[b]
Mortality		
Overall survival	Median: 10.3 vs. 8.2 months HR: 0.78 [0.66; 0.93] p = 0.006 probability: "indication"	Outcome category: "mortality" $0.85 \leq CI_u < 0.95$ Added benefit, extent: "considerable"
Morbidity		
Health status (EQ-5D VAS)	Mean: −7.35 vs. −2.77 MD: −4,59 [ND] p < 0.001 Hedges' g: −0.26 [−0.41; −0.10][c]	Lesser benefit/added benefit not proven
Health-related quality of life		
Outcomes from this category were not recorded		
Side effects		
SAEs	Median: 10.8 vs. 10.5 months HR: 1.31 [1.02; 1.69] HR: 0.76 [0.59; 0.98][d] p = 0.035 probability: "hint"	Outcome category: serious/severe side effects $0.90 \leq CI_u < 1.00$ greater harm, extent: "minor"
Severe AEs (CTCAE grade ≥ 3)	Median: 1.0 vs. 4.1 months HR: 2.60 [2.13; 3.18] HR: 0.38 [0.31; 0.47][d] p < 0.001 probability: "hint"	Outcome category: serious/severe side effects $CI_u < 0.75$ and risk ≥ 5% greater harm, extent: "major"
Discontinuation due to AEs	Median: 19.7 vs. NA months HR: 1.64 [1.18; 2.28] HR: 0.61 [0.44; 0.85][d] p = 0.003 probability: "indication"	Outcome category: serious/severe side effects $0.75 \leq CI_u < 0.90$ greater harm, extent: "considerable"
Nervous system disorders (CTCAE grade ≥ 3)	Median: NA vs. NA HR: 4.10 [1.62; 10.37] HR: 0.24 [0.10; 0.62][d] p = 0.001 probability: "hint"	Outcome category: serious/severe side effects $CI_u < 0.75$ and risk ≥ 5% greater harm, extent: "major"

(continued)

Table 16: Extent of added benefit at outcome level: cabozantinib vs. BSC (continued)

Outcome category **Outcome**	**Cabozantinib vs. BSC** **Median time to event (months) or mean value of the change from baseline to end of study** **Effect estimation [95% CI]** **p-value** **Probability[a]**	**Derivation of extent[b]**
Decreased appetite (CTCAE grade ≥ 3)	Median: NA vs. NA HR: 5.75 [1.36; 24.27] HR: 0.17 [0.04; 0.74][d] p = 0.007 probability: "hint"	Outcome category: serious/severe side effects CI_u < 0.75 and risk ≥ 5% greater harm, extent: "major"
Diarrhoea (CTCAE grade ≥ 3)	Median: NA vs. NA HR: 5.34 [1.92; 14.86] HR: 0.19 [0.07; 0.52][d] p < 0.001 probability: "hint"	Outcome category: serious/severe side effects CI_u < 0.75 and risk ≥ 5% greater harm, extent: "major"
Fatigue (CTCAE grade ≥ 3)	Median: NA vs. NA HR: 2.66 [1.35; 5.24] HR: 0.38 [0.19; 0.74][d] p = 0.003 probability: "hint"	Outcome category: serious/severe side effects CI_u < 0.75 and risk ≥ 5% greater harm, extent: "major"
Hypertension (CTCAE grade ≥ 3)	Median: NA vs. NA HR: 8.31 [3.36; 20.54] HR: 0.12 [0.05; 0.30][d] p < 0.001 probability: "hint"	Outcome category: serious/severe side effects CI_u < 0.75 and risk ≥ 5% greater harm, extent: "major"
Palmar-plantar erythrodysaesthesia syndrome (CTCAE grade ≥ 3)	Median: NA vs. NA HR: NC[e] p < 0.001 probability: "hint"	Outcome category: serious/severe side effects greater harm, extent: "major"
Mucosal inflammation	Median: NA vs. NA HR: 7.40 [2.98; 18.35] HR: 0.14 [0.05; 0.34][d] p < 0.001 probability: "hint"	Outcome category: non-serious/non-severe side effects CI_u < 0.80 greater harm, extent: "considerable"
Stomatitis	Median: NA vs. NA HR: 7.34 [2.96; 18.21] HR: 0.14 [0.05; 0.34][d] p < 0.001 probability: "hint"	Outcome category: non-serious/non-severe side effects CI_u < 0.80 greater harm, extent: "considerable"

(continued)

Table 16: Extent of added benefit at outcome level: cabozantinib vs. BSC (continued)

a: Probability provided if a statistically significant and relevant effect is present. b: Estimations of effect size are made depending on the outcome category with different limits based on the CI_u. c: If the CI of Hedges' g is fully outside the irrelevance range [−0.2; 0.2], this is interpreted to be a relevant effect. In other cases, the presence of a relevant effect cannot be derived. d: Institute's calculation, reversed direction of effect to enable use of limits to derive the extent of the added benefit. e: Since no events occurred in the comparator arm, the HR cannot be calculated. In the present situation, the Institute conducted an asymptotic calculation of the RR only for the approximate determination of the extent: 87.85 [5.47; 1410.22]; inverse direction of effect: RR: 0.01 [0.00; 0.18] (see Section 2.7.4.3.2 of the full dossier assessment). AE: adverse event; BSC: best supportive care; CI: confidence interval; CI_u: upper limit of confidence interval; CTCAE: Common Terminology Criteria for Adverse Events; EQ-5D: European Quality of Life-5 Dimensions; HR: hazard ratio; MD: mean difference; NA: not achieved; RCT: randomized controlled trial; RR: relative risk; SAE: serious adverse event; VAS: visual analogue scale; vs.: versus

2.5.2 Overall conclusion on added benefit

Table 17 summarizes the results considered in the overall conclusion on the extent of the added benefit.

Table 17: Positive and negative effects from the assessment of cabozantinib in comparison with BSC

Positive effects	**Negative effects**
Mortality ▪ Overall survival: indication of an added benefit – extent: "considerable"	Serious/severe side effects ▪ SAEs: hint of greater harm – extent: "minor" ▪ severe AEs (CTCAE grade ≥ 3): hint of greater harm – extent: "major" ▪ discontinuation due to AEs: indication of greater harm – extent: "considerable" ▪ specific AEs, including nervous system disorders (CTCAE grade ≥ 3), decreased appetite (CTCAE grade ≥ 3), diarrhoea (CTCAE grade ≥ 3), fatigue (CTCAE grade ≥ 3), hypertension (CTCAE grade ≥ 3), and plantar erythrodysaesthesia syndrome (CTCAE grade ≥ 3): in each case hint of greater harm – extent: "major"
	Non-serious/non-severe side effects ▪ specific AEs, including mucosal inflammation and stomatitis: in each case hint of greater harm – extent: "considerable"
Health-related quality of life: outcomes from this category were not recorded	
AE: adverse event; BSC: best supportive care; CTCAE: Common Terminology Criteria for Adverse Events; SAE: serious adverse event	

The overall assessment showed one positive and several negative effects of cabozantinib in comparison with BSC. There was a positive effect for the outcome "overall survival". This was accompanied by several negative effects, mainly in the category of serious/severe side effects,

mostly with the extent “major”. There were no data for the outcome category “health-related quality of life”. The negative effects and the missing data on health-related quality of life did not completely outweigh the advantage in overall survival, but resulted in a downgrading of the extent of the added benefit.

In summary, there is an indication of a minor added benefit of cabozantinib in comparison with the ACT BSC for patients with HCC who have previously been treated with sorafenib.

The result of the assessment of the added benefit of cabozantinib in comparison with the ACT is summarized in Table 18.

Table 18: Cabozantinib – probability and extent of added benefit

Therapeutic indication	**ACT[a]**	**Probability and extent of added benefit**
Adult patients with hepatocellular carcinoma (HCC) who have previously been treated with sorafenib[b]	Best supportive care (BSC)[c]	Indication of minor added benefit
a: Presentation of the ACT specified by the G-BA. b: The relevant study included patients with Child-Pugh class A and an ECOG PS of 0 or 1. It remains unclear whether the observed effects can be transferred to patients with Child-Pugh class B and/or an ECOG PS of > 1 (see Section 2.3.2). c: BSC refers to the therapy that provides the patient with the best possible, individually optimized, supportive treatment to alleviate symptoms and improve the quality of life. ACT: appropriate comparator therapy; BSC: best supportive care; ECOG PS: Eastern Cooperative Oncology Group Performance Status; G-BA: Federal Joint Committee; HCC: hepatocellular carcinoma		

The assessment described above deviates from that of the company, which overall derived an indication of non-quantifiable added benefit.

The approach for deriving an overall conclusion on the added benefit is a proposal by IQWiG. The G-BA decides on the added benefit.

2.6 List of included studies

Abou-Alfa GK, Meyer T, Cheng A-L, El-Khoueiry AB, Rimassa L, Ryoo BY et al. Cabozantinib in patients with advanced and progressing hepatocellular carcinoma. N Engl J Med 2018; 379(1): 54-63.

Exelixis. A study of cabozantinib (XL184) vs placebo in subjects with hepatocellular carcinoma who have received prior sorafenib (CELESTIAL): study details [online]. In: ClinicalTrials.gov. 19.10.2017 [Accessed: 21.12.2018]. URL: https://ClinicalTrials.gov/show/NCT01908426.

Exelixis. Eine randomisierte, doppelblinde, kontrollierte Studie der Phase 3 zu Cabozantinib (XL184) gegenüber Placebo bei Patienten mit hepatozellulärem Karzinom, die vorher Sorafenib erhalten haben [online]. In: Deutsches Register Klinischer Studien. 5 December 2018 [Accessed: 21.12.2018]. URL: http://www.drks.de/DRKS00005304.

Exelixis. A phase 3, randomized, double-blind, controlled study of cabozantinib (XL184) vs placebo in subjects with hepatocellular carcinoma who have received prior sorafenib [online]. In: EU Clinical Trials Register. [Accessed: 21.12.2018]. URL: https://www.clinicaltrialsregister.eu/ctr-search/search?query=eudract_number:2013-001001-91.

Exelixis. A phase 3, randomized, double-blind, controlled study of cabozantinib (XL184) vs placebo in subjects with hepatocellular carcinoma who have received prior sorafenib: study XL184-309; clinical study protocol [unpublished]. 2016.

Exelixis. A phase 3, randomized, double-blind, controlled study of cabozantinib (XL184) vs placebo in subjects with hepatocellular carcinoma who have received prior sorafenib: study XL184-309; statistical analysis plan [unpublished]. 2016.

Exelixis. A phase 3, randomized, double-blind, controlled study of cabozantinib (XL184) vs placebo in subjects with hepatocellular carcinoma who have received prior sorafenib: study XL184-309; clinical study report addendum [unpublished]. 2018.

Exelixis. A phase 3, randomized, double-blind, controlled study of cabozantinib (XL184) vs placebo in subjects with hepatocellular carcinoma who have received prior sorafenib: study XL184-309; clinical study report [unpublished]. 2018.

Ipsen Pharma. A phase 3, randomized, double-blind, controlled study of cabozantinib (XL184) vs placebo in subjects with hepatocellular carcinoma who have received prior sorafenib: study XL184-309; Zusatzanalysen [unpublished]. 2018.

References for English extract

Please see full dossier assessment for full reference list.

1. Institute for Quality and Efficiency in Health Care. General methods: version 5.0 [online]. 10.07.2017 [Accessed: 04.06.2018]. URL: https://www.iqwig.de/download/General-Methods_Version-5-0.pdf.

2. Skipka G, Wieseler B, Kaiser T, Thomas S, Bender R, Windeler J et al. Methodological approach to determine minor, considerable, and major treatment effects in the early benefit assessment of new drugs. Biom J 2015; 58(1): 43-58.

3. Ipsen Pharma. Cabometyx 20 mg/40 mg/60 mg Filmtabletten: Fachinformation [online]. 11.2018 [Accessed: 14.12.2018]. URL: https://www.fachinfo.de/.

The full report (German version) is published under https://www.iqwig.de/en/projects-results/projects/drug-assessment/a18-85-cabozantinib-hepatocellular-carcinoma-benefit-assessment-according-to-35a-social-code-book-v.11201.html.