IQWiG Reports – Commission No. A19-73

Ramucirumab (hepatocellular carcinoma) –

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

Extract

[1] Translation of Sections 2.1 to 2.6 of the dossier assessment *Ramucirumab (hepatozelluläres Karzinom) – Nutzenbewertung gemäß § 35a SGB V* (Version 1.0; Status: 28 November 2019). Please note: This translation is provided as a service by IQWiG to English-language readers. However, solely the German original text is absolutely authoritative and legally binding.

Publishing details

Publisher:

Institute for Quality and Efficiency in Health Care

Topic:

Ramucirumab (hepatocellular carcinoma) – Benefit assessment according to §35a Social Code Book V

Commissioning agency:

Federal Joint Committee

Commission awarded on:

29 August 2019

Internal Commission No.:

A19-73

Address of publisher:

Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen
Im Mediapark 8
50670 Köln
Germany

Phone: +49 221 35685-0
Fax: +49 221 35685-1
E-mail: berichte@iqwig.de
Internet: www.iqwig.de

Medical and scientific advice:

- Henning Schulze-Bergkamen, Marien-Hospital Wesel gGmbH, Wesel, Germany

IQWiG thanks the medical and scientific advisor for his contribution to the dossier assessment. However, the advisor was not involved in the actual preparation of the dossier assessment. The responsibility for the contents of the dossier assessment lies solely with IQWiG.

IQWiG employees involved in the dossier assessment:

- Anne-Kathrin Petri
- Judith Gibbert
- Petra Kohlepp
- Matthias Maiworm
- Dominik Schierbaum
- Ulrike Seay
- Volker Vervölgyi
- Siw Waffenschmidt

Keywords: Ramucirumab, Carcinoma – Hepatocellular, Benefit Assessment, NCT01140347, NCT02435433

Table of contents

List of tables[2]

Page

[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
AFP	alpha fetoprotein
BCLC	Barcelona Clinic Liver Cancer
BSC	best supportive care
CTCAE	Common Terminology Criteria for Adverse Events
ECOG PS	Eastern Cooperative Oncology Group Performance Status
EQ-5D	European Quality of Life-5 Dimensions
FACT	Functional Assessment of Cancer Therapy
FHSI-8	FACT Hepatobiliary Symptom Index-8
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 ramucirumab. 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 29 August 2019.

Research question

The aim of the present report is the assessment of the added benefit of ramucirumab in comparison with the appropriate comparator therapy (ACT) in patients with advanced or unresectable hepatocellular carcinoma (HCC) who have a serum alpha fetoprotein (AFP) of ≥ 400 ng/mL and who have been previously treated with sorafenib.

Table 2: Research questions of the benefit assessment of ramucirumab

Research question	Therapeutic indication	ACT[a]
1	Adult patients with advanced or unresectable hepatocellular carcinoma (HCC) who have a serum alpha fetoprotein of ≥ 400 ng/mL and who have been previously treated with sorafenib	**Best supportive care**[b] or cabozantinib

a: Presentation of the respective ACT specified by the G-BA. In cases where the company, because of the G-BA's specification of the ACT, could choose a comparator therapy from several options, the respective choice of the company is printed in **bold**.
b: Best supportive care 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; G-BA: Federal Joint Committee; HCC: hepatocellular carcinoma

Following the G-BA, the company chose best supportive care (BSC) as ACT.

The assessment was conducted by means of patient-relevant outcomes on the basis of the data presented 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

The studies REACH and REACH-2 were included in the benefit assessment. The studies had a very similar study design and are described together below, unless otherwise stated. Both studies were randomized, placebo-controlled, double-blind multicentre studies. The studies compared treatment with ramucirumab + BSC with placebo + BSC. They included adult patients with advanced or unresectable HCC who had received prior sorafenib therapy. Patients had to be in Barcelona Clinic Liver Cancer (BCLC) stage C. Patients in BCLC stage B could also be eligible if their disease was not amenable or refractory to locoregional therapy. Patients

with an Eastern Cooperative Oncology Group Performance Status (ECOG PS) of 0 or 1 and with only mild liver impairment (Child Pugh class A) were enrolled.

Patients were included in the REACH study regardless of their serum AFP levels at baseline. The company presented analyses of a relevant subpopulation who had baseline serum AFP levels of ≥ 400 ng/mL. These were 119 patients in the ramucirumab + BSC arm and 131 patients in the placebo + BSC arm.

The REACH-2 study only included patients with serum AFP levels of ≥ 400 ng/mL at baseline. The study included 292 patients, randomly allocated in a 2:1 ratio either to treatment with ramucirumab + BSC (N = 197) or to placebo + BSC (N = 95).

In both studies, treatment with ramucirumab was in compliance with the Summary of Product Characteristics (SPC). According to the study protocols, the investigators had been instructed to provide the patients with individual supportive therapies in the sense of BSC to alleviate symptoms and complications.

Primary outcome of both studies was overall survival. Patient-relevant secondary outcomes were symptoms, health status and adverse events (AEs).

Risk of bias

The risk of bias across outcomes of both studies was rated as low. The risk of bias for the results on the outcomes "overall survival" and "discontinuation due to AEs" was also rated as low. The risk of bias of the results on the outcomes of the category of side effects was rated as high.

Mortality

Overall survival

The meta-analysis showed a statistically significant difference between the treatment groups in favour of ramucirumab + BSC in comparison with placebo + BSC for the outcome "overall survival". This resulted in proof of an added benefit of ramucirumab + BSC versus BSC for the outcome "overall survival".

Morbidity

Symptoms (recorded using FHSI-8) and health status (recorded using EQ-5D VAS)

There were no usable data for the outcomes "symptoms" (Functional Assessment of Cancer Therapy [FACT]-Hepatobiliary Symptom Index-8 [FHSI-8]) and "health status" (European Quality of Life-5 Dimensions visual analogue scale [EQ-5D VAS]). In each case, this resulted in no hint of an added benefit of ramucirumab + BSC in comparison with BSC; an added benefit is therefore not proven.

Health-related quality of life

No outcomes in the category of health-related quality of life were recorded in the studies REACH and REACH-2. This resulted in no hint of an added benefit of ramucirumab + BSC in comparison with BSC in this outcome category; an added benefit is therefore not proven.

Side effects

Serious adverse events, severe adverse events (CTCAE grade ≥ 3) and discontinuation due to adverse events

The meta-analysis showed no statistically significant difference between the treatment groups for the outcomes "serious AEs (SAEs)", "severe AEs" (Common Terminology Criteria for Adverse Events [CTCAE] grade ≥ 3]) and "discontinuation due to AEs". In each case, this resulted in no hint of greater or lesser harm from ramucirumab + BSC in comparison with BSC; an added benefit is therefore not proven.

Specific adverse events

- Gastrointestinal disorders (System Organ Class [SOC], severe AEs [CTCAE grade ≥ 3]), hyperbilirubinaemia (Preferred Term [PT]), severe AEs [CTCAE grade ≥ 3]), investigations (SOC, severe AEs [CTCAE grade ≥ 3])

  The meta-analysis showed a statistically significant difference in favour of ramucirumab + BSC versus placebo + BSC for each of the following outcomes: gastrointestinal disorders, hyperbilirubinaemia and investigations. This resulted in an indication of lesser harm from ramucirumab + BSC in comparison with BSC in each case.

- Oedema peripheral (PT, AE), reproductive system and breast disorders (SOC, AE), headache (PT, AE) and hypertension (PT, severe AE [CTCAE grade ≥ 3])

  A statistically significant difference to the disadvantage of ramucirumab + BSC versus placebo + BSC was shown for each of the following outcomes: oedema peripheral, reproductive system and breast disorders, headache, and hypertension. This resulted in an indication of greater harm from ramucirumab + BSC in comparison with BSC in each case.

- Renal and urinary disorders (SOC, AE) and injury, poisoning and procedural complications (SOC, AE)

  A statistically significant difference to the disadvantage of ramucirumab + BSC was shown for each of the outcomes "renal and urinary disorders" and "injury, poisoning and procedural complications". The effect in each of these non-serious/non-severe AEs was no more than marginal, however. In each case, this resulted in no hint of greater or lesser harm from ramucirumab + BSC in comparison with BSC; an added benefit is therefore not proven.

- Bleeding/haemorrhagic events and hepatic encephalopathy

  No statistically significant difference between the treatment groups was shown for each of the outcomes "bleeding/haemorrhagic events" and "hepatic encephalopathy". This resulted in no hint of greater or lesser harm from ramucirumab + BSC in comparison with BSC; an added benefit is therefore not proven.

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

Based on the results presented, probability and extent of the added benefit of the drug ramucirumab in comparison with the ACT are assessed as follows:

The overall consideration showed both positive and negative effects of ramucirumab + BSC in comparison with BSC. The positive effect with the extent "major" and the probability "proof" for the outcome "overall survival" is decisive for the overall conclusion on the added benefit. This is accompanied by several negative effects in the outcome categories of serious/severe side effects and non-serious/non-severe side effects with an extent up to "considerable" and the probability "indication" in each case. There are further positive effects in the outcome category of serious/severe side effects with an extent up to "considerable" and also the probability "indication" in each case. It is questionable, however, whether these positive effects should be allocated to the outcome category of side effects or whether they rather reflect symptoms of the disease. The negative effects did not outweigh the advantage in overall survival, but resulted in a downgrading of the extent of the added benefit.

In summary, there is proof of considerable added benefit of ramucirumab + BSC versus the ACT placebo + BSC for patients with advanced or unresectable HCC who have a serum AFP of ≥ 400 ng/mL and who have been previously treated with sorafenib.

Table 3 shows a summary of probability and extent of the added benefit of ramucirumab.

[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].

Table 3: Ramucirumab – probability and extent of added benefit

Therapeutic indication	**ACT**[a]	**Probability and extent of added benefit**
Adult patients with advanced or unresectable hepatocellular carcinoma (HCC) who have a serum alpha fetoprotein of ≥ 400 ng/mL and who have been previously treated with sorafenib	**Best supportive care**[b] or cabozantinib	Proof of considerable added benefit[c]

a: Presentation of the respective ACT specified by the G-BA. In cases where the company, because of the G-BA's specification of the ACT, could choose a comparator therapy from several options, the respective choice of the company is printed in **bold**.
b: Best supportive care 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.
c: The studies REACH and REACH-2 only included patients with an ECOG PS of 0 or 1 and with Child Pugh class A. It therefore remains unclear whether the observed effects can be transferred to patients with ECOG PS ≥ 2 or Child-Pugh class B or C.

ACT: appropriate comparator therapy; 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 is the assessment of the added benefit of ramucirumab in comparison with the ACT in patients with advanced or unresectable HCC who have a serum AFP of ≥ 400 ng/mL and who have been previously treated with sorafenib.

This resulted in one research question for the assessment, for which the G-BA specified the ACT presented in Table 4.

Table 4: Research questions of the benefit assessment of ramucirumab

Research question	**Therapeutic indication**	**ACT**[a]
1	Adult patients with advanced or unresectable hepatocellular carcinoma (HCC) who have a serum alpha fetoprotein of ≥ 400 ng/mL and who have been previously treated with sorafenib	**Best supportive care**[b] or cabozantinib

a: Presentation of the respective ACT specified by the G-BA. In cases where the company, because of the G-BA's specification of the ACT, could choose a comparator therapy from several options, the respective choice of the company is printed in **bold**.
b: Best supportive care 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; G-BA: Federal Joint Committee; HCC: hepatocellular carcinoma

The G-BA specified the ACT listed in Table 4 (status: August 2019) at the same time as the company submitted the dossier. In comparison with its decision of June 2017 (BSC), the G-BA expanded the comparator therapy to include the option of cabozantinib with this specification.

This had no consequence for the assessment. The comparator therapy BSC cited by the company is comprised by the alternatives of the ACT specified by the G-BA.

The assessment was conducted by means of patient-relevant outcomes on the basis of the data presented 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 ramucirumab (status: 3 July 2019)
- bibliographical literature search on ramucirumab (last search on 3 July 2019)
- search in trial registries for studies on ramucirumab (last search on 3 July 2019)

To check the completeness of the study pool:

- search in trial registries for studies on ramucirumab (last search on 5 September 2019)

The check identified no additional relevant study.

2.3.1 Studies included

The studies listed in the following table were included in the benefit assessment.

Table 5: Study pool – RCT, direct comparison: ramucirumab + BSC vs. placebo + 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)
I4T-IE-JVBF (REACH[b])	Yes	Yes	No
I4T-MC-JVDE (REACH-2[b])	Yes	Yes	No
a: Study sponsored by the company. b: In the following tables, the study is referred to with this abbreviated form. BSC: best supportive care; RCT: randomized controlled trial; vs.: versus			

The study pool for the benefit assessment of ramucirumab concurs with that of the company. It includes the 2 studies REACH and REACH-2, which compared ramucirumab + BSC with placebo + BSC.

Section 2.6 contains a reference list for the studies included.

2.3.2 Study characteristics

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

Table 6: Characteristics of the studies included – RCT, direct comparison: ramucirumab + 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]
REACH	RCT, double-blind, parallel	Adults with ▪ histologically or cytologically confirmed advanced or unresectable HCC[b, c, d] ▪ prior therapy with sorafenib ▪ Child-Pugh class A[e] ▪ ECOG PS 0 or 1	▪ Ramucirumab + BSC (N = 283) ▪ placebo + BSC (N = 282) Relevant analysed subpopulation thereof[f]: ▪ ramucirumab + BSC (n = 119) ▪ placebo + BSC (n = 131)	▪ Screening: within 14 days ▪ Treatment: until disease progression, unacceptable toxicity, withdrawal of consent to study participation ▪ Observation[g]: outcome-specific, at most until death or end of study	154 centres in: Australia, Austria, Belgium, Brazil, Bulgaria, Canada, Czech Republic, Finland, France, Germany, Hong Kong, Hungary, Israel, Italy, Japan, Korea, Netherlands, Norway, Philippines, Portugal, Romania, Spain, Sweden, Switzerland, Taiwan, Thailand, USA 11/2010–03/2015 Data cut-off: 3/2014[h]	Primary: overall survival Secondary: symptoms, health status, AEs
REACH-2	RCT, double-blind, parallel	Adults with ▪ histologically or cytologically confirmed advanced or unresectable HCC[b, i, j] ▪ AFP ≥ 400 ng/mL ▪ prior therapy with sorafenib ▪ Child-Pugh class A ▪ ECOG PS 0 or 1	▪ Ramucirumab + BSC (N = 197) ▪ placebo + BSC (N = 95)	▪ Screening: within 21 days ▪ Treatment: until disease progression, unacceptable toxicity, withdrawal of consent to study participation ▪ Observation[g]: outcome-specific, at most until death or end of study	92 centres in: Australia, Austria, Belgium, Brazil, Canada, China, Czech Republic, France, Germany, Hong Kong, Israel, Italy, Japan, Korea, Poland, Spain, Switzerland, Taiwan, United Kingdom, USA 07/2015–ongoing[k] Data cut-off: 3/2018[l]	Primary: overall survival Secondary: symptoms, health status, AEs

(continued)

Table 6: Characteristics of the studies included – RCT, direct comparison: ramucirumab + BSC vs. placebo + BSC (continued)

a: Primary outcomes include information without consideration of the relevance for this benefit assessment. Secondary outcomes only include information on relevant available outcomes for this benefit assessment.
b: Patients in BCLC stage C at randomization; patients in BCLC stage B could be eligible if their disease was not amenable or refractory to locoregional therapy.
c: Patients with fibrolamellar carcinoma were excluded from the study.
d: In the absence of a histologically confirmed diagnosis, patients had to have clinical, biochemical or radiological findings consistent with the diagnosis of liver cirrhosis on study entry, and a liver mass measuring at least 2 cm with characteristic vascularization seen on either triphasic computed tomography (CT) scan or magnetic resonance imaging (MRI) with gadolinium.
e: According to versions 1.0–4.0 of the protocol, patients with Child-Pugh score < 9 were included in the study (CP-A or CP-B). Version 5.0 of the protocol (4 September 2012) specified that patients in CP-B should be excluded from inclusion in the study (due to imbalances in hepatic AEs in the ramucirumab + BSC arm).
f: The relevant subpopulation comprised patients with serum AFP levels of ≥ 400 ng/mL at baseline.
g: Outcome-specific information is provided in Table 8.
h: Final analysis of a total of 438 deaths corresponding to the predefined data cut-off for the primary outcome “overall survival”.
i: In the absence of histological findings, a diagnosis of liver cirrhosis and HCC with classical imaging techniques was acceptable.
j: Patients with fibrolamellar HCC or mixed hepatocellular cholangiocarcinoma were excluded from the study.
k: Planned end of study 6/2020.
l: Final analysis of a total of 221 deaths, corresponding to the predefined data cut-off for the primary outcome “overall survival”.

AE: adverse event; AFP: alpha fetoprotein; BCLC: Barcelona Clinic Liver Cancer; BSC: best supportive care; CP-A: Child-Pugh class A; CP-B: Child-Pugh class B; ECOG PS: Eastern Cooperative Oncology Group Performance Status; HCC: hepatocellular carcinoma; n: relevant subpopulation; N: number of randomized patients; RCT: randomized controlled trial; vs.: versus

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

Study	Intervention	Comparison
REACH	Ramucirumab, 8 mg/kg[a], day 1 of each cycle (every 2 weeks), IV (over about 60 minutes) + BSC (at the investigator's discretion)	Ramucirumab placebo, day 1 of each cycle (every 2 weeks), IV (over about 60 minutes) + BSC (at the investigator's discretion)
	Up to 2 dose adjustments due to AEs permitted: ▪ dose reduction: ▫ 1st: 8 mg/kg → 6 mg/kg (every 2 weeks) ▫ 2nd: 6 mg/kg → 5 mg/kg (every 2 weeks) ▪ treatment discontinuation in case of unacceptable toxicity (e.g. the following CTCAE grade 3 or 4 events: infusion-related reaction, bleeding/haemorrhagic event) ▪ dose delays were permitted	
	Permitted pretreatment ▪ pretreatment with sorafenib (until at most 14 days before randomization) as the only systemic therapy of the advanced HCC **Non-permitted pretreatment** ▪ systemic, targeted therapy with VEGF inhibitors or VEGF receptor inhibitors (except sorafenib) ▪ hepatic locoregional therapy within 28 days before randomization ▪ any transfusion of blood components, erythropoietin, an albumin preparation, or G-CSF within 14 days before randomization[b] ▪ radiation to any nonhepatic site (e.g. bone metastases) within 14 days before randomization ▪ major surgery within 28 days before randomization, or central venous access device placement within 7 days before randomization ▪ liver transplantation **Permitted concomitant treatment** ▪ premedication with histamine H1 antagonists (e.g. diphenhydramine hydrochloride) recommended[c] ▪ BSC as clinically appropriate for the treatment of all symptoms and complications ▪ supportive treatment, e.g. with anticoagulants, antidiarrhoeal drugs, antiemetics, analgesics, antibiotics, antiviral therapy, appetite stimulants, growth factors and blood transfusions **Non-permitted concomitant treatment** ▪ radiation[d], chemotherapy, biologic reaction modifiers or other experimental anticancer drugs[e] ▪ chronic therapy with antiplatelet agents, including NSAIDs, therapeutic anticoagulation with warfarin, low molecular weight heparin, or similar agents	
REACH-2[f]	see REACH study	

a: A recalculation of the dose was necessary if the change in body weight was more than 10% of the body weight at the previous dose calculation.
b: REACH-2: transfusion with blood products not permitted 7 days before baseline examinations, otherwise no restrictions.
c: REACH-2: premedication mandated.
d: REACH-2: palliative radiotherapy permitted (if necessary from a medical perspective and after consultation with the sponsor).
e: REACH-2: other systemic anticancer therapy, hormonal cancer therapy, curative surgery/procedures for cancer treatment not permitted.
f: Differences to the REACH study are given as footnotes.

AE: adverse event; BSC: best supportive care; CTCAE: Common Terminology Criteria for Adverse Events; G-CSF: granulocyte colony-stimulating factor; HCC: hepatocellular carcinoma; IV: intravenous; NSAID: nonsteroidal anti-inflammatory drug; RCT: randomized controlled trial; VEGF: vascular endothelial growth factor; vs.: versus

The studies REACH and REACH-2 had a very similar study design and are described together below, unless otherwise stated. Both studies were randomized, placebo-controlled, double-blind multicentre studies. The studies compared treatment with ramucirumab + BSC with placebo + BSC. They included adult patients with advanced or unresectable HCC who had received prior sorafenib therapy. Patients had to be in BCLC stage C. Patients in BCLC stage B could also be eligible if their disease was not amenable or refractory to locoregional therapy. Patients with an ECOG PS of 0 or 1 and with only mild liver impairment (Child Pugh class A) were enrolled.

The approval of ramucirumab in the present therapeutic indication comprises patients with advanced or unresectable HCC who have a serum AFP of ≥ 400 ng/mL and who have been previously treated with sorafenib [3]. Patients were included in the initial REACH study regardless of their serum AFP levels at baseline. The study included 565 patients, randomly allocated in a 1:1 ratio to the 2 treatment arms ramucirumab + BSC (N = 283) or placebo + BSC (N = 282). Randomization was stratified by geographical region and aetiology of the disease at baseline (hepatitis B virus [HBV]/hepatitis C virus [HCV]/other). The company presented analyses of a subpopulation who had baseline serum AFP levels of ≥ 400 ng/mL. These were 119 patients in the ramucirumab + BSC arm and 131 patients in the placebo + BSC arm. The analyses presented by the company comprised the relevant subpopulation of the REACH study and were used for the benefit assessment. The following information refers to the relevant subpopulations.

The REACH-2 study only included patients with serum AFP levels of ≥ 400 ng/mL at baseline. 292 patients were randomly allocated in a 2:1 ratio either to treatment with ramucirumab + BSC (N = 197) or to placebo + BSC (N = 95). Randomization in the REACH-2 study was stratified by geographical region, macrovascular invasion (yes/no) and ECOG PS (0/1).

According to the SPC, ramucirumab should be used with caution in patients with Child-Pugh B or C [3], but these patients are not excluded from the therapeutic indication. Patients with an ECOG PS of > 1 are also comprised by the therapeutic indication. Hence, regarding disease stage, the populations of the studies REACH and REACH-2 do not completely cover the therapeutic indication of ramucirumab. It remains unclear whether the observed effects can be transferred to patients with Child-Pugh class B or C or an ECOG PS of > 1.

In both studies, treatment with ramucirumab was conducted according to the regimen described in Table 7 and was in compliance with the SPC. Concurring with the SPC, the dose of the study medication was to be reduced in case of unacceptable toxicity in both studies. In the REACH study, 29 (24.4%) patients in the ramucirumab + BSC arm and 18 (14.1%) patients in the placebo + BSC arm had AEs leading to dose adjustments. In the REACH-2 study, such dose adjustments due to AEs were necessary in 67 (34.0%) patients in the ramucirumab + BSC arm and in 12 (12.6%) patients in the placebo + BSC arm. According to the study protocols, the investigators had been instructed to provide the patients with individual supportive therapies in the sense of BSC to alleviate symptoms and complications.

In both studies, treatment was until disease progression, unacceptable toxicity or withdrawal of consent.

Primary outcome of both studies was overall survival. Patient-relevant secondary outcomes were symptoms, health status and AEs.

The final analysis for the total population of the REACH study was planned after 438 deaths. The final analysis was conducted in March 2015. In the REACH-2 study, the final analysis was planned after 221 deaths. This analysis was conducted with the data cut-off in March 2018.

Other subsequent systemic or local therapies could be conducted without restrictions after discontinuation of the study medication. In the REACH study, 36.1% of the patients received systemic, non-radiological cancer treatment in the ramucirumab + BSC arm, and 24.4% in the placebo + BSC arm. In the REACH-2 study, these proportions were 26.9% in the ramucirumab + BSC arm and 28.4% in the placebo + BSC arm (see Table 29 of the full dossier assessment). Both studies allowed continuation of ramucirumab treatment in the ramucirumab arm after the end of study. In the REACH-2 study, patients were also allowed to be switched from the control arm to ramucirumab. No patients received ramucirumab as subsequent therapy, however.

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: ramucirumab + BSC vs. placebo + BSC

Study **Outcome category** **Outcome**	**Planned follow-up observation**
REACH	
Mortality	
Overall survival	▪ at most until end of study
Morbidity	
Health status (EQ-5D VAS)	▪ within 7 days after discontinuation of study treatment
Symptoms (FHSI-8)	▪ within 7 days after discontinuation of study treatment
Health-related quality of life	▪ not recorded
Side effects	
AEs, severe AEs (CTCAE grade ≥ 3)	▪ 30–45 days after administration of the last dose of study medication
SAEs, discontinuation due to AEs	▪ until resolution or stabilization of the event
REACH-2	
Mortality	
Overall survival	▪ at most until end of study
Morbidity	
Health status (EQ-5D VAS)	▪ within 7 days after discontinuation of study treatment
Symptoms (FHSI-8)	▪ within 7 days after discontinuation of study treatment
Health-related quality of life	▪ not recorded
Side effects	▪
All outcomes in the category "side effects"	▪ 30 days (±7 days) after administration of the last dose of study medication

AE: adverse event; BSC: best supportive care; CTCAE: Common Terminology Criteria for Adverse Events; EQ-5D: European Quality of Life-5 Dimensions; FHSI-8: Functional Assessment of Cancer Therapy-Hepatobiliary Symptom Index-8; RCT: randomized controlled trial; SAE: serious adverse event; VAS: visual analogue scale; vs.: versus

The observation periods for the outcomes on morbidity and side effects were systematically shortened because they were only recorded for the time period of treatment with the study medication (plus 30 to 45 days for AEs). 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.

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

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

Study Characteristics Category	REACH		REACH-2	
	Ramucirumab + BSC	Placebo + BSC	Ramucirumab + BSC	Placebo + BSC
	Na = 119	Na = 131	Na = 197	Na = 95
Age [years], median [min; max]	62 [34; 84]	59 [25; 83]	64 [30; 88]	64 [26; 85]
Sex [F/M], %	23/77	16/84	22/78	17/83
Family origin, n (%)				
Asian	66 (55.5)	78 (59.5)	102 (51.8)	45 (47.4)
Caucasian	50 (42.0)	49 (37.4)	60 (30.5)	31 (32.6)
Other[b]	3 (2.5)[c]	4 (3.1)[c]	35 (17.8)[c, d]	19 (20.0)[c, d]
Geographical region, n (%)				
Europe	43 (36.1[c])	42 (32.1[c])	82 (41.6[c])	43 (45.3[c])
Rest of the world	76 (63.9[c])	89 (67.9[c])	115 (58.4[c])	52 (54.7[c])
ECOG PS, n (%)				
0	60 (50.4)	63 (48.1)	113 (57.4)	55 (57.9)
1	59 (49.6)	68 (51.9)	84 (42.6)	40 (42.1)
Child-Pugh class at baseline, n (%)				
A – 5 points	67 (56.3)	81 (61.8)	123 (62.4)	54 (56.8)
A – 6 points	48 (40.3)	48 (36.6)	74 (37.6)	41 (43.2)
B – 7 points	1 (0.8)	2 (1.5)	0 (0)	0 (0)
B – 8 points	3 (2.5)	0 (0)	0 (0)	0 (0)
BCLC stage at baseline				
Stage B	11 (9.2)	9 (6.9)	34 (17.3)	20 (21.1)
Stage C	108 (90.8)	122 (93.1)	163 (82.7)	75 (78.9)
Aetiology of liver disease				
Hepatitis B	53 (44.5)	66 (50.4)	71 (36.0)	36 (37.9)
Hepatitis C	35 (29.4)	28 (21.4)	48 (24.4)	28 (29.5)
Hepatitis A	ND	ND	0 (0)	1 (1.1)
Hepatitis, non-A, non-B, non-C	ND	ND	2 (1.0)	1 (1.1)
Significant prior alcohol consumption	23 (19.3)	22 (16.8)	48 (24.4)	21 (22.1)
Steatohepatitis (NASH, fatty liver)	7 (5.9)	7 (5.3)	19 (9.6)	4 (4.2)
Haemochromatosis	1 (0.8)	1 (0.8)	1 (0.5)	0 (0)
Primary biliary cirrhosis	ND	ND	2 (1.0)	2 (2.1)
Cryptogenic cirrhosis	ND	ND	12 (6.1)	4 (4.2)
Other/unknown	15 (12.6)[c]	19 (14.5)[c]	12 (6.1)	3 (3.2)
Macrovascular invasion	43 (36.1)	44 (33.6)	70 (35.5)	33 (34.7)

(continued)

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

Study Characteristics Category	REACH		REACH-2	
	Ramucirumab + BSC	Placebo + BSC	Ramucirumab + BSC	Placebo + BSC
	N[a] = 119	N[a] = 131	N[a] = 197	N[a] = 119
Extrahepatic spread	85 (71.4)	101 (77.1)	141 (71.6)	70 (73.7)
Baseline AFP [ng/mL], median [Q1; Q3]	5293.0 [1295; 29 100]	7022.0 [1322; 30 027]	3920.0 [12 003; 22 534]	2741.0 [1321; 21 538]
Treatment discontinuation, n (%)	ND[e]	ND[e]	186 (94.4)[f]	95 (100.0)[f]
Study discontinuation, n (%)	ND	ND	ND	ND

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: Referring to the following categories: black or African American, several ethnicities, missing and other.
c: Institute's calculation.
d: Family origin was not recorded from patients in France; family origin did not need to be recorded outside the United States; instructions in the eCRF: "If the information was not provided by the study participant, please enter 'not applicable'."
e: Data on patients who discontinued treatment are only available for the total population of the REACH study.
f: Thereof discontinuation due to progression, n (%): ramucirumab + BSC: 129 (65.5) vs. placebo + BSC: 77 (81.1).
AFP: alpha fetoprotein; BCLC: Barcelona Clinic Liver Cancer; BSC: best supportive care; ECOG PS: Eastern Cooperative Oncology Group Performance Status; eCRF: electronic case report form; F: female; M: male; max: maximum; min: minimum; n: number of patients in the category; N: number of randomized (or included) patients; NASH: nonalcoholic steatohepatitis; ND: no data; Q1: first quartile; Q3: third quartile; RCT: randomized controlled trial; vs.: versus

The demographic and clinical characteristics of the patients are largely comparable both between the studies REACH and REACH-2 and between the treatment arms. About 80% of the study participants were male, which is due to the higher disease rate among men [4]. At baseline, most patients were in BCLC stage C with good liver function (Child-Pugh class A). In the REACH study, the median serum AFP level of about 6000 ng/mL at baseline was markedly higher than in the REACH-2 study with about 3500 ng/mL. In both studies, the proportion of patients of Asian family origin was about 50%. The proportion of patients with hepatitis B or hepatitis C in the aetiology of their liver disease was over 50% in both studies.

In summary, the demographic and clinical characteristics of the patients were sufficiently balanced between the studies.

Table 10 shows the average treatment duration and observation period for both studies.

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

Study **Duration of the study phase** **Outcome category**	**Ramucirumab + BSC**	**Placebo + BSC**
REACH	N = 119	N = 131
Treatment duration [weeks]		
Median [min; max]	8.0 [ND]	6.1 [ND]
Mean (SD)	ND	ND
Observation period [months]		
Overall survival	ND	ND
Morbidity	ND	ND
Health-related quality of life	Outcome not recorded	
Side effects	ND	ND
REACH-2	N = 197	N = 95
Treatment duration [weeks]		
Median [min; max]	12.00 [2.00; 107.29]	8.00 [2.00; 43.00]
Mean (SD)	20.05 (19.93)	10.45 (7.69)
Observation period [months]		
Overall survival		
Median [min; max]	7.9 [0.2; 27.0]	6.6 [0.5; 22.2]
Mean (SD)	ND	ND
Morbidity	ND	ND
Health-related quality of life	Outcome not recorded	
Side effects	ND	ND

BSC: best supportive care; max: maximum; min: minimum; N: number of analysed patients; ND: no data; RCT: randomized controlled trial; SD: standard deviation; vs.: versus

In the REACH study, the median treatment duration was markedly longer in the ramucirumab + BSC arm (8.0 weeks) than in the placebo + BSC arm (6.1 weeks); as was the case in the REACH-2 study (12.0 versus 8.0 weeks). The observation period was only provided for overall survival in the REACH-2 study, where it was 7.9 months in the ramucirumab + BSC arm compared with 6.6 months in the placebo + BSC arm. There was no information on the observation periods for the outcomes "morbidity" and "AEs". Morbidity outcomes were to be observed until treatment discontinuation, and AE outcomes until 30 or 45 days after treatment discontinuation. It can be concluded from this that the observation periods for the outcomes "morbidity" and "AEs" were markedly longer in the ramucirumab + BSC arms of both studies than in the placebo + BSC arms.

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: ramucirumab + 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			
REACH	Yes	Yes	Yes	Yes	Yes	Yes	Low
REACH-2	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 both studies. 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
  - symptoms (FHSI-8)
  - health status (EQ-5D VAS)
- Health-related quality of life
- Side effects
  - SAEs
  - severe AEs (CTCAE grade ≥ 3)
  - discontinuation due to AEs
  - if applicable, further specific AEs

The choice of patient-relevant outcomes deviated from that of the company, which used further outcomes in the dossier (Module 4 A) (see Section 2.7.4.3.2 of the full dossier assessment).

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

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

Study	Outcomes							
	Overall survival	**Health status (EQ-5D VAS)**	**Symptoms (FHSI-8)**	**Health-related quality of life**	**SAEs**	**Discontinuation due to AEs**	**Severe AEs (CTCAE grade ≥ 3)**	**Further specific AEs[a]**
REACH	Yes	No[b]	No[b]	No[c]	Yes	Yes	Yes	Yes
REACH-2	Yes	No[b]	No[b]	No[c]	Yes	Yes	Yes	Yes

a: The following events are considered (MedDRA coding): oedema peripheral (PT, AE), reproductive system and breast disorders (SOC, AE), renal and urinary disorders (SOC, AE), headache (PT, AE), injury, poisoning and procedural complications (SOC, AE), gastrointestinal disorders (SOC, CTCAE grade ≥ 3), hypertension (PT, CTCAE grade ≥ 3), hyperbilirubinaemia (PT, CTCAE grade ≥ 3), investigations (SOC, CTCAE grade ≥ 3), bleeding/haemorrhagic events (prespecified compilation of PTs), hepatic encephalopathy (PT, SAE).
b: No usable data available; for reasons, see Section 2.7.4.3.2 of the full dossier assessment.
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; FHSI-8: Functional Assessment of Cancer Therapy-Hepatobiliary Symptom Index-8; 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: ramucirumab + BSC vs. placebo + BSC

Study	Study level	Outcomes							
		Overall survival	Health status (EQ-5D VAS)	Symptoms (FHSI-8)	Health-related quality of life	SAEs	Discontinuation due to AEs	Severe AEs (CTCAE grade ≥ 3)	Further specific AEs[a]
REACH	L	L	–[b]	–[b]	–[c]	H[d]	L[e]	H[d]	H[d]
REACH-2	L	L	–[b]	–[b]	–[c]	H[d]	L[e]	H[d]	H[d]

a: The following events are considered (MedDRA coding): oedema peripheral (PT, AE), reproductive system and breast disorders (SOC, AE), renal and urinary disorders (SOC, AE), headache (PT, AE), injury, poisoning and procedural complications (SOC, AE), gastrointestinal disorders (SOC, CTCAE grade ≥ 3), hypertension (PT, CTCAE grade ≥ 3), hyperbilirubinaemia (PT, CTCAE grade ≥ 3), investigations (SOC, CTCAE grade ≥ 3), bleeding/haemorrhagic events (prespecified compilation of PTs), hepatic encephalopathy (PT, SAE).
b: No usable data available; for reasons, see Section 2.7.4.3.2 of the full dossier assessment.
c: Outcome not recorded.
d: Incomplete observations for potentially informative reasons.
e: Despite low risk of bias, a restricted certainty of results was assumed for the outcome "discontinuation due to AEs" (see Section 2.7.4.2 of the full dossier assessment).
AE: adverse event; BSC: best supportive care; CTCAE: Common Terminology Criteria for Adverse Events; EQ-5D: European Quality of Life-5 Dimensions; FHSI-8: Functional Assessment of Cancer Therapy-Hepatobiliary Symptom Index-8; 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.

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". The reason for this are incomplete observations for potentially informative reasons. The company considered the overall risk of bias for the results on AEs and rated it as low.

The certainty of conclusions for the outcome "discontinuation due to AEs" was restricted despite low risk of bias (see Section 2.7.4.2 of the full dossier assessment).

2.4.3 Results

Table 14 summarizes the results of the comparison of ramucirumab + BSC with placebo + BSC in patients with advanced or unresectable HCC who have a serum AFP of ≥ 400 ng/mL and

who have been previously treated with sorafenib. Where necessary, calculations conducted by the Institute are provided in addition to the data from the company's dossier. If available, Kaplan-Meier curves on the outcomes included are presented in Appendix A of the full dossier assessment.

Tables with the common AEs, SAEs, severe AEs and discontinuations due to AEs can be found in Appendix B of the full dossier assessment.

Table 14: Results (mortality, morbidity, health-related quality of life, side effects) – RCT, direct comparison: ramucirumab + BSC vs. placebo + BSC

Outcome category **Outcome** **Study**	**Ramucirumab + BSC** **N**	**Median time to event in months [95% CI]** **Patients with event n (%)**	**Placebo + BSC** **N**	**Median time to event in months [95% CI]** **Patients with event n (%)**	**Ramucirumab + BSC vs. placebo + BSC** **HR [95% CI]; p-value[a]**
Mortality					
Overall survival					
REACH	119	7.82 [5.82; 9.33] 99 (83.2)	131	4.21 [3.68; 4.76] 116 (88.5)	0.67 [0.51; 0.90]; 0.006[b]
REACH-2	197	8.51 [7.00; 10.58] 147 (74.6)	95	7.29 [5.42; 9.07] 74 (77.9)	0.71 [0.53; 0.95]; 0.020[b]
Total[c]	316	8.08 [6.87; 9.30] 246 (77.8)	226	5.03 [4.34; 6.08] 190 (84.1)	0.69 [0.57; 0.84]; < 0.001
Morbidity					
Symptoms (FHSI-8)	No usable data				
Health status (EQ-5D VAS)	No usable data				
Health-related quality of life	Outcome not recorded				
Side effects[d]					
AEs (supplementary information)					
REACH	119	0.23 [0.10; 0.39] 115[e] (96.6)	128	0.43 [0.30; 0.49] 124[e] (96.9)	–
REACH-2	197	0.33 [0.20; 0.39] 191 (97.0)	95	0.46 [0.26; 0.56] 82 (86.3)	–
SAEs					
REACH	119	14.49 [5.85; NC] 43[e] (36.1)	128	6.74 [3.09; NC] 47[e] (36.7)	0.94 [0.62; 1.42]; 0.754
REACH-2	197	16.39 [7.62; NC] 66[e] (33.5)	95	6.14 [3.94; 9.86] 27[e] (28.4)	0.81 [0.51; 1.29]; 0.375
Total[c]	316	14.49 [7.62; NC] 109 (34.5)	223	6.74 [3.94; 18.07] 74 (33.2)	0.88 [0.64; 1.20]; 0.413

(continued)

Table 14: Results (mortality, morbidity, health-related quality of life, side effects) – RCT, direct comparison: ramucirumab + BSC vs. placebo + BSC (continued)

Outcome category Outcome Study	Ramucirumab + BSC N	Ramucirumab + BSC Median time to event in months [95% CI] Patients with event n (%)	Placebo + BSC N	Placebo + BSC Median time to event in months [95% CI] Patients with event n (%)	Ramucirumab + BSC vs. placebo + BSC HR [95% CI]; p-value[a]
Severe AEs (CTCAE grade ≥ 3)					
REACH	119	3.25 [2.00; 7.13] 65 (54.6)	128	2.33 [1.87; 3.42] 74[e] (57.8)	0.89 [0.64; 1.25]; 0.484
REACH-2	197	3.65 [2.60; 5.16] 116 (58.9)	95	5.06 [2.79; 6.14] 42 (44.2)	1.04 [0.73; 1.49]; 0.837
Total[c]	316	3.61 [2.63; 4.67] 181 (57.3)	223	3.09 [2.33; 3.91] 116 (52.0)	0.96 [0.75; 1.22]; 0.713
Discontinuation due to AEs					
REACH	119	24.18 [14.62; 24.18] 17[e] (14.3)	128	NA [7.56; NC] 13 (10.2)	1.09 [0.52; 2.27]; 0.827
REACH-2	197	19.55 [13.37; NC] 35 (17.8)	95	NA 10 (10.5)	1.07 [0.51; 2.22]; 0.865
Total[c]	316	19.55 [14.62; NC] 52 (16.5)	223	NA 23 (10.3)	1.08 [0.64; 1.81]; 0.783
Oedema peripheral (PT, AE)					
REACH	119	7.85 [5.52; NC] 42 (35.3)	128	NA [6.11; NC] 25 (19.5)	1.83 [1.11; 3.01]; 0.016
REACH-2	197	16.59 [8.80; NC] 50 (25.4)	95	NA 13 (13.7)	1.58 [0.85; 2.93]; 0.142
Total[c]	316	16.59 [8.77; NC] 92 (29.1)	223	NA 38 (17.0)	1.73 [1.17; 2.55]; 0.005
Reproductive system and breast disorders (SOC, AE)					
REACH	119	ND 4 (3.3)[f]	128	ND 0 (0)[f]	NC[g]; ND
REACH-2	197	NA [13.57; NC] 11 (5.6)	95	NA 0 (0)	NC[g]; 0.111
Total[c]	316	NA 15 (4.7)	223	NA 0 (0)	NC[g]; 0.022
Renal and urinary disorders (SOC, AE)					
REACH	119	NA [7.95; NC] 25 (21.0)	128	NA [6.74; NC] 17 (13.3)	1.35 [0.72, 2.51]; 0.351
REACH-2	197	NA [9.26; NC] 49 (24.9)	95	NA [6.44; NC] 8 (8.4)	2.27 [1.06; 4.87]; 0.030
Total[c]	316	NA [9.26; NC] 74 (23.4)	223	NA [6.74; NC] 25 (11.2)	1.69 [1.05; 2.70]; 0.028

(continued)

Table 14: Results (mortality, morbidity, health-related quality of life, side effects) – RCT, direct comparison: ramucirumab + BSC vs. placebo + BSC (continued)

Outcome category Outcome Study	Ramucirumab + BSC N	Ramucirumab + BSC Median time to event in months [95% CI] Patients with event n (%)	Placebo + BSC N	Placebo + BSC Median time to event in months [95% CI] Patients with event n (%)	Ramucirumab + BSC vs. placebo + BSC HR [95% CI]; p-value[a]
Headache (PT, AE)					
REACH	119	NA 25 (21.0)	128	NA [7.52; NC] 9 (7.0)	3.16 [1.48; 6.78]; 0.002
REACH-2	197	ND 28 (14.2)	95	ND 5 (5.3)	2.69 [1.03; 6.97]; ND
Total[c]	316	NA 53 (16.8)	223	NA 14 (6.3)	2.97 [1.63; 5.41]; < 0.001
Injury, poisoning and procedural complications (SOC, AE)					
REACH	119	NA 11 (9.2)	128	NA 5 (3.9)	2.12 [0.73, 6.14]; 0.156
REACH-2	197	22.47 [13.34; 22.47] 26 (13.2)	95	NA 4 (4.2)	2.40 [0.83, 7.00]; 0.098
Total[c]	316	22.47 [NC] 37 (11.7)	223	NA 9 (4.0)	2.26 [1.07; 4.79]; 0.029
Gastrointestinal disorders (SOC, CTCAE grade ≥ 3)					
REACH	119	13.54 [10.15; NC] 17 (14.3)	128	18.07 [4.24; NC] 27 (21.1)	0.56 [0.30; 1.04]; 0.061
REACH-2	197	NA 20 (10.2)	95	9.86 [NC] 9 (9.5)	0.74 [0.33; 1.65]; 0.457
Total[c]	316	NA [15.41; NC] 37 (11.7)	223	18.07 [9.86; NC] 36 (16.1)	0.62 [0.38; 1.004]; 0.0499
Hypertension (PT, CTCAE grade ≥ 3)					
REACH	119	NA 14 (11.8)	128	NA 3 (2.3)	4.60 [1.32; 16.09]; 0.009
REACH-2	197	NA 24 (12.2)	95	NA 5 (5.3)	1.98 [0.75; 5.23]; 0.161
Total[c]	316	NA 38 (12.0)	223	NA 8 (3.6)	2.87 [1.32; 6.24]; 0.006
Hyperbilirubinaemia (PT, CTCAE grade ≥ 3)					
REACH	119	NA 3 (2.5)	128	15.87 [15.87; NC] 12 (9.4)	0.22 [0.06, 0.78]; 0.010
REACH-2	197	NA 0 (0)	95	NA 0 (0)	NC[g]
Total[c]	316	NA 3 (0.9)	223	15.87 [15.87; NC] 12 (5.4)	0.22 [0.06; 0.78]; 0.010

(continued)

Table 14: Results (mortality, morbidity, health-related quality of life, side effects) – RCT, direct comparison: ramucirumab + BSC vs. placebo + BSC (continued)

Outcome category Outcome Study	Ramucirumab + BSC N	Ramucirumab + BSC Median time to event in months [95% CI] Patients with event n (%)	Placebo + BSC N	Placebo + BSC Median time to event in months [95% CI] Patients with event n (%)	Ramucirumab + BSC vs. placebo + BSC HR [95% CI]; p-value[a]
Investigations (SOC, CTCAE grade ≥ 3)[h]					
REACH	119	NA 16 (13.4)	128	NA [6.44; NC] 29 (22.7)	0.52 [0.28; 0.96]; 0.034
REACH-2	197	17.51 [11.99; NC] 28 (14.2)	95	NA 11 (11.6)	0.68 [0.32, 1.42]; 0.295
Total[c]	316	NA [13.83; NC] 44 (13.9)	223	NA [8.25; NC] 40 (17.9)	0.58 [0.36; 0.92]; 0.020
Bleeding/haemorrhagic events (prespecified compilation of PTs)					
REACH	119	13.37 [5.55; NC] 31[e] (26.1)	128	16.62 [4.24; NC] 28[e] (21.9)	1.10 [0.66; 1.85]; 0.717
REACH-2	197	19.55 [11.99; NC] 48 (24.4)	95	9.86 [NC] 12 (12.6)	1.46 [0.77; 2.78]; 0.242
Total[c]	316	13.83 [11.99; NC] 79 (25.0)	223	16.62 [9.86; NC] 40 (17.9)	1.24 [0.83; 1.84]; 0.296
Hepatic encephalopathy (PT, SAE)					
REACH	119	NA 3 (2.5)	128	NA 0 (0)	NC[g]; 0.071
REACH-2	197	NA 3 (1.5)	95	NA 0 (0)	NC[g]; 0.431
Total[c]	316	NA 6 (1.9)	223	NA 0 (0)	NC[g]; 0.053

a: Unless stated otherwise, HR and CI: unstratified Cox proportional hazards model; p-value: unstratified log-rank test; for pooled analysis stratified by study.
b: Analysis stratified by the randomization strata of the respective study.
c: IPD meta-analysis.
d: Events caused by progression of the underlying disease are also recorded as AEs (see Section 2.3.2).
e: Discrepancy between information in Module 4 and Module 5 of the dossier. The data presented are from additional analyses on Module 4 and are identical with this. The discrepancy is marginal and therefore not relevant.
f: Institute's calculation.
g: Since no event occurred in at least one treatment arm, the HR cannot be estimated.
h: Includes the PTs "aspartate aminotransferase increased" and "blood bilirubin increased".

AE: adverse event; BSC: best supportive care; CI: confidence interval; CTCAE: Common Terminology Criteria for Adverse Events; EQ-5: European Quality of Life-5 Dimensions; FHSI-8: Functional Assessment of Cancer Therapy-Hepatobiliary Symptom Index-8; HR: hazard ratio; IPD: individual patient data; N: number of analysed patients; n: number of patients with event; NA: not achieved; NC: not calculable; ND: no data; PT: Preferred Term; RCT: randomized controlled trial; SAE: serious adverse event; SOC: System Organ Class; VAS: visual analogue scale; vs.: versus

Based on the available data, at most proof, e.g. of an added benefit, can be determined for the outcome "overall survival". Due to the high risk of bias in the outcomes "SAEs", "severe AEs" (CTCAE grade ≥ 3), "discontinuation due to AEs" and "specific AEs", at most indications, e.g. of an added benefit, can be determined.

Mortality

Overall survival

The meta-analysis showed a statistically significant difference between the treatment groups in favour of ramucirumab + BSC in comparison with placebo + BSC for the outcome "overall survival". This resulted in proof of an added benefit of ramucirumab + BSC versus BSC for the outcome "overall survival".

This concurs with the company's assessment.

Morbidity

Symptoms (recorded using FHSI-8)

There were no usable data for the outcome "symptoms" recorded with the FHSI-8. This resulted in no hint of an added benefit of ramucirumab + BSC in comparison with BSC; an added benefit is therefore not proven.

This deviates from the company's assessment. The company derived proof of an added benefit for the outcome "symptoms" (FHSI-8).

Health status (recorded using the EQ-5D VAS)

There were no usable data for the outcome "health status" recorded with the EQ-5D VAS. This resulted in no hint of an added benefit of ramucirumab + BSC in comparison with BSC; an added benefit is therefore not proven.

This deviates from the company's assessment. The company derived proof of an added benefit for the outcome "health status" (EQ-5D VAS).

Health-related quality of life

No outcomes in the category of health-related quality of life were recorded in the studies REACH and REACH-2. This resulted in no hint of an added benefit of ramucirumab + BSC in comparison with BSC in this outcome category; an added benefit is therefore not proven.

This concurs with the company's assessment.

Side effects

Besides treatment-related AEs, the outcomes on the overall rates of side effects – i.e. AEs, serious AEs, severe AEs, discontinuation due to AEs – also contain disease-related AEs. On the one hand, these are AEs caused by the tumour disease itself, for example the progression of a malignant neoplasm. On the other, AEs related to liver diseases were also included. Common

accompanying diseases of a liver disease include ascites, bleeding oesophageal varices, or laboratory parameters such as increased bilirubin levels in the blood [4]. The proportions of treatment-related and disease-related AEs contained in the overall AE rates in the studies REACH and REACH-2 are unclear. This uncertainty was taken into account in the interpretation of the results.

Serious adverse events, severe adverse events (CTCAE grade ≥ 3) and discontinuation due to adverse events

The meta-analysis showed no statistically significant difference between the treatment groups for the outcomes "SAEs", "severe AEs" (CTCAE grade ≥ 3) and "discontinuation due to AEs". As described above, events attributable to the underlying disease were also considered in these outcomes. Mostly advantages of ramucirumab were shown in these events (see section 2.5.2 of the full dossier assessment). However, it is assumed that there would be no greater harm from ramucirumab even without the progression-related or disease-related events contained in the overall rates. Overall, this resulted in no hint of greater or lesser harm from ramucirumab + BSC in comparison with BSC; an added benefit is therefore not proven.

This concurs with the company's assessment.

Specific adverse events

Gastrointestinal disorders, hyperbilirubinaemia, investigations

The meta-analysis showed a statistically significant difference in favour of ramucirumab + BSC versus placebo + BSC for each of the following outcomes: gastrointestinal disorders, hyperbilirubinaemia and investigations. This resulted in an indication of lesser harm from ramucirumab + BSC in comparison with BSC in each case.

The company did not use these outcomes for the derivation of the added benefit.

Oedema peripheral, reproductive system and breast disorders, headache and hypertension

A statistically significant difference to the disadvantage of ramucirumab + BSC versus placebo + BSC was shown for each of the following outcomes: oedema peripheral, reproductive system and breast disorders, headache, and hypertension. This resulted in an indication of greater harm from ramucirumab + BSC in comparison with BSC in each case.

The assessment largely deviates from that of the company. The company only used hypertension and oedema peripheral for the derivation of an added benefit and derived proof of greater harm from ramucirumab + BSC in comparison with BSC in each case.

Renal and urinary disorders and injury, poisoning and procedural complications

A statistically significant difference to the disadvantage of ramucirumab + BSC was shown for each of the outcomes "renal and urinary disorders" and "injury, poisoning and procedural complications". The effect in each of these non-serious/non-severe AEs was no more than

marginal, however. In each case, this resulted in no hint of greater or lesser harm from ramucirumab + BSC in comparison with BSC; an added benefit is therefore not proven.

The company did not use these outcomes for the derivation of the added benefit.

Bleeding/haemorrhagic events and hepatic encephalopathy

No statistically significant difference between the treatment groups was shown for each of the outcomes "bleeding/haemorrhagic events" and "hepatic encephalopathy". In each case, this resulted in no hint of greater or lesser harm from ramucirumab + BSC in comparison with BSC; an added benefit is therefore not proven.

The company did not use these outcomes for the derivation of the added benefit.

2.4.4 Subgroups and other effect modifiers

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

- sex (male; female)
- age (< 65 years; ≥ 65 years)
- geographical region (Europe; rest of the world)
- aetiology of the liver disease (hepatitis B; hepatitis C; other)
- disease severity according to BCLC stage (stage B versus stage C)

Except for geographical region, all subgroups mentioned above were prespecified.

Subgroup analyses on the characteristics mentioned above were available for the following outcomes: overall survival, SAEs, severe AEs, and discontinuation due to AEs.

Interaction tests were performed if at least 10 patients per subgroup were included in the analysis. For binary data, there must be 10 events in at least one subgroup.

Only 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

Probability and extent of the added benefit at outcome level are presented below. The various outcome categories and the effect sizes were taken into account. The methods used for this purpose are explained in the *General Methods* of IQWiG [1].

The approach for deriving an overall conclusion on the 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 15).

Determination of the outcome category for the outcomes on side effects

The dossier does not provide information for every outcome considered in the present benefit assessment whether it was serious/severe or non-serious/non-severe. The classification of these outcomes is justified below.

The majority of the events that occurred in the following specific AEs were non-serious/non-severe: oedema peripheral, reproductive system and breast disorders, renal and urinary disorders, headache, as well as injury, poisoning and procedural complications. These outcomes were therefore allocated to the outcome category of non-serious/non-severe side effects.

Table 15: Extent of added benefit at outcome level: ramucirumab + BSC vs. placebo + BSC

Outcome category **Outcome**	**Ramucirumab + BSC vs. placebo + BSC** **Median time to event or proportion of events (%)** **Effect estimation [95% CI]** **p-value** **Probability[a]**	**Derivation of extent[b]**
Mortality		
Overall survival	7.82−8.51 vs. 4.21−7.29 months[c] HR: 0.69 [0.57; 0.84] p < 0.001 probability: “proof”	Outcome category: “mortality” CI_u < 0.85 added benefit, extent: “major”
Morbidity		
Symptoms (FHSI-8)	No usable data	Lesser benefit/added benefit not proven
Health status (EQ-5D VAS)	No usable data	Lesser benefit/added benefit not proven
Health-related quality of life		
Outcomes from this category were not recorded		
Side effects		
SAEs	14.49−16.39 vs. 6.14−6.74 months[c] HR: 0.88 [0.64; 1.20] p = 0.413	Greater/lesser harm not proven
Severe AEs (CTCAE grade ≥ 3)	3.25−3.65 vs. 2.33−5.06 months[c] HR: 0.96 [0.75; 1.22] p = 0.713	Greater/lesser harm not proven

(continued)

Table 15: Extent of added benefit at outcome level: ramucirumab + BSC vs. placebo + BSC (continued)

Outcome category **Outcome**	**Ramucirumab + BSC vs. placebo + BSC** **Median time to event or proportion of events (%)** **Effect estimation [95% CI]** **p-value** **Probability**[a]	**Derivation of extent**[b]
Discontinuation due to AEs	19.55−24.18 vs. NA months[c] HR: 1.08 [0.64; 1.81] p = 0.783	Greater/lesser harm not proven
Oedema peripheral (PT, AE)	7.85–16.59 vs. NA months[c] HR: 1.73 [1.17; 2.55] HR: 0.58 [0.39; 0.85][d] p = 0.005 probability: "indication"	Outcome category: non-serious/non-severe side effects $0.80 \leq CI_u < 0.90$ Greater harm, extent: "minor"
Reproductive system and breast disorders (SOC, AE)	Proportions of events: 3.3–5.6% vs. 0%[c] HR: NC p = 0.022 probability: "indication"	Outcome category: non-serious/non-severe side effects greater harm, extent: "non-quantifiable"
Renal and urinary disorders (SOC, AE)	NA vs. NA months[c] HR: 1.69 [1.05; 2.70] HR: 0.59 [0.37; 0.95][d] p = 0.028	Outcome category: non-serious/non-severe side effects $0.90 \leq CI_u < 1.00$ Greater/lesser harm not proven[e]
Headache (PT, AE)	ND–NA vs. ND–NA months[c] HR: 2.97 [1.63; 5.41] HR: 0.34 [0.18; 0.61][d] p < 0.001 probability: "indication"	Outcome category: non-serious/non-severe side effects $CI_u < 0.80$ Greater harm, extent: "considerable"
Injury, poisoning and procedural complications (SOC, AE)	NA–22.47 vs. NA months[c] HR: 2.26 [1.07; 4.79] HR: 0.44 [0.21; 0.94][d] p = 0.029	Outcome category: non-serious/non-severe side effects $0.90 \leq CI_u < 1.00$ Greater/lesser harm not proven[e]
Gastrointestinal disorders (SOC, CTCAE grade ≥ 3)	NA–13.54 vs. 9.86–18.07 months[c] HR: 0.62 [0.38; 1.004] p = 0.0499 probability: "indication"	Outcome category: serious/severe side effects $CI_u \geq 0.90$ lesser harm, extent: "minor"
Hypertension (PT, CTCAE grade ≥ 3)	NA vs. NA months[c] HR: 2.87 [1.32; 6.24] HR: 0.35 [0.16; 0.76][d] p = 0.006 probability: "indication"	Outcome category: serious/severe side effects $0.75 \leq CI_u < 0.90$ greater harm, extent: "considerable"

(continued)

Table 15: Extent of added benefit at outcome level: ramucirumab + BSC vs. placebo + BSC (continued)

Outcome category **Outcome**	**Ramucirumab + BSC vs. placebo + BSC** **Median time to event or proportion of events (%)** **Effect estimation [95% CI]** **p-value** **Probability**[a]	**Derivation of extent**[b]
Hyperbilirubinaemia (PT, CTCAE grade ≥ 3)	NA vs. NA–15.87 months[c] HR: 0.22 [0.06; 0.78] p = 0.010 probability: "indication"	Outcome category: serious/severe side effects $0.75 \leq CI_u < 0.90$ lesser harm, extent: "considerable"
Investigations (SOC, CTCAE grade ≥ 3)	NA–17.51 vs. NA months[c] HR: 0.58 [0.36; 0.92] p = 0.020 probability: "indication"	Outcome category: serious/severe side effects $0.90 \leq CI_u < 1.00$ lesser harm, extent: "minor"
Bleeding/haemorrhagic events (prespecified compilation of PTs)	13.37–19.55 vs. 9.86–16.62 months[c] HR: 1.24 [0.83; 1.84] p = 0.296	Greater/lesser harm not proven
Hepatic encephalopathy (PT, SAE)	Proportions of events: 1.5–2.5% vs. 0%[c] HR: NC p = 0.053	Greater/lesser harm not proven

a: Probability provided if statistically significant differences were present.
b: Estimations of effect size are made depending on the outcome category with different limits based on the upper limit of the confidence interval (CI_u).
c: Minimum and maximum quantiles of the time to event in the studies included.
d: Institute's calculation, reversed direction of effect to enable use of limits to derive the extent of the added benefit.
e: The extent of the effect in this non-serious/non-severe outcome was no more than marginal.

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; FHSI-8: Functional Assessment of Cancer Therapy-Hepatobiliary Symptom Index-8; HR: hazard ratio; NA: not achieved; ND: no data; PT: Preferred Term; RCT: randomized controlled trial; SAE: serious adverse event; SOC: System Organ Class; VAS: visual analogue scale; vs.: versus

2.5.2 Overall conclusion on added benefit

Table 16 summarizes the results considered in the overall conclusion on the extent of added benefit.

Table 16: Positive and negative effects from the assessment of ramucirumab + BSC compared with placebo + BSC

Positive effects	**Negative effects**
Mortality ▪ overall survival: proof of an added benefit – extent: "major"	
Serious/severe side effects ▪ gastrointestinal disorders (SOC, severe AEs [CTCAE grade ≥ 3]): indication of lesser harm – extent: "minor" ▪ hyperbilirubinaemia (PT, severe AEs [CTCAE grade ≥ 3]): indication of lesser harm – extent: "considerable" ▪ investigations (SOC, severe AEs [CTCAE grade ≥ 3]): indication of lesser harm – extent: "minor"	Serious/severe side effects ▪ hypertension (PT, severe AEs [CTCAE grade ≥ 3]): indication of greater harm – extent: "considerable"
	Non-serious/non-severe side effects ▪ reproductive system and breast disorders (SOC, AE): indication of greater harm – extent: "non-quantifiable" ▪ oedema peripheral (PT, AE): indication of greater harm – extent: "minor" ▪ headache (PT, AE): indication of greater harm – extent: "considerable"
Morbidity: no usable data	
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; PT: Preferred Term; SOC: System Organ Class	

The overall consideration showed both positive and negative effects of ramucirumab + BSC in comparison with BSC. The positive effect with the extent "major" and the probability "proof" for the outcome "overall survival" is decisive for the overall conclusion on the added benefit. This is accompanied by several negative effects in the outcome categories of serious/severe side effects and non-serious/non-severe side effects with an extent up to "considerable" and the probability "indication" in each case. There are further positive effects in the outcome category of serious/severe side effects with an extent up to "considerable" and also the probability "indication" in each case. It is questionable, however, whether these positive effects should be allocated to the outcome category of side effects or whether they rather reflect symptoms of the disease. The negative effects did not outweigh the advantage in overall survival, but resulted in a downgrading of the extent of the added benefit.

In summary, there is proof of considerable added benefit of ramucirumab + BSC versus the ACT BSC for patients with advanced or unresectable HCC who have a serum AFP of ≥ 400 ng/mL and who have been previously treated with sorafenib.

The result of the assessment of the added benefit of ramucirumab in comparison with the ACT is summarized in Table 17.

Table 17: Ramucirumab – probability and extent of added benefit

Therapeutic indication	**ACT[a]**	**Probability and extent of added benefit**
Adult patients with advanced or unresectable hepatocellular carcinoma (HCC) who have a serum alpha fetoprotein of ≥ 400 ng/mL and who have been previously treated with sorafenib	**Best supportive care[b]** or cabozantinib	Proof of considerable added benefit[c]

a: Presentation of the respective ACT specified by the G-BA. In cases where the company, because of the G-BA's specification of the ACT, could choose a comparator therapy from several options, the respective choice of the company is printed in **bold**.
b: Best supportive care 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.
c: The studies REACH and REACH-2 only included patients with an ECOG PS of 0 or 1 and with Child Pugh class A. It therefore remains unclear whether the observed effects can be transferred to patients with ECOG PS ≥ 2 or Child-Pugh class B or C.

ACT: appropriate comparator therapy; 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 proof of major 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

REACH

Chau I, Park JO, Ryoo BY, Yen CJ, Poon R, Pastorelli D et al. Alpha-fetoprotein kinetics in patients with hepatocellular carcinoma receiving ramucirumab or placebo: an analysis of the phase 3 REACH study. Br J Cancer 2018; 119: 19-26.

Chau I, Peck-Radosavljevic M, Borg C, Malfertheiner P, Seitz JF, Park JO et al. Ramucirumab as second-line treatment in patients with advanced hepatocellular carcinoma following first-line therapy with sorafenib: patient-focused outcome results from the randomised phase III REACH study. Eur J Cancer 2017; 81: 17-25.

Chau I, Peck-Radosavljevic M, Borg C, Malfertheiner P, Seitz JF, Park JO et al. Corrigendum to 'Ramucirumab as second-line treatment in patients with advanced hepatocellular carcinoma following first-line therapy with sorafenib: patient-focused outcome results from the randomised phase III REACH study' [Eur J Canc 81 (2017) 17-25]. Eur J Cancer 2018; 100: 135-136.

Eli Lilly. Eine multizentrische, randomisierte, doppelblinde Phase-3-Studie zum Vergleich des Arzneimittels Ramucirumab (IMC-1121B) und der besten unterstützenden Behandlung(BSC) gegen Placebo und der besten unterstützenden Behandlung als Zweitlinientherapie bei Patienten mit hepatozellulärem Karzinom nach Erstlinientherapie mit Sorafenib [online]. In: Deutsches Register Klinische Studien. [Accessed: 31.10.2019]. URL: http://www.drks.de/DRKS00003671.

Eli Lilly. A study of ramucirumab (IMC-1121B) drug product (DP) and best supportive care (BSC) versus placebo and BSC as 2nd-Line treatment in participants with hepatocellular carcinoma after 1st-line therapy with sorafenib: study results [online]. In: ClinicalTrials.gov. 28.12.2015 [Accessed: 09.09.2019]. URL: https://clinicaltrials.gov/ct2/show/results/NCT01140347.

Eli Lilly. A study of ramucirumab (IMC-1121B) drug product (DP) and best supportive care (BSC) versus placebo and BSC as 2nd-line treatment in participants with hepatocellular carcinoma after 1st-line therapy with sorafenib: study details [online]. In: ClinicalTrials.gov. 28.12.2015 [Accessed: 09.09.2019]. URL: https://ClinicalTrials.gov/show/NCT01140347.

Eli Lilly Japan. A multicenter, randomized, double-blind, phase 3 study of ramucirumab (IMC-1121B) drug product and best supportive care (BSC) versus placebo and BSC as second-line treatment in patients with hepatocellular carcinoma following first-line therapy with sorafenib (REACH) [online]. In: Japic Clinical Trials Information. 17.12.2018 [Accessed: 09.09.2019]. URL: https://www.clinicaltrials.jp/user/showCteDetailE.jsp?japicId=JapicCTI-101318.

ImClone. A multicenter, randomized, double-blind; phase 3 study of ramucirumab (IMC-1121B) drug product and best supportive care (BSC) versus placebo and bsc as second-line treatment in patients with hepatocellular carcinoma following first-line therapy with sorafenib: study 14T-IE-JVBF (REACH); clinical study report [unpublished]. 2014.

ImClone. A multicenter, randomized, double-blind, phase 3 study of ramucirumab (IMC-1121B) drug product and best supportive care (BSC) versus placebo and BSC as second-line treatment in patients with hepatocellular carcinoma following first-line therapy with sorafenib: study 14T-IE-JVBF (REACH); Zusatzanalysen [unpublished]. 2019.

ImClone. A multicenter, randomized, double-blind, phase 3 study of ramucirumab (IMC-1121B) drug product and best supportive care (BSC) versus placebo and BSC as second-line treatment in patients with hepatocellular carcinoma following first-line therapy with sorafenib: clinical trial results [online]. In: EU Clinical Trials Register. 02.04.2016 [Accessed: 09.09.2019]. URL: https://www.clinicaltrialsregister.eu/ctr-search/trial/2010-019318-26/results.

ImClone. A multicenter, randomized, double-blind, phase 3 study of ramucirumab (IMC-1121B) drug product and best supportive care (BSC) versus placebo and BSC as second-line treatment in patients with hepatocellular carcinoma following first-line therapy with sorafenib [online]. In: EU Clinical Trials Register. [Accessed: 09.09.2019]. URL: https://www.clinicaltrialsregister.eu/ctr-search/search?query=eudract_number:2010-019318-26.

Kudo M. Systemic therapy for hepatocellular carcinoma: 2017 update. Oncology 2017; 93(Suppl 1): 135-146.

Park JO, Ryoo BY, Yen CJ, Kudo M, Yang L, Abada PB et al. Second-line ramucirumab therapy for advanced hepatocellular carcinoma (REACH): an East Asian and non-East Asian subgroup analysis. Oncotarget 2016; 7(46): 75482-75491.

Zhu AX, Baron AD, Malfertheiner P, Kudo M, Kawazoe S, Pezet D et al. Ramucirumab as second-line treatment in patients with advanced hepatocellular carcinoma: analysis of reach trial results by child-pugh score. JAMA Oncol 2017; 3(2): 235-243.

Zhu AX, Park JO, Ryoo BY, Yen CJ, Poon R, Pastorelli D et al. Ramucirumab versus placebo as second-line treatment in patients with advanced hepatocellular carcinoma following first-line therapy with sorafenib (REACH): a randomised, double-blind, multicentre, phase 3 trial. Lancet Oncol 2015; 16(7): 859-870.

REACH-2

Eli Lilly. A study of ramucirumab (LY3009806) versus placebo in participants with hepatocellular carcinoma and elevated baseline alpha-fetoprotein: study details [online]. In: ClinicalTrials.gov. 17.05.2019 [Accessed: 31.10.2019]. URL: https://ClinicalTrials.gov/show/NCT02435433.

Eli Lilly. Randomized, double-blind, placebo-controlled, phase 3 study of ramucirumab and best supportive care (BSC) versus placebo and BSC as second-line treatment in patients with hepatocellular carcinoma and elevated baseline alpha-fetoprotein (AFP) following first-line therapy with sorafenib [online]. In: EU Clinical Trials Register. [Accessed: 09.09.2019]. URL: https://www.clinicaltrialsregister.eu/ctr-search/search?query=eudract_number:2014-005068-13.

Eli Lilly. A study of ramucirumab (LY3009806) versus placebo in participants with hepatocellular carcinoma and elevated baseline alpha-fetoprotein: study results [online]. In: ClinicalTrials.gov. 17.05.2019 [Accessed: 09.09.2019]. URL: https://clinicaltrials.gov/ct2/show/results/NCT02435433.

Eli Lilly. Randomized, double-blind, placebo-controlled, phase 3 study of ramucirumab and best supportive care (BSC) versus placebo and BSC as second-line treatment in patients with hepatocellular carcinoma and elevated baseline alpha-fetoprotein (AFP) following first-line therapy with sorafenib; study JVDE (REACH-2); clinical study report [unpublished]. 2018.

Eli Lilly. Randomized, double-blind, placebo-controlled, phase 3 study of ramucirumab and best supportive care (BSC) versus placebo and BSC as second-line treatment in patients with hepatocellular carcinoma and elevated baseline alpha-fetoprotein (AFP) following first-line therapy with sorafenib; study JVDE (REACH-2); Zusatzanalysen [unpublished]. 2019.

Eli Lilly Japan. Randomized, double-blind, placebo-controlled, phase 3 study of ramucirumab and best supportive care (BSC) versus placebo and BSC as second-line treatment in patients with hepatocellular carcinoma and elevated baseline alpha-fetoprotein (AFP) following first-line therapy with sorafenib [online]. In: Japic Clinical Trials Information. 17.12.2018 [Accessed: 09.09.2019]. URL: https://www.clinicaltrials.jp/user/showCteDetailE.jsp?japicId=JapicCTI-152971.

Zhu AX, Kang Y, Yen CJ, Finn RS, Galle PR, Llovet JM et al. Ramucirumab after sorafenib in patients with advanced hepatocellular carcinoma and increased α-fetoprotein concentrations (REACH-2): a randomised, double-blind, placebo-controlled, phase 3 trial. Lancet Oncol 2019; 20(2): 282-296.

References for English extract

Please see full dossier assessment for full reference list.

The reference list contains citations provided by the company in which bibliographical information may be missing.

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. Lilly. Cyramza 10 mg/ml Konzentrat zur Herstellung einer Infusionslösung: Fachinformation [online]. 09.2019 [Accessed: 31.10.2019]. URL: https://www.fachinfo.de/.

4. European Association for the Study of the Liver. EASL Clinical Practice Guidelines: management of hepatocellular carcinoma. J Hepatol 2018; 69(1): 182-236.

The full report (German version) is published under https://www.iqwig.de/en/projects-results/projects/drug-assessment/a19-73-ramucirumab-hepatocellular-carcinoma-benefit-assessment-according-to-35a-social-code-book-v.12575.html.