27 June 2019
EMA/635673/2019
Committee for Medicinal Products for Human Use (CHMP)

CHMP extension of indication variation assessment report

Cyramza

International non-proprietary name: ramucirumab

Procedure No. EMEA/H/C/002829//II/0027

Note

Assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

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List of abbreviations

ADA	antidrug antibody
AE	adverse event
AFP	alpha-fetoprotein
ALT	alanine aminotransferase
AST	aspartate aminotransferase
ATE	arterial thromboembolic event
BCLC	Barcelona Clinic Liver Cancer
BQL	below the quantifiable lower limit of the assay
BSC	best supportive care
CHF	congestive heart failure
CELESTIAL	cabozantinib vs placebo in subjects with hepatocellular carcinoma who have received prior sorafenib
CI	confidence interval
CIOMS	Council for International Organizations of Medical Sciences
Cmax	maximum serum concentration
Cmin	minimum serum concentration
C-P	Child-Pugh
CR	complete response
CRF	case report form
CRO	contract research organization
CRP	clinical research physician
CSR	clinical study report
CT	computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
CV	coefficient of variation
CYP	Cytochrome P450
DDI	drug-drug interaction
DNA	eoxyribonucleic acid
DCR	disease control rate
EC	Exclusion Criterion
ECG	electrocardiogram
ECHO	echocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic case report form
ELISA	enzyme-linked immunosorbent assay
ERB	ethics review board
EQ-5D	EuroQol 5 Dimensions
EQ-5D-5L	EuroQol 5 Dimensions 5-Level
EU	European Union
FACT	Functional Assessment of Cancer Therapy
FACT-Hep	Functional Assessment of Cancer Therapy Hepatobiliary
FDA	Food and Drug Administration
FHSI-8	Functional Assessment of Cancer Therapy Hepatobiliary Symptom Index-8
G-CSF	granulocyte colony-stimulating factor
GCP	good clinical practice
GI	gastrointestinal
GM-CSF	granulocyte macrophage colony-stimulating factor
HBV	hepatitis B virus
HCC	hepatocellular carcinoma
HCV	hepatitis C virus
HR	hazard ratio
IC	Inclusion Criterion
ICF	informed consent form
ICH	International Conference on Harmonisation
IDMC	Independent Data Monitoring Committee
INR	international normalized ratio
IRR	infusion-related reaction
ITT	intent-to-treat
IV	intravenous(ly)
IWRS	interactive web response system
Max	maximum

MedDRA	Medical Dictionary for Regulatory Activities
Min	minimum
MRI	magnetic resonance imaging
mTKI	multi-targeted tyrosine kinase inhibitor
MUGA	multiple-gated acquisition
NCI	National Cancer Institute
NP	not provided
ORR	objective response rate
OS	overall survival
PD	progressive disease
PDT	post-discontinuation therapy
PFS	progression-free survival
PFO	patient-focused outcome
PI	principal investigator
PI	product information
PK	pharmacokinetic(s)
PopPK	population pharmacokinetic(s)
PP	per-protocol
PR	partial response
PRO	patient-reported outcome
PS	performance status
PSUR	periodic safety update report
PT	preferred term
QoL	quality of life
Q2W	every two weeks
REACH	ramucirumab drug product and best supportive care (BSC) versus placebo and BSC as 2nd-line treatment in participants with hepatocellular carcinoma after 1st-line therapy with sorafenib
REACH-2	ramucirumab versus placebo in participants with hepatocellular carcinoma and elevated baseline alpha-fetoprotein
RECIST	Response Evaluation Criteria in Solid Tumours
REGARD	ramucirumab monotherapy for previously treated advanced gastric or gastro-oesophageal junction adenocarcinoma
RESORCE	regorafenib for patients with hepatocellular carcinoma who progressed on sorafenib treatment
RNA	ribonucleic acid
RPLS	reversible posterior leukoencephalopathy syndrome
SAE	serious adverse event
SAP	statistical analysis plan
SD	standard deviation
SD	stable disease
SHARP	Sorafenib Hepatocarcinoma Assessment Randomized Protocol
SMQ	standardized MedDRA query
SOC	System Organ Class
sVEGFR	soluble vascular endothelial growth factor receptor
TE	treatment-emergent
TEAE	treatment-emergent adverse event
Tmax	time to maximum serum concentration
TTD	time to deterioration
TTP	time to radiographic progression
ULN	upper limit of institutional normal value
US	United States
VAS	visual analog scale
VEGF	vascular endothelial growth factor
VEGFR	vascular endothelial growth factor receptor
VTE	venous thromboembolic event

1. Background information on the procedure

1.1. Type II variation

Pursuant to Article 16 of Commission Regulation (EC) No 1234/2008, Eli Lilly Nederland B.V. submitted to the European Medicines Agency on 23 July 2018 an application for a variation.

The following variation was requested:

Variation requested		**Type**	**Annexes affected**
C.I.6.a	C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	Type II	I and IIIB

Extension of indication to include Cyramza as monotherapy for the treatment of adult patients with hepatocellular carcinoma who have an alpha fetoprotein (AFP) of ≥ 400 ng/mL, after prior sorafenib therapy; as a consequence, sections 4.1, 4.2, 4.4, 4.8, 5.11 and 5.2 of the SmPC are updated in accordance. The Package Leaflet is updated in accordance. RMP version 8.1 has been submitted.

The requested variation proposed amendments to the Summary of Product Characteristics and Package Leaflet and to the Risk Management Plan (RMP).

Information on paediatric requirements

Pursuant to Article 8 of Regulation (EC) No 1901/2006, the application included an EMA Decision P/0282/2017 on the granting of a product-specific waiver.

Information relating to orphan market exclusivity

Similarity

Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the applicant did not submit a critical report addressing the possible similarity with authorised orphan medicinal products because there is no authorised orphan medicinal product for a condition related to the proposed indication.

MAH request for additional market protection

The MAH requested consideration of its application in accordance with Article 14(11) of Regulation (EC) 726/2004 - one year of market protection for a new indication. During the procedure, the MAH withdrew its application.

Scientific advice

The MAH did not seek Scientific advice at the CHMP in relation to the current pivotal study REACH-2 and the target population of HCC patients with AFP ≥400 ng/ml. However, scientific advice on ramucirumab in an all-comer second-line HCC indication was sought in 2009 (Procedure No.: EMEA/H/SA/1505/1/2010/II).

1.2. Steps taken for the assessment of the product

The Rapporteur and Co-Rapporteur appointed by the CHMP were:

Rapporteur: Paula Boudewina van Hennik Co-Rapporteur: Kolbeinn Gudmundsson

Timetable	Actual dates
Submission date	23 July 2018
Start of procedure:	18 August 2018
CHMP Rapporteur Assessment Report	11 October 2018
CHMP Co-Rapporteur Assessment Report	12 October 2018
PRAC Rapporteur Assessment Report	12 October 2018
PRAC members comments	24 October 2018
Updated PRAC Rapporteur Assessment Report	25 October 2018
PRAC Outcome	31 October 2018
CHMP members comments	05 November 2018
Updated CHMP Rapporteur(s) (Joint) Assessment Report	8 November 2018
Request for supplementary information (RSI)	15 November 2018
CHMP Rapporteur Assessment Report	26 February 2019
PRAC Rapporteur Assessment Report	1 March 2019
PRAC members comments	06 March 2019
Updated PRAC Rapporteur Assessment Report	07 March 2019
PRAC Outcome	14 March 2019
CHMP members comments	18 March 2019
Updated CHMP Rapporteur Assessment Report	21 March 2019
Request for Supplementary Information	28 March 2019
Joint Rapporteur's assessment report circulated on:	11 June 2019
PRAC Outcome	13 June 2019
CHMP member's comments	17 June 2019
Updated CHMP Rapporteur Assessment Report	19 June 2019
CHMP opinion:	27 June 2019

2. Scientific discussion

2.1. Introduction

2.1.1. Problem statement

Disease or condition

The sought indication in this application is for the treatment of adult patients with hepatocellular carcinoma who have an alpha fetoprotein (AFP) of ≥ 400 ng/mL, after prior sorafenib therapy.

Epidemiology

Liver cancer is the sixth most common cancer and the fourth most frequent cause of cancer-related death globally, with 841,080 new cases and 781,631 deaths per year, accounting for 8.2% of all cancer-related deaths. In Europe, there were 82,466 new cases diagnosed and 77,375 deaths reported in 2018 (GLOBOCAN 2018). Hepatocellular carcinoma (HCC) represents about 90% of primary liver cancers. The incidence of HCC varies from 3 out of 100 000 in Western countries, to more than 15 out of 100 000 in certain areas of the world, mapping the geographical distribution of viral hepatitis B (HBV) and hepatitis C (HCV), the most important causes of chronic liver disease and HCC. HCC has a strong male preponderance, with a male to female ratio estimated to be 2–2.5:1. In European men, mortality rates have been stable during the last decade (3.5/100,000). Mortality rates in women are 3- to 5-fold lower than men in most regions (EASL Clinical Practice Guidelines. J Hepatol. 2018; C. Verslype et al. Annals of Oncology 2012; Bertuccio et al. J Hepatol. 2017).

Alpha-fetoprotein (AFP, α-fetoprotein; also called alpha-1-fetoprotein, alpha-fetoglobulin, or alpha fetal protein) is a major plasma protein produced by the yolk sac and the foetal liver during foetal development. It is thought to be the foetal analog of serum albumin. AFP binds to copper, nickel, fatty acids and bilirubin and is found in monomeric, dimeric and trimeric forms (NCBI). The function of AFP in adult humans is largely unknown. It is estimated that globally, patients with an AFP ≥400 ng/mL comprise approximately half of patients with HCC on systemic therapy, including those with disease progression on or after prior sorafenib therapy (Jelic et al. 2010; Zhu et al. 2015; Bruix et al. 2017).

Biologic features

An association has been demonstrated between increased angiogenesis in HCC and blood alpha-fetoprotein (AFP) concentration.

Blood AFP concentration has been found to be associated with elevated vascular endothelial growth factor receptor (VEGFR) expression, and poor prognosis in HCC (Gomaa et al. 2009; Guo et al. 2012; Mukozu et al. 2013; Berretta et al. 2017).
AFP concentration in blood is accepted as a tumour marker and prognostic biomarker in patients with HCC, and has been incorporated into several HCC prognostic scoring systems (Pons et al. 2005). Patients with HCC and elevated AFP have a particularly poor prognosis, with an AFP level of e.g. ≥400 ng/mL having been defined as a poorer prognostic group in different treatment settings (CLIP Investigators 1998; Tangkijvanich et al. 2000; Zhang et al. 2009; Mailey et al. 2011). This is illustrated by the information in Table 1, wherein median OS is shown by patient subgroup with different baseline AFP level for both treatment arms in several phase 3 studies in advanced HCC, both in first- as well as in second-line treatment. Alpha-fetoprotein is a continuous variable reaching very high levels in some patients (up to several hundred thousand), and the relationship between poorer prognosis and elevated AFP has been reported to be continuous beyond the threshold of 400 ng/mL (Hsu et al. 2015; Zhu et al. 2015; Silva et al. 2017). Indeed, the percentage of patients with an AFP ≥400 ng/mL in the three second-line advanced HCC studies in Table 1 was 41-45%.

Table 1: Median OS in several phase 3 studies in advanced HCC by baseline AFP level

Patient population	**Study treatment**	**Control treatment**	**mOS study treatment arm** (months)	**mOS control treatment arm** (months)	**Difference between treatment arms** (months)	**HR** (95% CI)
First-line treatment of advanced HCC						
Sorafenib SHARP study (Llovet et al. N Engl J Med 2008; Raoul et al. J Hepatol. 2012)						
Overall	Sorafenib	Placebo	10.7	7.9	2.8	0.69 (0.55-0.87)
Subgroup with AFP ≤ULN			12.4	9.5	2.9	0.76 (0.51-1.13)
Subgroup with AFP >ULN to 400 ng/mL			10.3	8.5	2.8	0.67 (0.43-1.04)
Subgroup with AFP >400 ng/mL			7.0	6.0	1.0	0.77 (0.54-1.08)
Lenvatinib REFLECT study (Kudo et al. Lancet. 2018)						
Overall	Lenvatinib	Sorafenib	13.6	12.3	1.3	0.92 (0.79-1.06)
Subgroup with AFP <200 ng/mL			19.5	16.3	3.2	0.91 (0.74-1.12)
Subgroup with AFP ≥200 ng/mL			10.4	8.2	2.2	0.78 (0.63-0.98)
Second-line treatment of advanced HCC						
Regorafenib RESORCE study (Stivarga HCC EPAR)						
Overall	Regorafenib	Placebo	10.6	7.8	2.8	0.63 (0.50-0.79)
Subgroup with AFP <400 ng/mL			13.5	9.4	4.1	0.67 (0.50-0.90)
Subgroup with AFP ≥400 ng/mL			7.4	5.8	1.6	0.68 (0.50-0.92)
Cabozantinib CELESTIAL study (Abou-Alfa et al. N Engl J Med. 2018)						
Overall	Cabozantinib	Placebo	10.2	8.0	2.2	0.76 (0.63-0.92)
Subgroup with AFP <400 ng/mL			13.9	10.3	3.6	0.81 (0.62-1.04)
Subgroup with AFP ≥400 ng/mL			8.5	5.2	3.3	0.71 (0.54-0.94)
Ramucirumab REACH study (Zhu et al. Lancet Oncol. 2015)						
Overall	Ramucirumab	Placebo	9.2	7.6	1.6	0.87 (0.72-1.05)
Subgroup with AFP <400 ng/mL			10.1	11.8	-1.7	1.09 (0.84-1.43)
Subgroup with AFP ≥400 ng/mL			7.8	4.2	3.6	0.67 (0.51-0.90)

Abbreviations: AFP = alpha-fetoprotein; CI = confidence interval; HR = hazard ratio; ULN = upper limit of institutional normal value. [a] Calculated as mOS in study treatment arm minus mOS in control treatment arm.

Clinical presentation, diagnosis

Patients with HCC may experience no symptoms until their disease is advanced. Disease-related symptoms include anorexia and unexplained weight loss, nausea and vomiting, hepato- or splenomegaly, abdominal or shoulder pain, abnormal bruising or bleeding, jaundice and fever. If the patient is cirrhotic, ascites, hepatic encephalopathy and GI bleeding may occur. Laboratory abnormalities, other than elevated liver function tests (LFTs), include hypercalcemia, hypoglycaemia, elevated serum cholesterol, erythrocytosis and thrombocytopenia.

Management

Treatment options and prognosis are determined by extent of HCC disease as well as the severity of the underlying cirrhosis. The Child-Pugh classification has been used to assess hepatic reserve in cirrhotic patients by scoring five variables (serum albumin, total bilirubin, ascites, encephalopathy and prothrombin time). Patients with a score of 5 or 6 are classified as Child-Pugh class A and are considered to have well-compensated liver disease. Child-Pugh B or C patients have higher scores and a worse prognosis. Various classification systems have been constructed to prescribe treatment and predict outcome in HCC.

The Barcelona Clinic Liver Cancer (BCLC) staging system is the staging system that is recommended for prognostic prediction and treatment allocation in HCC. Intermediate HCC (BCLC stage B) patients have multinodular tumours with preserved liver function and Eastern Cooperative Oncology Group (ECOG) 0. Advanced HCC (BCLC stage C) patients have cancer-related symptoms (symptomatic tumours, ECOG 1-2), macrovascular invasion (either segmental or portal invasion) or extrahepatic spread (lymph node involvement or metastases), but preserved liver function. These patients bear a poor prognosis with expected median survival times of 6–8 months if left untreated and are (in principle) candidates for palliative systemic treatment (EASL Clinical Practice Guidelines. J Hepatol. 2018).

First-line treatment of advanced HCC

HCC is recognised as being among the most chemo-resistant tumour types, and until 2007 no systemic drug was recommended for patients with advanced tumours (EASL Clinical Practice Guidelines. J Hepatol. 2018).

Individual treatment decisions largely depend on the stage of disease, but not on its aetiology. Surgical resection, transplantation, and ablation are potential curative options for early-stage disease, whereas chemoembolisation is recommended for patients with preserved liver function and disease confined to the liver generally without vascular invasion. In most HCC patients, the disease is diagnosed at advanced stages, when curative treatments, including resection, liver transplantation, and ablation, are no longer suitable.

The multikinase inhibitor sorafenib, was the first drug to demonstrate an overall survival benefit in patients with HCC who have not received prior systemic treatment (Llovet et al. N Engl J Med. 2008). Nexavar (sorafenib) was approved by the CHMP in 2007 for the treatment of HCC (Nexavar-H-C-690-II-05 EPAR). In the pivotal phase 3 SHARP study treatment with sorafenib reduced the hazard of death by 31% (HR 0.69, 95% CI: 0.55-0.87, p<0.001). Median OS was 10.7 months in the sorafenib group compared with 7.9 months in the placebo group, i.e. a 2.8-month improvement in favour of sorafenib.
Lenvima (lenvatinib, also a multikinase inhibitor) was recently approved for the treatment of adult patients with advanced or unresectable HCC who have received no prior systemic therapy, and is thereby expected to become an alternative first-line treatment option (Lenvima HCC EPAR). This approval was based on the pivotal REFLECT study in which lenvatinib was non-inferior to sorafenib in OS in untreated advanced HCC (Kudo et al. Lancet. 2018). Median OS was 13.6 months for lenvatinib versus (vs.) 12.3 months for sorafenib (HR 0.92, 95% CI: 0.79-1.06).

Second-line treatment of advanced HCC

Stivarga (regorafenib, another multikinase inhibitor) was approved in September 2017 for the treatment of adult patients with HCC who have been previously treated with sorafenib (Stivarga HCC EPAR). Approval was based on results from the pivotal phase 3, placebo-controlled RESORCE study (Bruix et al. Lancet. 2018). Treatment with regorafenib reduced the hazard of death by 37% (HR 0.63, 95% CI: 0.50-0.79, p<0.0001). Median OS was 10.6 months for regorafenib vs. 7.8 months for placebo, resulting in a 2.8 months increase. Importantly, patients who were intolerant to sorafenib were excluded from the RESORCE study.

Cabozantinib (yet another multikinase inhibitor) in the pivotal phase 3, placebo-controlled CELESTIAL study increased median OS with 2.2 months, as median OS was 10.2 months for cabozantinib vs. 8.0 months for placebo (HR 0.76; 95% CI, 0.63-0.92, p=0.005) (Abou-Alfa et al. 2018). This study was the basis for the very recent approval of Cabometyx (cabozantinib) for the treatment of HCC in adults who have previously been treated with sorafenib (Cabometyx HCC EPAR).

Notwithstanding the above-mentioned medicinal products, the prognosis of advanced HCC is still poor and new treatment options are needed.

About the product

Ramucirumab is a human receptor-targeted antibody that specifically binds Vascular Endothelial Growth Factor (VEGF) Receptor 2 and blocks binding of its activating ligands VEGF-A, VEGF-C, and VEGF-D. VEGF Receptor 2 is the key mediator of VEGF induced angiogenesis. As a result, ramucirumab inhibits ligand stimulated activation of VEGF Receptor 2 and its downstream signalling components, including p44/p42 mitogen-activated protein kinases, neutralising ligand-induced proliferation and migration of human endothelial cells (Cyramza SmPC).

Rationale for ramucirumab in hepatocellular carcinoma with elevated blood alpha-fetoprotein

Hepatocellular carcinoma (HCC) is a highly vascular neoplasm (Yang and Poon 2008). Circulating VEGF-A levels are increased in HCC and have been shown to correlate with tumour VEGF expression (Poon et al. 2001, 2003). High tumour microvessel density and increased local and circulating VEGF are associated with rapid disease progression and reduced survival (Miura et al. 1997; Poon et al. 2001).

In the EU, Cyramza is approved for the second-line treatment of advanced gastric cancer (as monotherapy or in combination with chemotherapy), locally advanced or metastatic non-small cell lung cancer (in combination with chemotherapy), and metastatic colorectal cancer (in combination with chemotherapy). The MAH applied for the following indication:

Cyramza monotherapy is indicated for the treatment of adult patients with hepatocellular carcinoma who have an alpha fetoprotein (AFP) of ≥ 400 ng/mL, after prior sorafenib therapy.

The following indication was adopted by the CHMP:

Cyramza monotherapy is indicated for the treatment of adult patients with advanced or unresectable hepatocellular carcinoma who have a serum alpha fetoprotein (AFP) of ≥ 400 ng/ml and who have been previously treated with sorafenib.

The recommended dose of ramucirumab as a single agent is 8 mg/kg every 2 weeks.

Patients with HCC should be selected based on a serum AFP concentration of ≥ 400 ng/ml with a validated AFP test prior to ramucirumab treatment.

2.2. Non-clinical aspects

No new non-clinical data have been submitted in this application, which was considered acceptable by the CHMP.

2.2.1. Ecotoxicity/environmental risk assessment

Ramucirumab is a protein, which is expected to be metabolised in the body and biodegrade in the environment. Thus, according to the "Guideline on the Environmental Risk Assessment of Medicinal Products for Human Use" (EMEA/CHMP/SWP/4447/00), ramucirumab is exempt from the submission of Environmental Risk Assessment studies as the product and excipients do not expect to pose a significant risk to the environment.

2.2.2. Discussion and conclusion on non-clinical aspects

The applicant did not submit studies for the ERA. According to the guideline, in the case of products containing proteins as active pharmaceutical ingredient(s), a justification for the lack of ERA studies is acceptable.

2.3. Clinical aspects

2.3.1. Introduction

GCP

The Clinical trials were performed in accordance with GCP as claimed by the applicant

The applicant has provided a statement to the effect that clinical trials conducted outside the community were carried out in accordance with the ethical standards of Directive 2001/20/EC.

- Tabular overview of clinical studies

Table 2: Overview of studies in the current dossier

Studies Supporting Ramucirumab Efficacy and Safety in Hepatocellular Carcinoma				
Study	**Description**	**Treatment**	**Number of Patients**	**Variables Evaluated**
REACH-2 (I4T-IE-JVDE)	Phase 3 study in patients with HCC and a baseline AFP ≥400 ng/mL after prior sorafenib therapy	Ramucirumab 8 mg/kg IV Q2W + BSC compared with placebo IV Q2W + BSC	ITT population: 292 Ramucirumab arm: 197 Placebo arm: 95 Safety population: 292 Ramucirumab arm: 197 Placebo arm: 95	Primary: OS Secondary: PFS, ORR, TTP, safety, PFOs, PK, and immunogenicity
REACH (I4T-IE-JVBF)	Phase 3 study in patients with HCC after prior sorafenib therapy	Ramucirumab 8 mg/kg IV Q2W + BSC compared with placebo IV Q2W + BSC	ITT population: Ramucirumab arm: 283 Placebo arm: 282 Population with a baseline AFP ≥400 ng/mL: Ramucirumab arm: 119 Placebo arm: 131	Primary: OS Secondary: PFS, ORR, TTP, safety, PFOs, PK, and immunogenicity
I4T-IE-JVBQ	Phase 2 study in patients with HCC not previously treated with systemic therapy	Ramucirumab 8 mg/kg IV Q2W	ITT population: 42 Safety population: 42	Primary: PFS Secondary: TTP, OS, ORR, DOR, safety, PK, and immunogenicity
I4T-CR-JVCQ (Safety only)	Phase 1b safety study in patients with HCC who had not previously treated with systemic therapy	Ramucirumab 8 mg/kg IV Q2W + FOLFOX4	Safety population: 8	Safety, PK, immunogenicity

Abbreviations: AFP = alpha-fetoprotein; BSC = best supportive care; DOR = duration of response; FOLFOX4 = 5-flourouracil/folinic acid/oxaliplatin; HCC = hepatocellular carcinoma; ITT = intent to treat; IV = intravenous; ORR = objective response rate; OS = overall survival; PFS = progression-free survival; PFO = patient-focused outcome; PK = pharmacokinetics; Q2W = every 2 weeks; TTP = time to progression.

2.3.2. Pharmacokinetics

The recommended dosing regimen of ramucirumab for HCC is 8 mg/kg on days 1 and 15 of a 28 day cycle. This is the same ramucirumab dosing regimen as for treatment of patients with colorectal cancer and patients with advanced gastric cancer.

The basis of this submission is the pivotal Phase 3 trial, REACH-2 (JVDE), a placebo-controlled study. Pharmacokinetic information in this HCC submission includes data from the 4 studies in patients with HCC (Table 2). Ramucirumab pharmacokinetics was evaluated by an update of the previously submitted RAISE popPK analysis. Exposure-response analyses based on REACH-2 and pooled data from REACH and REACH-2, and updated immunogenicity data are also presented.

No changes have been made to the approved commercial formulations (Process C1 and C2) described in previous submissions.

Methods

Bioanalytical methods.

Ramucirumab concentrations were measured in serum samples using a validated enzyme-linked immunosorbent assay as detailed in previous submissions. The bioanalytical method was cross-validated with acceptable results.

Anti-drug antibodies (ADA) in patient sera were detected and characterised using modified ELISA formats with a 4-tiered approach as detailed in previous submissions.

PopPK analysis

Studies REACH and REACH-2 had only sparse PK data i.e. blood samples for the determination of serum ramucirumab concentrations were collected prior to infusion (trough) and within 1 to 1.5 hours after the end of the infusion (peak) for Cycles 1, 2, 4, 7, and 10 (Weeks 0, 2, 6, 12, and 18). Study JVCQ had rich PK data collection in 8 Chinese patients with HCC.

The previously submitted RAISE population pharmacokinetic (PopPK) analysis (see mCRC submission, EMEA/H/C/002829/II/0004) was updated with the PK data from studies REACH-2 and JVCQ in patients with HCC. PK data in patients with HCC from studies REACH and JVBQ were already included in RAISE popPK analysis. Further, PK data from 2 studies in patients with urothelial carcinoma (RANGE [I4T-MC-JVDC] and Study 14Y-IE-JCDC [JCDC]), and 2 studies in patients with gastric or gastroesophageal junction adenocarcinoma (Studies I4T-MC-JVDB [JVDB] and I4T-MC-JVCZ [JVCZ]) were included in the updated popPK analysis. In total, there are 17 studies included in the updated PopPK analysis, the so-called REACH-2 PopPK report. The final analysis included 11,256 ramucirumab concentrations from 2522 patients.

Effects of different patient factors, including body weight, age, sex, race, cancer indication, serum albumin, AFP, ALT, AST, ALP, TBI, total protein, CLcr, renal function, and measures of liver cirrhosis prognosis and patient functioning (C-P score and ECOG performance status [PS] score, respectively) on ramucirumab PK were investigated in the PopPK analysis. Covariates were included in the model when there was a >6.635 point drop in MOF ($p<0.01$) and a decrease (≥10%) in the relative inter-individual (patient) variability (IIV) estimate in the relevant parameter and demonstration of clinical relevance, criterion: 20% influence on the PK model parameter. Body weight was the only significant covariate identified in this analysis. The final model parameter estimates are shown in Table 3.

Table 3: Pharmacokinetic Parameters in Final Population Model for Ramucirumab

Parameter[a] Description	Population Estimate (%SEE)	Inter-Patient Variability (%SEE)	Calculated 95% CI Based on Objective Function Mapping
Clearance			
Parameter for CL (L/hr)	0.0205 (3.23)	36.6 (7.92)	(0.0199, 0.0214)
Effect of body weight on CL[b]	0.487 (6.49)	–	(0.426, 0.548)
Central Volume of Distribution			
Parameter for V_1 (L)	3.31 (0.671)	23.0 (6.82)	(3.27, 3.36)
Effect of body weight on V_1[c]	0.572 (4.93)	–	(0.518, 0.627)
Inter-compartmental clearance; Q (L/hr)	0.0269 (12.9)	–	(0.0222, 0.0327)
Peripheral volume of distribution; V_2 (L)	1.23 (8.70)	88.5 (22.7)	(1.10, 1.36)
Maximum change in CL; T_{max}	-0.418 (12.2)	67.6 (21.4)	(-0.480, -0.369)
Time to half-maximal change in CL; T_{50} (hr)	647 (10.4)	–	(568, 719)
Hill coefficient	1.67 (18.5)	–	(1.34, 2.04)
Inter-patient variability correlation coefficient			
CL and V_1	0.567 (6.72)	–	
CL and T_{max}	-0.474 (25.2)	–	
Residual Error			
Additive (µg/mL)	2.34 (12.5)	–	
Proportional	21.1 (6.03)	–	

Abbreviations: CI = confidence interval; CL = clearance; Q = inter-compartmental clearance; SEE = standard error of the estimate; T_{50} = time to half-maximal change in CL; T_{max} = maximum change in clearance; V_1 = central volume of distribution; V_2 = peripheral volume of distribution.

[a] ETA shrinkage (%): CL: 17.8, V_1: 24.2, V_2: 57.6, T_{max}: 51.3; EPS shrinkage (%): 18.5.

[b] $CL = 0.0205 * (\text{body weight}/68)^{0.487}$, where 68 is the median baseline body weight.

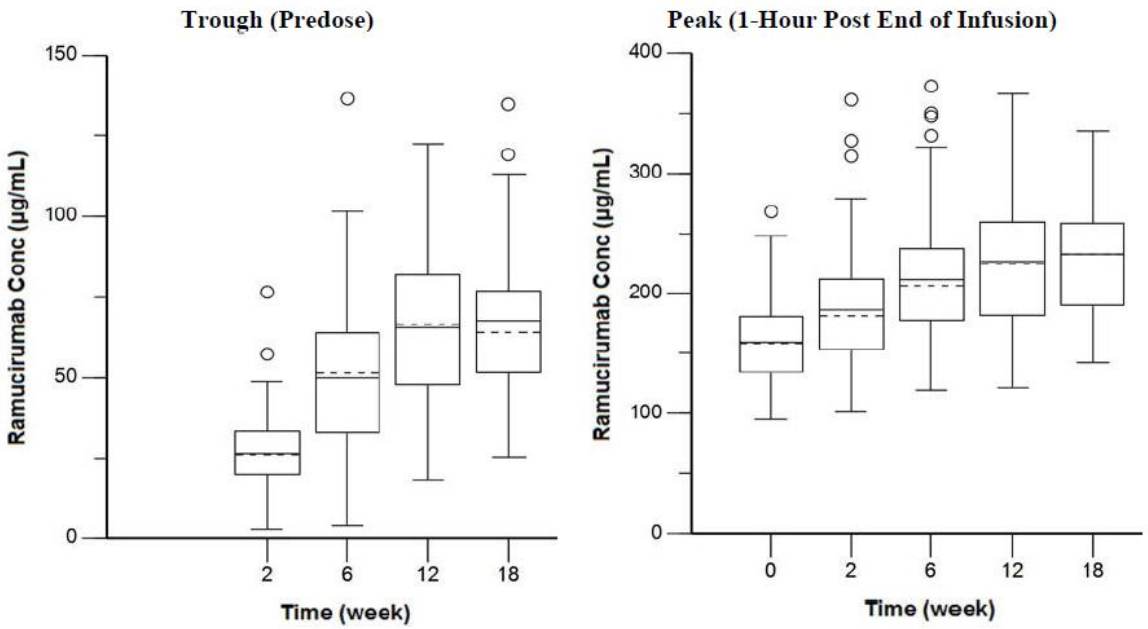
[c] $V_1 = 3.31 * (\text{body weight}/68)^{0.572}$, where 68 is the median baseline body weight.

Source: I4T-MC-JVDE Population Pharmacokinetic Parameters Report, Table 8.2.

Results

REACH-2

Ramucirumab trough and peak concentration data following administration of 8 mg/kg ramucirumab every 2-weeks are shown in Figure 1. Geometric mean trough concentrations at Day 1 of Cycles 2, 4, 7, and 10 (Weeks 2, 6, 12, and 18) were 23.5 µg/mL (range of 2.9-76.5 µg/ml) (n=162), 44.1 µg/mL (range of 4.2-137 µg/ml) (n=120), 60.2 µg/mL (range of 18.3-123 µg/ml) (n=69), and 63.2 µg/mL (range of 25.4-135 µg/ml) (n=45), respectively. Peak concentrations also increased, with a geometric mean of 156 µg/mL following the first dose and 228 µg/mL following the tenth dose. Trough and peak concentrations appeared to stabilise by Week 12.



Outline of box shows the 25th and 75th percentile with inside lines being the arithmetic mean (solid) and median (dashed). Whiskers show lowest and highest values within 1.5 times the difference between the first and third quartile. Individual observations outside the whiskers are shown with open circles.
Source: REACH-2 Clinical Study Report, Figure JVDE.11.12.

Figure 1: Summary of ramucirumab trough and peak concentrations for patients in REACH-2 with hepatocellular carcinoma following administration of 8 mg/kg of ramucirumab every 2 weeks as an intravenous infusion over approximately 1 hour.

Ramucirumab CL was found to decrease over time, with a mean maximal reduction from baseline of approximately 34% at steady state. The decrease in CL was shown to occur rapidly, such that approximately 90% of the decrease in CL was achieved by Week 12 after start of treatment. Relative to the CL obtained from the two-compartment linear model CL model, CL at steady state obtained from the time-varying CL model was only 12.3% lower. Steady state ramucirumab PopPK model-derived estimates for time-varying CL and two-compartment linear model are summarised in Table 4.

Table 4: Post Hoc Estimates of Population Pharmacokinetic Parameters

	Geometric Mean (%CV)		
	REACH-2[a] Time-Varying CL Model	REACH-2 Constant CL Model	RAISE Constant CL Model
Clearance; CL (L/hr)	0.0136 (30.4)	0.0155 (31.8)	0.0147 (30.0)
Volume of distribution at steady state; V_{ss} (L)	4.57 (19.6)	6.12 (19.0)	5.38 (15.0)
Terminal half-life; $t_{1/2}$ (days)	10.1 (27.7)	15.8 (25.6)	14.2 (20.0)
N	2522	2522	1639

Abbreviations: %CV = percent coefficient of variation; N = number of patients.
[a] Parameter estimates at steady state.
Source: I4T-MC-JVDE Population Pharmacokinetic Parameters Report, Table APP.7.1.

Body weight effect (baseline range: 30 to 169 kg) was similar to that seen previously, and was retained in the current model as a significant covariate due to an updated model selection criterion. Because the ramucirumab dosing regimen is based on body weight, there was only an approximately 20% difference in

average concentration at steady state (Cave,ss) when patients in the 5th (47.7 kg) or 95th (99.5 kg) percentile for weight were compared with those with median weight (68.2 kg).

Sex (1722 males, 800 females), age (range, 19 to 88 years), and race (the majority of which were White [1768; 70%] or Asian [602; 24%]) had no significant effect on the PK of ramucirumab.

Renal function was assessed continuously based on levels of serum creatinine [baseline range, 18 to 284 µmol/L] and Cockcroft-Gault creatinine clearance (CLcr) [baseline range, 19.6 to 303 mL/min]), and categorically based on CLcr classification [normal (N=1031; 41%) and mild (N=1033; 41%), moderate (N=431; 17%), or severe (N=14; <1%) dysfunction], with 13 missing values [<1%]). None were found to have a significant effect on the disposition of ramucirumab.

Hepatic function, as assessed by continuous covariates (alanine aminotransferase; baseline range, 3 to 742 IU/L, aspartate aminotransaminase; baseline range, 2 to 567 IU/L, alkaline phosphatase; baseline range, 25 to 2210 IU/L, total bilirubin baseline range, 1.03 to 61.0 micromol/L, total protein levels range, 29 to 140 g/L) and categorical covariates (hepatic function score with baseline levels of normal [N=1683; 67%], mild hepatic impairment [N=734; 29%], moderate hepatic impairment [N=28; 1%], and 77 missing values [3%]) were investigated for the influence on the PK of ramucirumab. None were found to have a significant effect on the disposition of ramucirumab.

Immunogenicity

Immunogenicity was assessed in 3059 patients treated with ramucirumab in 25 studies including the 4 studies in HCC (REACH-2, REACH, Study JVBQ, and Study JVCQ). Across all studies, 94/3059 (3.1%) of ramucirumab-treated patients tested positive for treatment emerging (TE) ADAs, and neutralizing antibodies were detected in 14 of the 94 patients who tested positive for treatment emerging ADAs. In the HCC studies, 10.5% (83/788) patients had antidrug antibodies (ADA) present at baseline; 24/427 (5.6%) of ramucirumab-treated patients tested positive for treatment-emerging ADAs, and neutralizing antibodies were detected in 2 of the 24 patients who tested positive for treatment-emerging ADAs. Neutralizing antibodies were detected in 1 patient at baseline.

Infusion-related reactions were reported at similar frequency between treatment-emerging ADA+ patients (18.4% [7/38]) and treatment emerging ADA– patients (13.6% [94/691]). The number of treatment-emerging ADA+ patients who reported infusion-related reactions across the HCC studies was low (7 patients in total: 5 ramucirumab-treated patients; 2 placebo-treated patients) and with no consistent temporal relationship with the presence of treatment-emerging ADAs. The majority of treatment-emerging ADA+ patients reported infusion-related reactions at times when treatment-emerging ADAs were not present. No analysis of the effect of immunogenicity on efficacy was conducted due to the low rate of ADA formation.

2.3.3. Pharmacodynamics

Mechanism of action

No new mechanism of action studies have been submitted with this application.

Primary and secondary pharmacology

No new primary and secondary pharmacology studies have been submitted with this application.

2.3.4. PK/PD modelling

The objectives of the performed exposure-response analysis were to:

• Evaluate the relationship between predicted ramucirumab exposure and selected efficacy outcomes of overall survival (OS) and progression-free survival (PFS) in patients with advanced hepatocellular carcinoma (HCC) with baseline alpha-fetoprotein (AFP) ≥400 ng/mL.

• Evaluate the relationship between predicted ramucirumab exposure and selected safety outcomes in patients with advanced HCC.

• Summarise dose modification (that is, dose delay, reduction, and omission) by ramucirumab exposure quartile group in patients with advanced HCC.

Exposure-effect relationship

The relationship between ramucirumab exposure and OS and PFS was evaluated using Kaplan-Meier (KM) methods, Cox models, and case-matched control analysis for 2 patient populations, the REACH-2 efficacy population and the pooled efficacy population REACH-2 and REACH subpopulation AFP ≥400 ng/mL. Model-predicted minimum concentration after first dose administration ($C_{min,1}$) was selected for exposure-efficacy analysis.

The following factors were evaluated for potential prognostic significance using stepwise Cox regression: baseline alpha-fetoprotein, BCLC, baseline ECOG PS, macrovascular invasion, aetiology of liver disease, extrahepatic metastases geographic region, prior locoregional therapy, reason for discontinuation of sorafenib, gender, age, and race. A stepwise Cox regression, with entry p-value <.05 and exit p-value ≥.10, was used to identify the baseline factors that were prognostic for OS or PFS, respectively. These significant factors were either adjusted in the multivariate models as covariates or used as matching factors for evaluating the relationship between efficacy and ramucirumab exposure measures. In the multivariate Cox regression analyses, separate models were fitted using exposure measures as either continuous or categorical variables (quartile groups).

Results

The number of patients in the exposure-response analysis of REACH-2 was 193 for the ramucirumab arm and 95 for the placebo arm. A statistically significant positive association was identified between OS and $C_{min,1}$ in both the univariate (p<0.0001) and multivariate (p<0.0001) Cox regression analyses for the REACH-2 efficacy population (Table 5).

Table 5: Analysis of Predicted $C_{min,1}$ and Overall Survival (REACH-2)

Efficacy Parameter Overall Survival	Hazard Ratio[a] (95% CI)	p-Value (Wald's)
REACH-2 Efficacy Population (N = 193/143 events)		
Univariate analysis	0.539 (0.426, 0.680)	<.0001
Multivariate analysis adjusting for significant factors[b]	0.567 (0.443, 0.726)	<.0001

Analysis of Predicted $C_{min,1}$ and Overall Survival

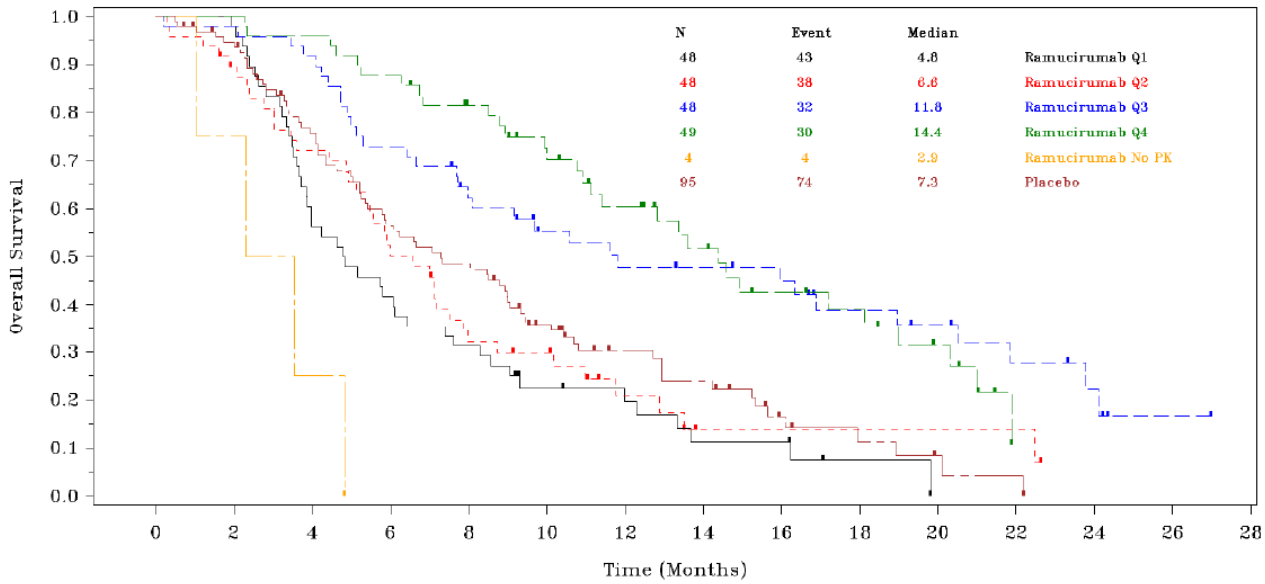
Abbreviations: AFP = alpha-fetoprotein; CI = confidence interval; $C_{min,1}$ = minimum concentration after first dose administration; CRF = case report form; ECOG PS = Eastern Cooperative Oncology Group performance status; HR = hazard ratio; N = number of patients; PK = pharmacokinetic.

a Log-2 transformation was applied before fitting the model, hence the HR should be interpreted as the change in hazard when the PK parameter doubles its value.

b Adjusted for macrovascular invasion (CRF); ECOG PS at baseline and baseline AFP (ng/mL) (log-transformed).

For the purpose of comparison with the placebo treatment group, patients who had non-missing ramucirumab concentration data were grouped into 4 quartiles ($C_{min,1}$: <25% (4.9-18.9 µg/ml), 25% to <50% (19.1-24.5 µg/ml), 50% to <75% (24.8-30.2 µg/ml), and ≥75% (30.2-76.0 µg/ml)).

The Kaplan-Meier plots of OS by $C_{min,1}$ quartiles for the REACH-2 efficacy population are presented in Figure 2. There was separation between the OS curves for the 4 exposure groups, indicating that quartiles that achieved higher exposures within the exposure range of 8 mg/kg demonstrated an association with longer survival. This approach did not adjust for the imbalanced prognostic factors among the quartiles and placebo group.



At Risk															
Ram Q1	48	47	27	20	15	9	7	4	4	1	0	0	0	0	0
Ram Q2	48	41	33	23	14	12	6	2	2	2	2	2	0	0	0
Ram Q3	48	47	44	35	28	22	19	18	18	12	10	7	4	1	0
Ram Q4	49	49	47	43	37	30	24	18	13	11	7	0	0	0	0
Ram (No PK)	4	3	1	0	0	0	0	0	0	0	0	0	0	0	0
Placebo	95	87	67	50	43	28	19	15	7	4	2	1	0	0	0

Cutoff Date: JVDE: 2018-03-15.

Abbreviations: BSC = best supportive care; $C_{min,1}$ = minimum concentration after first dose administration; PK = pharmacokinetics; Q = quartile; Ram=ramucirumab.

Figure 2: Kaplan-Meier plots of overall survival by predicted $C_{min,1}$ quartiles for the REACH-2 population.

A multivariate Cox regression analysis was conducted to account for the significant prognostic factors associated with OS, including macrovascular invasion (case report form [CRF]), ECOG PS at baseline, and baseline AFP (ng/mL). The comparison between the placebo and ramucirumab quartile groups is shown in Table 6. After adjusting for the baseline factors that were significantly associated with OS, a significant improvement (smaller hazard ratio [HR]) in OS was observed in the Q3 and Q4 groups, and the lowest exposure groups Q1 and Q2 appeared to have no improvement in OS with ramucirumab vs. placebo.

Table 6: Multivariate Cox Regression Analysis of Overall Survival by $C_{min,1}$ Quartiles (REACH-2)

Efficacy Parameter Overall Survival	Placebo N[a]	Ramucirumab N[a]	Hazard Ratio (95% CI)	p-Value (Wald's)
REACH-2 Efficacy Population[b]				
Q1 vs. Placebo	95	48	1.335 (0.910, 1.958)	0.1394
Q2 vs. Placebo	95	48	1.060 (0.706, 1.591)	0.7782
Q3 vs. Placebo	95	48	0.481 (0.306, 0.754)	0.0014
Q4 vs. Placebo	95	49	0.445 (0.285, 0.696)	0.0004

Abbreviations: AFP = alpha-fetoprotein; CI = confidence interval; $C_{min,1}$ = minimum concentration after first dose administration; CRF = case report form; ECOG PS = Eastern Cooperative Oncology Group performance status; N = number of patients contributing to analysis; Q = quartile.

a Patients with missing baseline covariate factors were omitted from analysis.

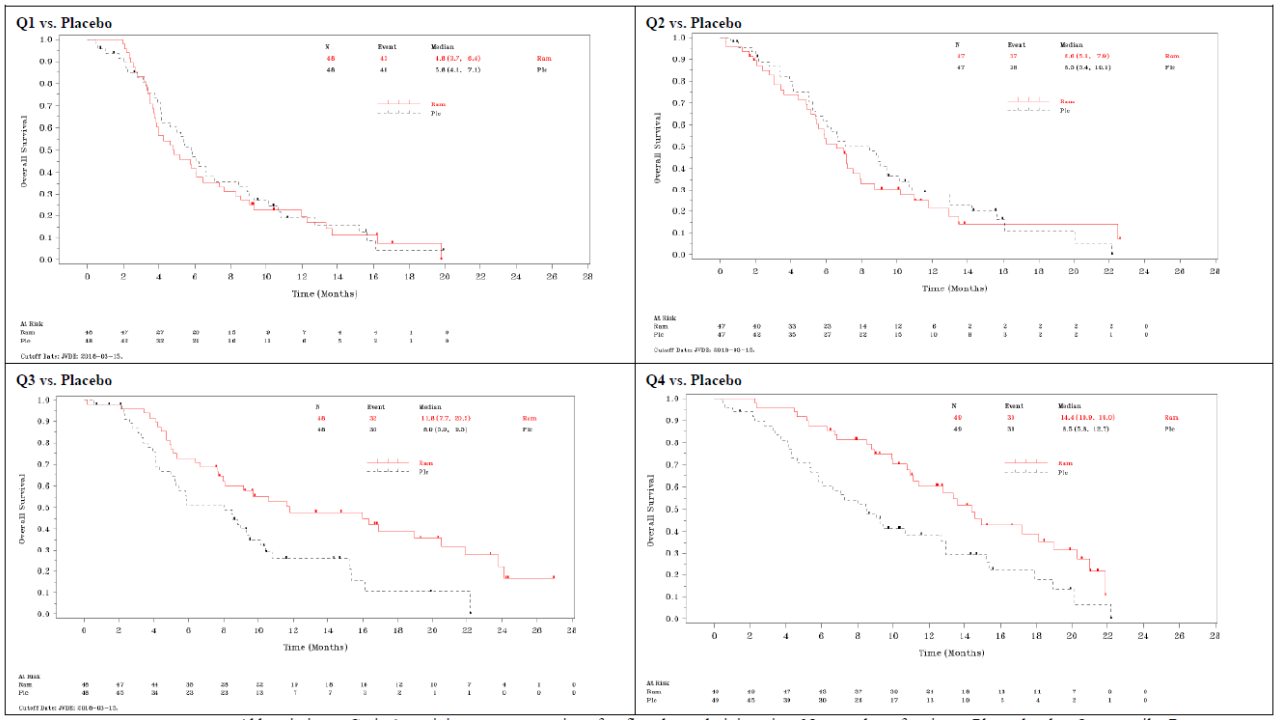
b Adjusted for macrovascular invasion (CRF); ECOG PS at baseline and baseline AFP (ng/mL) (log-transformed).

Note:

Q1 = ramucirumab-treated patients with $C_{min,1}$ <25%;
Q2 = ramucirumab-treated patients with $C_{min,1}$ 25% – <50%;
Q3 = ramucirumab-treated patients with $C_{min,1}$ 50% – <75%;
Q4 = ramucirumab-treated patients with $C_{min,1}$ ≥75%.

As another way to adjust for potential impact of imbalance in baseline characteristics and important prognostic factors between the treatments within each exposure group, case-matched control analyses for OS were explored to evaluate the exposure-efficacy relationship. The matching was performed separately for each of the 4 exposure quartiles (Q1 to Q4) of $C_{min,1}$ in the ramucirumab treatment group. There were 3 matching factors to be adjusted for OS in the REACH-2 efficacy population: macrovascular invasion (CRF); ECOG PS at baseline, and baseline AFP (ng/mL) (log-transformed). Based on Mahalanobis metric matching, 48, 47, 48, and 49 patients from the placebo treatment group were selected to match 1:1 with the Q1 group, Q2 group, Q3 group, and Q4 group, respectively.

To compare the 2 treatment groups in each of the 4 case-control groups, Kaplan-Meier curves for OS in each group are shown in Figure 3. Separation of the OS curves was observed in the matched Q3 and Q4 groups, but not the Q1 and Q2 groups. Cox regression models including the interaction term of treatment by each case-control group demonstrated results that are consistent with the exposure response association as observed in Table 6 with statistical significant treatment effects in the Q3 and Q4 groups and no treatment effect in the Q1 and Q2 groups.



Abbreviations: Cmin,1 = minimum concentration after first dose administration; N = number of patients; Plc = placebo; Q = quartile; Ram = ramucirumab.
Note: Mahalanobis metric matching (with a caliper size of 1/4 standard deviation of the logit score) was used (D'Agostino 1998).
Source: I4T-MC-JVDC Exposure-Response Analysis Report, Figure 8.3.

Figure 3: Kaplan-Meier plots of overall survival for the Mahalanobis distance matched subgroups by $C_{min,1}$ quartiles in the REACH-2 efficacy population.

Exposure-safety relationship

The overall safety population (REACH2 + REACH) consisted of 466 for the ramucirumab treatment arm and 371 for the placebo arm. Exposure-safety relationship was evaluated by 2 exposure parameters, $C_{min,1}$ and minimum concentration at steady state (Cmin,ss). Safety endpoints were Grade ≥3 *fatigue* (consolidated term), Grade ≥3 hypertension (preferred term), *liver failure/liver injury* (consolidated term; any grade and Grade ≥3), *hepatic encephalopathy* (consolidated term; any grade and Grade ≥3), and *ascites* (consolidated term; any grade and Grade ≥3). In addition, dose modifications were summarised by different exposure quartile groups.

The highest ramucirumab exposure group appeared to have the greatest incidence of Grade ≥3 hypertension in the pooled safety population (baseline AFP ≥400 ng/mL), the REACH-2 safety population, and the pooled overall safety population in patients with HCC over the range of exposures achieved by a dosage of 8 mg/kg given every 2 weeks (see Table 7). Increasing ramucirumab exposure did not appear to be associated with higher incidences for other safety endpoints, including Grade ≥3 *fatigue* (consolidated term), any grade and Grade ≥3 *hepatic encephalopathy* (consolidated term), any grade and Grade ≥3 *ascites* (consolidated term), and any grade and Grade ≥3 *liver failure/liver injury* (consolidated term), in the pooled safety population (AFP ≥400 ng/mL), the REACH-2 safety population, or the pooled overall safety population over the range of exposures achieved by a dosage of 8 mg/kg given every 2 weeks.

Table 7: Observed Treatment-Emergent Adverse Event Incidence by Quartile of Minimum Ramucirumab Concentration at Steady-State (Cmin,ss) REACH-2 Safety Population

		Ramucirumab + BSC				
			$C_{min,ss}$			
	Placebo + BSC	Overall	First Quartile	Second Quartile	Third Quartile	Fourth Quartile
Ramucirumab Concentration Range (µg/mL)	---	11.571 – 165.390	11.571 – <45.983	≥45.983 – <59.754	≥59.754 – <74.976	≥74.976 – 165.390
Grade ≥3	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**n (%)**
Fatigue[a]	1 (2.0)	10 (5.2)	4 (8.3)	3 (6.3)	2 (4.2)	1 (2.0)
Hypertension[b]	5 (5.3)	24 (12.4)	3 (6.3)	6 (12.5)	5 (10.4)	10 (20.4)
Liver Failure/ Liver Injury[a]	15 (15.8)	35 (18.1)	7 (14.6)	16 (33.3)	5 (10.4)	7 (14.3)
Ascites[a]	2 (2.1)	8 (4.2)	3 (6.3)	4 (8.3)	1 (2.1)	0 (0)
Hepatic Encephalopathy[a]	0 (0)	6 (3.1)	0 (0)	3 (6.3)	1 (2.1)	2 (4.1)
Any Grade						
Liver Failure/ Liver Injury[a]	28 (29.5)	76 (39.4)	21 (43.8)	27 (56.3)	11 (22.9)	17 (34.7)
Ascites[a]	7 (7.4)	35 (18.1)	11 (22.9)	13 (27.1)	4 (8.3)	7 (14.3)
Hepatic Encephalopathy[a]	0 (0)	8 (4.2)	0 (0)	4 (8.3)	1 (2.1)	3 (6.1)
Number of Patients (N)	95	193	48	48	48	49

Abbreviations: % = percentage of patients experiencing adverse event grade; AFP = alpha-fetoprotein; BSC = best supportive care; $C_{min,ss}$ = minimum concentration at steady-state; N = number of patients; n = number of patients experiencing an adverse event.

[a] Consolidated term.

[b] Preferred term.

Source: I4T-MC-JVDE Exposure-Response Analysis Report, Table 8.11.

A summary of dose modifications over the range of exposures achieved by a dosage of 8 mg/kg given every 2 weeks is included in Table 8.

Table 8: Summary of Dose Modifications by $C_{min,1}$ Quartiles in the Pooled Safety Population (AFP ≥400 ng/mL) and REACH-2 Safety Population

REACH-2 Safety Population	Placebo	Ramucirumab $C_{min,1}$ Quartiles			
		Q1	Q2	Q3	Q4
	N=95	N=48	N=48	N=48	N=49
	n (%)	n (%)	n (%)	n (%)	n (%)
Dose modifications of ramucirumab/placebo					
Patients with at least 1 dose modification	26 (27.4)	22 (45.8)	20 (41.7)	20 (41.7)	21 (42.9)
Dose delay	7 (7.4)	3 (6.3)	8 (16.7)	12 (25.0)	5 (10.2)
Dose omission	20 (21.1)	21 (43.8)	17 (35.4)	14 (29.2)	18 (36.7)
Dose reduction	2 (2.1)	3 (6.3)	3 (6.3)	1 (2.1)	2 (4.1)

Pooled Safety Population (AFP ≥400 ng/mL)	Placebo	Ramucirumab $C_{min,1}$ Quartiles			
		Q1	Q2	Q3	Q4
	N=223	N=77	N=78	N=78	N=78
	n (%)	n (%)	n (%)	n (%)	n (%)
Dose modifications of ramucirumab/placebo					
Patients with at least 1 dose modification	35 (15.7)	28 (36.4)	25 (32.1)	26 (33.3)	27 (34.6)
Dose delay	12 (5.4)	6 (7.8)	7 (9.0)	15 (19.2)	7 (9.0)
Dose omission	25 (11.2)	27 (35.1)	22 (28.2)	18 (23.1)	22 (28.2)
Dose reduction	3 (1.3)	5 (6.5)	5 (6.4)	4 (5.1)	2 (2.6)

Abbreviations: AFP = alpha-fetoprotein; $C_{min,1}$ = minimum concentration after the first dose; N = number of patients; n = number of patients with at least 1 dose modification, delay, omission, or reduction; Q = quartile.
Source: I4T-MC-JVDE Exposure-Response Analysis Report, Table 8.14.

2.3.5. Discussion on clinical pharmacology

Ramucirumab pharmacokinetics in HCC were evaluated by an updated popPK analysis including PK data of all 4 studies in patients with HCC. Exposure-response analyses based on REACH-2 and pooled data from REACH and REACH-2, and updated immunogenicity data were also presented.

The observed Ctrough and peak ramucirumab concentrations in HCC were comparable with previous values for ramucirumab in gastric cancer (Cyramza gastric cancer EPAR). Pharmacokinetics of ramucirumab were adequately described by a time-dependent clearance model. Based on this PopPK, the following covariates were found to have no impact on ramucirumab disposition: age, sex, race, and albumin levels. These and other factors investigated had < 20 % effect on ramucirumab disposition. Only body-weight was considered a significant co-variate of ramucirumab pharmacokinetics supporting the dosing based on body weight (see SmPC section 5.2). Because the ramucirumab dosing regimen is based on body weight, there was only an approximately 20% difference in average concentration at steady state (Cave,ss) when patients in the 5th (47.7 kg) or 95th (99.5 kg) percentile for weight were compared with those with median weight (68.2 kg). These results support the body weight-based dosing regimen for the majority of patients. The applicant was requested to discuss if capping of ramucirumab dose is necessary because the effect of body-weight on the pharmacokinetics is less than proportional. Given the exposure-effect relationship i.e. no benefit in subjects with low ramucirumab exposure it was also questioned whether ramucirumab dosing needs adjustment in subjects with a low body-weight. In reply, the applicant showed that the percentage of subjects with a high body weight (≥90 kg) was relatively low (~12%) and the highest body weight was 128 kg. Patients with a high bodyweight had on average a 20-25% higher ramucirumab exposure, however, there was a great overlap in exposures with patients weighing <90 kg. To further evaluate if ramucirumab dosing should be adjusted for patients with a low body weight, a Cox regression analysis was completed and the relationship between body weight and OS and PFS was assessed. Bodyweight was not a prognostic factor for OS and PFS

and increasing body weight did not appear to increase the safety risk for all 3 selected safety events. In conclusion, dose adjustment for high or low body weight is not considered necessary.

Hepatic impairment was not a significant covariate in the popPK model. However, only 1% of the population had moderate hepatic impairment and no subjects with severe hepatic impairment were included in the popPK analyses. Hence, limited information on the effect of hepatic impairment on pharmacokinetics of ramucirumab is available (see section 4.4 of the SmPC). Liver failure any grade was higher in patients with the lowest two ramucirumab exposure quartiles, which may be related to the apparent interaction between clearance of monoclonal antibodies and health condition as further discussed below.

The relationship between ramucirumab exposure and OS was evaluated using Kaplan-Meier methods, Cox models, and case-matched control analysis for the REACH-2 population. Model-predicted trough concentration after first dose administration was selected for exposure-efficacy analysis. As only one dose of 8 mg/kg was investigated in this study, Ctrough, Cave and clearance are highly correlated. Ctrough following the first administration is considered an acceptable exposure measure to evaluate exposure-efficacy relations of ramucirumab in HCC, because mean PFS is being reached before steady-state has been reached, which would result in bias by drop-out of patients with an early PFS. Therefore, an exposure measure following the first ramucirumab administration is supported.

A positive association between ramucirumab exposure and OS was observed in REACH-2 over the range of exposures achieved by a dosage of 8 mg/kg given every 2 weeks. Patients with low ramucirumab exposure (Q1 and Q2) appeared to have a shorter survival than the placebo arm, while the quartiles with higher exposures (Q3 and Q4) demonstrated an association with longer survival. However, there was an imbalance in baseline factors, including prognostic factors, between the exposure quartiles: patients with poorer prognostic factors, including ECOG PS (1), macrovascular invasion, etiology of disease, C-P (6) had lower ramucirumab exposure. Multivariate and matched-control analyses for REACH-2 indeed indicated that the apparent shorter survival in patients with low exposure compared to placebo was due to imbalance in baseline factors; however, patients with the lowest ramucirumab exposures in Q1 and Q2 (highest ramucirumab clearance) had no benefit from ramucirumab treatment. Only patients with higher ramucirumab exposure had a longer survival than the matched placebo arm. It should be noted that factors such as presence of ascites, the cachexia-related factor weight loss, and baseline albumin were not reported or tested as covariates in the popPK analysis nor in the multivariate analysis. These factors were predictors for OS in another multivariate analysis submitted as part of the type II variation (EMEA/H/C/002829/II/0023/G) evaluating various dosing regimens (6 mg/kg QW, 8 mg/kg Q2W, 8 mg/kg Q3W and 12 mg/kg Q2W) for ramucirumab. Therefore, it is uncertain whether other unknown confounding factors could have contributed to the remaining relationship or whether this is a true exposure-response relationship.

It was discussed whether these findings meant that the ramucirumab dose of 8 mg/kg Q2W was not high enough to achieve effective ramucirumab exposures. This phenomenon of lower monoclonal antibody exposure in patients with risk factors for survival compared to subjects with better disease severity/health status has been observed for other monoclonal antibodies in treatment of cancer (cetuximab, bevacizumab, trastuzumab, ipilimumab, nivolumab, pembrolizumab; Azzopradi et al. 2011, Han et al. 2014, Cosson et al. 2014, Feng et al. 2013,Bajaj et al. 2017, Wang et al. 2017, Turner et al. 2018). For nivolumab and pembrolizumab, retrospective analyses of studies with more than one treatment dose, indicated that clearance rather than exposure was a significant predictor of overall survival (Bajaj et al. 2017, Wang et al. 2017, Turner et al. 2018). When evaluating a single dose, a steep exposure-effect relationship was observed, similar to the exposure-effect relationship of ramucirumab in REACH-2. However, when an antibody is not dosed at the flat part of the dose-response curve, increase of exposure may improve OS (as has been shown for ipilimumab [Feng et al. 2013, Ascierto et al. 2017]).

No dose-finding study was conducted for ramucirumab for the treatment of patients with advanced HCC. The same dose 8 mg/kg Q2W as has been approved for treatment of advanced gastric cancer was selected. At time of approval of MAA, it was uncertain whether ramucirumab was dosed at the flat part of the dose-response curve and a post-approval measure to evaluate various dosing regimen was requested. Recently, this post-approval measure (EMEA/H/C/002829/II/0023/G) has been evaluated comparing the 8 mg/kg Q2W dose with 12 mg/kg Q2W for combination with paclitaxel and monotherapy in advanced gastric cancer. A small numerical increase in OS was observed in patients treated with 12 mg/kg ramucirumab compared to 8 mg/kg in both the monotherapy study and in combination with paclitaxel in gastric cancer. The studies were, however, not powered for formal statistical comparisons of OS and the results were considered inconclusive.

In the REACH-2 study for HCC, a relevant exposure-efficacy association was observed for ramucirumab which showed that only patients with above-median exposure experienced an improvement in OS, compared to placebo, and these exposure-efficacy relationships remained after attempts to adjust for other prognostic factors. A treatment effect on PFS was observed for all exposure levels produced by 8 mg/kg ramucirumab given every 2 weeks (see section 5.2 of the SmPC).

Taking into consideration that the included population in REACH-2 is a selected population with a potentially relatively good disease severity/health status compared to the real life population with HCC after treatment with sorafenib, and that disease severity/health status interacts with ramucirumab clearance.

As data from trials of other monoclonal antibodies for cancer treatment report similar patterns of exposure-response relationships (cetuximab, bevacizumab, trastuzumab, ipilimumab, nivolumab, pembrolizumab), one might hypothesise that antibody clearance as predictor of overall survival might be generalizable to oncology treatment with monoclonal antibodies. It was discussed if and how ramucirumab exposure/clearance can be used as a biomarker to select the population who benefits most from this treatment. Irrespective of whether ramucirumab clearance is a true or a confounded factor, ramucirumab clearance is a strong predictive factor for OS. Ackowledging the potential hurdles to implement ramucirumab clearance as a biomarker for patient selection, in clinical practice, given that the same phenomenon of high monoclonal antibody clearance with poor survival probability is observed for other monoclonal antibodies in treatment of cancer, selection on the basis of antibody clearance may be considered for future applications.

Exposure-safety analyses showed that the incidence of Grade ≥3 hypertension was highest in patients with the highest ramucirumab exposure (see section 5.2 of the SmPC). This was in line with previous findings, and the AEs were manageable. There was no relationship between ramucirumab exposure and the incidence of other safety parameters, including Grade ≥3 fatigue, any grade and Grade ≥3 liver failure/liver injury, any grade and Grade ≥3 hepatic encephalopathy, and any grade and Grade ≥3 ascites. Liver failure any grade was higher in patients with the lowest two ramucirumab exposure quartiles, which is consistent with apparent interaction disease severity/health status and antibody clearance in oncology. These results were consistent results among the pooled REACH-2 and REACH and the entire ramucirumab-treated patient population.

There was no apparent relationship observed between ramucirumab exposure and dose modifications, although there was a higher percentage of dose modifications in the ramucirumab treatment group compared with the placebo treatment group.

Like most therapeutic proteins, ramucirumab should not metabolised by liver cytochrome P450 (CYP) or other drug-metabolizing enzymes, and is unlikely to have an effect on CYPs or other metabolizing enzymes in terms of inhibition or induction (Lobo et al. 2004). Therefore, ramucirumab is unlikely to have significant metabolism-based DDI.

Rates of treatment-emergent anti-drug antibodies and neutralizing antibodies in HCC were low and comparable to the rate of anti-drug antibody formation in the entire ramucirumab-treated patient

population. Infusion-related reactions did not occur more often in the anti-drug antibody positive population compared to the anti-drug antibody negative population. It is agreed that due to the low rate of formation of anti-drug antibodies,no conclusions could be drawn on the potential effect of anti-drug antibodies on PK or efficacy in HCC.

2.3.6. Conclusions on clinical pharmacology

No dose-response studies have been submitted for the requested HCC indication and hence there is uncertainty as to whether the selected dose of 8 mg/kg Q2W is optimal. A relevant exposure-efficacy association was demonstrated in HCC, which showed that only half of the patients (those with above-median exposure) appeared to benefit from ramucirumab treatment. This exposure-efficacy relationship remained after attempts to adjust for other prognostic factors.
Based on the observed exposure-response relationship in HCC, there is uncertainty whether patients with below-median exposure would benefit from ramucirumab treatment. While findings may be due to clearance still being confounded by prognosis despite the performed adjustments, it cannot be concluded from the presented findings whether the dose of ramucirumab in HCC is adequate for all patients in the proposed indication, and this remains an uncertainty. The MAH is encouraged to further investigate the optimal dose for ramucirumab in the applied indication.

2.4. Clinical efficacy

The pivotal study for this submission is REACH-2, a global, randomised (2:1), double-blind, placebo-controlled phase 3 study evaluating the efficacy and safety of ramucirumab 8 mg/kg IV Q2W as a single agent for the treatment of patients with HCC and a baseline AFP ≥400 ng/mL after prior sorafenib therapy.

Data from REACH, a global, randomised (1:1), double-blind phase 3 study of ramucirumab in HCC after prior sorafenib therapy, irrespective of baseline AFP level, were also included as a supportive study (Zhu et al. Lancet Oncol. 2015).

Supportive efficacy and safety data are included from Study JVBQ, a phase 2 study of ramucirumab as monotherapy in patients with HCC who had not received prior systemic therapy (Zhu et al. Clin Cancer Res. 2013). For completeness, a phase 1b Study I4T-CR-JVCQ (JVCQ) of ramucirumab in combination with 5-fluorouracil/folinic acid and oxaliplatin (FOLFOX4) in 8 patients with HCC who had not received prior systemic treatment, was also included (Table 2).

2.4.1. Dose response study

No dose-response studies have been submitted for the requested indication.

2.4.2. Main study

REACH-2 (I4T-MC-JVDE): 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

Methods

Study participants

Key inclusion criteria were as follows:

- The patient had a histopathologically or cytologically confirmed diagnosis of HCC. In the absence of a histologic confirmation, a diagnosis of cirrhosis and HCC with classical imaging characteristics was acceptable.
- The patient had a Child Pugh Class A score of <7 and stage C BCLC disease. Patients with stage B BCLC disease were eligible if their disease was not amenable or had become refractory to locoregional therapy.
- The patient had ≥1 measurable lesion per RECIST v. 1.1 that had not been previously treated with locoregional therapy. Patients with lesion(s) previously treated with locoregional therapy were eligible if the lesion was documented as progression and was measureable.
- The patient had received prior sorafenib treatment as the only systemic therapeutic intervention for advanced HCC for at least 14 days and had discontinued sorafenib treatment ≥14 days prior to randomisation. The patient experienced radiographically confirmed disease progression during or after discontinuation of sorafenib therapy or discontinued sorafenib treatment because of intolerance despite appropriate sorafenib management and supportive care.
- The patient had a baseline AFP ≥400 ng/mL, as determined by local laboratory testing.
- The patient had an ECOG PS of 0 or 1 and adequate organ function, including only mildly impaired renal function at worst (creatinine clearance ≥60 mL/min).
- The patient was at least 18 years of age or of an acceptable age according to local regulations and agreed to local requirements regarding methods and duration of contraception.

Key exclusion criteria were as follows:

- Patients with or who had previous fibrolamellar carcinoma or mixed hepatocellular cholangiocarcinoma.
- Patients with or who had a previous concurrent malignancy. Patients with carcinoma in situ of any origin and patients with prior malignancies who were in remission and whose likelihood of recurrence was very low were eligible for this study.
- Patients with documented brain metastases, leptomeningeal disease, or uncontrolled spinal cord compression.
- Patients with a history of hepatic encephalopathy or clinically meaningful ascites. Patients who were on a stable medical regimen (for ≥3 months) to manage ascites were eligible if they showed no evidence of ascites upon clinical examination that would require further intervention.
- Patients who had confirmed hepatorenal syndrome within 6 months prior to randomisation.
- Patients who had a liver transplant.
- Patients who were on systemic therapy with VEGF inhibitors or VEGFR inhibitors other than sorafenib for treatment of HCC.
- Patients who had received hepatic locoregional therapy (including radiation, surgery, hepatic arterial embolization, chemoembolization, radiofrequency ablation, cryoablation, or percutaneous ethanol injection) following sorafenib or within 28 days prior to randomisation. Use of locoregional therapy prior to sorafenib was allowed.
- Patients with a history of GI perforation and/or fistulae within 6 months prior to randomisation or a history of bowel obstruction, inflammatory enteropathy or extensive intestinal resection or Crohn's disease, ulcerative colitis, or chronic diarrhoea.
- Patients who had symptomatic congestive heart failure (New York Heart Association II-IV) or symptomatic or poorly controlled cardiac arrhythmia.
- Patients who had undergone major surgery within 28 days prior to randomisation, or subcutaneous venous access device placement within 7 days prior to first dose of study treatment were excluded, except if the procedure was minimally invasive and the investigator did not anticipate any significant bleeding.

- Patients who had experienced any arterial thromboembolic event (ATE), including myocardial infarction, unstable angina, cerebrovascular accident, or transient ischemic attack, within 6 months prior to randomisation.
- Patients who received chronic therapy with nonsteroidal anti-inflammatory agents or other anti-platelet agents prior to first dose of study treatment. Aspirin use at doses up to 100 mg/day was permitted.
- Patients who had uncontrolled hypertension prior to initiating study treatment, despite antihypertensive intervention.
- Patients who experienced any bleeding episode considered life-threatening, or any grade 3 or 4 GI/variceal bleeding episodes in the 3 months prior to randomisation requiring transfusion or endoscopic or operative intervention.
- Patient who had oesophageal or gastric varices that required immediate intervention or represented a high bleeding risk. Patients with evidence of portal hypertension or any prior history of variceal bleeding were required to have had endoscopic evaluation within the 3 months immediately prior to randomisation.

Treatments

A treatment cycle was defined for all patients as 2 weeks. On Day 1 of each cycle, each patient received 1 of the following treatments (based on the treatment group to which they were randomised). All patients received BSC.

- Arm A: Ramucirumab (8 mg/kg IV) over approximately 60 minutes;
- Arm B: Equivalent volume of placebo to 8 mg/kg ramucirumab (IV) over approximately 60 minutes.

The initial dose of ramucirumab or placebo was dependent upon the patient's baseline body weight in kilograms. Recalculation of this dose was required in the event of a greater than 10% change in body weight from the previous dose calculation; a ±5% variance in the administered dose from the calculated dose was allowed for ease of dose administration. Ramucirumab or placebo was administered every 2 weeks until disease progression, the development of unacceptable toxicity, noncompliance, withdrawal of consent by the patient, or until other criteria for treatment discontinuation were met.

Premedication with agents including histamine H1 antagonists such as diphenhydramine hydrochloride 50 mg (or equivalent) was required prior to administration of ramucirumab or placebo, with additional premedication provided at investigator discretion. Premedication with a histamine H1 antagonist (such as diphenhydramine), dexamethasone (or equivalent), and acetaminophen was required in the setting of a prior Grade 1 or 2 infusion-related reaction (IRR). Study treatment was discontinued in the setting of prior Grade ≥3 IRR.

Post-Discontinuation Anti-Cancer Therapy

Per protocol, there was no unblinding at the time of disease progression. The use of post-discontinuation anti-cancer therapy was not specified per protocol and, following study therapy discontinuation, patients could receive additional anti-cancer therapy at the discretion of the investigator.

Objectives

Primary Objective

The primary objective of this study was to compare OS for ramucirumab vs. placebo in patients with advanced HCC after intolerance or progression on prior sorafenib treatment.

Secondary Objectives

The secondary objectives of this study were to evaluate:

- PFS
- Time to radiographic progression (TTP)
- Objective response rate (ORR)
- Safety profile of ramucirumab
- Ramucirumab pharmacokinetics (PK)
- Immunogenicity of ramucirumab
- Time to deterioration in Functional Assessment of Cancer Therapy Hepatobiliary Symptom Index-8 (FHSI-8)
- Time to deterioration in ECOG PS
- Other patient-reported outcome (PRO) measures of disease-specific symptoms (FHSI-8) and health-related QoL (EuroQol 5 Dimensions 5-Level [EQ-5D-5L])

Exploratory Objectives

The exploratory objectives of this study were to investigate biomarkers relevant to ramucirumab, angiogenesis, and the disease state, and to correlate these markers to clinical outcome.

Outcomes/endpoints

Primary endpoint

The primary endpoint of the study was OS, defined as the time from the date of randomization to the date of death from any cause. If the patient was alive at the end of the follow-up period (at data cut-off for this report [15 March 2018]) or was lost to follow-up or withdrew consent, OS data was censored on the last date the patient was known to be alive.

Secondary endpoints

Secondary efficacy endpoints included PFS, TTP, and ORR. Assessment for response, according to RECIST and assessed by investigators was performed every 6 weeks (±3 days) randomization for the first 6 months, and every 9 weeks (±3 days) thereafter until there was radiographic documentation of PD.

Progression-Free Survival: defined as the time from the date of randomisation until the date of PD as determined by the investigator, or death due to any cause.

Time to Radiographic Progression: defined as the time from the date of randomization until the date of radiographic progression according to RECIST as determined by the investigator.

Objective Response Rate: calculated as the number of patients who achieve a best response of complete response (CR) or partial response (PR) using the investigator response assessments. The disease control rate (DCR) was calculated as the number of patients who achieve a best response of CR, PR, or stable disease (SD) using investigator response assessments.

Patient-Focused Outcomes: included disease-specific symptoms and health status, which were assessed using FHSI-8, ECOG PS, and EQ-5D-5L. The FHSI-8 and EQ-5D-DL were administered together with the FHSI-8 presented first, followed by presentation of the EQ-5D-5L.

Sample size

The sample size was determined based on the following assumptions:

- Hazard ratio (treatment/control) of 0.67, with median OS of 4.5 months in the placebo arm and 6.7 months in the ramucirumab arm
- Randomisation ratio of 2:1 (ramucirumab:placebo)

- Overall significance level controlled at 1-sided 0.025 (2-sided 0.05)
- Type II error rate of 20%.

The study was planned to randomise approximately 279 patients (that is, 20% censoring rate including dropouts, with approximately 186 patients randomised to the ramucirumab arm and 93 patients randomised to the placebo arm) to achieve at least 221 deaths.

Randomisation

Upon completion of all screening evaluations, to confirm a patient's eligibility, the site registered the patient via the interactive web response system (IWRS). Randomisation was stratified by the following factors:

- Geographic region (Region 1: Americas, Europe, Israel, and Australia vs. Region 2: Asia [except Japan] vs. Region 3: Japan)
- Macrovascular invasion (yes vs. no)
- ECOG PS (0 vs. 1)

Blinding (masking)

The study was a double-blind study. Patients, investigators, and all other personnel involved in the conduct of the study were blinded to individual treatment assignments for the duration of the study. Unblinding did not occur until the reporting database was validated and locked for final statistical analysis. Unblinding occurred on 23 March 2018.

Statistical methods

The analysis of OS was based on a log-rank test, stratified by randomization strata (geographic region, macrovascular invasion, ECOG PS) collected by interactive web response system [IWRS]). Additionally, OS curves were presented using the Kaplan-Meier method by treatment arm, together with a summary of associated statistics. The HR and its two-sided 95% confidence interval (CI) were estimated using a stratified Cox regression model. An exploratory restricted mean survival analysis was performed.
A gatekeeping approach to selected secondary endpoints was applied to protect the study-wise Type I error rate and to enable inferential statements; each hypothesis was inferentially tested only if each of the preceding hypotheses were rejected. The sequential order of the confirmatory testing after OS in the intent-to-treat (ITT) population was: (1) PFS; (2) Time to deterioration (TTD) on FHSI-8; and (3) TTD on ECOG PS.

The following sensitivity analyses on OS were performed:

- Analysis of OS based on the PP population
- Analysis of OS in the ITT population with an unstratified log-rank test
- Stratified analysis of OS in the ITT population using stratification factors as reported in the eCRF
- Analysis of OS in the ITT population with baseline AFP ≥400 ng/mL based on central laboratory result
- An analysis of OS adjusting the treatment effect for significant prognostic factors.

Secondary endpoints were analysed at the same level of significance as OS.
Progression-free survival (PFS) and time to radiographic progression (TTP) was similarly analysed as OS. The ORR and DCR observed in each treatment arm were compared using exact Cochran-Mantel-Haenszel test adjusting for the stratification variables as captured by IWRS. Patients who did not have a tumour response assessment for any reason were considered non-responders and were included in the denominator

when calculating the ORR or DCR. Frequencies for best overall response were presented by treatment arm, as well as ORR and DCR observed in each treatment arm together with 95% CI.

The PFS censoring rules are shown below in **Table 9**.

Table 9: PFS censoring rules

Situation	Event / Censor	Date of Event or Censor
Tumor progression or death	Event	Earliest date of PD or death
No tumor progression and no death	Censored	Date of last adequate radiological assessment or date of randomization (whichever is later)
unless		
No baseline radiological tumor assessment available	Censored	Date of randomization
No adequate post baseline radiological tumor assessment available and death reported after 2 scan intervals following randomization	Censored	Date of randomization
New anticancer treatment started and no tumor progression or death within 14 days	Censored	Date of adequate radiological assessment prior to (start of new therapy +14 days) or date of randomization (whichever is later)
Tumor progression or death documented immediately after 2 or more scan intervals following last adequate radiological tumor assessment or randomization (whichever is later)	Censored	Date of last adequate radiological assessment or date of randomization (whichever is later)

Abbreviations: CR = complete response; PD = progressive disease; PFS = progression-free survival; PR = partial response; SD = stable disease.

Notes:

1. Clinical progression (that is, symptomatic progressions, which are not radiologically confirmed) will not be considered as progressions.
2. Adequate radiological tumor assessment refers to an assessment with one of the following responses: CR, PR, SD, or PD.
3. If target, non-target and new lesion assessments have different dates within a visit, then the earliest of those dates will be considered as the date of the tumor assessment if the assessment for that visit is PD; otherwise, the latest date will be used.

In sensitivity analyses on PFS, only one alternative rule was applied as listed below in Table 10, the other rules were as above.

Table 10: PFS sensitivity analyses

Sensitivity Analysis	Situation	Date of Progression or Censor	Outcome
Count clinical progression as progression	Documented progression or clinical progression	Date of documented progression (New Lesion, Unequivocal Progression of Non-Target Lesion, or Progression of Target Lesion). If a tumor assessment was performed on multiple days, use the earliest date for that visit. Or date of clinical progression, whichever occurred first.	Progressed
Ignore new anticancer treatment	New therapeutic anticancer treatment started prior to documented progression or death	Date of progression or death based on subsequent tumor assessments	Progressed
Ignore missing tumor assessments	Death or documented progression after ≥ two consecutively missed tumor assessment visits	Date of first scheduled tumor assessment within the time period of the consecutively missed visits	Progressed
Treat lost to follow up as progression (worst case scenario)	Patient lost to follow-up without documented progression or death	Date of next scheduled tumor assessment after last tumor assessment	Progressed

Abbreviation: PFS = progression-free survival.

Missing data in EQ-5D-5L and FHSI-8 were investigated using the following imputations: last observation carried forward, worst observation carried forward, and multiple imputation using Markov Chain Monte Carlo methodology.

Results

Participant flow

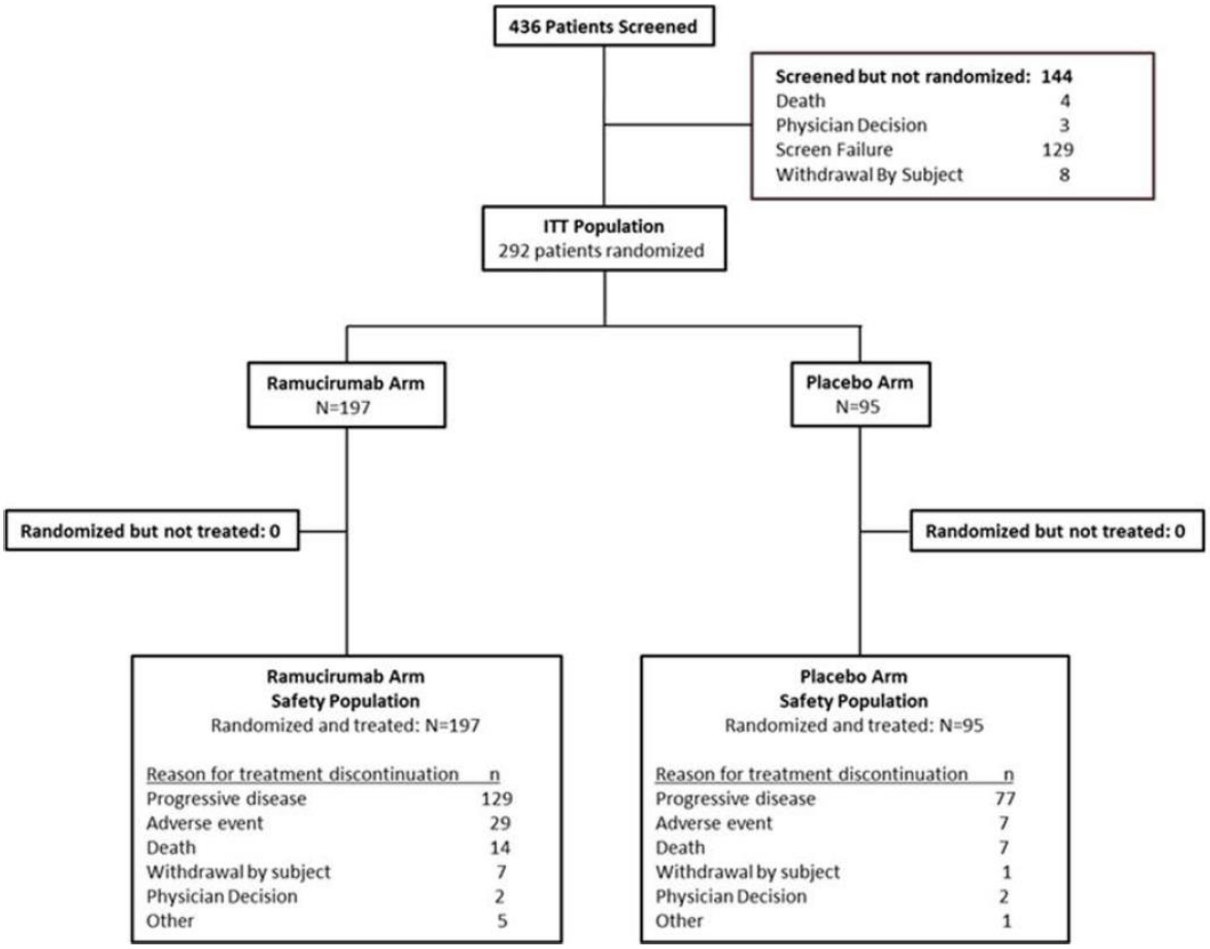


Figure 4: Patient flow

Recruitment

This study was conducted at 92 investigative sites in 20 countries, in three main geographic regions.

Region 1 included: Australia, Brazil, Canada, Europe (Austria, Belgium, Czech Republic, France, Germany, Italy, Poland, Spain, Switzerland, and United Kingdom), Israel, and the United States; region 2 included: Asian countries except Japan (China, Hong Kong, Korea, and Taiwan); and region 3 included Japan only.

Conduct of the study

Protocol deviations

Important protocol deviations are summarised in Table 11. A total of 41 (14.0%) randomised patients were reported to have important protocol deviations, including 30 (15.2%) patients in the ramucirumab arm and 11 (11.6%) patients in the placebo arm. The most common category of deviations was important dose

modifications not performed per protocol (ramucirumab arm vs. placebo arm: 4.6% vs. 3.2%). Violations of at least 1 IC/EC were reported for 6.6% and 5.3% of patients in the ramucirumab arm and placebo arm, respectively. The majority of significant premedication errors were a result of premedication (histamine H1 antagonist) not being administered to the patient prior to the infusion of ramucirumab/placebo by the site.

Table 11: Summary of Important Protocol Deviations

Deviation Category/ Deviation Subcategory	Ram + BSC N = 197 n (%)	Placebo + BSC N = 95 n (%)	Total N = 292 n (%)
Any Important Protocol Deviation	30 (15.2)	11 (11.6)	41 (14.0)
Exclusion Criteria Met but Enrolled[a]	5 (2.5)	2 (2.1)	7 (2.4)
Exclusion criterion 18	2 (1.0)	0	2 (0.7)
Exclusion criterion 20	1 (0.5)	1 (1.1)	2 (0.7)
Exclusion criterion 23	1 (0.5)	0	1 (0.3)
Exclusion criterion 24	1 (0.5)	0	1 (0.3)
Exclusion criterion 40	0	1 (1.1)	1 (0.3)
Inclusion Criteria Not Met but Enrolled[a]	8 (4.1)	3 (3.2)	11 (3.8)
Inclusion criterion 04	1 (0.5)	0	1 (0.3)
Inclusion criterion 09	1 (0.5)	1 (1.1)	2 (0.7)
Inclusion criterion 12	1 (0.5)	1 (1.1)	2 (0.7)
Inclusion criterion 13	1 (0.5)	0	1 (0.3)
Inclusion criterion 33	4 (2.0)	1 (1.1)	5 (1.7)
Investigational Product	16 (8.1)	5 (5.3)	21 (7.2)
Important dose modifications not performed per protocol	9 (4.6)	3 (3.2)	12 (4.1)
Infusion of study treatment at rate greater than 25 mg/min	0	1 (1.1)	1 (0.3)
Significant premedication errors	7 (3.6)	1 (1.1)	8 (2.7)
Unacceptable drug related toxicity but not discontinued from study treatment	1 (0.5)	0	1 (0.3)
Study Procedures	4 (2.0)	1 (1.1)	5 (1.7)
Inadequate monitoring of vital signs	3 (1.5)	1 (1.1)	4 (1.4)
Laboratories important to ensure patient safety were not adequately assessed	1 (0.5)	0	1 (0.3)

Abbreviations: BSC = best supportive care; ITT = intent-to-treat; N = number of randomized patients; n = number of patients in category; Ram = ramucirumab.

[a] For the complete list of inclusion and exclusion criteria, refer to Section 7.1 and 7.2 of the protocol, provided in an appendix to this report (Protocol and Addenda).

Protocol amendments

The original protocol was approved on 20 February 2015. The protocol was amended 3 times: Amendment (a) on 06 October 2015, Amendment (b) on 13 May 2016, and Amendment (c) on 24 April 2017. Important changes made in the protocol amendments are summarised in the sections below.

Protocol Amendment (a)

- Revisions of inclusion criteria to allow patients to enter the study if they had a lesion(s) which had previously been treated with locoregional therapy, if the lesion had documented progression after locoregional treatment and was measureable
- Discontinuation criterion added if a patient became pregnant while on study treatment
- Patient registration and stratification were changed to being collected via the IWRS

Protocol Amendment (b)

- The addition of an interim analysis for unequivocal efficacy, which was planned to be conducted when approximately 60% of the planned OS events (191 events) were observed in the ITT

population, with a planned nominal significance level for the efficacy analysis of 0.0044 (2-sided). This interim analysis was not performed.

Protocol Amendment (c)

Important changes included:

- Removal of the interim analysis of efficacy to consolidate to a single final OS analysis with a power of 80% and using an OS HR assumption of 0.67, resulting in a study size reduction from 399 to 279 patients.

Changes in the Planned Analyses

The SAP (version 2) was finalised prior to the database lock and all statistical analyses followed the SAP, with the following exceptions to accommodate the data in the final locked database. Given that baseline AFP was one of the most important prognostic factors, and median baseline AFP was imbalanced between the 2 treatment arms in the locked database, the following additional analyses adjusting for baseline AFP (as a continuous variable with log10- transformation) were to be conducted:

1) Analyses of OS adjusting for baseline AFP with Cox models (stratified and unstratified), as well as adjusted Kaplan-Meier curves with median OS estimates at the mean.
2) For the stepwise analysis adjusting for covariates, an additional analysis was performed to include baseline AFP in the covariate selection.

Baseline data

The patient and disease characteristics of the population enrolled in the main study are shown in the tables below.

Table 12: Patient Demographic and Baseline Characteristics (ITT population)

Parameter	Ram + BSC (N = 197)	Placebo + BSC (N = 95)	Total (N = 292)
Sex, n (%)			
Male	154 (78.2)	79 (83.2)	233 (79.8)
Female	43 (21.8)	16 (16.8)	59 (20.2)
Age (years)			
Median age (range)	64 (30-88)	64 (26-85)	64 (26-88)
Age group, n (%)			
Age <65 years	102 (51.8)	49 (51.6)	151 (51.7)
Age ≥65 years	95 (48.2)	46 (48.4)	141 (48.3)
Age 65 to <75 years	58 (29.4)	35 (36.8)	93 (31.8)
Age ≥75 years	37 (18.8)	11 (11.6)	48 (16.4)
Age 75 to <85 years	35 (17.8)	10 (10.5)	45 (15.4)
Age ≥85 years	2 (1.0)	1 (1.1	3 (1.0)
Race, n (%)			
Asian	102 (51.8)	45 (47.4)	147 (50.3)
Black or African American	1 (0.5)	1 (1.1)	2 (0.7)
White	60 (30.5)	31 (32.6)	91 (31.2)
Multiple	0	1 (1.1)	1 (0.3)
Missing[a]	34 (17.3)	17 (17.9)	51 (17.5)
Ethnicity, n (%)			
Hispanic or Latino	12 (6.1)	9 (9.5)	21 (7.2)
Non Hispanic or Latino	129 (65.5)	58 (61.1)	187 (64.0)
Not Applicable[b]	56 (28.4)	28 (29.5)	84 (28.8)
ECOG PS, n (%)			
0	113 (57.4)	55 (57.9)	168 (57.5)
1	84 (42.6)	40 (42.1)	124 (42.5)
Geographic Region[c], n (%)			
Region 1	101 (51.3)	50 (52.6)	151 (51.7)
Region 2	55 (27.9)	27 (28.4)	82 (28.1)
Region 3	41 (20.8)	18 (18.9)	59 (20.2)

Abbreviations: BSC = best supportive care; CRF = case report form; ECOG PS = Eastern Cooperative Oncology Group performance status; ITT = intent-to-treat; N = total population size; n = number of patients; Ram = ramucirumab.

Note: All variables are based on CRF data.

[a] Race of patients from France was not collected.

[b] Ethnicity was not required to be collected outside of the United States. Electronic case report form instructions stated "if the information was not provided by the subject, please enter 'not applicable'."

[c] Region 1: Australia, Brazil, Canada, Europe (Austria, Belgium, Czech Republic, France, Germany, Israel, Italy, Poland, Spain, Switzerland, and United Kingdom), and the United States. Region 2: Asian countries (China, Hong Kong, Korea, and Taiwan). Region 3: Japan only.

Table 13: Summary of Baseline Disease Characteristics (ITT population)

Parameter	Ram + BSC (N = 197)	Placebo + BSC (N = 95)	Total (N = 292)
Duration of Disease (months)[a]			
n	195	94	289
Mean (SD)	33.43 (40.92)	29.26 (31.54)	32.08 (38.12)
Median	20.14	17.64	18.27
Min – Max	2.27-259.68	1.12-160.10	1.12-259.68
Baseline Child-Pugh Score, n (%)			
A - 5 points	123 (62.4)	54 (56.8)	177 (60.6)
A - 6 points	74 (37.6)	41 (43.2)	115 (39.4)
Baseline BCLC Score, n (%)			
Stage B	34 (17.3)	20 (21.1)	54 (18.5)
Stage C	163 (82.7)	75 (78.9)	238 (81.5)
Etiology of Liver Disease[b]			
Hepatitis B	71 (36.0)	36 (37.9)	107 (36.6)
Hepatitis C	48 (24.4)	28 (29.5)	76 (26.0)
Significant Prior Alcohol Use	48 (24.4)	21 (22.1)	69 (23.6)
Steatohepatitis (NASH, Fatty Liver)	19 (9.6)	4 (4.2)	23 (7.9)
Hemachromatosis	1 (0.5)	0	1 (0.3)
Primary Biliary Cirrhosis	2 (1.0)	2 (2.1)	4 (1.4)
Hepatitis A	0	1 (1.1)	1 (0.3)
Hepatitis, Non-A, Non-B, Non-C	2 (1.0)	1 (1.1)	3 (1.0)
Cryptogenic Cirrhosis	12 (6.1)	4 (4.2)	16 (5.5)
Other	12 (6.1)	3 (3.2)	15 (5.1)
Number of Organs with HCC Metastases, n (%)			
0	60 (30.5)	29 (30.5)	89 (30.5)
1	85 (43.1)	38 (40.0)	123 (42.1)
2	43 (21.8)	21 (22.1)	64 (21.9)
≥3	9 (4.6)	7 (7.4)	16 (5.5)
Macrovascular Invasion Present			
Yes	70 (35.5)	33 (34.7)	103 (35.3)
No	127 (64.5)	62 (65.3)	189 (64.7)
Extrahepatic Spread Present			
Yes	141 (71.6)	70 (73.7)	211 (72.3)
No	56 (28.4)	25 (26.3)	81 (27.7)
Baseline Alpha-fetoprotein (ng/mL)[c]			
Median (Q1, Q3)	3920.0 (1175.0, 20000.0)	2741.0 (1178.0, 11681.0)	3394.0 (1176.5, 16811.5)
Min – Max	408-230500	419-473163	408-473163

Abbreviations: AFP = alpha-fetoprotein; BCLC = Barcelona Clinic Liver Cancer; BSC = best supportive care; HCC = hepatocellular carcinoma; ITT = intent-to-treat; Max = maximum; Min = minimum; N = number of randomized patients; n = number of patients in category; NASH = nonalcoholic steatohepatitis; Q = quartile; Ram = ramucirumab; SD = standard deviation.

a Duration of disease is the time from date of initial diagnosis to date of randomization.

b More than 1 etiology may be reported per patient.

c AFP was based on local lab results, except central lab results were used for 1 patient whose local baseline results were not available.

Table 14: Summary of Prior Anti-Cancer Treatment (ITT population)

Parameters	Ram + BSC (N=197)	Placebo + BSC (N=95)	Total (N=292)
Prior locoregional therapy for HCC, n (%)			
Yes[a]	127 (64.5)	59 (62.1)	186 (63.7)
TACE	104 (52.8)	51 (53.7)	155 (53.1)
Radiofrequency ablation	35 (17.8)	19 (20.0)	54 (18.5)
Prior anti-cancer therapy, n (%)			
Surgical procedure	87 (44.2)	39 (41.1)	126 (43.2)
Radiotherapy	36 (18.3)	19 (20.0)	55 (18.8)
Systemic therapy	197 (100.0)	95 (100.0)	292 (100.0)
Reason for discontinuation of sorafenib, n (%)			
Progressive Disease	166 (84.3)	76 (80.0)	242 (82.9)
Intolerance	31 (15.7)	19 (20.0)	50 (17.1)
Duration of prior sorafenib treatment, n (%)			
<5 months	110 (55.8)	57 (60.0)	167 (57.2)
≥5 months	87 (44.2)	38 (40.0)	125 (42.8)
Time from last sorafenib treatment to randomization, n (%)			
<1 months	102 (51.8)	54 (56.8)	156 (53.4)
≥1 months	95 (48.2)	41 (43.2)	136 (46.6)

Abbreviations: BSC = best supportive care; HCC = hepatic cell carcinoma; ITT = intent-to-treat; N = number of randomized patients; n = number of patients in category; Ram = ramucirumab; TACE = transarterial chemoembolization.

[a] Includes percutaneous ethanol injection, microwave ablation, and other therapies in addition to those presented in this table (TACE and radiofrequency ablation). Table JVDE.14.24 provides a complete set of data.

Numbers analysed

Data cut-off occurred on 15 March 2018 after 221 OS events were observed in the ITT population. The reporting database was validated and subsequently locked for analysis on 23 March 2018. Primary and secondary efficacy endpoints were analysed using the ITT population (with allocation of patients to treatment arms considered as "randomised"). The ITT population (N = 292 patients) included 197 patients randomised to receive ramucirumab plus BSC and 95 patients randomised to receive placebo plus BSC.

Outcomes and estimation

Primary endpoint (overall survival)

Overall survival data and the Kaplan-Meier plot of OS for the ITT population are shown in Table 15 and Figure 5, respectively.

Table 15: Summary of Overall Survival (ITT population, primary endpoint)

	Ram + BSC (N = 197)	Placebo + BSC (N = 95)	Treatment Difference
Number of deaths, n (%)	147 (74.6)	74 (77.9)	
Number censored, n (%)	50 (25.4)	21 (22.1)	
Median survival – months (95% CI)	8.51 (7.00, 10.58)	7.29 (5.42, 9.07)	1.22
Log-rank p-value (2-sided)			
Stratified[a]	0.0199		
Unstratified	0.0408		
Hazard ratio (95% CI)			
Stratified[a]	0.710 (0.531, 0.949)		
Unstratified	0.744 (0.561, 0.988)		
Survival rate, % (95% CI)[b]			
3-month	88.2 (82.8, 92.0)	84.7 (75.6, 90.7)	3.5 (-5.1, 12.2)
6-month	62.1 (54.9, 68.5)	56.5 (45.6, 66.0)	5.6 (-6.8, 17.9)
12-month	36.8 (29.8, 43.8)	30.3 (20.8, 40.3)	6.5 (-5.6, 18.6)
18-month	24.5 (18.0, 31.6)	11.3 (4.6, 21.5)	13.2 (2.2, 24.2)
21-month	17.1 (11.1, 24.3)	4.2 (0.5, 15.6)	12.9 (3.1, 22.7)
24-month	10.2 (4.6, 18.3)	0	10.2 (- , -)

Abbreviations: BSC = best supportive care; CI = confidence interval; ITT = intent-to-treat; N = number of randomized patients; n = number of patients in category; Ram = ramucirumab.

Note: Medians and survival rates, along with 95% CIs, were estimated using the Kaplan-Meier method. Hazard ratio and 95% CI (Wald) were estimated using the Cox model.

a Primary analysis; Stratified by the randomization strata (ie, geographical region; macrovascular invasion, ECOG PS).

b 95% CIs for treatment difference were calculated using a normal approximation.

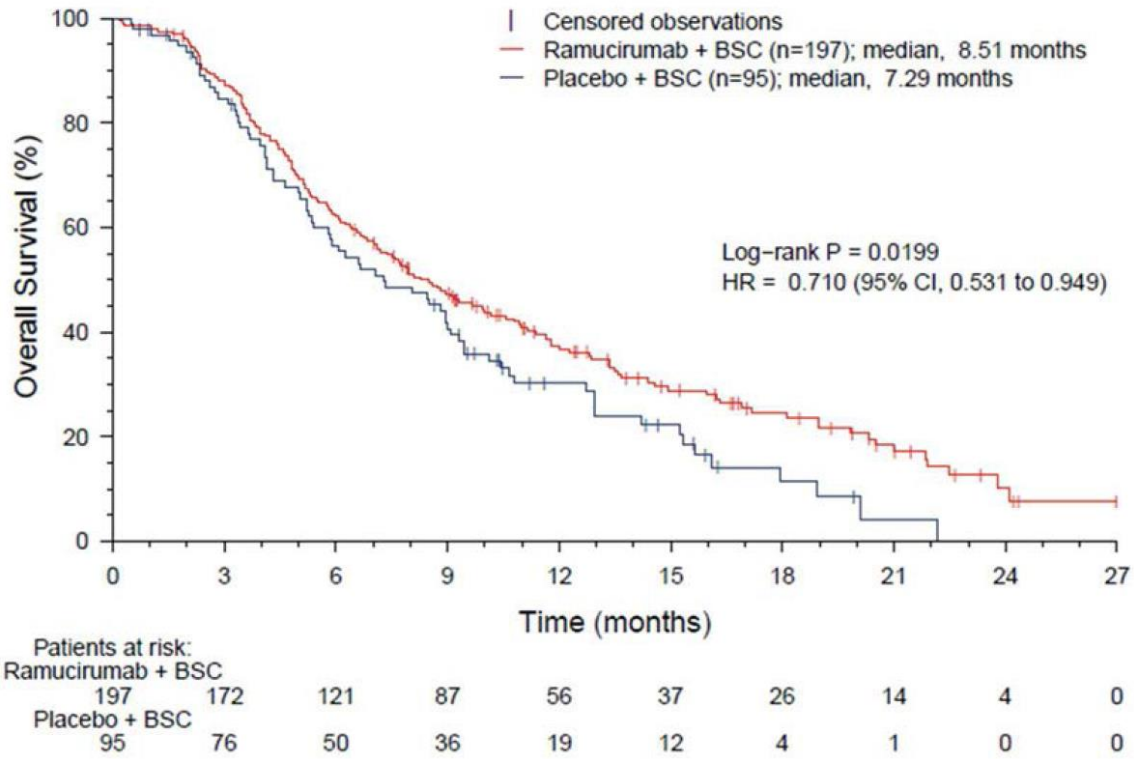


Figure 5: Overall survival on ITT population (primary endpoint)

Secondary endpoints

Progression-free survival

Table 16 summarises PFS data and Figure 7 displays the Kaplan-Meier plot of PFS for the ITT population.

Table 16: Summary of Progression-Free Survival (ITT population)

	Ram + BSC (N = 197)	Placebo + BSC (N = 95)	Treatment Difference
Number of events, n (%)	172 (87.3)	86 (90.5)	
Number censored, n (%)	25 (12.7)	9 (9.5)	
Median PFS – months (95% CI)	2.83 (2.76, 4.11)	1.61 (1.45, 2.69)	1.22
Restricted Mean			
Log-rank p-value (2-sided)			
Stratified[a]		<0.0001	
Unstratified		<0.0001	
Hazard ratio (95% CI)			
Stratified[a]		0.452 (0.339, 0.603)	
Unstratified		0.469 (0.357, 0.616)	
PFS rate, % (95% CI)[b]			
1.5-month	73.1 (66.3, 78.8)	54.4 (43.6, 64.0)	18.7 (6.7, 30.8)
3-month	47.6 (40.4, 54.5)	19.1 (11.5, 28.1)	28.6 (17.6, 39.6)
6-month	25.8 (19.7, 32.3)	6.4 (2.4, 13.1)	19.5 (11.2, 27.8)
9-month	16.2 (11.2, 22.0)	0.0 (- , -)	16.2 (- , -)
12-month	8.3 (4.6, 13.4)	0.0 (- , -)	8.3 (- , -)

Abbreviations: BSC = best supportive care; CI = confidence interval; ECOG = Eastern Cooperative Oncology Group; ITT = intent to treat; N = number of randomized patients; n = number of patients in category; PFS = progression-free survival; PS = performance status; Ram = ramucirumab.

Note: Medians, and survival rates, along with 95% CIs, were estimated using the Kaplan-Meier method. Hazard ratio and 95% CI (Wald) were estimated using the Cox model.

a Stratified by the randomization strata (geographical region, macrovascular invasion, and ECOG PS).

b 95% CI and p-value for treatment effect/difference were calculated using a normal approximation.

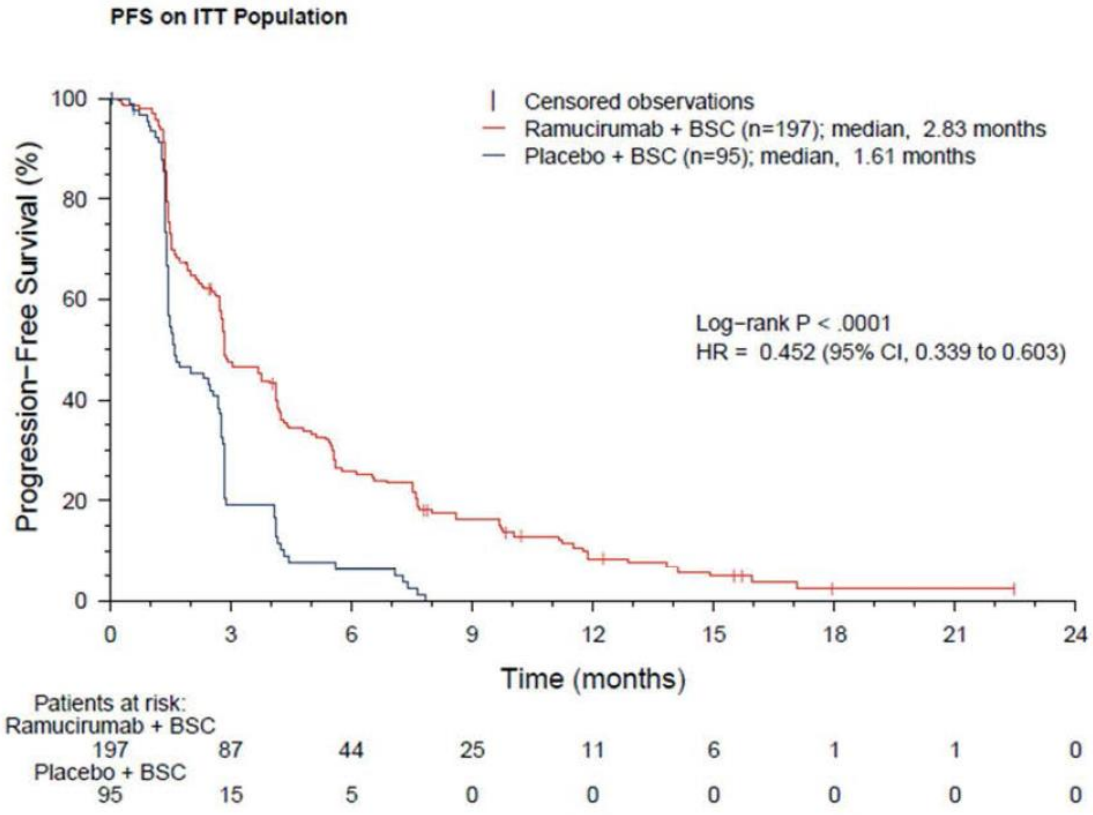


Figure 6: Progression-free survival (ITT population)

Time to Radiographic Progression

Treatment with ramucirumab reduced the hazard of radiographic progression by 57.3% (HR = 0.427; 95% CI: 0.313, 0.582; p<0.0001), with a 1.41-month longer median TTP in the ramucirumab arm over the placebo arm (3.02 vs. 1.61 months, respectively). The 1.5-, 3-, and 6-month radiographic progression-free rates were (ramucirumab vs. placebo) 74.2% vs. 55.2%, 50.4% vs. 19.9%, and 30.5% vs. 7.7%, respectively.

Objective response rate

Table 17: Summary of results for objective response rate

	Ram + BSC (N = 197) n (%)	Placebo +BSC (N = 95) n (%)	p-Value*
Best overall response[a]			
Complete response (CR)	0 (0)	0 (0)	
Partial response (PR)	9 (4.6)	1 (1.1)	
Stable disease (SD)	109 (55.3)	36 (37.9)	
Progressive disease (PD)	66 (33.5)	48 (50.5)	
Non-evaluable	13 (6.6)	10 (10.5)	
Objective response (CR+PR) rate			
ORR, n (%)	9 (4.6)	1 (1.1)	
(95% CI)[b]	(1.7 - 7.5)	(0.0 - 3.1)	
Odds ratio (95% CI)[c]	4.6 (0.6 - 37.3)		0.1697
Disease control (CR+PR+SD) rate			
DCR, n (%)	118 (59.9)	37 (38.9)	
(95% CI)[b]	(53.1 - 66.7)	(29.1 - 48.8)	
Odds ratio (95% CI)[c]	2.4 (1.4 - 4.0)		0.0006

Abbreviations: BSC = best supportive care; CI = confidence interval; DCR = disease control rate; ECOG = Eastern Cooperative Oncology Group; IWS = interactive web response system; N = total population size; n = number of patients; ORR = objective response rate; PS = performance status; Ram = ramucirumab; RECIST = Response Evaluation Criteria In Solid Tumors.

a Response criteria used was RECIST v 1.1.

b Confidence intervals are based on normal approximation.

c Stratified by Geographical Region (IWRS), Macrovascular invasion (IWRS), ECOG PS at Baseline (IWRS)

d p-value is calculated by Exact Cochran-Mantel-Haenszel test stratified by the randomization strata geographical region (IWRS), macrovascular invasion (IWRS), and ECOG PS at baseline (IWRS).

Patient-focused outcomes – FHSI-8 Analyses

In Table 18 the results are shown of the measurements using the FHSI-8 instrument.

Table 18: Summary of FHSI-8 – Time to First Deterioration

	Ram +BSC N = 197				Placebo + BSC N = 95				Hazard Ratio[a]		Log Rank
Criteria for Deterioration	n	Censored/ Events[a]	Median (months)[b]	95% CI	n	Censored/ Events[a]	Median (months)[b]	95% CI[c]	HR[c]	95% CI	p-Value
Time to Deterioration of FHSI-8 by 3 pts	197	96/101	3.71	(2.79, 4.40)	95	53/42	2.79	(1.64, 2.89)	0.799	(0.545, 1.171)	0.2382
Time to Deterioration of FHSI-8 by 2 pts	197	84/113	2.83	(1.61 ,4.17)	95	50/45	1.84	(1.48, 2.89)	0.875	(0.607, 1.261)	0.4615
Time to Deterioration of FHSI-8 by 4 pts	197	117/80	4.73	(4.17, 7.89)	95	40/35	2.89	(2.60, 4.37)	0.746	(0.486, 1.146)	0.1625

Abbreviations: BSC = best supportive care; CI = confidence interval; ECOG PS = Eastern Cooperative Oncology Group performance status; FHSI-8 = Functional Assessment of Cancer Therapy Hepatobiliary Symptom Index-8; HR = hazard ratio; ITT = intent-to-treat; n = number of patients in censored; N = number of randomized patients; pts =points; Ram = ramucirumab.

a Patients without any postbaseline assessments were censored at the randomization date.

b Estimated by the Kaplan-Meier method.

c Patients without any postbaseline assessments were censored at the randomization date.

Patient-focused outcomes – Time to Deterioration in ECOG Performance Status

Table 19 shows the results of the analysis of time to deterioration in ECOG PS.

Table 19: Summary of Time to Deterioration in ECOG Performance Status

	Ram + BSC N = 197				Placebo + BSC N = 95				Hazard Ratio[a]		Log Rank
Criteria for Deterioration	n	Censored/ Events[b]	Median (months)[c]	95% CI[c]	n	Censored/ Events[b]	Median (months)[c]	95% CI	HR	95% CI	p-Value
Deterioration to ECOG PS ≥ 2	197	141/56	NA	(9.33, NA)	95	75/20	NA	(5.26, NA)	1.082	(0.639, 1.832)	0.7671
Deterioration to ECOG PS ≥ 3	197	186/11	NA	NA	95	86/9	NA	NA	0.354	(0.135, 0.930)	0.0275
ECOG PS Deterioration by ≥ 2 Levels	197	170/27	NA	NA	95	81/14	NA	NA	0.625	(0.315, 1.239)	0.1762

Abbreviations: BSC = best supportive care; CI = confidence interval; ECOG = Eastern Cooperative Oncology Group; HR = hazard ratio; ITT = intent-to-treat; n = number of patients in censored; N = number of randomized patients; NA = not applicable (unable to estimate); PS = performance status; Ram = ramucirumab.

a Hazard ratio and 95% CI (Wald) were estimated using a stratified Cox model.

b Patients without any postbaseline assessments were censored at the randomization date.

c Estimated by the Kaplan-Meier method.

Patient-focused outcomes – EQ-5D-5L Analyses

In Table 20 and Table 21 the results of the analysis using EQ-5D-5L index and VAS are shown for the first 19 weeks.

Table 20: Summary of EQ-5D Index by Visit (up to week 19)

			LY3009806+BSC (N=197)		Placebo+BSC (N=95)	
Parameter	Visit		Actual Scores	Change from Baseline	Actual Scores	Change from Baseline
EQ-5D index	BASELINE	n	193		95	
		Mean	0.863		0.873	
		SD	0.138		0.149	
		Median	0.893		0.924	
		Minimum	0.226		0.330	
		Maximum	1.000		1.000	
	WEEK7	n	136	135	48	48
		Mean	0.825	-0.050	0.848	-0.043
		SD	0.201	0.163	0.209	0.128
		Median	0.878	-0.006	0.912	0.000
		Minimum	-0.178	-1.029	-0.016	-0.625
		Maximum	1.000	0.314	1.000	0.218
	WEEK13	n	95	93	22	22
		Mean	0.850	-0.029	0.868	-0.021
		SD	0.161	0.112	0.179	0.147
		Median	0.893	0.000	0.910	0.000
		Minimum	0.010	-0.321	0.162	-0.447
		Maximum	1.000	0.380	1.000	0.259
	WEEK19	n	65	65	11	11
		Mean	0.877	-0.002	0.827	-0.039

Cutoff Date: 2018-03-15.
Abbreviations: N = number of subjects in Intent-to-Treat Population; n = number of subjects in the specified category;
EQ-5D = EuroQol 5-Dimension 5-Level, VAS = visual analogue scale.
SD = standard deviation.
Note: A visit window of scheduled visit date +/- 3 weeks is applied. If there are multiple assessment within 1 visit window, the last assessment is used for calculation.

Table 21: Summary of EQ-5D VAS by Visit (up to week 19)

Parameter	Visit		LY3009806+BSC (N=197) Actual Scores	LY3009806+BSC (N=197) Change from Baseline	Placebo+BSC (N=95) Actual Scores	Placebo+BSC (N=95) Change from Baseline
EQ-5D VAS	BASELINE	n	195		95	
		Mean	74.656		73.263	
		SD	17.416		16.025	
		Median	80.000		75.000	
		Minimum	20.000		3.000	
		Maximum	100.000		100.000	
	WEEK7	n	136	136	49	49
		Mean	73.522	-2.750	69.327	-5.061
		SD	18.442	14.887	22.568	20.443
		Median	75.000	0.000	70.000	-5.000
		Minimum	20.000	-50.000	25.000	-50.000
		Maximum	100.000	40.000	100.000	47.000
	WEEK13	n	95	94	22	22
		Mean	73.989	-1.617	72.955	-1.273
		SD	16.460	14.081	16.666	21.211
		Median	75.000	0.000	80.000	-5.000
		Minimum	10.000	-54.000	35.000	-35.000
		Maximum	100.000	49.000	95.000	47.000
	WEEK19	n	65	65	11	11
		Mean	73.446	-3.138	73.636	4.727

Cutoff Date: 2018-03-15.
Abbreviations: N = number of subjects in Intent-to-Treat Population; n = number of subjects in the specified category;
EQ-5D = EuroQol 5-Dimension 5-Level, VAS = visual analogue scale.
SD = standard deviation.

Exploratory Biomarker Research in REACH-2

Vascular endothelial growth factor-A (VEGF-A), VEGF-C, and VEGF-D analyses were performed in relation to efficacy (Table 22, Table 23 and Table 24).

Table 22: Correlative Analyses by Median VEGF-A Level

Clinical Outcome	Parameter	High VEGF-A[a]		Low VEGF-A[b]	
		Ram + BSC	Placebo + BSC	Ram + BSC	Placebo + BSC
	N	86	42	89	39
OS	Median, months	5.91	5.22	11.14	8.74
	Treatment HR[c]	0.95		0.65	
	95% CI for HR[c]	(0.62, 1.48)		(0.42, 1.01)	
	p-value[d]	0.8113		0.0566	
	Interaction p-value[e]	0.2200			
PFS	Median, months	2.73	1.64	4.14	1.54
	Treatment HR[c]	0.53		0.37	
	95% CI for HR[c]	(0.35, 0.80)		(0.25, 0.57)	
	p-value[d]	0.0031		0.0000	
	Interaction p-value[e]	0.2402			

Abbreviations: BSC = best supportive care; CI = confidence interval; HR = hazard ratio; N = number of patients in category; OS = overall survival; PFS = progression-free survival; Ram = ramucirumab; TR = translational research; VEGF-A = vascular endothelial growth factor A.

[a] Patients with high protein expression level, as identified by a biomarker value at or above the median biomarker value. Median VEGF-A level = 0.482205.

[b] Patients with low protein expression level, as identified by a biomarker value below the median biomarker value. Median VEGF-A level = 0.482205.

[c] Hazard ratio for the time to event outcome comparing ramucirumab vs. placebo within sVEGFR-A expression level.

[d] p-value for treatment effect within sVEGFR-A expression level obtained using a likelihood ratio test.

[e] p-value for testing the interaction obtained using a likelihood ratio test. p-value not adjusted for testing multiple biomarkers.

Table 23: Correlative Analyses by Median VEGF-C Level

Clinical Outcome	Parameter	High VEGF-C[a]		Low VEGF-C[a]	
		Ram + BSC	Placebo + BSC	Ram + BSC	Placebo + BSC
	N	88	40	88	39
OS	Median, months	6.65	7.06	9.99	8.05
	Treatment HR	0.82		0.67	
	95% CI for HR	(0.54 - 1.27)		(0.43 - 1.05)	
	p-Value	0.3589		0.0778	
	Interaction p-value[b]	0.5123			
PFS	Median, months	2.92	2.33	2.83	1.45
	Treatment HR	0.49		0.35	
	95% CI for HR	(0.32 - 0.74)		(0.23 - 0.55)	
	p-Value	0.0010		0.0	
	Interaction p-value[b]	0.2861			

Abbreviations: BSC = best supportive care; CI = confidence interval; HR = hazard ratio; N = number of patients in category; PFS = progression-free survival; OS = overall survival; Ram = ramucirumab; TR = translational research; VEGF-C = vascular endothelial growth factor C.

[a] Median VEGF-C level = 73.68 pg/mL. Low VEGF-C: < median. High VEGF-C: ≥ median.

[b] p-Value for treatment by VEGF-C level interaction.

Table 24: Correlative Analyses by Median VEGF-D Level

Clinical Outcome	Parameter	High VEGF-D[a]		Low VEGF-D[a]	
		Ram + BSC	Placebo	Ram + BSC	Placebo + BSC
	N	87	43	90	38
OS	Median, months	8.08	5.22	9.07	9.00
	Treatment HR	0.73		0.74	
	95% CI for HR	(0.49 - 1.12)		(0.48 - 1.18)	
	p-Value	0.1479		0.1978	
	Interaction p-value[b]	0.9762			
PFS	Median, months	2.83	1.61	2.83	1.48
	Treatment HR	0.44		0.43	
	95% CI for HR	(0.30 - 0.67)		(0.28 - 0.66)	
	p-value	0.0001		0.0002	
	Interaction p-value[b]	0.9208			

Abbreviations: BSC = best supportive care; CI = confidence interval; HR = hazard ratio; N = number of patients in category; PFS = progression-free survival; OS = overall survival; Ram = ramucirumab; TR = translational research; VEGF-D = vascular endothelial growth factor D.

[a] Median VEGF-D level = 0.229 ng/mL. Low VEGF-D: < median. High VEGF-D: ≥ median.

[b] p-Value for treatment by VEGF-D level interaction.

Soluble vascular endothelial growth factor receptor (sVEGFR)-1 was not assessed in REACH-2, but sVEGFR-2 and sVEGFR-3 were (Table 25 and Table 26).

Table 25: Correlative Analyses by Median sVEGFR-2 Level

Clinical Outcome	Parameter	High sVEGFR-2[a]		Low VEGFR-2[b]	
		Ram + BSC	Placebo + BSC	Ram + BSC	Placebo + BSC
	N	82	38	82	38
OS	Median, months	7.69	8.97	10.58	5.42
	Treatment HR[c]	1.12		0.44	
	95% CI for HR[c]	(0.72, 1.79)		(0.28, 0.68)	
	p-value[d]	0.6150		0.0004	
	Interaction p-value[e]	0.0033			
PFS	Median, months	2.83	2.50	2.83	1.46
	Treatment HR[c]	0.61		0.29	
	95% CI for HR[c]	(0.40, 0.96)		(0.19, 0.45)	
	p-value[d]	0.0332		0.0000	
	Interaction p-value[e]	0.0135			

Abbreviations: BSC = best supportive care; CI = confidence interval; HR = hazard ratio; N = number of patients in category; OS = overall survival; PFS = progression-free survival; Ram = ramucirumab; sVEGFR-2 = soluble vascular endothelial growth factor receptor 2; TR = translational research.

[a] Patients with high protein expression level, as identified by a biomarker value at or above the median biomarker value. Median sVEGFR-2 level = 17.49 ng/mL.

[b] Patients with low protein expression level, as identified by a biomarker value below the median biomarker value. Median sVEGFR-2 level = 17.49 ng/mL.

[c] Hazard ratio for the time to event outcome comparing ramucirumab vs. placebo within sVEGFR-2 expression level.

[d] p-value for treatment effect within sVEGFR-2 expression level obtained using a likelihood ratio test.

[e] p-value for testing the interaction obtained using a likelihood ratio test. p-value not adjusted for testing multiple biomarkers.

Table 26: Correlative Analyses by Median sVEGFR-3 Level

Clinical Outcome	Parameter	High sVEGFR-3[a]		Low sVEGFR-3[b]	
		Ram + BSC	Placebo + BSC	Ram + BSC	Placebo + BSC
	N	89	40	88	41
OS	Median, months	6.08	8.80	11.76	7.33
	Treatment HR[c]	1.13		0.49	
	95% CI for HR[c]	(0.74, 1.78)		(0.32, 0.76)	
	p-value[d]	0.5663		0.0019	
	Interaction p-value[e]	0.0072			
PFS	Median, months	2.79	2.50	4.17	1.45
	Treatment HR[c]	0.65		0.29	
	95% CI for HR[c]	(0.43, 0.98)		(0.19, 0.44)	
	p-value[d]	0.0417		0.0000	
	Interaction p-value[e]	0.0063			

Abbreviations: BSC = best supportive care; CI = confidence interval; HR = hazard ratio; N = number of patients in category; OS = overall survival; PFS = progression-free survival; Ram = ramucirumab; sVEGFR-3 = soluble vascular endothelial growth factor receptor 3; TR = translational research.

[a] Patients with high protein expression level, as identified by a biomarker value at or above the median biomarker value. Median sVEGFR-3 level = 160.6 ng/mL.

[b] Patients with low protein expression level, as identified by a biomarker value below the median biomarker value. Median sVEGFR-3 level = 160.6 ng/mL.

[c] Hazard ratio for the time to event outcome comparing ramucirumab vs. placebo within sVEGFR-3 expression level.

[d] p-value for treatment effect within sVEGFR-3 expression level obtained using a likelihood ratio test.

[e] p-value for testing the interaction obtained using a likelihood ratio test. p-value not adjusted for testing multiple biomarkers.

Ancillary analyses

Subgroup analyses for OS

The forest plot for the unstratified subgroup analysis of overall survival (ITT population) is shown in **Error! Reference source not found.**.

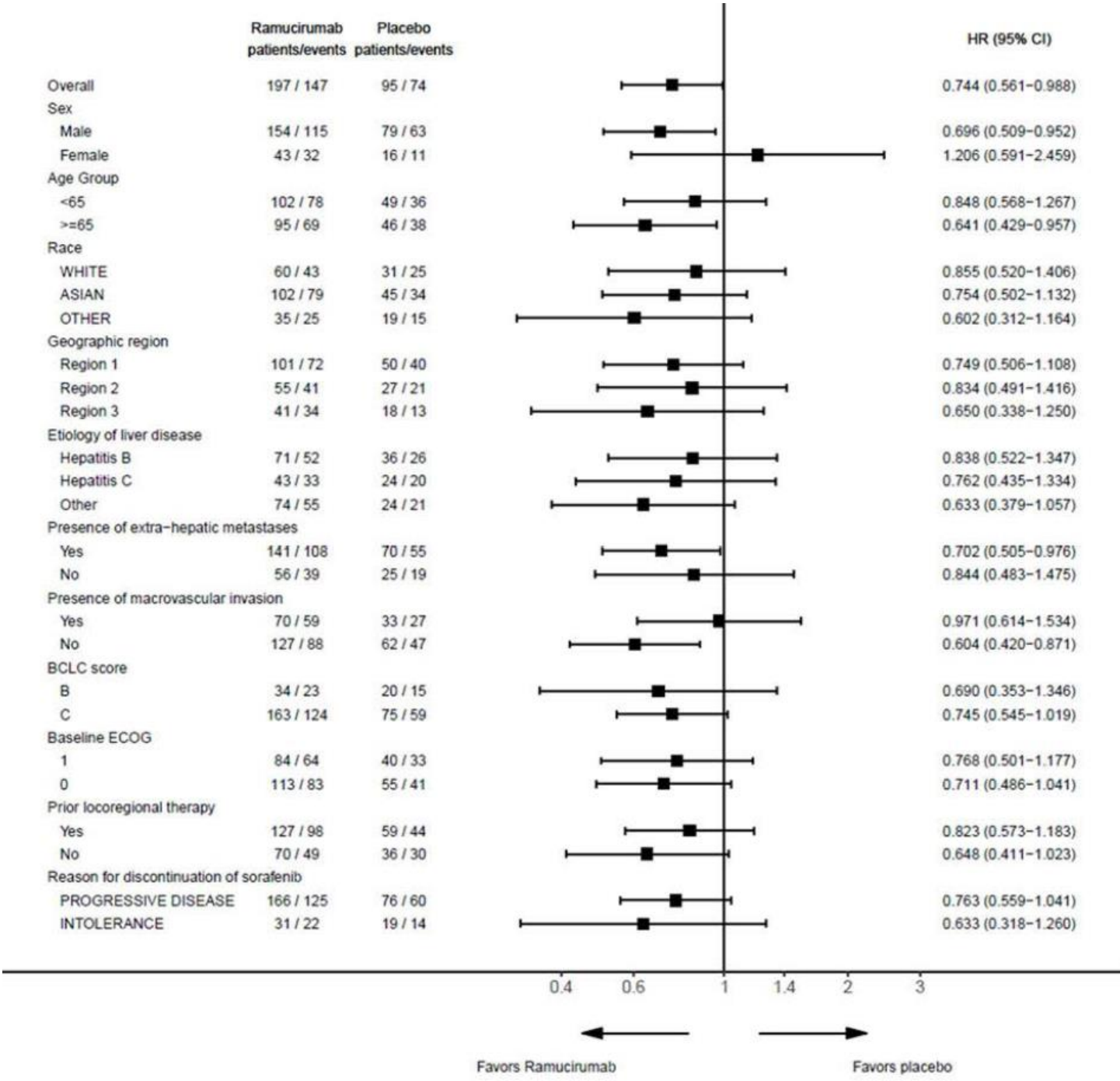


Figure 7: Forest plot for unstratified subgroup analysis of overall survival (ITT population)

In the PP population, ramucirumab-treated patients demonstrated a statistically significant improvement in OS compared with placebo-treated patients.

Table 27: Overall Survival - Per-Protocol Population

	LY3009806+BSC (N=195)	Placebo+BSC (N=94)	Treatment Effect/Difference / p-value*f
Number of Deaths, n (%)	145 (74.4)	73 (77.7)	
Number of Patients Censored, n (%)	50 (25.6)	21 (22.3)	
Alive, n (%)	46 (23.6)	16 (17.0)	
Lost to Follow Up, n (%)	2 (1.0)	2 (2.1)	
Withdrawal by Subject, n (%)	2 (1.0)	3 (3.2)	
Minimum *a, month	0.20	0.49	
25th percentile (95% CI)	4.60(3.68, 5.13)	4.11(3.09, 5.03)	
Median (95% CI)	8.57(7.00, 10.78)	7.29(5.36, 9.00)	1.28
75th percentile (95% CI)	17.18(13.67, 20.99)	12.94(10.41, 16.10)	
Maximum	26.97+	22.18	
Restricted Mean (95% CI) with restriction time = 22.18 month *b	10.71(9.65, 11.77)	8.97(7.64, 10.31)	1.73(0.03, 3.44) p = 0.0458*e
p-value (2-sided) - Log Rank Unstratified			p = 0.0360
- Log Rank Stratified*c			p = 0.0164
Hazard Ratio (95% CI) - UnStratified			0.737(0.555, 0.980)
- Stratified*c			0.700(0.522, 0.939)

Abbreviations: CI = Confidence Interval; N = total number of subjects in the population within the treatment group; n = number of patients; NC = not calculable.
Note: Quartiles and OS rates were estimated using the Kaplan-Meier method. Corresponding 95% CIs were estimated using the methods of Brookmeyer and Crowley, and Greenwood, respectively.
*a - For minimum and maximum, + indicates a censored observation;
*b - Restriction time is defined by the latest time where the standard error of the survival estimates are <=0.075.
*c - Stratified by Geographical Region (IWRS), Macrovascular invasion (IWRS), ECOG PS at Baseline (IWRS)
*d - 95% CIs and 2-sided p-values for the Difference between rates were calculated based on normal approximation.
*e - 2-sided p-value based on normal approximation
*f - Treatment Effect/Difference/p-values are computed based on comparator Placebo+BSC
Cutoff Date: 2018-03-15.

Sensitivity analyses for OS

The following other OS sensitivity analyses were pre-specified in the SAP:

- An unstratified analysis: An HR of 0.744 (95% CI: 0.561, 0.988) that was statistically significant (p=0.0408) was observed, from an unstratified Cox proportional hazards model.
- Using CRF data for stratified analysis: A pre-specified analysis was conducted to assess the sensitivity of the primary analysis to the source of data for the stratification factors (Note: the primary analysis was based on the IWRS data). The stratified Cox model and log-rank test using the stratification factors based on the data as recorded on the CRF had an HR of 0.716 (95% CI: 0.535, 0.958) that was statistically significant (p=0.0236).
- Analysis of ITT population with baseline AFP ≥400 ng/mL based on central laboratory result:

Table 28: Summary of Overall Survival, Baseline with Central Baseline AFP ≥400 ng/mL - ITT Population

	LY3009806+BSC (N=195)	Placebo+BSC (N=93)	Treatment Effect /Difference / p-value
Number of Deaths, n (%)	146 (74.9)	72 (77.4)	
Number of Patients Censored, n (%)	49 (25.1)	21 (22.6)	
Alive	45 (23.1)	16 (17.2)	
Lost to Follow Up	2 (1.0)	2 (2.2)	
Withdrawal by Subject	2 (1.0)	3 (3.2)	
Minimum *a, month	0.20	0.49	
25th percentile (95% CI)	4.47 (3.68, 4.99)	4.11 (3.09, 4.99)	
Median (95% CI)	8.51 (7.00, 10.58)	7.29 (5.42, 9.07)	1.22
75th percentile (95% CI)	17.18 (13.60, 20.99)	12.94 (10.12, 17.94)	
Maximum	26.97	22.18	
Restricted Mean (95% CI) with restriction time = 22.18 months *b	10.63(9.57,11.68)	8.96(7.62,10.30)	1.67 (-0.04, 3.38) p = 0.0553 *e
p-value (2-sided) - Log-rank Unstratified			0.0446
- Log-rank Stratified *c			0.0187
Hazard Ratio (95% CI) - Unstratified			0.746 (0.560, 0.993)
- Stratified*c			0.705 (0.526, 0.946)

Cutoff Date: 2018-03-15.
Abbreviations: CI = Confifence Interval; N = total number of subjects who had objective response in intent-to-treat population within the treatment group; n = number of subjects in specified category;
Note: Quartiles and Survival rates, along with 95% CIs , were estimated using the Kaplan-Meier method
Note: 4 patients were excluded due to baseline AFP <400 ng/mL or missing based on central lab.
*a - For minimum and maximum, + indicates a censored observation;
*b - Restriction time is defined by the latest time where the standard error of the survival estimates are <=0.075;
*c - Stratified by Geographical region(IWRS), Macrovascular invasion presence(IWRS),and ECOG PS(IWRS)
*d - 95% CIs and 2-sided p-values for the difference between rates were calculated based on normal approximation
*e - 2-sided p-value based on normal approximation.

- Adjusting for potential prognostic factors:

Table 29: Overall Survival, Stratified by Subgroups - ITT Population

	LY3009806+BSC				Placebo+BSC				Hazard Ratio			
	n	Events	Median* a (month)	95% CI	n	Events	Median* a (month)	95% CI	HR*b	95% CI	p-value *c	Inter-action p-value*d
Overall	197	147	8.51	(7.00, 10.58)	95	74	7.29	(5.42, 9.07)	0.744	(0.561, 0.988)	0.0408	
Gender												0.2166
F	43	32	8.80	(5.82, 13.37)	16	11	9.07	(5.88, 17.94)	1.206	(0.591, 2.459)	0.6032	
M	154	115	8.08	(6.74, 10.58)	79	63	6.60	(5.22, 8.97)	0.696	(0.509, 0.952)	0.0234	
Age group												0.2566
<65	102	78	8.74	(6.57, 10.97)	49	36	9.00	(5.36, 10.68)	0.848	(0.568, 1.267)	0.4245	
>=65	95	69	7.98	(6.08, 11.63)	46	38	6.08	(4.63, 8.80)	0.641	(0.429, 0.957)	0.0287	
Race												0.7138
ASIAN	102	79	8.80	(6.74, 10.78)	45	34	8.51	(3.94, 10.12)	0.754	(0.502, 1.132)	0.1745	
OTHER	35	25	8.28	(4.83, 13.67)	19	15	6.24	(3.09, 9.33)	0.602	(0.312, 1.164)	0.1264	
WHITE	60	43	7.41	(5.49, 12.29)	31	25	7.29	(5.36, 12.94)	0.855	(0.520, 1.406)	0.5368	
Geographical region												0.9040
Region 1	101	72	7.98	(6.11, 12.29)	50	40	7.06	(5.22, 9.07)	0.749	(0.506, 1.108)	0.1475	
Region 2	55	41	8.74	(5.16, 9.99)	27	21	9.00	(3.71, 10.68)	0.834	(0.491, 1.416)	0.5051	
Region 3	41	34	10.18	(6.67, 11.79)	18	13	5.42	(3.35, 12.71)	0.650	(0.338, 1.250)	0.1926	

Abbreviations: n = number of subjects in the subgroup;

*a - estimated using the Kaplan-Meier method;
*b - Hazard ratio and 95% CI (Wald) were estimated from unstratified Cox model;
*c - two-sided p-value from unstratified log-rank test;
*d - Wald test of treatment-by-subgroup interaction from unstratified Cox model;
Hazard ratio based on comparator: Placebo+BSC.
Cutoff Date: 2018-03-15.

Subgroup analyses for PFS

The forest plot for unstratified subgroup analysis of progression-free survival (ITT population) is shown in Figure 8.

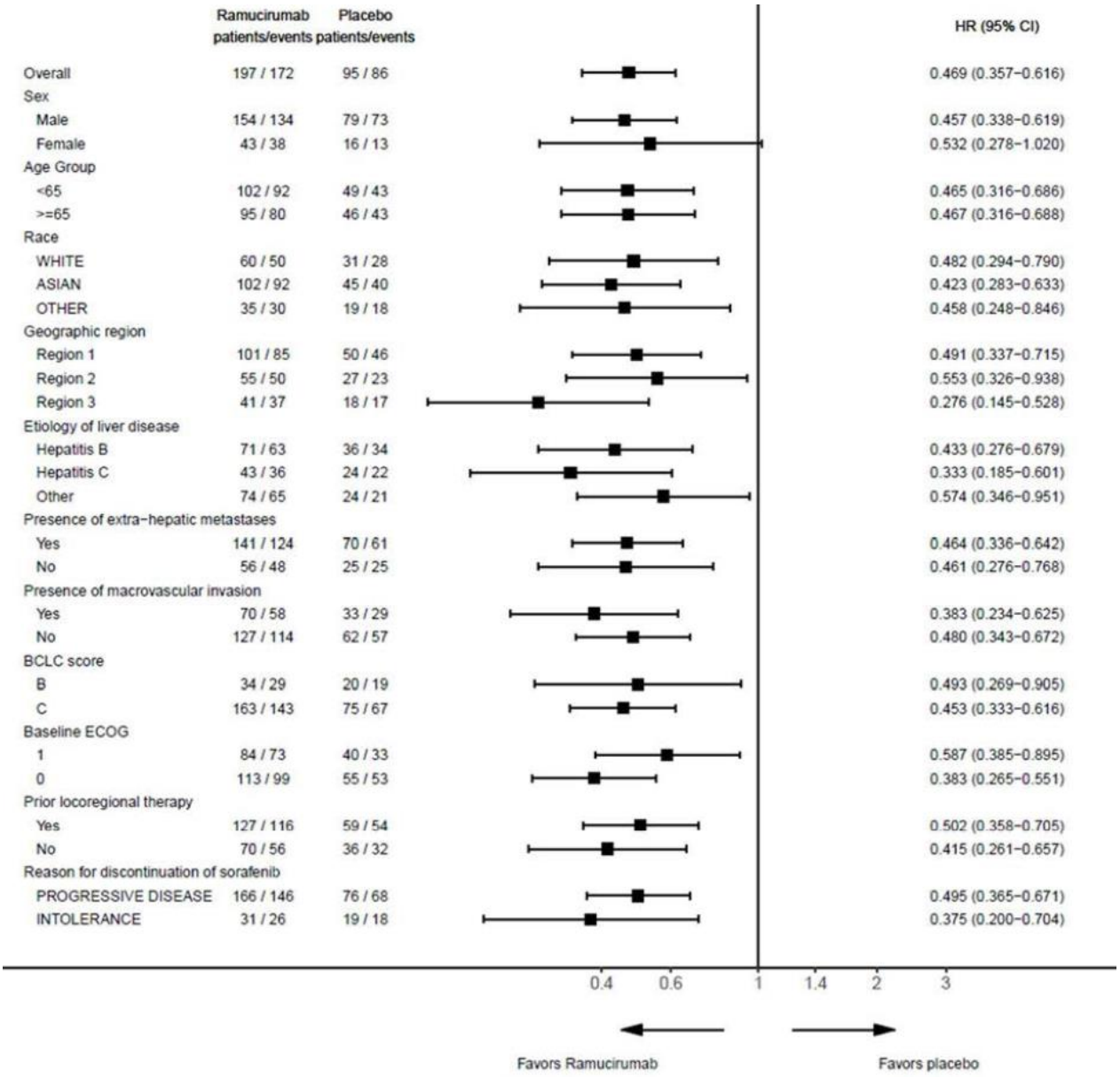


Figure 8: Forest plot for unstratified subgroup analysis of progression-free survival (ITT population)

The statistical significance and magnitude of treatment effect of the PFS analysis were supported by the performed pre-specified sensitivity analyses, which demonstrated HRs between 0.434 and 0.488 with $p<0.0001$ across all analyses, favouring the ramucirumab arm.

Post-hoc sensitivity analyses (not pre-specified in the SAP):

- The applicant also performed a post-hoc analysis in which there was adjustment for baseline AFP levels, since an imbalance in baseline AFP levels between treatment arms was observed. A multivariate unstratified Cox regression analysis of OS adjusting for baseline AFP as well as other prognostic factors (the selected factors included in the final model were ECOG PS, macrovascular invasion, and baseline AFP) demonstrated an HR of 0.752 (95% CI: 0.567, 0.999) for the comparison of ramucirumab with placebo (p=0.0489).

- An analysis where adjustment was only performed for AFP was also performed. This AFP-adjusted, stratified analysis (without adjustment for other prognostic factors) demonstrated a reduction in the hazard of death of 30.3% (HR = 0.697, 95% CI: 0.520, 0.934; p=0.0156).

Correlational analyses between AFP measured at local laboratories vs. AFP measured centrally were performed, which showed high concordance (Figure 9).

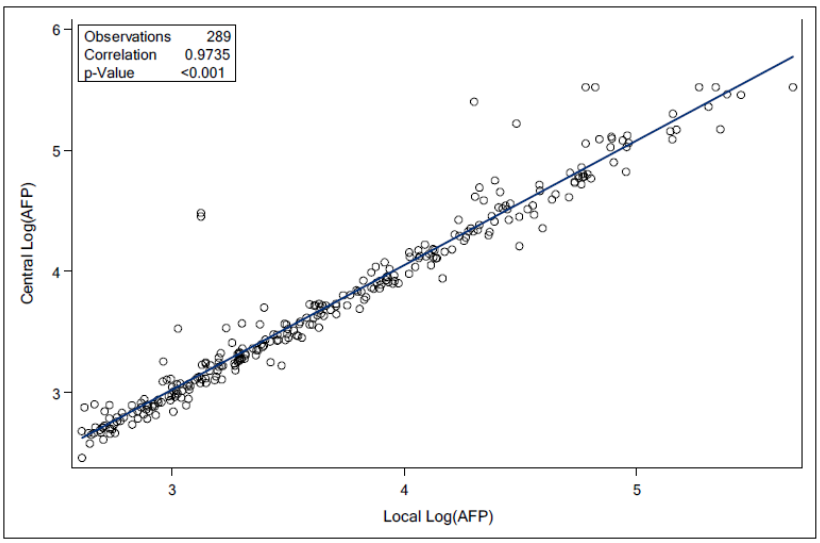


Figure 9: Correlational analyses between AFP measured at local laboratories versus AFP measured centrally

Post-Discontinuation Anti-Cancer Therapy

Overall, similar percentages of patients in the ramucirumab and placebo arms received additional anti-cancer systemic post-discontinuation anti-cancer therapy (53 [26.9%] patients in the ramucirumab arm and 27 [28.4%] patients in the placebo arm).

Summary of main study

The following table summarises the efficacy results from the main study supporting the present application. This summary should be read in conjunction with the discussion on clinical efficacy as well as the benefit risk assessment (see later sections).

Table 30: Summary of Efficacy for REACH-2 study

Title: 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 identifier	REACH-2; I4T-MC-JVDE; NCT02435433; EudraCT: 2014-005068-13	
Design	Phase 3, global, randomised, double-blind, placebo-controlled	
	Duration of main phase:	Patients were treated until there was evidence of progressive disease (PD), unacceptable toxicity, withdrawal of consent, or until other withdrawal criteria were met.
Hypothesis	Superiority	
Treatments groups	**Ramucirumab**	Ramucirumab: 8 mg/kg intravenously (IV) on Day1 once every 14-days + best supportive care (BSC) N = 197 (ITT population)
	Placebo	Placebo IV on Day 1 once every 14-days + BSC N = 95 (ITT population)

Endpoints and definitions	Primary endpoint	Overall survival (OS)	Defined as the time measured from the date of randomization to the date of death from any cause.	
	Secondary endpoint	Progression-free survival (PFS)	Defined as the time from the date of randomization to the date of first observation of objective progression or death from any cause (by investigator's assessment).	
	Secondary endpoint	Time to radiographic progression (TTP)	Defined as the time from the date of randomization to the date of first observation of objective progression according to Response Evaluation Criteria in Solid Tumors version 1.1 (RECIST 1.1) by investigator's assessment.	
	Secondary endpoint	Objective response rate (ORR)	Equal to the percentage of patients achieving a best overall response of complete response (CR) or partial response (PR) by investigator's assessment. Best overall response was classified based on the overall responses assessed by study investigators according to RECIST Version 1.1.	
	Secondary endpoint	Disease control rate (DCR)	Equal to the proportion of randomised patients achieving a best overall response of CR, PR, or stable disease (SD) per RECIST v.1.1.	
	Secondary endpoint	Time to deterioration in FACT hepatobiliary Symptom Index 8 (TTD FHSI-8)	Defined as the time from the date of randomization to the first date observing a decrease of ≥3-points from baseline.	
	Secondary endpoint	Time to deterioration in Eastern Cooperative Oncology Group performance status (TTD ECOG PS)	Defined as the time from the date of randomization to the first date observing ECOG PS ≥2 (that is, deterioration from baseline status of 0 or 1).	
Database lock	23 March 2018 (based on a data cut-off date of 15 March 2018)			
Results and Analysis				
Analysis description	**Primary Analysis**			
Analysis population and time point description	Intent-to-Treat Data cut-off date: 15 March 2018			
Descriptive statistics and estimate variability	Treatment group		**Ramucirumab**	**Placebo**
	Number of subjects		197	95
	OS Median, months (95% CI)		8.51 (7.00, 10.58)	7.29 (5.42, 9.07)
Effect estimate per comparison	Hazard ratio (95% CI)		0.710 (0.531, 0.949)	
	p-value		0.0199	
Analysis description	**Secondary Analysis**			
Analysis population and time point description	Intent-to-Treat Data cut-off date: 15 March 2018			
Descriptive statistics and estimate variability	Treatment group		**Ramucirumab**	**Placebo**
	Number of subjects		197	95
	PFS median, months (95% CI)		2.83 (2.76, 4.11)	1.61 (1.45, 2.69)
	TTP median, months, (95% CI)		3.02 (2.79, 4.17)	1.61 (1.45, 2.73)

	ORR % (95% CI)		4.6 (1.7, 7.5)	1.1 (0.0, 3.1)
	DCR % (95% CI)		59.9 (53.1, 66.7)	38.9 (29.1, 48.8)
	TTD FSHI-8 by ≥3 points, median, months (95% CI)		3.71 (2.79, 4.40)	2.79 (1.64, 2.89)
	TTD ECOG PS to ≥2, median, months (95% CI)		NE (9.33, NE)	NE (5.26, NE)
Effect estimate per comparison	Comparison groups		**Ramucirumab**	**Placebo**
	PFS	Hazard ratio (95% CI)	0.452 (0.339, 0.603)	
		p-value	<0.0001	
	TTP	Hazard ratio (95% CI)	0.427 (0.313, 0.582)	
		p-value	0.0001	
	ORR	p-value	0.1697	
	DCR	p-value	0.0006	
	TTD FHSI-8 by ≥3 points	Hazard ratio (95% CI)	0.799 (0.545, 1.171)	
		p-value	0.2382	
	TTD ECOG PS to ≥2	Hazard ratio (95% CI)	1.082 (0.639, 1.832)	
		p-value	0.7671	

Abbreviations: CI = confidence interval; NE = not estimable.

Analysis performed across trials (pooled analyses and meta-analysis)

A pooled efficacy analysis has been performed by the applicant in which the main study REACH-2 was pooled with the supportive study REACH. In the pooled efficacy population (AFP ≥400 ng/mL), ramucirumab treatment reduced the hazard of death by 31% (OS HR = 0.694; 95% CI: 0.571, 0.842; p=0.0002).

Clinical studies in special populations

The numbers of patients age 65 through 74, 75 through 84, and 85+ years who were enrolled in controlled and non-controlled trials in HCC are shown in the following table. Refer also to forest plot of subgroup analyses (Figure 6). In addition, efficacy in patients ≥75 years old (n = 37 ramucirumab vs. 11 placebo; unstratified OS HR = 0.617; 95% CI: 0.304, 1.252; p = 0.1771) was comparable to efficacy in patients <75 years old (n = 160 ramucirumab vs. 84 placebo; unstratified OS HR = 0.776; 95% CI: 0.570, 1.058; p = 0.1092), and in the overall population in REACH-2.

Table 31: Numbers of patients in age subgroups - HCC controlled and non-controlled trials Summary of efficacy for the REACH-2 study

	Age 65-74 (# patients/total number)	**Age 75-84 (# patients/total number)**	**Age 85+ (# patients/total number)**
Controlled trials (JVDE [REACH-2], JVBF [REACH])	ITT: 143/480 AFP ≥400 ng/mL: 93/316	ITT: 80/480 (AFP ≥400 ng/mL: 49/316	ITT: 5/480 AFP ≥400 ng/mL: 2/316
Non-controlled trials (JVBQ)	ITT: 12/42 AFP ≥400 ng/mL: 4/15	ITT: 2/42 AFP ≥400 ng/mL: 1/15	ITT: 1/42 AFP ≥400 ng/mL: 0/15

Abbreviations: # = number; AFP = alpha-fetoprotein; HCC = hepatocellular carcinoma; ITT = intent-to-treat.

2.4.3. Supportive studies

Supportive Phase 3 Study REACH – ITT Population with Baseline AFP ≥400 ng/mL

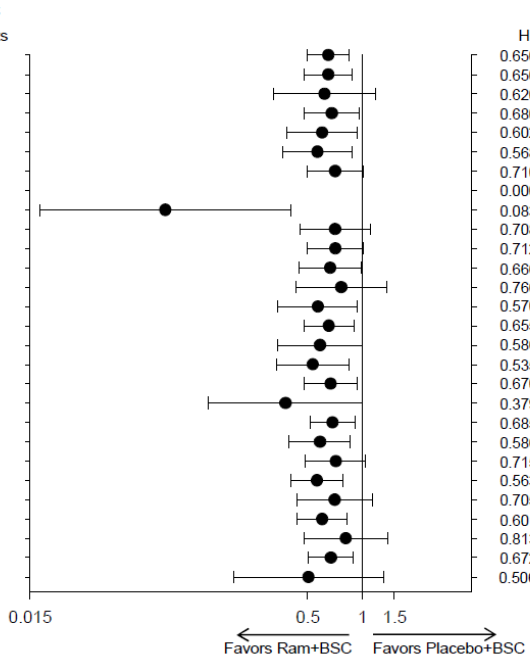
REACH was the first randomised, double-blind Phase 3 study of ramucirumab plus BSC vs. placebo plus BSC in HCC with disease progression after or intolerance to prior sorafenib. Patients were included irrespective of baseline AFP level (Zhu et al. Lancet Oncol. 2015). A total of 565 patients with a C-P score A were included in the overall ITT population: 283 in the ramucirumab arm and 282 in the placebo arm.

While REACH did not meet its primary objective of showing a survival benefit in ramucirumab compared with placebo (OS HR=0.866; 95% CI: 0.717, 1.046; p=0.139), in the pre-specified subgroup of patients with a baseline AFP of ≥400 ng/mL (n=250), ramucirumab reduced the hazard of death by 33% (OS HR = 0.674; 95% CI: 0.508, 0.895; p=0.0059; median OS = 7.8 months for ramucirumab vs. 4.2 months for placebo). Patients with baseline AFP <400 ng/mL in the REACH study did not experience a survival benefit (OS HR=1.093; 95% CI: 0.836, 1.428; p=0.5059).

Inclusion and exclusion criteria in REACH were highly similar to criteria in REACH-2.

In the subgroup with AFP ≥400 ng/mL, there was internal consistency across efficacy endpoints with improvements in PFS, ORR, and the results of subgroup analyses (Figure 10 and Figure 11).

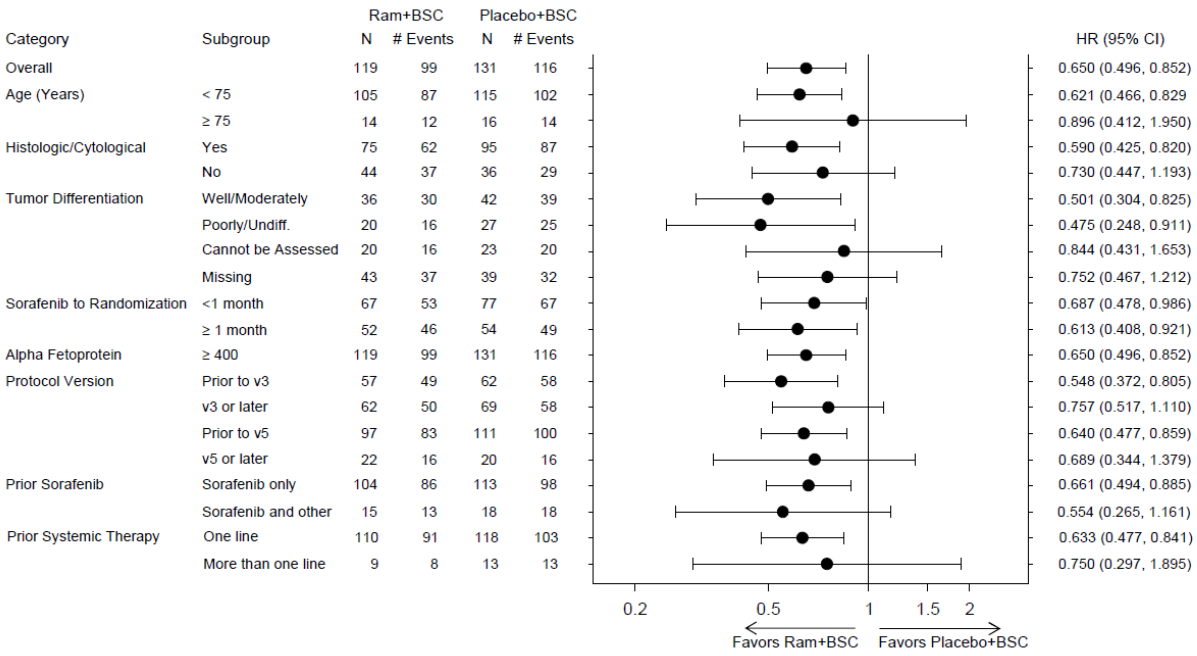
		Ram+BSC		Placebo+BSC		
Category	Subgroup	N	# Events	N	# Events	HR (95% CI)
Overall		119	99	131	116	0.650 (0.496, 0.852)
Sex	Male	92	77	110	98	0.650 (0.481, 0.878)
	Female	27	22	21	18	0.620 (0.326, 1.181)
Age (Years)	< 65	70	61	84	74	0.680 (0.483, 0.958)
	≥ 65	49	38	47	42	0.602 (0.386, 0.937)
Race	White	50	38	49	45	0.568 (0.366, 0.880)
	Asian	66	59	78	68	0.710 (0.499, 1.010)
	Other	3	2	4	3	0.000 (0.000 -) *
Geographical Region	Region 1	9	4	10	9	0.083 (0.017, 0.406)
	Region 2	44	36	48	44	0.708 (0.454, 1.104)
	Region 3	66	59	73	63	0.712 (0.498, 1.020)
Etiology of Liver Disease	Hepatitis B	50	46	63	56	0.666 (0.449, 0.990)
	Hepatitis C	32	27	26	21	0.766 (0.431, 1.361)
	Other	37	26	42	39	0.570 (0.344, 0.943)
Extra-hepatic Metastases	Yes	85	69	101	90	0.655 (0.476, 0.900)
	No	34	30	30	26	0.586 (0.344, 0.998)
Macrovascular Invasion	Yes	43	39	44	39	0.535 (0.338, 0.848)
	No	76	60	87	77	0.670 (0.477, 0.940)
BCLC Score	B	11	10	9	9	0.379 (0.143, 1.006)
	C	108	89	122	107	0.685 (0.516, 0.909)
ECOG PS	0	60	50	63	56	0.586 (0.397, 0.864)
	1	59	49	68	60	0.715 (0.489, 1.045)
Duration of Sorafenib	< 5 months	81	70	81	75	0.563 (0.404, 0.785)
	≥ 5 months	38	29	50	41	0.705 (0.437, 1.138)
Prior Locoregional	Yes	89	74	90	82	0.601 (0.438, 0.826)
	No	30	25	41	34	0.813 (0.481, 1.373)
Discont. Of Sorafenib	PD	108	89	122	107	0.672 (0.506, 0.892)
	Toxicity	11	10	9	9	0.506 (0.196, 1.309)



* The Race-Other Hazard Ratios are not shown due to the small number of patients/events.

Abbreviations: AFP = alpha fetoprotein; BCLC = Barcelona Clinic Liver Cancer; BSC = best supportive care; CI = confidence interval; Discont. = discontinuation; ECOG PS = Eastern Cooperative Oncology Group Performance Status; HR = hazard ratio; ITT = intent-to-treat; Ram = ramucirumab; PD = progressive disease.

Figure 10: Forest plot for subgroup analysis of overall survival in REACH study (patients with AFP ≥400 ng/mL only), part 1 of 2



Abbreviations: AFP = alpha fetoprotein; BSC = best supportive care; CI = confidence interval; HR = hazard ratio; ITT = intent-to-treat; Ram = ramucirumab; v = version.

Figure 11: Forest plot for subgroup analysis of overall survival in REACH study (patients with AFP ≥400 ng/mL only), part 2 of 2

Phase 2 study JVBQ

Study JVBQ was a single-arm, open-label, non-randomised, multicentre phase 2 trial to evaluate PFS in 42 patients with unresectable or metastatic HCC without prior systemic anticancer therapy. Secondary objectives included OS, TTP, and ORR. Ramucirumab 8 mg/kg was administered as an IV infusion Q2W. In study JVBQ, median PFS was 4.0 months, median TTP was 4.2 months, and median OS was 12.0 months.

2.4.4. Discussion on clinical efficacy

The proposed indication for Cyramza in HCC is: Cyramza monotherapy is indicated for the treatment of adult patients with advanced or unresectable hepatocellular carcinoma who have a serum alpha fetoprotein (AFP) of ≥400 ng/ml and who have been previously treated with sorafenib. This target population is acknowledged and appears in line with the submitted pivotal study.

The most important studies submitted in this application in relation to assessing the benefit/risk balance of ramucirumab in HCC are one pivotal study (REACH-2), and a supportive study (REACH). REACH-2 was a randomised (2:1), double-blind, placebo-controlled study evaluating the efficacy and safety of ramucirumab 8 mg/kg IV Q2W as monotherapy in conjunction with BSC for the treatment of patients with HCC and a baseline AFP ≥400 ng/mL after prior sorafenib therapy. The REACH study was an overall negative study in HCC patients not selected based on baseline AFP level, but was hypothesis-generating with respect to the efficacy of ramucirumab in HCC patients with baseline AFP levels ≥400 ng/mL. REACH-2 was intended to confirm the hypothesis of an OS benefit in HCC patients with baseline AFP levels ≥400 ng/mL.

Dose selection

No dose-response studies have been submitted for the requested HCC indication, and hence there is uncertainty as to whether the selected dose of 8 mg/kg Q2W is optimal (see discussion on clinical pharmacology). The applicant argues that the dose is adequate because a favourable benefit-risk profile has been demonstrated in patients with metastatic colorectal cancer and patients with gastric cancer. However, both in the initial application for metastatic gastric cancer and the application for metastatic colorectal

cancer there was uncertainty regarding the adequacy of the selected dose of 8 mg/kg Q2W (Cyramza gastric cancer EPAR; Cyramza colorectal cancer EPAR). Also in gastric cancer and colorectal cancer very limited data to support dose selection were presented. A relevant exposure-efficacy association was demonstrated in HCC, which showed that only half of the patients (with above-median exposure) appeared to benefit from ramucirumab treatment, (see discussion on clinical pharmacology). These exposure-efficacy relationships remained after attempts to adjust for other prognostic factors. Also in gastric cancer and colorectal cancer such an exposure-efficacy relationship was seen. As a result, there remains uncertainty the chosen dose of 8 mg/kg Q2W for monotherapy treatment in HCC for all patients is optimal.

Design and conduct of clinical studies

Study design: The randomised, double-blind, placebo-controlled design that was used in the pivotal study REACH-2 is considered adequate to evaluate the benefits and risks of ramucirumab in the second-line treatment of HCC. Overall survival was the primary endpoint of the pivotal study which is considered appropriate for the proposed target population considering the relatively short life expectancy. The most relevant secondary endpoints (PFS, ORR) were also included in the study, assessed according to RECIST 1.1 criteria by the investigators. No central evaluation of imaging was performed. Since OS was the primary endpoint and the effect on OS is considered the most important in the assessment of efficacy, lack of central evaluation of imaging for PFS/ORR can be accepted in this case.
The control arm, placebo + BSC, is acceptable in this case as the study was initiated at a time when regorafenib was not yet approved for HCC second-line treatment and thus no comparator other than (placebo +) BSC was available.

Patient population: The enrolled patient population is relatively selected compared to patients with HCC treated in clinical practice as they had to have C-P class A, ECOG PS ≤1, and were not allowed to have a number of comorbidities (in particular cardiovascular) or a history of HCC disease-related complications. The inclusion criteria with regard to disease stage (BCLC stage: patients had to be stage C, or stage B if not amenable or had become refractory to locoregional therapy) and liver function (patients had to be C-P class A) were, however, comparable to those in the pivotal studies of regorafenib (Stivarga HCC EPAR) and cabozantinib (Cabometyx HCC EPAR). Both studies were performed in a similar second-line setting after sorafenib.
The overall patient mix enrolled in the current pivotal study of ramucirumab is similar to that in the pivotal study of regorafenib with the exception of the selection of patients with high AFP in the current study and, importantly, the fact that in the regorafenib study "*Permanent discontinuation of sorafenib due to toxicity*" was an exclusion criterion, while in the current study both patients who did and who did not tolerate sorafenib were eligible. Another difference between the two studies is that in the regorafenib study patients had to be randomised within 10 weeks after last treatment with sorafenib while there was no such treatment interval-related criterion in the current study. However, time since last sorafenib treatment appears comparable in the current study and the regorafenib pivotal study (current study: ~50% of patients received last sorafenib <1 months ago and ~50% ≥1 month ago, while median time since last sorafenib treatment was ~26 days in the regorafenib study).

Statistical analysis: The censoring rules for the primary and sensitivity analyses of PFS are not in accordance with the EMA preferred analysis. Given the difference in reasons for discontinuation (AE, withdrawal, physician decision, other), an analysis as per EMA rules could have been less positive and was therefore requested (and provided) as further discussed below. Considering having no tumour assessments for whatever reasons as a non-response in ORR and DCR is a conservative strategy which is considered acceptable. The fact that the interim analysis was dropped, strengthens the analysis of the trial. In addition, REACH-2 trial replicates the subgroup result of an earlier trial (REACH). Otherwise, the statistical methods used are considered standard and adequate.

Efficacy data and additional analyses

Baseline patient characteristics were well balanced between treatment groups, as were prior treatments. Median baseline AFP levels were somewhat higher in the ramucirumab arm than in the placebo arm (3920 vs. 2741 ng/mL, respectively). However, the performed sensitivity analysis in which adjustment was made for baseline AFP as well as other prognostic factors, showed a HR in line with the primary efficacy analysis and thus the slight imbalances in prognostic factors did not have a relevant impact on the primary efficacy analysis.

Primary endpoint – OS: The effect of ramucirumab on OS relative to placebo resulted in a HR of 0.71 (95% CI: 0.53-0.95, p=0.0199), with median OS of 8.5 months for ramucirumab vs. 7.3 months for placebo, reflecting a difference in median OS of 1.2 months. Of note, the uncertainty in the curves is large after around the 9-month time point because patient numbers become very low (especially in the placebo arm). The treatment effect for the OS sensitivity analyses (both pre-specified in the SAP as well as post-hoc) was in general consistent with the results of the primary OS analysis.

The clinical relevance of 1.2 months median OS benefit was questioned. Because the enrolled patient population appears to be a highly selected population compared to patients with HCC treated in clinical practice (who are generally frailer with more comorbidities), the external validity of the results was also questioned. The main uncertainty was on whether the already limited benefit will be maintained in clinical practice. This uncertainty is mitigated by adequate reflection of the eligibility criteria of the study in section 5.1 of the SmPC.

The supportive study REACH, which was the hypothesis-generating study that led to the initiation of REACH-2, showed a HR for OS of 0.67; 95% CI: 0.508-0.895, p=0.0059, with a median OS of 7.8 months for ramucirumab vs. 4.2 months for placebo. This effect as reflected in the HR is slightly larger than in the confirmatory study REACH-2, which could be expected in view of the fact that the selection of the subgroup of patients within REACH with baseline AFP ≥400 ng/mL was the result of post-hoc subgroup analyses, and hence the effect size in this subgroup might be inflated compared to the true effect size. For this reason, it is considered that the effect size observed in REACH-2 is more likely to be reflective of the true effect size. It is not considered informative to pool the data from REACH and REACH-2. The resulting pooled effect size is likely to be also biased slightly towards a more favourable effect size for ramucirumab as a result of inclusion of the data from the hypothesis-generating study REACH.

Nevertheless, and although REACH-2 is the single confirmatory study submitted in this application, the results from REACH, which are largely in line with those of REACH-2, do substantiate the observed (small) effect on OS observed in REACH-2.

Acknowledging the limitations, cross-study comparisons can be made with an authorised second-line treatment option for advanced HCC, i.e. regorafenib (see **Error! Reference source not found.** and discussion about patient population above). In the subgroup of patients with AFP ≥400 ng/mL in the regorafenib RESORCE study, the median OS (mOS) for regorafenib-treated patients was 7.4 months vs. 5.8 months for placebo-treated patients (Δ 1.6 months, HR=0.677 [95% CI: 0.50-0.92]). This suggests that benefit may be comparable between ramucirumab and regorafenib in patients with elevated AFP. Cabozantinib is another authorised second-line treatment option (CD issued on 12/11/2018). In the subgroup of patients with AFP ≥400 ng/mL in the cabozantinib CELESTIAL study, the mOS for cabozantinib-treated patients was 8.5 months vs. 5.2 months for placebo-treated patients (Δ 3.3 months, HR=0.71 [95% CI: 0.54-0.94]). Despite the larger difference in median survival, the HR is similar to that for ramucirumab in the pivotal study REACH-2. Cross-study comparison should be interpreted with caution as, although the studies had similar designs, the patient population definition was slightly different.

Secondary endpoints – PFS, ORR: The secondary endpoint PFS also showed a benefit with a HR of 0.45 (0.34-0.60, p<0.0001, stratified analysis), and median PFS of 2.8 months in the ramucirumab arm vs. 1.6

months in the placebo arm. The observed PFS effect therefore supports the observed OS effect. However, the PFS main analysis followed FDA censoring rules and, initially, no sensitivity analysis (fully) compliant with EMA censoring rules was performed. A post hoc sensitivity analysis for PFS as per EMA censoring rules were in line with the original analysis (stratified HR = 0.489; 95% CI: 0.370, 0.646; p<0.0001; mPFS ramucirumab: 2.86 months vs. placebo: 1.63 months). The ORR was numerically (but not statistically significantly) higher in patients in the ramucirumab arm as compared to the placebo arm (4.6% vs. 1.1%, respectively, p=0.1697). The low ORR is in line with what is known from other VEGF inhibitors; their effect is likely to be associated more with stabilising disease than actually reducing disease.

Secondary endpoints – Patient-focused outcomes: The applicant measured different disease/health-related quality of life instruments, i.e., FHSI-8, time to Deterioration in ECOG PS, and EQ-5D-5L. None of these instruments showed overall statistically significant or clinically relevant results.

Biomarker analyses: The applicant performed biomarker analyses for VEGF-C and VEGF-D in relation to efficacy. No predictive relationship was identified between these markers and clinical efficacy of ramucirumab in REACH-2. While the applicant has performed biomarker analyses for VEGF-D and VEGF-C, analyses have not been performed for other biomarkers which have previously been associated with efficacy of angiogenesis inhibitors including ramucirumab. The applicant provided the results of exploratory analyses that were conducted in REACH-2 for VEGF-A, sVEGFR-2, and sVEGFR-3. sVEGFR-1 was not assessed in REACH-2. There was no clear correlation between VEGF-A and ramucirumab efficacy outcomes. In contrast, sVEGFR-2 and sVEGFR-3 did show a trend for improved OS benefit with lower levels of sVEGFR, but due to the exploratory nature of these analyses and the inconsistencies in the results regarding these markers in other trials, the value of these biomarkers is somewhat unclear. Therefore, the data is not considered sufficient to conclude that these markers are predictive biomarkers.

Efficacy in subgroups: Analyses of the primary endpoint in pre-defined subgroups were performed. Likely due to low patient numbers, some apparently inconsistent effects are observed, e.g. according to gender and presence of macrovascular invasion. However, when looking at the subgroup data from the supportive study REACH, no inconsistencies are observed in the population of patient with baseline AFP level ≥400 ng/mL (consistent subgroup effects are observed). Therefore, there are no concerns regarding efficacy in specific subgroups in the studied population.

Baseline AFP level is a prognostic factor in HCC, with prognosis becoming increasingly poorer with increasing baseline AFP level (see **Error! Reference source not found.**). The applicant has shown that baseline AFP level is predictive of ramucirumab efficacy, with patients who have low AFP level having no benefit from ramucirumab while patients with baseline AFP ≥400 ng/mL do. In view of these findings, and because the cut-off of 400 ng/mL is in principle chosen arbitrarily, it is important to determine whether the chosen cut-off is adequate, and determine what the relative benefit from ramucirumab treatment is for different groups of patients according to baseline AFP level within the targeted population, e.g. for four quartiles above 400 ng/mL within the patient population studied in the pivotal study. Subpopulation Treatment Effect Pattern Plot (STEPP) analyses of REACH and REACH-2 were submitted in addition to the associated forest plots by AFP quartile (data not shown), to assess whether the chosen cut-off was adequate and to determine what the relative benefit from ramucirumab treatment was for different groups of patients according to baseline AFP level within the targeted population. Based on this data, it was concluded that the chosen cut-off of ≥400 ng/mL can be considered adequate and the relative benefit from ramucirumab treatment across the different groups of patients according to baseline AFP level within the targeted population can be considered similar.

Special populations: *Elderly patients:* patients up to above 75 years of age were treated in the pivotal study. The subgroup analyses showed that efficacy both in patients above 65 years of age, as well as in patients above 75 years of age was similar to efficacy in the overall population.

2.4.5. Conclusions on the clinical efficacy

Although limited, ramucirumab did demonstrate a statistically significant OS benefit of 1.2 months (HR 0.71) in the confirmatory phase 3 study REACH-2 in the second-line setting in HCC in patients with AFP ≥400 ng/mL, without an apparent detrimental effect on QoL. The fact that the patient population in the pivotal study can be regarded as relatively selected is mitigated by adequate information in section 5.1 of the SmPC reflecting the eligibility criteria of the study. Also, the relevant data on the observed exposure-response relationship have been described in section 5.2 of the SmPC.

2.5. Clinical safety

Introduction

Of the currently approved indications, i.e. the treatment of gastric cancer, non-small cell lung cancer and colorectal cancer, ramucirumab as monotherapy is only approved for the treatment of gastric cancer. The most common adverse drug reactions observed in single-agent ramucirumab-treated gastric cancer patients at a rate of ≥5% and ≥2% higher than placebo were hypertension, diarrhoea, headache, and hyponatraemia. The most serious adverse reactions associated with ramucirumab treatment (across all approved indications and thus as a single agent or in combination with cytotoxic chemotherapy) were: gastrointestinal (GI) perforation, severe GI haemorrhage, and arterial thromboembolic events (ATEs).

Patient exposure

The safety analysis of ramucirumab in patients with HCC and AFP ≥400 ng/mL, after intolerance to or disease progression on or after prior sorafenib, focused on the pooled safety data from the safety population from the pivotal REACH-2 study plus the subpopulation of patients from the supportive REACH study with baseline AFP ≥400 ng/mL (hereafter referred to as the "pooled safety population (AFP ≥400 ng/mL)") (see Table 32). In this pooled safety population (AFP ≥400 ng/mL), the ramucirumab treatment group included 316 patients (197 from REACH-2 and 119 from REACH) and the placebo treatment group included 223 patients (95 from REACH-2 and 128 from REACH). For a description of both studies refer to section 2.4.2. Main study and 2.4.3 Supportive studies.

For completeness, the results of this safety analysis were compared with a safety analysis from the pooled population of REACH-2 and REACH regardless of AFP level (hereafter referred to as the "pooled overall safety population" (see Table 32). In addition, the results of this safety analysis were compared with the safety analysis from the ramucirumab monotherapy-treated gastric cancer patient population from the pivotal study I4T-IE-JVBD (REGARD) (Cyramza gastric cancer EPAR) (hereafter referred to as the "REGARD gastric cancer safety population").

Table 32: Analysis populations for safety

Population	Definition	No. of patients in safety population (ramucirumab vs. placebo)
Pooled safety population (AFP ≥400 ng/mL)	Population that included the REACH-2 safety population plus the subgroup of patients in the REACH safety population with AFP ≥400 ng/mL.	539 (316 vs. 223)
Pooled overall safety population	Population that included the REACH-2 safety population plus the REACH safety population, irrespective of baseline AFP.	845 (474 vs. 371)

Abbreviations: AFP = alpha-fetoprotein; No. = number.

As a result of the eligibility criteria for both the REACH-2 and the REACH study, all patients in the pooled safety population (AFP ≥400 ng/mL) had a C-P score of <7 (C-P Class A only), an ECOG PS <2, and only

mildly impaired renal function at worst (creatinine clearance ≥60 mL/min for REACH-2 and >50 mL/min for REACH). Patients with esophageal or gastric varices that required immediate intervention or represented a high bleeding risk were excluded, as were patients with a history of hepatic encephalopathy, and patients receiving chronic anti-platelet therapy (e.g. clopidogrel, ticlopidine, dipyridamole, or anagrelide) or nonsteroidal anti-inflammatory drugs. In addition, patients with evidence of portal hypertension or any prior history of variceal bleeding were required to have had endoscopic evaluation within the 3 months prior to randomisation.

The treatment groups were generally balanced in terms of baseline demographics and baseline disease characteristics. The median age was 63 years (range, 26 to 88 years), the majority of patients were male (80.1%), 35.1% of patients were white and 53.6% of patients were Asian, and 53.6% of patients had an ECOG PS of 0. Approximately 86% of patients had BCLC Stage C HCC, 73% had extrahepatic spread, 35% of patients had macrovascular invasion, 42% of patients had hepatitis B, and 26% of patients had hepatitis C. Patients who were intolerant to sorafenib made up 13% of the pooled safety population (AFP ≥400 ng/mL).

Apart from baseline AFP level, the baseline demographics and baseline disease characteristics in the pooled overall safety population were generally consistent with those in the pooled safety population (AFP ≥400 ng/mL).

Ramucirumab 8 mg/kg or placebo was administered IV Q2W in REACH-2 and REACH. Treatment continued until disease progression, occurrence of intolerable toxicity, or when another criterion for discontinuation was met. At the time of the data cut-off date (15 March 2018), 13 (4.1%) patients in the ramucirumab treatment group of the pooled safety population (AFP ≥400 ng/mL) and no patients in the placebo treatment group were on study treatment. The majority of treatment discontinuations were due to disease progression (ramucirumab: 69.0%; placebo: 83.9%). The median duration of therapy was 11.93 weeks (with a median of 5 cycles received) in the ramucirumab vs. 7.00 weeks (with a median of 3 cycles received) in the placebo treatment group, respectively (see Table 33). The overall duration of exposure expressed in Patient Year (PY) was 111.7 for the ramucirumab treatment group and 45.9 for the placebo treatment group. The median cumulative dose of ramucirumab was greater than the median cumulative dose of placebo (40.0 mg/kg vs. 25.0 mg/kg, respectively). The median relative dose intensity was high and consistent with the targeted dose in both treatment groups (ramucirumab: 98.25%; placebo: 99.61%).

Table 33: Summary of extent of exposure in pooled safety population (AFP ≥400 ng/mL)

	Ramucirumab + BSC N = 316	**Placebo + BSC N = 223**
Duration of Therapy (weeks)		
Mean (SD)	18.45 (19.19)	10.75 (10.38)
Median	11.93	7.00
Min-Max	2.00-107.29	2.00-77.00
Cycles Received Per Patient (%)[a]		
Mean (SD)	8.76 (9.04)	5.27 (5.00)
Median	5	3
Min-Max	1-51	1-38
Cumulative Dose (mg/kg)		
Mean (SD)	69.02 (71.11)	41.86 (39.41)
Median	40.00	24.97
Min-Max	7.73-411.64	7.90-293.42
Dose Intensity (mg/kg/week)[b]		
Mean (SD)	3.81 (0.38)	3.95 (0.22)
Median	3.93	3.98
Min-Max	1.65-4.38	2.48-4.51
Relative Dose Intensity (%)[c]		
Mean (SD)	95.21 (9.48)	98.65 (5.55)
Median	98.25	99.61
Min-Max	41.35-109.38	62.10-112.66

Abbreviations: AFP = alpha-fetoprotein; BSC = best supportive care; Max = maximum; Min = minimum; N = number of patients in the safety population; SD = standard deviation.
[a] Patient is considered to have received a treatment cycle after receiving at least 1 dose of study drug, ramucirumab or placebo, either partial or complete.
[b] Dose intensity is defined as actual cumulative amount of mg/kg per week.
[c] Relative dose intensity is calculated as (dose intensity / planned weekly dose intensity [8 mg/kg / 2 weeks]) * 100%.

Dose reductions occurred at a low incidence in both treatment groups (ramucirumab: 5.1% vs. placebo: 1.3%). A higher incidence of dose delays and dose omissions was observed in the ramucirumab treatment group compared with placebo (delays: 11.4% vs. 5.4%, respectively; omissions: 28.2% vs. 11.2%, respectively), the majority being a single dose delay or omission (single delay: 7.6% vs. 4.5, respectively; single omission: 17.1% vs. 9.4%, respectively).

The median duration of therapy and median (relative) dose intensity of ramucirumab in the pooled safety population (AFP >400 ng/mL) were generally consistent with that of the pooled overall safety population, and of the REGARD gastric cancer population.

Adverse events

In the pooled safety population (≥400 ng/mL), most patients experienced at least 1 TEAE of any grade (ramucirumab: 96.8%; placebo: 92.4%) (see Table 34). The percentages in almost all AE categories are (numerically) higher for the ramucirumab treatment group compared with the placebo treatment group.

Table 34: Overview of Adverse Events in pooled safety population (AFP ≥400 ng/mL)

Adverse Event Category[a]	Ramucirumab + BSC N = 316 n (%)	Placebo + BSC N = 223 n (%)
Patients with ≥1 TEAE	306 (96.8)	206 (92.4)
Related to Study Treatment[b]	226 (71.5)	105 (47.1)
Patients with ≥1 TEAE CTCAE Grade ≥3	181 (57.3)	116 (52.0)
Related to Study Treatment[b]	72 (22.8)	28 (12.6)
Patients with ≥1 SAE	112 (35.4)	75 (33.6)
Related to Study Treatment[b]	32 (10.1)	17 (7.6)
Patients who discontinued study treatment due to AE	52 (16.5)	23 (10.3)
Related to Study Treatment[b]	30 (9.5)	8 (3.6)
Patients who discontinued study treatment due to SAE	33 (10.4)	18 (8.1)
Related to Study Treatment[b]	18 (5.7)	8 (3.6)
Patients who died due to AE on study treatment or within 30 days of discontinuation from study treatment[c,d]	10 (3.2)	6 (2.7)
Related to Study Treatment[b]	4 (1.3)	2 (0.9)

Abbreviations: AE = adverse event; AFP = alpha-fetoprotein; BSC = best supportive care; CTCAE = Common Terminology for Regulatory Activities; n = number of patients in the specified category; N = number of patients in the safety population; SAE = serious adverse event; TEAE = treatment-emergent adverse event.
[a] Patients may be counted in more than 1 category.
[b] Includes events that were considered related to study treatment as judged by the investigator.
[c] Patients who died due to AE within 30 days of discontinuation from study treatment does not include the patients who died due to AE on study treatment.
[d] Deaths are also included as SAEs and discontinuations due to AEs.

The incidence of AEs in all AE categories in the pooled overall safety population was generally consistent with that in the pooled safety population (AFP ≥400 ng/mL) as summarised in Table 31.

Table 35 presents TEAEs occurring in ≥10% of patients in the ramucirumab treatment groups in the pooled safety population (AFP ≥400 ng/mL). Most of the TEAEs in the pooled safety population (AFP ≥400 ng/mL) seem consistent with the underlying disease state of HCC and the percentages of most reported any-grade TEAEs were similar between treatment groups. However, any-grade TEAEs reported in ≥10% of patients in the ramucirumab treatment group and for which the incidence was ≥5 percentage points higher in the ramucirumab treatment group than in the placebo treatment group, respectively, were peripheral oedema (29.1% vs. 17.0%), fatigue (24.1% vs. 17.5%), ascites (20.9% vs. 14.8%), hypertension (20.9% vs. 9.0%), diarrhoea (18.4% vs. 11.7%), proteinuria (17.7% vs. 5.4%), headache (16.8% vs. 6.3%), pyrexia

(12.7% vs. 6.3%), epistaxis (12.3% vs. 5.4%), asthenia (11.7% vs. 6.3%), and hypoalbuminemia (11.4% vs. 4.9%).

The majority of Grade ≥3 TEAEs occurring in both treatment groups were Grade 3 events (ramucirumab: 43.0%; placebo: 34.1%). Grade 4 TEAEs (ramucirumab: 5.1%; placebo: 9.0%) and Grade 5 TEAEs (ramucirumab: 9.2%; placebo: 9.0%) occurred at similar incidences in both treatment groups. Of note, the reported incidence of Grade 5 TEAEs is much higher than the reported incidence of deaths due to AEs while on treatment or within 30 days after discontinuation from study treatment in Table 34 above. The reason is that the reported percentages also included the cases where, based on the AE CRF, the AE outcome was reported as 'FATAL', where most death events reported by the investigator were attributed to disease, rather than assigned as AE. Hypertension was the only Grade ≥3 TEAE for which the incidence was ≥5 percentage points higher in the ramucirumab than in the placebo treatment group (12.0% vs. 3.6%, respectively; no Grade 4 or 5).

Table 35: Treatment-Emergent Adverse Events occurring in ≥10% of patients in ramucirumab arm by decreasing incidence in pooled safety population (AFP ≥400 ng/mL)

MedDRA Preferred Term	Ramucirumab + BSC N = 316 n (%)		Placebo + BSC N = 223 n (%)	
	Any Grade	Grade ≥3	Any Grade	Grade ≥3
Patients with ≥1 TEAE	**306 (96.8)**	**181 (57.3)**	**206 (92.4)**	**116 (52.0)**
Oedema peripheral	92 (29.1)	3 (0.9)	38 (17.0)	0
Fatigue	76 (24.1)	8 (2.5)	39 (17.5)	6 (2.7)
Decreased appetite	70 (22.2)	4 (1.3)	46 (20.6)	1 (0.4)
Ascites	66 (20.9)	15 (4.7)	33 (14.8)	9 (4.0)
Hypertension	66 (20.9)	38 (12.0)	20 (9.0)	8 (3.6)
Nausea	62 (19.6)	0	36 (16.1)	0
Abdominal pain	61 (19.3)	5 (1.6)	41 (18.4)	9 (4.0)
Diarrhoea	58 (18.4)	1 (0.3)	26 (11.7)	1 (0.4)
Proteinuria	56 (17.7)	4 (1.3)	12 (5.4)	0
Headache	53 (16.8)	1 (0.3)	14 (6.3)	1 (0.4)
Constipation	43 (13.6)	1 (0.3)	34 (15.2)	2 (0.9)
Pyrexia	40 (12.7)	0	14 (6.3)	0
Epistaxis	39 (12.3)	1 (0.3)	12 (5.4)	0
Asthenia	37 (11.7)	9 (2.8)	14 (6.3)	1 (0.4)
Aspartate aminotransferase increased	36 (11.4)	15 (4.7)	35 (15.7)	25 (11.2)
Cough	36 (11.4)	1 (0.3)	15 (6.7)	0
Hypoalbuminaemia	36 (11.4)	2 (0.6)	11 (4.9)	1 (0.4)
Vomiting	35 (11.1)	2 (0.6)	29 (13.0)	0
Back pain	32 (10.1)	1 (0.3)	19 (8.5)	5 (2.2)

Abbreviations: AFP = alpha-fetoprotein; BSC = best supportive care; MedDRA = Medical Dictionary for Regulatory Activities, Version 20.1; N = number of patients in the pooled safety population; TEAE = treatment-emergent adverse event.

The TEAEs (both any Grade as well as Grade ≥3) and their reported incidences in the pooled overall safety population were generally consistent with those reported in the pooled safety population (AFP ≥400 ng/mL). When compared with the known safety profile of single-agent ramucirumab from the REGARD gastric cancer population, no new safety signals were identified in the assessment of TEAEs in the pooled safety population (AFP ≥400 ng/mL).

An additional analysis of TEAEs was performed in which clinically synonymous Medical Dictionary for Regulatory Activities (MedDRA) PTs were consolidated (Table 33). The results of this consolidated term TEAE

analysis did not reveal any new safety concerns or new notable findings. The consolidated terms of fatigue (35.4% vs. 23.3%), thrombocytopenia (14.9% vs. 4.5%), hypoalbuminemia (12.7% vs. 4.9%), and neutropenia (7.0 vs. 2.5%) were reported with a higher (≥5 percentage point difference) incidence in the ramucirumab than the placebo treatment group. In this analysis, there was no Grade ≥3 TEAE for which the incidence was ≥5 percentage points higher in the ramucirumab than in the placebo treatment group.

Table 36: Summary of selected consolidated Treatment-Emergent Adverse Events occurring in ≥5% of patients in ramucirumab arm by decreasing incidence in pooled safety population (AFP ≥400 ng/mL)

Consolidated Term MedDRA Preferred Term	Ramucirumab + BSC N = 316 n (%)		Placebo + BSC N = 223 n (%)	
	Any Grade	Grade ≥3	Any Grade	Grade ≥3
Fatigue	**112 (35.4)**	**17 (5.4)**	**52 (23.3)**	**7 (3.1)**
Fatigue	76 (24.1)	8 (2.5)	39 (17.5)	6 (2.7)
Asthenia	37 (11.7)	9 (2.8)	14 (6.3)	1 (0.4)
Abdominal Pain	**79 (25.0)**	**6 (1.9)**	**55 (24.7)**	**10 (4.5)**
Abdominal pain	61 (19.3)	5 (1.6)	41 (18.4)	9 (4.0)
Abdominal pain upper	22 (7.0)	2 (0.6)	13 (5.8)	1 (0.4)
Abdominal pain lower	2 (0.6)	0	1 (0.4)	0
Hepatic pain	2 (0.6)	0	1 (0.4)	0
Gastrointestinal pain	0	0	1 (0.4)	0
Thrombocytopenia	**47 (14.9)**	**16 (5.1)**	**10 (4.5)**	**2 (0.9)**
Thrombocytopenia	25 (7.9)	10 (3.2)	8 (3.6)	1 (0.4)
Platelet count decreased	22 (7.0)	6 (1.9)	2 (0.9)	1 (0.4)
Hypoalbuminaemia	**40 (12.7)**	**2 (0.6)**	**11 (4.9)**	**1 (0.4)**
Hypoalbuminaemia	36 (11.4)	2 (0.6)	11 (4.9)	1 (0.4)
Blood albumin decreased	4 (1.3)	0	0	0
Hyperbilirubinaemia	**37 (11.7)**	**13 (4.1)**	**38 (17.0)**	**29 (13.0)**
Blood bilirubin increased	31 (9.8)	10 (3.2)	24 (10.8)	17 (7.6)
Hyperbilirubinaemia	7 (2.2)	3 (0.9)	14 (6.3)	12 (5.4)
Anemia	**32 (10.1)**	**12 (3.8)**	**19 (8.5)**	**5 (2.2)**
Anaemia	30 (9.5)	12 (3.8)	19 (8.5)	5 (2.2)
Hematocrit decreased	0	0	1 (0.4)	0
Hemoglobin decreased	2 (0.6)	0	1 (0.4)	0
Rash	**23 (7.3)**	**0**	**16 (7.2)**	**0**
Rash	20 (6.3)	0	13 (5.8)	0
Rash pruritic	1 (0.3)	0	0	0
Dermatitis	0	0	1 (0.4)	0
Rash maculo-papular	1 (0.3)	0	2 (0.9)	0
Rash pustular	2 (0.6)	0	0	0
Neutropenia	**22 (7.0)**	**8 (2.5)**	**2 (0.9)**	**1 (0.4)**
Neutrophil count decreased	12 (3.8)	4 (1.3)	0	0
Neutropenia	10 (3.2)	4 (1.3)	2 (0.9)	1 (0.4)
Hyperkalaemia	**19 (6.0)**	**5 (1.6)**	**8 (3.6)**	**0**
Hyperkalaemia	19 (6.0)	5 (1.6)	8 (3.6)	0
Hyponatraemia	**17 (5.4)**	**16 (5.1)**	**9 (4.0)**	**5 (2.2)**
Hyponatraemia	17 (5.4)	16 (5.1)	9 (4.0)	5 (2.2)

Abbreviations: AFP = alpha-fetoprotein; BSC = best supportive care; MedDRA = Medical Dictionary for Regulatory Activities, Version 20.1; N = number of patients in the safety population; n = number of patients in the specified category.

The consolidated terms and their reported incidences in the pooled overall safety population were generally consistent with those reported in the pooled safety population (AFP ≥400 ng/mL).

Adverse events of special interest

Adverse events of special interest consist of pre-specified selected AEs that are given special consideration because they have been associated with other agents in a similar class of drugs as ramucirumab, such as agents that inhibit VEGF- or VEGF Receptor 2-mediated angiogenesis; or were observed in preclinical evaluation or previous clinical studies.

The following terms are considered AESIs for ramucirumab: infusion-related reactions (IRRs), hypertension, proteinuria, arterial thromboembolic events (ATEs), venous thromboembolic events (VTEs), bleeding/haemorrhagic events, gastrointestinal (GI) perforation, congestive heart failure (CHF), wound healing complications, fistula, liver failure/liver injury, and reversible posterior leukoencephalopathy syndrome (RPLS).

No wound healing complications or reversible posterior leukoencephalopathy syndrome events were observed in the pooled safety population (AFP ≥400 ng/mL). For a summary of the other AESIs reported in the pooled safety population (≥400 ng/mL) see Table 37.

Table 37: Adverse Events of Special Interest in pooled safety population (AFP ≥400 ng/mL)

AESI term[a]	**Ramucirumab + BSC N = 316 n (%)**		**Placebo + BSC N = 223 n (%)**	
	Any Grade	**Grade ≥3**	**Any Grade**	**Grade ≥3**
Patients with any treatment emergent AESI	159 (50.3)	63 (19.9)	71 (31.8)	30 (13.5)
Infusion-related reactions[b,c,d]				
Narrow events on date of ramucirumab administration[e]	30 (9.5)	1 (0.3)	7 (3.1)	0
Broad events on date of ramucirumab administration[e]	83 (26.3)	1 (0.3)	30 (13.5)	1 (0.4)
Narrow events after date of ramucirumab administration[f]	27 (8.5)	1 (0.3)	20 (9.0)	0
Broad events after date of ramucirumab administration[f]	NP	NP	NP	NP
Hypertension	68 (21.5)	40 (12.7)	20 (9.0)	8 (3.6)
Proteinuria	59 (18.7)	4 (1.3)	12 (5.4)	0
Arterial thromboembolic events	5 (1.6)	3 (0.9)	3 (1.3)	2 (0.9)
Venous thromboembolic events	3 (0.9)	1 (0.3)	6 (2.7)	5 (2.2)
Bleeding/hemorrhagic events	79 (25.0)	15 (4.7)	40 (17.9)	15 (6.7)
Gastrointestinal perforation	2 (0.6)	2 (0.6)	2 (0.9)	2 (0.9)
Congestive heart failure	1 (0.3)	1 (0.3)	1 (0.4)	1 (0.4)
Fistula	1 (0.3)	0	0	0
Liver failure/liver injury	140 (44.3)	63 (19.9)	87 (39.0)	59 (26.5)

Abbreviations: AESI = Adverse Events of Special Interest; N = number of subjects in safety population; n = number of subjects in the specified category; NP = not provided.
[a] All AESIs are composite terms.
[b] Infusion-related reactions includes hypersensitivity and anaphylactic reactions.
[c] Infusion-related reactions were classified as either events occurring on the day of drug administration, or events occurring after the day of drug administration but prior to the next drug administration.
[d] 'Narrow' events include Preferred Terms that are highly likely to represent the condition of interest, while 'broad' terms include additional Preferred Terms that may represent the condition of interest, but may also prove to be of little or no interest upon closer inspection. 'Broad' events after date of ramucirumab
[e] Event timing was captured in addition to event date; if event timing was missing but an event occurred on the drug administration date, that event was included in all time categories <24 hours.
[f] Event timing was captured in addition to event date; if event timing was missing but an event occurred on the drug administration date, that event was included in this report.

Any-grade AESIs for which the incidence was ≥5 percentage points higher in the ramucirumab treatment group than in the placebo treatment group, respectively, were infusion-related reactions (9.5% vs. 3.1%), hypertension (21.5% vs. 9.0%), proteinuria (18.7% vs. 5.4%), bleeding/haemorrhagic events (25.0% vs. 17.9%), and liver failure/liver injury (44.3% vs. 39.0%) (Table 34). These 5 AESIs are discussed below in more detail. The majority of Grade ≥3 AESIs that occurred in both treatment groups occurred at similar incidences in both treatment groups. Hypertension was the only Grade ≥3 AESI for which the incidence was

≥5 percentage points higher in the ramucirumab than in the placebo treatment group (12.7% vs. 3.6%, respectively).

Infusion-related reactions

Infusion-related reactions (IRRs) includes hypersensitivity and anaphylactic reactions. IRRs were classified as either events occurring on the day of drug administration, or events occurring after the day of drug administration but prior to the next drug administration.

Per the REACH-2 protocol, premedication with a histamine H1 antagonist, such as diphenhydramine hydrochloride (or equivalent), was required prior to infusion of ramucirumab/placebo. It was recommended in REACH.

The incidence of any-grade IRRs occurring on the day of drug administration was higher in the ramucirumab than in the placebo treatment group (9.5% vs. 3.1%, respectively) (Table 34). One (0.3%) patient in the ramucirumab treatment group vs. no patient in the placebo treatment group experienced Grade 3 IRRs. No Grade 4 or Grade 5 events were reported in either treatment group. No anaphylactic reactions were observed.

The incidence of any-grade potential IRRs occurring after the day of drug administration but prior to the next drug administration was similar between treatment groups (ramucirumab: 8.5%; placebo: 9.0%) (Table 34). There was 1 Grade 3 event in the ramucirumab treatment group vs. no Grade 3 event in the placebo treatment group. No Grade 4 or Grade 5 events were reported in either treatment group. Three patients (0.9%) in the ramucirumab treatment group vs. no patient (0%) in the placebo treatment group discontinued study treatment due to infusion-related reactions.

Hypertension

In the pooled safety population (AFP ≥400 ng/mL), a higher incidence of hypertension was observed in patients receiving ramucirumab (21.5%) than in patients receiving placebo (9.0%) (Table 34). The incidence of Grade ≥3 hypertension was also higher in the ramucirumab than in the placebo treatment group (12.7% vs. 3.6%, respectively). No Grade 4 or Grade 5 hypertension events were observed in either treatment group. No patients in either treatment group discontinued study treatment due to hypertension events.

Proteinuria

In the pooled safety population (AFP ≥400 ng/mL), a higher incidence of proteinuria was observed in patients receiving ramucirumab (18.7%) than in patients receiving placebo (5.4%) (Table 34). The majority of proteinuria events were Grade 1-2 in both treatment groups. Four patients (1.3%) in the ramucirumab treatment group vs. no patient (0%) in the placebo treatment group experienced Grade ≥3 proteinuria. Six patients (1.9%) in the ramucirumab treatment group vs. no patient (0%) in the placebo treatment group discontinued study treatment due to proteinuria events.

Bleeding/haemorrhagic events

In the pooled safety population (AFP ≥400 ng/mL), any-grade bleeding/haemorrhagic events were observed at a higher incidence in the ramucirumab than the placebo treatment group (25.0% vs. 17.9%, respectively) (Table 34). Epistaxis was the most frequently reported bleeding event in both treatment groups (ramucirumab: 12.3%; placebo: 5.4%). No difference was observed between the ramucirumab and placebo treatment groups in the incidence of GI haemorrhagic events of any grade (7.6% vs. 8.5%, respectively). The incidence of Grade ≥3 bleeding/haemorrhagic events was lower in the ramucirumab than in the placebo treatment group (4.7% vs. 6.7%, respectively). Eight patients (2.5%) in the ramucirumab treatment group vs. 5 patients (2.2%) in the placebo treatment group discontinued study treatment due to bleeding/haemorrhagic events.

Liver failure/liver injury

In the pooled safety population (AFP ≥400 ng/mL), the incidence of any-grade clinical and laboratory liver failure/liver injury events was higher in the ramucirumab than in the placebo treatment group (44.3% vs. 39.0%, respectively) (Table 34). These any-grade clinical and laboratory liver failure/liver injury events were predominantly Grade 1-2 ascites (16.1% vs. 10.8%) and Grade 1-2 hypoalbuminemia (10.8% vs. 4.5%). In contrast, the incidence of Grade ≥3 clinical and laboratory liver failure/liver injury was lower in the ramucirumab than in the placebo treatment group (19.9% vs. 26.5%, respectively). The incidence of Grade 5 clinical and laboratory liver failure/liver injury was 1.3% in both treatment groups. When adjusted for the duration of exposure to study treatment, the incidence rates per 100 PY of any-grade clinical and laboratory liver failure/liver injury events were 125.3 for ramucirumab and 189.5 for placebo. Sixteen patients (5.1%) in the ramucirumab treatment group vs. 10 patient (4.5%) in the placebo treatment group discontinued study treatment due to clinical and laboratory liver failure/liver injury events.

Hepatic encephalopathy is of particular interest and is a clinically significant AE which may occur in HCC patients in the setting of deteriorating hepatic function due to underlying chronic liver disease and/or progressive disease. During the REACH study conduct, a numeric imbalance of liver-related AEs, specifically for hepatic encephalopathy, between the 2 treatment arms was observed from the Independent Data Monitoring Committee. Based on this safety finding, the study was modified including (a) inclusion of patients with C-P A only, (b) exclusion of patients with cirrhosis (any degree) **and** a history of hepatic encephalopathy or clinically meaningful ascites resulting from cirrhosis, and (c) an additional criterion for discontinuation of study drug (ramucirumab or placebo) for the new occurrence of hepatic encephalopathy and/or hepatorenal syndrome resulting from liver cirrhosis. The REACH-2 protocol also included these criteria, thus among others excluding patients with a history of hepatic encephalopathy. All protocols assessing ramucirumab subsequent to REACH, irrespective of indication, were amended during this timeframe, as appropriate.

Any-grade hepatic encephalopathy (including hepatic coma) was observed in 15 patients (4.7%) in the ramucirumab treatment group compared with 2 patients (0.9%) in the placebo treatment group in the pooled safety population (AFP ≥400 ng/mL), and Grade ≥3 in 11 patients (3.5%) vs. 1 patient (0.4%), respectively. Of these patients, 8 ramucirumab- and both placebo-treated were reported in the setting of progressive disease. The incidence of any-Grade and Grade ≥3 hepatic encephalopathy events assessed by the investigators as related to study-treatment was 1.9% (n = 6) and 1.3% (n = 4) in ramucirumab-treated patients, respectively. There were no hepatic encephalopathy events assessed by the investigators as related to study-treatment in placebo-treated patients. Four patients (1.3%) in the ramucirumab treatment group vs. no patient (0%) in the placebo treatment group discontinued study treatment due to hepatic encephalopathy. In the pivotal REACH-2 study, any-Grade and Grade ≥3 hepatic encephalopathy (including hepatic coma) was observed in 9 (4.6%) and 7 patients (3.6%), respectively in the ramucirumab treatment group - thus at a comparable incidence to the pooled safety population (AFP ≥400 ng/mL) - compared with no patient (0%) in the placebo treatment group. In the supportive REACH study (in the overall patient population, regardless of AFP level), any-Grade and Grade ≥3 hepatic encephalopathy (including hepatic coma) was observed in 19 (7.0%) and 9 patients (3.3%), respectively in the ramucirumab treatment group, compared with 3 (1.1%) and 2 patients (0.7%), respectively in the placebo treatment group.

Hepatorenal syndrome is of particular interest in the advanced HCC disease setting and was observed in 1.3% of patients (n = 4) in the ramucirumab treatment group compared with no patients in the placebo treatment group. All events in the ramucirumab treatment group were Grade ≥3. Two events occurred in the setting of disease progression and were not considered related to study drug. Two patients (0.6%) in the ramucirumab treatment group discontinued study treatment due to hepatorenal syndrome.

In the pooled overall safety population the incidence of AESIs in all categories was generally consistent with that in the pooled safety population (AFP ≥400 ng/mL) as summarised in Table 37. When compared with the

known safety profile of ramucirumab (as monotherapy) in the REGARD gastric cancer population, the incidence of the AESIs hypertension and proteinuria were higher in the ramucirumab treatment group in the pooled safety population (AFP ≥400 ng/mL), so was the incidence of the AESIs bleeding/haemorrhagic events and liver failure/liver injury but these two in both treatment groups (which could be expected given the HCC disease setting). The incidence of the AESI infusion-related reactions was higher than in the REGARD gastric cancer population, but was similar to the incidence observed in ramucirumab phase 2 gastric cancer studies, i.e. 11.5%.

Adverse drug reactions

For the monotherapy and combination therapy ADR tables in section 4.8 of the SmPC, the MAH integrated the safety data from the clinical database of the pivotal phase 3 clinical trials for the currently approved indications and HCC, as appropriate based on the trial study treatment regimen. These safety data for each clinical study were created at their primary outcome analyses.

The monotherapy ADR table is based on the pooled safety cohort comprising of 2 datasets of single-agent ramucirumab from Phase 3 studies: REGARD (I4T-IE-JVBD) and REACH-2 (I4TMC-JVDE)/REACH (I4T-IE-JVBF) (alpha fetoprotein ≥400 ng/mL).

Table 38: ADRs reported in patients treated with ramucirumab as monotherapy in phase 3 clinical trials (REGARD, REACH-2 and REACH patients with alpha fetoprotein ≥ 400 ng/ml)

System Organ Class	ADR	Cyramza (N=552) All grades toxicity (%)	Frequency
Blood and lymphatic system disorders	Thrombocytopenia[a]	10.5	Very common
	Neutropenia[a]	6.0	Common
Metabolism and nutrition disorders	Hypokalaemia[a,b]	1.1	Common
	Hyponatraemia[a]	3.1	Common
	Hypoalbuminaemia[a]	7.2	Common
Nervous system disorders	Hepatic encephalopathy[c]	2.7	Common
	Headache	13.6	Very common
Vascular disorders	Hypertension[a,d]	19.2	Very common
	Arterial thromboembolic events[a]	1.6	Common
Respiratory, thoracic, and mediastinal disorders	Epistaxis	9.1	Common
Gastrointestinal disorders	Intestinal obstruction[a]	1.6	Common
	Gastrointestinal perforation[a]	0.7	Uncommon
	Abdominal pain[a,e]	14.3	Very common
	Diarrhoea	16.7	Very common
Skin and subcutaneous tissue disorders	Rash[a]	6.0	Common
Renal and urinary disorders	Proteinuria[a,f]	12.0	Very common
General disorders and administration site disorders	Infusion-related reactions[a]	6.3	Common
	Peripheral oedema	20.3	Very common

[a] Terms represent a group of events that describe a medical concept rather than a single event or preferred term.
[b] Includes: hypokalaemia and blood potassium decreased.
[c] Based on study REACH-2 and REACH (single-agent ramucirumab in HCC). Includes hepatic encephalopathy and hepatic coma.
[d] Includes: blood pressure increased and hypertension.
[e] Includes: abdominal pain, abdominal pain lower, abdominal pain upper, and hepatic pain.
[f] Includes one case of nephrotic syndrome.

The combination therapy ADR table is based on the pooled safety cohort comprising of 3 Phase 3 clinical trials in licensed indications in which ramucirumab is used in combination with chemotherapy: RAINBOW (I4T-IE-JVBE), REVEL (I4T-MC-JVBA), and RAISE (I4T-MCJVBB).

Table 39: ADRs reported in patients treated with ramucirumab in combination with chemotherapy in phase 3 clinical trials (RAINBOW, REVEL and RAISE)

System Organ Class	ADR	Cyramza (N=1483) All grades toxicity (%)	Frequency
Infections and infestations	Sepsis[a,b]	1.4	Common
Blood and lymphatic system disorders	Neutropenia[a]	56.2	Very common
	Leukopenia[a,c]	21.2	Very common
	Thrombocytopenia[a]	18.7	Very common
	Febrile neutropenia[d]	8.7	Common
Metabolism and nutrition disorders	Hypoalbuminaemia[a]	6.3	Common
	Hyponatraemia[a]	3.9	Common
Vascular disorders	Hypertension[a,e]	19.4	Very common
Respiratory, thoracic, and mediastinal disorders	Epistaxis	26.5	Very common
Gastrointestinal disorders	Gastrointestinal haemorrhage events[a,f]	7.8	Common
	Gastrointestinal perforation[a]	1.3	Common
	Stomatitis	25.2	Very common
	Diarrhoea	41.9	Very common
Skin and subcutaneous tissue disorders	Palmar-plantar erthyrodysaesthesia syndrome[g]	5.8	Common
Renal and urinary disorders	Proteinuria[a,h]	11.2	Very common
General disorders and administration site disorders	Fatigue[a,i]	56.2	Very common
	Mucosal inflammation[d]	13.7	Very common
	Peripheral oedema	19.7	Very common

[a] Terms represent a group of events that describe a medical concept rather than a single event or preferred term.
[b] Based on study RAINBOW (ramucirumab plus paclitaxel).
[c] Based on study RAINBOW (ramucirumab plus paclitaxel). Includes: leukopenia and white blood cell count decreased.
[d] Based on study REVEL (ramucirumab plus docetaxel).
[e] Includes: blood pressure increased, hypertension, and hypertensive cardiomyopathy.
[f] Based on study RAINBOW (ramucirumab plus paclitaxel) and study RAISE (ramucirumab plus FOLFIRI). Includes: anal haemorrhage, diarrhoea haemorrhage, gastric haemorrhage, gastrointestinal haemorrhage, haematemesis, haematochezia, haemorrhoidal haemorrhage, Mallory-Weiss syndrome, melaena, oesophageal haemorrhage, rectal haemorrhage, and upper gastrointestinal haemorrhage.
[g] Based on study RAISE (ramucirumab plus FOLFIRI).
[h] Includes cases of nephrotic syndrome.
[i] Based on study RAINBOW (ramucirumab plus paclitaxel) and study REVEL (ramucirumab plus docetaxel). Includes: fatigue and asthenia.

The ADR frequencies for monotherapy and combination therapy were determined from the incidence rates of any-grade events in ramucirumab-treated patients in the pooled monotherapy and combination therapy safety cohorts, respectively.

Serious adverse event/deaths/other significant events

Table 40 presents SAEs occurring in ≥1% of patients in the ramucirumab treatment group in the pooled safety population (AFP ≥400 ng/mL). A similar percentage of patients in both treatment groups had any-grade SAEs (ramucirumab: 35.4%; placebo: 33.6%) and Grade ≥3 SAEs (ramucirumab: 27.8%; placebo: 30.0%). No individual SAE occurred at higher incidence and with a difference of ≥2% in the ramucirumab group compared with placebo. In both treatment groups, all SAE terms were reported at an

incidence <5%. Hepatic encephalopathy was reported as a SAE in 6 patients (1.9%) in the ramucirumab treatment group vs. no patient (0%) in the placebo treatment group.

Table 40: Serious Adverse Events occurring in ≥1% of patients in ramucirumab arm, by decreasing incidence in pooled safety population (AFP ≥400 ng/mL)

MedDRA Preferred Term	Ramucirumab + BSC N = 316 n (%)		Placebo + BSC N = 223 n (%)	
	Any Grade	Grade ≥3	Any Grade	Grade ≥3
Patients with any SAE	**112 (35.4)**	**88 (27.8)**	**75 (33.6)**	**67 (30.0)**
Malignant neoplasm progression [a]	13 (4.1)	13 (4.1)	10 (4.5)	10 (4.5)
Ascites	9 (2.8)	5 (1.6)	3 (1.3)	3 (1.3)
Abdominal pain	6 (1.9)	3 (0.9)	5 (2.2)	4 (1.8)
Hepatic encephalopathy	6 (1.9)	5 (1.6)	0	0
Pneumonia	6 (1.9)	4 (1.3)	3 (1.3)	2 (0.9)
General physical health deterioration	5 (1.6)	5 (1.6)	2 (0.9)	2 (0.9)
Pyrexia	5 (1.6)	0	1 (0.4)	0
Dyspnoea	4 (1.3)	1 (0.3)	3 (1.3)	2 (0.9)
Oesophageal varices haemorrhage	4 (1.3)	4 (1.3)	8 (3.6)	8 (3.6)

Abbreviations: AFP = alpha-fetoprotein; BSC = best supportive care; MedDRA = Medical Dictionary for Regulatory Activities, Version 20.1; N = number of patients in the safety population; n = number of patients in specified category; SAE = serious adverse event.
[a] In REACH, malignant neoplasm progression could be entered by investigators as an adverse event regardless of whether this was considered related to study treatment. However, in REACH-2, malignant neoplasm progression was not considered as an adverse event unless related to study treatment.

The evaluation of SAEs in the pooled overall safety population was generally consistent with that in the pooled safety population (AFP ≥400 ng/mL). In the REGARD gastric cancer population the incidence of SAEs was higher in both treatment groups (ramucirumab: 44.9%; placebo: 44.3%) than in the pooled safety population (AFP ≥400 ng/mL).

Deaths in the pooled safety population (AFP ≥400 ng/mL) are summarised in Table 41. The incidence of deaths while on treatment or within 30 days after discontinuation from study treatment was 15.8% in the ramucirumab treatment group and 11.2% in the placebo treatment group, but the percentage of deaths due to AEs was similar (ramucirumab: 3.2%; placebo: 2.7%) and the majority of the deaths were due to disease progression, as reported by the investigator. The incidence of deaths due to AEs that occurred on treatment or within 30 days of after discontinuation from study treatment was similar in both treatment groups (ramucirumab: 3.2%; placebo: 2.7%). The AEs that lead to death in the ramucirumab treatment group were pneumonia (n = 2), acute kidney injury (n = 1), asthenia (n = 1), generalised oedema (n = 1), hepatorenal syndrome (n = 1), multiple organ dysfunction syndrome (n = 1), myocardial infarction (n = 1), renal failure (n = 1), and sudden death (n = 1).

Table 41: Deaths in pooled safety population (AFP ≥400 ng/mL)

	Ramucirumab + BSC N = 316 n (%)	Placebo + BSC N = 223 n (%)
All Deaths	**246 (77.8)**	**187 (83.9)**
Deaths on Therapy	**19 (6.0)**	**9 (4.0)**
Adverse Events	8 (2.5)	4 (1.8)
Adverse Events Related to Study Treatment	4 (1.3)	1 (0.4)
Study Disease	11 (3.5)	5 (2.2)
Deaths on Therapy or within 30 days of Treatment Discontinuation	**50 (15.8)**	**25 (11.2)**
Adverse Events	10 (3.2)	6 (2.7)
Adverse Events Related to Study Treatment	4 (1.3)	2 (0.9)
Study Disease	40 (12.7)	19 (8.5)

Abbreviations: AE = adverse event; AFP = alpha-fetoprotein; BSC = best supportive care; CRF = case report form; N = number of patients in safety population; n = number of patients in specified category.
Note: Summary of death data was collected on a disposition CRF page (REACH-2) or the Death CRF page (REACH) where the site entered reason for death.
Note: "Deaths on Therapy" are included in "Deaths on Therapy or within 30 days of Treatment Discontinuation."
Note: "Adverse events" as reasons for death include "Adverse events related to study treatment."

The evaluation of deaths and deaths due to TEAEs in the pooled overall safety population was generally consistent with that in the pooled safety population (AFP ≥400 ng/mL). In the REGARD gastric cancer population the incidence of death due to an AE while on treatment or within 30 days after discontinuation from study treatment was higher in both treatment groups (ramucirumab: 9.3%; placebo: 13.0%) than in the pooled safety population (AFP ≥400 ng/mL).

Laboratory findings

Low-grade (Grade 1-2) abnormalities were noted in baseline levels of alanine aminotransferase (ALT), aspartate aminotransferase (AST), and alkaline phosphatase in a high proportion of patients in both treatment groups, and similar shifts were observed in these parameters.

Safety in special populations

Additional analyses for the pooled safety population (AFP ≥400 ng/mL) summarising TEAEs by subgroups, including age, gender, race, and geographic region are provided in Table 42.

Regarding the special patient population with impaired hepatic/renal function, the eligibility criteria for both the REACH-2 and the REACH study included: total bilirubin ≤1.5 times upper limit of institutional normal value (ULN), aspartate transaminase (AST) and alanine transaminase (ALT) ≤5 × ULN, and creatinine clearance ≥60 mL/min for REACH-2 and >50 mL/min for REACH.

Table 42: Subgroup analysis of Treatment-Emergent Adverse Events pooled safety population (AFP ≥400 ng/mL)

AE Category [a]	Ramucirumab + BSC			Placebo + BSC		
	N	Any Grade n (%)	Grade ≥3 n (%)	N	Any Grade n (%)	Grade ≥3 n (%)
Age, years						
<65	172	165 (95.9)	93 (54.1)	130	118 (90.8)	64 (49.2)
≥65	144	141 (97.9)	88 (61.1)	93	88 (94.6)	52 (55.9)
Gender						
Male	246	237 (96.3)	136 (55.3)	186	171 (91.9)	103 (55.4)
Female	70	69 (98.6)	45 (64.3)	37	35 (94.6)	13 (35.1)
Race[b]						
Asian	168	159 (94.6)	80 (47.6)	121	110 (90.9)	58 (47.9)
White	110	109 (99.1)	72 (65.5)	79	75 (94.9)	45 (57.0)
Other	38	38 (100.0)	29 (76.3)	23	21 (91.3)	13 (56.5)
Region[c]						
Region 1	154	152 (98.7)	102 (66.2)	107	101 (94.4)	61 (57.0)
Region 2	101	95 (94.1)	45 (44.6)	76	68 (89.5)	37 (48.7)
Region 3	61	59 (96.7)	34 (55.7)	40	37 (92.5)	18 (45.0)

Abbreviations: AE = adverse event; AFP = alpha-fetoprotein; BSC = best supportive care; N = number of treated patients in the safety population; n = number of patients in specified category; SD = standard deviation.
[a] Patients may be counted in more than 1 category.
[b] In REACH-2, the race of patients from France was not collected.
[c] For the pooled safety population (AFP ≥400 ng/mL), regions were redefined as Region 1 (Australia, Austria, Belgium, Brazil, Bulgaria, Canada, Czech Republic, Finland, France, Germany, Hungary, Israel, Italy, Netherlands, New Zealand, Norway, Poland, Portugal, Romania, Spain, Sweden, Switzerland, United Kingdom, and the United States), Region 2 (China, Hong Kong, Korea, Malaysia, Philippines, and Taiwan), and Region 3 (Japan).

Age

The pooled safety population (AFP ≥400 ng/mL) included 44.0% patients aged ≥65 years, 14.5% patients aged ≥75 years (n = 78), and 0.6% patients aged ≥85 years (n = 3). As shown in Table 43, in both treatment groups, patients aged ≥65 years had a higher incidence of both any-grade as well as Grade ≥3 events compared with those aged <65 years, but within each age group the difference in incidence between treatment groups was similar. Table 43 provides a summary of safety by age intervals (<65, 65-74, 75-84, and ≥85 years) for the pooled safety population (AFP ≥400 ng/mL). Herein over twice as high percentages are reported for patients aged 75-84 in the ramucirumab treatment group when compared to the placebo treatment group, for the categories/MeDRA terms "Serious AEs – Total", "Fatal AE", "Hospitalization/prolong

existing hospitalization", "Life-threatening", and "AEs leading to drop-out". However, all SAEs that occurred in patients aged 75 to 84 years, occurred in a single patient only, and (thus) no specific type(s) of AEs caused the observed differences.

Table 43: Summary of selected Adverse Events by age interval pooled safety population (AFP ≥400 ng/mL)

MedDRA Terms	Ramucirumab + BSC				Placebo + BSC			
	Age <65 N = 172 n (%)	Age 65-74 N = 93 n (%)	Age 75-84 N = 49 n (%)	Age 85+ N = 2 n (%)	Age <65 N = 130 n (%)	Age 65-74 N = 66 n (%)	Age 75-84 N = 26 n (%)	Age 85+ N = 1 n (%)
Total AEs	**166 (96.5)**	**92 (98.9)**	**47 (95.9)**	**2 (100.0)**	**119 (91.5)**	**61 (92.4)**	**26 (100.0)**	**1 (100.0)**
Serious AEs – Total	58 (33.7)	33 (35.5)	21 (42.9)	0	40 (30.8)	29 (43.9)	5 (19.2)	1 (100.0)
Fatal AE	14 (8.1)	7 (7.5)	8 (16.3)	0	10 (7.7)	8 (12.1)	2 (7.7)	0
Hospitalization/prolong existing hospitalization	58 (33.7)	31 (33.3)	19 (38.8)	0	38 (29.2)	29 (43.9)	4 (15.4)	1 (100.0)
Life-threatening	6 (3.5)	3 (3.2)	4 (8.2)	0	1 (0.8)	5 (7.6)	1 (3.8)	0
Disability/incapacity	2 (1.2)	1 (1.1)	0	0	0	0	0	0
Other (medically significant)	3 (1.7)	4 (4.3)	0	0	0	0	0	0
AEs leading to drop-out[a]	23 (13.4)	20 (21.5)	9 (18.4)	0	11 (8.5)	11 (16.7)	1 (3.8)	0
Psychiatric disorders	20 (11.6)	17 (18.3)	5 (10.2)	0	14 (10.8)	11 (16.7)	3 (11.5)	0
Nervous system disorders	61 (35.5)	34 (36.6)	11 (22.4)	0	23 (17.7)	17 (25.8)	7 (26.9)	1 (100.0)
Accidents and injuries	13 (7.6)	9 (9.7)	6 (12.2)	0	2 (1.5)	3 (4.5)	2 (7.7)	0
Cardiac disorders	5 (2.9)	5 (5.4)	2 (4.1)	0	2 (1.5)	4 (6.1)	1 (3.8)	0
Vascular disorders	39 (22.7)	29 (31.2)	15 (30.6)	1 (50.0)	16 (12.3)	12 (18.2)	6 (23.1)	1 (100.0)
Cerebrovascular disorders	2 (1.2)	0	2 (4.1)	0	1 (0.8)	1 (1.5)	1 (3.8)	0
Infections and infestations	46 (26.7)	29 (31.2)	21 (42.9)	1 (50.0)	26 (20.0)	13 (19.7)	8 (30.8)	1 (100.0)
Anticholinergic syndrome	46 (26.7)	25 (26.9)	12 (24.5)	0	30 (23.1)	13 (19.7)	6 (23.1)	1 (100.0)
Sum of postural hypotension, falls, black outs, syncope, dizziness, ataxia, fractures[b]	14 (8.1)	9 (9.7)	5 (10.2)	0	12 (9.2)	4 (6.1)	3 (11.5)	1 (100.0)

Abbreviations: AE = adverse event; BSC = best supportive care; AFP = alpha-fetoprotein; MedDRA = Medical Dictionary for Regulatory Activities, Version 20.1; N = number of patients in the safety population; n = number of patients in the specified category; SMQ = standardized MedDRA query.
Note: Accidents and injuries, Cerebrovascular disorders, and Anticholinergic syndrome were searched based on the narrow and broader term of SMQ.
[a] AEs leading to drop-out: discontinuation of study treatment.
[b] Sum of postural hypotension, falls, black outs, syncope, dizziness, ataxia, fractures: summary of respective MedDRA preferred terms.

Gender

The pooled safety population (AFP ≥400 ng/mL) included 80.1% male and 19.9% female patients. In Table 42 the difference between the percentages of reported any-grade TEAEs for the ramucirumab- vs. the placebo-treated group is similar for male and female patients. For male patients the percentage of reported Grade ≥3 TEAEs was almost identical for the ramucirumab- vs. the placebo-treated group with 55.3% vs. 55.4%, respectively.

For female patients the percentage of reported Grade ≥3 TEAEs was much higher for the ramucirumab-treated group (64.3%) than for the placebo-treated group (35.1%). This difference in the percentage of reported Grade ≥3 TEAEs was due to differences in the percentages of the Grade 3 TEAEs hypertension, hyponatremia, ascites, general physical health deterioration, and thrombocytopenia. However, apart from a 6.3% difference between genders for hyponatraemia (ramucirumab-treated female

patients: 10.0%; ramucirumab-treated male patients: 3.7%), the differences in incidence of these Grade 3 TEAEs between female and male patients were all <5%. The differences between both treatment groups in reported incidence of SAEs, discontinuations due to (S)AEs, and deaths due to AEs were similar for male and female patients.

No full overview of AEs by gender was provided for the pooled overall safety population. No relevant differences in type or frequency of TEAEs were seen among subgroups defined by gender in the REGARD gastric cancer population.

Immunological events

Rates of treatment-emergent (TE) anti-drug antibodies (ADAs) and neutralizing antibodies were low in the HCC studies REACH-2 and REACH, as 18/402 (4.5%) of ramucirumab-treated patients tested positive for TE ADAs, and neutralizing antibodies were detected in one of the 18 ramucirumab-treated patients who tested positive for TE ADAs (1/402 = 0.2% overall). In studies REACH-2 and REACH the number of TE ADA+ ramucirumab-treated patients who reported infusion-related reactions (IRRs) was very low, i.e. 2 and 1 patient(s), respectively. No anaphylactic reactions were observed among TE ADA+ ramucirumab-treated patients. Refer to section 5.3.2. Pharmacokinetics - *Immunogenicity* for more information on this matter.

Safety related to drug-drug interactions and other interactions

No formal drug-drug interaction (DDI) studies were conducted to support this submission of ramucirumab as a monotherapy in HCC patients.

Discontinuation due to adverse events

In the pooled safety population (AFP ≥400 ng/mL), the overall incidence of TEAEs leading to the discontinuation of study treatment was higher in the ramucirumab compared with the placebo treatment group (16.5% vs. 10.3%, respectively). The most commonly reported TEAE (any-grade) for ramucirumab was the AESI proteinuria (ramucirumab: 1.9%; placebo: 0%), and for placebo it was oesophagus varices haemorrhage (placebo: 1.8%; ramucirumab: 1.3%). Consistent with protocol guidelines in REACH-2 and in REACH, 4 (1.3%) patients, all in the ramucirumab treatment group, discontinued treatment due to the AESI hepatic encephalopathy, and 2 (0.6%) patients, all in the ramucirumab treatment group, discontinued treatment due to the AESI hepatorenal syndrome.

The incidence and types of TEAEs leading to discontinuation of study treatment in the pooled overall safety population were generally consistent with those in the pooled safety population (AFP ≥400 ng/mL). In the REGARD gastric cancer population the incidence of discontinuations due to an AE was somewhat lower in both treatment groups (ramucirumab: 10.5%; placebo: 6.0%) than in the pooled safety population (AFP ≥400 ng/mL).

The overall incidence of TEAEs leading to dose adjustment (i.e. dose reductions, dose delays, dose omissions) was higher in the ramucirumab compared with the placebo treatment group (any Grade: 30.4% vs. 13.5%, respectively; Grade ≥3: 16.5% vs. 9.4%, respectively). The most common (occurring in ≥2% of patients) any-grade TEAEs leading to dose adjustment were hypertension (4.7% vs. 0.4%, respectively), proteinuria (3.5% vs. 0%, respectively), and ascites (2.2% vs. 0.6%, respectively).

Post marketing experience

Ramucirumab was first authorised in 2014 and is currently approved in several regions, including the European Union, the United States and Japan, both as a single agent and in combination with different chemotherapy regimens for the treatment of gastric cancer, non-small cell lung cancer and colorectal

cancer. Cumulatively, as of 21 April 2018, approximately 6086 patients have received ramucirumab in the ramucirumab clinical program. An estimated 1368 patients received single-agent ramucirumab and 4718 patients received ramucirumab in combination with chemotherapeutic agents. Also, as of 30 April 2018, cumulatively an estimated 75,800 patients have received ramucirumab worldwide. The latest periodic safety update report (PSUR) from ramucirumab summarised safety and other pertinent data up to 21 April 2018, and the PSUR review confirmed the previously established favorable benefit-risk profile for ramucirumab in the currently approved indications. No off-label use events have been reported for the use of ramucirumab for the treatment of HCC.

2.5.1. Discussion on clinical safety

The safety analysis of ramucirumab in patients with HCC and AFP ≥400 ng/mL, after intolerance to or disease progression on or after prior sorafenib, focused on the pooled safety data from the safety population from the pivotal REACH-2 study plus the subpopulation of patients from the supportive REACH study with baseline AFP ≥400 ng/mL, i.e. the pooled safety population (AFP ≥400 ng/mL). The results of this safety analysis were compared with the gastric cancer safety population from the ramucirumab monotherapy-treated gastric cancer patient population in the pivotal REGARD study (Cyramza gastric cancer EPAR).

It should be noted that as a result of the eligibility criteria for both the REACH-2 and the REACH study, all patients in the pooled safety population (AFP ≥400 ng/mL) had a C-P score <7 (C-P class A only), an ECOG PS ≤1, and only mildly impaired renal function at worst (creatinine clearance ≥60 mL/min for REACH-2 and >50 mL/min for REACH). The to-be-treated patient population in clinical practice is expected to include more frail patients with e.g. ECOG PS of 2 and/or more impaired renal function and more comorbidities. Therefore, it is uncertain if the observed toxicity in the selected pooled safety population (AFP ≥400 ng/mL) is truly representative of the to-be-treated patient population. The eligibility criteria of the pivotal regorafenib RESORCE study (Stivarga HCC EPAR) and the pivotal cabozantinib CELESTIAL study (Abou-Alfa et al. N Engl J Med. 2018) were generally similar to the main ramucirumab studies (REACH and REACH-2), as they also included a C-P score <7 and an ECOG PS ≤1. In contrast to the two ramucirumab studies, in both the RESORCE study as well as in the CELESTIAL study patients with a history of hepatic encephalopathy and patients receiving chronic anti-platelet therapy (including nonsteroidal anti-inflammatory drugs) were allowed to enrol, as were patients with moderately impaired renal function.

The median duration of therapy was rather short but longer in the ramucirumab treatment group compared to the placebo treatment group. The rather short duration of therapy prevents assessment of the long-term safety, but is in accordance with the observed relatively short PFS in this setting.

Overall, there were no unexpected findings in the assessment of TEAEs, with the known ADRs peripheral oedema (ramucirumab: 29.1%; placebo 17.0%), hypertension (ramucirumab: 21.5%; placebo 9.0%), proteinuria (ramucirumab: 18.7%; placebo 5.4%), headache (ramucirumab: 16.8%; placebo 6.3%), and thrombocytopenia (ramucirumab: 14.9%; placebo 4.5%) being among the most frequently reported (any-Grade) TEAEs with ramucirumab. Hypertension was the only Grade ≥3 TEAE with a ≥5 percentage points higher incidence for ramucirumab (12.0%) than placebo (3.6%).

Most patients experienced at least 1 treatment-emergent adverse event of any grade, and the majority experienced Grade ≥3 events. Most TEAEs seem consistent with the underlying disease state of HCC and the percentages of most reported any-grade TEAEs were similar between treatment groups. When compared with the known safety profile of single-agent ramucirumab from the REGARD gastric cancer population, no new safety signals were identified, although the incidence of the adverse events of special interest hypertension and proteinuria was higher in the ramucirumab treatment group in the HCC pooled safety population (AFP ≥400 ng/mL). The incidence of the AESIs bleeding/haemorrhagic events and liver failure/liver injury was higher in both HCC treatment groups when compared with the REGARD gastric cancer population, as could be expected given the HCC disease setting.

Regarding the AESI bleeding/haemorrhagic events, even though the incidence of any-Grade events was higher in the ramucirumab than in the placebo treatment group, it was the other way round for Grade ≥3 events. Then again, patients with oesophageal or gastric varices that required immediate intervention or represented a high bleeding risk were excluded from REACH-2 and REACH and thus the pooled safety population (AFP ≥400 ng/mL), and patients with evidence of portal hypertension or any prior history of variceal bleeding were only allowed to enrol if they had been screened by endoscopic evaluation within the 3 months immediately prior to randomisation. Moreover, patients receiving chronic anti-platelet therapy (including nonsteroidal anti-inflammatory drugs) were excluded, and the to-be-treated patient population in clinical practice may be expected to include patients receiving these medications. Therefore, the incidence of bleeding/haemorrhagic events to be expected in clinical practice is uncertain, and may be higher. A precautionary statement in section 4.4 of the SmPC is deemed necessary, stating that for HCC patients with evidence of portal hypertension or prior history of oesophageal variceal bleeding, screening for and treatment of oesophageal varices should be performed as per standard of care before starting ramucirumab treatment.

Regarding the AESI liver failure/liver injury, even though the incidence of any-Grade events was higher in the ramucirumab than in the placebo treatment group, it was the other way round for Grade ≥3 events. Although infrequent, hepatic encephalopathy and hepatorenal syndrome were observed at a higher incidence in ramucirumab than in placebo-treated patients. However, approximately half of the events in the ramucirumab treatment group were reported in the setting of progressive disease and thus were not necessarily related to study drug. While patients with a history of hepatic encephalopathy were excluded from REACH-2 and REACH, and thus from the pooled safety population (AFP ≥400 ng/mL), the to-be-treated patient population in clinical practice may be expected to include patients with a history of hepatic encephalopathy. Therefore, the incidence of hepatic encephalopathy to be expected in clinical practice is more uncertain.

The eligibility criteria of REACH were amended to prevent hepatic encephalopathy only after a numeric imbalance of liver-related AEs, specifically for hepatic encephalopathy, had been observed between the 2 treatment arms from the Independent Data Monitoring Committee. The same, strict eligibility criteria were thereafter applied in REACH-2. Probably as a result thereof, the incidence of hepatic encephalopathy was numerically lower in both treatment groups of REACH-2 when compared with both treatment groups of REACH. However, in REACH-2 the incidence of hepatic encephalopathy was still higher in ramucirumab than in placebo-treated patients, and the difference between both treatment groups was similar for REACH-2 and REACH (REACH-2: +4.6 percentage points; REACH: +5.9 percentage points). Moreover, the incidence of Grade ≥3 hepatic encephalopathy in the ramucirumab treatment group in REACH-2 was also higher than that in the ramucirumab treatment group in REACH (REACH-2: 3.6%; REACH: 3.3%). Therefore, the more strict eligibility criteria could not negate the increase in hepatic encephalopathy caused by ramucirumab treatment. In general, it can be concluded that an increased severity of underlying liver disease as assessed by C-P class status at baseline suggests a greater risk of occurrence of hepatic encephalopathy while receiving ramucirumab, and other precipitating factors appear to be related to the underlying cancer and general condition of the patients. Patients should be monitored for clinical signs and symptoms of hepatic encephalopathy. Ramucirumab should be permanently discontinued in the event of hepatic encephalopathy or hepatorenal syndrome (see sections 4.2, 4.4 and 4.8 of the SmPC). Hepatic encephalopathy in patients with HCC has been added as an important identified risk to the list of safety concerns (see RMP).

The adverse drug reactions (ADRs) proposed by the MAH in section 4.8 of the SmPC are acceptable. Of note, separate tables of ADRs were previously reflected in section 4.8 of the SmPC for each approved indication/pivotal study. During the procedure and further to the CHMP request, the MAH has presented ADRs in two tables, i.e. one with all ADRs for ramucirumab when administered as monotherapy (which include the ADRs observed in the pooled safety population [AFP ≥400 ng/mL] in this procedure), and one with all ADRs for ramucirumab when administered in combination with chemotherapy. Due to differences in

safety profile between ramucirumab monotherapy and ramucirumab in combination with chemotherapy, two separate tables are acceptable in section 4.8 of the SmPC.

A similar percentage of patients in both treatment groups had any-grade serious adverse events. The incidence of death (while on treatment or within 30 days after discontinuation from study treatment) was higher in the ramucirumab treatment group than in the placebo treatment group, but the percentage of deaths due to AEs was similar. However, it should also be taken into account that the median duration of therapy was longer in the ramucirumab treatment group compared with the placebo treatment group. Therefore, a higher incidence of death in the ramucirumab treatment group is not unexpected. Moreover, the incidence of death due to an AE was lower (in both treatment groups) than in the REGARD gastric cancer population.

Regarding laboratory findings, the assessments of analyses for haematology and serum chemistry laboratory toxicity shifts from baseline to worst grade post-baseline were consistent with the AE data. Low-grade (Grade 1-2) abnormalities were noted in baseline levels of alanine aminotransferase (ALT), aspartate aminotransferase (AST), and alkaline phosphatase in a high proportion of patients in both treatment groups, and similar shifts were observed in these parameters.

Regarding the safety in special populations, a summary of selected AEs by age interval showed over twice as high percentages for several selected AEs for patients aged 75-84 in the ramucirumab treatment group (n = 49) when compared to the placebo treatment group (n = 26), whereas no such differences were apparent for the other age categories. However, no specific type(s) of AEs caused the observed differences. Therefore, the observed differences could simply be due to chance, due to the relatively small number of placebo-treated patients aged 75-84.

In addition, for female patients the percentage of reported Grade ≥3 TEAEs was much higher for the ramucirumab-treated group than for the placebo-treated group, whereas for male patients the percentage was almost identical for both treatment groups. This difference in the percentage of reported Grade ≥3 TEAEs was due to differences in the percentages of the Grade 3 TEAEs hypertension, hyponatremia, ascites, general physical health deterioration, and thrombocytopenia. Importantly however, apart from a 6.3% difference between genders for hyponatraemia, the differences in incidence of these Grade 3 TEAEs between female and male patients were all <5%. Also, the differences between both treatment groups in reported incidence of SAEs, discontinuations due to (S)AEs, and deaths due to AEs were similar for male and female patients. It remains unclear why the percentage of reported Grade ≥3 TEAEs in placebo-treated female patients was rather low, i.e. 20% lower than in placebo-treated male patients, but this might simply be due to the limited number of female patients in the placebo group.

Analyses in special populations showed no meaningful differences in the TEAE profile with respect to race, or between different geographic regions.

Regarding immunological events, rates of treatment-emergent (TE) anti-drug antibodies (ADAs) and neutralising antibodies in the REACH-2 and REACH studies were low and very low, respectively.

The overall incidence of TEAEs leading to the discontinuation of study treatment was higher in the ramucirumab compared with the placebo treatment group. The discontinuation rate of 1 in 6 ramucirumab-treated patients could be considered acceptable, but was higher than the rate of 1 in 10 in the REGARD gastric cancer population.

When compared with other second-line treatment options for advanced HCC, i.e. regorafenib and cabozantinib, the safety profile of ramucirumab as observed in the pooled safety population (AFP ≥400 ng/mL) could be considered somewhat more favourable, though with the caveat of cross-study comparisons. The incidence of hepatic encephalopathy with ramucirumab was 4.7% and 3.5% in the pooled safety population (AFP ≥400 ng/mL) for both any-Grade as well as Grade≥3 respectively). The eligibility criteria of REACH were amended to exclude patients with a history of hepatic encephalopathy, and these

patients were also excluded from REACH-2, whereas they were allowed to be enrolled in the regorafenib RESORCE and cabozantinib CELESTIAL studies.

Results from the phase 2 study I4T-IE-JVBQ and phase 1b study I4T-CR-JVCQ in HCC patients are not presented and discussed as both studies were non-comparative and conducted in previously untreated patients. The safety findings in the single-agent ramucirumab Study JVBQ were generally consistent with those observed in REACH-2 and REACH. No additional safety findings for ramucirumab were identified from the review of studies JVBQ or JVCQ that would have a significant impact on product labeling (new warnings, precautions or contraindications) for ramucirumab.

From the safety database all the adverse reactions reported in clinical trials <and post-marketing> have been included in the Summary of Product Characteristics

2.5.2. Conclusions on clinical safety

Overall, there were no unexpected findings in the assessment of TEAEs in the pooled safety population (AFP ≥400 ng/mL), with the known ADRs peripheral oedema, hypertension, proteinuria, headache, and thrombocytopenia being among the most frequently reported. When compared with the known safety profile of single-agent ramucirumab from the REGARD gastric cancer population, no new safety signals were identified, but the discontinuation rate in HCC patients was somewhat higher.

As patients with evidence of portal hypertension or any prior history of variceal bleeding were only allowed to enrol in REACH-2 and REACH if they had been screened for and (if considered necessary) treated for oesophageal varices, a precautionary statement in section 4.4 of the SmPC is deemed necessary. Also, hepatic encephalopathy is qualified as a new ADR and has been included in section 4.8 of the SmPC and as an identified risk in the RMP.

Overall, the safety profile as observed in the pooled safety population (AFP ≥400 ng/mL) can be considered manageable.

2.5.3. PSUR cycle

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

2.6. Risk management plan

The CHMP received the following PRAC Advice on the submitted Risk Management Plan:

The PRAC considered that the risk management plan version 8.3 is acceptable.

The CHMP endorsed the Risk Management Plan version 8.3 with the following content:

Safety concerns

Summary of safety concerns	
Important identified risks	Arterial thromboembolic events Hypertension Proteinuria including nephrotic syndrome Gastrointestinal perforation Haemorrhagic events Liver failure/liver injury Hepatic encephalopathy in patients with HCC
Important potential risks	Serious infection secondary to neutropenia Posterior reversible encephalopathy syndrome Severe clinical outcomes of venous thromboembolic events Reproductive and developmental toxicity
Missing information	Not applicable

As a result of the data submitted as part of this extension of indication, "hepatic encephalopathy in patients with HCC" has been added as an important identified risk to the list of safety concerns.

Pharmacovigilance plan

Study Status	**Summary of objectives**	**Safety concerns addressed**	**Milestones**	**Due dates**
Category 1 - Imposed mandatory additional pharmacovigilance activities that are conditions of the marketing authorisation				
None				
Category 2 – Imposed mandatory additional pharmacovigilance activities that are Specific Obligations in the context of a conditional marketing authorisation or a marketing authorisation under exceptional circumstances				
None				
Category 3 - Required additional pharmacovigilance activities				
I4T-MC-JVDD: Safety and Effectiveness of Ramucirumab in Patients with Advanced Gastric Cancer in the European Union and North America: A Prospective Observational Registry Ongoing	**Primary objective**: To describe the safety profile of ramucirumab administered as monotherapy or in combination therapy for second-line treatment of adult patients with advanced gastric cancer under real-world disease conditions in the EU and North America **Secondary objectives:** To describe the effectiveness of ramucirumab administered as monotherapy or in combination therapy for second-line treatment of adult	Potential safety signals in special populations, such as elderly, patients with cardiac comorbidities, hepatic impairment and renal impairment	Protocol submitted[a]	12 December 2014
			First patient enrolled	9 December 2015
			Last patient enrolled	Estimated Q4 2020

Study Status	Summary of objectives	Safety concerns addressed	Milestones	Due dates
	patients with advanced gastric cancer under real-world disease conditions in the EU and North America. To describe the safety profile in the following subgroups: • Elderly patients • Patients with cardiac comorbidities • Patients with hepatic impairment • Patients with renal impairment		Final study report	Estimated Q4 2021

No changes were made to the pharmacovigilance plan as a result of the data submitted for this extension of indication.

Risk minimisation measures

Safety Concern	Risk Minimisation Measures	Pharmacovigilance Activities
Important Identified Risks		
Arterial thromboembolic events	**Routine risk minimisation measures:** SmPC Ssections 4.2, 4.4, and 4.8 PL Sections 2, 3, and 4 SmPC Sections 4.2 and 4.4 advise: • Permanent discontinuation of ramucirumab in the event of severe ATEs. PL Sections 2 and 4 advise patients: • To tell their health care professional immediately if they experience any symptoms or signs of blockage of the artery by a blood clot either during treatment with ramucirumab or anytime thereafter, including symptoms of a heart attack or stroke.	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** • Thromboembolism follow-up form **Additional pharmacovigilance activities:** None
Hypertension	**Routine risk minimisation measures:** SmPC Ssections 4.2, 4.4, 4.8, and 5.2 PL Sections 2, 3, and 4 SmPC Sections 4.2 and 4.4 advise: • Blood pressure should be monitored prior to each ramucirumab administration and treated as clinically indicated. • Ramucirumab therapy should be temporarily discontinued in the event of severe hypertension, until controlled with medical management; if there is medically significant hypertension that cannot be controlled safely with antihypertensive therapy, ramucirumab therapy should be permanently discontinued.	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** • Hypertension follow-up form **Additional pharmacovigilance activities:** None

Safety Concern	Risk Minimisation Measures	Pharmacovigilance Activities
	SmPC Section 4.4 advises: • Ramucirumab treatment should not be initiated in patients with uncontrolled hypertension until and unless their pre-existing hypertension is controlled. PL Section 2 advises patients: • To tell their doctor or nurse before being given ramucirumab if they have high blood pressure. PL Section 4 advises patients: • To tell their doctor if they experience the side effect of high blood pressure.	
Proteinuria including nephrotic syndrome	**Routine risk minimisation measures:** SmPC Ssections 4.2, 4.4, and 4.8 PL Sections 2, 3, and 4 SmPC Sections 4.2 and 4.4 advise that: • Patients should be monitored for the development or worsening of proteinuria during ramucirumab therapy. If the urine protein is ≥2+ on a dipstick, a 24 hour urine collection should be performed. Ramucirumab therapy should be temporarily discontinued if the urine protein level is ≥2 g/24 hours. A ramucirumab dosing table for resumption of treatment at reduced dose(s) once the urine protein level returns to <2 g/24 hours is provided. • Ramucirumab therapy should be permanently discontinued if the urine protein level is >3 g/24 hours or in the event of nephrotic syndrome. PL Sections 2 advises patients: • To tell their doctor or nurse immediately if they have an abnormal urine test ("proteinuria") during treatment with ramucirumab or anytime thereafter. PL Section 4 advises patients: • To tell their doctor if they experience the side effect of protein in their urine (abnormal urine test).	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** • Proteinuria follow-up form **Additional pharmacovigilance activities:** None
Gastrointestinal perforation	**Routine risk minimisation measures:** SmPC Ssections 4.2, 4.4, and 4.8 PL Sections 2, 3, and 4 SmPC Sections 4.2 and 4.4 advise that: • Ramucirumab therapy should be permanently discontinued in the event of gastrointestinal perforation. PL Sections 2 and 4 advise patients: • To tell their health care professional immediately if they develop any symptoms of a hole in the wall of their gut ('gastrointestinal perforation') including abdominal pain, vomiting, fever or chills during treatment with ramucirumab or anytime	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** • Gastrointestinal perforation and/or fistula follow-up form **Additional pharmacovigilance activities:** None

Safety Concern	Risk Minimisation Measures	Pharmacovigilance Activities
	thereafter.	
Haemorrhagic events	**Routine risk minimisation measures:** SmPC Sections 4.2, 4.3, 4.4, and 4.8 PL Sections 2, 3, and 4 SmPC Sections 4.2 and 4.4 advise that: • Ramucirumab should be permanently discontinued in the event of severe bleeding (NCI CTCAE Grade 3 or 4). SmPC Section 4.3 states that: • For patients with NSCLC, ramucirumab is contraindicated where there is tumour cavitation or tumour involvement of major vessels. SmPC Section 4.4 advises that: • Blood counts and coagulation parameters should be monitored in patients with conditions predisposing to bleeding, and in those treated with anticoagulants or other concomitant medicinal products that increase the risk of bleeding. • For HCC patients with evidence of portal hypertension or prior history of oesophageal variceal bleeding, screening for and treatment of oesophageal varices should be performed as per standard of care before starting ramucirumab treatment. PL Section 2 advises patients before they receive ramucirumab: • To talk to their doctor or nurse if they have any condition that increases the risk of bleeding. • To tell their doctor if they are taking any medicines that may increase the risk of bleeding or that affect blood clotting ability. • To talk to their doctor or nurse if they have lung cancer and have had recent bleeding in the lung (coughing up bright red blood) or are regularly taking non-steroidal anti-inflammatory medicines, or medicines that affect blood clotting ability. • To talk to their doctor or nurse if they have liver cancer and have had previous bleeding from enlarged veins in the food pipe (oesophagus) or have high blood pressure in the portal vein, which carries the blood from the bowel and spleen to the liver. PL Sections 2 and 4 advise patients: • To tell their health care professional immediately if they experience symptoms of severe bleeding or severe bleeding in the gut, including extreme tiredness, weakness, dizziness or changes in the colour of stools, either during treatment with ramucirumab or any time thereafter.	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** • General bleeding follow-up form **Additional pharmacovigilance activities:** None
Liver ~~injury~~failure/liver ~~failure~~ injury	**Routine risk minimisation measures:** SmPC Sections 4.2, 4.4, 4.8, and 5.2 PL Sections 2, 3, and 4	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal**

Safety Concern	Risk Minimisation Measures	Pharmacovigilance Activities
	SmPC Section 4.2: • Provides advice to check blood chemistry prior to each paclitaxel infusion, and includes liver function test criteria to be met prior to each paclitaxel administration. • Ramucirumab should be permanently discontinued in the event of hepatic encephalopathy or hepatorenal syndrome. SmPC Section 4.4 advises that: • Ramucirumab should be used with caution in patients with severe liver cirrhosis (Child-Pugh B or C), cirrhosis with hepatic encephalopathy, clinically significant ascites due to cirrhosis, or hepatorenal syndrome. ~~In these patients, r~~Ramucirumab should only be used in these patients if the potential benefits of treatment are judged to outweigh the potential risk of progressive hepatic failure. • Patients should be monitored for clinical signs and symptoms of hepatic encephalopathy. • Ramucirumab should be permanently discontinued in the event of hepatic encephalopathy or hepatorenal syndrome. PL Section 2 advises patients: • To talk to their doctor or nurse prior to being given ramucirumab if they have severe liver disease ('cirrhosis') and associated conditions, such as excessive accumulation of fluid in the abdomen ('ascites'). PL Section 4 advises patients with chronic liver problems: • To tell their doctor if they experience common side effects of confusion and/or disorientation.	**detection:** • Hepatic disorder follow-up form **Additional pharmacovigilance activities:** None
Hepatic encephalopathy in patients with HCC	**Routine risk minimisation measures:** SmPC Sections 4.2, 4.4, and 4.8 PL Sections 2, 3, and 4 SmPC Section 4.2 advises that: • Ramucirumab should be permanently discontinued in the event of hepatic encephalopathy or hepatorenal syndrome. SmPC Section 4.4 advises that: • Ramucirumab should be used with caution in patients with severe liver cirrhosis (Child-Pugh B or C), cirrhosis with hepatic encephalopathy, clinically significant ascites due to cirrhosis, or hepatorenal syndrome. Ramucirumab should only be used in these patients if the potential benefits of treatment are judged to outweigh the potential risk of progressive hepatic failure. • Patients should be monitored for clinical signs and symptoms of hepatic encephalopathy.	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** • Hepatic disorder follow-up form **Additional pharmacovigilance activities:** None

Safety Concern	Risk Minimisation Measures	Pharmacovigilance Activities
	• Ramucirumab should be permanently discontinued in the event of hepatic encephalopathy or hepatorenal syndrome. PL Section 2 advises patients: • To talk to their doctor or nurse prior to being given ramucirumab if they have severe liver disease ('cirrhosis'). PL Section 4 advises patients with chronic liver problems: • To tell their doctor if they experience confusion and/or disorientation.	
Important Potential Risks		
Serious infection secondary to neutropenia	**Routine risk minimisation measures:** SmPC Sections 4.2, 4.8, and 5.2 PL Sections 2 and 4 SmPC Section 4.2 includes: • Advice to check complete blood count prior to each paclitaxel infusion, and provides neutrophil count criteria to be met prior to each paclitaxel administration. • Paclitaxel dose reduction guidance for Grade 4 haematological toxicity. • FOLFIRI dose reduction guidance for Grade 2 to Grade 4 neutropenia and febrile neutropenia. • Docetaxel dose adjustments for neutropenia and febrile neutropenia. PL Section 2 advises patients: • To tell their doctor or nurse immediately if they experience fever and infection or symptoms of infection such as sweating, headache, pain in the limbs, or decreased appetite either during treatment with ramucirumab or any time thereafter. PL Section 4 advises patients: • To tell their doctor if they experience low white blood cell counts (may increase the risk of infection), fever accompanied by low white blood cell counts, or serious infection (sepsis).	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** None **Additional pharmacovigilance activities:** None
Posterior reversible encephalopathy syndrome	**Routine risk minimisation measures:** None	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** • Posterior reversible encephalopathy syndrome follow-up form **Additional pharmacovigilance activities:** None
Severe clinical outcomes of venous	**Routine risk minimisation measures:** None	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:**

Safety Concern	Risk Minimisation Measures	Pharmacovigilance Activities
thromboembolic events		• Thromboembolism follow-up form **Additional pharmacovigilance activities:** None
Reproductive and developmental toxicity	**Routine risk minimisation measures:** SmPC Sections 4.6 and 5.3 PL Section 2 SmPC Section 4.6 states that: • Women should be advised to avoid becoming pregnant while on ramucirumab. • Women of child-bearing potential should use effective contraception during and up to 3 months after the last dose of ramucirumab treatment. • Ramucirumab is not recommended during pregnancy and in women of child-bearing potential not using contraception. Ramucirumab should only be used if the potential benefit to the mother justifies the potential risk during pregnancy. • Breast-feeding should be discontinued during treatment with ramucirumab and for at least 3 months after the last dose. PL Section 2 advises patients: • To tell their doctor if they are pregnant or breast-feeding, suspect they may be pregnant, or are planning to become pregnant before starting treatment. • To avoid getting pregnant while receiving this medicine and for at least 3 months after the last dose. • If planning to have a baby, to talk to their doctor about the best contraception for them. • That ramucirumab should not be used during pregnancy. • That breast-feeding should be avoided during treatment and for at least 3 months after the last dose.	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** • Pregnancy outcome maternal follow-up form **Additional pharmacovigilance activities:** None
Missing Information		
None	Not applicable	Not applicable

Routine risk minimisation activities remain sufficient to manage the safety concerns of the medicinal product.

2.7. Update of the Product information

As a consequence of this new indication, sections 4.1, 4.2, 4.4, 4.8, 5.1 and 5.2 of the SmPC have been updated. Particularly, a new warning has been added to the product information to inform prescribers of the

higher rate of hepatic encephalopathy reported in the ramucirumab-treated patients compared to the placebo-treated patients. The Package Leaflet has been updated accordingly.

2.7.1. User consultation

A justification for not performing a full user consultation with target patient groups on the package leaflet has been submitted by the MAH and has been found acceptable for the following reasons:

- The addition of the new indication for the treatment of HCC targets a similar patient demographic group as made up the representative test population for the user testing previously performed.
- The proposed text modifications to the package leaflet resulting from the addition of this new indication are minor and do not include text that is significantly different from that already user tested.
- Overall, the structure and design of the revised Cyramza Package Leaflet has not changed due to the new information and the revisions do not significantly affect the overall readability.

3. Benefit-Risk Balance

3.1. Therapeutic Context

3.1.1. Disease or condition

The proposed new therapeutic indication for Cyramza in this procedure is for the treatment of adult patients with advanced or unresectable hepatocellular carcinoma who have a serum alpha fetoprotein (AFP) of ≥400 ng/mL and who have been previously treated with sorafenib.

Liver cancer is the sixth most common cancer and the fourth most frequent cause of cancer-related death globally. In Europe, there were 82,466 new cases diagnosed and 77,375 deaths reported in 2018 (GLOBOCAN 2018). Hepatocellular carcinoma (HCC) represents about 90% of primary liver cancers. Patients with advanced HCC have an expected median OS of 6–8 months if left untreated, and are candidates for palliative systemic treatment when performance status is adequate. Increased alpha-fetoprotein (AFP) is associated with poorer prognosis and reduced survival in advanced HCC (EASL Clinical Practice Guidelines. J Hepatol. 2018). HCC patients with an AFP ≥400 ng/mL comprise almost half of patients on systemic therapy, including those in the second-line treatment setting (Jelic et al. 2010; Zhu et al. 2015; Bruix et al. 2017).

3.1.2. Available therapies and unmet medical need

Since 2007 the first-line standard of care for patients with advanced HCC has been sorafenib (Nexavar HCC EPAR). Recently however, lenvatinib was approved for the first-line treatment of advanced HCC as well, based on the results of a non-inferiority study (Lenvima HCC EPAR). Lenvatinib is therefore expected to become an alternative first-line treatment option.

For second-line treatment, regorafenib was until very recently the only authorised medicinal product. It was approved in September 2017 based on the results of the placebo-controlled RESORCE study (Stivarga HCC EPAR). However, in January 2019 cabozantinib was also approved for the second-line treatment of advanced HCC, based on the results of the placebo-controlled CELESTIAL study (Cabometyx HCC EPAR). The median OS in this setting ranges from 7.4 months to 13.9 months.

Notwithstanding the above-mentioned medicinal products, the prognosis of advanced HCC is still poor and new treatment options are needed.

3.1.3. Main clinical studies

The pivotal study in this procedure was REACH-2, a randomised, double-blind, placebo-controlled, phase 3 study evaluating the efficacy and safety of ramucirumab for the treatment of patients with HCC who had an AFP ≥400 ng/mL after prior sorafenib therapy. Supportive data were provided from the study REACH, a randomised, double-blind, placebo-controlled, phase 3 study of ramucirumab as second-line treatment in patients with HCC following first-line sorafenib, but only from a subgroup analysis of patients with baseline AFP of ≥400 ng/mL.

Ramucirumab was administered as 8 mg/kg every 2 weeks as an intravenous infusion over approximately 60 minutes, which is consistent with the existing approved posology for ramucirumab as monotherapy in adult patients with advanced gastric cancer (or gastro-oesophageal junction adenocarcinoma).

3.2. Favourable effects

REACH-2 study

REACH-2 demonstrated a statistically significant improvement in OS in patients with HCC and AFP ≥400 ng/mL after prior sorafenib therapy (intended target population) who were treated with ramucirumab + BSC compared with placebo + BSC. In the ITT analysis, treatment with ramucirumab reduced the hazard of death by 29% (OS HR of 0.710; 95% CI: 0.531, 0.949; p=0.0199, stratified log-rank test). Median OS was 8.51 months (95% CI: 7.00, 10.58) in the ramucirumab arm compared with 7.29 months (95% CI: 5.42, 9.07) in the placebo arm, resulting in a median improvement of 1.22 months.

REACH-2 demonstrated a statistically significant improvement in the secondary endpoint of PFS in the ramucirumab arm compared with the placebo arm. Treatment with ramucirumab reduced the hazard of disease progression or death by 55% (stratified HR = 0.452; 95% CI: 0.339, 0.603; p<0.0001), representing a 1.22 month longer median PFS in the ramucirumab arm compared with the placebo arm (2.83 months vs. 1.61 months, respectively).

The objective response rate (ORR; complete responses + partial responses) was numerically higher in patients in the ramucirumab arm as compared to the placebo arm but was not statistically significantly different (4.6% vs. 1.1%, respectively; odds ratio = 4.6; 95% CI: 0.6, 37.3; p=0.1697).

REACH study

In the exploratory subgroup analysis of the supportive REACH study in patients with a baseline AFP of ≥400 ng/mL (n=250), ramucirumab reduced the hazard of death by 33% (OS HR = 0.674; 95% CI: 0.508-0.895; p=0.0059), with median OS of 7.8 months for ramucirumab vs. 4.2 months for placebo. Patients with baseline AFP <400 ng/mL in the REACH study did not experience a survival benefit (OS HR=1.093; 95% CI: 0.836, 1.428; p=0.5059).

3.3. Uncertainties and limitations about favourable effects

The enrolled patient population appears to be a relatively selected population compared to patients with HCC treated in clinical practice (who for example may be more frail and have more comorbidity), the external validity of the results is therefore uncertain and these limitations have been reflected in section 5.1 of the SmPC.

No dose-response studies have been submitted for the requested HCC indication, and hence there is uncertainty as to whether the selected dose of 8 mg/kg Q2W is optimal. A relevant exposure-efficacy association was demonstrated in HCC, which showed that only half of the patients (those with above-median exposure) appeared to benefit from ramucirumab treatment. This exposure-efficacy relationship remained after attempts to adjust for other prognostic factors.

Based on the observed exposure-response relationship in HCC, there is uncertainty whether patients with below-median exposure would benefit from ramucirumab treatment. While findings may be due to clearance still being confounded by prognosis despite the performed adjustments, it cannot be concluded from the presented findings whether the dose of ramucirumab in HCC is adequate for all patients in the proposed indication, and this remains an uncertainty as reflected in section 5.2 of the SmPC. The MAH is encouraged to further investigate the optimal dose for ramucirumab in the applied indication.

3.4. Unfavourable effects

In the pooled safety population from the pivotal REACH-2 study plus the subpopulation of patients with baseline AFP ≥400 ng/mL from the supportive REACH study, the incidence of AEs in the different AE categories for ramucirumab vs. placebo were: any-Grade TEAs: 96.8% vs. 92.4%; Grade ≥3 TEAEs: 57.3% vs. 52.0%; SAEs: 35.4% vs. 33.6%; discontinuation due to an AE: 16.5% vs. 10.3%; death due to an AE: 3.2% vs. 2.7%.

Overall, there were no unexpected findings in the assessment of TEAEs, with the known ADRs peripheral oedema (ramucirumab: 29.1%; placebo 17.0%), hypertension (ramucirumab: 21.5%; placebo 9.0%), proteinuria (ramucirumab: 18.7%; placebo 5.4%), headache (ramucirumab: 16.8%; placebo 6.3%), and thrombocytopenia (ramucirumab: 14.9%; placebo 4.5%) being among the most frequently reported (any-Grade) TEAEs. Hypertension was the only Grade ≥3 TEAE with a ≥5 percentage points higher incidence for ramucirumab (12.0%) than placebo (3.6%).

Hepatic encephalopathy was reported in 4.7% of ramucirumab- vs. 0.9% of placebo-treated patients. It is considered a new ADR for single-agent ramucirumab in the treatment of HCC and as such was included in the product information.

3.5. Uncertainties and limitations about unfavourable effects

All patients in the pooled safety population (AFP ≥400 ng/mL) had C-P score <7 (C-P class A only), ECOG PS <2, and only mildly impaired renal function at worst. The to-be-treated patient population in clinical practice is expected to include more frail patients with e.g. ECOG PS of 2 and/or impaired renal function, and possibly also C-P class B. The limitations related to the studied patient population are reflected in sections 4.4 and 5.1 of the SmPC)

Patients with evidence of portal hypertension or any prior history of variceal bleeding were only allowed to enrol in REACH-2 and REACH if they had been screened and (if considered necessary) treated for oesophageal varices (see section 4.4 of the SmPC).

Regarding hepatic encephalopathy, patients with a history of hepatic encephalopathy were excluded from the pivotal and supportive studies, and thus the pooled safety population (AFP ≥400 ng/mL). Nevertheless, the incidence of hepatic encephalopathy was higher in ramucirumab-treated than in placebo-treated patients. It is uncertain if the observed incidence of hepatic encephalopathy is truly representative of the to-be-treated patient population. However, the information on hepatic encephalopathy that is to be included in the SmPC, is considered sufficient and therefore acceptable.

3.6. Effects Table

Table 44: Effects Table for Cyramza (ramucirumab) monotherapy for the treatment of adult patients with hepatocellular carcinoma who have an alpha fetoprotein (AFP) of ≥400 ng/mL, after prior sorafenib therapy (data cut-off: 15 March 2018)

Effect	Short description	Unit	Treatment	Control	Uncertainties / Strength of evidence	References
Favourable Effects						
OS	Time from the date of randomisation to the date of death from any cause.	Months	8.51	7.29	HR=0.710 (95% CI: 0.531-0.949) P=0.0199	Section *2.4 Clinical efficacy*
PFS	Time from randomisation to date of first progression or death from any cause (by investigator's assessment).	Months	2.83	1.61	HR=0.452 (95% CI: 0.339-0.603) P<0.0001	Section *2.4 Clinical efficacy*
ORR	Percentage of patients with complete response (CR) or partial response (PR) by investigator's assessment (RECIST 1.1)	%	4.6	1.1	P=0.1697	Section *2.4 Clinical efficacy*
Unfavourable Effects						
Grade ≥3 TEAEs	Patients with ≥1 TEAE CTCAE Grade ≥3	%	57.3	52.0		Section *2.5. Clinical safety*
SAEs	Patients with ≥1 SAE	%	35.4	33.6		
Discontinuations	Patients who discontinued study treatment due to AE	%	16.5	10.3		
Deaths	Patients who died due to AE on study treatment or within 30 days of treatment discontinuation	%	3.2	2.7		
Hypertension	Any Grade	%	21.5	9.0		
	Grade ≥3	%	12.7	3.6		
Proteinuria	Any Grade	%	18.7	5.4		
	Grade ≥3	%	1.3	0		
Thrombocytopenia	Any Grade	%	14.9	4.5		
	Grade ≥3	%	5.1	0.9		
Hepatic encephalopathy	Any Grade	%	4.7	0.9	Patients with a history of hepatic encephalopathy were excluded	
	Grade ≥3	%	3.5	0.4		

Abbreviations: CI = confidence interval; CR = complete response; CTCAE = Common Terminology for Regulatory Activities; DCR = disease control rate; HR = hazard ratio; ORR = objective response rate; OS = overall survival; PFS = progression-free survival; PR = partial response; RECIST = Response Evaluation Criteria in Solid Tumors; SAE = serious adverse event; SD = stable disease; TEAE = treatment-emergent adverse event.

3.7. Benefit-risk assessment and discussion

3.7.1. Importance of favourable and unfavourable effects

The prognosis of patients with advanced HCC, and progressive disease on or after prior sorafenib treatment, is poor, as shown by the 7-month median OS in the placebo arm of the submitted pivotal study. There are few treatment options available for HCC patients who progress on first-line systemic therapy and thus new treatment options are necessary in this setting.

The OS benefit observed for ramucirumab vs. placebo in the current application was small (1.2 month). Importantly, this benefit needs to be considered in light of the need for patients to undergo treatment for which they have to attend the hospital for receiving infusions every two weeks. On the other hand, the effect on OS was consistent across subgroups (when considering both REACH and REACH-2), supported by sensitivity analyses and an increase in PFS, although of equally small magnitude, 1.22 months or approximately 5 weeks.

The observed exposure-response relationship brings into question whether the dosage of ramucirumab of 8 mg/kg Q2W is adequate. A relevant exposure-efficacy association was demonstrated in HCC, which showed that only half of the patients (i.e. those with above-median exposure; Q3 and Q4) appeared to benefit from ramucirumab treatment. These exposure-efficacy relationships remained after attempts to adjust for other prognostic factors. Of interest, similar exposure-response relationships have been observed for many other monoclonal antibodies in cancer treatment suggesting this phenomenon might be generalizable. This information has been reflected in section 5.2 of the SmPC.

The toxicity profile of ramucirumab appears quite manageable, even though it is non-negligible and the treatment duration is in general short (for all indications). The following three comments should be made.

Firstly, given the fact that ramucirumab may potentially increase the risk of (severe) bleeding in HCC (like other VEGF-targeted drugs), and that there is an increased risk of oesophageal varices bleeding due to portal hypertension, HCC patients with evidence of portal hypertension or any prior history of variceal bleeding were only allowed to enrol in REACH-2 and REACH if they had been screened and (if considered necessary) treated for oesophageal varices. The proposed precautionary statement on this matter included in section 4.4 of the SmPC, is considered sufficient.

Secondly, hepatic encephalopathy is considered a new ADR for single-agent ramucirumab in the treatment of HCC and as such is included in the revised product information and as an identified risk in the RMP.

Thirdly, when compared with regorafenib and cabozantinib, the safety profile of ramucirumab as observed in the pooled safety population (AFP ≥400 ng/mL) may be somewhat more favourable, however, as this involves cross study comparisons, no definitive conclusions can be drawn.

An uncertainty important for the benefit-risk assessment for ramucirumab in HCC is the fact that the patient population studied in the pivotal study was relatively selected (e.g. in terms of C-P class, ECOG PS, and comorbidities) compared to what can be expected in clinical practice.

Overall, although limited, ramucirumab did demonstrate a statistically significant OS benefit in the confirmatory phase 3 study REACH-2, without an apparent detrimental effect on QoL, and showing a manageable toxicity profile. The fact that the patient population in the pivotal study can be regarded as relatively selected can be negated by adequately reflecting the eligibility criteria of the study in section 5.1 of the SmPC. Also, the relevant data on the observed exposure-response relationship are described in section 5.2.

3.7.2. Balance of benefits and risks

Patients with advanced HCC not amenable to curative treatment options have a very poor prognosis even with currently available treatment options, and novel treatments for these patients are therefore necessary.

Ramucirumab treatment resulted in a small but statistically significant OS benefit vs. placebo in the ITT population of the pivotal study REACH-2 in a relatively selected population (e.g. in terms of C-P class, ECOG PS, and comorbidities) compared to what can be expected in clinical practice. In addition, a relevant exposure-efficacy association was demonstrated, which showed that half of the patients (i.e. those with below-median exposure) did not have any OS benefit. Available information concerning these topics are adequately reflected in the SmPC.

The safety profile of ramucirumab, even though non-negligible, appears quite manageable.

In conclusion, the benefit-risk balance for ramucirumab for the treatment of adult patients with advanced or unresectable hepatocellular carcinoma who have a serum alpha fetoprotein (AFP) of ≥400 ng/mL and who have been previously treated with sorafenib, could be considered positive pending resolution of the last outstanding issues. It is left up to the treating physician and the patient to make an informed decision to start treatment with either ramucirumab or one of the other two approved second-line treatment options.

3.8. Conclusions

The overall B/R of Cyramza (ramucirumab) for the treatment of adult patients with advanced or unresectable hepatocellular carcinoma who have a serum alpha fetoprotein (AFP) of ⩾400 ng/mL and who have been previously treated with sorafenib, is positive.

4. Recommendations

Outcome

Based on the review of the submitted data, the CHMP considers the following variation acceptable and therefore recommends the variation to the terms of the Marketing Authorisation, concerning the following change:

Variation accepted		**Type**	**Annexes affected**
C.I.6.a	C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	Type II	I and IIIB

Extension of indication to include Cyramza as monotherapy for the treatment of adult patients with hepatocellular carcinoma who have an alpha fetoprotein (AFP) of ≥ 400 ng/mL, after prior sorafenib therapy; as a consequence, sections 4.1, 4.2, 4.4, 4.8, 5.1 and 5.2 of the SmPC are updated in accordance. The Package Leaflet is updated in accordance. RMP version 8.3 has been agreed.

The variation leads to amendments to the Summary of Product Characteristics and Package Leaflet and to the Risk Management Plan (RMP).

5. EPAR changes

The EPAR will be updated following Commission Decision for this variation. In particular the EPAR module 8 "*steps after the authorisation*" will be updated as follows:

Scope

Extension of indication to include Cyramza as monotherapy for the treatment of adult patients with hepatocellular carcinoma who have an alpha fetoprotein (AFP) of ≥ 400 ng/mL, after prior sorafenib therapy; as a consequence, sections 4.1, 4.2, 4.4, 4.8, 5.1 and 5.2 of the SmPC are updated in accordance. The Package Leaflet is updated in accordance. RMP version 8.3 has been agreed.

Summary

Please refer to the Scientific Discussion EMEA/H/C/002829/II/0027

Attachments

1. Product Information (changes highlighted), as adopted by the CHMP on 27 June 2019.

Reminders to the MAH

1. In accordance with Article 13(3) of Regulation (EC) No 726/2004 the Agency makes available a European Public Assessment Report (EPAR) on the medicinal product assessed by the Committee for Medicinal Products for Human Use. The EPAR is first published after the granting of the initial marketing authorisation (MA) and is continuously updated during the lifecycle of the medicinal product. In particular, following a major change to the MA, the Agency further publishes the assessment report of the CHMP and the reasons for its opinion in favour of granting the change to the authorisation, after deletion of any information of a commercially confidential nature.

   Should you consider that the CHMP assessment report contains commercially confidential information, **please provide the EMA Procedure Assistant your proposal for deletion of commercially confidential information** (CCI) in "track changes" and with detailed justification by 15 July 2019. The principles to be applied for the deletion of CCI are published on the EMA website at https://www.ema.europa.eu/documents/regulatory-procedural-guideline/principles-be-applied-deletion-commercially-confidential-information-disclosure-emea-documents_en.pdf.

2. The MAH is reminded that, within 30 calendar days of the receipt of the Opinion, an updated version of Annex I of the RMP template, reflecting the final RMP agreed at the time of the Opinion should be submitted to h-eurmp-evinterface@emea.europa.eu.

3. If the approved RMP is using Rev. 2 of the 'Guidance on the format of the RMP in the EU' and the RMP 'Part VI: Summary of the risk management plan' has been updated in the procedure, the MAH is reminded to provide to the EMA Procedure Assistant by Eudralink a PDF version of the 'Part VI: Summary of the risk management plan' as a standalone document, within 14 calendar days of the receipt of the CHMP Opinion. The PDF should contain only text and tables and be free of metadata, headers and footers.

4. The MAH is reminded to submit an eCTD closing sequence with the final documents provided by Eudralink during the procedure (including final PI translations, if applicable) within 15 days after the Commission Decision, or prior to the next regulatory activity, whichever is first.