4 July 2017
EMA/467788/2017
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Stivarga

International non-proprietary name: regorafenib

Procedure No. EMEA/H/C/002573/II/0020

Note

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

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List of abbreviations

AASLDA	American Association for Study of Liver Disease Adverse drug reaction
AE	Adverse event
AESI	Adverse events of special safety interest
AF	Alpha-fetoprotein
AJCC	American Joint Committee on Cancer
ALT	Alanine aminotransferase (also known as SGPT)
AST	Aspartate aminotransferase (also known as SGOT)
BCLC	Barcelona Clinic Liver Cancer
BCRP	Breast cancer resistant protein
BMI	Body mass index
BSC	Best supportive care
CI	Confidence interval
CNS	Central nervous system
CR	Complete response
CSR	Clinical Study Report
CT	Computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
DCR	Disease control rate
DMC	Data Monitoring Committee
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
EQ-5D	EuroQoL-5 Dimensions questionnaire
EU	European Union
FACT-Hep	Functional Assessment of Cancer Therapy-Hepatobiliary
FAS	Full Analysis Set
FDA	Food and Drug Administration
FFPE	Formalin-fixed paraffin-embedded FWB Functional well-being
GCP	Good Clinical Practice
GFR	Glomerular filtration rate
GGT	Gamma glutamyl transferase
GIST	Gastrointestinal stromal tumor

GMP	Good Manufacturing Practices
HBV	Hepatitis B virus
HCC	Hepatocellular carcinoma
HCS	Hepatobiliary Cancer Subscale
HCV	Hepatitis C virus
HFSR	Hand foot skin reaction
HGF	Hepatocyte growth factor
HR	Hazard ratio
HRQoL	Health-related quality of life
ICH	International Conference on Harmonization
ITT	Intention to treat
IVRS	Interactive voice response system
KIT	Gene encodes the ligand of the tyrosine-kinase receptor
LDH	Lactic dehydrogenase
MedDRA	Medical Dictionary for Regulatory Activities
MEK	Mitogen activated protein kinase
MID	minimally important difference
mRECIST	modified Response Evaluation Criteria in Solid Tumors
MRI	Magnetic Resonance Imaging
NA	Not assessed
NASH	Non-Alcoholic steatohepatitis
NCI	National Cancer Institute
NRAS	Neuroblastoma RAS viral oncogene homolog New York Heart Association
OD	once daily
ORR	Objective tumor response rate
OS	Overall survival
PBT	Persistent, Bioaccumulative and toxic
PD	Progressive disease
PFS	Progression-free survival
PK	Pharmacokinetics
p.o.	per os (by mouth)
PR	Partial response
PRO	Patient reported outcome

PS	Performance status score
QoL	Quality of life
RAVE	validated electronic system for data collection
RECIST	Response Evaluation Criteria in Solid Tumors
ROW	Rest of the World
SAE	Serious adverse event
SAS	Safety analysis set
SAP	Statistical analysis plan
SD	Stable disease
SOC	System organ class
TACE	transcatheter arterial chemoembolization
TEAE	Treatment-emergent adverse event
TESAE	Treatment-emergent serious adverse event
TKI	Tyrosine kinase inhibitor
TNM	Tumor, node, metastasis
TOI	Trial Outcome Index
TTP	Time to progression
VAS	Visual analog scale
VEGF	Vascular endothelial growth factor
VEGFR	Vascular endothelial growth factor receptor

1. Background information on the procedure

1.1. Type II variation

Pursuant to Article 16 of Commission Regulation (EC) No 1234/2008, Bayer Pharma AG submitted to the European Medicines Agency on 3 November 2016 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, IIIA and IIIB

Extension of indication for Stivarga to include treatment of adult patients with hepatocellular carcinoma (HCC) who have been previously treated with one systemic therapy; as a consequence, sections 4.1, 4.2, 4.4, 4.8 and 5.1 of the EU Summary of Product Characteristics (SmPC) are updated. The package leaflet and Risk Management Plan (RMP; version 5.0) are updated accordingly. Furthermore, the Product Information (PI) is brought in line with the latest Quality Review of Documents (QRD) template version 10.0.

The requested variation proposed amendments to the SmPC, Labelling and Package Leaflet and to the RMP.

Information on paediatric requirements

Pursuant to Article 8 of Regulation (EC) No 1901/2006, the application included EMA Decision P/0190/2016 on the granting of a class 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 application included a critical report addressing the possible similarity with authorised orphan medicinal product.

Derogation from market exclusivity

Pursuant to Article 8 of Regulation (EC) No. 141/2000, the applicant submitted a claim addressing the following derogation laid down in Article 8.3 of the same Regulation: the holder of the marketing authorisation for the original orphan medicinal product has given his consent to the applicant.

Scientific advice

The applicant did not seek Scientific Advice at the CHMP.

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: N/A

Timetable	Actual dates
Submission date	3 November 2016
Start of procedure:	26 November 2016
CHMP Rapporteur Assessment Report	20 January 2017
PRAC Rapporteur Assessment Report	20 January 2017
PRAC members comments	01 February 2017
PRAC Outcome	9 February 2017
CHMP members comments	13 February 2017
Updated CHMP Rapporteur(s) (Joint) Assessment Report	21 February 2017
Request for supplementary information (RSI)	23 February 2017
CHMP Rapporteur Assessment Report	14 April 2017
PRAC Rapporteur Assessment Report	14 April 2017
PRAC members comments	26 April 2017
PRAC Outcome	5 May 2017
CHMP members comments	8 May 2017
Updated CHMP Rapporteur Assessment Report	12 May 2017
2nd Request for supplementary information (RSI)	18 May 2017
CHMP Rapporteur Assessment Report	7 June 2017
PRAC Rapporteur Assessment Report	7 June 2017
PRAC members comments	12 June 2017
PRAC Outcome	9 June 2017
CHMP members comments	12 June 2017
Updated CHMP Rapporteur Assessment Report	15 June 2017
Opinion via written procedure	4 July 2017
The CHMP adopted a report on similarity of Stivarga with Nexavar	4 July 2017

2. Scientific discussion

2.1. Introduction

Problem statement

Disease or condition

The company applied for the following indication:

Hepatocellular carcinoma (HCC) in adult patients who have been previously treated with one systemic therapy.

Epidemiology

HCC is a cancer that usually occurs in the setting of liver cirrhosis, because of chronic infections with hepatitis B virus or hepatitis C virus, alcohol consumption, non-alcoholic steatohepatitis, or diabetes (EASL&EORTC 2012).

It is the third-leading cause of cancer-related death, and the global incidence is rising, with approximately 700,000 cases diagnosed worldwide in 2012 alone (Lozano et al. 2010, Torre et al. 2015).

In the US, the incidence of HCC is approximately 9.18 per 100,000 persons, in Southern Europe 9.8/3.2, in Western Europe 7.2/2.1, and in Northern Europe 3.8/1.6 (male/female, respectively) per 100,000 persons (Jemal et al. 2011). The incidence of HCC is rising in the last decennia and it varies geographically largely due to variations in the incidences of hepatitis B and C infection, with the majority of the cases (> 80%) occurring in sub-Saharan Africa and eastern Asia. One country alone, China, accounts for 40% to 50% of worldwide cases.

Management

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. For patients who are not or who are no longer candidates for loco regional therapy, the oral multikinase inhibitor sorafenib is the only systemic treatment currently approved in the EU. The approval was based on the results of a large Phase-3 clinical trial (Study 100554 SHARP) conducted in 602 HCC patients (Llovet et al. 2008). The study demonstrated significantly increased survival under sorafenib (plus BSC) compared to placebo (plus BSC) (HR 0.69; p=0.0005), with a median survival rate for the sorafenib arm of 10.6 months, compared with 7.9 months for the placebo arm. Another trial (Study 11849) similarly designed as SHARP and conducted in Asian subjects, confirmed the favourable SHARP results (Cheng et al. 2009). Subgroup analyses from studies conducted with sorafenib have demonstrated that the survival benefit of sorafenib is independent of the underlying aetiology of liver disease and independent of prior treatments such as TACE (transarterial chemoembolization) which is usually administered in intermediate-stage HCC. Other compounds (e.g., the anti-PD1 antibody nivolumab, the multiple TKIs lenvatinib and tivantinib) are currently tested in clinical trials as first line treatment options in comparison with sorafenib.

Currently, there is no second-line treatment approved for HCC patients whose disease has progressed under first-line sorafenib treatment. All recent global Phase-3 trials with novel agents (e.g., brivanib, ramucirumab, everolimus) in second-line systemic treatment of patients with advanced HCC who progressed during sorafenib treatment have failed to meet their primary endpoint of survival improvement. Based on the placebo-arm data from these trials, it can be estimated that patients progressing under sorafenib treatment have a median life expectancy of about 7-8 months if left untreated. Therefore there is a clear unmet medical need for this patient population.

About the product

Regorafenib is an oral tumour deactivation agent that potently blocks multiple protein kinases, including kinases involved in tumour angiogenesis (VEGFR1, -2, -3, TIE2), oncogenesis (KIT, RET, RAF-1, BRAF, BRAFV600E), metastasis (VEGFR3, PDGFR, FGFR) and tumour immunity (CSF1R). In particular, regorafenib inhibits mutated KIT, a major oncogenic driver in gastrointestinal stromal tumours, and thereby blocks tumour cell proliferation. Regorafenib was approved in the EU on 26 August 2013 as Stivarga 40 mg, film-coated tablets for the treatment of adult patients with

- metastatic colorectal cancer (mCRC) who have been previously treated with, or are not considered candidates for, available therapies. These include fluoropyrimidine-based chemotherapy, an anti-VEGF therapy and an anti-EGFR therapy (see section 5.1).
- unresectable or metastatic gastrointestinal stromal tumours (GIST) who progressed on or are intolerant to prior treatment with imatinib and sunitinib.

With this variation application, the results of a Phase 3 trial (RESORCE study) are submitted, supporting the extension of indication to patients with HCC after sorafenib.

No addendum to the non-clinical part of the dossier is submitted with this application since preclinical data, i.e. activity of regorafenib in the respective animal model (hepatoma in mice) were already part of the approved nonclinical dossier for Stivarga. The Environmental Risk Assessment has been updated based on the expected wider use of Stivarga due to the new indication.

An RMP (version 5.0) has been provided which covers the new indication with this variation. The adult indication of this extension is covered by a respective paediatric class waiver. Furthermore, the Applicant has included a critical report addressing the possible similarity with authorised orphan medicinal products (Nexavar (INN: sorafenib tosylate) in the HCC condition.

2.2. Non-clinical aspects

No new non-clinical data have been submitted in this application.

2.2.1. Ecotoxicity / environmental risk assessment

The updated ERA summary is presented in the table below.

Table 1. EPAR: table with environmental endpoints.

Substance (INN/Invented Name): regorafenib			
CAS-number (if available): 755037-03-7 (free base); 1019206-88-2 (monohydrate)			
PBT screening		Result	**Conclusion**
Bioaccumulation potential – log K_{ow}	OECD 117	3.9	see below
PBT-assessment			
Parameter	**Result relevant for conclusion**		**Conclusion**
Bioaccumulation	log K_{ow}	3.9 (HPLC determined)	
	BCF	2018 L/kg 3241 L/kg	B
Persistence	ready biodegradability	not readily biodegradable	
	$DT50_{water}$ $DT50_{system}$ $DT50_{soil}$	< 1 d >>100 d at 22-24°C 181 d at 20±2°C	vP
Toxicity	NOEC algae NOEC Daphnia NOEC fish	0.008 µg/L 11 µg/L 0.0075 µg/L	T
	CMR	not fully investigated	

PBT-statement	regorafenib is considered PBT, not vPvB				
Phase I					
Calculation	**Value**	**Unit**			**Conclusion**
$PEC_{surfacewater}$	0.6	µg/L			> 0.01 threshold
$PEC_{surfacewater}$, refined with published 5 y prevalence data for two indications (CRC, GIST) as well as SimpleTreat (STP) simulation	0.022	µg/L			
Other concerns (e.g. chemical class)	antineoplastic				
Phase II Physical-chemical properties and fate					
Study type	**Test protocol**	**Results**			**Remarks**
Adsorption-Desorption	OECD 121	K_{oc} = 398107 L/kg			1 value (HPLC)
	OECD 106	$K_{oc\ sludge}$ 36,700; 47,400 L/kg $K_{oc\ soil}$ 198,000; 78,500; 165,000 L/kg			2 sewage sludges 3 soil types
Ready Biodegradability Test	OECD 301	not readily biodegradable			
Aerobic and Anaerobic Transformation in Aquatic Sediment systems	OECD 308	$DT_{50,\ water}$ = <1 d $DT_{50,\ sediment}$ = >>100 d $DT_{50,\ whole\ system}$ = >>100 d % shifting to sediment = 68-81% at day 2			T=22-24°C
Phase IIa Effect studies					
Study type	**Test protocol**	**Endpoint**	**value**	**Unit**	**Remarks**
Algae, Growth Inhibition Test / *D. subspicatus*	OECD 201	NOEC EC10	0.021 0.19	µg/L µg/L	growth rate growth rate
Daphnia sp. Reproduction Test	OECD 211	NOEC EC10 NOEC NOEC	11 5.1 11 25	µg/L	mortality mortality intr. growth rate nr of offspringg
Fish, Early Life Stage Toxicity Test	OECD 210	NOEC EC10	0.007 5 0.009 6	µg/L	28 d survival, most senstive endpoint
Activated Sludge, Respiration Inhibition Test	OECD 209	EC10 EC50	$>S_w$ [a] $>S_w$ [a]	µg/L µg/L	S_w <56 µg/L
Phase IIb Studies					
Bioaccumulation in fish *L. macrochirus*	OECD 305	BCF	2018 3241	L/kg L/kg	normalised to 5% lipids
Aerobic and anaerobic transformation in soil	OECD 307	DT50 %CO_2	181 1.1	d %	extrapolated DT50; one soil tested
Soil Micro organisms: Nitrogen Transformation Test	OECD 216	%effect	8.9	%	at 1250 mg/kg_{dw}. Not significant acc. to OECD 216 criteria
Terrestrial Plants, Growth Test / *P.sativum, R. sativus, Z. mays*	OECD 208	NOEC	≥197	mg/kg_{dw}	emergence and growth, normalised to 2% o.c.
Earthworm, Acute Toxicity Tests	OECD 207	LC50	>40	mg/kg_{dw}	normalised to 2% o.c.
Collembola, Reproduction Test *F. candida*	OECD 232	NOEC	≥40	mg/kg_{dw}	reproduction and mortality, normalised to 2% o.c.

Sediment dwelling organism / *C. riparius*	OECD 218	EC10= NOEC	2.7	mg/kg_{dw}	total nr or midges and mortality

[a] *The water solubility was not determined (reported as a < value), hence the result of the study can not be displayed correctly. Since no effect was observed at the highest tested concentration, the result is displayed as $>S_w$ for practical reasons.*

2.2.2. Discussion and conclusion on the non-clinical aspects

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

With regards to the Environmental Risk Assessment (ERA), regorafenib is a Persistent, Bioaccumulative and toxic (PBT) substance. A risk to the sediment and surface water compartment is identified. A risk to the sewage treatment plant (STP), soil and groundwater compartments is not identified.

Hence, the following statement is provided in section 5.3 of the SmPC:

"Environmental Risk Assessment (ERA)

Environmental risk assessment studies have shown that regorafenib has the potential to be persistent, bioaccumulative and toxic to the environment and may pose a risk to the surface water and to the sediment compartment (see section 6.6)."

Because of the expected risks of regorafenib to the surface water and sediment compartment and the PBT characteristics of the substance, all measures possible to prevent release of the substance to the environment should be taken.

The updated data submitted in this application lead to a significant increase in environmental exposure further to the use of regorafenib.

Therefore, considering the above data, regorafenib should be used according to the precautions stated in the SmPC and section 5 of the package leaflet in order to minimise any potential risks to the environment.

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

			Number of patients		
Study	**Phase**	**Dosages (regorafenib)**	**Regorafenib**	**Placebo**	**Endpoints**
15982 (RESORCE)	III	160 mg OD 3 wks on-1wks off	379	194	**1°: OS 2°: PFS, TTP, ORR, DCR, QoL, Safety**

14596	II	160 mg OD 3 wks on-1wks off	36	-	**1°: Safety 2°: TTP, ORR, OS**
Total			415	194	

OD: Once daily, wks: weeks, OS: overall survival, PFS: progression free survival, TTP: time to progression, ORR: overall response rate, DCR: disease control rate, QoL: quality of life.

2.3.2. Pharmacokinetics

The proposed dose regimen of regorafenib for HCC is 160 mg qd for 3 weeks /1 week off. This is the same dose regimen currently approved for mCRC and GIST.

New clinical pharmacology data obtained in the analyses based on data from Study 15982 (RESORCE) have been submitted. Sparse data sampling was conducted and the pharmacokinetic analyses consist of a population PK (popPK) and covariate model-based analysis comprised of a total of 16 regorafenib studies including the RESORCE trial and an exploratory analysis of the exposure-response relationships in the RESORCE trial.

Two metabolites of regorafenib, M-2 and M-5, have demonstrated *in vitro* pharmacologic activity similar to that of unchanged regorafenib. Therefore, the evaluation of metabolite PK for M-2 and M-5 was included in all PK studies.

A summary of key pharmacokinetic parameters of regorafenib and metabolites M-2 and M-5 in patients with mCRC and GIST is provided in the table below.

Table 2. Pharmacokinetic parameters of regorafenib, M-2 and M-5 in plasma following multiple daily oral doses of 160 mg regorafenib in CRC and GIST patients Data are geom. Mean (CV%), median (range) for $T_{max,ss}$

parameter	Regorafenib	M-2	M-5
CRC patients (day 21 cycle 1, extension cohort study 11650, N=19)			
$AUC_{0-24,ss}$ (mg*h/L)	50.3 (86%)	48.0 (89%)	64.6 (182%)
$C_{max,ss}$ (mg/L)	3.5 (86%)	3.2 (42%)	4.0 (174%)
$T_{max,ss}$ (h)	2.85 (0.5-10.2)	4.1 (0.5-24)	3.0 (0.5-24)
$T_{1/2}$ (h)	28 (35%)	25 (24%)	51 (31%)
GIST patients (Day 15 cycle 1, study 14935, N=16)			
$AUC_{0-24,ss}$ (mg*h/L)	59.7 (63%)	33.6 (110%)	18.1 (145%)[1]
$C_{max,ss}$ (mg/L)	4.0 (61%)	2.1 (106%)	1.2 (140%)[1]
$T_{max,ss}$ (h)	2.0 (0-24)	2 (0-24)	1.3 (0-24)

[1] M-5 is not a steady-state at day 15.

Methods - analysis of data submitted

The same validated LC-MS/MS methods were used to analyse regorafenib and metabolites M-2 and M-5 in plasma as for the MAA.

PopPK analysis

A previously developed popPK model for regorafenib ("the integrated PK model"; R-8931) was applied to the PK data collected in Study 15982. Data from 16 studies were included in the popPK model. It consists of two sub-models, a parent PK sub-model and a metabolite PK sub-model (see figure below). The objectives were to determine the PK in patients with HCC and calculation of individual exposure estimates based on the empirical Bayes' estimates derived and second to evaluate the exposure-covariate relationships across 16 clinical regorafenib.

Population PK analyses were performed by means of non-linear mixed-effects modelling using NONMEM (version 7.2; Icon Development Solutions, Ellicott City, Maryland, USA). Diagnostic graphics, exploratory analyses, and post-processing of NONMEM output was performed using S-Plus (version 8.2 Professional, Insightful Corp., Seattle, USA). The covariate analysis was performed using R (version 3.2.2, The R foundation for Statistical Computing) and RStudio (Version 0.99.486, RStudio Inc, Boston, USA).

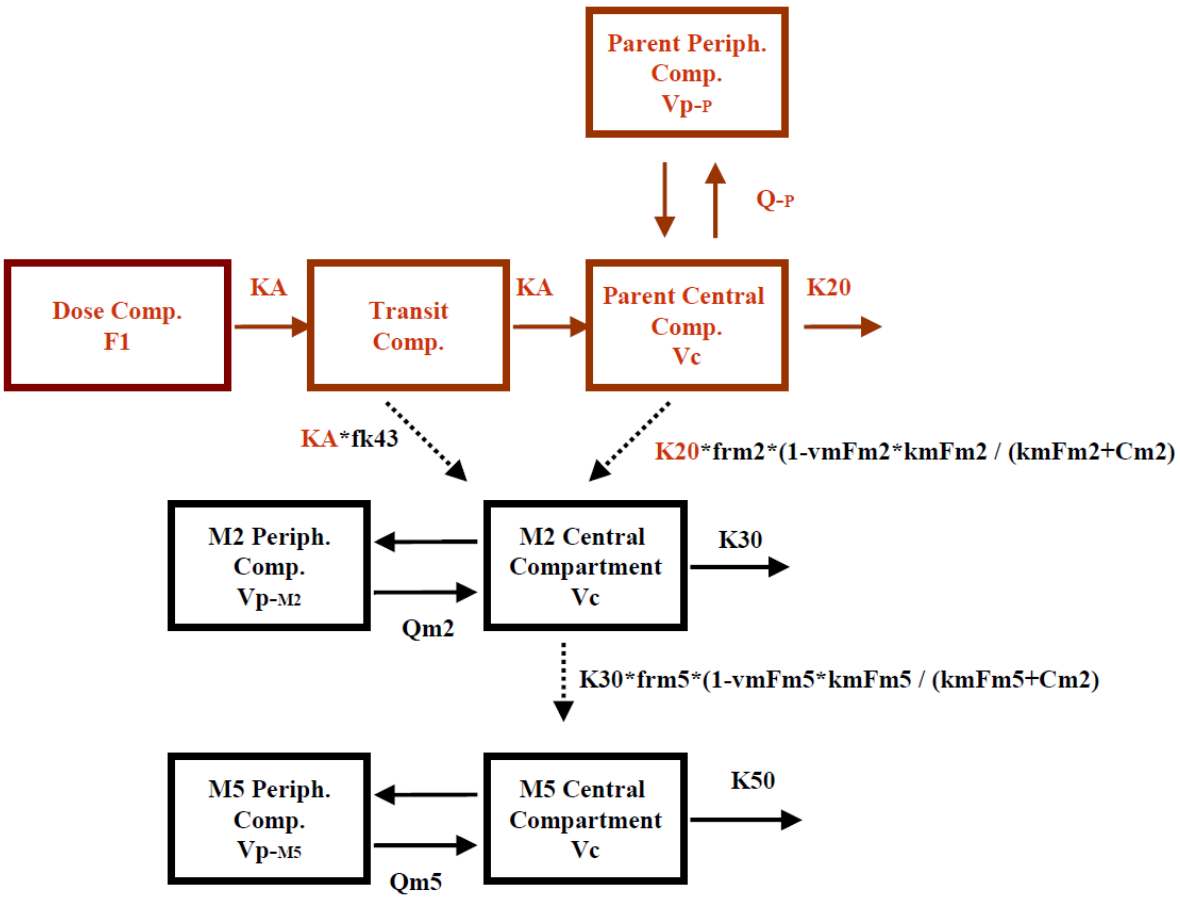


Figure 1: Schematic representation of the final popPK model of regorafenib and its metabolites M2 and M5

In study 15982, blood samples for PK analysis of regorafenib and its metabolites M-2 and M-5 were collected from all subjects pre-dose on Day 15 of Cycle 1 and on Day 1 and Day 15 of Cycle 2. In a subset of patients, an additional sample was collected on the same days between 2 and 4 h post-dose, i.e. around the time of the expected (daily) maximum concentrations of regorafenib.

To ensure timely delivery of the exposure estimates for the exposure-response modelling and the (multivariate) covariate analysis, the analysis started prior to database lock, when concentration data from approximately 80% of the patients were available. Once the data for all patients became available, the same analysis was performed again for the 100% population. The comparison of the distributions of

the estimated exposures to regorafenib (parent and total) in the 80% popPK population and in the 100% population investigated later showed that the regorafenib exposure was very similar in the two populations. Since the two populations were also similar with regards to demographic and baseline disease characteristics, it can be assumed that the results of the covariate analyses based on the 80% dataset can be extrapolated to the whole population. The 80% dataset consisted of 2534 observations from 276 subjects. These 2534 observations were almost equally distributed among regorafenib, M-2 and M-5 (846, 828 and 860 observations, respectively). The 100% dataset consisted of 3210 observations from 339 subjects. The actually administered dose (i.e. 160 mg, corresponding to no dose reduction, 120 or 80 mg, corresponding to a dose reduction, or 0 mg, corresponding to a dose interruption/delay, including the 7 days off drug), and dosing time were implemented based on the start- and end-date and available dose information from the clinical dataset. The number of subjects per dose level is summarised in the table below.

Table 3. Number of subjects at time point of exposure calculation (popPK analysis R-1108 complete dataset)

	Cycle 1 Day 15	Cycle 2 Day 1	Cycle 2 Day 15
0 mg	30	77	44
80 mg	7	7	16
120 mg	24	46	67
160 mg	278	186	190
Total	339	316	304

In the popPK covariate analysis across 16 studies (R-11104), subject status (patient or healthy volunteer), sex, age, BMI, and haemoglobin / albumin at baseline (HB0 / ALB0) were identified as having a statistically significant influence on exposure to regorafenib parent. The impact of these covariates on regorafenib exposure is graphically illustrated in Figure 2 for the population of cancer patients.

Age and haemoglobin at baseline significantly increased both the exposure of parent and the total nominal exposure (regorafenib+M-2+M-5). Of the 1337 subjects in the popPK analysis, 117 subjects were ≥75 years of age. An increase in 10 years of results in 3.8% and 4.9% increase in parent and the total nominal exposure, respectively.

BMI and plasma albumin (ALB0) at baseline increased the parent nominal exposure but not the total nominal exposure. An increase in BMI of 5 kg/m^2 results in 4.7% increase in parent nominal exposure.

Body weight and the liver enzymes ALT (ALT0) at baseline had a decreasing effect on the total nominal exposure but no significant influence on parent nominal exposure. An increase in body weight of 10 kg results in 3.1% decrease in total nominal exposure.

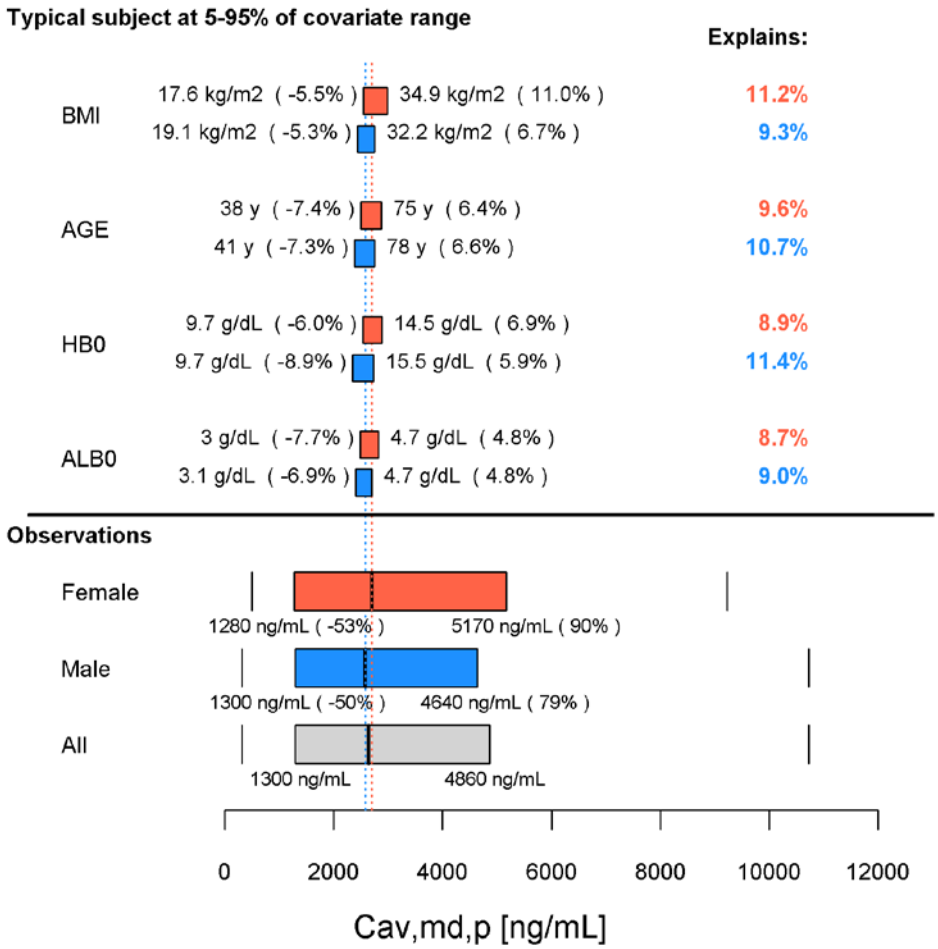


Figure 2. Exposure to regorafenib parent: Impact of covariates.

Range bars show difference between the 5th to 95th percentile and the median of parent nominal exposure (Cav,md,p) in all cancer patients. Covariate bars show the predicted difference between Cav,md,p at the 5th to 95th percentile of the covariate and Cav, md,p at the median of the covariate in all cancer patients. BMI: body mass index; HB0: baseline hemoglobin; ALB0: baseline albumin; Blue: males; red: females; grey: all patients. Source: Module 5.3.3.5, R-11104, Figure 7.2:19.

Results

HCC population

The PK parameters in patients with HCC from study 15982 are summarised in the table below.

Table 4: PK parameters of regorafenib, M-2, M-5 and free aggregate as estimated averages over the first cycle or first two cycles in HCC patients (study 15982)

Parameter	Unit	n	Geom. Mean	Geom. SD	Geom. CV(%)	Arithm. Mean	Arithm. SD	Arithm. CV(%)	Min	Median	Max
Regorafenib average exposure in cycle 1 using actual dosing	ng/mL	329	1867.1	1.52	43.76	2027.5	821.0	40.50	485	1920.0	7160
M-2 average exposure in cycle 1 using actual dosing	ng/mL	329	1139.5	2.00	78.60	1425.1	996.0	69.88	103	1200.0	7830
M-5 average exposure in cycle 1 using actual dosing	ng/mL	329	671.25	2.90	144.82	1206.50	2139.55	177.34	35.2	644.00	32100.0
Free aggregate average exposure in cycle 1 using actual dosing	nmol/L	329	24.630	1.58	48.07	27.182	12.228	44.99	5.48	25.726	92.43
Regorafenib AUC in cycle 1 using actual dosing	mcg*h/mL	329	1254.7	1.52	43.76	1362.5	551.7	40.50	326	1290.2	4812
M-2 AUC in cycle 1 using actual dosing	mcg*h/mL	329	765.77	2.00	78.60	957.69	669.28	69.88	69.2	806.40	5261.8
M-5 AUC in cycle 1 using actual dosing	mcg*h/mL	329	451.08	2.90	144.82	810.77	1437.78	177.34	23.7	432.77	21571.2
Free aggregate AUC in cycle 1 using actual dosing	mcmol*h/L	329	16.552	1.58	48.07	18.267	8.217	44.99	3.68	17.288	62.11
Regorafenib average exposure in cycles 1 and 2 using actual dosing	ng/mL	232	1495.8	1.54	45.08	1634.0	701.2	42.91	365	1555.0	5900
M-2 average exposure in cycles 1 and 2 using actual dosing	ng/mL	232	891.71	2.08	84.00	1147.43	881.87	76.86	98.8	936.50	6470.0
M-5 average exposure in cycles 1 and 2 using actual dosing	ng/mL	232	507.70	2.99	152.66	968.07	2101.95	217.13	30.1	491.50	28900.0
Free aggregate average exposure in cycles 1 and 2 using actual dosing	nmol/L	232	19.596	1.61	50.64	21.898	10.854	49.57	5.07	20.612	77.96
Regorafenib AUC in cycles 1 and 2 using actual dosing	mcg*h/mL	232	2010.4	1.54	45.08	2196.1	942.4	42.91	491	2089.9	7930
M-2 AUC in cycles 1 and 2 using actual dosing	mcg*h/mL	232	1198.5	2.08	84.00	1542.1	1185.2	76.86	133	1258.7	8696
M-5 AUC in cycles 1 and 2 using actual dosing	mcg*h/mL	232	682.35	2.99	152.66	1301.09	2825.02	217.13	40.5	660.58	38841.6
Free aggregate AUC in cycles 1 and 2 using actual dosing	mcmol*h/L	232	26.337	1.61	50.64	29.430	14.588	49.57	6.82	27.702	104.77

Note: Calculation of free aggregate: C regorafenib/ MWp * FUp + C M-2/MWm2 * FUm2 + C M-5/MWm5 * FUm5
Note: Where the molecular weights p, m2 and m5 are given as Regorafenib: 482.83 g/mol, M-2: 498.82 g/mol, M-5: 484.80 g/mol.
Note: Where the plasma FU p, m2 and m5 are given as Regorafenib: 0.488 %, M-2: 0.188 %, M-5: 0.053 %
Global Integrated Analysis: /by-sasp/patdb/ia/734506/stat/2017/prod_0130_ema_q/pgms/t_q2_pksummary.sas ertiv 02MAR2017 15:59
End of table

Figure 3 shows that the individual exposure to regorafenib parent was similar in HCC patients and CRC patients and slightly higher than the exposure in GIST patients. However, the exposures observed in GIST patients were completely within the range of the exposures observed in CRC and HCC patients, indicating that the exposure to regorafenib parent was very similar in the three patient populations.

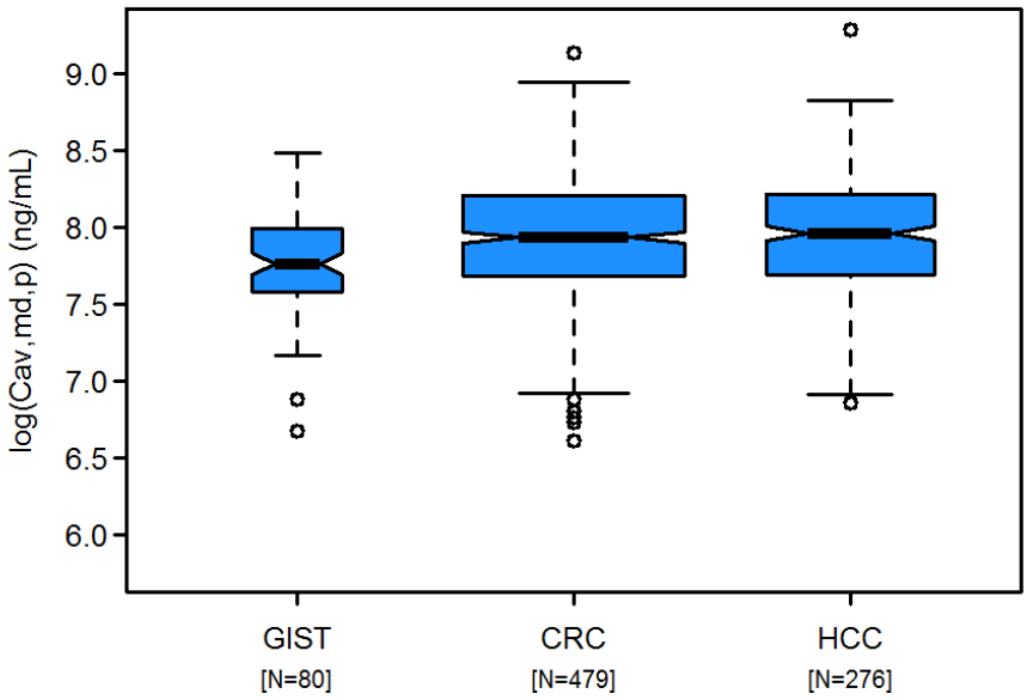
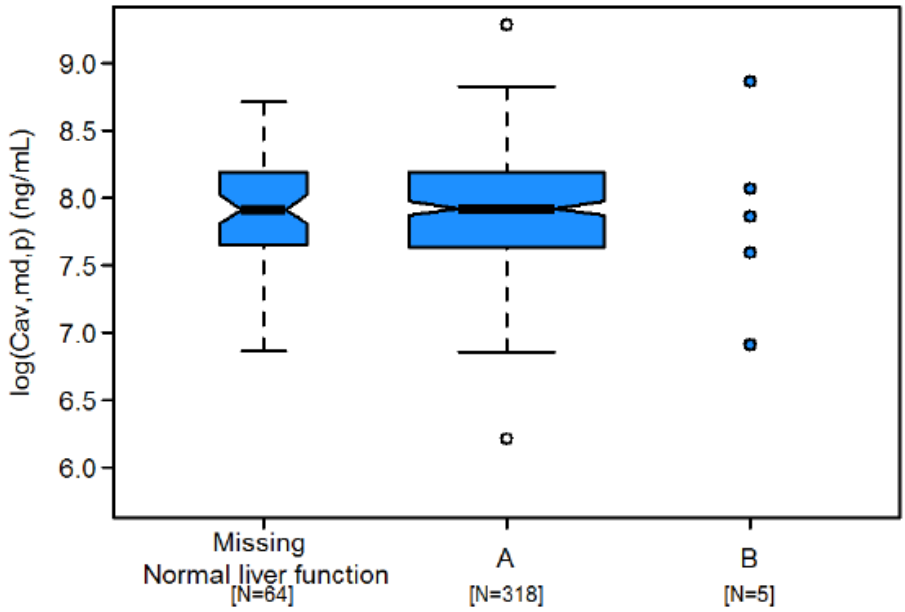


Figure 3: Exposure to regorafenib parent in patients with different types of cancer across four Phase 3 studies (Studies 15982, 14387, 14874, and 15808).

In addition, effect of hepatic function on PK of regorafenib was graphically explored. In study 15982, only 6 patients were classified as Child-Pugh B at baseline and PK data were available for only one. Across all studies with HCC patients (15982, 14596, 11651), PK data for 5 patients with Child-Pugh B and 318 patients with Child-Pugh A were available. Exposure in subjects with Child-Pugh class B function was comparable to that in patients with Child-Pugh class A function and that in patients with normal liver function (Figure 4). However a quantitative assessment could not be made because of the limited number of patients with Child-Pugh class B function. For 76 of 373 patients, their HCC was attributed to alcohol consumption. No notable impact of this factor was observed on the PK of regorafenib.



HCC (15982, 14596, 11651) studies

Figure 4: Distribution of exposure to regorafenib parent in patients with different Child-Pugh score levels across HCC studies

2.3.3. Pharmacodynamics

Mechanism of action

Regorafenib is an oral anti-tumour agent that can inhibit multiple protein kinases, including kinases involved in tumour angiogenesis (VEGFR1, -2, -3, TIE2), oncogenesis (KIT, RET, RAF-1, BRAF, BRAFV600E), and the tumour microenvironment (PDGFR, FGFR). In preclinical studies, regorafenib has demonstrated anti-tumour activity in a broad spectrum of tumour models including colorectal cancer models. Major human metabolites (M-2 and M-5) exhibited efficacy similar to regorafenib in both *in vitro* and *in vivo* models.

Biomarkers

In the RESORCE trial, retrospective explorative biomarker analyses are in progress aiming to identify biomarker candidates which might help to predict response to regorafenib.

The following types of correlative biomarker analyses are in progress:

- Expression data from approximatively 800 circulating miRNA isolated from plasma at baseline from subjects who granted genetic consent to identify individual miRNAs or miRNA signatures associated with the clinical endpoints OS and TTP.
- Determination of an immune profile on the basis of targeted gene expression on archival tumor tissue samples from approximately 65 subjects subjected to analysis
- Determination of the tumour mutational landscape using targeted Next-Generation DNA sequencing on archival tumor tissue samples from approximatively 22 subjects subjected to analysis

The results of the correlative biomarker analyses will be reported in separate non-genetic and genetic biomarker reports.

2.3.4. PK/PD modelling

The objective of the exploratory exposure-response (PKPD) analysis for Study 15982 was to assess the relationship between the exposure to regorafenib and its two pharmacologically active metabolites M-2 and M-5 on the one hand and efficacy- and safety-related responses on the other hand in HCC patients. For this purpose, different exposure parameters, which were estimated using a popPK model and various efficacy and safety variables, were correlated. In the absence of studies generating data comparable to those of Study 15982, the analysis was based on the data from Study 15982 only. A univariate (report PH-39209) and a multivariate (report PH39309) analysis were conducted.

The PK/PD population included 337 patients, 297 men (88.1%) and 40 women (11.9%). The median age was 64.0 years (range: 19 to 85 years). Approximately 40% of the subjects were Asians and 40% were non- Asians (ethnicity not reported: approx. 20%). For 76 of 337 patients (22.6%), their HCC was attributed to alcohol consumption.

For the univariate analysis, subgroups for analyses were defined based on exposure quartiles. For each parameter, the subjects were assigned to three mutually exclusive exposure groups defined as follows: low = 1st quartile, medium = 2nd and 3rd quartiles, high = 4th quartile of the respective exposure parameter. Exposure, defined as the average concentration (CAV) during the time interval, was estimated for regorafenib parent and for the sum of regorafenib parent, M-2, and M-5 concentrations corrected for differences in molecular weight and protein binding (free aggregate). Given the low peak-trough fluctuation at steady-state, the average concentration is an adequate parameter to describe the extent of exposure to regorafenib and its active metabolites.

There were some minor imbalances in demographic and baseline characteristics among the three exposure groups: there were more females in the high exposure group than in the two other groups (27% vs ≤ 10% in the other two groups) and the percentage of mainland Chinese patients was higher in the high exposure group than in the other two groups (42% vs ≤20% in the other two groups) (see Table 5). Also baseline disease characteristics ECOG status 1 and percentage of patients with increased levels of AST/ALT was slightly higher in the low exposure group.

Table 5: Study 15982 – Demographics by exposure to free aggregate in Cycle 1

Characteristic	Free aggregate exposure group			
	Low n=83 (100%)	Medium n=163 (100%)	High n=83 (100%)	Total n=329 (100%)
Sex (n [%])				
Male	81 (97.6%)	147 (90.2%)	61 (73.5%)	289 (87.8%)
Female	2 (2.4%)	16 (9.8%)	22 (26.5%)	40 (12.2%)
Race group 1 (n [%])				
Asian	35 (42.2%)	62 (38.0%)	44 (53.0%)	141 (42.9%)
Non-Asian	29 (34.9%)	68 (41.7%)	28 (33.7%)	125 (38.0%)
Not reported	19 (22.9%)	33 (20.2%)	11 (13.3%)	63 (19.1%)
Race-group 2 (n [%])				
Japanese	7 (8.4%)	15 (9.2%)	7 (8.4%)	29 (8.8%)
Chinese	11 (13.3%)	32 (19.6%)	35 (42.2%)	78 (23.7%)
Other Asian	17 (20.5%)	15 (9.2%)	2 (2.4%)	34 (10.3%)
Non-Asian	29 (34.9%)	68 (41.7%)	28 (33.7%)	125 (38.0%)
Not reported	19 (22.9%)	33 (20.2%)	11 (13.3%)	63 (19.1%)
Race-group 3 (n [%])				
Chinese / Taiwanese	16 (19.3%)	42 (25.8%)	36 (43.4%)	94 (28.6%)
Other	48 (57.8%)	88 (54.0%)	36 (43.4%)	172 (52.3%)
Not reported	19 (22.9%)	33 (20.2%)	11 (13.3%)	63 (19.1%)
Age (years)				
n	83	163	83	329
Mean (range)	62.8 (32 - 85)	63.4 (19 - 84)	58.4 (27 - 82)	62.0 (19 - 85)
Median	62.0	65.0	60.0	64.0
Baseline BMI (kg/m^2)				
n	82	157	82	321
Mean (range)	25.0 (14.8 - 44.8)	25.5 (16.1 - 40.8)	23.7 (17.3 - 35.1)	24.9 (14.8 - 44.8)
Median	24.2	25.4	23.3	24.6
Baseline ECOG status (n [%])				
0	50 (60.2%)	116 (71.2%)	58 (69.9%)	224 (68.1%)
1	33 (39.8%)	47 (28.8%)	25 (30.1%)	105 (31.9%)
Baseline hepatic impairment (n [%])				
AST/ALT ≤ 1.5*ULN	40 (48.2%)	98 (60.1%)	56 (67.5%)	194 (59.0%)
1.5*ULN < AST/ALT ≤ 3*ULN	35 (42.2%)	51 (31.3%)	22 (26.5%)	108 (32.8%)
ALT > 3*ULN OR AST > 3*ULN	8 (9.6%)	14 (8.6%)	5 (6.0%)	27 (8.2%)
BCLC stage at study entry				
Missing	0	1 (0.6%)	0	1 (0.3%)
A (early stage)	0	1 (0.6%)	0	1 (0.3%)
B (intermediate stage)	14 (16.9%)	22 (13.5%)	11 (13.3%)	47 (14.3%)
C (advanced stage)	69 (83.1%)	139 (85.3%)	72 (86.7%)	280 (85.1%)

'Japanese' is defined as race = Asian and Country = Japan, 'Chinese' is defined as race = Asian and country = mainland China.

Exposure-effect relationships

Univariate analysis indicated that there was a trend towards shorter OS in the low exposure group compared to the medium and high exposure group. The median survival times for subjects in low, median or high exposure groups (free aggregate) were 261, 374 or 499 days, respectively, with the median survival of 343 days (N=329) for the overall population. The median overall survival in the placebo group in the RESORCE trial was 237 days (95% CI: 192, 269 days; N = 194).

Table 6: Study 15982 – median overall survival (OS) [days] by exposure to regorafenib parent and free aggregate

Median (95% confidence interval)

Analyte	Exposure group	Classification based on exposure in Cycle 1 ($C_{av}D28$) N_{total} = 329	Classification based on exposure in Cycles 1 plus 2 ($C_{av}D56$) N_{total} = 232
Parent	Low	260 (194, 331)	324 (232, 430)
	Medium	374 (272, 451)	451 (344, 560)
	High	472 (341, 655)	403 (292, -)
Free aggregate	Low	261 (194, 339)	331 (232, 431)
	Medium	374 (272, 425)	447 (395, 532)
	High	499 (316, 644)	366 (239, 655)

Source: PH-39209, Section 14, Table 4/1 to Table 4/6

There were no consistent differences between exposure groups regarding time to progression (TTP). When the subjects were grouped by exposure in Cycle 1 (parent and free aggregate), the lowest median TTP was seen in the low exposure groups (Table 7). When the subjects were grouped by exposure in Cycles 1 plus 2, the relation was inverted, i.e. the longest median TTP was seen in the low exposure groups. In both cases, the 95% CIs were largely overlapping.

Table 7: Study 15982 – median time to progression (TTP) [days] by exposure to regorafenib parent and free aggregate

Median (95% confidence interval)

Analyte	Exposure group	Classification based on exposure in Cycle 1 ($C_{av}D28$) N_{total} = 329	Classification based on exposure in Cycles 1 plus 2 ($C_{av}D56$) N_{total} = 232
Parent	Low	85 (53, 120)	168 (121, 194)
	Medium	129 (91, 168)	165 (127, 204)
	High	128 (89, 144)	129 (92, 171)
Free aggregate	Low	85 (66, 128)	168 (120, 194)
	Medium	127 (87, 144)	148 (127, 204)
	High	128 (89, 168)	137 (126, 177)

Source: PH-39209, Section 14, Table 4/7 to Table 4/12

Source: PH 39209, Section 14, Table 4/7 to Table 4/12.

The exposure-response relationship for Overall Survival (OS) was further investigated using multivariate Cox proportional regression analysis to evaluate the correlation between exposure quartiles and efficacy while taking the effect of predefined baseline covariates into consideration. Table 8 shows that Cox proportional-hazard analysis identified three significant baseline risk factors for OS: ECOG performance score ($p < 0.001$), AFP baseline value (AFP category, $p < 0.001$) and hepatic function according to AST/ALT baseline levels (AST/ALT levels > 3 times the upper limit of normal, $p < 0.001$). While no statistically significant exposure-response relationship could be identified between (continuous) individual exposure for OS in the regorafenib group, the analysis of the exposure-response relationship shows a trend for OS to increase with increasing exposure to regorafenib.

Table 8: Results of the Cox regression analysis with the reduced model for OS based on all patients using imputed exposure estimates (N=567). Reference category for each covariate is indicated by the HR estimate of '1'

Covariate	Category	HR estimate ER analysis set	HR estimate	LLCI[a]	ULCI[b]	p-value of category	p-value of covariate
CAVD28	Placebo		1	na	na	na	<0.001
	Q1		0.7138	0.524	0.9724	0.03254	
	Q2		0.5277	0.3769	0.739	<0.001	
	Q3		0.8482	0.6451	1.115	0.2383	
	Q4		0.4606	0.3239	0.6549	<0.001	
ECOG stage	0		1	na	na	na	<0.001
	>=1		1.7	1.372	2.107	<0.001	
AFP level	<400 ng/mL		1	na	na	na	<0.001
	>=400 ng/mL		1.964	1.591	2.424	<0.001	
max of AST and ALT	<=1.5*ULN		0.8428	0.671	1.059	0.1417	
	>1.5*ULN to <=3*ULN		1	na	na	na	<0.001
	>3*ULN		2.087	1.463	2.978	<0.001	

[a] Lower limit (2.5%) confidence interval [b] Upper limit (97.5%) confidence interval
na = not applicable
Source: 19107/Reporting/06_Exploratory_output/OS/imp19107-SA-reduced-cox-model-OS-v1.csv, 19107/Reporting/06_Exploratory_output/OS/imp19107-SA-reduced-cox-model-LRT-OS-v1.csv

a; Lower limit (2.5%) confidence interval. b; Upper limit (97.5%) confidence interval. na = not applicable.
Source: 19107/Reporting?06_Exploratory_output/OS/imp19107-SA-reduced-cox-model-OS-v1.csv,19107/Reporting?06_Exploratory_output/OS/imp19107-SA-reduced-cox-model-LRT-OS-v1.csv.

In addition, OS in average dose subgroups of <140 mg and ≥140 mg was evaluated by Kaplan-Meier analysis. Results from these (exploratory) analyses are provided in Table 9. The OS was shorter in the regorafenib group with an average dose <140 mg (median of 224 days in 99 subjects) versus a median of 360 days in 275 subjects in the ≥140 mg average dose group. For the placebo group, a substantial difference in OS between the <140 mg average dose group and the≥140 mg average dose group was observed also, with a median of 47 (18 subjects) and 248 (175 subjects) days, respectively.

Table 9: Study 15982 - Median OS by average dose group

Cycle	Average dose group	Placebo n	Placebo OS (95% CI) (days)	Regorafenib n	Regorafenib OS (95% CI) (days)
Cycle 1	< 140 mg	18	47 (31;100)	99	224 (178;323)
	≥ 140 mg	175	248 (202;282)	275	360 (293;421)
Cycle 1+2	< 140 mg	39	182 (94;280)	126	303 (237;343)
	≥ 140 mg	134	260 (228;294)	211	401 (323;493)

Exposure – safety relationships

The number of subjects with, as well as the incidence of any ≥ Grade 3 TEAE, any TESAE, and individual AEs of asthenia/fatigue, diarrhoea, HFSR, haemorrhage, hepatic encephalopathy, hypertension, mucositis, liver failure, rash, and elevated ALT, AST, total bilirubin and changes in platelet counts were investigated.

The analyses demonstrated that there were no correlations between selected relevant TEAEs (total and ≥ NCI CTCAE Grade 3) and exposure to regorafenib or free aggregate when considering Cycle 1 as well as TEAEs reported for the whole treatment period and drug exposure in Cycle 1 plus 2.

A trend for an exposure-dependent increase was observed for the number of subjects with elevated total bilirubin and for total events of mucositis (mostly driven by events of Grade 1 and few events of Grade 2 and 3). Furthermore, a slight increase of total incidence of haemorrhage and decreased platelets was seen (mostly driven by Grade 1 and 2 events) and the total incidence for HFSR slightly increased with exposure to regorafenib and free aggregate which are also driven by an increase in Grade 1 and 2 events.

Exposure – dose modification relationship

The planned dose regimen for regorafenib (160 mg once daily, 3 weeks on / 1 week off) was modified for 146 of 329 (evaluable) subjects in Cycle 1 (44.4%), for 216/329 subjects (65.7%) in Cycles 1 plus 2 and for 316/329 subjects (96.0%) during the whole treatment period. The median time to first modification (dose reduction or interruption/delay) was 16 days in the 146 subjects with dose modifications in Cycle 1.

Any modifications and dose interruptions or delays were more common in the low exposure group than in the medium exposure group and in particular in the high exposure group. This is shown in Table 10 for exposure to free aggregate but the results were similar when the subjects were grouped by exposure to regorafenib parent. Subjects in the low exposure group experienced more TEAEs during the first cycle which resulted in dose modifications. The time to first interruption or delay during Cycle 1 was also shorter in the low exposure group and the number of subjects who discontinued regorafenib was higher in this group than in the two other groups (8/83 subjects (9.6%)) in the low exposure group vs 4/163 subjects (2.5%) in the medium exposure group and 0/83 subjects (0%) in the high exposure group). The number of subjects with dose reductions and the time to first dose reduction was similar in the three groups. The primary reason for dose interruptions or delays was the occurrence of adverse events in all exposure groups. The most common treatment-emergent adverse events (TEAEs) that led to dose interruption in subjects randomized to regorafenib were diarrhoea, fatigue, AST increased, blood bilirubin increased, and HFSR.

Table 10: Study 15982–dose modifications in Cycle 1 by exposure to free aggregate in Cycle1

Number of subjects affected (%) (95% confidence interval)

Exposure group	N	Type of dose modification			Median time [days] to first	
		Any modification	Reduction	Interruption or delay	reduction	interruption or delay
Low	83	51 (61.4) (50.1 - 71.9)	13 (15.7) (8.6 - 25.3)	47 (56.6) (45.3 - 67.5)	15	16
Medium	163	71 (43.6) (35.8 - 51.5)	26 (16.0) (10.7 - 22.5)	60 (36.8) (29.4 - 44.7)	15	20
High	83	24 (28.9) (19.5 - 39.9)	12 (14.5) (7.7 - 23.9)	19 (22.9) (14.4 - 33.4)	13	29

A subsequent analysis of the average dose groups stratified by no or at least one interruption/delay, shows that the average dose group with <140 mg with no interruption/delay has a shorter OS compared to the average dose group with <140 mg with at least one dose interruption/delay in both the placebo and the regorafenib treatment group.

Table 11: Study 15982 - Median OS by average dose group and/or interruptions/delays group

Cycle	Average dose group	Number of interruption/delay	Placebo n	Placebo OS (95% CI) (days)	Regorafenib n	Regorafenib OS (95% CI) (days)
Cycle 1	< 140 mg	≥ 1	5	126 (47;534)	69	292 (196;332)
		none	13	34 (16;100)	30	96 (46;316)
	≥ 140 mg	≥ 1	37	237 (127;411)	61	343 (269;451)
		none	138	260 (208;282)	214	374 (293;432)
Cycle 1+2	< 140 mg	≥ 1	18	280 (84;411)	99	324 (241;383)
		none	21	142 (88;278)	27	233 (109;316)
	≥ 140 mg	≥ 1	35	248 (148;571)	64	402 (276;539)
		none	99	260 (214;288)	147	401 (298;503)

2.3.5. Discussion on clinical pharmacology

Regorafenib is an oral anti-tumour agent that can inhibit multiple protein kinases, including kinases involved in tumour angiogenesis (VEGFR1, -2, -3, TIE2), oncogenesis (KIT, RET, RAF-1, BRAF, BRAFV600E), and the tumour microenvironment (PDGFR, FGFR).

In study 15982 (RESORCE), regorafenib is given after treatment with sorafenib has failed. Though it seems counter-intuitive to initiate a treatment with a multikinase inhibitor after another multikinase inhibitor has failed, there is increasing evidence that sequential use and switch upon progression of multikinase inhibitors with partially overlapping but distinct kinase inhibitor profiles is associated with clinical benefit and prolongation of survival. In renal cell cancer and GIST, sequential use of several multikinase inhibitors such as imatinib, sunitinib, sorafenib, or axitinib has become an element of the standard of care in these patients. The findings from the RESORCE trial of a significantly increased survival compared to placebo in HCC patients after prior treatment with sorafenib is therefore consistent with the data regarding the clinical benefit of multikinase inhibitor sequence treatments in RCC and GIST.

For the current application in HCC, pharmacokinetic data of regorafenib was obtained in the pivotal phase 3 study 15982 (sparse PK data). The original popPK analysis based on 14 studies including the phase 3 studies for mCRC and GIST was updated with data from the pivotal study 15982. Further an exploratory exposure-response analysis for both efficacy and safety was conducted for the Phase 3 study 15982.

The pharmacokinetics of regorafenib are comparable between HCC and mCRC patients. Exposure of M-2 and M-5 in HCC patients seemed somewhat lower than in CRC patients but high inter-individual variability in exposure of these active metabolites was observed (Table 4).

The limited pharmacokinetic data in patients with Child-Pugh B (N=6) do not indicate a different exposure to regorafenib, data on M-2 and M-5 were not reported. It is agreed that the data are too limited to provide a recommendation for starting dose in section 4.2 for Child-Pugh B. During treatment with regorafenib, ~30% of the patients became classified as Child-Pugh B, and dose reductions are proposed for liver function (ALT, AST and bilirubin), which should be controlled on regular basis. This is adequately addressed in sections 4.2 and 4.4 of the SmPC.

In the phase 3 study 15982, exposure-efficacy analysis showed a trend for longer OS but not TTP with higher regorafenib exposure. Previously, no correlation between exposure and efficacy was observed for mCRC and GIST. HCC patients with the lowest regorafenib exposure had a lower average dosage due to dose reductions and more dose interruptions than patients with higher regorafenib exposures. Further,

the percentage of subjects with baseline ECOG status 1 was higher in subjects with lower average dosage in cycle 1 compared to subjects with 160 mg dosage in both the placebo as the regorafenib group. In addition, patients with a lower average dose seemed to withdraw more frequently. Both in the placebo and regorafenib group patients with a lower average dosage had a shorter OS. Hence, the trend for longer OS with higher regorafenib exposure can be explained (in part) by differences in baseline characteristics regarding performance status and subsequently dose interruption, reductions and study withdrawal. This is in agreement with the COX multivariate analysis, where ECOG performance score, AFP baseline value and hepatic function according to AST/ALT baseline levels were significant baseline risk factors for OS.

There were no correlations between selected relevant TEAEs ≥ Grade 3 and regorafenib exposure. A trend for an exposure-dependent increase was observed for the number of subjects with elevated total bilirubin and for total events of mucositis and rash (mostly driven by events of Grade 1 and few events of Grade 2 and 3). Furthermore, a slight increase of total incidence of haemorrhage and decreased platelets was seen (mostly driven by Grade 1 and 2 events). This is consistent with the exposure-toxicity correlations observed in mCRC and GIST patients.

Exploratory biomarker analysis to potentially identify mechanisms involved and to select patients who benefit most from regorafenib treatment is ongoing; results from the non-genetic analyses have been provided during review and the results on the genetic biomarker analyses will be submitted by the MAH once available.

2.3.6. Conclusions on clinical pharmacology

The clinical pharmacology package for the extension of indication for treatment of patients with HCC, who have been previously treated with one systemic therapy, is considered acceptable.

2.4. Clinical efficacy

In support of this type II variation application, to extend the use of regorafenib to patients with HCC who have been previously treated with one systemic therapy the MAH has submitted one pivotal Phase III 15982 (RESORCE) study. In addition, the results of the phase II 14596 study, also conducted in patients with HCC (in EU and South Korea) after failure (defined as radiological progression) of sorafenib treatment has been presented as supportive.

The proposed dosing regimen of regorafenib (160 mg orally OD (i.e., once daily) according to a 3 weeks on followed by 1 week off schema) in patients with HCC pre-treated with sorafenib is in line with the already approved indication in metastatic colorectal cancer and GIST.

2.4.1. Main study

Study 15982: A randomized, double blind, placebo-controlled, multicenter phase III study of regorafenib in patients with hepatocellular carcinoma (HCC) after sorafenib (RESORCE)

Study 15982 is a pivotal multi-centre, multi-national, randomized, double-blind, placebo-controlled phase III trial comparing regorafenib plus best supportive care (BSC) versus placebo plus BSC in patients with HCC who have progressed after sorafenib. A total of 573 patients were randomized (2:1) to receive either regorafenib or matching placebo 160 mg OD orally for 3 weeks followed by 1 week off therapy (cycle of 4

weeks).

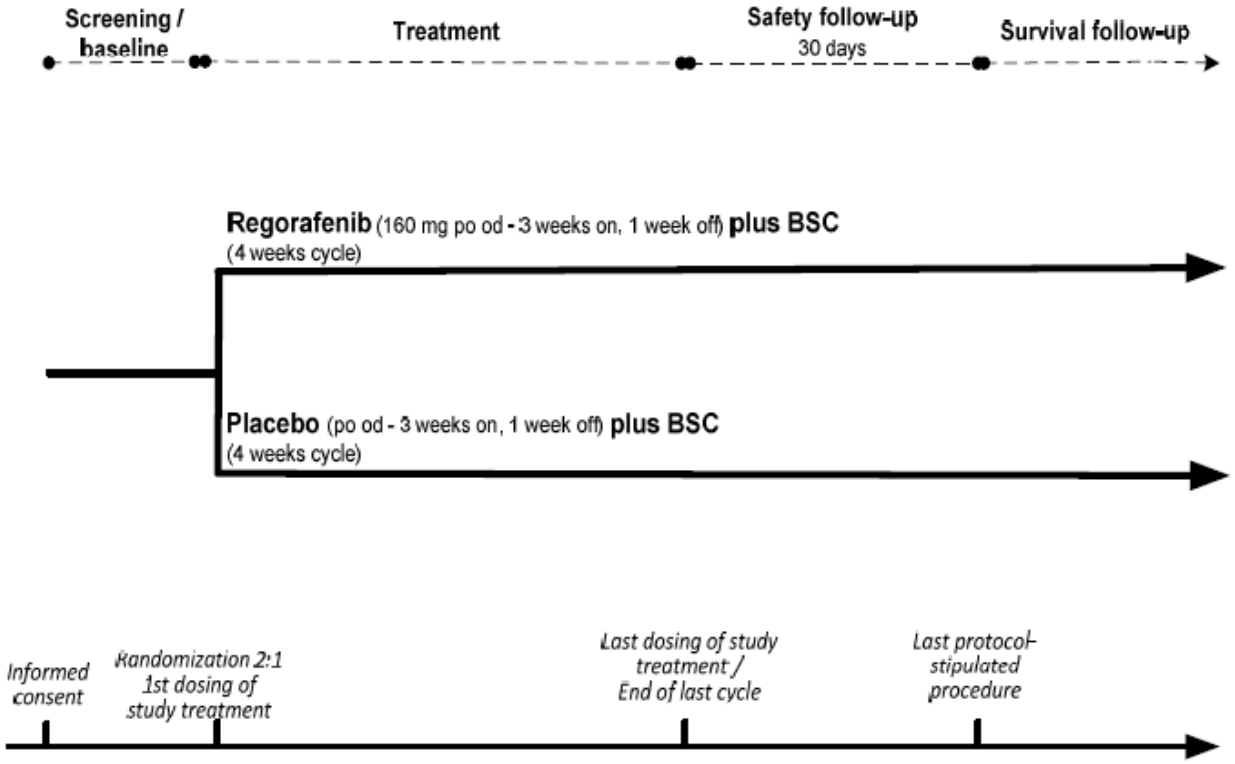


Figure 5: Design of the pivotal 15982 study.

Methods

Study participants

Key inclusion criteria:

- Histologically or cytologically confirmed HCC or with non-invasive diagnosis of HCC as per American Association for Study of Liver Disease (AASLD) criteria, with Barcelona Clinic Liver Cancer (BCLC) criteria B or C who could not benefit from treatments with established efficacy and higher priority like resection, local ablation, chemoembolisation, and who had failure prior therapy with sorafenib according to the radiology charter.

- Patients randomized within 10 weeks after the last treatment with sorafenib,

- Liver function status Child-Pugh Class A and ECOG performance status ≤1.

- Measurable disease according to RECIST criteria (version 1.1)

- Adequate bone marrow and renal function (GFR ≥30 mL/min/1.73 m^2).

Key exclusion criteria:

- Any CNS metastases

- Large oesophageal varices at risk of bleeding not treated with conventional medical intervention (i.e., beta blockers or endoscopic treatment),

- Uncontrolled hypertension, or with cardiac arrhythmias requiring anti-arrhytmic therapy (excluding beta blockers or digoxin), or with congestive heart failure New York Association (NYHA) >1, or with unstable

angina or myocardial infarction or arterial or venous thrombotic or embolic events with 6 months from enrolment.

- Permanent discontinuation of sorafenib due to toxicity, or with tolerability of prior treatment with sorafenib less than 20 days at a minimum daily dose of 400 mg QD within the last 28 days prior to withdrawal as well as with any other prior systemic treatment for HCC (excluding sorafenib).

- Significant bleeding within 30 days prior to randomization,

- Proteinuria, uncontrolled pleural effusion/ascites, presence of non-healing wounds, ulcer or bone fracture, any kind of malabsorption, interstitial lung disease, pheochromocytoma and previous liver transplantation.

Treatments

Patients were to receive either regorafenib or matching placebo 160 mg (4 x 40 mg tablets) OD orally for 3 weeks followed by 1 week off therapy (cycle of 4 weeks) plus BSC (Best Supportive Care). Doses of study drug were to be taken following a light meal.

Up to two regorafenib dose-reductions due to toxicity were allowed (from 160 mg to 120 mg to 80 mg. Biomarker analyses on whole blood and plasma samples and archived diagnostic tumour biopsies were performed (voluntary patients with a separate consent).

Patients were treated until disease progression according to mRECIST or RECIST 1.1 criteria, clinical progression, unacceptable toxicity, and/or consent withdrawal. Dosing beyond disease progression was allowed under special circumstances (i.e. expected benefit by continued therapy) and in consultation with the sponsor. Cross-over was not allowed.

Objectives

Primary objective:

To show superiority of regorafenib plus BSC versus placebo plus BSC in terms of Overall Survival (OS).

Secondary objectives:

Comparison between the two study arms of Progression Free Survival (PFS), Time to Progression (TTP), objective tumour response rate (ORR), and disease control rate (DCR= CR+PR+SD).

Tertiary objectives:

Duration of objective response, duration of stable disease, evaluation of health related quality of life and utility values, safety and pharmacokinetics. A biomarker analysis was also included as exploratory.

Outcomes/endpoints

Primary endpoint:

OS, defined as the time (days) from randomization to death due to any cause.

Secondary endpoints:

TTP: time [days] from randomization to radiological or clinical disease progression.

PFS: time [days] from randomization to first observed disease progression [radiological or clinical, as assessed by investigators] or death due to any cause, if death occurred before disease progression was documented.

ORR: percentage of patients with complete response [CR] or partial response [PR] according to RECIST 1.1 and the modified RECIST criteria.

DCR: percentage of patients with CR, PR or stable disease [SD]. In order to be counted as a responder in DCR, stable disease had to be maintained for at least 6 weeks. Of note, the RECIST modified for HCC (mRECIST) does not include necrotic tissue into the measurement but only viable parts of tumour lesions.

Tertiary endpoints:

Duration of response: time from the first documented objective response of CR of PR, whichever was noted earlier, to disease progression or death [if death occurred before progression], in patients achieving CR or PR according to both RECIST 1.1 and mRECIST,

Duration of stable disease: time from randomization to disease progression or death, calculated only in patients who failed to achieve CR or PR)

Evaluation of patient reported outcomes (PROs) including evaluation of Health Related Quality of life (according to the FACT-Hep and the EQ-5D questionnaires).

(Optional) biomarker analysis included evaluation of mutation of genes of interest (e.g., BRAF, KRAS, PI3KCA), expression of several genes (eg, VEGFR, PDGFR, FGFR, c-KIT, TIE2) on archival tumour biopsies and/or blood/plasma samples.

Sample size

The sample size was based on the primary efficacy endpoint (OS). The targeted improvement was a 43% increase in median OS compared to placebo (i.e. assuming a median OS under placebo of 8 months, the median OS under regorafenib was expected to be at least 11.4 months). The associated hazard ratio of regorafenib over placebo was 0.7. Approximately 370 events were required assuming a one-sided $\alpha = 0.025$, a targeted improvement in median survival of 43%, a power of 90%, and a randomization ratio of 2:1 between regorafenib and placebo. Approximately 560 subjects were planned to be randomized in order to conduct the study in a reasonable time frame. The study data were to be considered mature and the final analysis performed after approximately 370 events (deaths) were observed.

Randomisation

Patients were randomized (2:1) to receive either regorafenib or matching placebo. Randomization was performed through a computer generated randomization list prepared by the Sponsor Randomization Manager. The randomization number for each eligible patient was provided to the Investigators through an interactive voice recognition system (IVRS).

Randomization was stratified by:

1- Geographical region (Asia of Rest of the World);

2- ECOG PS (0 vs 1);

3- Alpha-feto protein (AFP) level (< 400 ng/mL vs ≥400 ng/mL);

4- Presence vs absence of extra-hepatic disease;

5- Presence vs absence of macrovascular invasion.

Blinding (masking)

Patients were randomized to receive regorafenib or matching placebo in a double-blind fashion, i.e. neither the investigator, nor the sponsor, nor the patient knew which agent was being administered.

Statistical methods

Analysis sets

All primary efficacy analyses were based on the Full Analysis Set (FAS), which comprised all randomized subjects, including subjects who withdrew regardless of the reason for withdrawal.

The population for safety analysis comprised all patients who received at least 1 dose of study medication.

Analysis methods

The final analysis of OS was to be performed using a 1-sided overall α of 0.025 when approximately 370 death events were observed. The hazard ratio (HR) for OS and its 95% confidence interval (CI) was to be calculated using the Cox model, stratified by the same factors as stated above. Kaplan-Meier (KM) estimates for OS and KM survival curves are presented for each treatment arm. Primary endpoint OS: Increase in median survival of 43%, 8.0 to 11.4 months; HR = 0.70. Significance level/power: 0.025 (one-sided) / 90%. Accrual period: 22.2 months (first patient first visit [FPFV] to last patient first visit [LPFV]). Accrual rate 25 patients/month, ramp- up 3 months). Study duration 32.7 months (until primary completion). Total number of events: 370. Total number of patients required: 560.

Interim analyses

In the original protocol one formal interim futility analysis and one formal interim efficacy analysis for OS was planned to be conducted during the study and evaluated by a DMC. However only the interim analysis for futility was performed as the other one was removed with protocol amendment 4 as by the time of the formal interim efficacy analysis for OS and in case of a hypothetical premature study stop, enrolment would not yet have been completed.

Handling of missing data

Missing or unevaluable tumour assessments (including scheduled assessments that were not done and incomplete assessments that did not result in an unambiguous tumour response evaluation according to RECIST 1.1 and mRECIST criteria) were not used in the calculation of derived efficacy variables related to tumour assessments unless a new lesion occurred or the lesions that were evaluated already showed progressive disease. No imputation was performed for missing lesion assessments and tumour response evaluation. For example, if a subject missed a scan visit and progressive disease (PD) was documented at the next available scan visit, the actual visit date of the first documented PD was used to calculate PFS and TTP. If a date was incomplete, (e.g. only the year and month of the tumour assessment or if the date of death was available), then day 15 of the month was used for the calculation of, for example, OS and PFS. If the actual scan date of the radiological progression was missing and radiological or clinical progression had been documented based on the criteria specified in the protocol, the scheduled scan date was to be used to calculate the time to progression.

Results

Participant flow

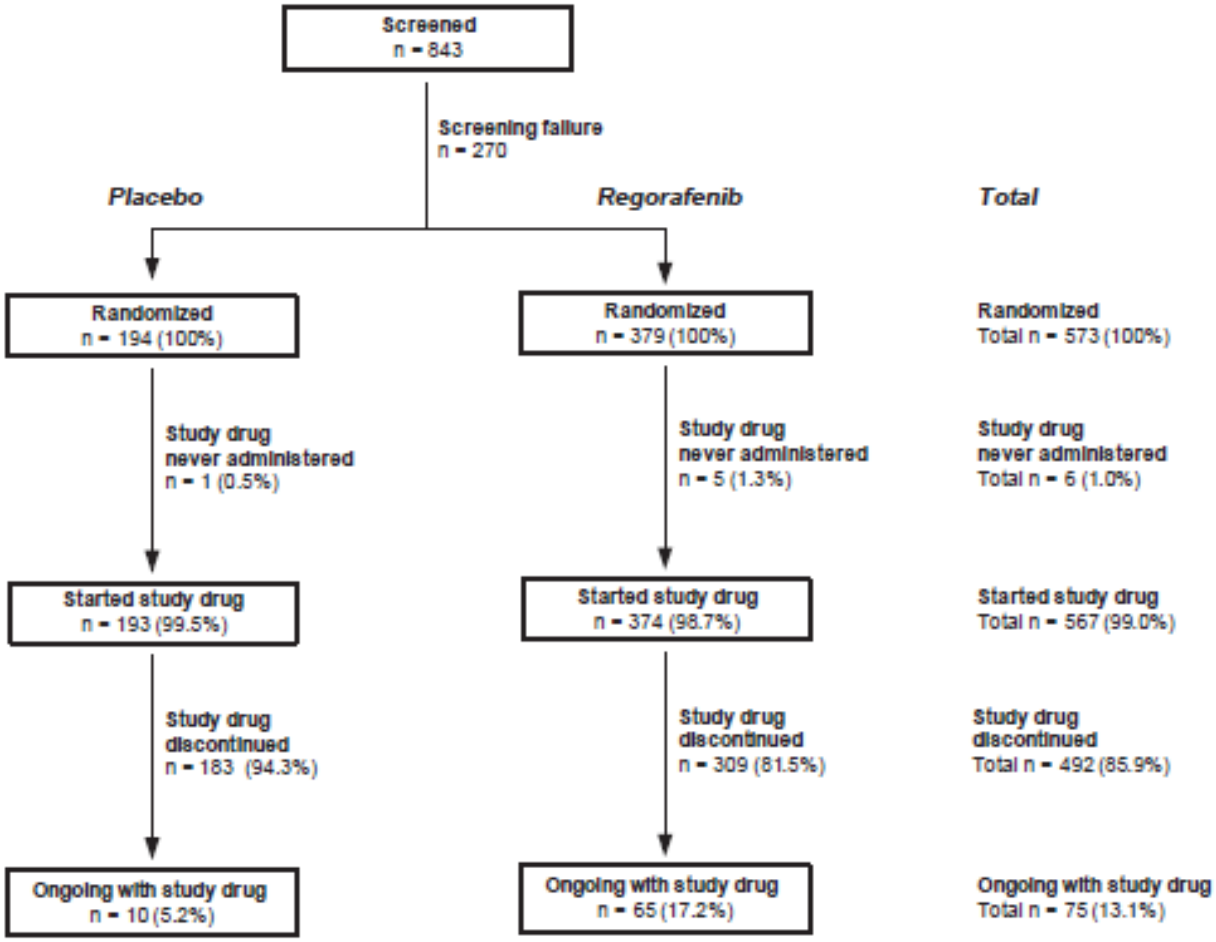


Figure 6. Participant flow Cut-off 29-02-2016.

Recruitment

A total of 573 patients were randomized into the study (ITT population), between 14 May 2013 and 29 February 2016, 379 in the regorafenib plus BSC group and 194 in the placebo plus BSC group, consistent with the planned 2:1 randomization. Five patients randomized to regorafenib and 1 randomized to placebo did not receive a single dose of study drug. Therefore, 567 patients received at least one dose of study medication and were included in the safety population.

As of the 29 February 2016 cut-off date 75 patients (13.1%) were still on study (65 [17.2%] in the regorafenib arm and 10 [5.2%] in the placebo arm). Thus, a total of 492 (85.9%) patients in the ITT population had discontinued the study, 309 (81.5%) in the regorafenib group and 183 (94.3%) in the placebo group.

The study was conducted at 152 study centers that enrolled patients in 21 countries. The participating countries were (number of centers in brackets): Japan (12), USA (17), France (20), Germany (11), Belgium (2), Australia (5), Czech Republic (3), The Netherlands (2), China (27), Hungary (3), Italy (16), Spain (9), Argentina (1), Austria (3), Brazil (2), Switzerland (2), Russia (3), Singapore (1), South Korea (4), Taiwan (4), United Kingdom (5).

Conduct of the study

The original study protocol was subsequently amended 5 times.

Amendment 1 (dated 02 May 2013) essentially clarified inclusion/exclusion criteria, in particular inclusion of HCV positive patients not requiring antiviral treatment was allowed, whereas concomitant therapy with antivirals for HCV was not allowed.

Amendment 2 (dated 13 December 2013) essentially changed the allowed time from last sorafenib treatment to randomization from 8 to 10 weeks, clarified exclusion of patients treated with non-occlusive arterial chemotherapies such as intra-arterial chemotherapy or lipiodolisation, and introduced the continuation of tumour evaluation for patients stopping treatment due to other reason than disease progression until progression was observed.

Amendment 3 (dated 11 November 2014) increased the number of patients to be enrolled from 530 to 560 in order to allow inclusion of 150 patients in China while at the same time adhering to the 40% cap for Asian patients (taking into account that 40 patients were required to be recruited in Japan and 32 patients had already been recruited in other Asian Countries) and allowed inclusion of patients pre-treated with intrahepatic intra-arterial chemotherapy with lipiodol.

Amendment 4 (dated 02 November 2015) essentially removed the second interim analysis, as, due to the unexpectedly slow recruitment of patients in China, the second interim analysis would have been conducted before full subject accrual into the study had been reached.

Amendment 5 (dated 1 December 2015) essentially added information regarding interaction of regorafenib with neomycin, breast cancer resistance protein (BCRP) UGT1A1, UGT1A9, P-glycoprotein substrates and bile salt-sequestering agents.

Baseline data

Table 12. Baseline Demographic Characteristics - RESORCE study.

	15982 RESORCE (FAS)	
	Placebo N=194	**Regorafenib N=379**
Sex, n (%)		
Male	171 (88.1%)	333 (87.9%)
Female	23 (11.9%)	46 (12.1%)
Race, n(%)		
White	68 (35.1%)	138 (36.4%)
Black	2 (1.0%)	6 (1.6%)
Asian	78 (40.2%)	156 (41.2%)
White, Black	1 (0.5%)	2 (0.5%)
Not reported [a]	45 (23.2%)	77 (20.3%)
Calculated age (year)		
n	194	379
Mean ± StD	61.1 (±11.6)	61.8 (±12.4)
Median (range)	62.0 (23-83)	64.0 (19-85)
Age group		
< 65 years	116 (59.8%)	199 (52.5%)
≥ 65 years	78 (40.2%)	180 (47.5%)
Geographic region		
Asia	73 (37.6%)	143 (37.7%)
ROW	121 (62.4%)	236 (62.3%)
ECOG performance status, n (%)		
0	130 (67%)	247 (65%)
1	64 (33%)	132 (35%)
Body mass index (kg/m^2)		
n	192	371
Mean (±StD)	24.4 (±4.2)	24.8 (±4.3)
Median (range)	23.9 (14.5-38.7)	24.6 (14.8-44.8)

Abbreviations: ECOG = Eastern Cooperative Oncology Group; FAS = full analysis set; ITT = intent-to-treat; N = number of subjects; ROW = rest of the world; StD = standard deviation.
a; Some participating countries do not require/allow reporting of race for demographic purposes.

Numbers analysed

The number of patients included in the efficacy analysis populations is reported in the table below.

Table 13. Efficacy analysis populations – RESORCE Study.

	Placebo N=194 (100%)	Regorafenib N=379 (100%)
Subjects valid for FAS	194 (100%)	379 (100%)
Subjects valid for SAF	193 (99.5%)	374 (98.7%)
Excluded from safety analysis	1 (0.5%)	5 (1.3%)
Not treated with study drug	1 (0.5%)	5 (1.3%)

Abbreviations: FAS = full analysis set; N = number of subjects; PK = pharmacokinetics; SAF = safety analysis set.

Table 14. Patient disposition RESORCE study.

	15982 RESORCE (FAS)	
Disposition all enrolled subjects	**Placebo N=194**	**Regorafenib N=379**
Number (%) of subjects		
Enrolled	843	
Screening failures	270	
Assigned to treatment (randomized)	194 (100%)	379 (100%)
Study drug never administered	1 (0.5%)	5 (1.3%)
Started treatment	193 (99.5%)	374 (98.7%)
Ongoing with study treatment	10 (5.2%)	65 (17.2%)
Discontinued study treatment	183 (94.3%)	309 (81.5%)
Ended safety follow-up [a]	177 (91.2%)	294 (77.6%)
Ended survival follow-up	102 (52.6%)	186 (49.1%)
Disposition FAS		
Number (%) of subjects		
Never treated	1 (0.5%)	5 (1.3%)
Started treatment	193 (99.5%)	374 (98.7%)
Terminated treatment	183 (94.3%)	309 (81.5%)
Primary reason		
AE	0	1 (0.3%)
AE associated with clinical disease progression	28 (14.4%)	56 (14.8%)
AE not associated with clinical disease progression	12 (6.2%)	47 (12.4%)
Death	0	5 (1.3%)
Non-compliance with study drug	0	2 (0.5%)
Other [b]	1 (0.5%)	0
Physician decision	0	1 (0.3%)
Progressive disease	1 (0.5%)	0
Progressive disease – clinical progression	14 (7.2%)	21 (5.5%)
Progressive disease – radiological progression	119 (61.3%)	149 (39.3%)
Withdrawal by subject	5 (2.6%)	26 (6.9%)
Protocol violation	3 (1.5%)	1 (0.3%)
Ongoing with treatment (as of LPLV)	10 (5.2%)	65 (17.2%)

Abbreviations: AE = adverse event; FAS = full analysis set; ITT = intent-to-treat; N = number of subjects. LPLV = last subject, last visit (29 FEB 2016); PD = progressive disease; screening failure = subject signed informed consent but did not meet inclusion criteria/met exclusion criteria. Screening failure = Subjects who were not randomized to study.
a; Subjects who took at least one treatment of study medication and completed or prematurely discontinued safety follow-up.
a; Reason for "other" was given as "ECOG performance status moved two points from baseline" on case report form.

Table 15. Baseline disease Characteristics - RESORCE study.

	15982 RESORCE (FAS)	
	Placebo N=194	Regorafenib N=379
Number of Target Lesions (RECIST [a])		
1	31 (16.0%)	67 (17.7%)
2	88 (45.4%)	175 (46.2%)
3	37 (19.1%)	68 (17.9%)
3-5	--	--
4	26 (13.4%)	43 (11.4%)
5	12 (6.2%)	19 (5.0%)
6-10	--	--
Time since Initial diagnosis to Start of Study Treatment (weeks)		
n	173	335
Mean (±StD)	115.9 (±94.9)	127.3 (±121.3)
Median (range)	87.9 (10.9-531.1)	92.7 (8.7-1129)
Time since the First Progression [b] to Start of Study Treatment (weeks)		
n	180	338
Mean (±StD)	52.8 (±55.2)	64.4 (±75.0)
Median (range)	34.2 (1.4-326.4)	38.9 (1.0-486.9)
Type of the First Progression [b] Assessment		
Measurement proven	180 (92.8%)	334 (88.1%)
Clinical judgment	5 (2.6%)	13 (3.4%)
Pathology proven	6 (3.1%)	16 (4.2%)
Measurement and pathology proven	3 (1.6%)	13 (3.4%)
TNM stage at initial diagnosis		
Stage I	38 (19.6%)	83 (21.9%)
Stage II	44 (22.7%)	89 (23.5%)
Stage IIIA	32 (16.5%)	65 (17.2%)
Stage IIIB	22 (11.3%)	39 (10.3%)
Stage IIIC	2 (1.0%)	12 (3.2%)
Stage IV	--	--
Stage IVA	12 (6.2%)	22 (5.8%)
Stage IVB	30 (15.5%)	47 (12.4%)
Unknown	--	--
TNM stage at study entry		
Stage I	0	2 (0.5%)
Stage II	12 (6.2%)	27 (7.1%)
Stage IIIA	16 (8.3%)	36 (9.5%)
Stage IIIB	18 (9.3%)	41 (10.8%)
Stage IIIC	0	5 (1.32%)
Stage IVA	17 (8.76%)	22 (5.80%)
Stage IV	--	--
Stage IVB	130 (67.0%)	245 (64.6%)
Unknown	--	--

Table 16: Baseline disease Characteristics - RESORCE study (Ctd)

			15982 RESORCE (FAS)	
			Placebo N=194	Regorafenib N=379
HCC diagnosis per AASLD[e] [n(%)]	Biopsy		124 (63.9%)	264 (69.7%)
	Non-invasive	Lesion >2 cm and 1 dynamic imaging technique	60 (30.9%)	98 (25.9%)
		Lesion 1-2 cm and two coincidental dynamic techniques	10 (5.2%)	16 (4.2%)
		Missing	0	1 (0.3%)
Hepatitis B Surface Antigen at Study Entry				
Negative			121 (62.4%)	244 (64.4%)
Positive			69 (35.6%)	125 (33.0%)
Hepatitis C Antibody at Study Entry				
Negative			149 (76.8%)	290 (76.5%)
Positive			41 (21.1%)	72 (19.0%)
Etiology of HCC [d]				
Alcohol use			55 (28.4%)	90 (23.8%)
Hepatitis B			73 (37.6%)	143 (37.7%)
Hepatitis C			41 (21.1%)	78 (20.6%)
Genetic / Metabolic			6 (3.1%)	16 (4.2%)
Non-alcoholic steatohepatitis (NASH)			13 (6.7%)	25 (6.6%)
Unknown			32 (16.5%)	66 (17.4%)
Other			4 (2.1%)	12 (3.2%)
BCLC stage at study entry				
A (Early Stage)			0	1 (0.3%)
B (Intermediate Stage)			22 (11.3%)	53 (14.0%)
C (Advanced Stage)			172 (88.7%)	325 (85.8%)
Alpha-fetoprotein (AFP) (ng/mL) (CRF)				
Missing			--	--
< 400 ng/mL			107 (55.2%)	217 (57.3%)
≥ 400 ng/mL			87 (44.9%)	162 (42.7%)
Macrovascular invasion (CRF)				
Absence			140 (72.2%)	269 (71.0%)
Presence			54 (27.8%)	110 (29.0%)
Extrahepatic disease (CRF)				
Absence			47 (24.2%)	114 (30.1%)
Presence			147 (75.8%)	265 (69.9%)
Macrovascular invasion and extrahepatic spread status (CRF)				
Macrovascular invasion present, but not extrahepatic spread			15 (7.7%)	39 (10.3%)
Extrahepatic spread present, but not macrovascular invasion			108 (55.7%)	194 (51.2%)
Both conditions present			39 (20.1%)	71 (18.7%)
Both conditions not present			32 (16.5%)	75 (19.8%)
Child-Pugh Score				
Missing			0	1 (0.3%)
5			118 (60.8%)	244 (64.4%)
6			70 (36.1%)	129 (34.0%)
7 •			5 (2.6%)	5 (1.3%)
8			1 (0.5%)	0
Child-Pugh Score				
Missing			0	1 (0.3%)
A			188 (96.9%)	373 (98.4%)
B •			6 (3.1%)	5 (1.3%)
Liver Cirrhosis (Medical History)				
No			50 (25.8%)	94 (24.8%)
Yes			144 (74.2%)	285 (75.2%)

Abbreviations: AASLD = American Association for Study of Liver Disease; AFP = alpha-fetoprotein; BCLC = Barcelona Clinic Liver Cancer ; CRF = case report form; ECOG = Eastern Cooperative Oncology Group; FAS = full analysis set; HCC = hepatocellular carcinoma; mRECIST = modified RECIST for HCC; NASH = non-alcoholic steatohepatitis; R0 = Complete tumor resection with all margins histologically negative; R1 = Incomplete tumor resection with microscopic surgical resection margin involvement (margins grossly uninvolved); R2 = Incomplete tumor resection with gross residual tumor that was not resected (primary tumor, regional nodes, macroscopic margin involvement); RECIST = Response Evaluation Criteria in Solid Tumors; StD = standard deviation; TNM = tumor, node, metastasis

a; mRECIST evaluation criteria for Study 15982.

b; "First progression" did not necessarily mean first progression while on sorafenib.

c; Non-invasive diagnosis of HCC was documented only when diagnosis was not proven by biopsy.

d; Subjects may have had more than one etiology of HCC.

e; The information in this table is based on the last observations on or before the first study drug intake. Changes may have occurred between the screening of subjects and their first day of study drug intake. During the study it was found that 3 subjects were on anticoagulant medication which, according to the study protocol, led to Child-Pugh classification of B.Baseline data were taken from the non-missing observation before or on the first day of study drug intake. Baseline values for ECOG, AFP, macroscopic vascular invasion and extrahepatic spread status collected on CRF were based on randomization date.

Table 17. Duration of treatment and time to progression with sorafenib.

		Placebo N=194 (100%)	Regorafenib N=379 (100%)
Time (days) from start of sorafenib to start of study medication	n	193	374
	N missing	1	5
	mean (±StD)	380.6 (324.4)	385.3 (344.6)
	median (range)	279 (56-2217)	261 (53-2204)
Time (days) from progression [a] while on sorafenib to start of study medication [b]	n	193	374
	N missing	1	5
	mean (±StD)	54.6 (53.1)	55.0 (42.7)
	median (range)	43.0 (8-522)	42.5 (4-299)
Time (days) from permanent discontinuation of sorafenib to start of study medication	n	193	374
	N missing	1	5
	mean (±StD)	31.1 (14.6)	31.5 (14.8)
	median (range)	26.0 (15-71)	26.5 (14-78)
Time (days) from start of sorafenib to progression while on sorafenib	n	193	374
	N missing	1	5
	median (95% CI)	217 (176, 266)	217 (184,245)
	(range)	(19-2185)	(1-2183)

Table 18. Systemic anti-cancer therapy during follow up (full analysis set).

ATC CLASSIFICATION SUBCLASS WHO-DD Version 3q2005	Placebo N=194 (100%)	Regorafenib 160 mg N=379 (100%)	Total N=573 (100%)
Number of subjects (%) with at least one medication	59 (30.4%)	88 (23.2%)	147 (25.7%)
ANTINEOPLASTIC AND IMMUNOMODULATING AGENTS	54 (27.8%)	76 (20.1%)	130 (22.7%)
ANTINEOPLASTIC AGENTS	54 (27.8%)	73 (19.3%)	127 (22.2%)
ENDOCRINE THERAPY	1 (0.5%)	2 (0.5%)	3 (0.5%)
IMMUNOSTIMULANTS	1 (0.5%)	2 (0.5%)	3 (0.5%)
IMMUNOSUPPRESSIVE AGENTS	2 (1.0%)	5 (1.3%)	7 (1.2%)

Outcomes and estimation

Primary endpoint – Overall Survival (OS)

Table 19: Overall survival – (Study 15982)

		15982 RESORCE (FAS)	
		Placebo N=194	Regorafenib N=379
Number (%) of patients	With event	140 (72.2%)	233 (61.5%)
	Censored	54 (27.8%)	146 (38.5%)
Overall survival (months)	Median (95% CI)	7.8 (6.3, 8.8)	10.6 (9.1, 12.1)
Range	(including censored values)	(0.4-31.1)	(0.3-32.1)**
	(without censored values)	(0.4-31.1)	(0.3-25.2)
Overall survival rate (95% CI) at:			
Month 3		0.82 (0.77, 0.88)	0.88 (0.84, 0.91)
Month 4		*not calculated*	
Month 5		*not calculated*	
Month 6		0.58 (0.51, 0.65)	0.68 (0.63, 0.73)
Month 9		0.42 (0.34, 0.49)	0.56 (0.50, 0.61)
Month 12		0.29 (0.22, 0.37)	0.45 (0.40, 0.51)
Month 18		0.15 (0.09, 0.22)	0.30 (0.25, 0.36)
Month 24		0.11 (0.05, 0.17)	0.21 (0.15, 0.26)
Month 30		0.09 (0.03, 0.15)	0.16 (0.10, 0.22)
IVRS-stratified	Hazard ratio [a] (95% CI)	0.627 (0.500, 0.785)	
	p-value [b]	0.000020	
RAVE-stratified	Hazard ratio [a] (95% CI)	0.661 (0.527, 0.829)	
	p-value [b]	0.000155	
Unstratified	p-value [b]	0.000107	

Abbreviations: CI = confidence interval; FAS = full analysis set; ITT = intent-to-treat; IVRS = interactive voice response system; N = number of subjects; RAVE = validated electronic system for data collection.
*** censored observation;*
a; The hazard ratio (regorafenib/placebo) and its 95% CI was based on Cox Regression Model. A hazard ratio < 1 indicates superiority of regorafenib over placebo.
b;. One-sided p-value from log rank test. Median, percentile and other 95% CIs computed using Kaplan-Meier estimates. Hazard ratio and its 95% CI was based on either a stratified (IVRS), stratified (RAVE), or non-stratified Cox Regression Model. Note: Durations manually converted from days (shown in source tables) to months (1 month = 30.44 days).

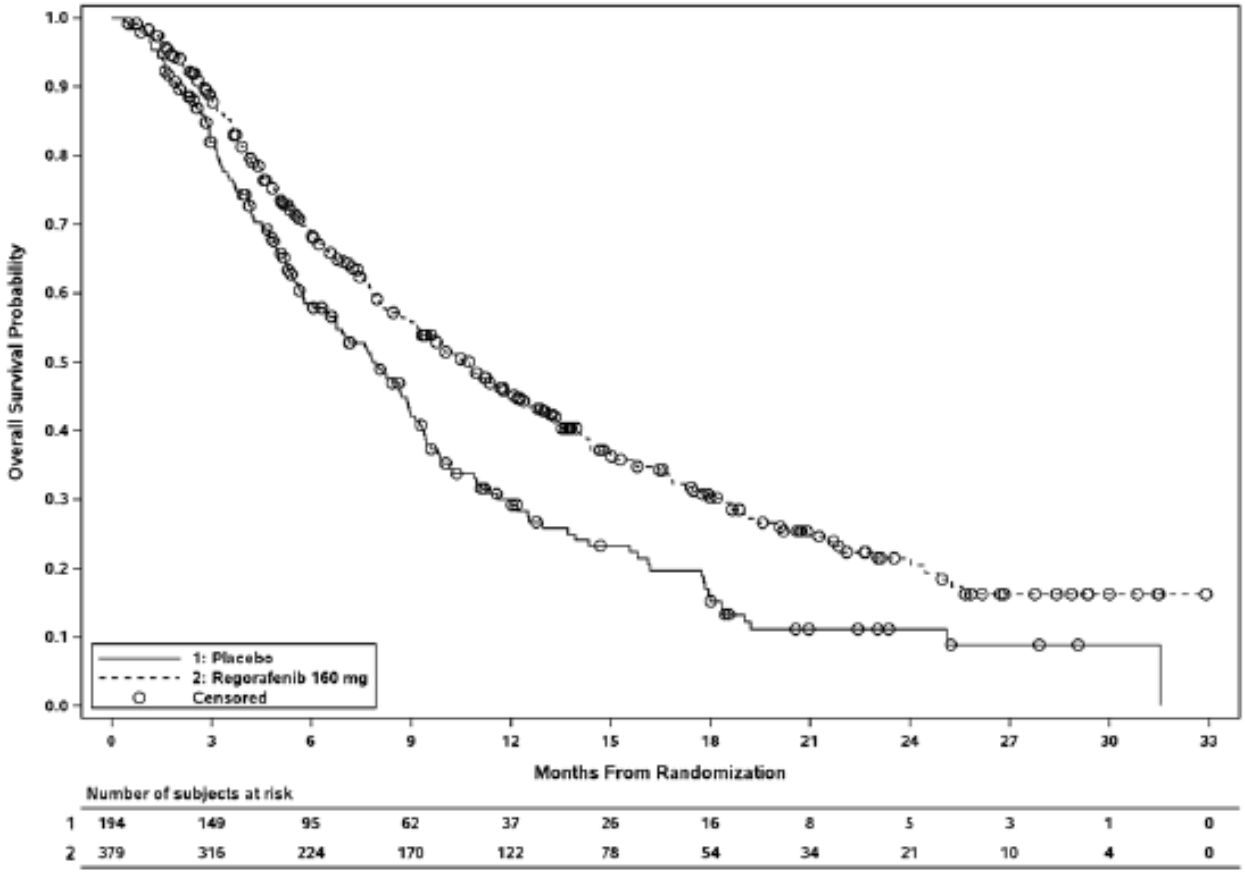


Figure 7 Kaplan-Meier curves of overall survival (Study 15982, FAS).

Forest Plots were provided according to several demographic and baseline characteristics.

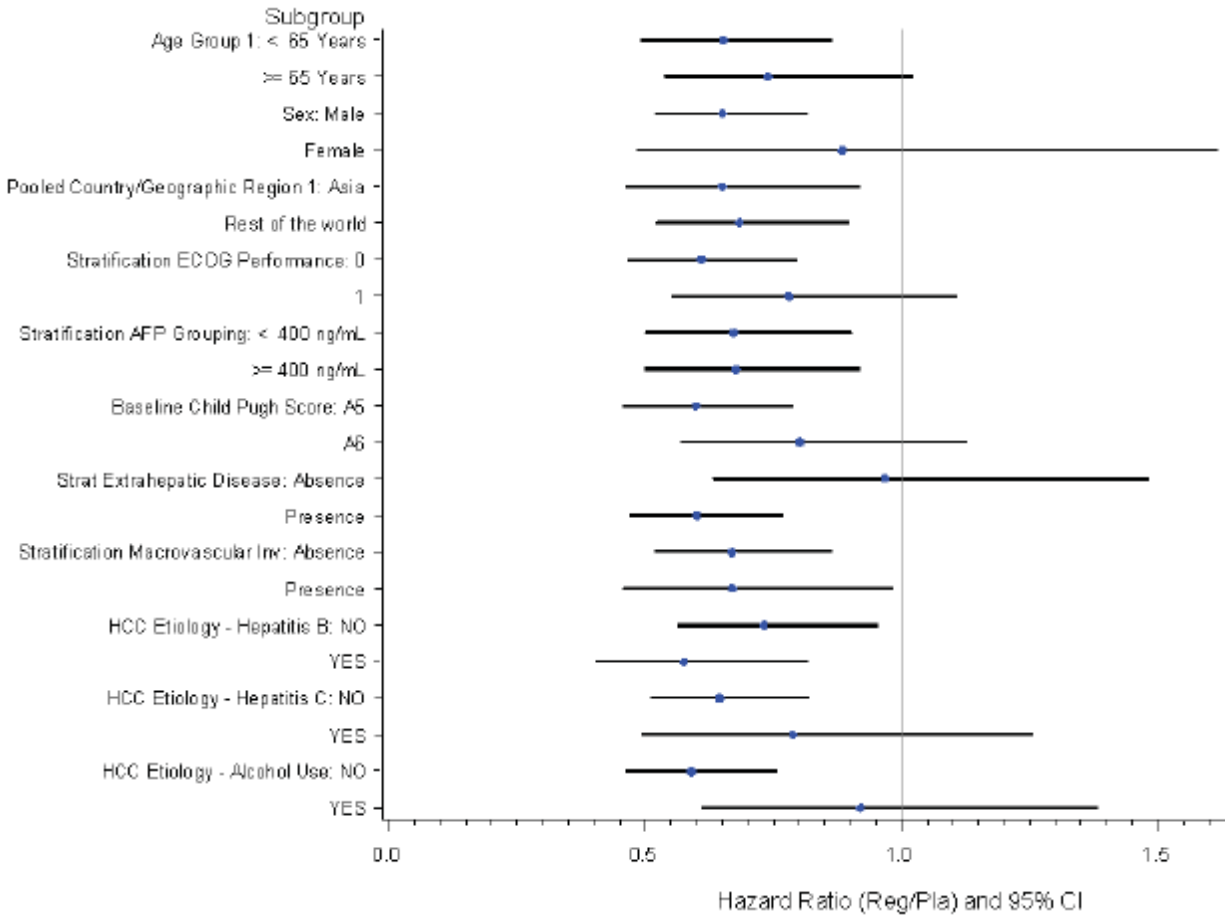


Figure 8: Forest Plots of OS (FAS)

Table 20: Subgroup analyses of OS (FAS)

					Hazard Ratio (Reg/Pla)		Median (Days)	
Variable	Subgroup	N	# Events	# Censored	Estimate	95% CI	Placebo	Regorafenib
Age Group	<65 years	315	205	110	0.653	(0.493, 0.865)	211 (156, 267)	298 (232, 341)
	≥ 65 years	258	168	90	0.740	(0.536, 1.021)	260 (202, 307)	354 (278, 405)
Sex	Male	504	327	177	0.651	(0.520, 0.815)	241 (173, 280)	324 (269, 383)
	Female	69	46	23	0.884	(0.484, 1.616)	233 (148, 297)	292 (114, 499)
Geographical Region	Asia	216	142	74	0.651	(0.462, 0.916)	158 (112, 268)	278 (214, 354)
	ROW	357	231	126	0.684	(0.523, 0.895)	253 (211, 288)	332 (278, 425)
ECOG PS (RAVE)	0	377	231	146	0.610	(0.468, 0.795)	260 (202, 288)	388 (323, 451)
	1	196	142	54	0.781	(0.551, 1.107)	192 (126, 260)	194 (161, 278)
AFP Grouping (RAVE)	<400 ng/mL	324	194	130	0.673	(0.502, 0.902)	282 (233, 366)	405 (343, 493)
	≥400 ng/mL	249	179	70	0.677	(0.499, 0.919)	174 (142, 244)	223 (178, 261)
Baseline Child Pugh Score	A5	362	222	140	0.599	(0.455, 0.788)	244 (174, 283)	360 (303, 432)
	A6	199	141	58	0.802	(0.570, 1.127)	228 (146, 268)	264 (184, 339)
Extrahepatic Disease (RAVE)	Absence	161	103	58	0.968	(0.632, 1.482)	296 (234, 430)	326 (261, 421)
	Presence	412	270	142	0.601	(0.470, 0.769)	196 (157, 260)	313 (248, 369)
Macrovascular Invasion (RAVE)	Absence	409	259	150	0.670	(0.520, 0.862)	260 (208, 284)	344 (293, 403)
	Presence	164	114	50	0.670	(0.457, 0.983)	157 (106, 253)	232 (180, 332)
HCC Etiology - Hep B	N	357	238	119	0.732	(0.562, 0.953)	260 (202, 296)	332 (278, 401)
	Y	216	135	81	0.576	(0.406, 0.817)	161 (127, 268)	269 (223, 366)
HCC Etiology - Hep C	N	454	295	159	0.646	(0.510, 0.819)	230 (167, 268)	313 (272, 372)
	Y	119	78	41	0.788	(0.494, 1.257)	267 (174, 294)	331 (225, 472)
HCC Etiology - Alcohol Use	N	428	273	155	0.591	(0.461, 0.757)	202 (161, 253)	313 (260, 366)
	Y	145	100	45	0.920	(0.613, 1.381)	296 (230, 484)	339 (240, 405)

Abberevations: AFP = alpha fetoprotein; CI = confidence interval; ECOG PF = Eastern Cooperative Oncology Group performance status; FAS = full analysis set; HCC hepatocellular carcinoma; Hep = hepatitis virus; IVRS = interactive voice response system; Pla =placebo; RAVE = validated electronic system for data collection; Reg = regorafenib (160

mg); ROW – rest of the world. A hazard ration <1 indicates superiority of regorafenib 160 mg (experimental) over placebo (control). Hazard ration and Cis are based on an unstratified Cox Regression Model.

Table 21: Time to death with sorafenib and study medication - descriptive statistics (Study 15982, FAS)

		Placebo N=194 (100%)	Regorafenib N=379 (100%
Time (days) from start of sorafenib to start of study medication	n	193	374
	N missing	1	5
	mean (±StD)	380.6 (324.4)	385.3 (344.6)
	median (range)	279 (56-2217)	261 (53-2204)
Time (days) from progression [a] while on sorafenib to start of study medication [b]	n	193	374
	N missing	1	5
	mean (±StD)	54.6 (53.1)	55.0 (42.7)
	median (range)	43.0 (8-522)	42.5 (4-299)
Time (days) from permanent discontinuation of sorafenib to start of study medication	n	193	374
	N missing	1	5
	mean (±StD)	31.1 (14.6)	31.5 (14.8)
	median (range)	26.0 (15-71)	26.5 (14-78)
Time (days) from start of sorafenib to progression while on sorafenib	n	193	374
	N missing	1	5
	median (95% CI)	217 (176, 266)	217 (184,245)
	(range)	(19-2185)	(1-2183)
Time (days) from start of sorafenib to progression on study medication	n	193	374
	N missing	1	5
	median (95% CI)	355 (317, 395)	455 (421, 505)
	(range)	(98-2216*)	(80*-2387*)
Time (days) from start of sorafenib to death	n	193	374
	N missing	1	5
	median (95% CI)	584 (497, 693)	791 (689, 856)
	(range)	(120-2230)	(91-2475)

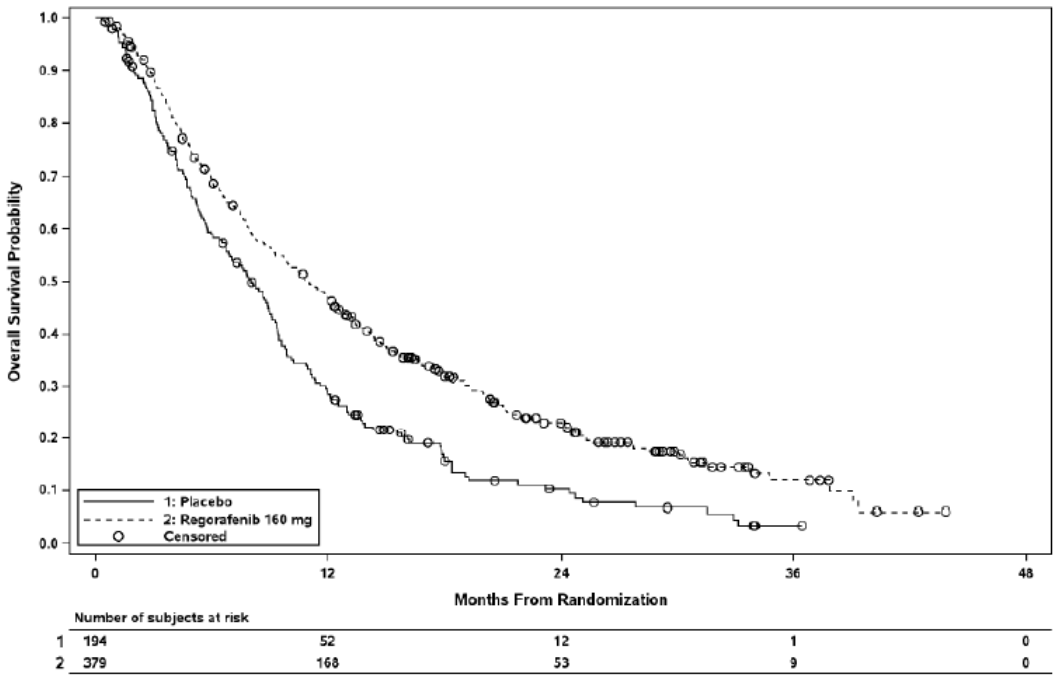
Abbreviations: CI = confidence interval; FAS = full analysis set; N = number of subjects; StD = standard deviation.
a Progression was to be radiologically confirmed per protocol.
b Time to progression while on sorafenib to start of regorafenib = (start date of regorafenib - date of progression on sorafenib) +1.
** censored values*

An updated analysis of OS has been performed with a database cut-off date of 23 January 2017 and submitted during the procedure.

Table 22: Overall survival – descriptive statistics (Study 15982, FAS, data cut-off 23 Jan 2017)

		Placebo (N=194)	Regorafenib 160 mg (N=379)	Total (N=573)
N		194	379	573
Number (%) of subjects with event		169 (87.1%)	290 (76.5%)	459 (80.1%)
Number (%) of subjects censored		25 (12.9%)	89 (23.5%)	114 (19.9%)
25th percentile [95% CI]	Days	117 (93, 142)	148 (126, 171)	135 (121, 150)
Median [95% CI]	Days	241 (196, 274)	326 (278, 372)	283 (260, 316)
75th percentile [95% CI]	Days	392 (340, 532)	636 (581, 758)	570 (523, 629)
Range (including censored values)	Days	(12-1093**)	(9-1316**)	(9-1316**)
Range (without censored values)	Days	(12-994)	(9-1180)	(9-1180)
Overall Survival rate at	Month 3 [95% CI]	0.822 (0.768,0.877)	0.879 (0.846,0.912)	0.860 (0.831,0.889)
	Month 6 [95% CI]	0.584 (0.514,0.654)	0.687 (0.639,0.734)	0.652 (0.612,0.691)
	Month 9 [95% CI]	0.432 (0.361,0.503)	0.563 (0.512,0.614)	0.519 (0.477,0.560)
	Month 12 [95% CI]	0.279 (0.214,0.344)	0.466 (0.415,0.517)	0.403 (0.362,0.444)
	Month 15 [95% CI]	0.216 (0.157,0.276)	0.367 (0.317,0.417)	0.316 (0.277,0.356)
	Month 18 [95% CI]	0.155 (0.100,0.210)	0.319 (0.270,0.368)	0.264 (0.226,0.302)
	Month 24 [95% CI]	0.102 (0.054,0.150)	0.219 (0.173,0.265)	0.180 (0.145,0.215)
	Month 30 [95% CI]	0.067 (0.025,0.109)	0.160 (0.114,0.206)	0.129 (0.096,0.163)

** censored observation
A: Value cannot be estimated due to censored data.
Median, percentile and other 95% CIs computed using Kaplan-Meier estimates.
Subjects who switched from Placebo to Regorafenib after study was unblinded were analyzed under Placebo arm in this analysis



Subjects who switched from Placebo to Regorafenib after study was unblinded were analyzed under Placebo arm in this analysis

Figure 9: Kaplan-Meier curves of OS (Study 15982, FAS, data cut-off 23 Jan 2017)

Secondary endpoints:

Progression Free Survival (PFS)

The PFS analysis was performed according to mRECIST (474 events [82.7%]) and RECIST 1.1. (472 events [82.3%]).

Table 23. Progression-free survival descriptive statistics (Study 15982, FAS).

			Placebo N=194 (100%)	Regorafenib N=379 (100%)
mRECIST	Number (%) of subjects	With event	181 (93.3%)	293 (77.3%)
		Censored	13 (6.7%)	86 (22.7%)
	PFS (Months)	Median (95% CI)	1.5 (1.4, 1.6)	3.1 (2.8, 4.2)
		Range (without censored values)	(0.2-15.2)	(0.3-26.0)
	Stratified (IVRS)	Hazard ratio (95% CI) [a]	0.455 (0.371, 0.558)	
		p-value [b]	<0.000001	
	Unstratified	Hazard ratio (95% CI) [a]	0.481 (0.398, 0.581)	
		p-value [b]	<0.000001	
RECIST1.1	Number (%) of subjects	With event	184 (94.8%)	288 (76.0%)
		Censored	10 (5.2%)	91 (24.0%)
	PFS (Months)	Median (95% CI)	1.5 (1.4, 1.5)	3.4 (2.9, 4.2)
		Range (without censored values)	(0.2-15.2)	(0.3-26.0)
	Stratified (IVRS)	Hazard ratio (95% CI) [a]	0.427 (0.348, 0.524)	
		p-value [b]	<0.000001	
	Unstratified	Hazard ratio (95% CI) [a]	0.453 (0.375, 0.548)	
		p-value [b]	<0.000001	

Abbreviations: : CI = confidence interval; FAS = full analysis set; IVRS = interactive voice response system; mRECIST =modified RECIST; PFS = progression-free survival; RECIST = Response Evaluation Criteria in Solid Tumors.
a; A Hazard ratio (Regorafenib/Placebo) < 1 indicates superiority of Regorafenib (experimental) over placebo (control). Hazard ratio and its 95% CI was based on stratified (IVRS) Cox Regression Model
b; One-sided p-value from log rank test Median, percentile and other 95% CIs computed using Kaplan-Meier estimates. Durations manually converted from days (shown in source tables) to months (1 month = 30.44 days).

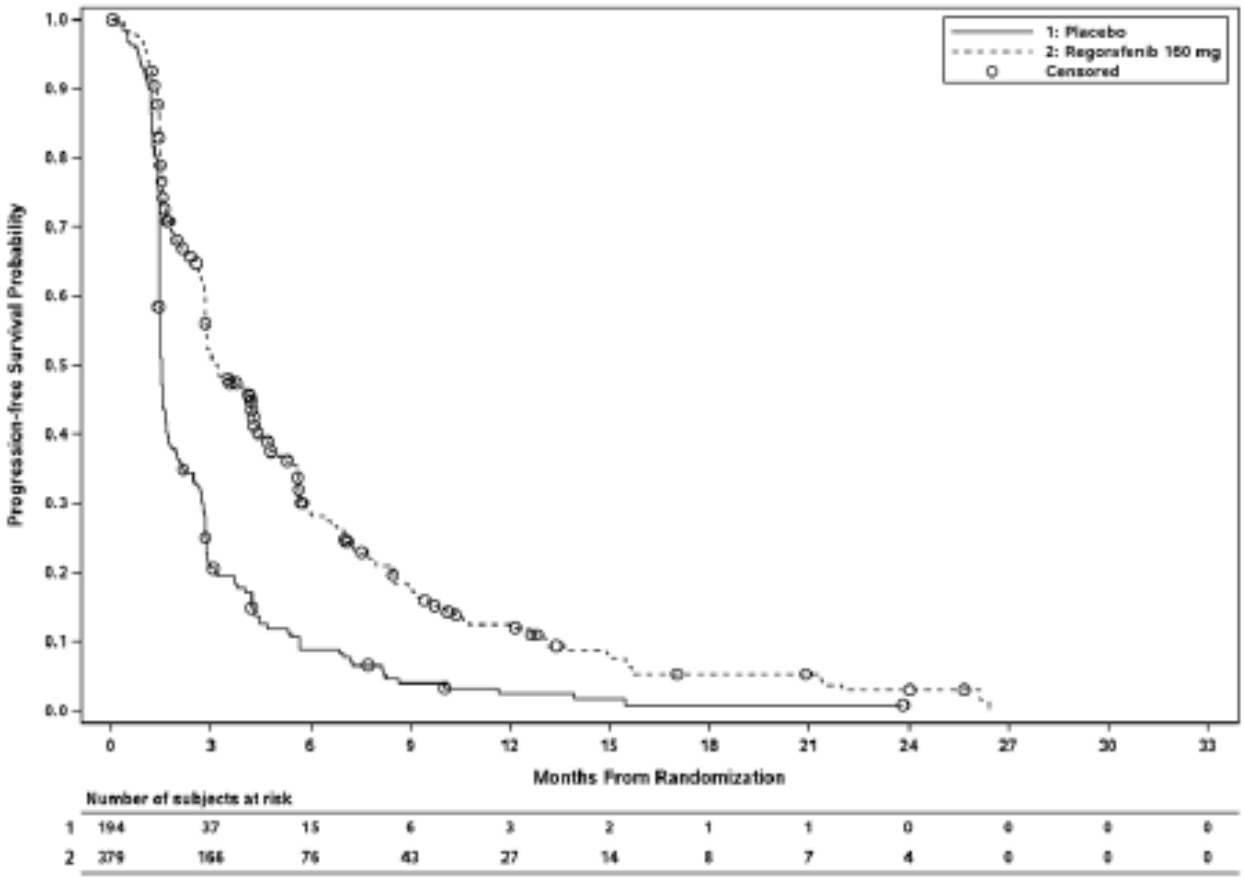


Figure 10: m RECIST; Kaplan-Meier curve for progression-free survival (Study 15982, FAS).

As documented by Forest Plot, treatment effect for regorafenib was observed across different subgroups.

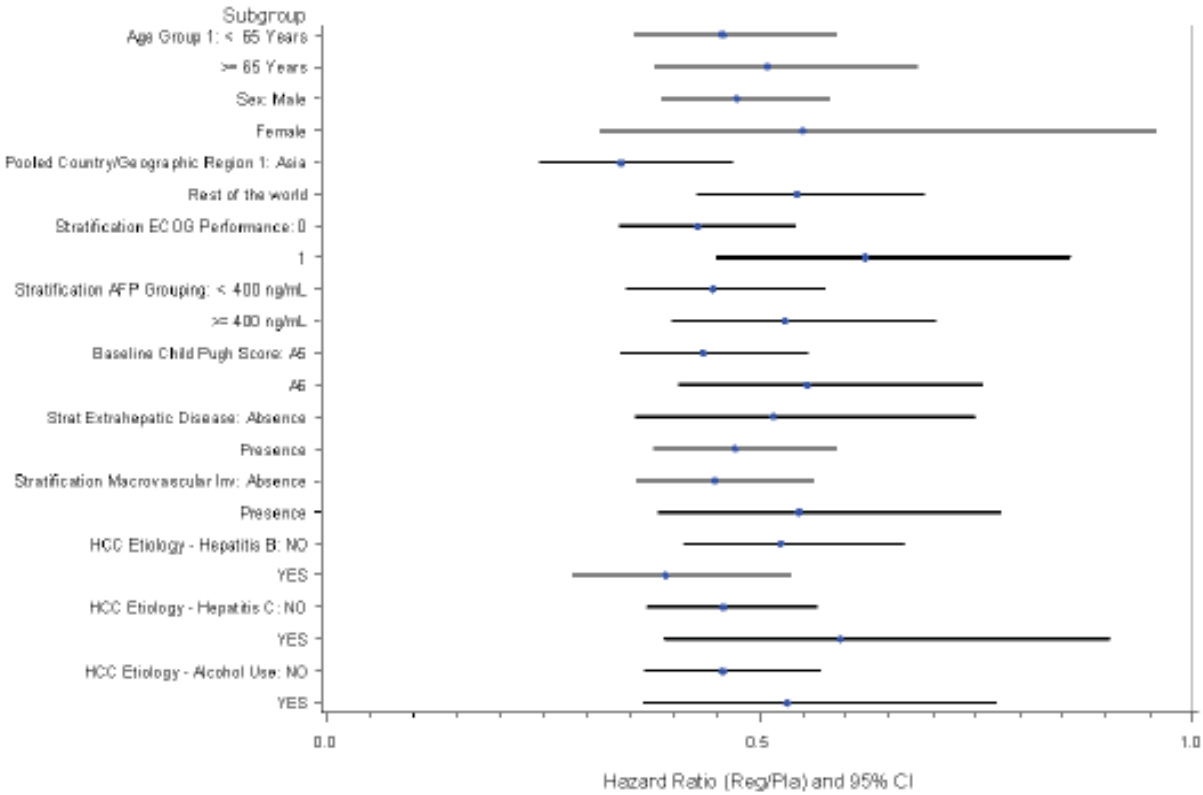


Figure 11. Forest plot for PFS by subgroup in 15982 (RESORCE) Study.

Time To Progression (TTP)

The TTP analysis was performed according to mRECIST (447 events [78%]) and RECIST 1.1. (445 events [77.6%]).

Table 24: Time to progression including sensitivity analyses descriptive statistics (Study 15982, FAS)

			Placebo N=194	Regorafenib N=379
mRECIST	Number (%) of subjects	With event	173 (89.2%)	274 (72.3%)
		Censored	21 (10.8%)	105 (27.7%)
	TTP (months)	Median (95% CI)	1.5 (1.4, 1.6)	3.2 (2.9, 4.2)
		Range (without censored values)	(0.2-15.2)	(0.4-26.0)
	Stratified (IVRS)	Hazard ratio (95% CI) [a]	0.442 (0.358, 0.545)	
		p-value [b]	<0.000001	
	Unstratified	Hazard ratio (95% CI) [a]	0.472 (0.389, 0.573)	
		p-value [b]	<0.000001	
RECIST 1.1	Number (%) of subjects	With event	175 (90.2%)	270 (71.2%)
		Censored	19 (9.8%)	109 (28.8%)
	TTP (months)	Median (95% CI)	1.5 (1.4, 1.6)	3.9 (2.9, 4.2)
		Range (without censored values)	(0.2-15.2)	(0.4-26.0)
	Stratified (IVRS)	Hazard ratio (95% CI) [a]	0.414 (0.335, 0.511)	
		p-value [b]	<0.000001	
	Unstratified	Hazard ratio (95% CI) [a]	0.443 (0.365,0.539)	
		p-value [b]	<0.000001	

Abbreviations: CI = confidence interval; FAS = full analysis set; IVRS = interactive voice response system; mRECIST = modified RECIST; RECIST = Response Evaluation Criteria in Solid Tumors; TTP = time to progression.

a Hazard ratio (Regorafenib/Placebo) < 1 indicates superiority of Regorafenib (experimental) over placebo (control). Hazard ratio and its 95% CI was based on stratified (IVRS) Cox Regression Model

b One-sided p-value from log rank test

Median, percentile and other 95% CIs computed using Kaplan-Meier estimates. . Durations manually converted from days (shown in source tables) to months (1 month = 30.44 days).

As documented by Forest Plot, treatment effect for regorafenib was observed across different subgroups.

Objective Response Rate (ORR) and Disease Control Rate (DCR)

Table 25: Response with respect to RECIST and inferential statistics (Study 15982, FAS)

Best overall response (mRECIST)	Placebo N=194 (100%) [95% CI]	Regorafenib N=379(100%) [95% CI]
Complete response (CR)	0	2 (0.5%) [0.1%; 1.9%]
Partial response (PR)	8 (4.1%) [1.8%; 8.0%]	38 (10.0%) [7.2%; 13.5%]
Stable disease (SD)	62 (32.0%) [25.5%; 39.0%]	206 (54.4%) [49.2%; 59.4%]
Non CR/Non PD	0	1 (0.3%) [0.0%; 1.5%]
Progressive disease (PD)	108 (55.7%) [48.4%; 62.8%]	86 (22.7%) [18.6%; 27.2%]
Not evaluable (NE)	8 (4.1%) [1.8%; 8.0%]	19 (5.0%) [3.0%; 7.7%]
Not assessed (NA)	8 (4.1%) [1.8%; 8.0%]	27 (7.1%) [4.7%; 10.2%]
Clinical progression	40 (20.6%) [15.2%; 27.0%]	86 (22.7%) [18.6%; 27.2%]
Response Rate	8 (4.1%)	40 (10.6%)
Disease Control Rate	70 (36.1%)	247 (65.2%)

Comparison of Treatments - Inferential Statistics: Regorafenib versus Placebo	Difference	[95% CI]	p-value
Objective Response	-6.61	[-10.84, -2.39]	0.004728
DCR	-29.31	[-37.52, -21.11]	<0.000001

Best overall response (RECIST 1.1)		
Complete response (CR)	0	0
Partial response (PR)	5 (2.6%) [0.8%; 5.9%]	25 (6.6%) [4.3%; 9.6%]
Stable disease (SD)	62 (32.0%) [25.5%; 39.0%]	223 (58.8%) [53.7%; 63.8%]
Non CR/Non PD	0	1 (0.3%) [0.0%; 1.5%]
Progressive disease (PD)	111 (57.2%) [49.9%; 64.3%]	85 (22.4%) [18.3%; 27.0%]
Not evaluable (NE)	9 (4.6%) [2.1%; 8.6%]	19 (5.0%) [3.0%; 7.7%]
Not assessed (NA)	7 (3.6%) [1.5%; 7.3%]	26 (6.9%) [4.5%; 9.9%]
Clinical progression	40 (20.6%) [15.2%; 27.0%]	86 (22.7%) [18.6%; 27.2%]
Response Rate	5 (2.6%)	25 (6.6%)
Disease Control Rate	67 (34.5%)	249 (65.7%)

Comparison of Treatments - Inferential Statistics: Regorafenib versus Placebo	Difference	[95% CI]	p-value
Objective response	-4.15	[-7.55, -0.75]	0.019991
DCR	-31.39	[-39.57, -23.22]	<0.000001

Abbreviations: CI = confidence interval, CR = complete response; FAS = full analysis set; HCC = hepatocellular carcinoma; mRECIST = modified RECIST for HCC; N = number of subjects; NA = not assessed; NE = not evaluable; PD = progressive disease; PR = partial response; RECIST = Response Evaluation Criteria in Solid Tumors; SD = stable disease

Duration of response (for patients achieving CR and PR)

Table 26: ***Duration of response - descriptive statistics (Study 15982, FAS)***

	Placebo (N=8)	Regorafenib (N=40)
mRECIST		
N	8	40
Number (%) of subjects with event	5 (62.5%)	30 (75.0%)
Number (%) of subjects censored	3 (37.5%)	10 (25.0%)
Median [95% CI] (Days)	81 (57, A)	106 (57, 138)
Range (including censored values) (Days)	(1[a] -673 [a])	(1[a] -708)
RECIST 1.1		
N	5	25
Number (%) of subjects with event	3 (60.0%)	16 (64.0%)
Number (%) of subjects censored	2 (40.0%)	9 (36.0%)
Median [95% CI] (Days)	169 (71, A)	179 (44, 256)
Range (including censored values) (Days)	(71-673[a])	(1[a] -708)

Abbreviations: A = Value cannot be estimated due to censored data; CI = confidence interval; FAS = full analysis set; mRECIST = modified RECIST for HCC; N = number of subjects; RECIST = Response Evaluation Criteria in Solid Tumors.** censored observation

a censored observation.

A: Value cannot be estimated due to censored data.

Median, percentile and other 95% CIs computed using Kaplan-Meier estimates.

Duration of stable disease

Table 27: Duration of stable disease - descriptive statistics (Study 15982, FAS)

	Placebo (N=62)	Regorafenib (N=206)
mRECIST		
N	62	206
Number (%) of subjects with event	56 (90.3%)	151 (73.3%)
Number (%) of subjects censored	6 (9.7%)	55 (26.7%)
Median [95% CI] (Days)	93 (86, 127)	168 (132, 171)
Range (without censored values) (Days)	(33-464)	(43-785)
RECIST 1.1		
N	62	223
Number (%) of subjects with event	57 (91.9%)	161 (72.2%)
Number (%) of subjects censored	5 (8.1%)	62 (27.8%)
Median [95% CI] (Days)	93 (86, 127)	168 (132, 171)
Range (including censored values) (Days)	(33-464)	(40-785)

Abbreviations: CI = confidence interval; FAS = full analysis set; mRECIST = modified RECIST for HCC; N = number of subjects; RECIST = Response Evaluation Criteria in Solid Tumors.

Median, percentile and other 95% CIs computed using Kaplan-Meier estimates.

Patient-Reported Outcomes: FACT-Hep and EQ-5D

FACT-Hep and EQ-5D questionnaires were administered at baseline and on Day 1 of all cycles and at the end of treatment visit. Higher scores of the FACT-Hep and EQ-5D represent a higher level of functioning and better HRQoL or fewer symptoms. The FACT-Hep score consists of the sum of the FACT-G (including 5 subscales related to well-being) and the hepatobiliary cancer subscale (HCS, assessing specific symptoms of hepatobiliary carcinoma and side effects of its treatment). In the FACT-Hep minimally important difference (MID) for the trial outcome index (TOI) was 7-8 whereas for the FACT-G subscales: 2-3, and for the FACT-G total score: 6-7. Changes of ≥7 points on the visual analogue scale (VAS) or ≥ 0.10 to 0.12 points on the EQ-5D index were considered as clinically meaningful (MID: minimally important difference).

Fact-Hep: During treatment questionnaire was completed by at least 80% of patients in both arms and in about 90% of patients in either treatment group were valid for analysis.

Table 28: FACT-Hep total score and change from baseline through Cycle 16 (Study 15982, FAS)

	Placebo					Regorafenib				
Cycle on Day 1	n	Mean	StD	Change from baseline	StD	n	Mean	StD	Change from baseline	StD
C1	185	134.4	21.7			367	135.5	22.9		
C2	164	134.0	23.6	-0.9	16.2	324	130.7	23.7	-6.0	17.1
C3	93	139.1	20.2	0.9	17.6	253	133.0	23.5	-5.2	16.0
C4	65	139.7	20.2	-0.3	19.3	212	134.0	23.2	-5.1	17.3
C5	49	139.3	20.6	-0.6	20.6	177	133.6	25.3	-6.3	21.2
C6	33	141.6	20.9	-2.0	18.4	153	134.3	23.0	-5.0	18.7
C7	28	138.9	21.4	-3.1	17.9	124	135.6	24.2	-4.8	18.4
C8	19	147.9	17.4	5.6	19.7	110	133.8	24.7	-7.3	21.1
C9	14	142.8	21.5	5.7	17.4	90	134.9	24.7	-5.4	19.7
C10	10	145.2	21.1	5.9	15.1	82	135.7	26.4	-2.4	18.6
C11	6	145.0	22.0	5.5	8.2	75	137.9	24.1	-3.0	19.4
C12	9	148.0	21.0	5.2	11.9	64	134.5	26.7	-5.8	23.9
C13	8	148.9	19.2	3.8	10.0	57	136.8	25.1	-2.8	19.8
C14	7	142.2	23.6	4.8	10.1	46	135.6	26.3	-3.8	21.0
C15	6	136.3	28.0	-3.6	15.2	44	135.4	27.6	-5.2	19.1
C16	5	149.1	12.3	0.6	15.3	37	134.7	29.3	-6.2	19.3
EOT Visit	111	122.9	26.3	-13.0	21.7	178	121.2	24.7	-15.0	22.1

Abbreviations: C = cycle number; D = day; EOT=End of treatment; MID = minimally important difference; N = number of subjects; StD = standard deviation.
Note: MID for FACT-Hep is >8-9.

EQ-5D: During treatment questionnaire was completed by at least 80% of patients in both arms and in about 90% of patients in either treatment group were valid for analysis.

Table 29: Mean EQ-5D and VAS scores through Cycle 16 (Study 15982, FAS)

	Placebo					Regorafenib				
EQ-5D	n	Mean	StD	Change from baseline	StD	n	Mean	StD	Change from baseline	StD
C1, Day 1	184	0.84	0.22	.	.	366	0.82	0.21	.	.
C2, Day 1	166	0.78	0.23	-0.06	0.19	324	0.76	0.24	-0.07	0.21
C3, Day 1	92	0.79	0.26	-0.07	0.20	249	0.80	0.21	-0.05	0.20
C4, Day 1	64	0.84	0.18	-0.02	0.19	210	0.80	0.20	-0.05	0.18
C4, Day 15 [a]	-	-	-	-	-	1	0.76	.	-0.24	.
C5, Day 1	48	0.82	0.21	-0.04	0.21	177	0.79	0.22	-0.06	0.21
C6, Day 1	33	0.82	0.21	-0.05	0.22	153	0.79	0.21	-0.07	0.20
C7, Day 1	27	0.76	0.26	-0.10	0.28	124	0.82	0.18	-0.05	0.17
C8, Day 1	19	0.86	0.13	-0.01	0.22	109	0.82	0.16	-0.05	0.18
C9, Day 1	14	0.86	0.18	-0.04	0.15	91	0.81	0.21	-0.06	0.21
C10, Day 1	10	0.92	0.13	0.07	0.14	82	0.83	0.20	-0.04	0.20
C11, Day 1	8	0.87	0.14	-0.04	0.05	75	0.82	0.21	-0.05	0.20
C12, Day 1	9	0.94	0.12	0.03	0.06	63	0.78	0.23	-0.07	0.23
C13, Day 1	9	0.88	0.15	-0.04	0.06	56	0.83	0.17	-0.03	0.18
C14, Day 1	8	0.90	0.14	-0.01	0.07	45	0.81	0.17	-0.08	0.16
C15 Day 1	6	0.90	0.17	-0.00	0.07	43	0.83	0.17	-0.07	0.13
C16 Day 1	5	0.93	0.10	-0.01	0.10	36	0.84	0.19	-0.07	0.16
EOT	110	0.67	0.32	-0.20	0.30	178	0.65	0.31	-0.17	0.30
EQ-VAS										
C1, Day 1	185	73.51	18.90	.	.	367	74.35	17.81	.	.
C2, Day 1	166	73.63	16.93	-0.85	17.13	326	71.93	17.87	-2.93	14.74
C3, Day 1	90	75.43	18.90	1.00	20.23	253	73.31	17.06	-1.93	15.43
C4, Day 1	63	77.10	16.77	0.67	16.07	213	73.64	16.66	-1.88	15.26
C4, Day 15 [a]	-	-	-	-	-	1	50.00	.	-35.00	.
C5, Day 1	47	76.49	17.50	1.79	17.28	179	74.82	15.84	-1.65	15.15
C6, Day 1	32	76.28	16.95	0.25	15.68	153	74.93	16.06	-1.68	16.09
C7, Day 1	26	76.35	19.65	1.04	16.81	123	75.80	17.60	-1.67	17.35
C8, Day 1	19	81.11	12.41	4.63	12.00	110	76.90	14.74	-2.30	14.84
C9, Day 1	13	82.46	14.30	9.54	15.27	92	74.57	16.73	-3.66	15.83
C10, Day 1	10	81.50	19.87	5.00	10.45	83	77.17	15.80	-0.90	15.39
C11, Day 1	8	84.38	12.04	11.25	12.33	75	76.17	16.30	-2.12	17.89
C12, Day 1	9	80.56	19.17	4.44	5.27	65	73.65	18.53	-3.59	19.15
C13, Day 1	8	80.13	17.04	6.38	4.90	57	74.54	16.97	-2.30	19.77
C14, Day 1	8	83.88	14.77	10.75	11.59	46	74.67	18.58	-1.94	21.10
C15, Day 1	6	79.00	19.95	10.67	12.61	44	76.96	13.94	-0.30	15.06
C16 Day 1	5	82.20	13.97	6.20	15.90	37	78.51	14.75	-2.16	12.12
EOT	112	67.39	20.20	-7.60	18.90	180	65.36	19.86	-9.26	18.88

Abbreviations: C = cycle number; EOT = End of Treatment; EQ-5D = EuroQoL-5 Dimensions questionnaire; StD = standard deviation; VAS = Visual Analogue Scale.
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Ancillary analyses

- Maximum percent target lesion reduction:

Table 30: Maximum percent change in the size of target lesions (Study 15982, FAS)

Maximum Percent Change in Target Sum of Longest Diameter	Placebo (N=194)	Regorafenib (N=379)
mRECIST		
n	194 (100%)	379 (100%)
Reduction >30%	10 (5.2%)	49 (12.9%)
Reduction ≥20% but <30%	3 (1.5%)	34 (9.0%)
Reduction ≥10% but <20%	9 (4.6%)	38 (10.0%)
Reduction ≥0% but <10%	22 (11.3%)	63 (16.6%)
Growth ≥0%	128 (66.0%)	141 (37.2%)
Not Assessed	22 (11.3%)	54 (14.2%)
RECIST		
n	194 (100%)	379 (100%)
Reduction >30%	5 (2.6%)	28 (7.4%)
Reduction ≥20% but <30%	3 (1.5%)	20 (5.3%)
Reduction ≥10% but <20%	7 (3.6%)	48 (12.7%)
Reduction ≥0% but <10%	13 (6.7%)	70 (18.5%)
Growth ≥0%	146 (75.3%)	165 (43.5%)
Not Assessed	20 (10.3%)	48 (12.7%)

Abbreviations: FAS = full analysis set; mRECIST = modified Response Evaluation Criteria in Solid Tumors; N = number of subjects

-Post-progression survival (PPS):

Post-progression survival was measured from the date of radiologically confirmed progression while on pre-study sorafenib treatment to death due to any cause.

Table 31: Post-sorafenib progression survival - descriptive statistics (Study 15982, FAS)

Category		Placebo (N=194)	Regorafenib (N=379)
N		194	379
Number (%) of subjects with event		140 (72.2%)	233 (61.5%)
Number (%) of subjects censored		54 (27.8%)	146 (38.5%)
Median [95% CI]	Months	9.6 (8.1, 10.6)	12.3 (10.6, 13.7)
Range (without censored values)	Months	(1.4-32.5)	(1-29.3)
Hazard ratio: (Reg/Pla) [95% CI] [a]		0.643 (0.514, 0.804)	
One-sided p-value from log rank test	Stratified (IVRS)		0.000049
Hazard ratio: (Reg/Pla) [95% CI] [a]		0.671 (0.544,0.829)	
One-sided p-value from log rank test	Unstratified		0.000095

Abbreviations: CI = confidence interval; FAS = full analysis set; IVRS = interactive voice response system; Pla = placebo; Reg = regorafenib (160 mg).
a A Hazard ratio <1 indicates superiority of Regorafenib 160 mg (experimental) over Placebo (control).
Hazard ratio and its 95% CI were based on either stratified (IVRS) or unstratified Cox Regression Model. Median, percentile and other 95% CIs computed using Kaplan-Meier estimates.

Summary of main study

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

Table 32. Summary of Efficacy for trial 15982 (RESORCE).

Title: A randomized, double blind, placebo-controlled, multicentre phase III study of regorafenib in patients with hepatocellular carcinoma (HCC) after sorafenib			
Study identifier	15982		
Design	Phase III, multicenter, multinational, randomized (2:1), double blind, placebo controlled study with a superiority design		
	First subject first visit: 14 May 2013 Last subject last visit: 29 February 2016		
Hypothesis	Superiority study of regorafenib plus BSC vs placebo plus BSC		
Treatments groups	Regorafenib plus BSC		160 mg OD orally for 3 weeks followed by 1 week off therapy (cycle of 4 weeks). N= 379
	Placebo plus BSC		Matching placebo. N= 194
Endpoints and definitions	Primary endpoint	OS	Overall Survival: defined as the time (days) from randomization to death due to any cause
	Secondary endpoint	PFS	Progression Free Survival: defined as the time [days] from randomization to first observed disease progression [radiological or clinical, as assessed by investigators] or death due to any cause, if death occurred before disease progression was documented
	Secondary endpoint	TTP	Time to Progression: defined as the time [days] from randomization to radiological or clinical disease progression
		ORR	Objective response rate: defined as the percentage of patients with complete response [CR] or partial response [PR] according to RECIST 1.1 and the modified RECIST criteria)
		DCR	Disease control rate: defined as the percentage of patients with CR, PR or stable disease [SD])
		QoL	Quality of life: evaluated according to the FACT-Hep and the EQ-5D questionnaires
Database lock	29 Feb 2016		

Results and Analysis				
Analysis description	**Primary Analysis**			
Analysis population and time point description	Intent to treat (all patients randomized)			
Descriptive statistics and estimate variability	Treatment group	Regorafenib	Placebo	
	Number of subject	N= 379	N=194	

	OS (median,mo) 95%CI	10.6 (9.1-12.1)	7.8 (6.3-8.8)	HR 0.627 (0.50-0.785) p=0.00002
	PFS (median, mo, mRECIST) 95%CI	3.1 (2.8-4.2)	1.5 (1.4-1.6)	HR 0.455 (0.371-0.558) p<0.000001
	TTP (median, mo, mRECIST) 95%CI	3.2 (2.9-4.2)	1.5 (1.4-1.6)	HR 0.442 (0.358-0.545) p<0.000001
	ORR (CR+PR, mRECIST)	10.5% (2+38 pts)	4.1% (0+8 pts)	-
	DCR (CR+PR+SD)	36.1%	64.5%	-

BSC: Best Supportive Care.

Supportive study - Study 14596

Study 14596 was a multi-centre, open-label, uncontrolled phase II safety study conducted with regorafenib in 36 patients with HCC and liver function status Child Pugh A that had experienced radiological disease progression during previous therapy with sorafenib. Primary endpoint was evaluation of safety. Secondary endpoints included TTP, ORR, DCR and OS. Patients received regorafenib 160 mg OS according to a 3 weeks on and 1 week off schema. Enrolment criteria were very similar to the ones of the pivotal RESORCE study.

More than 80% of the subjects were male (88.9%), more than two-thirds were White (72.2%), 27.8% were Asians whereas none were Hispanic or Latino. Most patients were enrolled in Europe (77.8%), whereas the rest was enrolled in Korea (22.2%). Approximately two-thirds were ≤ 65 years of age (61.1%, median 61.0 years [range 40 to 76 years]) and both the mean (SD±3.9) and median BMI (range 16.6 to 33.2 kg/m2) were < 25 kg/m2.

Per protocol, all subjects had a medical history of HCC. In addition 24 of 36 (66.7%) subjects had a medical history of liver cirrhosis. Frequent and relevant medical history findings were: Hepatitis B Virus (HBV) in 18 subjects, 3 of whom had chronic HBV infections and Hepatitis C Virus (HCV) in 13 subjects, 3 of whom had chronic HCV infections.

All enrolled subjects (36 [100%]) received prior systemic anticancer therapy (sorafenib). The median duration of prior treatment with sorafenib was 137 days (range 15 to 993 days).

Results: The ORR was 2.8% (95% CI 0.1- 14.5%, CR= 0, PR= 1). More than two-thirds of the subjects (25 [69.4%]) achieved stable disease. The DCR was 72.2% (n= 26 pts, 95% CI 54.8%- 85.8%). One-third of the subjects (12 [33.3%]) showed a reduction in the sum of longest diameters of target lesions.

Among the 36 subjects evaluated for OS, 8 (22.2%) were censored before or were alive at the cut-off date. Median OS was 419 days (13.8 months, range: 18 to 981 days). The OS rate at 90 days was 0.88 (95% CI 0.72 - 0.95) and at 180 days was 0.79 (95% CI 0.61 - 0.89). The median KM estimate for TTP was 131 days (approximately 4.3 months).

2.4.2. Discussion on clinical efficacy

The proposed regorafenib dose regimen is 160 mg OD administered according to a 3 weeks on/one week off schema, in line with the already approved indications in patients with metastatic colorectal cancer and in GIST. No dose finding studies with regorafenib have been specifically conducted in patients with HCC, but the dose regimen is considered acceptable based on the provided data. Dose reductions in case of toxicity have been adequately described in the SmPC.

Design and conduct of clinical studies

The evidence of efficacy of regorafenib in patients with HCC is based on the results of one pivotal study (15982 or RESORCE), supported by the data of the phase II single arm 14596 study, both enrolling patients with HCC and Child Pugh A as liver function previously treated with sorafenib. As in all studies performed to date with regorafenib in HCC, patients who had to discontinue sorafenib due to toxicity were excluded.

Study 15982 (RESORCE) is a pivotal, phase III, multicentre, multinational, randomized, double blind, placebo-controlled study. A total of 573 patients with HCC and Child Pugh A as liver function score previously treated with sorafenib were randomized (2:1) to receive oral regorafenib 160 mg OD (3 weeks on/1 week off) plus BSC or matching placebo plus BSC. The two arms design of the study with placebo plus BSC as comparator is considered acceptable, as patients enrolled in the trial had received all the standard treatment options currently available in the EU.

OS was the primary study endpoint which is considered appropriate for the proposed target population, considering the relatively short life expectancy and the absence of alternative treatment options to date. PFS, TTP and ORR were secondary endpoints, all assessed by the investigator according to mRECIST or RECIST 1.1 criteria. Evaluation of health related quality of life (according to FACT-Hep and EQ-5D questionnaires) was also performed which is agreed, in view of the palliative treatment setting and the known significant regorafenib-related toxicity. However, obvious differences in treatment induced toxicities between study regimens (regorafenib and placebo) might potentially have compromised the double-blind nature of this trial. A biomarker analysis was also planned as exploratory. However, collection of archival and fresh tumour biopsies as well as of plasma for biomarker evaluation was not mandatory in the study, and, as a result, no biomolecular data were available for the majority of patients. Considering that regorafenib is a TKI, the results of such analysis could have been employed to identify parameters for patient selection, even though results of biomarker analyses to date with regorafenib in advanced colorectal cancer and GIST have failed to identify analytes capable of reliably predict clinical outcome. During the procedure, the MAH submitted the report on the analysis of non-genetic biomarkers. Although the data suggest that the treatment benefit for regorafenib versus the placebo group is maintained for the vast majority of patients, no firm conclusions can be drawn from these exploratory analyses. Hence, the CHMP recommends the submission of retrospective exploratory genetic biomarker analyses to identify biomarker candidates which might help to predict response to regorafenib. The biomarker report is expected to be available for submission in Q3/2017.

Of note, in the original study protocol two interim analyses were planned, one for early stop due to futility and a second one for efficacy. However, given the slow recruitment rate in China, it was expected that the second interim analysis would have been performed before accrual in the pivotal study was completed. As a consequence, the second interim analysis was removed by a protocol amendment. This is considered not to have impacted the results of the trial.

Efficacy data and additional analyses

Demographic and baseline characteristics appeared comparable between the two study arms.

The results of the final OS analysis based on 373 events (65%) (cut-off 29 Feb 2016) show a statistically significant improvement in OS for regorafenib compared with placebo (HR 0.627, 95% CI 0.50-0.785, p=0.00002), with a gain in median PFS of about 2.8 months in favour of regorafenib (median OS 10.6 vs 7.8 months, respectively). The robustness of the OS effect is supported by several sensitivity analyses, the results of which are in line with the primary analysis (i.e. an unstratified analysis and an analysis using stratification information from the RAVE). The effect on OS was observed in most subgroups of the population. In particular no significant difference was observed by race and by geographical region.

Regarding the secondary endpoints, consistency was observed in terms of PFS according to both mRECIST (HR 0.455, 95% CI 0.371-0.558, median PFS 1.5 and 3.1 months with regorafenib and placebo, respectively) and RECIST 1.1 (HR 0.427, 95% CI 0.348-0.524, median PFS 1.5 vs 3.4 months, respectively), as well as TTP (mRECIST: HR 0.442, 95% CI 0.358-0.545, median TTP 3.2 vs 1.5 months, respectively).

The ORR observed in the regorafenib arm (mRECIST 10.6%) suggests no improvement of cancer related symptoms related to tumour shrinkage in the majority of patients. The observed improvement in OS and PFS appears to be essentially driven by patients experiencing disease stabilisation under treatment. The Quality of life analysis, showing no clinically meaningful difference between the two study arms; however, a trend for better scores in patients treated with placebo in particular at later cycles of treatment could be seen.

Finally, consistent results in terms of median OS, TTP, ORR and DCR were reported in the supportive phase II single arm 14596 study compared with the pivotal phase III RESORCE study (median OS 13.8 months, median TTP 4.3 months, ORR: 2.8%, DCR: 72.2%). Of note, enrolment criteria were quite similar in the two studies but in the 14596 trial the majority of patients (72%) were Whites.

Evaluation of cancer related symptoms showed no significant difference between the two study arms. However, a numerical trend towards lower scores (and therefore worse quality of life and more symptoms) for patients treated with regorafenib is observed especially at later cycles. The reason for this difference observed between the two treatment arms favouring placebo at late treatment cycles is unclear.

2.4.3. Conclusions on the clinical efficacy

A statistically significant improvement in OS with regorafenib plus BSC compared with placebo plus BSC has been observed in the pivotal RESORCE study in patients with HCC previously treated with sorafenib. The results appear mature and robust, and supported by the secondary study endpoints and by the results of the additional phase II 14596 study. The low ORR reported with regorafenib in both studies is disappointing, indicating that the treatment effect is essentially driven by patients experiencing disease stabilisation. This is also reflected by the results of the quality of life evaluation. The lack of compelling biomarker data (that can be foreseen in view of the very limited number of patients consenting for the optional biomarker analysis) is considered a deficiency of the submitted dossier. In effect, considering that regorafenib is presented as a targeted therapy (multikinase inhibitor) and that treatment with regorafenib is associated with substantial toxicity, evaluation of biomarkers could potentially help in addressing proper patient selection.

The CHMP recommends the submission of retrospective explorative biomarker analyses to identify biomarker candidates which might help to predict response to regorafenib as follows:

(i) Expression data from approximatively 800 circulating miRNA isolated from plasma at baseline from subjects who granted genetic consent to identify individual miRNAs or miRNA signatures associated with the clinical endpoints OS and TTP.

(ii) Determination of an immune profile on the basis of targeted gene expression on archival tumor tissue samples from approximately 65 subjects subjected to analysis

(iii) Determination of the tumour mutational landscape using targeted Next-Generation DNA sequencing on archival tumor tissue samples from approximatively 22 subjects subjected to analysis.

2.5. Clinical safety

Introduction

The main safety data for regorafenib treatment of subjects with HCC is derived from the pivotal Phase 3 placebo-controlled study in 567 subjects (n=374 regorafenib) with HCC (Study 15982, RESORCE). The results of the phase 2 study in 36 subjects with HCC (Study 14596) are considered supportive and briefly reported. A phase 1 study including 23 subjects with HCC (Study 1165) is included in the overall pooled safety data. The phase 1 and phase 2 study have been previously submitted within the initial MAA for PK-analysis.

Additional supportive data for Stivarga is provided based on the overall safety database from 15 completed (i.e. final or interim clean database available) company-sponsored monotherapy trials in subjects with cancer in any indication (n=4518) and briefly discussed as part of the supportive data. For adverse events of special interest, the results are compared to those observed in phase 3 placebo-controlled studies in CRC (n=636 patients on regorafenib) and GIST (n=132 patients on regorafenib) for which the same dosing schedule was used.

Patient exposure

The overall median duration of treatment (including time interrupted) as of cut-off date of 29 FEB 2016 in the regorafenib group was 15.6 weeks compared to 8.4 weeks in the placebo group (Table 33). About one third (n=125, 33.4%) of patients had a treatment duration ≥ 6 months compared to 13.9% (n=24) on placebo. A total of 13.9% on regorafenib and 4.1% on placebo had a treatment duration ≥ 12 months. The median daily dose was 159.3 mg (range: 82.4-160), with approximately half of the subjects (49.2%) receiving 160 mg/day. Dose modifications were observed in 84.0% of subjects in the regorafenib group, and in 58.5% of subjects in the placebo group. At the data cut-off date treatment was ongoing in 65 (17.2%) of subjects in the regorafenib group vs. 10 (5.2%) in the placebo group.

Table 33. Extent of exposure to study drug (SAF).

	Placebo N=193 (100%)	Regorafenib N=374 (100%)
Overall time under treatment (including time off drug/interruptions) (weeks)		
Mean (±StD)	14.5 (±17.0)	25.4 (±26.2)
Median (range)	8.4 (0.7-119.0)	15.6 (0.1-128.0)
Actual time under treatment (excluding time off drug/interruptions) (weeks)		
Mean (±StD)	11.2 (±12.6)	18.6 (±19.2)
Median (range)	6.1 (0.7-86.6)	11.8 (0.1-94.7)
Actual average daily dose [a] (mg/day)		
Mean (±StD)	157.4 (±10.3)	144.1 (±21.3)
Median (range)	160 (80-160)	159.3 (82.4-160)
Total Amount of Dose [b] (mg)		
Mean (±StD)	12239.4 (±13736.6)	18162.8 (±18367.8)
Median (range)	6880 (800-96960)	11100 (160-93160)
Total Amount of Dose categorical		
≤2000 mg	6 (3.1%)	18 (4.8%)
>2000 to 5000 mg	26 (13.5%)	63 (16.8%)
>5000 to 8000 mg	69 (35.8%)	59 (15.8%)
>8000 to 11000 mg	32 (16.6%)	46 (12.3%)
>11000 mg	60 (31.1%)	188 (50.3%)
No. (%) of subjects with any modification [c]	113/193 (58.5%)	314/374 (84.0%)
No. (%) of subjects with at least 1 interruption [d]	110/193 (57.0%)	297/374 (79.4%)
Total no. of interruptions	191	825
Primary reason for interruption		
Lab or test abnormality per protocol	0	1 (0.1%)
Adverse event	86 (45.0%)	464 (56.2%)
Subject error	52 (27.2%)	171 (20.7%)
Site error	1 (0.5%)	5 (0.6%)
Logistical difficulty	39 (20.4%)	142 (17.2%)
Other	13 (6.8%)	37 (4.5%)
No. of interruptions per subject [d]		
1	66 (60.0%)	107 (36.0%)
2	26 (23.6%)	73 (24.6%)
3	13 (11.8%)	43 (14.5%)
4	1 (0.9%)	30 (10.1%)
5	0	15 (5.1%)
6 to 16	4 (3.6%)	29 (9.6%)
No. (%) of subjects with at least 1 dose reduction	21/193 (10.9%)	189/374 (50.5%)
Total no. of reductions	25	301
Adverse event	19 (76.0%)	280 (93.0%)
Subject error	4 (16.0%)	11 (3.7%)
Other	2 (8.0%)	9 (3.0%)
No. of reductions per subject [b]		
1	17 (81.0%)	102 (54.0%)
2	4 (19.0%)	75 (39.7%)
3	0	6 (3.2%)
4	0	2 (1.1%)
5	0	2 (1.1%)
6 to 7	0	2 (1.1%)
No. (%) of subjects with at least 1 re-escalation	3 (1.6%)	47 (12.6%)
Total no. of re-escalations	3	78
Missing	2 (66.7%)	57 (73.1%)
Adverse event per protocol	0	1 (1.3%)
Adverse event	0	1 (1.3%)
Subject error	1 (33.3%)	6 (7.7%)
Other	0	13 (16.7%)

Abbreviations: N = number of subjects: SAF = safety analysis set; StD = standard deviation.
a; Average daily dose across the length of treatment.
b; Over the length of treatment
c; in case of multiple events per subject, only the longest duration was taken.
d; the denominators in the placebo and regorafenib groups here are "No. (%) of subjects with at least 1 interruption.
Notes: Counts of zero are not displayed. Dose modification had to be selected as applicable (e.g. reduction, interruption/delay etc.). The descriptive statistics for duration of modification is event-based, not subject-based.

Adverse events

Most patients in both treatment groups reported at least one TEAE (100% for regorafenib vs 92.7% for placebo) (Table 34). Drug-related TEAEs were reported at a higher frequency in the regorafenib group (92.5%) compared with the placebo group (51.8%). Treatment-emergent SAEs were reported at comparable rates (44.4% for regorafenib vs 46.6% for placebo), but confounded by the fact that subjects who were hospitalized within 30 days after their last dose of study medication intake due to progression of HCC were required to be included as treatment-emergent SAEs. Drug-related TESAEs were reported at a higher frequency in the regorafenib group (10.4% vs 2.6% for placebo). TEAEs of Grade ≥3 were

reported in 79.7% of the regorafenib treated compared with 58.5% in the placebo group. Deaths were reported in 13.4% in the regorafenib group vs 19.7% in the placebo group. The incidence of TEAEs leading to permanent treatment discontinuation was 24.9% in the regorafenib group versus 19.2% in the placebo group. TEAEs that led to dose modifications occurred more frequently during regorafenib treatment; 68.2% versus 31.1% in the placebo group.

Table 34. Overview of treatment-emergent adverse events (SAF).

Overview	Placebo N=193 (100%)	Regorafenib N=374 (100%)
Number of subjects (%) with:		
Any AE	179 (92.7%)	374 (100%)
Worst CTCAE grade:		
Grade 1	30 (15.5%)	16 (4.3%)
Grade 2	36 (18.7%)	60 (16.0%)
Grade 3	61 (31.6%)	208 (55.6%)
Grade 4	14 (7.3%)	40 (10.7%)
Grade 5 (death)	38 (19.7%)	50 (13.4%)
Grade 3 or 4	75 (38.9%)	248 (66.3%)
Grade 3, 4 or 5	113 (58.5%)	298 (79.7%)
Serious	90 (46.6%)	166 (44.4%)
Non-serious [a]	176 (91.2%)	371 (99.2%)
Leading to dose modification [b]	60 (31.1%)	255 (68.2%)
Leading to permanent discontinuation of study drug	37 (19.2%)	93 (24.9%)
Related to protocol-required procedure	3 (1.6%)	13 (3.5%)
Any drug-related AE	100 (51.8%)	346 (92.5%)
Worst CTCAE grade:		
Grade 1	43 (22.3%)	42 (11.2%)
Grade 2	23 (11.9%)	110 (29.4%)
Grade 3	31 (16.1%)	173 (46.3%)
Grade 4	1 (0.5%)	14 (3.7%)
Grade 5 (death)	2 (1.0%)	7 (1.9%)
Grade 3 or 4	32 (16.6%)	187 (50.0%)
Grade 3, 4 or 5	34 (17.6%)	194 (51.9%)
Serious	5 (2.6%)	39 (10.4%)
Non-serious [a]	99 (51.3%)	346 (92.5%)
Leading to dose modification [b]	20 (10.4%)	202 (54.0%)
Leading to permanent discontinuation of study drug	7 (3.6%)	39 (10.4%)
Related to protocol-required procedure	2 (1.0%)	10 (2.7%)

Abbreviations; AE = adverse events; CTCAE = Common Terminology Criteria for Adverse Events; SAE = serious adverse event.Notes: 'Any AE' also includes subjects with grade not available for all AEs. Table contains deaths only if due to a treatment-emergent AE. CTCAE Version 4.03 used.
a; This category includes all subjects who had at least one non-serious AE, irrespective of the occurrence of SAEs.
b; Modifications included interruptions and reductions.

Overall, AEs were most commonly reported within the SOCs of gastrointestinal disorders (77.5%), general disorders and administration site conditions (69.5%), and skin and subcutaneous tissue disorders (64.0%). AEs with a higher incidence (≥10%) in the regorafenib group than the placebo group included HFSR (51.6% vs 7.3%), diarrhoea (41.2% vs. 15.0%), hypertension (30.7% vs. 6.2%), decreased appetite (30.7% vs. 14.0%), pyrexia (19.8% vs. 6.7%), and dysphonia (17.9% vs. 1.6%).

The most commonly reported TEAEs (≥10%) in regorafenib treated subjects were in general in the same range as that reported previously for CRC and GIST. Adverse events like AST/ALT increased, bilirubin increased, oedema peripheral, ascites, hypoalbuminemia, abdominal pain upper and general health physical deterioration were reported at somewhat higher frequencies but this was also seen in the placebo group. Dysphonia was reported at lower rates in HCC compared to CRC and GIST.

Table 35. Incidence rates of TEAEs (any grade) occurring in ≥5% of all subjects in either treatment group (SAF).

System Organ Class (SOC) Preferred term	Placebo N=193 (100%)	Regorafenib N= 374 (100%)
Blood and lymphatic disorders		
Anemia	21 (10.9%)	51 (13.6%)
Endocrine disorders		
Hypothyroidism	0	24 (6.4%)
Gastrointestinal disorders		
Abdominal distension	10 (5.2%)	18 (4.8%)
Abdominal pain	30 (15.5%)	79 (21.1%)
Abdominal pain upper	17 (8.8%)	47 (12.6%)
Ascites	31 (16.1%)	58 (15.5%)
Constipation	21 (10.9%)	65 (17.4%)
Diarrhea	29 (15.0%)	154 (41.2%)
Dry mouth	9 (4.7%)	21 (5.6%)
Nausea	26 (13.5%)	64 (17.1%)
Stomatitis	4 (2.1%)	31 (8.3%)
Vomiting	13 (6.7%)	47 (12.6%)
General disorders and administration site conditions		
Asthenia	18 (9.3%)	56 (15.0%)
Edema peripheral	26 (13.5%)	56 (15.0%)
Fatigue	47 (24.4%)	107 (28.6%)
General physical health deterioration	27 (14.0%)	44 (11.8%)
Malaise	5 (2.6%)	22 (5.9%)
Pyrexia	13 (6.7%)	74 (19.8%)
Investigations		
Alanine aminotransferase increased	21 (10.9%)	54 (14.4%)
Aspartate aminotransferase increased	38 (19.7%)	92 (24.6%)
Blood alkaline phosphatase increased	8 (4.1%)	22 (5.9%)
Blood bilirubin increased	31 (16.1%)	91 (24.3%)
GGT increased	12 (6.2%)	22 (5.9%)
Lipase increased	6 (3.1%)	27 (7.2%)
Platelet count decreased	2 (1.0%)	34 (9.1%)
Weight decreased	8 (4.1%)	50 (13.4%)
Metabolism and nutrition disorders		
Decreased appetite	27 (14.0%)	115 (30.7%)
Hypoalbuminemia	14 (7.3%)	52 (13.9%)
Hypokalemia	5 (2.6%)	26 (7.0%)
Hyponatremia	6 (3.1%)	21 (5.6%)
Hypophosphatemia	4 (2.1%)	36 (9.6%)
Musculoskeletal and connective tissue disorders		
Arthralgia	11 (5.7%)	14 (3.7%)
Back pain	17 (8.8%)	45 (12.0%)
Muscle spasms	4 (2.1%)	38 (10.2%)
Musculoskeletal pain	11 (5.7%)	17 (4.5%)
Pain in extremity	6 (3.1%)	26 (7.0%)
Nervous system disorders		
Headache	12 (6.2%)	24 (6.4%)
Psychiatric disorders		
Insomnia	8 (4.1%)	24 (6.4%)
Renal and Urinary disorders		
Proteinuria	2 (1.0%)	32 (8.6%)
Respiratory, thoracic and mediastinal disorders		
Cough	13 (6.7%)	41 (11.0%)
Dysphonia	3 (1.6%)	67 (17.9%)
Dyspnea	15 (7.8%)	28 (7.5%)
Pleural effusion	11 (5.7%)	15 (4.0%)
Skin and subcutaneous tissue disorders		
Alopecia	5 (2.6%)	26 (7.0%)
Palmar-plantar erythrodysesthesia syndrome [a]	13 (6.7%)	192 (51.3%)
Pruritus	14 (7.3%)	19 (5.1%)
Rash	14 (7.3%)	20 (5.3%)
Vascular disorders		
Hypertension	12 (6.2%)	115 (30.7%)

Abbreviations: GGT = gamma glutamyltransferase; N = number of subjects; SOC = system organ class; SAF = safety analysis set; TAEE = treatment- emergent adverse event.
a; Hand foot skin reation (HFSR) per CTCAE v 3.0 terminology.

Majority of the most common TEAEs were of CTCAE Grade 1 or 2, with the exception of blood bilirubin increases (n=41 Grade 3 and n=5 Grade 4 event; 50.8% (18/39) in the placebo group; 30.8% (28/91) in the regorafenib group) and increases in AST levels (56 Grade 3 and 7 Grade 4 events; 57.9% (22/38) in the placebo group; 44.6% (41/92) in the regorafenib group). HFSR was the most common TEAE and occurred at a notably higher frequency in the regorafenib group with 51.6% compared with 7.3% in the

placebo group (frequencies corrected further to errors identified by the MAH). A total of 46 (46/192, 24.0%) of these cases in the regorafenib group were CTCAE Grade 3.

A treatment group comparison of the incidence of CTCAE Grade 3 and 4 TEAEs occurring in at least 1% of the subjects in either treatment group in the SAF classified according to MedDRA SOC and preferred term is presented in Table 36. The most common (>5% of subjects) Grade 3 AEs by MedDRA preferred term in the regorafenib arm were hypertension (14.7% regorafenib vs 4.7% placebo), HFSR (12.3% regorafenib vs 0.5% placebo), AST increased (9.9% regorafenib vs 9.8% placebo), hypophosphatemia (7.8% regorafenib vs 1.6% placebo), blood bilirubin increased (7.5% regorafenib vs 6.7% placebo) and fatigue (5.9% regorafenib vs 3.6% placebo).

Table 36. CTCAE Grade 3 and 4 TEAEs with incidence rates in at least 1% in either treatment group (SAF).

System Organ Class (SOC) Preferred term	Placebo N=193 (100%)		Regorafenib N=374 (100%)	
Number (%) of subjects with:	**Grade 3**	**Grade 4**	**Grade 3**	**Grade 4**
Blood and lymphatic system disorders	11 (5.7%)	1 (0.5%)	22 (5.9%)	3 (0.8%)
Anemia	11 (5.7%)	0	14 (3.7%)	1 (0.3%)
Thrombocytopenia	0	0	4 (1.1%)	1 (0.3%)
Cardiac disorders	0	0	5 (1.3%)	1 (0.3%)
Gastrointestinal disorders	22 (11.4%)	2 (1.0%)	59 (15.8%)	3 (0.8%)
Abdominal pain	5 (2.6%)	0	10 (2.7%)	0
Abdominal pain upper	2 (1.0%)	0	2 (0.5%)	0
Ascites	11 (5.7%)	0	16 (4.3%)	0
Diarrhea	0	0	12 (3.2%)	0
Gastrointestinal hemorrhage	2 (1.0%)	0	1 (0.3%)	0
General disorders and administration site conditions	11 (5.7%)	3 (1.6%)	45 (12.0%)	2 (0.5%)
Asthenia	2 (1.0%)	0	14 (3.7%)	0
Fatigue	7 (3.6%)	0	22 (5.9%)	0
General physical health deterioration	6 (3.1%)	3 (1.6%)	13 (3.5%)	2 (0.5%)
Hepatobiliary disorders	14 (7.3%)	4 (2.1%)	18 (4.8%)	9 (2.4%)
Bile duct stenosis	4 (2.1%)	0	0	0
Hepatic failure	2 (1.0%)	2 (1.0%)	3 (0.8%)	3 (0.8%)
Hepatic function abnormal	4 (2.1%)	0	2 (0.5%)	0
Hyperbilirubinemia	2 (1.0%)	1 (0.5%)	6 (1.6%)	1 (0.3%)
Jaundice	3 (1.6%)	0	2 (0.5%)	0
Infections and infestations	10 (5.2%)	1 (0.5%)	23 (6.1%)	2 (0.5%)
Abdominal infection	2 (1.0%)	0	3 (0.8%)	0
Pneumonia	1 (0.5%)	0	5 (1.3%)	0
Injury, poisoning and procedural complications	3 (1.6%)	0	3 (0.8%)	0
Investigations	31 (16.1%)	9 (4.7%)	102 (27.3%)	14 (3.7%)
Alanine aminotransferase increased	5 (2.6%)	0	9 (2.4%)	2 (0.5%)
Amylase increased	0	0	6 (1.6%)	0
Aspartate aminotransferase increased	19 (9.8%)	3 (1.6%)	37 (9.9%)	4 (1.1%)
Bilirubin conjugate increased	1 (0.5%)	0	5 (1.3%)	0
Blood alkaline phosphatase increased	4 (2.1%)	0	7 (1.9%)	0
Blood bilirubin increased	13 (6.7%)	5 (2.6%)	28 (7.5%)	0
GGT increased	4 (2.1%)	1 (0.5%)	12 (3.2%)	0
Lipase increased	3 (1.6%)	0	18 (4.8%)	7 (1.9%)
Neutrophil count decreased	1 (0.5%)	0	4 (1.1%)	0
Platelet count decreased	0	0	10 (2.7%)	0
Weight decreased	0	0	7 (1.9%)	0
White blood cell decreased	0	0	4 (1.1%)	0
Metabolism and nutrition disorders	17 (8.8%)	5 (2.6%)	66 (17.6%)	9 (2.4%)
Anorexia	3 (1.6%)	0	10 (2.7%)	0
Dehydration	0	0	5 (1.3%)	0
Diabetes mellitus	2 (1.0%)	0	0	0
Hyperglycemia	3 (1.6%)	1 (0.5%)	4 (1.1%)	1 (0.3%)
Hyperkalemia	1 (0.5%)	1 (0.5%)	4 (1.1%)	0
Hypoalbuminemia	1 (0.5%)	0	6 (1.6%)	0
Hypokalemia	2 (1.0%)	0	9 (2.4%)	0
Hyponatremia	4 (2.1%)	2 (1.0%)	12 (3.2%)	3 (0.8%)
Hypophosphatemia	3 (1.6%)	0	29 (7.8%)	2 (0.5%)
Musculoskeletal and connective tissue disorders	8 (4.1%)	0	16 (4.3%)	1 (0.3%)
Back pain	2 (1.0%)	0	7 (1.9%)	1 (0.3%)
Musculoskeletal pain	2 (1.0%)	0	1 (0.3%)	0
Neoplasms benign, malignant and unspecified (including cysts and polyps)	1 (0.5%)	0	10 (2.7%)	0
Tumor pain	1 (0.5%)	0	5 (1.3%)	0
Nervous system disorders	6 (3.1%)	0	16 (4.3%)	3 (0.8%)
Hepatic encephalopathy	1 (0.5%)	0	4 (1.1%)	2 (0.5%)
Psychiatric disorders	2 (1.0%)	0	3 (0.8%)	1 (0.3%)
Renal and urinary disorders	3 (1.6%)	1 (0.5%)	13 (3.5%)	0
Acute kidney injury	2 (1.0%)	0	1 (0.3%)	0
Proteinuria	1 (0.5%)	0	7 (1.9%)	0
Reproductive system and breast disorders	2 (1.0%)	0	0	0
Respiratory, thoracic and mediastinal disorders	5 (2.6%)	1 (0.5%)	10 (2.7%)	3 (0.8%)
Haemoptysis	2 (1.0%)	0	1 (0.3%)	1 (0.3%)
Pleural effusion	2 (1.0%)	0	3 (0.8%)	0
Skin and subcutaneous tissue disorders	2 (1.0%)	0	51 (13.6%)	0
Palmar-plantar erythrodysaesthesia syndrome [a]	1 (0.5%)	0	46 (12.3%)	0
Vascular disorders	11 (5.7%)	0	56 (15.0%)	1 (0.3%)
Hypertension	9 (4.7%)	0	55 (14.7%)	0

Abbreviations: CTCAE = Common Terminology Criteria for Adverse Events; N = number of subjects; SOC = system organ class; SAF = safety analysis set; TEAE = treatment-emergent adverse event.
a; Hand foot skin reaction (HFSR) per CTCAE v 3.0 terminology

Drug-related TEAEs that occurred in at least 5% of all subjects for any CTCAE grade in the SAF according to MedDRA is presented in Table 37. The most common drug-related TEAEs in the regorafenib group were

HFSR (50.8% regorafenib vs 5.7% placebo), diarrhea (33.4% regorafenib vs 9.3% placebo), decreased appetite (23.5% regorafenib vs 5.7% placebo), hypertension (23.0% regorafenib vs 4.7% placebo), fatigue (21.1% regorafenib vs 13.5% placebo), blood billirubine increased (15.8% regorafenib vs 2.6% placebo), dysphonia (15.8% regorafenib vs 1.0% placebo), AST increased (13.1% regorafenib vs 7.8% placebo), asthenia (11.2% regorafenib vs 5.7% placebo), and nausea (10.7% regorafenib vs 6.7% placebo). Most common drug-related TEAES in the placebo group were fatigue (13.5%), diarrhoea (9.3%), and AST increased (7.8%).

Grade 3 drug-related TEAEs that occurred at a higher frequency (at least 4% of the subjects) in the regorafenib group during the study were hypertension (12.8%), HFSR (12.3%), blood bilirubin increased (5.1%), AST increased (4.5%), hypophosphatemia (4.3%), and lipase increased (4.0%). Drug-related CTCAE Grade 4 events occurred very infrequently in the regorafenib group and twice in the placebo group (1 event of AST increased and 1 event of renal failure). Grade 4 events that occurred in the regorafenib in at least two subjects were ALT increased (0.8%), AST increased (0.5%) and hypophosphatemia (0.5%). All other events occurred in a single subject.

Table 37. Incidence rates of drug-related TEAEs (any grade) occurring in ≥5% of all subjects in either treatment group (SAF).

System Organ Class (SOC) Preferred Term	Placebo N=193 (100%)	Regorafenib N=374 (100%)
Blood and lymphatic system disorders		
Anemia	2 (1.0%)	22 (5.9%)
Gastrointestinal disorders		
Abdominal pain	4 (2.1%)	26 (7.0%)
Constipation	3 (1.6%)	24 (6.4%)
Diarrhea	18 (9.3%)	125 (33.4%)
Nausea	13 (6.7%)	40 (10.7%)
Stomatitis	3 (1.6%)	28 (7.5%)
Vomiting	5 (2.6%)	27 (7.2%)
General disorders and administration site conditions		
Asthenia	11 (5.7%)	42 (11.2%)
Fatigue	26 (13.5%)	79 (21.1%)
Investigations		
Alanine aminotransferase increased	8 (4.1%)	28 (7.5%)
Aspartate aminotransferase increased	15 (7.8%)	49 (13.1%)
Blood bilirubin increased	5 (2.6%)	59 (15.8%)
Weight decreased	2 (1.0%)	26 (7.0%)
Metabolism and nutrition disorders		
Decreased appetite	11 (5.7%)	88 (23.5%)
Hypophosphatemia	2 (1.0%)	22 (5.9%)
Musculoskeletal and connective tissue disorders		
Muscle spasms	1 (0.5%)	23 (6.1%)
Renal and urinary disorders		
Proteinuria	2 (1.0%)	21 (5.6%)
Respiratory, thoracic and mediastinal disorders		
Dysphonia	2 (1.0%)	59 (15.8%)
Skin and subcutaneous tissue disorders		
Alopecia	5 (2.6%)	25 (6.7%)
Palmar-plantar erythrodysaesthesia syndrome [a]	11 (5.7%)	190 (50.8%)
Vascular disorders		
Hypertension	9 (4.7%)	86 (23.0%)

Abbreviations: N= number of subjects; SOC = system organ class; SAF = safety analysis set; TEAE = treatment-emergent adverse event.
a; Hand foot skin reaction (HFSR) per CTCAE v 3.0 terminology

Time to first onset of selected treatment-emergent adverse events and outcomes

Common treatment-emergent AEs with an incidence of >5% overall in any group by MedDRA PT, v. 19.0 were analysed by interval-specific and cumulative event rates. For most analysed common events, the highest event rate in the regorafenib group of Study 15982 (Pool 2) was in the first cycle. Time to first onset for the most frequent regorafenib ADRs (>25%) showed that the majority of regorafenib adverse

reactions - in particular HFSR (median 14 days, Q3: 24 days), hypertension (median: 15 days; Q3: 37 days), fatigue (median 15 days; Q3: 42.5days) and decreased appetite (median 16 days; Q3:66.5 days) - occur within first weeks of treatment. Fatigue and decreased appetite occurred earlier in regorafenib-treated subjects as compared to subjects in placebo arm (fatigue median 28 days, Q3: 54 days), decreased appetite median 29 days, Q3: 64 days). Diarrhoea (median: 26.5 days; Q3: 71 days) and infection (median 62 days; Q3: 128 days) events in subjects treated with regorafenib occur later during treatment and do not show a clear-cut difference in onset pattern as compared to placebo subjects.

Outcome data for the most frequent regorafenib adverse reactions (>25% of regorafenib treatment group) have been reviewed for any potential data which would indicate that dose modifications or concomitant medications did not lead to an improvement of respective events. For decreased appetite, 62.7% of events resolved (vs 36.4% placebo), for diarrhoea 82.7% of events resolved (vs 69.0% placebo), for fatigue 47.6% of events resolved (vs 34.9% placebo), for hypertension 61.0% events resolved (vs 66.7% placebo), for infections and infestations, 81.8% resolved (vs 76.7% placebo), and for HFSR 66.5% resolved (vs 45.5% placebo).

Adverse events of special interest (AESI)

AEs of special interest include cardiac safety, renal safety, hepatobiliary events, haemorrhage, skin AE, vascular safety, GI safety, wound healing and infections. The important identified risks of regorafenib were severe drug-induced liver injury (DILI), cardiac ischemic events, hypertension and hypertensive crisis, haemorrhage, HFSR, posterior reversible encephalopathy syndrome (PRES), gastrointestinal perforation and fistulae, Stevens-Johnson Syndrome (SJS)/Toxic epidermal necrolysis (TEN). Special attention has been given to hepatoxicity and haemorrhage in the HCC trial.

Of note, the frequency of several AESIs (e.g., hepatobiliary disorders, proteinuria, pancreatitis, etc.) has been updated in the SmPC by the MAH, as the results of pooled analyses.

Cardiac safety

Cardiac ischemic events were reported at low rates but at a higher frequency in patients on regorafenib versus placebo (1.9% vs 0%). There does not appear to be an increased risk in patients with cardiovascular risk factors. Using the SMQ ischemic heart disease, events were reported in 2.4% (n=9) of patients on regorafenib versus 0.5% of patients on placebo (n=1). Five events in the regorafenib group were of grade 1-2, 2 of grade 3 and 1 each of grade 4 and 5. Corresponding rates for CRC were 1.6% regorafenib vs 0.3% placebo, and for GIST: 1.5% regorafenib vs 0% placebo.

The incidence of cardiac arrhythmia (SMQ) events in general were low in patients subjects treated with regorafenib (n=14, 3.7% on regorafenib and n=4, 2.1% on placebo) and was mainly related to atrial fibrillation events (n=5, 1.3%). Atrial fibrillation is classified as an important potential risk for regorafenib. There were 3 cases of worst grade 1-2 severity, and two events of grade 3. Overall rates of atrial fibrillation were slightly higher than for placebo in all indications (HCC: 1.3% vs 0%; CRC: 1.4% vs 0%; GIST: 0.8% vs 0%). The event was resolved in the majority of cases. Permanent study drug discontinuation did not become necessary.

Events of congestive heart failure occurred at similar rates (16.8% on regorafenib and 14.5% on placebo) and events were more commonly in those patients with baseline risk factors.

ECGs were not standard performed during follow-up. Previous data did not indicate clinically significant effect of regorafenib on QTc.

Renal safety

Adverse events in the SOC of renal and urinary disorders were more commonly reported in the regorafenib group (16.8% vs 9.3% placebo). The most commonly reported event was proteinuria (8.6% for regorafenib vs 1.0% placebo) and mostly grade 1 to 2. The incidence of renal failure was higher for placebo than for regorafenib (4.1% vs 1.9%). There was no detrimental effects seen on estimated GFR or GFR using Risk Injury Failure criteria (RIFLE).

Hepatobiliary disorders

Regorafenib is known to increase transaminases and blood bilirubin levels and high frequencies were reported in HCC. ALT abnormalities were reported in 70.4% of regorafenib treated patients (vs 58.6% placebo). AST abnormalities occurred in 92.7% of regorafenib treated patients (vs 84.9% placebo). Billirubin abnormalities were reported in 78.2% and 54.2% in regorafenib and placebo-treated patients, respectively. AEs in the SOC of hepatobiliary disorders were reported in a similar percentage of subjects in both treatment groups (16.1% in the placebo group and 14.7% in the regorafenib group). In the regorafenib group, the most commonly reported AEs were hyperbilirubinemia (3.7%), hepatic failure (2.4%), and jaundice (2.1%). Hepatic failure was reported in 4.7% of subjects the placebo group and 2.4% of subjects in the regorafenib group, and was the most commonly reported AE in the placebo group. There were two drug-related Grade-4 hepatobiliary disorders events in the regorafenib group (hyperbilirubinaemia and hepatic failure), and none in the placebo group. There were two drug-related Grade-5 hepatobiliary disorders event in the placebo group (both hepatic failure), and none in the regorafenib group. No cases of drug-induced liver injury (DILI) were reported.

Compared to other indications CRC and GIST, laboratory abnormalities were reported at higher frequencies in both regorafenib and placebo am (ALT abnormalities: CRC: 47.4% regorafenib vs 30.1% placebo; GIST: both groups 40.9%; AST abnormalities: CRC: 66.2% regorafenib vs 23.8% placebo; GIST: 59.1% regorafenib vs 48.5% placebo; bilirubin abnormalities: CRC: 49.7% of regorafenib vs 20.4% placebo; GIST: 34.4% regorafenib vs 12.1% placebo). Overall incidence rate of MEdDRA SMQ hepatic disorders (broad) was also higher for patients on regorafenib and highest in patients with HCC but also for the placebo group (55.1% vs 43.5%; CRC: 42.3% vs 25.6%; GIST: 24.2% vs 15.2%). SAEs in this SMQ were also higher for regorafenib in HCC compared to other indications and also placebo rates were higher (HCC:11.0% vs 15.0%; CRC: 6.3% vs 4.4%; GIST: 5.30% vs 1.5%). However, in HCC SAEs were reported at a higher incidence in the placebo group. Overall review of potential Hy's Law cases and cases compatible with regorafenib-induced severe liver injury confirmed severe liver injury as a clinically serious (with potential fatal outcome) but uncommon adverse drug reaction for regorafenib. In that respect, for HCC subjects no new safety finding was observed.

Skin and subcutaneous disorders

Skin and subcutaneous AEs were common in subjects treated with regorafenib (65.5% vs 30.6% placebo). Most commonly reported events are hand and foot syndrome (51.6%), alopecia (7.0%), and rash (5.3%). There was one serious event of HFSR reported. HFSR events were reported as recovered/resolved in 100 of 191 regorafenib treated patients with such events, including the serious case. HFSR events led to dose reductions in 75 (20.1%) and to permanent study drug discontinuation in 7 (1.9%) of regorafenib-treated patients. There were no fatal outcomes.

The SMQ "severe cutaneous reactions (narrow) yielded 5 results in the regorafenib group (1.3%) versus none in the placebo group. Low rates were seen before (CRC: 2.5% vs 0.6%; GIST: 0% vs 0%). SJS and TEN have been previously determined as ADRs (frequency category: "rare") for regorafenib. No SJS/TEN events with fatal outcome have been observed.

Vascular disorders and thromboembolic events

Hypertension is common among subjects treated with regorafenib (30.7% vs 6.2% placebo). The majority of hypertension occurred during the first cycle of treatment. Most events were of grade 2 or 3. One SAE of hypertensive crisis was reported in the regorafenib group, there were no fatal outcomes. About 16.6% of events were reported as resolved, ten events (2.7%) led to a dose reduction, in one case the study drug needed to be discontinued.

Frequencies of hypertension were also high in CRC (29.6% vs 7.5%) and GIST (60.6% vs 25.8%). In general, the incidence of hypertension is slightly higher in subjects with baseline history of hypertension, the same trend has been observed in placebo treated subjects. Overall, hypertension events in 3 patients in the placebo-controlled trials were considered serious, none were fatal.

For pulmonary and other venous embolism, the incidence was higher in the placebo group than in the regorafenib groups. Regarding arterial thromboembolism, the incidence was higher in the regorafenib group than in the placebo groups (2.9% for regorafenib vs 0.5% for placebo) in HCC, overall higher incidences on regorafenib had been reported before. No new safety signals were identified based on the study in HCC compared to the known safety profile.

Gastrointestinal disorders

AEs in the SOC of gastrointestinal disorders were reported more frequently in the regorafenib group (77.5%) than in the placebo group (59.1%). Diarrhoea (41.2% vs 15.0% placebo) and abdominal pain (21.1% vs 15.5%) were the most common gastrointestinal disorders in the regorafenib group, and the majority of cases were mild to moderate severity. Stomatitis was reported in 8.3% of subjects in the regorafenib group and 2.1% of subjects in the placebo group.

Overall, 7 cases of pancreatitis (0.61%) have been reported within pooled placebo-controlled Phase 3 trials in regorafenib treated patients compared to one in placebo-treated patients using the MedDRA Labeling Group (MLG) pancreatitis (including the following MedDRA PTs: Pancreatitis, Pancreatitis acute, Oedematous pancreatitis, Pancreatitis relapsing). Thereof 6 cases, have been reported from pivotal study 15982 (RESORCE) with 3 of them reported as serious. The remaining 2 cases (one case each for regorafenib and placebo arm) were reported from the pivotal CRC CORRECT study. In most cases the increase in laboratory values was accompanied by clinical symptoms.

The majority of the pancreatitis events were grade 1 or 2 and no Grade 4 or 5 events were reported. No fatal events were reported. Pancreatitis has now been reflected in section 4.8 of the SmPC.

Gastrointestinal perforation by MEdDRA SMQ was reported infrequently across all indications (HCC: 1.3% vs 1.6%; CRC: 1.9% vs 0.6%; GIST: 3.0% vs 0%). SAEs on regorafenib, occurred in 0.8% HCC, 0.9% CRC and 1.5% GIST. In the RESORCE trial, there was one SAE of duodenal perforation (resulting in death) in a regorafenib-treated subject, and there were no GI fistula SAEs.

Respiratory, thoracic and mediastinal disorders

There was no indication of an increased risk of severe or significant respiratory, thoracic and mediastinal adverse events with regorafenib treatment. The incidence of AEs was higher in the regorafenib group than the placebo group (41.2% regorafenib vs 22.3% placebo), largely driven by the higher incidence of dysphonia in the regorafenib group (17.9% vs 1.6%). Only 3 subjects in the regorafenib group had reported worst Grade 4 events (haemoptysis, respiratory distress, and tracheal disorder).

Interstitial lung disease had been identified as an important potential risk. There were 5 subjects (1.3%) with events included in the SMQ of interstitial lung disease in the regorafenib group (4 subjects with pneumonitis and 1 subject with interstitial lung disease) and no subjects in the placebo group. No cases

of pneumonitis or interstitial lung disease were drug-related. Corresponding incidences in CRC were 0.5% regorafenib vs 0.6% placebo and none within GIST.

Metabolic and nutrition disorders

Decreased appetite was the most commonly AE reported (30.7% regorafenib vs 14.0% placebo), the majority were non-serious.

Haemorrhage

The incidence of haemorrhagic events in the regorafenib group (17.6%) was similar to that in the placebo group (16.1%). The most common haemorrhagic events were epistaxis, haematuria, and haemoptysis, all reported at a higher incidence in the regorafenib group than in the placebo group. A total of 44/66 patients on regorafenib with bleeding events recovered compared to 12/31 on placebo.

SAEs occurred in 5.1% (n=19) of regorafenib treated group and 8.3% in the placebo group. In 10 of these 19 patients on regorafenib, the outcome was recovered/resolved and in 4 patients the events had a fatal outcome, compared to 7 fatal outcomes in the placebo group. Three patients discontinued the study drug and 4 patients had to reduce the dose due to a bleeding event. There was a higher incidence of upper gastrointestinal haemorrhage (placebo 2.1%, regorafenib 1.1%) and gastrointestinal haemorrhage (placebo 2.1%, regorafenib 0.5%) in the placebo group compared to the regorafenib groups. There were 3 cases of haemorrhagic shock in the regorafenib group of which 2 were grade 5 and one case of hypovolemic shock, grade 5. No events of shock occurred in the placebo group. Grade 5 haemorrhagic events were more common in the placebo group (3.6% vs 1.1% placebo).

Most events were of grade 1 or 2. SAEs on regorafenib occurred at low frequencies but at somewhat higher rates in HCC (HCC: 5.1% vs 8.3%; CRC: 2.4% vs 0.6%, GIST: 3.8% vs 0%). Grade 5 events were low but again higher in HCC (HCC: 1.1% vs 3.6%; CRC: 0.6% vs 0%, GIST: 0%), however also for placebo.

Infections

The incidence of AEs in the SOC of infections and infestations was 31.3% for regorafenib versus 18.1% for placebo. Bronchitis (3.7%), nasopharyngitis (3.5%) and urinary tract infection (3.5%) were the most commonly reported AEs in the regorafenib group. Other infections reported were pneumonia (2.4% vs 1.0%), upper respiratory infections (2.1% vs 1%), influenza (1.6% vs 0.5%), and sepsis (0.8% vs 0%). SAEs in the SOC of infections and infestations were also reported more frequently in the regorafenib group than in the placebo group (3.1%). Pneumonia was reported as SAE in 1.6% of subjects in the regorafenib group, and 0.5% of subjects in the placebo group. The respective Grade 5 incidence rate was 1.3% (n=5) in the regorafenib group, compared with 0% in the placebo group. None of these were reported as drug-related by the treating physician; 2 cases were lung infection, 2 cases were sepsis-related events, and 1 case was peritonitis.

Infection related events were frequently reported across all indications and at comparable rates in the regorafenib group (CRC: 31.1% vs 19%; GIST: 34.8% vs 6.1%).

Table 38: Incidence rates of infections including fatal events in the placebo-controlled phase III trials

SOC Infections & Infestations	HCC: RESORCE 15982		CRC: CORRECT / CONCUR 14387 /15808		GIST: GRID 14874 (double-blind phase)	
	REG (n=374)	PLA (n=193)	REG (n=636)	PLA (n=321)	REG (n=132)	PLA (n=66)
TEAEs (independent of study drug relationship assessment)						
All grades	31.3%	18.1%	31.1%	19.0%	34.9%	6.1%
Grade 5	1.3%	0%	0.8%	0.6%	0.8%	0%

Posterior reversible encephalopathy syndrome (PRES)

Using the MedDRA search strategy pertaining to PRES, excluding headache, 7 patients were identified in the regorafenib group (1.9%) compared to 7 patients in the placebo group (3.6%). Most of these were of grade 3 in the regorafenib group. Headache was reported as similar percentages in both treatment arms (about 6 Comparable frequencies for the PRES search strategy were seen in CRC (1.6% vs 2.8%) and GIST (0.8% vs 3.0%). No confirmed case with PT PRES has been reported in HCC. Overall, the PT PRES has been reported once in the placebo-controlled trials in a patient with GIST.

Thrombotic microangiopathies (TMA)

There were no cases of interest regarding the identified potential risk thrombotic microangiopathies (TMA) in the study. Overall, one case was reported in CRC based on the placebo-controlled studies.

Wound healing complications

Using Product-specific Bayer MedDRA query (PBMQ), there were 5 (1.3%) cases in the regorafenib group vs none in the placebo group. No serious cases were reported, and the majority has been reported as recovered. Corresponding rates for CRC were 0.16% vs 0.62% and for GIST: 1.5% vs 1.3%).

Serious adverse event / deaths / other significant events

Overall, 256 (45.1%) subjects in the SAF were reported to have had SAEs. There were 10.4% (n=39) of drug-related SAEs in the regorafenib group compared with 2.6% (n=5) in the placebo group. SAEs are shown in the table below (Table 39).

Table 39. Incidence rates of treatment-emergent SAEs and drug-related SAEs (any grade) occurring in ≥ 1% of the subjects in either treatment group with respect to SOC or preferred term (SAF).

	Overall Incidence		Drug-related	
System Organ Class (SOC) Preferred Term	Placebo N=193 (100%)	Regorafenib N=374 (100%)	Placebo N=193 (100%)	Regorafenib N=374 (100%)
Blood and lymphatic system disorders	2 (1.0%)	4 (1.1%)	–	–
Cardiac disorders	1 (0.5%)	7 (1.9%)	0	4 (1.1%)
Gastrointestinal disorders	22 (11.4%)	32 (8.6%)	0	9 (2.4%) [a]
Abdominal pain	4 (2.1%)	2 (0.5%)	–	–
Ascites	6 (3.1%)	9 (2.4%)	–	–
Esophageal hemorrhage	1 (0.5%)	4 (1.1%)	–	–
Gastrointestinal hemorrhage	2 (1.0%)	1 (0.3%)	–	–
Intra-abdominal hemorrhage	2 (1.0%)	0	–	–
Upper gastrointestinal hemorrhage	3 (1.6%)	3 (0.8%)	–	–
General disorders and administration site conditions	27 (14.0%)	49 (13.1%)	1 (0.5%)	8 (2.1%) [a]
General physical health deterioration	24 (12.4%)	39 (10.4%)	1 (0.5%)	5 (1.3%)
Pyrexia	1 (0.5%)	5 (1.3%)	–	–
Hepatobiliary disorders	21 (10.9%)	22 (5.9%)	4 (2.1%)	2 (0.5%)
Bile duct stenosis	2 (1.0%)	0	–	–
Hepatic failure	9 (4.7%)	9 (2.4%)	3 (1.6%)	1 (0.3%)
Hepatic function abnormal	3 (1.6%)	2 (0.5%)	–	–
Hepatic hemorrhage	2 (1.0%)	2 (0.5%)	–	–
Jaundice	2 (1.0%)	1 (0.3%)	–	–
Infections and infestations	6 (3.1%)	28 (7.5%)	–	–
Liver abscess	2 (1.0%)	2 (0.5%)	–	–
Pneumonia	1 (0.5%)	6 (1.6%)	–	–
Injury, poisoning, and procedural complications	3 (1.6%)	4 (1.1%)	–	–
Investigations	2 (1.0%)	4 (1.1%)	–	–
Blood bilirubin increased	2 (1.0%)	1 (0.3%)	–	–
Metabolism and nutrition disorders	6 (3.1%)	10 (2.7%)	–	–
Decreased appetite	3 (1.6%)	1 (0.3%)	–	–
Hypercalcemia	2 (1.0%)	0	–	–
Musculoskeletal and connective tissue disorders	5 (2.6%)	13 (3.5%)	–	–
Back pain	2 (1.0%)	6 (1.6%)	–	–
Neoplasms benign, malignant and unspecified (including cysts and polyps)	2 (1.0%)	9 (2.4%) [a]	–	–
Tumor pain	0	4 (1.1%)	–	–
Nervous system disorders	10 (5.2%)	20 (5.3%)	0	4 (1.1%) [a]
Encephalopathy	3 (1.6%)	3 (0.8%)	–	–
Hepatic encephalopathy	3 (1.6%)	7 (1.9%)	–	–
Renal and urinary disorders	3 (1.6%)	5 (1.3%)	–	–
Acute kidney injury	2 (1.0%)	0	–	–
Respiratory, thoracic, and mediastinal disorders	8 (4.1%)	20 (5.3%) [a]	–	–
Dyspnea	2 (1.0%)	5 (1.3%)	–	–
Hemoptysis	2 (1.0%)	3 (0.8%)	–	–
Pleural effusion	1 (0.5%)	4 (1.1%)	–	–
Respiratory failure	3 (1.6%)	1 (0.3%)	–	–
Vascular disorders	2 (1.0%)	6 (1.6%)	–	–

Abbreviations: CTCAE = Common Terminology Criteria for Adverse Events; N = number of subjects; NCI National cancer institute; SAE = serious adverse events; SAF safety analysis set; system organ class.
a; overall percentage by SOC may not equal number of events shown by preferred term of may only appear due to cut-off ≥1% incidence for other treatment group without having individual qualifying events.

Most of these drug-related SAEs were CTCAE Grade 3 in both treatment groups (n=21, 5.6% regorafenib and n=3, 1.6% placebo). Most Grade 3 events were related to the following SOCs: General disorders and administration site conditions (6 events), Gastrointestinal disorders (5 events), and Infections and infestations (3 events).

Serious adverse events leading to hospitalization

Overall, 40.6% in the regorafenib group and 38.3% of the SAEs resulted in hospitalization. Most frequently reported SAEs leading to hospitalisation on regorafenib and with a difference of 1% compared to placebo were general physical health deterioration (7.8% regorafenib vs 5.7% placebo), and pneumonia (1.6% regorafenib vs 0.5% placebo). The incidence of the SAEs of pneumonia, pyrexia, and

dyspnoea leading to hospitalisation was higher in the regorafenib group, while the incidence of the SAEs of hepatic function abnormal, decreased appetite, and respiratory failure was higher in the placebo group. The majority of events leading to hospitalisation in regorafenib-treated subjects are comparable with respect to frequencies and affected organ sites to respective events reported for subjects treated within placebo arm. There was a slight increase (~3%) in reported Grade 3 events leading to hospitalisation in regorafenib arm. This difference is mainly due to an increase of reported SOC infection Grade 3 events (n=19; 5.1%) leading to hospitalisation.

Death

An overview of all deaths during treatment and up to 30 days post permanent treatment discontinuation is shown below (Table 40).

Table 40. Overview of deaths during treatment and up to 30 days post permanent treatment discontinuation (SAF).

	Placebo N=193 (100%) n (%)	**Regorafenib N=374 (100%) n (%)**	**Total N=567 (100%) n (%)**
All	38 (19.7%)	50 (13.4%)	88 (15.5%)
AE associated with clinical disease progression	21 (10.9%)	31 (8.3%)	52 (9.2%)
AE not associated with clinical disease progression	6 (3.1%)	12 (3.2%)	18 (3.2%)
Progressive disease	11 (5.7%)	7 (1.9%)	18 (3.2%)

A treatment group comparison of the incidence of CTCAE Grade 5 TEAEs (deaths) for the SAF is presented in Table 41. Altogether, 88 subjects died due to Grade 5 TEAEs during the study, 38 (19.7%) in the placebo group and 50 (13.4%) in the regorafenib group. Incidence rates were in general comparable or slightly lower in the regorafenib group. A higher frequency of deaths was reported for regorafenib in the SOC Infections and infestations (1.3% vs 0 placebo) and vascular disorders (0.8% vs 0% placebo).

Table 41. Incidence rates of Grade 5 TEAEs by preferred term (SAF).

System Organ Class (SOC) Preferred term	Placebo N=193 (100%)	Regorafenib N=374 (100%)
Any event	38 (19.7%)	50 (13.4%)
Cardiac disorders	1 (0.5%)	1 (0.3%)
Cardiac arrest	1 (0.5%)	0
Myocardial infarction	0	1 (0.3%)
Gastrointestinal disorders	5 (2.6%)	3 (0.8%)
Ascites	1 (0.5%)	2 (0.5%)
Duodenal perforation	0	1 (0.3%)
Esophageal varices hemorrhage	1 (0.5%)	0
Intra-abdominal hemorrhage	1 (0.5%)	0
Upper gastrointestinal hemorrhage	2 (1.0%)	0
General disorders and administration site conditions	17 (8.8%)	24 (6.4%)
Death	0	1 (0.3%)
General physical health deterioration	16 (8.3%)	23 (6.1%)
Multi-organ failure	1 (0.5%)	0
Hepatobiliary disorders	8 (4.1%)	5 (1.3%)
Acute hepatic failure	0	1 (0.3%)
Hepatic failure	5 (2.6%)	3 (0.8%)
Hepatic hemorrhage	2 (1.0%)	0
Hepatorenal syndrome	1 (0.5%)	1 (0.3%)
Infections and infestations	0	5 (1.3%)
Lung infection	0	1 (0.3%)
Peritonitis bacterial	0	1 (0.3%)
Pneumonia	0	1 (0.3%)
Sepsis	0	1 (0.3%)
Septic shock	0	1 (0.3%)
Injury, poisoning, and procedural complications	0	1 (0.3%)
Craniocerebral injury	0	1 (0.3%)
Investigations	0	1 (0.3%)
Blood pressure decreased	0	1 (0.3%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	1 (0.5%)	0
Tumor hemorrhage	1 (0.5%)	0
Nervous system disorders	2 (1.0%)	3 (0.8%)
Encephalopathy	1 (0.5%)	0
Intracranial hemorrhage	0	1 (0.3%)
Hepatic encephalopathy	1 (0.5%)	1 (0.3%)
Meningorrhagia	0	1 (0.3%)
Respiratory, thoracic and mediastinal disorders	5 (2.6%)	4 (1.1%)
Bronchial obstruction	0	1 (0.3%)
Dyspnea	1 (0.5%)	2 (0.5%)
Pleural effusion	1 (0.5%)	0
Respiratory failure	3 (1.6%)	1 (0.3%)
Vascular disorders	0	3 (0.8%)
Hypovolemic shock	0	1 (0.3%)
Shock hemorrhagic	0	2 (0.5%)

Abbreviations: N = number of subjects; SAF = safety analysis set; SOC = system organ class; TEAE = Treatment-emergent adverse event.
Source: Table 14.3.2/155

Abbreviations: N = number of subjects; SAF = safety analysis set; SOC =system organ class; TEAE = treatment-emergent adverse event.

In total, at the time of the database cut-off, there were 9 TEAEs with a fatal outcome (Grade 5) within 30 days of last study drug that were reported as treatment-related in the clinical database. Two subjects' deaths were considered study drug-related in the placebo group (acute hepatic failure) compared with 7 subjects' deaths in the regorafenib group. Within the regorafenib group the cause of death was duodenal perforation, meningorrhagia, hemorrhagic shock, hepatic encephalopathy, myocardial infarction, general physical health deterioration, or death. All were single cases.

Laboratory findings

Treatment-emergent laboratory abnormalities observed in the RESORCE trial are shown in the below table.

Table 42: Treatment-emergent laboratory test abnormalities reported in placebo-controlled phase III trials in patRESORCE)

Laboratory Parameter	Stivarga plus BSC (n= 374)	Placebo plus BSC (n=193)	Stivarga plus BSC (n= 374)	Placebo plus BSC (n=193)
	Grade [a]			
	All Grades %		**Grade 3/4 %**	
Blood and lymphatic system disorders				
Hemoglobin decreased	72.5	71.3	6.0	4.8
Thrombocytopenia	63.1	50.0	5.4	0
Neutropenia	13.6	14.9	3.0	1.0
Lymphopenia	67.8	58.5	17.4	11.7
Metabolism and nutrition disorders				
Hypocalcemia	23.4	10.1	0.3	0
Hypokalemia	30.7	9.0	4.3	2.1
Hypophosphatemia	70.4	31.4	33.9	6.9
Hepatobiliary disorders				
Hyperbilirubinemia	78.2	54.5	15.9	15.7
Increased AST	92.7	84.3	17.8	19.9
Increased ALT	70.4	58.6	6.2	4.7
Renal and urinary disorders				
Proteinuria	50.8	36.7	16.7	3.2
Investigations				
Increased INR*	44.2	35.4	0.7	2.1
Increased Lipase	40.5	27.0	14.2	8.7
Increased Amylase	23.0	19.0	2.8	2.7

[a] Common Terminology Criteria for Adverse Events (CTCAE), Version 4.0

* International normalized ratio

BSC = Best Supportive Care

Vital signs

No notable treatment group differences were observed regarding changes seen in the mean changes from baseline in heart rate, body mass index, respiration rate, temperature, and body weight during the study in either treatment group.

ECOG performance status

There were no marked treatment differences with respect to the proportion of subjects with ECOG performance status at any given visit up to Cycle 18 during the course of the study. Altogether 60% of the placebo subjects and 69% of regorafenib subjects maintained ECOG performance status 0 up to Cycle 18 of the study. At end of treatment visit, 41% of the placebo subjects and 30% of the regorafenib subjects maintained performance status of 0.

Child-Pugh assessment

The proportion of subjects with Child-Pugh classification A ranged from 98.7% at Baseline to 55.7% at End of Treatment in the regorafenib group and from 97.4% to 62.2% of the subjects in the placebo group. The proportion of subjects with Child-Pugh classification B ranged from 1.1% at Baseline to 31.6% at End of Treatment in the regorafenib group and 2.6% to 27.6% in the placebo group.

Safety in special populations

Age

Specific categories of adverse events were analysed by age subgroup and results are provided in Table 43. Within the regorafenib group, serious ADRs were reported more frequently in subjects 75 years of age and older (54.7%) than in in subjects 65 to 74 years of age (35.5%) and below 65 years (47.7). In contrast, frequencies within the placebo group were comparable for subjects ≥75 years and between 65-74 years (about 37%-38%). Within the regorafenib group, especially AEs in the SOC vascular disorders were reported more frequently in subjects 75 years of age and older (52.8%) than in in subjects 65 to 74 years of age (39.5%) and below 65 years (29.2%). The same trend was seen in the placebo group. Also AEs in the SOC infections and infestations were reported more frequently in patients of 75 years and older compared to patients 65-74 years (37.7% vs 29.0%), and notably more often in the regorafenib group ≥75 years compared to placebo ≥75 years (37.7% vs 9.5%). For common AEs (>10% overall in regorafenib group) and in subjects 65 years and older, diarrhoea, fatigue, and peripheral oedema were seen more frequently in the regorafenib group in subjects 75 years of age and older than in subjects 65 to 74 years of age. Hypoalbuminemia and anaemia were also seen more frequently in subjects 75 years of age and older than in subjects 65 to 74 years of age. Overall incidences of worst Grade 3, 4, or 5 AEs in placebo subjects were 62.6% and 52.6%, respectively, for subjects <65 and ≥65 years of age.

Table 16. Overview of treatment-emergent adverse events according to specific categories by age (SAF).

	Regorafenib			
	<65 years N=195	65 -74 years N=124	75 -84 years N=53	>85 years N=2
MedDRA PT, v. 19.0	n (%)	N (%)	n (%)	n (%)
Total ADRs	**195 (100.0)**	**124 (100.0)**	**53 (100.0)**	**2 (100.0)**
Serious ADRs - Total	93 (47.7)	44 (35.5)	29 (54.7)	0
- Fatal	29 (14.9)	14 (11.3)	7 (13.2)	0
-Hospitalization/prolong existing hospitalization	86 (44.1)	40 (32.3)	26 (49.1)	0
- Life-threatening	13 (6.7)	7 (5.6)	4 (7.5)	0
- Disability/incapacity	2 (1.0)	2 (1.6)	0	0
- Other (medically significant)	5 (2.6)	7 (5.6)	7 (13.2)	0
AE leading to drop-out	40 (20.5)	35 (28.2)	17 (32.1)	1 (50.0)
Psychiatric disorders (SOC)	20 (10.3)	18 (14.5)	6 (11.3)	1 (50.0)
Nervous system disorders (SOC)	42 (21.5)	34 (27.4)	16 (30.2)	0
Accidents and injuries (SMQ)	9 (4.6)	6 (4.8)	6 (11.3)	0
Cardiac disorders (SOC)	16 (8.2)	7 (5.6)	4 (7.5)	0
Vascular disorders (SOC)	57 (29.2)	49 (39.5)	28 (52.8)	0
Central nervous system vascular disorders (SMQ)	2 (1.0)	1 (0.8)	1 (1.9)	0
Infections and infestations (SOC)	61 (31.3)	36 (29.0)	20 (37.7)	0
Quality of life decreased (PT)	0	0	0	0
	Placebo			
	<65 years N=115	65 -74 years N=57	75 -84 years N=21	>85 years N=0
Total ADRs	**107 (93.0)**	**55 (96.5)**	**17 (81.0)**	0
Serious ADRs - Total	61 (53.0)	21 (36.8)	8 (38.1)	0
- Fatal	25 (21.7)	11 (19.3)	2 (9.5)	0
-Hospitalization/prolong existing hospitalization	48 (41.7)	20 (35.1)	6 (28.6)	0
- Life-threatening	7 (6.1)	3 (5.3)	0	0
- Disability/incapacity	1 (0.9)	0	0	0
- Other (medically significant)	6 (5.2)	2 (3.5)	2 (9.5)	0
AE leading to drop-out	24 (20.9)	10 (17.5)	3 (14.3)	0
Psychiatric disorders (SOC)	7 (6.1)	6 (10.5)	4 (19.0)	0
Nervous system disorders (SOC)	25 (21.7)	18 (31.6)	6 (28.6)	0
Accidents and injuries (SMQ)	4 (3.5)	5 (8.8)	3 (14.3)	0
Cardiac disorders (SOC)	3 (2.6)	2 (3.5)	4 (19.0)	0
Vascular disorders (SOC)	13 (11.3)	6 (10.5)	7 (33.3)	0
Central nervous system vascular disorders (SMQ)	2 (1.7)	1 (1.8)	1 (4.8)	0
Infections and infestations (SOC)	20 (17.4)	13 (22.8)	2 (9.5)	0
Quality of life decreased (PT)	0	0	0	0

Abbreviations: AE = Adverse event; SOC = system organ class; PT = preferred term; SMQ = standardized MedDRA query; SAF = safety analysis set; MedDRA = Medical Dictionary for Regulatory Activities; ADR = adverse drug reaction.

Across all clinical trials, cardiac disorder events (all grades) have been more often (13.7% vs. 6.5%) reported in Stivarga-treated patients aged 75 years or older (N=410), compared to Stivarga-treated patients below 75 years (N=4108).

Gender

Since HCC is a male dominant disease, 88% of the subjects were male, and a much smaller number of female subjects were analysed. A few large (≥10%) differences in incidence rates between male and female subjects were observed. Of AEs that were most common (>10% overall), the most commonly reported AEs with a higher frequency in the regorafenib group in female subjects than male subjects by 10 or more percent were HFSR, pyrexia, nausea, constipation, anaemia, and vomiting. Except for constipation, there was a higher frequency of these AEs also in females in the placebo group, but not by 10 or more percent.

Overall incidences of worst Grade ≥3 in placebo subjects were 60.6% and 43.5%, respectively, for male and female subjects; and 78.0% and 91.3%, respectively in the regorafenib group. Grade 5 AEs were reported in the placebo group in 21.2% of males and 8.7% of females; and in the regorafenib group, in 11.9% of males and 23.9% of females. No deaths in females were assessed by the investigator as drug-related, and most deaths in females were due to general physical health deterioration. Drug-related deaths were reported in 7 males in the regorafenib group, and 2 males in the placebo group.

The popPK covariate analysis across 16 studies confirmed no relevant influence of sex on the PK of regorafenib, M-2 and M-5 which is in line with previous findings.

Race

In the regorafenib treated patients, there was a higher incidence in Asians of HFSR; 67.1% and 42.2%, respectively, for Asian and White subjects. The overall incidence of hand-foot skin reaction (74.8%, CRC, 88.2%, GIST and 67.1%, HCC) was higher in Stivarga-treated Asian patients, compared to other ethnicities. The incidence of Grade 3 hand-foot skin reaction in Asians was 20.5% (CRC), 23.5% (GIST) and 13.5% (HCC).The incidence of Grade 3 hand-foot skin reaction in Asians was 20.5% (CRC), 23.5% (GIST) and 13.5% (HCC). This is currently reflected in sections 4.2, 4.4 and 4.8 of the SmPC. Other AEs reported more frequently in Asian subjects (>10% difference) included ALT increased (20.6% vs 8.1%), AST increased (36.8% vs 13.3%), and hypoalbuminaemia (23.2% vs 5.9%). AEs reported more frequently in White subjects included fatigue (37.8% vs 16.8%) and hypothyroidism (13.3% vs 3.2%).

Increased incidence of HFSR and ALT/AST increases is in line with previous observations. The popPK covariate analysis across 16 studies indicated no relevant influence of race on the PK of regorafenib, M-2 and M-5.

Hepatic impairment

Regorafenib is eliminated mainly via the hepatic route. A total of 124/374 subjects in the regorafenib group and 54/193 in the placebo group had mildly impaired hepatic function at baseline (baseline AST and ALT 1.5 x ULN to 3 x ULN) and 35/374 in the regorafenib group and 16/193 in the placebo group had mildly impaired hepatic function (baseline AST and ALT > 3 x ULN). Overall, there were no notable differences in the incidence of AEs within the different hepatic function categories in the regorafenib treatment group, except for ALT increased, AST increased, hypoalbuminemia, and ascites, all of which had an approximately twofold higher incidence in the 'baseline AST and ALT 1.5 x ULN to 3 x ULN' than in the category 'baseline AST and ALT ≤1.5 x ULN'. Except for hypoalbuminemia, this trend was also seen in placebo subjects.

The proportion of subjects with Child-Pugh classification A ranged from 98.7% at baseline to 55.7% at end of treatment in the regorafenib group and from 97.4% to 62.2% of the subjects in the placebo group. The proportion of subjects with Child-Pugh classification B ranged from 1.1% at baseline to 31.6% at end of treatment in the regorafenib group and 2.6% to 27.6% in the placebo group.

No clinically important differences in exposure were observed between subjects with mild (Child-Pugh A) or moderate (Child-Pugh B) hepatic impairment compared to subjects with normal hepatic function. However, the dataset in moderate hepatic impairment is too limited to provide dose recommendations. No dose adjustment is required in subjects with mild hepatic impairment. Regorafenib has not been studied in subjects with severe hepatic impairment (Child-Pugh C).

Renal impairment

Over 94% of the subjects had normal kidney function at baseline, thus making it difficult to draw meaningful conclusions about comparison of adverse event rates by renal function in this study. Available clinical data indicate similar exposure of regorafenib and its metabolites M-2 and M-5 in subjects with mild, moderate or severe renal impairment compared to subjects with normal renal function. There are no safety signals identified based on the recently completed study (Study 16653) in patients with severe renal impairment (n=6 regorafenib). No dose adjustment is therefore required in patients with mild, moderate or severe renal impairment.

Body mass index/body weight

The overall incidence of any AE and the incidence of most of the common AEs, including hypertension, HFSR, diarrhoea, and fatigue was similar among BMI subgroups (BMI <20, 20 – 25, 25 -30, ≥ 30 kg/m2).

Safety related to drug-drug interactions and other interactions

No new clinically relevant drug-drug interaction signals have been identified by the data submitted for the present Type II variation.

Supportive data

Phase 2 study 14596

Within the phase 2 study, thirty-six patients were treated with intermittent dosing (3 weeks on/1 week off treatment) of regorafenib (160 mg p.o.). The median (mean) overall time under treatment (including interruptions) was 19.5 weeks (34.7 weeks) (range 2 - 127 weeks). The safety profile was in general consistent with that seen in the pivotal trial and did not give rise to new safety signals.

Pooled safety data

Additional supportive data for Stivarga is provided based on the overall safety database from 15 completed (i.e. final or interim clean database available) company-sponsored monotherapy trials in subjects with cancer in any indication (Pool 1). In total, 4518 regorafenib-treated subjects are included in this pool (phase 1 to phase 3). Of note, 2864 (63.4%) of the subjects in Pool 1 were from one study (Study 15967, CONSIGN) in subjects with metastatic CRC. It also includes data with a different dosing schedule and data of subjects, who after unblinding, crossed over from placebo to regorafenib treatment. Pool 2 consists of safety data from HCC (Study 15982, RESORCE). Pool 3 consists of safety data (regorafenib vs placebo) from 4 randomized, double-blind, placebo-controlled Phase 3 studies for the indications CRC (n=636), GIST (n=132), and HCC (n=374). In total, 1142 regorafenib-treated subjects and 580 placebo subjects are included in this pool. Only the blinded treatment phase data are included.

Median time of exposure for regorafenib (including time off drug/interruptions) was 25.4 weeks (range 0.1-95) in pool 2, 18.8 weeks (range 0-193) in pool 1 and 19 weeks (range 0-128) in pool 3. Median dose was 160 mg and ranged from 80-160 mg in pool 2 and pool 3 and from 10-220 mg in pool 1. Patients included in the safety population were mostly male (61.7% pool 1 and 70.4% pool 3 compared to 87.7% pool 2). Median age was around 61, range 18-89. About 60% was below 65 years of age (pool 1 and pool 3). Median BMI was about 25 kg/m^2 and ranged from 13.6 – 55.1 kg/m^2. With regard to race, the overall patient population treated (Pool 1) was White (75%) followed by Asian (12%). Within Pool 3, 54% of patients were White and 35% Asian.

The most common TEAEs reported in the different safety pools are presented in the table below.

Table 17: Most common (>10% overall in any regorafenib treatment group) treatment-emergent adverse events by MedDRA PT (SAF)

	15982 (RESORCE) (Pool 2)		Monotherapy (Pool 1)	Placebo-controlled (Pool 3)	
MedDRA PT, v. 19.0	Placebo N = 193 n (%)	Regorafenib N = 374 n (%)	Regorafenib N = 4518 n (%)	Placebo N = 580 n (%)	Regorafenib N = 1142 n (%)
Any event	**179 (92.7)**	**374 (100.0)**	**4493 (99.4)**	**544 (93.8)**	**1140 (99.8)**
Palmar-plantar erythro-dysesthesia syndrome [a]	13 (6.7)	192 (51.3)	2103 (46.5)	44 (7.6)	607 (53.2)
Diarrhoea	29 (15.0)	154 (41.2)	1620 (35.9)	83 (14.3)	473 (41.4)
Decreased appetite	27 (14.0)	115 (30.7)	1630 (36.1)	120 (20.7)	413 (36.2)
Hypertension	12 (6.2)	115 (30.7)	1568 (34.7)	53 (9.1)	381 (33.4)
Fatigue	47 (24.4)	107 (28.6)	1827 (40.4)	148 (25.5)	388 (34.0)
AST increased	38 (19.7)	92 (24.6)	577 (12.8)	69 (11.9)	182 (15.9)
Blood bilirubin increased	31 (16.1)	91 (24.3)	710 (15.7)	52 (9.0)	194 (17.0)
Abdominal pain	30 (15.5)	79 (21.1)	917 (20.3)	96 (16.6)	238 (20.8)
Pyrexia	13 (6.7)	74 (19.8)	973 (21.5)	64 (11.0)	268 (23.5)
Dysphonia	3 (1.6)	67 (17.9)	1231 (27.2)	25 (4.3)	309 (27.1)
Constipation	21 (10.9)	65 (17.4)	896 (19.8)	94 (16.2)	242 (21.2)
Nausea	26 (13.5)	64 (17.1)	883 (19.5)	98 (16.9)	224 (19.6)
Ascites	31 (16.1)	58 (15.5)	239 (5.3)	42 (7.2)	91 (8.0)
Asthenia	18 (9.3)	56 (15.0)	870 (19.3)	70 (12.1)	213 (18.7)
Oedema peripheral	26 (13.5)	56 (15.0)	316 (7.0)	49 (8.4)	115 (10.1)
ALT increased	21 (10.9)	54 (14.4)	440 (9.7)	42 (7.2)	134 (11.7)
Anemia	21 (10.9)	51 (13.6)	507 (11.2)	49 (8.4)	136 (11.9)
Hypoalbuminemia	14 (7.3)	52 (13.9)	162 (3.6)	23 (4.0)	89 (7.8)
Weight decreased	8 (4.1)	50 (13.4)	1225 (27.1)	45 (7.8)	245 (21.5)
Vomiting	13 (6.7)	47 (12.6)	696 (15.4)	70 (12.1)	170 (14.9)
Abdominal pain upper	17 (8.8)	47 (12.6)	331 (7.3)	35 (6.0)	102 (8.9)
Back pain	17 (8.8)	45 (12.0)	567 (12.5)	53 (9.1)	138 (12.1)
General physical health deterioration	27 (14.0)	44 (11.8)	479 (10.6)	58 (10.0)	100 (8.8)
Cough	13 (6.7)	41 (11.0)	434 (9.6)	52 (9.0)	125 (10.9)
Muscle spasms	4 (2.1)	38 (10.2)	275 (6.1)	11 (1.9)	86 (7.5)
Stomatitis	4 (2.1)	31 (8.3)	599 (13.3)	17 (2.9)	154 (13.5)
Dyspnoea	15 (7.8)	28 (7.5)	618 (13.7)	57 (9.8)	133 (11.6)
Headache	12 (6.2)	24 (6.4)	504 (11.2)	36 (6.2)	105 (9.2)
Rash	14 (7.3)	20 (5.3)	637 (14.1)	28 (4.8)	183 (16.0)
Mucosal inflammation	0	11 (2.9)	621 (13.7)	5 (0.9)	120 (10.5)
Hypophosphataemia	4 (2.1)	36 (9.6)	455 (10.1)	6 (1.0)	79 (6.9)

a: Hand foot skin reaction (HFSR) per CTCAE v 3.0 terminology.
MedDRA = Medical Dictionary for Regulatory Activities; PT = Preferred term; AST = Aspartate aminotransferase; ALT = Alanine aminotransferase; SAF = Safety analysis Set
Order of AEs: descending frequency in regorafenib treatment group of Study 15982 (Pool 2).

In the placebo-controlled phase III trials (pool 3), the overall incidence of haemorrhage was 18.2% in patients treated with regorafenib and 9.5% in patients receiving placebo. Most cases of bleeding events in patients treated with regorafenib were mild to moderate in severity (Grades 1 and 2: 15.2%), most notably epistaxis (6.1%). Fatal outcome in patients treated with regorafenib was uncommon (0.7%), and included cerebral, respiratory, gastrointestinal and genitourinary events (see section 4.8 of the SmPC).

In the placebo-controlled phase III trials (pool 3), infections were more often observed in patients treated with regorafenib, compared to patients receiving placebo (all grades: 31.6% vs. 17.2%). Most infections in patients treated with regorafenib were mild to moderate in severity (Grades 1 and 2: 23.0%), and

included urinary tract infections (5.7%), nasopharyngitis (4.0%), mucocutaneous and systemic fungal infections (3.3%) as well as pneumonia (2.6%). Fatal outcomes associated with infection were observed more often in patients treated with regorafenib (1.0%), compared to patients receiving placebo (0.3%), and were mainly respiratory events(see section 4.8 of the SmPC).

In the placebo-controlled phase III trials (pool 3), the overall incidence of hand-foot skin reaction was higher in patients treated with regorafenib, compared to patients receiving placebo (all grades: 51.4% vs. 6.5% CRC, 66.7% vs. 15.2% GIST and 51.6% vs.7.3% HCC). Most cases of hand-foot skin reaction in patients treated with regorafenib appeared during the first cycle of treatment and were mild to moderate in severity (Grades 1 and 2: 34.3%%, CRC, 44.7%, GIST and 39.3%, HCC). The incidence of Grade 3 hand-foot skin reaction was 17.1% (CRC), 22.0% (GIST) and 12.3% (HCC).

In the placebo-controlled phase III trials (pool 3), the overall incidence of hypertension was higher in patients treated with regorafenib, compared to patients receiving placebo (29.6% vs. 7.5% CRC, 60.6% vs. 25.8% GIST and 31.0% vs. 6.2% HCC). Most cases of hypertension in patients treated with regorafenib appeared during the first cycle of treatment and were mild to moderate in severity (Grades 1 and 2: 20.9%, CRC, 31.1%, GIST and 15.8% HCC). The incidence of Grade 3 hypertension was 8.7% (CRC), 27.3% (GIST) and 15.2% (HCC). One case of Grade 4 hypertension was reported in the GIST trial.

In the placebo-controlled phase III trials (pool 3), the overall incidence of treatment emergent proteinuria was 9.1% in patients treated with regorafenib, compared to 1.9% in patients receiving placebo. Of these events, 35.6% in the regorafenib arm and 54.5% in the placebo arm have been reported as not recovered/not resolved.

Adverse drug reactions

The table of ADRs in section 4.8 of the SmPC has been updated to reflect the new clinical data available. The denominator (4,800) used for the calculation of frequencies includes all cancer patients treated with regorafenib either in monotherapy or in combination with other anticancer drugs (i.e. FOLFOX, FOLFIRI) studied in completed and ongoing company-sponsored clinical trials as of July 2016.

Frequencies of all 47 ADRs previously determined based on pooled data from placebo-controlled phase III trials 14387-CORRECT and 14874-GRID were reassessed based on updated pooled data also including placebo-controlled studies 15808-CONCUR and 15982-RESORCE. Few changes have been reflected for increases in transaminases (shift from “common” to “very common” category), alopecia and headache (shift from “very common” to “common” category). Pancreatitis was the only new ADR included in the frequency category “uncommon”. The ADR “Musculoskeletal stiffness” has been reworded to “Muscle spasms” in section 4.8 of the SmPC as it reflects the majority of PTs reported.

Table 18: Frequencies (crude incidence) of ADRs based on review of TEAE data from placebo-controlled phase III trials

ADR	*Frequency category in current ADR table*	Updated pooled frequency data (regorafenib arm; n=1142) Studies 14387-CORRECT, 14874-GRID, 15808-CONCUR + 15982-RESORCE
Pain*	*very common*	55.78%
Hand-foot skin reaction	*very common*	53.24%
Asthenia/fatigue	*very common*	50.44%
Diarrhea	*very common*	41.51%
Decreased appetite and food intake	*very common*	36.16%
Hypertension	*very common*	33.63%
Infection	*very common*	31.61%
Dysphonia	*very common*	27.06%
Hyperbilirubinemia	*very common*	24.78%
Fever	*very common*	23.47%
Weight loss	*very common*	21.45%
Rash	*very common*	20.14%
Nausea	*very common*	19.61%
Hemorrhage	*very common*	18.21%
Increase in transaminases	*common*	17.69%
Vomiting	*very common*	14.89%
Anemia	*very common*	14.01%
Stomatitis	*very common*	13.49%
Thrombocytopenia	*very common*	12.43%
Mucosal inflammation	*very common*	10.51%
Alopecia	*very common*	9.54%
Headache	*very common*	9.19%
Proteinuria	*common*	9.11%
Hypokalaemia	*common*	8.14%
Hypophosphatemia	*common*	8.14%
Musculoskeletal stiffness	*common*	7.79%
Leukopenia	*common*	7.09%
Hypothyroidism	*common*	6.92%
Increase in lipase	*common*	6.65%
Hyponatremia	*common*	5.78%
Taste disorders	*common*	5.69%
Dry skin	*common*	5.25%
Dry mouth	*common*	4.99%
Hypocalcemia	*common*	4.20%
Increase in amylase	*common*	2.63%
Hypomagnesemia	*common*	2.36%
Exfoliative rash	*common*	1.84%
Tremor	*common*	1.40%
Abnormal International normalized ratio	*common*	1.14%
Gastroesophageal reflux	*common*	1.14%
Gastroenteritis	*common*	1.05%
Hyperuricemia	*common*	1.05%
Gastrointestinal fistula	*uncommon*	0.79%
Erythema multiforme	*uncommon*	0.61%
Myocardial ischemia	*uncommon*	0.61%
Nail disorder	*uncommon*	0.53%
Myocardial infarction	*uncommon*	0.26%

* Pool of relevant PTs according MLG concept has been augmented compared to last frequency determination

There were no changes in the frequencies of 8 SAEs (gastrointestinal perforation, hypersensitivity reaction, severe liver injury, hypertensive crisis, keratoacanthoma/squamous cell carcinoma of the skin, PRES, SJS, and TEN).

Discontinuation due to adverse events

There was a higher frequency of withdrawals of study medication due to TEAEs in the regorafenib group with 24.9% (n=93) of subjects compared with 19.2% (n=37) of subjects in the placebo group. The majority of these TEAEs were CTCAE grades 3 (15.0% regorafenib vs 13.0% placebo) or 4 (4.8% regorafenib vs 4.7% placebo). TEAEs leading to discontinuation of study drug ≥1% of subjects in the regorafenib group were general physical health deterioration (3.7%), AST increased (2.4%) and blood bilirubin increased (2.1%), HFSR (1.9%), hepatic failure (1.6%) and asthenia (1.1%). TEAEs leading to discontinuation of study drug in the placebo group were blood bilirubin increased (3.6%), general physical health deterioration (2.1%), ascites (2.1%), fatigue, hepatic failure, hepatic function abnormal and AST increased (each 1.6%), and asthenia and hepatic haemorrhage (each 1.0%).

The incidence of drug-related AEs leading to discontinuation of study drug was 10.4% in the regorafenib group and 3.6% in the placebo group. In the regorafenib group, the most common AEs leading to discontinuation of study drug were HFSR (1.9%) and AST increased (2.4%). All other drug-related AEs leading to discontinuation were reported in <1% of subjects in the placebo group or regorafenib group.

Overall, the incidence of AEs leading to permanent discontinuation of study drug were higher than previously reported in the combined placebo-controlled trials for CRC and GIST (15.2% regorafenib vs 11.6% placebo (EMEA/H/C/002573/II/0001).

Dose interruptions due to TEAEs

There was a higher frequency of interruptions of study medication due to TEAEs in the regorafenib group with 58.3% of subjects compared with 29.0% of subjects in the placebo group. The majority of these TEAEs were CTCAE Grade 3 (41.2% regorafenib vs 19.7% placebo). Grade 4 TEAEs were reported in 5.1% of patients on regorafenib and 3.1% on placebo. Treatment-emergent AEs leading to dose interruptions in at least 4% of subjects in the regorafenib treatment group included HFSR (11.2%), blood bilirubin increased (5.9%), AST increased (5.1%), fatigue (4.5%), and diarrhoea (4.0%).

Dose reductions due to TEAEs

Overall the frequency of dose reductions due to TEAEs was notably higher in the regorafenib group at 47.9% compared with 7.8% in the placebo group. The majority of the TEAEs were CTCAE Grade 2 or 3. Treatment-emergent AEs leading to dose reductions in at least 4% of subjects in the regorafenib treatment group included HFSR (20.1%), and diarrhoea (4.3%). The majority of TEAEs was of Grade 2 (n=78, 20.9%) and Grade 3 (n=62, 16.6%) severity.

Overall, dose modifications due to AEs were frequently reported in the RESORCE trial (68.2% vs 31.1% placebo), and in line with that reported previously for CRC and GIST (67.2% vs 21.3%).

Post marketing experience

The first approval for regorafenib (Stivarga) was granted in the USA on 27 SEP 2012. As of 31 May 2016 and based on current sales data, at present around 90% of the commercial regorafenib tablets are used

to treat CRC patients and around 10% to treat GIST patients. It is estimated that up to 31 May 2016 around 79,026 patients have been exposed to regorafenib in post marketing setting.

The SAEs reported so far in the post-marketing setting (as of 01 JUL 2016) are consistent with the known safety profile of regorafenib outlined in current product information. To date, no new safety signal for regorafenib has been observed based on the received post-marketing reports.

2.5.1. Discussion on clinical safety

The safety data for regorafenib in HCC is primarily derived from one placebo-controlled phase 3 study including 374 patients treated with a regorafenib starting dose of 160 mg once daily for three weeks followed by one week off treatment. The median dose was 159.3 mg (82.4-160) with approximately half of the patients (49.2%) receiving 160 mg/day. The median duration of treatment (including time interrupted) was 15.6 weeks (range 0.1-128 weeks), 13.9% of patients had a treatment duration ≥12 months. Therefore, limited long-term safety data is available in HCC. However, long-term safety data for regorafenib is available from other indications and post-marketing and this does not indicate delayed toxicity. Further, the patient population with HCC has a reduced life expectancy. Therefore it is sufficient to follow-up long-term safety in HCC through regular pharmacovigilance activities.

Patients included in the study had progressed on sorafenib therapy, whereas subjects were excluded in case of permanent discontinuation of sorafenib therapy due to sorafenib-related toxicity. The safety in patients with HCC not tolerating sorafenib is therefore unknown. As sorafenib belongs to the same pharmacological class, there is a risk of underreporting of certain adverse events and especially serious adverse events in HCC. As a consequence, a warning has been included in section 4.4 of the SmPC to reflect that the tolerability of regorafenib has not been established in patients who discontinued sorafenib therapy due to sorafenib-related toxicity or only tolerated a low dose (< 400 mg daily) of sorafenib.

It should be noted that patients included in the study were relatively healthy with mostly ECOG PS=0 (about 66%), well preserved liver function (Child Pugh: 98%) and lack of significant comorbidities like cardiac disease, uncontrolled hypertension and presence of untreated large oesophageal varices. Hence, the MAH will conduct a non-interventional PASS in order to provide additional information on safety in a less healthy population excluded from the pivotal study (see RMP).

Adverse events

AEs were most frequently reported in the SOCs gastrointestinal disorders, general disorders and administration site disorders and skin and subcutaneous disorders. Most frequently reported adverse events were HFSR (51.6% vs 7.3% placebo), diarrhoea (41.2% vs 15.0% placebo), decreased appetite (30.7% vs 14.0% placebo), hypertension (30.7% vs 6.2% placebo) and fatigue (28.6% vs 24.4% placebo). Grade 3/4 events were reported at a higher frequency for regorafenib than for placebo (66.3% vs 38.9%). The most common grade 3 AEs in the regorafenib arm were hypertension (14.7% regorafenib vs 4.7% placebo) and HFSR (12.3% regorafenib vs 0.5% placebo). The most common (≥ 1%) Grade-4 events in the regorafenib group included lipase increased (regorafenib group 1.9% vs placebo group 0.0%) and AST increased (regorafenib group 1.1% vs placebo group 1.6%).

HFSR, diarrhoea, decreased appetite, hypertension, and fatigue were also the most commonly reported drug-related AEs occurring ≥20% of patients. Grade 3/4 drug-related events were reported at a higher frequency for regorafenib than for placebo. The most common grade 3 AEs in the regorafenib arm were hypertension (12.8% regorafenib vs 3.1% placebo) and HFSR (12.3% regorafenib vs 0.5% placebo).

HSFR, hypertension, decreased appetite and fatigue most frequently occurred within the first weeks of treatment, whereas diarrhoea occurred later during treatment. Most cases were of grade 1-2 severity and most events resolved by dose modifications and application of standard of care treatment.

The overall safety profile resembles that known for regorafenib and for drugs affecting VEGFR and other tyrosine kinase-mediated pathways in general. Pancreatitis was the only new ADR identified reported in 1.6% of regorafenib treated patients in HCC (0% placebo), the majority of events being of mild to moderate severity whereas only one SAE (grade 1) was considered drug-related. Pancreatitis has now been added to section 4.8 (frequency "uncommon") of the SmPC. No fatal events were reported and no additional warnings are required.

AEs were in general comparable within the subgroups analysed. HFSR and increases in transaminases had a higher incidence in Asians, which has been observed before. Although some AEs occurred more frequently in female, the overall female population was limited since HCC is a male dominant disease and no firm conclusions can be drawn. At the moment, there are no clear signals for gender differences based on the known PK profile of regorafenib and previous studies performed. Further, cardiovascular events and AEs in the SOC infections and infestations appear higher in patients of 75 years and older, but number of patients are limited (n=53 for regorafenib and n=21 placebo). No clear signals for differential exposure were identified based on pharmacokinetics over the studied range of 29 to 85 years. In addition, in the popPK covariate analysis across 16 studies which included evaluation within different age categories, age had no relevant influence on the PK of regorafenib, M-2 and M-5 which is in line with previous findings. No dose adjustment is therefore considered necessary in elderly patients.

Serious adverse events / Death / Other significant effects

Similar frequencies of occurrence of SAEs were observed in both treatment groups with 46.6% in the placebo group and 44.4% in the regorafenib group. Drug-related SAEs were reported at higher frequencies for regorafenib (10.4% vs 2.6%). The most commonly reported SAEs in the regorafenib arm were general physical health deterioration, ascites and hepatic failure which were reported at comparable or higher frequencies in the placebo-group. These mostly likely reflect the underlying malignancy.

Deaths occurred more often in the placebo arm (19.7% vs 13.4% regorafenib), mainly due to clinical progression of disease. Seven cases were reported as treatment-related, fatal adverse events occurred in a single subject and no pattern was seen.

A higher incidence of grade 5 infections with fatal outcome was reported for regorafenib in HCC (1.3% vs 0%) and infection has been added newly as an important identified risk. This is agreed upon based on the overall increased risk in placebo-controlled trials (1% regorafenib vs 0.3% placebo). Most fatal infections concerned respiratory infections and none was reported as drug-related. Infections are a known commonly occurring ADR and concern those typically seen in cancer subjects (e.g. respiratory, urinary tract, and sepsis). The pathomechanism of regorafenib-related infection is unknown, and different potential mechanisms are discussed by the MAH in the RMP. These include blockade of haematopoietic stem-cell cycling, differentiation and haematopoietic recovery after bone-marrow suppression, or modulation of immune cells (T cells) that are present in the tumour microenvironment and consequent host response to infections. The review of the 7 cases of fatal infectious events in the RESORCE trial and literature data on treatment of cancer patients with VEGFR-TKIs in general, did not reveal any potential risk factors for (fatal) infectious events. The apparent higher number of fatal infectious events in patients with HCC on regorafenib compared to GIST and CRC could be a chance finding.

In cases of worsening infection events, interruption of regorafenib treatment should be considered. Follow-up through routine risk minimisation measures and risk mitigation by a warning in section 4.4 of the SmPC is considered sufficient.

There were no other new safety signals based on the HCC study taking into account the identified important and potential risks. Special attention had been given to hepatoxicity and haemorrhage in the HCC trial given the known toxicity of regorafenib. Laboratory abnormalities of ALT, AST, and bilirubin and hepatic failure/injury events were higher than for other indications, however, this was also seen in the placebo group. SAEs were reported at higher frequencies in placebo than for regorafenib and hepatic failure events of grade 3 and more were more frequently reported in the placebo group (4.7% vs 2.4% regorafenib). Currently, the data do not indicate differences in susceptibility towards regorafenib-induced severe liver injury between distinct underlying tumour types. However, it may be difficult to detangle drug-related from disease-related events in HCC. Most patients had mildly impaired hepatic function. Within the group of patients with moderate hepatic impairment, ALT/AST increased, hypoalbuminemia, and ascites, had an approximately twofold higher incidence which, except for hypoalbuminemia, was also seen in placebo subjects. Close monitoring of safety is already recommended for patients with moderate hepatic impairment including dose modification recommendations, and use in patients with severe hepatic impairment is not recommended. These risk management measures are also considered adequate for patients with HCC.

Overall incidence of haemorrhagic events was comparable between treatment groups, and in line with that reported for other indications for regorafenib (CRC: 19.3% vs 6.9%; GIST: 14.4% vs 3.0%). SAEs occurred at low frequencies but was somewhat higher for both regorafenib and especially placebo in HCC (5.1% vs 8.3%) than for CRC (2.4% vs 0.6%) and GIST (3.8% vs 0%). Patients with HCC may be at an increased risk of upper gastrointestinal haemorrhages and especially oesophageal varices bleeding due to portal hypertension. Only patients screened for oesophageal varices and treated were included in the study, which may reduce the risk of bleedings. A precautionary statement has been included in section 4.4 of the SmPC to recommend that screening for and subsequent treatment of large oesophageal varices in patients with liver cirrhosis should be performed as per standard of care before starting treatment with regorafenib.

Overall, the laboratory toxicity profile in the RESORCE trial was as expected for this class of drug and was consistent with that previously observed during the regorafenib clinical development program. However, as expected in HCC subjects owing to the underlying liver disease (e.g. cirrhosis, hepatitis) elevations in AST, ALT, and bilirubin were more frequently recorded in the RESORCE trial than previously seen in the CRC and GIST subjects. There were no new signals based on laboratory parameters.

Discontinuations/dose modifications

No dose finding was performed for HCC and the dose was similar to that of CRC and GIST. Dose reduction and/or temporary interruption of regorafenib is already recommended within the SmPC in case of specific adverse events/laboratory abnormalities, the minimal recommended dose is 80 mg. Dose modifications due to AEs were frequently reported for regorafenib (68.2%), it remains uncertain whether a lower starting dose could reduce the frequency of AEs at comparable efficacy. Nevertheless, comparable high dose modification rates were reported previously for CRC and GIST. In most cases, treatment could be continued; permanent discontinuation was reported in 24.9% regorafenib vs 19.2% placebo. The difference in drug discontinuation appears related to AEs not associated with clinical disease progression (12.4% vs 6.2%) whereas discontinuation due to progressive disease was comparable among treatment groups (14%-15%). The latter may be explained by the fact that regorafenib rather stabilises disease and patients on regorafenib had longer follow-up. Most common AEs leading to permanent discontinuation were general physical health deterioration (3.7%), AST increased (2.4%) and blood bilirubin increased (2.1%). There was no increase in specific adverse events leading to permanent discontinuation. The overall discontinuation rate may be considered acceptable taking into account the observed benefit in the patient population with severe disease and limited treatment options.

Pooled data

The applicant compared the safety data as reported for HCC to pool 1 (regorafenib monotherapy) and pool 3 (placebo-controlled studies) data. In general, the safety profile was comparable between all pools. Consistent with the underlying disease in HCC subjects, the incidences of ascites, peripheral oedema, and hypoalbuminemia were higher (with a difference of at least 5%) in the regorafenib treated subjects pool 2 than for those in pool 1 and pool 3. For ascites and peripheral oedema, the incidences in the placebo group in pool 2 were considered similar to those in the regorafenib treatment group (about 14%-16%); for hypoalbuminemia, the incidence in the placebo group of pool 2 was lower than for regorafenib (7.3% vs 13.9%) but higher than that in the placebo group of pool 3 (4.0%). The incidences of AST increased, ALT increased and bilirubin increased were also higher in both treatment groups in pool 2 than in pools 1 and 3. On the other hand, the incidences of fatigue, stomatitis, rash, and mucosal inflammation were higher in the regorafenib groups of pool 1 and pool 3 (with a difference of at least 5%) compared to pool 2. There were no new signals based on laboratory parameters. As expected in HCC subjects owing to the underlying liver disease (e.g. cirrhosis, hepatitis) elevations in AST, ALT, and bilirubin were more frequently recorded in the RESORCE trial than previously seen in the CRC and GIST subjects.

The incidences of dose modifications were comparable across the pools, however, the incidence of AEs leading to discontinuation of study drug were highest in HCC in both regorafenib and placebo group.

Overall, there was no pattern seen in grade 5 adverse events and the events were distributed across different MedDRA SOCs.

Overall, the safety profile as reported in the pool 3 and pool 1 did not raise new safety signals except for pancreatitis which was classified as a new ADR and infection which has been added newly as an important identified risk based on the additional cases reported in the RESORCE study.

2.5.2. Conclusions on clinical safety

The safety profile for regorafenib in patients with HCC has been demonstrated in a reasonable number of patients with HCC which allow determination of uncommon adverse events. The overall safety profile is in line with that is known for regorafenib and mainly related to its primary mechanism of actions as a tyrosine kinase inhibitor. Most events were of grade 3 severity and can be resolved by dose modifications and concomitant medications. Pancreatitis is the only new ADR, whereas infections have been newly added as important identified risk. A warning on infections has been included in section 4.4 of the SmPC as well which is considered sufficient. Follow-up through routine pharmacovigilance activities for long-term safety in HCC is considered sufficient. There does not appear to be an increased risk of severe liver toxicity in patients with HCC. Only patients screened for large oesophageal varices and treated were included in the study. A precautionary statement has been included in section 4.4 of the SmPC to address the known risk of bleedings.

The main uncertainty in the safety data concerns the exclusion of patients who permanently discontinued sorafenib therapy due to sorafenib-related toxicity. The safety in patients with HCC not tolerating sorafenib is therefore unknown. As sorafenib belongs to the same pharmacological class, there might have been an underreporting of certain adverse events and especially serious adverse events in HCC.

The CHMP considers the following measures necessary to address issues related to safety:

The MAH will conduct a non-interventional PASS to address uncertainties on safety related to certain populations excluded from the pivotal trial: e.g. Child Pugh B and ECOG PS2 and patients stopping previous treatment with sorafenib due to toxicity.

2.5.3. PSUR cycle

The PSUR cycle remains unchanged.

The next data lock point will be 26 September 2017.

The annex II related to the PSUR, refers to the EURD list which remains unchanged.

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 5 could be acceptable if the applicant implements the changes to the RMP as described in the PRAC endorsed PRAC Rapporteur assessment report.

The applicant implemented the changes in the RMP as requested by PRAC and CHMP.

The CHMP endorsed the Risk Management Plan version 5.2 with the following content:

Safety concerns (changes shown in red)

Summary of safety concerns	
Important identified risks	- Severe drug-induced liver injury (DILI) - Cardiac ischemic events - Hypertension and hypertensive crisis - Haemorrhage - Hand-foot skin reaction (HFSR) - Posterior reversible encephalopathy syndrome (PRES) - Gastrointestinal (GI) perforation and fistulae - Stevens-Johnson syndrome (SJS)/Toxic epidermal necrolysis (TEN) - *Infection*
Important potential risks	- Wound healing complications - Interstitial lung disease (ILD) - Atrial fibrillation - Reproductive and developmental toxicity - Thrombotic microangiopathies (TMA)
Missing information	- Safety in severe hepatic impairment - Safety in children - Safety in patients with a cardiac history - ~~Safety in severe renal impairment~~ - Activity in ~~KRAS mutated tumours or other~~ biomarker-defined tumour subtypes - *Safety in HCC patients who discontinued prior sorafenib therapy due to sorafenib-related toxicity*

For the current application for HCC, the risk of 'infections' was added as an important identified risk to the list of safety specifications. Furthermore following completion of a phase I study which evaluated the pharmacokinetics and safety of regorafenib in cancer subjects with severe renal impairment the missing information 'safety in patients with severe renal impairment' was deleted from the safety concerns.

Finally patients who experienced severe drug toxicity of sorafenib leading to permanent discontinuation of treatment were excluded from the pivotal phase III trial in HCC patients. As a consequence "Safety in HCC patients who discontinued prior sorafenib therapy due to sorafenib-related toxicity" was included as missing information.

Pharmacovigilance plan (changes shown in red)

Study / activity type, title and category (1-3)	Objectives	Safety concerns addressed	Status (planned, started)	Date for submission of interim or final reports (planned or actual)
Study 19244: REFINE: Regorafenib observational study in hepatocellular carcinoma (category 3)	The primary objective of this study is to evaluate the safety of regorafenib in patients with unresectable HCC, including incidence of all treatment-emergent adverse events (TEAEs) and dose modifications due to TEAEs in real-world practice conditions.	Missing information: Safety in HCC patients who discontinued prior sorafenib therapy due to sorafenib-related toxicity	Protocol finalized (07 MAR 2017) Planned FPFV: Q2/3 2017	Final study report Oct 2022

A PASS category 3 study was added to the Pharmacovigilance plan in order to address the newly added missing information "Safety in HCC patients who discontinued prior sorafenib therapy due to sorafenib-related toxicity"

Risk minimisation measures (changes shown in red)

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
Important identified risks		
Severe drug-induced liver injury (DILI)	**SmPC Sections:** 4.2 Posology and method of administration 4.4 Special warnings and precautions for use 4.8 Undesirable effects.	Not applicable

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
Cardiac ischemic events	**SmPC Sections:** 4.4 Special warnings and precautions for use 4.8 Undesirable effects.	Not applicable
Hypertension and hypertensive crisis	**SmPC Sections:** 4.4 Special warnings and precautions for use 4.8 Undesirable effects.	Not applicable
Hemorrhage	**SmPC Sections:** 4.4 Special warnings and precautions for use 4.8 Undesirable effects.	Not applicable
Hand-foot skin reaction (HFSR)	**SmPC Sections:** 4.2 Posology and method of administration 4.4 Special warnings and precautions for use 4.8 Undesirable effects.	Not applicable
Posterior reversible encephalopathy syndrome (PRES)	**SmPC Sections:** 4.4 Special warnings and precautions for use 4.8 Undesirable effects.	Not applicable
Gastrointestinal (GI) perforation and fistulae	**SmPC Sections:** 4.4 Special warnings and precautions for use 4.8 Undesirable effects.	Not applicable
Stevens-Johnson syndrome (SJS)/Toxic epidermal necrolysis (TEN)	**SmPC Sections:** 4.8 Undesirable effects.	Not applicable
Infection	***SmPC Sections:*** *4.4 Special warnings and precautions for use* *4.8 Undesirable effects*	*Not applicable*
Important potential risks		
Wound healing complications	**SmPC Sections:** 4.4 Special warnings and precautions for use	Not applicable
Interstitial Lung Disease (ILD)	None	Not applicable
Atrial fibrillation	None	Not applicable
Reproductive and developmental toxicity	**SmPC Sections:** Section 4.6. 'Fertility, pregnancy and lactation'	Not applicable
Thrombotic microangiopathies (TMA)	None	Not applicable
Missing information		
Safety in severe hepatic impairment	**SmPC Sections:** Section 4.2 ('Posology and method of administration'), Section 4.4 ('Warnings and Precautions')	Not applicable

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
	Section 5.2 ('Pharmacokinetic Properties')	
Safety in children	**SmPC Sections:** Section 4.2 'Posology and method of administration'	Not applicable
Safety in patients with a cardiac history	**SmPC Sections:** Section 4.4 'Warnings and precautions for use'	Not applicable
~~Safety in severe renal impairment~~	~~**SmPC Sections:**~~ ~~Section 4.2 'Posology and method of administration'~~	~~Not applicable~~
Activity in ~~KRAS mutated tumours or other~~ biomarker-defined tumour subtyps	None	Not applicable
Safety in HCC patients who discontinued prior sorafenib therapy due to sorafenib-related toxicity	SmPC Sections: Section 4.4 'Warnings and precautions for use'	Not applicable

The table of risk minimisation measures was adjusted to reflect the changes to the list of safety concerns, but routine risk minimisation measures were considered sufficient to minimise the newly added risks of the regorafenib in the new indication.

2.7. Update of the Product information

As a consequence of this new indication, sections 4.1, 4.2, 4.4, 4.8 and 5.1 of the SmPC have been updated. Particularly, new warnings with regard to the increased incidence of infections, screening for large oesophageal varices and in patients who had issues in tolerating sorafenib has been added to the product information. The Package Leaflet has been updated accordingly.

In addition, the list of local representatives in the PL has been revised to amend contact details for the representatives of United Kingdom.

2.7.1. User consultation

A user consultation with target patient groups on the package leaflet has been performed on the basis of a bridging report making reference to Stivarga. The bridging report submitted by the MAH has been found acceptable.

3. Benefit-Risk Balance

3.1. Therapeutic Context

3.1.1. Disease or condition

HCC is a cancer that usually occurs in the setting of liver cirrhosis, because of chronic infections with hepatitis B virus or hepatitis C virus, alcohol consumption, non-alcoholic steatohepatitis, or diabetes (EASL&EORTC 2012).

It is the third-leading cause of cancer-related death, and the global incidence is rising, with approximately 700,000 cases diagnosed worldwide in 2012 alone (Lozano et al. 2010, Torre et al. 2015).

3.1.2. Available therapies and unmet medical need

For patients who are not or who are no longer candidates for loco regional therapy, the oral multikinase inhibitor sorafenib is the only systemic treatment currently approved in the EU. The approval was based on the results of a large Phase-3 clinical trial (Study 100554 SHARP) conducted in 602 HCC patients (Llovet et al. 2008). The study demonstrated significantly increased survival under sorafenib (plus BSC) compared to placebo (plus BSC) (HR 0.69; p=0.0005), with a median survival rate for the sorafenib arm of 10.6 months, compared with 7.9 months for the placebo arm.

3.1.3. Main clinical studies

The pivotal study supporting this application is study 15982 (RESORCE), a multi-centre, multi-national, randomized, double-blind, placebo-controlled phase III trial comparing regorafenib plus BSC versus placebo plus BSC in patients with HCC who have progressed after sorafenib. A total of 573 patients were randomized (2:1) to receive either regorafenib or matching placebo 160 mg OD orally for 3 weeks followed by 1 week off therapy (cycle of 4 weeks).

3.2. Favourable effects

The results of the final OS analysis based on 373 events (65%) (cut-off 29 Feb 2016) show a statistically significant improvement in OS for regorafenib compared with placebo (HR 0.627, 95% CI 0.50-0.785, p=0.00002), with a gain in median OS of about 2.8 months in favour of regorafenib (median OS 10.6 vs 7.8 months, respectively). The robustness of the OS effect is supported by several sensitivity and subgroup analyses, the results of which are essentially in line with the primary analysis. No significant imbalance in post-study therapies was observed. An updated OS analysis (cut-off date 23 January 2017) has been provided confirming the results of the primary analysis

Regarding the secondary endpoints, consistency was observed in terms of PFS according to both mRECIST (HR 0.455, 95% CI 0.371-0.558, median PFS 1.5 and 3.1 months with placebo and regorafenib, respectively) and RECIST 1.1 (HR 0.427, 95% CI 0.348-0.524, median PFS 1.5 vs 3.4 months, respectively), as well as TTP (mRECIST: HR 0.442, 95% CI 0.358-0.545, median TTP 3.2 vs 1.5 months, respectively).

Overall response rate (ORR: CR+PR) in regorafenib treated patients was low (10.6%), but higher than the placebo arm (4.1%). Disease control rate was significantly higher in the regorafenib arm compared to the placebo arm (64.5% vs 36.1%, respectively).

Consistent results in terms of median OS, TTP, ORR and DCR were reported in the supportive phase II single arm 14596 study (median OS 13.8 months, median TTP 4.3 months, ORR: 2.8%, DCR: 72.2%). Of note, enrolment criteria were quite similar in the two (RESORCE and 14596) studies, but in the 14596 trial the majority of patients (72%) were Whites.

3.3. Uncertainties and limitations about favourable effects

In the 15982 and 14596 studies, patients who had to discontinue sorafenib due to toxicity or for whom the sorafenib dose had to be reduced to less than 400 mg OD were excluded. Therefore, no data on the efficacy and safety of regorafenib in this subgroup of the population are available. This has been reflected as a warning in section 4.4 of the SmPC.

In contrast with the population included in the pivotal and supportive studies (as indicated by their enrolment criteria) the HCC patient population treated in clinical practice is very heterogeneous in terms of disease burden/presence of comorbidity and includes also patients with ECOG PS >1, Child Pugh B and C, with significant renal impairment, with cardiovascular co-morbidities, with untreated/uncontrolled oesophagus varices, requiring anti-viral therapy for HBV and HCV and/or patients stopping sorafenib due to unacceptable toxicity. Such patients were not enrolled in the RESORCE study and this has been reflected in section 5.1 of the SmPC.

The OS effect appears less pronounced (and not statistically significant) in several subgroups of the population (females, patients with ECOG PS 1, with underlying hepatitis C or alcohol abuse as well as in absence of extra-hepatic disease). This could be related to the relatively limited sample size of these subgroups.

The low ORR observed in the regorafenib arm (10.6%) is disappointing. The significant difference between the two study arms in DCR, PFS and OS appears to be essentially driven by patients experiencing disease stabilisation under treatment, with therefore minor effects on disease-related symptoms.

Indeed, assessments of Quality of Life/PRO's in the pivotal RESORCE trial according to the EQ-5D and the Fact Hep scores showed no remarkable difference between the two study arms regarding deterioration of Quality of Life. However, a numerical trend towards lower scores (and therefore worse Quality of Life and more symptoms) for patients treated with regorafenib is consistently observed in the evaluation of the single domains of the questionnaires, in particular at the later cycles of treatment, achieving also the MID, suggesting a potential detrimental effect of regorafenib due to treatment-related toxicity.

It is regrettable that submission of tumour material/plasma was optional and not mandatory for patients enrolled in the pivotal RESORCE study. Indeed, considering that regorafenib is presented as a multiple tyrosine kinase inhibitor, a compelling biomolecular analysis could have helped to identify a marker predictive for tumour response. The MAH is recommended to provide the results of the genetic biomarker analysis once available.

3.4. Unfavourable effects

The safety profile of regorafenib in patients with HCC in general resembles what is known for the already authorised indications of CRC and GIST and what is known for products inhibiting VEGFR and other tyrosine kinase-mediated pathways. Over 90% of patients on regorafenib experienced at least one TEAE or a drug-related TEAE. The most frequently reported adverse events for regorafenib were HFSR (51.6%), diarrhoea (41.2%), and hypertension (30.7%). Hypertension (14.7%) and HFSR (12.3%) were also the most commonly reported grade 3 AEs in the regorafenib arm. Most commonly reported grade 4 AEs were lipase increased (1.9%) and AST increased (1.1%). HFSR, diarrhoea, decreased appetite,

hypertension, and fatigue were also the most commonly reported drug-related AEs occurring ≥20% of patients. HFSR, hypertension, decreased appetite and fatigue most frequently occurred within the first weeks of treatment, whereas diarrhoea occurred later during treatment. Most cases were of grade 1-2 severity, for hypertension events this was grade 2 or 3, and most events resolved by dose modifications and/or application of standard of care treatment. Dose modification due to regorafenib was seen in 68.2% of patients; permanent discontinuation occurred in 24.9% on regorafenib compared to 19.2% on placebo.

Pancreatitis was the only new ADR identified reported in 1.6% of regorafenib treated patients in HCC (0% placebo), the majority of events being of mild to moderate severity. The overall incidence in placebo-controlled studies accumulates to 0.5% and pancreatitis has been added to section 4.8 of the SmPC.

Drug-related SAEs were reported at higher frequencies for regorafenib (10.4% vs 2.6%). The most commonly reported SAEs in the regorafenib arm were general physical health deterioration, ascites and hepatic failure which were reported at comparable or higher frequencies in the placebo group.

Incidence rates of transaminases and bilirubin increased were high and more often seen in the regorafenib arm than in the placebo arm.

Overall, a higher incidence of grade 5 infections with fatal outcome was reported for regorafenib (1.3% vs 0%) and infection has been added now as an important identified risk. Most fatal infections concerned respiratory infections. A warning has been included in section 4.4 with reference to section 4.8. In cases of worsening infection events, interruption of regorafenib treatment should be considered.

3.5. Uncertainties and limitations about unfavourable effects

Patients that discontinued prior sorafenib therapy due to sorafenib-related toxicity are not included in the study. Therefore, safety in those patients with HCC is unknown. As sorafenib belongs to the same pharmacological class, there might have been an underreporting of certain adverse events and especially serious adverse events in HCC. The impact on the reported safety profile for regorafenib in HCC is unknown. No information is available on the extent to which patients with HCC discontinue treatment due to sorafenib toxicity and whether these patients are distinct from the HCC population tolerating sorafenib. A warning has been included in section 4.4 of the SmPC to reflect this limitation.

Only patients screened for oesophageal varices and treated were included in the study. Given the known risk of bleedings for regorafenib and the fact that patients with HCC are at risk for oesophageal varices bleedings due to portal hypertension, a precautionary statement has been included in section 4.4 of the SmPC.

The current data do not indicate an increased risk of hepatotoxicity in patients with HCC. However, it may be difficult to disentangle drug-related from disease-related events. Close monitoring of safety is already recommended for patients with moderate hepatic impairment including dose modification recommendations, and use in patients with severe hepatic impairment is not recommended. These risk management measures are also considered adequate for patients with HCC.

The overall patient population with HCC included in the study was relatively healthy (ECOG PS=0 in 65% patients) and excluding patients with severe cardiovascular comorbidities. This is adequately addressed in sections 4.4 and 5.1 of the SmPC.

Long-term safety data for regorafenib in HCC is limited. Given the known long-term safety data from other indications and the reduced life expectancy of the patient population, follow-up through regular pharmacovigilance activities is considered sufficient.

3.6. Effects Table

Effect	Short Description	Unit	Regorafenib	Placebo	Uncertainties / Strength of evidence	
Favourable Effects						
OS	Overall Survival	mo	10.6	7.8	Results obtained in a selected population as defined by strict enrolment criteria.	HR 0.624 p=0.000017
PFS (mRECIST)	Progression Free Survival	mo	3.1	1.5	Investigator assessed	HR 0.453 P<0.000001
TTP	Time to Progression	mo	3.2	1.5	Investigator assessed	HR 0.439 p<0.000001
ORR	Objective Response Rate	%	10.6	4.1		
DCR	Disease Control Rate (CR+PR+SD)	%	64.5	36.1		
Unfavourable Effects						
HFSR	Hand-foot skin reaction	%	51.6	7.3		
Diarrhoea		%	41.2	15.0		
Hypertension		%	30.7	6.2		
Pancreatitis		%	1.6	0		New ADR
Haemorrhages		%	17.6	16.1		
Fatal infections		%	1.3	0		None reported as drug-related
Hepatic failure		%	2.4	4.7		
Laboratory abnormalities						
AST increase	Aspartate aminotransferase increased	%	92.7	84.3		
ALT increase	Alanine aminotransferase increased	%	70.4	58.6		
Bilirubin increase		%	78.2	54.5		

Note: The MAH provided updated figures for OS, PFS and TPP during review which are based on an Errata. The additional findings reported by the MAH do not impact the B/R. The corrected figures are shown in the effects table above and are reflected in the SmPC.

3.7. Benefit-risk assessment and discussion

3.7.1. Importance of favourable and unfavourable effects

Hepatocellular carcinoma, metastatic or not amenable for local therapy, progressive after systemic treatment with sorafenib, is a highly invalidating and life-threatening condition with an overall infaust prognosis. Currently there are no treatment options authorised in the EU for this patient population. Therefore, an unmet medical need for such population is acknowledged. In this scenario with no other treatment options available and a bad prognosis, an improvement in survival associated with acceptable toxicity would represent a conventional outcome measure for patient benefit.

The benefits of regorafenib for the new proposed indication are essentially based on a statistically significant improvement in OS supported by a consistent improvement in PFS, TTP and ORR. Results appear mature, robust and consistent in the different sensitivity and subgroup analyses provided. The magnitude of the improvement (2.8 months for median OS) is of potential clinical relevance.

However, due to the stringent enrolment criteria of the pivotal RESORCE and supportive 14596 studies, a relatively healthier and more homogeneous HCC population has been studied compared to the heterogeneous patient population encountered in clinical practice. The HCC patient population treated in clinical practice would also include patients with ECOG PS >1, Child Pugh liver score B and C, with significant renal impairment, with cardiovascular co-morbidities, with untreated/uncontrolled oesophagus varices, requiring anti-viral therapy for HBV and HCV. Risk minimisation measures, including warnings and close monitoring/dose adjustment, together with a description of the most important characteristics of the population in section 5.1 of the SmPC, are considered sufficient to address limitation in terms of the included population and disease characteristics.

The efficacy findings are also associated with a treatment related toxicity that appears substantial. In line with the already known safety profile of regorafenib, HFSR, diarrhoea, decreased appetite, hypertension and fatigue were the AEs most frequently reported. No significant increase of major bleedings events was reported in the regorafenib arm compared with the placebo arm. However, strict selection criteria were used in the studies in order to avoid inclusion of patients with untreated/uncontrolled oesophagus varices, which represent a bleeding risk factor. Evaluation of cancer related symptoms showed no significant difference between the two study arms. However, a numerical trend towards lower scores (and therefore worse quality of life and more symptoms) for patients treated with regorafenib is observed especially at later cycles. Unfortunately, no compelling biomarker analysis, which could potentially help to identify parameters for patient selection, was submitted by the applicant. The applicant is recommended to submit the genetic biomarker analysis once available.

3.7.2. Balance of benefits and risks

In view of the poor prognosis of the HCC population, metastatic and/or not amenable for local therapy and experiencing disease progression after sorafenib, the results of the pivotal RESORCE trial are considered of clinical relevance. The observed 2.8 months gain in median OS, confirmed by the updated analysis (cut off 23 January 2017) and supported by consistent improvement in PFS and TTP, is considered of clinical benefit and able to outweigh the substantial treatment related toxicity.

The lack of efficacy and in particular of safety data in patients discontinuing previous sorafenib treatment due to toxicity remains an unresolved issue, which is adequately addressed by a warning in section 4.4 of the SmPC. These patients should not be excluded from regorafenib treatment beforehand given that no other treatment options are currently available.

The uncertainties regarding the lack of data in patients with ECOG PS >1 and/or Child Pugh B are considered sufficiently addressed at this time by the proposed SmPC. In addition, the risk of severe bleeding in patients with oesophageal varices and the risk of infections are addressed by a precautionary statement in section 4.4.

3.8. Conclusions

The overall B/R of Stivarga is positive.

4. Recommendations

Outcome

Based on the review of the submitted data, the CHMP considers the following variation acceptable and therefore recommends by consensus 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, IIIA and IIIB

Extension of indication for Stivarga to include treatment of adult patients with hepatocellular carcinoma (HCC) who have been previously treated with sorafenib; as a consequence, sections 4.1, 4.2, 4.4, 4.8 and 5.1 of the EU SmPC are updated. The package leaflet and RMP (version 5.2) have been updated accordingly. Furthermore, the PI is brought in line with the latest QRD template version 10.0.

Similarity with authorised orphan medicinal products

The CHMP by consensus is of the opinion that Stivarga is similar to Nexavar within the meaning of Article 3 of Commission Regulation (EC) No. 847/200. See appendix 1.

Derogation from market exclusivity

The CHMP by consensus is of the opinion that pursuant to Article 8 of Regulation (EC) No. 141/2000 and the following derogation laid down in Article 8.3 of the same Regulation applies: the holder of the marketing authorisation for Nexavar has given his consent to the applicant.

5. EPAR changes

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

Scope

Extension of indication for Stivarga to include treatment of adult patients with hepatocellular carcinoma (HCC) who have been previously treated with sorafenib; as a consequence, sections 4.1, 4.2, 4.4, 4.8

and 5.1 of the EU SmPC are updated. The package leaflet and RMP (version 5.2) have been updated accordingly. Furthermore, the PI is brought in line with the latest QRD template version 10.0.

Summary

Please refer to the scientific discussion Stivarga-H-C-2573-II-0020