Post Authorization Study Information

Acronym/Title	REFINE: Regorafenib observational study in hepatocellular carcinoma
Protocol version identifier	v 1.0
Date of last version of protocol	07 MAR 2017
IMPACT study number	19244
Study type/Study phase	☐ non-PASS ☒ PASS Joint PASS: ☐ YES ☒ NO Phase IV
EU PAS register number	Study not yet registered
Active substance	ATC L01XE21, Protein kinase inhibitors, Regorafenib
Medicinal product	STIVARGA®, regorafenib
Product reference	EU marketing authorization number: EU/1/13/858/001 (28 tablets) EU/1/13/858//002 (3x28 tablets)
Procedure number	EU procedure number EMEA/H/C/002573/II/0020
Study Initiator and Funder	Bayer AG, 51368 Leverkusen, Germany
Reference therapy	N/A
Research question and objectives	The purpose of this observational study is to evaluate, in real-world practice conditions, the safety and effectiveness of regorafenib in patients with unresectable hepatocellular carcinoma (uHCC) for whom a decision to treat with regorafenib has been made before study enrollment. The study will also evaluate regorafenib treatment in a variety of HCC patient subsets, such as grouping by Child–Pugh score regionally and globally, that were not addressed in the RESORCE study, as well as provide information on treatment patterns and outcomes for patients with uHCC in the real-world setting. The primary objective of this study is to evaluate the safety of regorafenib in patients with uHCC, including incidence

	of all treatment-emergent adverse events (TEAEs) and dose modifications due to TEAEs in real-world practice conditions. Secondary objectives are: • To describe the effectiveness of regorafenib, including overall survival (OS), progression-free survival (PFS), time to progression (TTP), and overall tumor response (ORR) • To describe the patterns of regorafenib treatment, including actual doses, duration of treatment (DOT), and other dosing parameters • To describe patient characteristics, comorbidities, and their influence on treatment and outcomes under real-life conditions • To describe physicians' practice patterns, including regional difference in management of and treatments for uHCC in real-world conditions Tertiary objectives are: • To describe sorafenib treatment prior to regorafenib treatment including doses, duration of treatment, best response, and reasons for discontinuation (in relevant patients) • To describe other therapies for HCC prior to regorafenib, including doses, duration of treatment, best response, and reasons for discontinuation (in relevant patients)
Country(-ies) of study	Approx. 30 countries in Europe (e.g. Austria, Benelux, France, Greece, Italy, Netherlands, Portugal, Russia, Scandinavia, Spain, Switzerland), North America (e.g. USA, Canada), Asia (e.g. Japan, Korea, Taiwan, Thailand, Hong Kong), Latin America (e.g. Argentina, Colombia, Mexico), Levant (e.g. Turkey, Lebanon), Middle East (e.g. UAE, Oman, Saudi Arabia) and North Africa (e.g. Egypt, Algeria). An updated list is available as stand-alone document (listed in Table 4, Annex 1).
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Marketing authorization holder

Marketing authorization holder(s)	Bayer AG, 51368 Leverkusen, Germany
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The study will be conducted in compliance with the protocol

and any applicable regulatory requirements.

Throughout this document, symbols indicating proprietary names (®, TM) may not be displayed. Hence, the appearance of product names without these symbols does not imply that these names are not protected.

1. Table of contents

2. List of abbreviations

AE	Adverse event
AR	Adverse reaction
AFP	Alpha-fetoprotein
ALP	Alkaline phosphatase
ALT	Alanine transaminase
AST	Aspartate transaminase
ATC	Anatomical Therapeutic Chemical (Classification System)
BCLC	Barcelona Clinic Liver Cancer
ChE	Cholinesterase
CFR	Code of Federal Regulations
CrCl	Creatinine clearance
CRF	Case Report Form
CRO	Contract Research Organization
CRP	C-reactive protein
CTCAE	Common Terminology Criteria Adverse Event
DCP	Des-gamma-carboxy prothrombin
DMP	Data Management Plan
DOT	Duration of treatment
EC	European Commission
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic Case Report Form
EDC	Electronic Data Capture
EFPIA	European Federation of Pharmaceutical Industries and Associations
EMA	European Medicine Agency
ENCePP	European Network of Centers in Pharmacoepidemiology and Pharmacovigilance
EU	European Union
FAS	Full analysis set
FDA	Food and Drug Administration
FGFR	Fibroblast growth factor receptor
GCP	Good Clinical Practice
GGT	Gamma-glutamyl-transferase
GIST	Gastrointestinal stromal tumors
GPP	Good Publication Practice
GVP	Good Pharmacovigilance Practice
HBV	Hepatitis B virus
HCC	Hepatocellular carcinoma
HCV	Hepatitis C virus
HEOR	Health Economics and Outcomes Research
ICD	International Classification of Diseases
ICH	International Conference of Harmonization

IEC	Independent Ethics Committee
INN	International Nonproprietary Name
INR	International normalized ratio
IRB	Institutional Review Board
IT	Information Technology
KM	Kaplan–Meier
LDH	Lactate dehydrogenase
LPLV	Last patient last visit
MAH	Marketing Authorization Holder
mCRC	Metastatic colorectal cancer
MedDRA	Medical Dictionary for Regulatory Activities
mRECIST	Modified Response Evaluation Criteria in Solid Tumors
MRP	Medical Review Plan
N/A	Not applicable
NASH	Nonalcoholic steatohepatitis
NCI	National Cancer Institute
NNH	Number Needed to Harm
ORR	Overall tumor response
OS	Overall survival
PAS	Post-authorization study
PASS	Post-authorization safety study
PDGFR	Platelet-derived growth factor receptor
PFS	Progression-free survival
PIVKA-II	Protein induced by vitamin K absence/antagonist-II
PMDA	Pharmaceuticals and Medical Devices
PSUR	Periodic Safety Update Report
PV	Pharmacovigilance
QPPV	Qualified person responsible for pharmacovigilance
QRP	Quality review plan
RESORCE	REgorafenib after SORafenib in patients with hepatoCEllular carcinoma
SAE	Serious adverse event
SAF	Safety analysis set
SAP	Statistical analysis plan
SHARP	Sorafenib Hepatocellular carcinoma Assessment Randomized Protocol
SmPC	Summary of product characteristics
STROBE	Strengthening the Reporting of Observational Studies in Epidemiology
TEAE	Treatment-emergent adverse event
TNM	Tumor, node, metastasis
TTP	Time to progression
uHCC	Unresectable hepatocellular carcinoma
VEGF	Vascular endothelial growth factor

VEGFR	Vascular endothelial growth factor receptor
WHO DD	World Health Organization Drug Dictionary

3. Responsible parties

3.1 Study initiator and funder

Contact details of the responsible parties at Bayer AG are available upon request.

3.2 Collaborators/Committees

Contact details on the coordinating and/or principal investigators, co-investigators and other site personnel for each country, and sites participating in the study are listed in a standalone document (see Table 4, Annex 1), which is available upon request.

Information on the Steering/Adjudication/Publication Committee Members is kept as a standalone document (see Table 4, Annex 1, and the respective Charters) and is available upon request.

Administrative changes of responsible persons and/or the composition of the committees will be documented by updating the respective lists, but do not require formal protocol amendments.

4. Abstract

Acronym/Title	REFINE: Regorafenib observational study in hepatocellular carcinoma
Protocol version identifier	v 1.0
Date of last version of protocol	07 MAR 2017
IMPACT study number	19244
Study type/Study phase	☐ non-PASS ☒ PASS Joint PASS: ☐ YES ☒ NO Phase IV
Author	Keiko Nakajima, 67 Whippany Road, Bayer HealthCare Pharmaceuticals Inc., Whippany, NJ, USA
Rationale and background	Liver cancer is the sixth most common cancer worldwide and the second most common cause of cancer-related death. Hepatocellular carcinoma (HCC) is the most common subtype of primary liver cancer, accounting for 70–85% of the total liver cancer burden worldwide. Regorafenib has been shown to prolong survival in patients with unresectable hepatocellular carcinoma (uHCC) who have progressed on the first-line therapy sorafenib. However, there are no real-world data available on the use of regorafenib in second line after first-line treatment with sorafenib. Therefore, this study will describe the safety and effectiveness of regorafenib under real-world treatment conditions, as well as provide information about management for uHCC in standard clinical practice.
Research question and objectives	The purpose of this observational study is to evaluate, under real-world practice conditions, the safety and effectiveness of regorafenib in patients with uHCC for whom a decision to treat with regorafenib has been made before study enrollment. The study will also evaluate regorafenib treatment in a variety of HCC patient subsets, such as in patients grouped by Child–Pugh score regionally and globally, that were not addressed in the RESORCE study, as well as provide information on treatment patterns and outcomes for patients with uHCC in the real-world setting.

	The primary objective of this study is: • To evaluate the safety of regorafenib in patients with uHCC, including incidences of all treatment-emergent adverse events (TEAEs) and dose modifications due to TEAEs under real-world practice conditions. Secondary objectives are: • To describe the effectiveness of regorafenib, including overall survival (OS), progression-free survival (PFS), time to progression (TTP), and overall tumor response (ORR) • To describe the patterns of regorafenib treatment, including actual doses, duration of treatment (DOT), and other dosing parameters • To describe patient characteristics, comorbidities, and their influence on treatment and outcomes under real-life conditions • To describe physicians' practice patterns, including regional difference in the management and treatment of uHCC under real-world conditions Tertiary objectives are: • To describe sorafenib treatment prior to regorafenib treatment, including doses, duration of treatment, best response, and reasons for discontinuation • To describe other therapies for HCC prior to regorafenib, including doses, duration of treatment, best response, and reasons for discontinuation (in relevant patients)
Study design	International, prospective, open-label, multicenter, observational study.
Population	Female and male patients with a diagnosis of uHCC in whom a decision to treat with regorafenib has been made by the treating physician at the time of study enrollment.
Variables	Variables for the primary objective are adverse events (AEs). Variables for secondary and tertiary objectives are demography, HCC classification, medical history/ comorbidities, prior systemic anti-cancer therapy and tolerability (including sorafenib), prior local anti-cancer therapy, prior medication, lifestyle records, vital signs, tumor status and metastases, Child–Pugh classification, BCLC staging, ECOG performance status, laboratory parameters,

	treatment with regorafenib (including AEs), and reason for ending the treatment and/or observation (including death). Other variables include eligibility for the study, informed consent and visit dates.
Data sources	Treatment-related data are documented during visits that take place in routine practice. Historic data are based on medical records or on interviewing the patient.
Study size	The study aims to enroll and collect data from 1000 patients, to enable observation of at least one patient with a particular AE, if the true incidence rate for the AE is 0.2%, with approximately 86% probability.
Data analysis	STATISTICAL CONSIDERATIONS Statistical analyses will be of explorative and descriptive nature. The study is not aimed to confirm or reject pre-defined hypotheses. All variables will be analyzed descriptively with appropriate statistical methods: categorical variables by frequency tables (absolute and relative frequencies) and continuous variables by sample statistics (i.e. mean, standard deviation, minimum, median, quartiles, 5th and 95th percentiles, and maximum). Continuous variables will be described by absolute value and as change from baseline per analysis time point, if applicable. Patients who took at least one dose of regorafenib will be included in the safety analysis set (SAF). Patients who took at least one dose of regorafenib, did not violate a major inclusion/exclusion criterion, and had at least one follow-up assessment after receiving regorafenib will be included in the full analysis set (FAS). Safety data will be analyzed on the SAF and effectiveness data on the FAS. Demographic and baseline data will be described for the SAF and the FAS. All analyses will be performed for the total study population (overall analysis) and separately for each participating country if patient numbers are sufficient and if required for local reasons. Whenever reasonable, data will be stratified by subgroups (e.g. age, gender, baseline characteristics). Retrospective sorafenib data prior to treatment with regorafenib will be described in patients who have received sorafenib prior to the study entry. Retrospective data relating to other therapies for HCC prior to treatment with regorafenib will be described

	in patients who have received such therapy prior to study entry. All statistical details including violation of inclusion/exclusion criteria and patient validity, derived variables for analysis, handling of missing data, and format and content of tables will be detailed in the Statistical Analysis Plan (SAP). The SAP will be finalized before study database lock.	
Milestones	First patient first visit: Last patient first visit: Last patient last visit: Final report:	Q2 2017 Q2 2020 Q2 2022 Q1 2023

5. Amendments

Table 1: Amendments

Amendment Number	Reason for Amendment	New version number	Effective Date
AM01	The global REFINE protocol has been revised to comply with Japanese regulations. The amendment was generated as proof of written-based study design specific in Japan and will be reviewed by Japanese regulatory authority (PMDA). To avoid redundant description or any conflict, the local Japanese amendment only focuses on critical information for PMDA communication (e.g. # patients, observation period, timing of interim/final analysis, etc.)	v 1.0_JP	07 MAR 2017

6. Milestones

Table 2 presents planned milestones for the project. These milestones are based on a timely review and approval of the project. Administrative changes to milestones due to delays in study preparation and enrolment do not require amendments to the protocol. Revised study timelines and milestones which do not constitute a need for a formal protocol amendment are kept as stand-alone document (Table 4, Annex 1) that is available upon request.

Table 2: Milestones

Milestone	Planned date
Start of data collection	Q2 2017
End of data collection	Q2 2022
Registration in the EU PAS register	not yet registered
Interim Analysis	When a minimum of 500 patients have been on study for at least 4 months
Final report of study results	Q1 2023

7. Rationale and background

The phase III RESORCE (REgorafenib after SORafenib in patients with hepatoCEllular carcinoma) study demonstrated that regorafenib prolongs survival in patients with unresectable hepatocellular carcinoma (uHCC) who have progressed on the first-line therapy of sorafenib. However, there are no real-world data available on the use of regorafenib in the second line after first-line treatment with sorafenib. This study will describe the safety and effectiveness of treatment with regorafenib in real-world settings. In addition, this study will provide information about baseline characteristics, treatments, and management of uHCC in real-world practice that will enable greater understanding of the disease and practice patterns.

Liver cancer is the sixth most common cancer worldwide, and the second most common cause of cancer-related death. [1] Globally, in 2012, there were an estimated 782,000 new cases of liver cancer. [1] Among primary liver cancers, hepatocellular carcinoma (HCC) is the most common subtype, accounting for 70–85% of the total liver cancer burden worldwide. [2] Liver cancer was estimated to be responsible for nearly 745,000 deaths in 2012. [1]

Regorafenib is an oral multikinase inhibitor that blocks various kinases within the mechanisms involved in tumor growth and progression (angiogenesis, oncogenesis, and the tumor microenvironment). In preclinical studies, regorafenib has been shown to inhibit several angiogenic vascular endothelial growth factor (VEGF) receptor (VEGFR) tyrosine kinases that play a role in tumor neoangiogenesis (the growth of new blood vessels). In addition to VEGFR 1–3, regorafenib also inhibits numerous oncogenic and tumor microenvironment kinases, including TIE-2, RAF-1, BRAF, BRAFV600, KIT, RET, platelet-derived growth factor receptor (PDGFR), and fibroblast growth factor receptor (FGFR), which individually and collectively control tumor growth, formation of a stromal microenvironment, and disease progression.

The efficacy and safety of regorafenib were evaluated in two different international, multicenter, randomized, double-blinded placebo controlled phase III trials. One study in metastatic colorectal cancer (mCRC) demonstrated significant improvement in survival with regorafenib compared with placebo [median overall survival (OS): 6.4 vs 5.0 months, P=0.0052]. Another study in gastrointestinal stromal tumors (GIST) demonstrated a significant improvement in progression free survival (PFS) for regorafenib compared with placebo (median PFS: 4.8 vs 0.9 months, respectively, P<0.0001). These studies resulted in regorafenib approvals for both mCRC and GIST.

For uHCC, sorafenib has been the only available systemic treatment. It demonstrated a statistically significant OS benefit, shown in two phase III randomized, placebo-controlled trials (SHARP and Asia Pacific study), [3] [4] and has been standard of care as the first-line option in patients with uHCC who are not suitable for curative treatments. [5] [6] [7] However, there has been no systemic therapy available after progression on sorafenib. A number agents have been evaluated for uHCC, none has shown a survival benefit, although recent reports from a phase III trial indicate that lenvatinib might be non-inferior to sorafenib as first-line treatment. [8] Recent data from the phase III RESORCE study showed clinically and statistically significant OS prolongation with regorafenib in patients with uHCC who have progressed on the first-line therapy of sorafenib. The median OS was 10.6 months for patients receiving regorafenib versus 7.8 months for those receiving placebo [HR 0.63 (95% CI: 0.50, 0.79); P<0.001], which translates to a 37% reduction in the risk of death over the study period. [9]

The phase III RESORCE data indicated that the safety profile of regorafenib in HCC was consistent with that reported in the phase III studies in mCRC and GIST. In all three indications, the most

common grade ≥3 adverse events (AEs) included hand–foot skin reaction, hypertension, fatigue, and diarrhea, and AEs leading to discontinuation were relatively low (6–18% among all three studies). [9] [10] [11] [12]

The purpose of this observational study is to describe the safety and effectiveness of regorafenib in patients with uHCC under real-world practice conditions. Patients enrolled will be those for whom a decision to treat with regorafenib has already been made, and will likely include a variety of HCC patient subsets, such as patients grouped by Child–Pugh score regionally and globally, that were not addressed in the RESORCE study. The study will also provide information on treatment patterns and outcomes for patients with uHCC in the real-world setting, and will collect baseline information, including retrospective data on sorafenib treatment.

8. Research questions and objectives

8.1 Primary objective

The primary objective of this international observational study is to evaluate the safety of regorafenib in patients with uHCC, including incidences of all treatment-emergent adverse events (TEAEs) and dose modifications due to TEAEs in real-world practice conditions.

8.2 Secondary objective(s)

Secondary objectives are:

- To describe the effectiveness of regorafenib, including overall survival (OS), progression-free survival (PFS), time to progression (TTP), and overall tumor response (ORR
- To describe the patterns of regorafenib treatment, including actual doses, duration of treatment (DOT), and other dosing parameters
- To describe patient characteristics, comorbidities, prior therapies, and assess their potential influence on treatment and outcomes under real-life conditions
- To describe the physicians' practice patterns, including regional difference in the management and treatment of uHCC under real-life conditions

8.3 Tertiary objective(s)

Additional objectives, based on patients' prior treatments, will be evaluated. Tertiary objectives include:

- To describe sorafenib treatment prior to regorafenib treatment, including doses, duration of treatment, best response, and reasons for discontinuation (in relevant patients)
- To describe other therapies for HCC prior to regorafenib, including doses, duration of treatment, best response, and reasons for discontinuation (in relevant patients)

9. Research methods

9.1 Study design

This is an international, prospective, open-label, multi-center, observational study. Patients with uHCC for whom a decision to treat with regorafenib has been made before enrollment will be

eligible for the study. The decision on the dose and duration of treatment is solely at the discretion of the treating physician, based on the recommendations written in the local product information. Examinations and the laboratory monitoring schedule will follow local label recommendations in line with local standard of care. No control arm is planned in this study because regorafenib is the only agent with proven survival benefit in patients with uHCC after prior sorafenib treatment; there is currently no alternative treatment available.

This study is designed to evaluate AEs in patients treated with regorafenib. It will also collect data to describe the effectiveness of regorafenib in uHCC, patterns of treatment, and the influence of baseline characteristics and treatment history.

Data will be collected from approximately 1000 patients globally over a total study period of 5 years, including 36 months' enrollment and 24 months' observation time from study entry. Interim data analyses for safety monitoring will be conducted with a minimum of 500 patients who have been observed for at least 4 months. The final analysis will be conducted after the final patient remaining in the study has been observed for 24 months or is no longer under observation due to withdrawal or death.

Patients will be observed from the time from the start of therapy with regorafenib until the end of observation owing to premature discontinuation, withdrawal of consent, or death, or until the end of the study.

Physicians participating in this study are recommended to include consecutive patients. The data for this study will be collected using an electronic case report form (CRF).

9.1.1 Primary endpoint(s)

The primary endpoint is the safety of regorafenib in patients with uHCC, defined as the frequency of documented TEAEs, including serious adverse events (SAEs).

Safety will be assessed in all patients who receive at least one dose of regorafenib regardless of prior treatment.

9.1.2 Secondary endpoint(s)

The secondary endpoints for all patients are:

- Overall survival (OS) is defined as the time (days) from the start of regorafenib treatment to the date of death, due to any reason. Patients alive or lost to follow-up at the time of analysis will be censored at their last date of follow-up.
- Progression-free survival (PFS) is defined as the time (days) from the start of regorafenib treatment to the date of first observed disease progression (radiological or clinical, whichever is earlier) or death due to any cause, if death occurs before progression is documented.
- Time to progression (TTP) is defined as the time (days) from the start of regorafenib treatment to the first documented disease progression.
- Best overall tumor response (ORR) will be defined for all patients using tumor assessment criteria, including modified Response Evaluation Criteria in Solid Tumors (mRECIST).

- Duration of regorafenib treatment, defined by the time interval from the start of regorafenib treatment to the day of permanent discontinuation of regorafenib (including death); mean dose and reasons for regorafenib discontinuation or dose modification will be recorded

9.1.3 Tertiary endpoint(s)

Tertiary endpoints, related to patient treatment history, will be evaluated. The tertiary endpoints for patients who received sorafenib prior to regorafenib are:

- Duration of sorafenib treatment, defined by the time interval from the start of sorafenib treatment to the day of permanent discontinuation of sorafenib
    - Reasons for sorafenib discontinuation will be recorded, as will doses of sorafenib given and time from sorafenib initiation to death, including time on regorafenib
- Response to sorafenib treatment, as assessed using mRECIST
- Overall survival, defined as the time interval from the start of sorafenib treatment to death due to any cause
- Frequency of adverse reactions experienced during treatment with sorafenib
- Time from discontinuation of sorafenib to start of regorafenib

Tertiary endpoints for prior treatments other than sorafenib are defined analogously.

9.1.4 Strengths of study design

The international, observational study design enables data to be collected from patients treated under local standard-of-care clinical practice; all decisions in terms of diagnostic procedures, treatments, management of the disease, and resource utilization are fully dependent on mutual agreement between the patient and the attending physician, without interference by the study protocol. This will enable assessment of treatment and subsequent outcomes based on local standards, and is likely to encompass a wider range of therapeutic decisions compared with the stricter, defined limits on therapy required by investigational study protocols. Decisions and outcomes made in real-world conditions are likely to be more applicable to wider clinical practice than those from interventional studies.

This study population is larger and likely to be more diverse than that observed in prior interventional trials, with a broader range of disease severity, prior treatments, comorbidities and concomitant medications. The sample size will enable comprehensive characterization of the regorafenib safety profile of all treated patients, as well as analysis of safety and effectiveness among different patient subsets (for example, by Child–Pugh status, prior treatment history).

9.2 Setting

9.2.1 Eligibility

Patients with uHCC and for whom a decision to treat with regorafenib has been made (by the treating physician) will be eligible for enrollment into the study. Patients considered for study enrollment and treatment with regorafenib should meet the criteria for regorafenib use according to the local health authority-approved product information, including indications and contraindications with respect to the local market authorization / summary of product characteristics (SmPC).

9.2.2 Inclusion criteria

- Patients with confirmed diagnosis of unresectable HCC
- Physician-initiated decision to treat with regorafenib (prior to study enrollment)
- Signed informed consent form

9.2.3 Exclusion criteria

- Participation in an investigational program with interventions outside of routine clinical practice
- Past treatment with regorafenib

9.2.4 Withdrawal

In this observational study, withdrawal from the study is independent of the underlying therapy and will not affect the patient's medical care. Each patient can refuse to further participate or may withdraw from the study at any time and without giving a reason. If a patient wants to terminate the study participation, no further data will be collected. However, the patient will be asked whether he/she agrees that the data collected so far can be used. In case the patient does not agree, these data will not be used for any patient level analysis of study data. This includes safety data, with the exception that data already captured in the company's safety database, which will be kept. However, data that are relevant for primary outcomes might be displayed on an aggregated level to assess a potential bias. In case a patient would like to withdraw the consent given earlier, he/she should inform his/her doctor and the site should document the withdrawal in the CRF as well as in the patient's medical records.

9.2.5 Replacement

Patients will not be replaced.

9.2.6 Representativeness

The patients documented in the study should be selected based only on eligibility according to inclusion and exclusion criteria (sections 9.2.1 – 9.2.3). No further selection should be applied. Physicians will be asked to sample consecutive patients whenever possible to avoid selection bias and thus increase the likelihood of representativeness. At each site, all screened patients will be documented consecutively in an anonymous screening log with reasons for non-participation (without recording patient-specific data).

9.2.7 Visits

The start of the study is the date from which information on the first patient can be first recorded in the study dataset (i.e. first informed consent obtained). The end of the study is the date after which the final patient remaining in the study has been in the study for 24 months, or is no longer under observation owing to being lost to follow-up, withdrawal, or death.

A visit is defined as any status assessment or new treatment decision the treating physician takes in the presence of the patient. The time interval between two documented status assessments is assumed to be 6–12 weeks, although this will be at the discretion of the treating physician.

The investigator will document the baseline / initial visit, follow-up visits and the end of observation / final visit for each patient in the CRF. Follow-up visits occur during routine practice; the study protocol does not define exact referral dates for those visits. The end of observation / final visit is to be documented after a patient has been on study for at least 24 months, is lost to follow-up, has withdrawn consent or has died, whichever comes first. If the documentation is stopped prematurely, the reasons for the end of observation must be given. If a patient joins an interventional clinical study during the course of observation, information on survival should be collected up to the end of this study. If a patient remains alive at time of study closure, this will be documented in the final visit.

Table 3: Tabulated overview on variables collected during the study

Variables	**Baseline / Initial visit***	**Follow-up visit(s)**	**End of observation / final visit**
Visit date	X	X	X
Eligibility assessment	X		
Patient information and consent	X		
Demography	X		
Co-morbidities (medical history, concomitant diseases)	X		
HCC classification	X		
Prior systemic anti-cancer therapy (including sorafenib) (see 9.3.3.6)	X		
Tolerability of prior systemic anti-cancer therapy (including sorafenib) (see 9.3.3.6)	X		
Prior local anti-cancer therapy	X		
Prior medication	X		
Lifestyle records (smoking & alcohol use)	X		
Vital signs	X		
BCLC Staging	X		
Tumor status and metastases (see 9.3.3.9)	X	X	X
Child-Pugh classification	X	X	X

ECOG performance status	X	X	X
Laboratory parameters (see 9.3.3.7)	X	X	X
Concomitant medication	X	X	X
Exposure/treatment with regorafenib (see 9.3.3.8)	X	X	X
Adverse events on regorafenib (see 9.3.3.11)	X	X	X**
Reason for end of observation			X
Death and reason for death			X
Survival assessment			X

*Initial visit is the visit when treatment with regorafenib is started. Baseline and Initial visit can be at the same day

**Adverse events (up to 30 days after the final treatment with regorafenib/ last treatment within the observation period)

9.3 Variables

The investigator collects historic data (demographic and clinical characteristics) from medical records if available, or else by interviewing the patient. Likewise, the investigator collects treatment related data during initial visit and follow-up visits. The investigator documents the study-relevant data for each patient in the CRF. The CRF is available upon request (see Table 4, Annex 1).

Information will be collected from laboratory tests performed according to the local standard of care. For potential TEAE reporting of any laboratory abnormalities please refer to section 11.

9.3.1 Variables to determine the primary endpoint(s)

The variables for the primary objective are:

- AEs and SAEs
- TEAEs leading to dose modifications (including reductions, interruptions and permanent discontinuation)

9.3.2 Variables to determine the secondary and tertiary endpoint(s)

The outcome variables for secondary objectives are:

- Demographic data and disease history
- Regorafenib use (including start/stop dates and dosage)
  - Initiation and termination dates
  - Dosage and dose modification
- Tumor assessment after initiation of regorafenib
- Date of radiological or clinical progression on regorafenib
- Child–Pugh score
- ECOG performance status
- Laboratory examination data
- Date of death

Outcome variables for tertiary endpoints include:

- Sorafenib treatment history (prior to study entry)
  - Initiation and termination dates
  - Tolerability of sorafenib treatment
  - Radiological progression on sorafenib
  - Best tumor response to sorafenib
- Previous systemic therapy other than sorafenib
  - Initiation and termination dates
  - Tolerability of systemic therapy
  - Radiological progression on therapy
  - Best tumor response to therapy

9.3.3 Detailed description of variables collected

9.3.3.1 Visits

Information collected relating to each visit (baseline, follow-up, end of observation) includes:

- Date of visit

9.3.3.2 Demography

For demographic/socio-demographic assessment, the following data will be recorded:

- Year of birth
- Age
- Sex
- Race [only where legally permitted]
- Ethnicity [only where legally permitted]

9.3.3.3 Vital signs

Information on vital signs to be documented includes:

- Height
- Weight
- Blood pressure
- Heart rate

9.3.3.4 Disease history

Disease history describes any medical findings that are relevant to the underlying disease and were present before inclusion into the study. Findings and diagnosis meeting the following criteria must be documented:

- Date, tumor stage [tumor, node, metastasis (TNM) and Barcelona Clinic Liver Cancer (BCLC) staging] and Child–Pugh status at initial diagnosis
- Tumor stage (TNM and BCLC), Child–Pugh status and ECOG performance status at the time of initial sorafenib treatment (if applicable)
- Etiology of HCC at the study entry
- Disease extent at the study entry (TNM, BCLC, metastatic lesions, extra hepatic spread, vascular invasion, portal vein thrombosis, tumor morphology)

- Child–Pugh score at the study entry
- ECOG performance status at the study entry
- Social history (smoking, alcohol use)

9.3.3.5 Co-morbidities (medical history, concomitant diseases)

Co-morbidities are any medical findings, whether or not they pertain to the study indication, that were present before the start of therapy with regorafenib, independent of whether or not they are still present. They have to be documented in the Medical History/Concomitant Diseases section. Co-morbidities that resolved more than three years prior to study entry and that are not considered relevant to current treatment do not require documentation.

The conditions of interest, which will be documented in the CRF, include:

- Ascites
- Encephalopathy
- Myocardial infarction
- Deep venous thrombosis
- Pulmonary embolism
- Transient ischemic attack
- Ischemic stroke
- Cerebral hemorrhage
- Hemorrhage, GI
- Diabetes mellitus type I
- Diabetes mellitus type II
- Hypertension
- Heart failure
- Phlebitis
- Gastrointestinal ulcer
- Angina pectoris
- Esophageal varices
- Upper GI bleeding

9.3.3.6 Prior and concomitant medication

All medication taken before study start (initiated and stopped before study start) is termed prior medication. Prior medication meeting the criteria listed below are considered to be relevant to the study indication must be documented:

- Treatment for HCC
    - Previous treatment with systemic therapy (including sorafenib)
        - Drug name
        - Start and stop date
        - Dose(s), including maximum tolerated dose
        - Therapy type and intent of treatment
        - Best response to treatment
        - Date of radiological progression, including type of progression (new lesion, new vascular invasion, progression of target lesion and quantification)
        - Tolerability of systemic treatment, including dose modifications relating to side effects

        - Reason for discontinuation
    - Previous local therapy
        - Procedure, drug name, dose, embolization agent, and intent
        - Administration date
        - Anatomic location
        - Best response to treatment
- Treatments for indications other than HCC

All medication taken in addition to regorafenib for any indication (either initiated before study start or during the study) is termed concomitant medication and has to be documented.

Information to be collected for medication includes:

- Trade name or INN
- Start date, stop date/ongoing
- Dose
- Unit
- Indication

9.3.3.7 Laboratory parameters

Laboratory parameters to be documented include (if available):

- Date of test
- Platelets
- Hemoglobin
- Erythrocytes
- Hematocrit
- Leukocytes
- International normalized ratio (INR)
- Alanine transaminase (ALT)
- Aspartate transaminase (AST)
- Alkaline phosphatase (ALP)
- Sodium
- Lactate dehydrogenase (LDH)
- Alpha fetoprotein (AFP) and AFP-L3
- C-reactive protein (CRP)
- Gamma-glutamyl-transferase (GGT)
- Creatinine
- Creatinine clearance (CrCl)
- Cholinesterase (ChE)
- Total bilirubin
- Albumin
- Des-Gamma-Carboxy Prothrombin (DCP)/ protein induced by vitamin K absence/antagonist-II (PIVKA-II)

9.3.3.8 Exposure/treatment

Information on regorafenib to be documented include:

- Start and stop date
- Dose modification
- Total daily dose
- Reason for dose modification

9.3.3.9 Assessment of therapy

Information on assessment of therapy to be documented includes:

- Tumor assessment according to criteria used within local guidance
    - Date of assessment
    - Tumor assessment [complete response, partial response, stable disease, or progressive disease (measurement proven or by clinical judgment)]
    - Location of metastases by organ (including lymph nodes)
    - Vascular invasion (location), portal vein thrombosis, extrahepatic spread
- Child–Pugh classification
- ECOG performance status

9.3.3.10 End of observation

If available, the primary reason for end of observation/study discontinuation should be stated:

- Regular end of study
- Patient lost to follow-up
- Patient withdrew consent
- Patient died
- Other

9.3.3.11 Adverse events/Adverse events of special interest

(Serious) adverse events need to be collected as described in section 11.2. Information collected includes:

- Diagnosis of AE or symptom (if diagnosis unknown)
- Start and stop date
- Seriousness
- Severity according to National Cancer Institute (NCI) Common Terminology Criteria Adverse Event (CTCAE) v4.03 severity grading
- Relatedness to regorafenib therapy
- Action taken
- Event outcome
- Other specific treatment(s) of AE

9.4 Data sources

The investigator collects historic data (demographic and clinical characteristics) from medical records if available. Likewise, the investigator collects treatment-related data during visits that take place in routine practice. Each patient is identified by a unique central patient identification code, which is only used for study purposes. For the duration of the study and afterwards, only the patient's treating physician or authorized site personnel are able to identify the patient based on the patient identification code.

9.5 Study size

Data collected from 1000 patients with uHCC treated with regorafenib globally should allow for sufficient evaluation of safety monitoring of all treated patients, as well as different subsets of patients, including evaluations between subgroups based on region etc. With this number of patients, it is possible to observe at least one patient with a particular adverse event, if the true incidence rate for the AE is 0.2% (2:1000), with approximately 86% probability. A particular event with a true incidence rate of 0.5% could be observed in at least two patients with 96% probability, and in at least three patients with 87% probability. The following tables show the probabilities of observing one, two, or three patients with the event for different true incidence rates, with a sample size of 1000 patients.

True incidence rate of a particular event (%)	Probability of observing the event in		
	At least one patient	At least two patients	At least three patients
0.1	0.6323	0.2642	0.0802
0.2	0.8649	0.5943	0.3233
0.3	0.9504	0.8013	0.5771
0.4	0.9818	0.9089	0.7625
0.5	0.9933	0.9599	0.8760

The sample size is also supported by the feasibility based on a previous global study in 3000 patients with uHCC who received sorafenib. Based on the information from external experts and market research, we consider 30-35% of patients who are treated with sorafenib would be subsequently treated with regorafenib; therefore, 1000 patients would be feasible for this observational study.

9.6 Data management

A Contract Research Organization (CRO) will be selected and assigned for EDC system development. The CRF will be part of the EDC system which allows documentation of all outcome variables and covariates by all participating sites in a standardized way. Information on the EDC system is available upon request (Table 4, Annex 1). Detailed information on data management, including procedures for data collection, retrieval and preparation are given in the Data Management Plan (DMP), which is available upon request (see Table 4, Annex 1).

For information on quality control, refer to section 9.8.

9.7 Data analysis

9.7.1 Statistical considerations

Statistical analyses will be of explorative and descriptive nature. The study is not aimed to confirm or reject pre-defined hypotheses.

All variables will be analyzed descriptively with appropriate statistical methods: categorical variables by frequency tables (absolute and relative frequencies) and continuous variables by sample statistics (i.e. mean, standard deviation, minimum, median, quartiles, 5th and 95th percentiles, and maximum). Continuous variables will be described by absolute value and as change from baseline per analysis time point, if applicable.

Patients who took at least one dose of regorafenib will be included in the safety analysis set (SAF).

Patients who took at least one dose of regorafenib, did not violate a major inclusion/exclusion criterion, and had at least one follow-up assessment after receiving regorafenib will be included in the full analysis set (FAS).

Safety data will be analyzed on the SAF, effectiveness data on the FAS. Demographic and baseline data will be described for the SAF and the FAS.

All analyses will be performed for the total study population (overall analysis) and separately for each participating country if patient numbers are sufficient and if required for local reasons. Whenever reasonable, data will be stratified by subgroups (e.g. age, gender, baseline characteristics, and prior treatment).

All therapies documented will be coded using the World Health Organization – Drug Dictionary (WHO-DD). Medical history, any diseases and AEs will be coded using the latest Medical Dictionary for Regulatory Activities (MedDRA) version.

All statistical details including violation of inclusion/exclusion criteria and patient validity, derived variables for analysis, handling of missing data, and format and content of tables will be detailed in the Statistical Analysis Plan (SAP). The SAP will be finalized before study database lock. The SAP is available upon request (see Table 4, Annex 1).

It is planned to have an interim analysis/analyses after minimum of 500 patients have been on study for at least 4 months, for the purpose of safety monitoring. The interim analysis will be detailed in the SAP. The final analysis will be performed after end of the study which is the date the analytical dataset is completely available.

9.7.2 Analysis of demography, disease details, prior and concomitant medication and other baseline data

All background data such as patient demographics, diagnosis and prior treatment for HCC, past medical history, concomitant diseases, and concomitant medication will be described by presenting frequency distributions and/or basic summary statistics.

9.7.3 Analysis of primary outcome(s)

Adverse events will be summarized for the safety population using NCI-CTCAE v4.03 as well as the Medical Dictionary for Regulatory Activities (MedDRA). Incidence proportions will be calculated based on the total number of patients valid for safety. Incidence proportions will be calculated by MedDRA system organ class, preferred term and worst CTCAE grade, for the MedDRA-based analyses, and by Event Category/NCI CTC Term and worst grade for the CTCAE-based analyses. These analyses will be performed for TEAEs, drug-related TEAEs, treatment-emergent SAEs, drug-related treatment-emergent SAEs, and TEAEs leading to dose reduction, dose interruption, or permanent dose discontinuation.

Subgroup analyses stratified by prognostic/predictive factors including liver function-related factors, tumor extent/stage, general condition such as ECOG performance status and comorbidities collected at baseline, including hepatic etiology [hepatitis C virus (HCV), hepatitis B virus (HBV), and alcoholic and nonalcoholic steatohepatitis (NASH)], as mentioned above, may be explored. For ECOG performance status, frequencies of recorded values and changes from performance status at baseline will be tabulated by visit. For vital signs, descriptive statistics will be calculated by visit. Where possible, laboratory data will be graded using the mapping provided within the NCI CTCAE manual version that is valid at time of analysis. CTCAE severity grading for laboratory abnormalities is mainly based on applicable laboratory threshold values outlined in NCI-CTCAE manuals. Frequency of laboratory abnormalities will be tabulated by NCI-CTCAE category and worst grade.

Changes in laboratory data and in CTCAE grades for laboratory data will also be analyzed.

9.7.4 Analysis of secondary outcome(s)

All summaries with respect to the effectiveness data will be descriptive. Effectiveness endpoints include OS, PFS, TTP, and best ORR. Investigator-assessed data, preferably per mRECIST according to local standard, will be used to evaluate the tumor response and radiological progression. Kaplan–Meier (KM) estimates and KM curves will be presented for OS, PFS, and TTP (as appropriate). Radiologically or clinically documented progression of tumor will be considered as disease progression. Subgroup analyses stratified with prognostic/predictive factors collected at baseline as mentioned above may be explored.

OS is defined as the time (days) from the start of regorafenib treatment to the date of death, due to any reason. Patients alive or lost to follow-up at the time of analysis will be censored at their last date of follow-up.

PFS is defined as the time (days) from the start of regorafenib treatment to the date of first observed disease progression (radiological or clinical, whichever is earlier) or death due to any cause, if death occurs before progression is documented.

TTP is defined as the time (days) from the start of regorafenib treatment to the first documented disease progression.

ORR will be defined for all patients using tumor assessment criteria, including mRECIST.

For regorafenib treatment, descriptive statistics will be calculated for the treatment duration, starting dose and average dose. The following frequencies will be calculated for regorafenib treatment: the number of patients with dose modification (e.g. reduction, interruption, re-challenge at protocol dose), number of dose modifications, and frequencies of reasons for dose modifications. These exposure analyses will be performed overall and by prior sorafenib dosing pattern.

9.7.5 Analysis of tertiary outcome(s)

In patients who had systemic anti-cancer therapy prior to the study, the treatment data will be summarized descriptively.

- Dosing of sorafenib treatment, including start/stop date, duration of treatment, given doses, reasons for discontinuation of sorafenib, time from discontinuation of sorafenib to start of regorafenib, and response to sorafenib will be retrospectively collected and summarized descriptively. Any potential side effects during prior sorafenib treatment (focusing on hand-

foot skin reactions, hypertension, fatigue, diarrhea and any other potential side effects leading to sorafenib dose modification) will be documented within a checklist in the past medical history section of CRF. Documented side effects under prior sorafenib treatment will be cumulatively reported within REFINE study report.
- Dosing of other treatment used prior to the study, including start/stop date, duration of treatment, given doses, reasons for discontinuation, and time from discontinuation of the treatment to start of regorafenib, will be retrospectively collected and summarized descriptively in the population enrolled in this study.

For the subgroup of patients with prior sorafenib treatment, the following analyses will be performed:

- Adverse events occurring after the start of regorafenib treatment will be correlated with adverse reactions occurring under prior sorafenib treatment.
- OS from the start of sorafenib treatment to death due to any cause will be analyzed using KM estimates and KM curves. Regorafenib exposure analyses will be performed by prior sorafenib dose.

These analyses might be also performed with respect to other prior therapies (e.g. lenvatinib), dependent on actual numbers of patients treated with such other prior therapies.

9.7.6 Analysis of safety data

Safety data comprise the primary endpoint of the study and the analysis is detailed in section 9.7.3.

9.8 Quality control

9.8.1 Data quality

Before study start at the sites, all investigators will be sufficiently trained on the background and objectives of the study and ethical as well as regulatory obligations. Investigators will have the chance to discuss and develop a common understanding of the OS protocol and the CRF.

A CRO will be selected and assigned for EDC system development, quality control, verification of the data collection, data analysis and data transfer to Bayer.

All outcome variables and covariates will be recorded in a standardized CRF. After data entry, missing or implausible data will be queried and the data will be validated. A check for multiple documented patients will be done.

Detailed information on checks for completeness, accuracy, plausibility and validity are given in the Data Management Plan (DMP). The same plan will specify measures for handling of missing data and self-evident corrections. The DMP is available upon request (see Table 4: List of stand-alone documents, Annex 1).

Medical Review of the data will be performed according to the Medical Review Plan (MRP). The purpose of the Medical Review is to verify the data from a medical perspective for plausibility, consistency, and completeness and to identify potential issues that could affect the robustness of the collected study data or the progress of the study. Detailed information on the Medical review will be described in the MRP, which is available upon request (see Table 4, Annex 1).

National and international data protection laws as well as regulations on observational studies will be followed. Electronic records used for capturing patient documentation (eCRF) will be validated according to 21 Code of Federal Regulations (CFR) Part 11 (FDA) [13]. The documentation is available upon request (Table 4, Annex 1).

9.8.2 Quality review

Quality review will be done in two steps:

In the first step, to assess the site's training status, telephone interviews will be conducted with 20% of the sites in each country (including at least one site in each country) without further selection criteria. Interviews should start when 20% of sites have started enrolment.

In the second step, source data verification will be conducted. The purpose is to review the documented data for completeness and plausibility, adherence to the OS protocol and verification with source documents. To accomplish this, study monitors will access medical records onsite for data verification. Data from a minimum of 125 patients, covering 1000 data items (such as date of birth, height, weight) or data item groups (such as concomitant diseases, adverse events), will be reviewed independent of the overall number of data items collected in the study. Onsite visits should occur no later than when 80% of patients have completed the study. This procedure is based on the exclusion of an error rate of 5%.

Detailed measures for quality reviews will be described in the Quality Review Plan (QRP). The QRP is available upon request (see Table 4, Annex 1).

9.8.3 Storage of records and archiving

The study initiator and funder will ensure that all relevant documents of this post-authorization safety study (PASS), including CRFs and other patient records, will be stored after the end or discontinuation of the study for at least 15 years. Other instructions for storage of medical records will remain unaffected.

The investigators participating in the study are required to archive documents at their sites according to local requirements, considering possible audits and inspections from the sponsor and/or local authorities. It is recommended to store documents for a retention period of at least 15 years.

Statistical programming performed to generate results will be stored in the productive area of the programming system for at least 15 years at the sponsor's site.

9.8.4 Certification/qualification of external parties

Not applicable.

9.9 Limitations of the research methods

Because of the non-interventional study design and limitations inherent to observational studies, findings generated from this study are subject to biases, such as selection bias, limitations to availability of historical medical data, and differences in treatment or reporting owing to local guidelines.

Results for secondary effectiveness variables PFS or TTP must be interpreted carefully because of the uncontrolled setting: time periods between follow-up visits are more variable than in controlled

clinical studies, in which a fixed visit schedule is maintained. The quality of the tumor status evaluation will differ from that in controlled clinical studies.

Comparison of outcomes after treatment with regorafenib versus treatment with a comparator cannot be performed in this single-arm study. Comparisons can only be performed with historical data from clinical or observational studies, which is prone to bias and confounding. Historical patient data collected with respect to prior sorafenib or other treatments may be incomplete and/or differ relating to sorafenib use and standard of care in local practice. Historical data provided by patient interview is prone to errant recall.

Although the study aims to include participants from a variety of geographic regions, there may be local limitations that reduce the representativeness of patients recruited, such as patient access to recruiting physicians (including differences in patient profile in specialized, recruiting sites vs local general practice), regorafenib availability and reimbursement, and decisions relating to local standard of care. In addition, the planned patient sample size to be recruited from Japan (150 patients) may result in comparative over-representation from this country with respect to other individual nations.

9.10 Other aspects

Not applicable.

10. Protection of human subjects

10.1 Ethical conduct of the study

This study is an observational study where regorafenib is prescribed in the customary manner in accordance with the terms of the marketing authorization. There is no assignment of a patient to a particular therapeutic strategy. The treatment decision falls within current practice and the prescription of the medicines is clearly separated from the decision to include the patient in the study. No additional diagnostic or monitoring process is required for participation or during the study. Epidemiological methods will be used for the analysis of the collected data.

10.2 Regulatory authority approvals/authorizations

The study will be carried out within an approved indication in accordance with guidelines and regulations of EMA, FDA and applicable local law(s) and regulation(s) (e.g. Regulation (EU) No 520/2012 [14]). Recommendations given by other organizations will be followed as well (e.g. EFPIA [15], ENCePP [16]). ICH-GCP guidelines will be followed whenever possible.

In addition, the guidelines on good pharmacovigilance practices (GVP module VI [17] and since the study qualifies as a PASS, GVP module VIII [18], [19]) will be followed.

10.3 Independent ethics committee (IEC) or institutional review board (IRB)

In all countries where reference to an IEC/IRB is required, documented approval from appropriate IECs/IRBs will be obtained for all participating centers prior to study start. When necessary, an extension, amendment or renewal of the IEC/IRB approval must be obtained and also forwarded to the MAH. The IEC/IRB must supply to the MAH, upon request, a list of the IEC/IRB members

involved in the vote and a statement to confirm that the IEC/IRB is organized and operates according to applicable laws and regulations.

10.4 Patient information and consent

Before documentation of any data, informed consent is obtained by the patient or a legal representative in writing. In countries where required by law or regulation, the investigator must have the IECs/IRB written approval / favorable opinion of the written informed consent form and any other written information to be provided to patients prior to the beginning of the observation.

10.5 Patient insurance

In this observational study, data on routine treatment of patients in daily practice are documented and analyzed with the help of epidemiological methods. Treatment including diagnosis and monitoring of therapy follows exclusively routine daily practice. Current medical daily practice is observed, and for the patient no risks beyond regular therapy exist – there is no additional hazard arising from study participation. As no study related risks exist, there is no need to protect the patient additionally by a patient insurance. The general regulations of medical law and the professional indemnity insurance of the investigators and, respectively, the institutions involved provide sufficient protection for both patient and investigator.

No study medication will be provided to participants. Thus, product insurance is covered by the existing product liability.

10.6 Confidentiality

Bayer as well as all investigators ensure adherence to applicable data privacy protection regulation. Data are transferred in encoded form only. The entire documentation made available to Bayer does not contain any data which, on its own account or in conjunction with other freely available data, can be used to re-identify natural persons. The investigators are obligated to ensure that no documents contain such data.

All records identifying the subject will be kept confidential and will not be made publicly available. Patient names will not be supplied to Bayer AG. If the patient name appears on any document, it must be obliterated before a copy of the document is supplied to Bayer AG. Study findings stored on a computer will be stored in accordance with local data protection laws.

The investigator will maintain a list to enable patients' records to be identified in case of queries. In case of a report of a serious adverse event (SAE), the responsible pharmacovigilance person may ask for additional clarification. In that case, the company is not allowed to directly contact the patient. All additional information will be provided by the investigator.

11. Management and reporting of adverse events/adverse reactions

11.1 Definitions

An adverse event (AE) is any untoward medical occurrence in a patient administered a medicinal product and which does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (e.g. an abnormal laboratory finding), symptom,

or disease temporally associated with the use of a medicinal product, whether or not considered related to this medicinal product [20].

The term also covers laboratory findings or results of other diagnostic procedures that are considered to be clinically relevant (e.g. that require unscheduled diagnostic procedures or treatments or result in withdrawal from the study).

All adverse events, including laboratory abnormalities, leading to dose modifications (i.e. interruptions, reductions, permanent discontinuation) need to be documented as AE.

The AE may be:

- A new illness
- Worsening of a sign or symptom of the condition under treatment or of a concomitant illness
- An effect of the study medication
- Off label use[1], occupational exposure, lack of drug effect, medication error, overdose, drug abuse, drug misuse or drug dependency itself, as well as any resulting event
- An effect related to a pre-existing condition having improved (unexpected therapeutic benefits are observed)
- Product exposure via mother/ father (exposure during conception, pregnancy, childbirth and breastfeeding)

New lesions per se should not be regarded as AEs. Instead, the associated signs and symptoms should be recorded as AEs. If progressive disease leads to signs and symptoms that meet the criteria of AE/SAE, the signs and symptoms must be reported as an AE/SAE and not the underlying (progressive) disease.

As mentioned above no causal relationship with a product is implied by the use of the term “adverse event”.

An Adverse Reaction (AR) is defined as a response to a medicinal product which is noxious and unintended. An AR is any AE judged as having a reasonable suspected causal relationship to regorafenib.

Causal relationship: The assessment of the causal relationship between an AE and the administration of treatment is a clinical decision based on all available information at the time of the completion of the CRF. The assessment is based on the question whether there was a "reasonable causal relationship" to the study treatment in question. Possible answers are "yes" or "no".

An assessment of "no" would include:

The existence of a clear alternative explanation (e.g. mechanical bleeding at surgical site)

[1] According to GVP Module VI, off label use "relates to situations where the medicinal product is intentionally used for a medical purpose not in accordance with the authorized product information". Off label use *per se* is an adverse event, even if no adverse reaction is reported, therefore it needs to be ensured that all relevant variables to identify such potential incidents are collected (e.g. indication).

Non-plausibility (e.g. the subject is struck by an automobile when there is no indication that the product caused disorientation that may have caused the event; cancer developing a few days after the first product administration)

An assessment of "yes" indicates that there is a reasonable suspicion that the AE is associated with the use of the study treatment. Factors to be considered in assessing the relationship of the AE to study treatment include:

The temporal sequence from product administration: The event should occur after the product is given. The length of time from product exposure to event should be evaluated in the clinical context of the event.

Recovery on product discontinuation (de-challenge), recurrence on product re-introduction (re-challenge): Subject's response after de-challenge or subjects response after re-challenge should be considered in the view of the usual clinical course of the event in question.

Underlying, concomitant, intercurrent diseases: Each event should be evaluated in the context of the natural history and course of the disease being treated and any other disease the subject may have.

Concomitant medication or treatment: The other products the subject is taking or the treatment the subject receives should be examined to determine whether any of them may be suspected to cause the event in question.

The pharmacology and pharmacokinetics of the study treatment: The pharmacokinetic properties (absorption, distribution, metabolism and excretion) of the study treatment, coupled with the individual subject's pharmacodynamics should be considered.

An AE is serious (SAE) if it:

- Results in death
- Is life-threatening
- Requires inpatient hospitalization or prolongation of existing hospitalization (see exceptions below)
- Results in persistent or significant disability or incapacity
- Is a congenital anomaly or birth defect
- Is medically important.

Death is usually the outcome of an underlying clinical event that causes it. Hence, it is the cause of death that should be regarded as the SAE. The one exception to this rule is 'sudden death' where no cause has been established. In this instance, 'sudden death' should be regarded as the AE and 'fatal' as its reason for being 'serious'.

Life-threatening: The term "life-threatening" in the definition of "serious" refers to an AE in which the subject was at risk of death at the time of the event. It does not refer to an AE which hypothetically might have caused death if it were more severe.

Hospitalization: Any AE leading to hospitalization or prolongation of hospitalization will be considered as serious, unless the admission is:

- planned before subject's inclusion in the study (i.e. elective or scheduled surgery) or

- ambulant (shorter than 12 hours) or
- part of the normal treatment or monitoring of the studied disease (i.e. not due to a worsening of the disease)

However it should be noted that invasive treatment during any hospitalization may fulfill the criteria of 'medically important' and as such may be reportable as a SAE dependent on clinical judgment. In addition where local regulatory authorities specifically require a more stringent definition, the local regulation takes precedent.

Disability means a substantial disruption of a person's ability to conduct normal life's functions.

Congenital anomaly (birth defect), i.e. any congenital anomaly observed in an infant, or later in a child, should be regarded as a SAE when:

- The mother had been exposed to a medicinal product at any stage during conception or pregnancy or during delivery
- The father was exposed to a medicinal product prior to conception

Other medically important serious event: any AE may be considered serious because it may jeopardize the patient and may require intervention to prevent another serious condition. Medically important events either refer to or might be indicative of a serious disease state. Such reports warrant special attention because of their possible association with serious disease state and may lead to more decisive action than reports on other terms.

11.2 Collection

Starting with the first application of regorafenib after enrollment into the study, all **non-serious AEs** must be documented on the AE Report Form or in the CRF/EDC system and forwarded to the MAH within 7 calendar days of awareness.

All **SAEs** must be documented and forwarded immediately (within one business day of awareness). For each AE, the investigator must assess and document the seriousness, duration, relationship to product, action taken and outcome of the event.

If a **pregnancy** occurs during the study, although it is not an SAE itself, it should be documented and forwarded to the MAH within the same time limits as a SAE. The result of a pregnancy will be followed-up according to applicable Bayer SOPs. Any data on abnormal findings concerning either the mother or the baby will be collected as AEs.

The documentation of any AE/SAE ends with the completion of the observation period of the patient. However, any AE/SAE - regardless of the relationship and the seriousness - occurring up to 30 days after the last dose of regorafenib within the study period has to be documented and forwarded to the MAH within the given timelines, even if this period goes beyond the end of observation.

As long as the patient has not received any regorafenib within the frame of the study AEs /SAEs do not need to be documented as such in this observational study. However, they are part of the patient's medical history.

For any serious product-related AE occurring after study end, the standard procedures that are in place for spontaneous reporting have to be followed.

All laboratory abnormalities leading to dose modifications (i.e. interruptions, reductions, permanent discontinuation) need to be documented as AE.

New lesions per se should not be regarded as AEs. Instead, the associated signs and symptoms should be recorded as AEs. If progressive disease leads to signs and symptoms that meet the criteria of AE/SAE the signs and symptoms must be reported as an AE/SAE and not the underlying (progressive) disease.

11.3 Management and reporting

Non-serious AEs

The outcome of all reported AEs will be followed up and documented. Where required, investigators might be contacted directly by the responsible study staff to provide further information.

Non-serious ARs

All non-serious ARs occurring under treatment with regorafenib that qualify for expedited reporting will be submitted to the relevant authorities according to EU PV legislation (Regulation (EU) No 1235/2010 and Directive 2010/84/EU, Module VI [17]) and according to national regulations by the MAH; however, all investigators must obey local legal requirements.

For non-serious ARs occurring under non-Bayer products the investigator has to account for and comply with the reporting system of the product's Marketing Authorization Holder within the frame of local laws and regulations as well as other locally applicable laws and regulations.

Serious AEs

Any SAE or pregnancy entered into the CRF/EDC system will be forwarded immediately (within one business day of awareness) to the pharmacovigilance country person being responsible for SAE processing. The outcome of all reported SAEs (resolution, death etc.) will be followed up and documented. Where required, investigators might be contacted directly by the pharmacovigilance country person in charge to provide further information.

Submission to the relevant authorities according to national regulations will be done by the MAH for SAEs related to regorafenib treatment; however, all investigators must obey local legal requirements.

For any serious drug-related AE occurring after study end, the standard procedures that are in place for spontaneous reporting have to be followed.

For SAEs that occurred while administering non-Bayer products the investigator has to account for and comply with the reporting system of the product's Marketing Authorization Holder within the frame of local laws and regulations as well as other locally applicable laws and regulations.

An isolated laboratory abnormality that is assigned Grade 4 according to NCI-CTCAE version 4.0 definition is not reportable as an SAE unless the investigator assesses that the event meets standard International Conference on Harmonization (ICH) criteria for an SAE.

11.4 Evaluation

Whenever new important safety information is received, e.g. case reports from an investigator, the reports are processed and entered into the global pharmacovigilance safety database. These reports will be reviewed on a regular basis (for information on collection, management and reporting of case

reports, refer to section 11.2 and 11.3). If a potential safety signal is suspected, an investigation of the suspected potential signal will be performed according to internal standard operating procedures, for further evaluation within the context of benefit risk.

12. Plans for disseminating and communicating study results

This study will be registered at “www.clinicaltrials.gov" and in in the EU PAS register at “http://www.encepp.eu/encepp_studies/indexRegister.shtml”. Results will be disclosed in a publicly available database within the standard timelines.

The results of this observational study are intended to be published in a peer-reviewed journal and as abstracts/presentations at medical congresses under the oversight of the MAH. Appropriate guidelines and recommendation on good publication practice will be followed (e.g. GPP3 Guidelines [21], STROBE [22]). No individual investigator may publish on the results of this study, or their own patients, without prior approval from the MAH.

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Annex 1: List of stand-alone documents

Table 4: List of stand-alone documents

Document Name	Final version and date (if available)*
19244_REFINE_Country & Site list	tbd
19244_REFINE_Investigator list	tbd
19244_REFINE_Steering Committee Members	tbd
19244_REFINE_Steering Committee Charter	tbd
19244_REFINE_CRF	v.06 (draft), 24 FEB 2017
EDC System	tbd
EDC System Validation	tbd
19244_REFINE_DMP	tbd
19244_REFINE_SAP	tbd
19244_REFINE_QRP	tbd
19244_REFINE_MRP	tbd

* Draft versions are indicated by <draft> in brackets and date. “tbd” indicates documents that are not available at the time of protocol creation, but will be issued at a later stage

Annex 2: ENCePP checklist for post-authorization safety study (PASS) protocols

Study title: REFINE: Regorafenib observational study in hepatocellular carcinoma

Study reference number: 19244

Section 1: Milestones	**Yes**	**No**	**N/A**	**Section Number**
1.1 Does the protocol specify timelines for				
1.1.1 Start of data collection[2]	☒	☐	☐	6
1.1.2 End of data collection[3]	☒	☐	☐	6
1.1.3 Study progress report(s)	☐	☐	☐	
1.1.4 Interim progress report(s)	☐	☐	☐	
1.1.5 Registration in the EU PAS register	☐	☐	☐	
1.1.6 Final report of study results.	☒	☐	☐	6

Comments:

Section 2: Research question	**Yes**	**No**	**N/A**	**Section Number**
2.1 Does the formulation of the research question and objectives clearly explain:	☒	☐	☐	7,8,9
2.1.1 Why the study is conducted? (e.g. to address an important public health concern, a risk identified in the risk management plan, an emerging safety issue)	☒	☐	☐	7
2.1.2 The objective(s) of the study?	☒	☐	☐	8
2.1.3 The target population? (i.e. population or subgroup to whom the study results are intended to be generalised)	☒	☐	☐	9
2.1.4 Which hypothesis(-es) is (are) to be tested?	☐	☐	☒	
2.1.5 If applicable, that there is no *a priori* hypothesis?	☒	☐	☐	9.7.1

Comments:

This is a prospective, observational study, so no hypothesis is being tested

[2] Date from which information on the first study is first recorded in the study dataset or, in the case of secondary use of data, the date from which data extraction starts.

[3] Date from which the analytical dataset is completely available.

Section 3: Study design		**Yes**	**No**	**N/A**	**Section Number**
3.1	Is the study design described? (e.g. cohort, case-control, cross-sectional, new or alternative design)	☒	☐	☐	9.1
3.2	Does the protocol specify whether the study is based on primary, secondary or combined data collection?	☒	☐	☐	9.1
3.3	Does the protocol specify measures of occurrence? (e.g. incidence rate, absolute risk)	☒	☐	☐	9.7.1
3.4	Does the protocol specify measure(s) of association? (e.g. relative risk, odds ratio, excess risk, incidence rate ratio, hazard ratio, number needed to harm (NNH) per year)	☒	☐	☐	9.7.3
3.5	Does the protocol describe the approach for the collection and reporting of adverse events/adverse reactions? (e.g. adverse events that will not be collected in case of primary data collection)	☒	☐	☐	9.2.7

Comments:

Section 4: Source and study populations		**Yes**	**No**	**N/A**	**Section Number**
4.1	Is the source population described?	☒	☐	☐	9.1
4.2	Is the planned study population defined in terms of:				
	4.2.1 Study time period?	☒	☐	☐	9.1
	4.2.2 Age and sex?	☐	☐	☒	
	4.2.3 Country of origin?	☒	☐	☐	9.1
	4.2.4 Disease/indication?	☒	☐	☐	9.1
	4.2.5 Duration of follow-up?	☒	☐	☐	9.1
4.3	Does the protocol define how the study population will be sampled from the source population? (e.g. event or inclusion/exclusion criteria)	☒	☐	☐	9.2.1

Comments:

Age and sex are not defined under the study population; consecutive patients fulfilling the inclusion criteria (of any age or sex) will be included

Section 5: Exposure definition and measurement		**Yes**	**No**	**N/A**	**Section Number**
5.1	Does the protocol describe how the study exposure is defined and measured? (e.g. operational details for defining and categorising exposure, measurement of dose and duration of drug exposure)	☒	☐	☐	9.3
5.2	Does the protocol address the validity of the exposure measurement? (e.g. precision, accuracy, use of validation sub-study)	☒	☐	☐	9.3
5.3	Is exposure classified according to time windows? (e.g. current user, former user, non-use)	☒	☐	☐	9.3

Section 5: Exposure definition and measurement	**Yes**	**No**	**N/A**	**Section Number**
5.4 Is exposure classified based on biological mechanism of action and taking into account the pharmacokinetics and pharmacodynamics of the drug?	☐	☒	☐	

Comments:

This is a non-interventional study, and all treatment decisions (including dosing and exposure) will be made by the treating physician without influence from the sponsor

Section 6: Outcome definition and measurement	**Yes**	**No**	**N/A**	**Section Number**
6.1 Does the protocol specify the primary and secondary (if applicable) outcome(s) to be investigated?	☒	☐	☐	9.1
6.2 Does the protocol describe how the outcomes are defined and measured?	☒	☐	☐	9.1
6.3 Does the protocol address the validity of outcome measurement? (e.g. precision, accuracy, sensitivity, specificity, positive predictive value, prospective or retrospective ascertainment, use of validation sub-study)	☒	☐	☐	9.1
6.4 Does the protocol describe specific endpoints relevant for Health Technology Assessment? (e.g. HRQoL, QALYs, DALYS, health care services utilisation, burden of disease, disease management)	☐	☒	☐	

Comments:

Health Technology Assessment endpoints are not included in the observational data

Section 7: Bias	**Yes**	**No**	**N/A**	**Section Number**
7.1 Does the protocol describe how confounding will be addressed in the study?	☒	☐	☐	9.1.3
7.1.1. Does the protocol address confounding by indication if applicable?	☒	☐	☐	9.7
7.2 Does the protocol address:	☐	☐	☐	
7.2.1. Selection biases (e.g. healthy user bias)	☒	☐	☐	9.9
7.2.2. Information biases (e.g. misclassification of exposure and endpoints, time-related bias)	☒	☐	☐	9.9
7.3 Does the protocol address the validity of the study covariates?	☒	☐	☐	9.9

Comments:

Section 8: Effect modification	**Yes**	**No**	**N/A**	**Section Number**
8.1 Does the protocol address effect modifiers? (e.g. collection of data on known effect modifiers, sub-group analyses, anticipated direction of effect)	☒	☐	☐	9.3

Comments:

Section 9: Data sources	**Yes**	**No**	**N/A**	**Section Number**
9.1 Does the protocol describe the data source(s) used in the study for the ascertainment of:				
9.1.1 Exposure? (e.g. pharmacy dispensing, general practice prescribing, claims data, self-report, face-to-face interview)	☒	☐	☐	9.4
9.1.2 Outcomes? (e.g. clinical records, laboratory markers or values, claims data, self-report, patient interview including scales and questionnaires, vital statistics)	☒	☐	☐	9.4
9.1.3 Covariates?	☒	☐	☐	9.3
9.2 Does the protocol describe the information available from the data source(s) on:				
9.2.1 Exposure? (e.g. date of dispensing, drug quantity, dose, number of days of supply prescription, daily dosage, prescriber)	☒	☐	☐	9.4
9.2.2 Outcomes? (e.g. date of occurrence, multiple event, severity measures related to event)	☒	☐	☐	9.4
9.2.3 Covariates? (e.g. age, sex, clinical and drug use history, co-morbidity, co-medications, lifestyle)	☒	☐	☐	9.4
9.3 Is a coding system described for:				
9.3.1 Exposure? (e.g. WHO Drug Dictionary, Anatomical Therapeutic Chemical (ATC) Classification System)	☒	☐	☐	9.7
9.3.2 Outcomes? (e.g. International Classification of Diseases (ICD)-10, Medical Dictionary for Regulatory Activities (MedDRA))	☒	☐	☐	9.7
9.3.3 Covariates?	☒	☐	☐	9.7
9.4 Is a linkage method between data sources described? (e.g. based on a unique identifier or other)	☒	☐	☐	9.8

Comments:

Section 10: Analysis plan	**Yes**	**No**	**N/A**	**Section Number**
10.1 Is the choice of statistical techniques described?	☒	☐	☐	9.7.1
10.2 Are descriptive analyses included?	☒	☐	☐	9.7
10.3 Are stratified analyses included?	☒	☐	☐	9.7

Section 10: Analysis plan	**Yes**	**No**	**N/A**	**Section Number**
10.4 Does the plan describe methods for adjusting for confounding?	☒	☐	☐	9.9
10.5 Does the plan describe methods for handling missing data?	☒	☐	☐	9.9
10.6 Is sample size and/or statistical power estimated?	☒	☐	☐	9.5

Comments:

Section 11: Data management and quality control	**Yes**	**No**	**N/A**	**Section Number**
11.1 Does the protocol provide information on data storage? (e.g. software and IT environment, database maintenance and anti-fraud protection, archiving)	☒	☐	☐	9.8
11.2 Are methods of quality assurance described?	☒	☐	☐	9.8
11.3 Is there a system in place for independent review of study results?	☒	☐	☐	9.8

Comments:

Section 12: Limitations	**Yes**	**No**	**N/A**	**Section Number**
12.1 Does the protocol discuss the impact on the study results of:				
12.1.1 Selection bias?	☒	☐	☐	9.9
12.1.2 Information bias?	☒	☐	☐	9.9
12.1.3 Residual/unmeasured confounding? (e.g. anticipated direction and magnitude of such biases, validation sub-study, use of validation and external data, analytical methods)	☒	☐	☐	9.9
12.2 Does the protocol discuss study feasibility? (e.g. study size, anticipated exposure, duration of follow-up in a cohort study, patient recruitment)	☒	☐	☐	9.5

Comments:

Section 13: Ethical issues	**Yes**	**No**	**N/A**	**Section Number**
13.1 Have requirements of Ethics Committee/ Institutional Review Board been described?	☒	☐	☐	10.3
13.2 Has any outcome of an ethical review procedure been addressed?	☐	☒	☐	
13.3 Have data protection requirements been described?	☒	☐	☐	10.6

Comments:

No relevant outcomes of an ethical review procedure are necessary for inclusion

Section 14: Amendments and deviations	**Yes**	**No**	**N/A**	**Section Number**
14.1 Does the protocol include a section to document amendments and deviations?	☒	☐	☐	5

Comments:

No amendments or deviations have been reported to date

Section 15: Plans for communication of study results	**Yes**	**No**	**N/A**	**Section Number**
15.1 Are plans described for communicating study results (e.g. to regulatory authorities)?	☒	☐	☐	12
15.2 Are plans described for disseminating study results externally, including publication?	☒	☐	☐	12

Comments:

Name of the main author of the protocol: Keiko Nakajima

Date: dd/Month/year

Signature: _____

Annex 3: Additional information

Not applicable

Annex 4: Description of amendments

AM01: Local Amendment for Japan

AM01; 07 MAR 2017	
Protocol section	**Description**
Cover Page	Local Amendment Cover Page (including signature field for Japanese Medical Director) added
Post Authorization Study Information	The specific hepatic safety interest in the Japanese population has been added to the primary objective
4. Abstract	The specific hepatic safety interest in the Japanese population has been added to the primary objective
8.1 Primary objective	Additional clarification of the specific hepatic safety interest in the Japanese population has been added
9.1 Study design	Additional information relating to interim and final analyses, and observation period for Japanese patients (2 years) and rationale included
9.2.2. Inclusion criteria	Japanese-subset-specific criterion added: "For Japanese population, uHCC patients are treated with regorafenib according to the product label in Japan"
9.3.3.11 Adverse events	Additional information relating to hepatic events added: "For the Japanese population, hepatic disorders are considered as the important safety focus." Further rationale is included
9.5 Study size	The number of planned Japanese patients for enrollment (150) and sample-size rationale is included
10.2 Regulatory authority approvals/authorizations	Clarification of conduct of study in accordance with Japanese regulations is included
Annex 5	Global signatories removed except for Medical Expert