Document Type:	Clinical Study Protocol
Official Title:	A single arm, open-label, multicenter Phase 2 study of regorafenib in participants who have been treated in a previous Bayer-sponsored regorafenib study (monotherapy or combination treatment) that has reached the primary completion endpoint or the main data analysis, or has been stopped prematurely.
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Title Page

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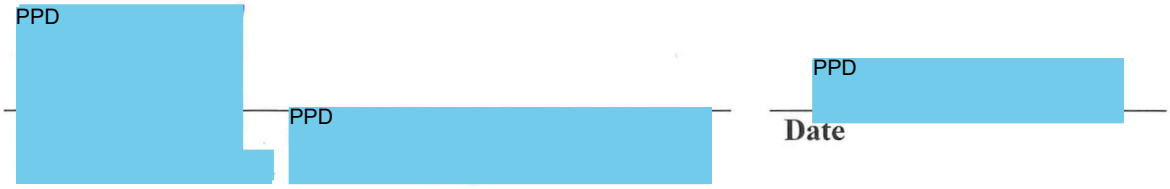
Protocol number:	20328
Compound Number:	BAY 73-4506
Study phase:	Phase 2
Short title:	Regorafenib rollover study.
Sponsor Name and Legal Registered Address:	**Sponsor (Non-US):** Bayer AG, D-51368 Leverkusen, Germany **Sponsor (US territory):** Bayer HealthCare Pharmaceuticals Inc., 100 Bayer Boulevard, P.O. Box 915, Whippany, New Jersey 07981-0915, USA
Regulatory Agency Identifier Number(s):	**EudraCT 2018-003650-24**
Approval Date:	20 NOV 2018

Sponsor Signatory



Medical Monitor Name and Contact Information will be provided separately.

Protocol Amendment Summary of Changes Table

DOCUMENT HISTORY	
Document	**Date**
Amendment 1	20 NOV 2018
Original Protocol	27 SEP 2018

Amendment 1 (20 NOV 2018)

This amendment is considered to be substantial based on the criteria set forth in Article 10(a) of Directive 2001/20/EC of the European Parliament and the Council of the European Union.

Overall Rationale for the Amendment:

Section # and Name	Description of Change	Brief Rationale
Synopsis, 3, 9, 9.1, 9.4.1, 9.4.2	Safety was upgraded to a second primary objective and a respective endpoint was added to the protocol. A respective endpoint was also added for the secondary objective tolerability.	These updates were done to ensure compliance with posting requirements on CT.gov following a review of the initial Protocol Registration Form.
11	List of 4 initial feeder studies in Section 11 was removed.	The feeder protocol titles were removed from the section “References” to avoid any future amendments to enable participants of other than the currently considered regorafenib studies to enter this roll-over study.

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1. Protocol Summary

1.1 Synopsis

Protocol Title: A single arm, open-label, multicenter Phase 2 study of regorafenib in participants who have been treated in a previous Bayer-sponsored regorafenib study (monotherapy or combination treatment) that has reached the primary completion endpoint, or main data analysis, or has been stopped prematurely.

Short Title: Regorafenib rollover study

Rationale: The primary purpose of the study is to enable participants, currently receiving regorafenib in a Bayer-sponsored clinical trial, to continue treatment after their respective study has reached the primary completion endpoint, main data analysis, or has been stopped prematurely, and the respective data have been cleaned. Participants will be able to continue treatment until the treating physician feels the participant is no longer benefiting from treatment.

Objectives

Objectives
Primary
• The primary purpose of the program is to enable participants, currently receiving regorafenib in a Bayer-sponsored clinical trial and assessed by the principal investigator (PI) to be benefitting, to continue regorafenib treatment after their respective study has reached the primary completion endpoint, or main data analysis, or has been stopped prematurely. • And the documentation of safety
Secondary
• Documentation of tolerability

Overall Design:

This is an open-label study that will enable participants currently receiving regorafenib in a completed Bayer-sponsored regorafenib clinical trial to continue treatment. A completed study is defined as one that has reached the primary completion endpoint, or main data analysis, or has been stopped prematurely, and the respective data have been cleaned.

Disclosure Statement: This is an open-label study that will enable participants currently receiving regorafenib in a completed Bayer-sponsored regorafenib clinical trial to continue treatment.

Number of Participants:

Participants who are currently receiving treatment in on-going regorafenib studies may be eligible to enroll in the study. There may be periods when there are no active participants in this study but it will remain open for enrollment.

Intervention Groups and Duration:

The start of the treatment period is defined by the first administration of regorafenib in the rollover study. Participants will be treated in 28-day cycles (ie, 3 weeks on, 1 week off) with once daily oral administration of regorafenib. Participants will continue regorafenib treatment until any of the discontinuation criteria specified in Section 7.2 occur.

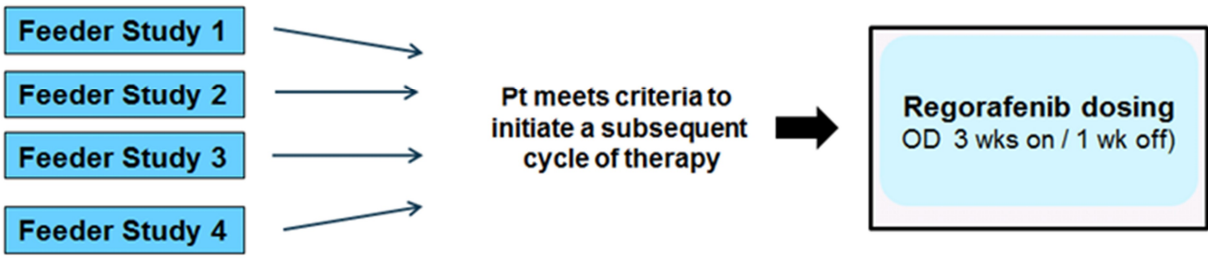
After permanent discontinuation from the study, an end of treatment (EoT) visit will be performed within 14 days after the last dose of regorafenib was administered. Following completion of the EoT evaluation, a phone call to monitor safety will take place 30-35 days after the last dose of regorafenib was administered.

Data Monitoring Committee: No

1.2 Schema

The design of the study is represented in Figure 1–1.

Figure 1–1: Study schema



1.3 Schedule of Activities (SoA)

Table 1–1: Schedule of activities

Procedure	Screening[a]	Intervention Period[b] [Cycles consisting of 4 weeks]		End of study treatment (up to 14 days after last dose)	Safety Follow-up (30-35 days after last dose, phone call)	Notes
		Cycle 1 Day 1[c]	Cycle 4 Day 1 + every 3 months (+/- 1 week)			
Informed consent	X					
Inclusion and exclusion criteria	X					Including pregnancy test done by treating physician.
Demography	X					
Tumor type	X					
Medical history	X					Medical important events, e.g. Grade 3/4 (S)AEs, since the start of treatment in the feeder study should be reported as medical history in this rollover study.
Study treatment		→→→→→→→				Recheck clinical status before 1st dose of study medication. Regorafenib dosing as per feeder study protocol.
Drug dispensing		X	X			
Drug accountability		X	X	X		
AE review	X	X	X	X	X	To be documented only: • AEs leading to dose reduction, interruption/delay and discontinuation • Any ongoing Grade 3 and 4 AEs, or Grade 2 AEs that affect vital organs (e.g. heart, liver) per feeder study protocol CTCAE version. These events need to be re-graded by the investigator

						according to CTCAE Ver 5.0. • Any new CTCAE Ver 5.0 Grade 3 and 4 AEs, or Grade 2 AEs that affect vital organs (e.g. heart, liver)
SAE review	X	X	X	X	X	To be documented any ongoing or new SAEs
Concomitant medication review	X	X	X	X	X	

Abbreviations: AE - adverse event; CTCAE - Common terminology criteria for adverse events; SAE - serious adverse event.
a During the screening period the participant will be on treatment under the umbrella of the feeder study. At the end of treatment visit of the feeder study, eligibility criteria will be reviewed and the participants should sign informed consent for the rollover study.
b Safety assessments should be done according to local standard of care and regorafenib label information by the treating physician.
c The treating investigator should ensure a seamless transition without a change in the treatment schedule. Any treatment interruption should not exceed 28 consecutive days including 1 week break.

2. Introduction

Experience has shown that in nearly all clinical trials with regorafenib (Stivarga®) there are participants who are continuing to receive regorafenib after the study has been completed. A completed study is defined as one that has reached the primary completion endpoint, main data analysis, or has been stopped prematurely, and the respective data have been cleaned. The intention of this rollover study is to enable these participants who are still benefiting from treatment to continue to receive regorafenib treatment.

2.1 Study Rationale

The primary purpose of the study is to enable participants, currently receiving regorafenib in a Bayer sponsored clinical trial, to continue treatment after their respective study has been completed. A completed study is defined as one that has reached the primary completion endpoint, main data analysis, or has been stopped prematurely, and the respective data have been cleaned. Participants will be able to continue treatment until the treating physician feels the participant is no longer benefiting from treatment.

2.2 Background

Approved indications of regorafenib include pre-treated metastatic colorectal cancer (CRC), hepatocellular carcinoma (HCC), and gastro-intestinal stromal tumors (GIST). Regorafenib is currently being studied in multiple solid tumors. This rollover study encompasses Phase 1-4 Bayer-sponsored clinical trials that have reached the primary completion endpoint, or main data analysis, or have been stopped prematurely, and the respective data have been cleaned, and are only kept open to ensure treatment of participants who are still benefiting from regorafenib treatment.

2.3 Benefit/Risk Assessment

Only participants who have been treated in a previous Bayer-sponsored regorafenib study and are still benefiting from treatment will be allowed to be enrolled in this study. They will continue treatment on the dose level that has been well tolerated before.

The site's principal investigator of the regorafenib study to which the subject is initially assigned, is expected to assess the overall benefit/risk for each participant. When the investigator deems there is a positive benefit/risk assessment the participant can be included in this rollover study.

More detailed information about the known and expected benefits and risks and reasonably expected adverse events of regorafenib may be found in the Investigator's Brochure (IB).

3. Objectives and Endpoints

Objectives	Endpoints
Primary	
• The primary purpose of the program is to enable participants, currently receiving regorafenib in a Bayer sponsored clinical trial and assessed by the PI to be benefitting, to continue regorafenib treatment after their respective study has met its primary completion date, or main data analysis, or has been stopped prematurely. • And the documentation of safety	• Frequency and severity of SAEs and protocol-specified AEs
Secondary	
• Documentation of tolerability	• Frequency of dose modifications

4. Study Design

This is an open-label study that will enable participants currently receiving regorafenib in a completed Bayer-sponsored regorafenib clinical trial to continue treatment. A completed study is defined as one that has reached the primary completion endpoint, main data analysis, or has been stopped prematurely, and the respective data have been cleaned.

4.1 Overall Design

The participants in this open-label program will continue receiving regorafenib monotherapy at the dose level previously assigned under the following conditions:

- as long as the interval of drug interruption does not exceed 4 weeks
- as long as the treating physician feels the participant is continuing to benefit from treatment
- until he/she withdraws consent
- until he/she is non-compliant
- until he/she is lost to follow up
- until an unacceptable toxicity or death occurs
- until patient starts a new anti-cancer treatment
- until the development of a second malignancy

- participants with a beta human chorionic gonadotropin (beta-hCG) test consistent with pregnancy. Pregnancy will be reported along the same timelines as a serious adverse event (SAE).

Prior to receiving study medication for this rollover study, participants will be required to complete at least their EoT visit in their feeder study. During this visit, criteria for the start of a subsequent cycle of therapy, as determined by the guidelines of the feeder protocol (eligibility criteria) will be reviewed and the participants should sign informed consent for the rollover study.

Participants should continue taking study medication dispensed under the umbrella of the feeder studies until first treatment in this rollover study. The participant needs to complete the last treatment cycle in the feeder study and will start treatment in the rollover study at Cycle 1 Day1. The treating investigator should ensure a seamless transition without a change in the treatment schedule. Any treatment interruption should not exceed 28 consecutive days including 1 week break.

Local standards of medical care should be applied to all participants. Details must be recorded in the patient's source documents and may be requested at the discretion of the Sponsor.

The investigator will continuously assess the benefit/risk of regorafenib treatment when the participant is seen in the clinic for his standard of care visits and will ensure that participants that achieve any of the withdrawal conditions above discontinue treatment.

Safety assessments should be done according to local standard of care and regorafenib label information by the treating physician.

Following the EoT assessments from the feeder study, the following information will be recorded in the rollover study eCRF:

- demography including study number, tumor type, and participant's identification number of the feeder study
- medical history: medical important events, e.g. Grade 3/4 (S)AEs, since the start of treatment in the feeder study should be reported as medical history in this rollover study
- any ongoing or new SAEs
- any AEs leading to dose reduction, interruption/delay and discontinuation of regorafenib
- any on-going Grade 3 / 4 AEs, or Grade 2 AEs that affect vital organs (e.g. heart, liver) per feeder study CTCAE version. These events need to be re-graded by the investigator according to CTCAE Ver 5.0.
- new CTCAE Ver 5.0 Grade 3 and 4 AEs, or Grade 2 AEs that affect vital organs (e.g. heart, liver)
- concomitant medications

4.2 Scientific rationale for Study Design

Not applicable for this rollover study.

4.3 Justification for Dose

Not applicable for this rollover study.

4.4 End of Study Definition

A participant is considered to have completed the study if he/she has discontinued treatment and/or has completed the Safety Follow-up visit.

The end of the study is defined as the date when the last participant has completed the study and the sponsor has decided to close enrollment.

5. Study Population

Participants who remain ongoing in a Bayer-sponsored Clinical Trial that has reached the primary completion date for data analysis and, in the opinion of the Investigator, are still benefiting from regorafenib treatment, will be eligible for entry into this study. The feeder studies must have completed all submissions and related regulatory requirements, e.g. 90 day safety update as required for US submissions.

5.1 Inclusion Criteria

Participants are eligible to be included in the study only if all of the following criteria apply:

Age

1. Participant must be age-eligible in the feeder study at the time of signing the informed consent.

Type of Participant and Disease Characteristics

2. Participant is currently participating in any Bayer-sponsored regorafenib study and is receiving study treatment.
3. Participant is currently benefiting from treatment with regorafenib monotherapy and meets criteria to initiate a subsequent cycle of therapy, as determined by the guidelines of the feeder protocol.
4. Any ongoing adverse events that require temporary treatment interruption must be resolved to baseline grade or assessed as stable and not requiring further treatment interruption by the investigator.

Sex

5. Male or female

Contraceptive use by men or women should be consistent with local regulations regarding the methods of contraception for those participating in clinical studies. This applies for the time between signing of the informed consent form and 2 months after the last administration of the study intervention.

Male participants:

In addition to the above methods, male trial participants and male partners of female trial participants must also use condoms during sex as an extra measure of protection against pregnancy.

Female participants:

The investigator or a designated associate is requested to advise sexually active participants on how to achieve highly effective birth control using one or more of the following methods:

- Hormonal contraception associated with inhibition of ovulation containing both estrogen and progestogen (oral, intravaginal or transdermal)
- Hormonal contraception associated with inhibition of ovulation containing only progestogen (oral, injectable or implantable)
- Intrauterine device (IUD) or intrauterine hormone-releasing system (IUS)
- Bilateral tubal occlusion
- Vasectomized partner (provided that partner is the sole sexual partner of the woman of childbearing potential who is the trial participant and that the vasectomized partner has received medical assessment of surgical success)

Women not considered to be of childbearing potential include those who biologically sterile, permanently sterilized (e.g. tubal occlusion, hysterectomy, bilateral salpingectomy) or postmenopausal. Postmenopausal women are defined as no menses for 12 months without an alternative medical cause. A high follicle stimulating hormone (FSH) level in the postmenopausal range may be used to confirm a postmenopausal state in women not using hormonal contraception or hormonal replacement therapy. However in the absence of 12 months of amenorrhea, a single FSH measurement is insufficient.

Informed Consent

6. Capable of giving signed informed consent as described in Appendix 1 (Section 10.1) which includes compliance with the requirements and restrictions listed in the informed consent form (ICF) and in this protocol

5.2 Exclusion Criteria

Participants are excluded from the study if any of the following criteria apply:

Medical Conditions

1. Ineligibility, for medical reasons, to start the next cycle in the respective feeder study
2. Patients with a beta-hCG test consistent with pregnancy.

Prior/Concomitant Therapy

3. Participants are using one or more of the prohibited medications listed in the respective feeder study protocol. A comprehensive list can be found in Section 6.5.

Prior/Concurrent Clinical Study Experience

4. Participant has been previously permanently discontinued from regorafenib treatment.

Diagnostic assessments

Not Applicable for this study.

Other Exclusions

5. Participant is unable to comply with the requirements of the study.

5.3 Lifestyle Considerations

Not Applicable for this study.

5.4 Screen Failures

Screen failures are defined as participants who consent to participate in the clinical study but are not subsequently entered in the study. A minimal set of screen failure information is required to ensure transparent reporting of screen failure participants to meet the Consolidated Standards of Reporting Trials (CONSORT) publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demography, screen failure details, eligibility criteria, and any SAE.

Individuals who do not meet the criteria for participation in this study (screen failure) may not be rescreened.

6. Study Intervention

The following investigational products will be used in the study:

- Regorafenib, 20 mg tablets
- Regorafenib, 40 mg tablets

Participants will be treated with the regorafenib dose taken during the last cycle of the feeder study. They will receive either 60, 80, 120, or 160 mg orally (p.o.) every day (qd) for 3 weeks of every 4 week cycle (i.e. 3 weeks on, 1 week off).

Study drug should be taken within 2 hours after a light meal with approximately 240 mL (8 fluid ounces) of water, preferably in the morning. If necessary, the study drug may be taken at different times of the day, but there should be consistency with respect to dosing intervals (the recommendation is to have at least a 20 hour interval between doses).

If a dose of study drug will be missed, the missed dose should be skipped (vomited tablets cannot be made up), and the next dose should be taken at the regular time. The subsequent dose of study drug should not be doubled. The investigator should be informed if the dose of regorafenib taken exceeded the scheduled dose.

Regorafenib will be provided by the sponsor as tablets.

The regorafenib 40 mg tablet is coated, not divisible, gray-orange-red, oval (length 16 mm, width 7, thickness 4.9-5.6) and 472 mg each in total weight. The 40 mg tablets are embossed with “40” on one side of the tablet, and “BAYER” on the other side. The packaging configuration is 30 tablets regorafenib 40mg and a 3 g desiccant capsule per bottle of regorafenib 40 mg.

The regorafenib 20 mg tablet is coated, not divisible, gray-orange-red, round, biconvex (diameter 9mm, thickness 3.5-4.0mm) and 238 mg each in total weight. The 20 mg tablets are not coded.

The packaging configuration is 65 tablets regorafenib 20 mg and a 3 g desiccant capsule per bottle of regorafenib 20 mg.

Regorafenib tablets are in an immediate-release dosage form with rapid dissolution characteristics under the in vitro test conditions.

6.1 Study Intervention(s) Administered

Participants will be treated with the regorafenib dose taken during the last cycle of the feeder study.

6.2 Preparation/Handling/Storage/Accountability

Regorafenib tablets will be packed in high density polyethylene (HDPE) bottles with a white child resistant closure and induction seal. Each bottle includes a desiccant cartridge inside. Once the drug has been received it has to be kept in a secure, dry location. The tablets have to be stored in the original bottle according to the labelled storage advice. The tablets have to be stored in the original pack provided in order to protect from moisture and swallowed immediately after they have been taken out. The bottle has to be kept tightly closed after first opening and the desiccant has to remain in the bottle. Once the bottle is opened, the tablets have to be discarded after 7 weeks.

Unused tablets must be returned to the trial site by the patient. Beyond that, no special precautions are required, when handling the study drug.

The bottles will have a label affixed containing study identification, product identification, and quantity of tablets.

The study drug must be exclusively used for the purpose specified in this protocol, and it will only be accessible to authorized staff. The investigator or designee must confirm the receipt of the drug by signing the drug acknowledgment form.

The study drug will be labeled according to the requirements of local law and legislation. Label text will be approved according to the sponsor's agreed procedures, and a copy of the labels will be made available to the study site upon request.

For the study drug, a system of numbering in accordance with all requirements of Good Manufacturing Practice (GMP) will be used, ensuring that each dose of study drug can be traced back to the respective bulk ware of the ingredients. Lists linking all numbering levels will be maintained by the sponsor's clinical supplies Quality Assurance group.

A complete record of batch numbers and expiry dates of all study drug as well as the labels will be maintained in the sponsor study file.

For more information about study drug, please refer to the Investigator's Brochure.

6.3 Measures to Minimize Bias: Randomization and Blinding

Not applicable. This is an open-label study.

6.4 Study Intervention Compliance

Participant compliance with study intervention will be assessed at each visit. Compliance will be assessed by counting returned tablets/capsules. Deviation(s) from the prescribed dosage regimen should be recorded in the eCRF.

6.5 Concomitant Therapy

All medication which is considered necessary for the subject's welfare, and which is not expected to interfere with the evaluation of the study drug, may be given at the discretion of the Investigator. All concomitant medications (including start/stop dates, dose frequency,

route of administration and indication) must be recorded in the subject's source documentation, as well as in the appropriate pages of the CRF.

6.5.1 Drug-drug interactions relevant for regorafenib

6.5.1.1 Inhibitors / inducers of CYP3A4

Administration of ketoconazole (400 mg for 18 days), a strong CYP3A4 inhibitor, with a single dose of regorafenib (160 mg on Day 5) resulted in an increase in mean exposure (AUC) of regorafenib of approximately 33%, and a decrease in mean exposure of the active metabolites, M-2 (N-oxide) and M-5 (N-oxide and N-desmethyl), of approximately 90**%. It is recommended to avoid concomitant use of strong inhibitors of CYP3A4 activity (**Appendix 10.6**) as their influence on the steady-state exposure of regorafenib and its metabolites has not been studied.**

Administration of rifampicin (600 mg for 9 days), a strong CYP3A4 inducer, with a single dose of regorafenib (160 mg on Day 7) resulted in a reduction in AUC of regorafenib of approximately 50%, a 3- to 4-fold increase in mean exposure of the active metabolite M-5, and no change in exposure of active metabolite M-2. Other CYP3A4 inducers (Appendix 10.6) may also increase metabolism of regorafenib. **Inducers of CYP3A4 should be avoided, or selection of an alternate concomitant medicinal product, with no or minimal potential to induce CYP3A4 should be considered.**

Appendix 10.6 provides an overview of the most commonly used strong CYP3A4 inhibitors and CYP3A4 inducers) that should be avoided during the study.

6.5.1.2 UGT1A1 and UGT1A9 substrates

In vitro data indicate that regorafenib as well as its active metabolites M-2 inhibit glucuronidation mediated by UGT1A1 and UGT1A9 whereas M-5 only inhibits UGT1A1 at concentrations which are achieved in vivo at steady state.

Administration of regorafenib with a 5-day break prior to administration of irinotecan resulted in an increase of approximately 44% in mean exposure (AUC) of SN-38, a substrate of UGT1A1 and an active metabolite of irinotecan. An increase in mean exposure (AUC) of irinotecan of approximately 28% was also observed. This indicates that **co-administration of regorafenib may increase systemic exposure to UGT1A1 and UGT1A9 substrates**. The clinical significance is unknown and is dependent on the substrate.

6.5.1.3 Breast cancer resistance protein and P-glycoprotein substrates

Administration of regorafenib (160 mg for 14 days) prior to administration of a single dose of rosuvastatin (5 mg), a breast cancer resistance protein (BCRP) substrate, resulted in a 3.9-fold increase in mean exposure (AUC) of rosuvastatin and a 4.6-fold increase in C_{max}. This indicates that co-administration of regorafenib may increase the plasma concentrations of other concomitant BCRP substrates (e.g. methotrexate, fluvastatin, atorvastatin). **Therefore, it is recommended to monitor patients closely for signs and symptoms of increased exposure to BCRP substrates.**

6.5.1.4 CYP isoform-selective substrates

A cytochrome P450 enzyme (CYP) probe substrate study in cancer patients was conducted to evaluate the effect of regorafenib on the pharmacokinetics of CYP2C9 substrate warfarin (10 mg), CYP2C19 substrate omeprazole (40 mg), CYP3A4 substrate midazolam (2 mg) and

CYP2C8 substrate rosiglitazone (4 mg) and to provide information about potential changes in exposure of these substrates when administered with regorafenib.

Overall, the PK data suggest that **regorafenib may be given concomitantly with substrates of CYP3A4, CYP2C8, CYP2C9, and CYP2C19 without the expectation of a clinically meaningful drug interaction**.

6.5.1.5 Antibiotics

The concentration-time profile indicates that regorafenib and its metabolites may undergo enterohepatic circulation. Co-administration with neomycin, a poorly absorbed antimicrobial agent used for eradicating the gastrointestinal microflora (which may interfere with the enterohepatic circulation of regorafenib) had no effect on the regorafenib exposure. There was an approximately 80% decrease in the exposure of the active metabolites M-2 and M-5. Effects of other antibiotics have not been studied. **The clinical significance of the neomycin effect and potential interactions with other antibiotics is unknown, but may result in a decreased efficacy of regorafenib.**

6.5.1.6 Bile salt-sequestering agents

Bile salt-sequestering agents may interact with regorafenib by forming insoluble complexes which may impact absorption (or reabsorption), thus resulting in potentially decreased exposure. **The clinical significance of these potential interactions is unknown, but may result in a decreased efficacy of regorafenib.**

6.5.2 Permitted concomitant therapies

All concomitant medications (including start / stop dates, total daily dose, and indication) must be recorded in the patient's source documentation and in the eCRF.

- Treatment with non-conventional therapies (e.g. herbs or acupuncture) and vitamin/mineral supplements is acceptable provided that they do not interfere with the study endpoints, in the opinion of the investigator. However, **St John's Wort (herbal preparation based on the plant species hypericum) is not permitted**.
- Patients who are therapeutically treated with an agent such as warfarin or heparin or novel oral anticoagulants (NOACs) such as dabigatran or rivaroxaban will be allowed to participate provided that no prior evidence of underlying abnormality in coagulation parameters exists. Close monitoring of at least weekly evaluations for patients on warfarin will be performed until INR is stable based on a measurement that is pre-dose as defined by the local standard of care.
- P-glycoprotein substrates: clinical data indicate that regorafenib has no effect on digoxin pharmacokinetics, therefore can be given concomitantly with p-glycoprotein substrates, such as digoxin, without a clinically meaningful drug interaction (see Section 6.5.1.3).
- Patients may receive palliative or supportive care for any underlying illness (e.g., Megestrol acetate (Megace®) as supportive care).
- Palliative and supportive care for the other disease-related symptoms and for toxicity associated with treatment will be offered to all patients on this trial. The use of anti-diarrheal or anti-emetics according to standard practice is strongly encouraged.
- Bisphosphonates and/or RANKL inhibitor therapies (such as denosumab) for bone metastases may be continued if treatment with an agent from one of these two classes

was initiated prior to signing informed consent. Bisphosphonates and/or RANKL inhibitor therapies cannot be initiated after informed consent has been signed, unless in the opinion of the investigator, the patient does not have PD.

- Radiotherapy:
  - Palliative radiotherapy during the study is allowed for local pain control after individual benefit-risk assessment provided that:
    - In the opinion of the investigator, the patient does not have PD,
    - No more than 25% of the patient's bone marrow is irradiated,
    - The radiation field does not encompass a lung field (to reduce the risk for ILD caused by irradiation pneumonitis).
  - Regorafenib may only be continued during palliative radiotherapy after an individual benefit-risk assessment. The investigator should consult the sponsor.

  Note: administration of palliative radiation therapy to a symptomatic solitary lesion or to the brain will be considered clinical progression
- Analgesics.
- Nutritional support.

Major surgery for any reason different than symptom management or tumor control should only be performed during the study period if, in the opinion of the investigator and after careful individual benefit / risk assessment (taking into account the potential wound healing complications that have been described with all anti-VEGF drugs), the surgery will be beneficial for the patient. It is recommended to stop regorafenib treatment two weeks before surgery. The decision to resume regorafenib after surgery should be based on clinical judgment of adequate wound healing. Patients should be placed back on study therapy within 4 weeks of the scheduled interruption of regorafenib.

Note:

- if treatment interruption of regorafenib will be >28 consecutive days - including the 1 week drug holiday - patient must be discontinued from regorafenib.

Patients may receive other medications that the investigator deems to be medically necessary.

6.5.3 Prohibited prior and concomitant therapies

Patients are prohibited from receiving the following therapies during the screening and treatment phase of this trial:

- **Disease-specific anti-neoplastic therapies**, including kinase inhibitors, immunotherapy, chemotherapy, or experimental therapies other than regorafenib are not allowed.
- Surgery for symptom management or tumor control.
- **Strong CYP 3A4 inhibitors / inducers**. Strong CYP3A4 inhibitors or CYP3A4 inducers (See Appendix 10.6) are not allowed.
- Any drug that targets angiogenesis, especially VEGF and VEGFR.

- Tyrosine-kinase inhibitors (TKIs)
- **Antiviral treatment for HCV**
- Bone marrow transplant or stem cell rescue.
- Prior and concomitant palliative radiation therapy is allowed if the target lesion(s) are not included within the radiation field and no more than 25% of the bone marrow is irradiated.
- Use of biologic response modifiers, such as granulocyte colony stimulating factor (G-CSF), within the 3 weeks prior to the randomization date.
  - G-CSF and other hematopoietic growth factors may be used during the study in the management of acute toxicity such as febrile neutropenia when clinically indicated or at the discretion of the investigator; however they may not be substituted for a required dose reduction.
  - Patients taking chronic erythropoietin are permitted.
- Patients taking narrow therapeutic index medications (e.g., warfarin, quinidine, and cyclosporine) should be monitored proactively.
- Investigational anti-tumor agents or anti-neoplastic chemo/hormonal/immunotherapy.

Therapeutic monitoring should be performed consistent with the local clinical standard of care following dose modification of the agent. In general, patients should be closely monitored for side effects of all concomitant medications regardless of path of elimination.

6.5.4 Documentation of prior and new concomitant therapies

Any medication or vaccine (including over-the-counter or prescription medicines, vitamins, and/or herbal supplements) that the participant is receiving at the time of enrollment or receives during the study must be recorded along with:

- Reason for use
- Dates of administration including start and end dates
- Dosage information including dose and frequency

The Medical Monitor should be contacted if there are any questions regarding concomitant or prior therapy.

6.6 Dose Modification

In case a dose reduction is necessary, the study treatment will be administered according to the following tables. Table 6–1 shows the dose modification levels for regorafenib. Table 6–2, Table 6–3, Table 6–4, and Table 6–5 show the dose modification plans for specific known drug-related toxicities.

Table 6–1: Dose modification levels for regorafenib

Dose Level	Daily Dose	Number of tablets
Dose level 0 (standard dose)	160 mg	4 tablets of regorafenib, 40 mg-tablet
Dose level -1	120 mg	3 tablets of regorafenib, 40 mg-tablet
Dose level -2	80 mg	2 tablets of regorafenib, 40 mg-tablet

Table 6–2: Dose Modification/Delay for Toxicities Related to Study Drug (Except Hand Foot Skin Reaction, Hypertension, and ALT and/or AST increases)[a,c]

Grade of Event	Dose Interruption	Dose modification	Dose for subsequent cycles
Grade 0-2	Treat on time	No change	No change
Grade 3	Delay until ≤ Grade 2[b]	Reduce 1 dose level	If toxicity remains ≤ Grade 2, dose re-escalation can be considered at the discretion of the treating investigator. If dose is re-escalated and toxicity (≤ Grade 3) recurs, institute permanent dose reduction.
Grade 4	Delay until ≤ Grade 2[b]	Reduce by 1 dose level. Permanent discontinuation can be considered at treating investigator's discretion.	

Abbreviations: ALT – alanine transaminase; AST – aspartate transaminase
a Excludes alopecia, non-refractory nausea/vomiting, non-refractory hypersensitivity, non-clinically significant and asymptomatic laboratory abnormalities.
b If no recovery after a 4-week delay, treatment should be permanently discontinued. In the event of severe bleeding necessitating urgent medical intervention, permanent discontinuation of regorafenib should be considered.
c In subjects who develop cardiac ischemia and/or infarction, interruption of regorafenib is recommended until resolution. The decision to re-initiate regorafenib therapy should be based on careful consideration of the potential benefits and risks of the individual subject. Regorafenib should be permanently discontinued if there is no resolution.

Table 6–3: Dose modifications for HFSR related to regorafenib (dose expansion phase) ("Palmar-plantar erythrodysesthesia syndrome")

Skin toxicity grade	Occurrence	Recommended dose modification and measures
Grade 1: Numbness, dysesthesia, paresthesia, tingling, painless swelling, erythema or discomfort of the hands or feet which does not disrupt the subject's normal activities	Any	Maintain dose level and immediately institute supportive measures for symptomatic relief.
Grade 2: Painful erythema and swelling of the hands or feet and/or discomfort which affects the subject's normal activities.	1st occurrence	Decrease dose by 40 mg (one tablet) and immediately institute supportive measures. If no improvement occurs despite dose reduction, interrupt therapy for a minimum of 7 days, until toxicity resolves to Grade 0-1. A dose re-escalation is permitted at the discretion of the treating physician.
	No improvement within 7 days or 2nd occurrence	Interrupt therapy until toxicity resolves to Grade 0-1. When resuming treatment, decrease dose by 40 mg (one tablet). A dose re-escalation is permitted at the discretion of the treating physician.
	3rd occurrence	Interrupt therapy until toxicity resolves to Grade 0-1. When resuming treatment, decrease dose by 40 mg (one tablet). A dose re-escalation is permitted at the discretion of the treating physician.
	4th occurrence	Discontinue treatment.
Grade 3: Moist desquamation, ulceration, blistering or severe pain of the hands or feet, or severe discomfort that causes the subject to be unable to work or perform activities of daily living.	1st occurrence	Institute supportive measures immediately. Interrupt therapy for a minimum of 7 days until toxicity resolves to Grade 0-1. When resuming treatment, decrease dose by 40 mg (one tablet). A dose re-escalation is permitted at the discretion of the treating physician.
	2nd occurrence	Institute supportive measures immediately. Interrupt therapy for a minimum of 7 days until toxicity resolves to Grade 0-1. When resuming treatment, decrease dose by 40 mg (one tablet).
	3rd occurrence	Discontinue treatment.

Abbreviations: HFSR – hand-foot-skin reaction

Table 6–4: Recommended dose modification and measures for hypertension

Hypertension grade	Occurrence	Recommended dose modification and measures [a]
Grade 1	Any	Maintain dose level. Consider increased BP monitoring.
Grade 2	Any	Institute antihypertensive treatment with the aim to achieve diastolic BP ≤ 90 mmHg: • If BP previously within normal limits, start antihypertensive monotherapy. • If subject already on antihypertensive medication, titrate up the dose. Continue regorafenib, or if symptomatic, hold regorafenib until symptoms resolve AND diastolic BP ≤ 90 mmHg.[b] When regorafenib is restarted, continue at the same dose level.
Grade 3	First occurrence	Institute antihypertensive treatment with the aim to achieve diastolic BP ≤ 90 mmHg: • Start antihypertensive medication AND/OR • Increase current antihypertensive medication AND/OR • Add additional antihypertensive medications. Hold regorafenib until diastolic BP ≤ 90 mm Hg, and if symptomatic, until symptoms resolve.[b] When regorafenib is restarted, continue at the same dose level. If BP is not controlled with the addition of new or more intensive therapy, reduce by 1 dose level.[c]
	Re-occurrence	If Grade 3 hypertension recurs despite dose reduction and antihypertensive therapy, reduce another dose level.[d]
Grade 4	Any	Discontinue therapy

Abbreviations: BP = blood pressure.
a A more conservative management of hypertension is allowed if judged medically appropriate by the investigator.
b Subjects requiring a delay of >4 weeks should go off regorafenib.
c If BP remains controlled for at least one full cycle, dose re-escalation is permitted at the investigator's discretion.
d Subjects requiring >2 dose level reductions (<80 mg reduction) should go off regorafenib.

Table 6–5: Dose modification/interruption for ALT/AST increases related to regorafenib

Observed elevations of ALT and / or AST	Occurrence	Recommended measures and dose modification
≤5 times ULN	Any occurrence	Continue regorafenib treatment. Monitor liver function weekly until transaminases return to <3 times ULN or baseline.
>5 times ULN to ≤20 times ULN	1st occurrence	Interrupt regorafenib treatment. Monitor transaminases weekly until return to <3 times ULN or baseline. Restart: If the potential benefit outweighs the risk of hepatotoxicity, re-initiate regorafenib treatment, reduce dose by 40 mg (one tablet), and monitor liver function weekly for at least 4 weeks.
	Re-occurrence	Discontinue treatment with regorafenib permanently.
>20 times ULN	Any occurrence	Discontinue treatment with regorafenib permanently.
>3 times ULN with concurrent bilirubin >2 times ULN	Any occurrence	Discontinue treatment with regorafenib permanently. Monitor liver function weekly until resolution or return to baseline. Exception: patients with Gilbert's syndrome who develop elevated transaminases should be managed as per the above outlined recommendations for the respective observed elevation of ALT and / or AST.

Abbreviations: ALT – alanine transaminase; AST – aspartate transaminase; ULN = upper limit of normal.

If a dose reduction has been performed within this study protocol intra subject dose reescalation can be considered up to the staring dose in this rollover study protocol at the discretion of the treating physician.

6.7 Intervention after the End of the Study

There is no planned intervention following the end of the study.

7. Discontinuation of Study Intervention and Participant Discontinuation/Withdrawal

7.1 Discontinuation of Study Intervention

In rare instances, it may be necessary for a patient to permanently discontinue study intervention. If study intervention is permanently discontinued, the participant will not remain in the study. See the SOA for data to be collected at the time of discontinuation of study intervention.

Patients *must* be withdrawn from the study intervention for the following reasons:

- At their own request or at the request of their legally acceptable representative. At any time during the study and without giving reasons, a subject may decline to participate further. The subject will not suffer any disadvantage as a result.

- If, in the investigator's opinion, continuation of the study would be harmful to the subject's well-being.
- At the specific request of the sponsor and in liaison with the investigator (e.g. obvious non-compliance, safety concerns).
- Severe allergic reactions, such as exfoliate erythroderma, anaphylaxis, or vascular collapse.
- Any other potential adverse reaction deemed sufficiently serious to warrant discontinuation of treatment by either the investigator or his designated associate(s).
- Substantial non-compliance with the requirements of the study.
- Use of illicit drugs or other substances that may, in the opinion of the investigator, have a reasonable chance of contributing to toxicity.
- Development of any intercurrent illness or situation which would, in the judgment of the investigator, may affect assessments of clinical status and study endpoints to a relevant degree.
- Clinical progression (e.g. defined as worsening of the ECOG PS ≥3 or symptomatic deterioration including increase in liver function tests).
- The development of a second malignancy.
- Subject lost to follow-up.
- Interruption in study drug administration for greater than 28 consecutive days (including the 1 week drug holiday in each cycle).
- More than 2 dose reductions of the study drug are necessary.

Patients with a beta-human chorionic gonadotropin (hCG) test consistent with pregnancy. Pregnancy will be reported as an SAE using the Pregnancy Monitoring Form.

7.1.1 Temporary Discontinuation

For temporary interruption of study drug please refer to Section 6.6. The interval of drug interruption should not exceed 4 weeks including 1 week break.

7.1.2 Rechallenge

Rechallenge should be done according to criteria specified in Section 6.6. The interval of drug interruption should not exceed 4 weeks including 1 week break.

7.2 Participant Discontinuation/Withdrawal from the Study

In case a participant is withdrawn from study intervention he/she will be withdrawn from the study after the safety follow-up visit.

7.3 Lost to Follow up

A participant will be considered lost to follow-up if he or she repeatedly fails to return for scheduled visits and is unable to be contacted by the study site.

The following actions must be taken if a participant fails to return to the clinic for a required study visit:

- The site must attempt to contact the participant and reschedule the missed visit as soon as possible and counsel the participant on the importance of maintaining the assigned visit schedule and ascertain whether or not the participant wishes to and/or should continue in the study.
- Before a participant is deemed lost to follow up, the investigator or designee must make every effort to regain contact with the participant (where possible, 3 telephone calls and, if necessary, a certified letter to the participant's last known mailing address or local equivalent methods). These contact attempts should be documented in the participant's medical record.
- Should the participant continue to be unreachable, he/she will be considered lost to follow-up.

Discontinuation of specific sites or of the study as a whole are handled as part of Appendix 1 (Section 10.1).

8. Study Assessments and Procedures

- Study procedures and their timing are summarized in the SoA. Protocol waivers or exemptions are not allowed.
- Immediate safety concerns should be discussed with the sponsor immediately upon occurrence or awareness to determine if the participant should continue or discontinue study intervention.
- Adherence to the study design requirements, including those specified in the SoA, is essential and required for study conduct.
- All screening activities must be completed and reviewed to confirm that potential participants meet all eligibility criteria. The investigator will maintain a screening log to record details of all participants screened and to confirm eligibility or record reasons for screening failure, as applicable.

8.1 Efficacy Assessments

There will be no formal assessments of efficacy during the rollover study.

8.2 Safety Assessments

Planned time points for all safety assessments are provided in the SoA.

8.3 Adverse Events and Serious Adverse Events

The definitions of an AE or SAE can be found in Appendix 3 (Section 10.3).

AE will be reported by the participant (or, when appropriate, by a caregiver, surrogate, or the participant's legally authorized representative or health care professional not involved in the study).

The investigator and any qualified designees are responsible for detecting, documenting, and recording events that meet the definition of an AE or SAE. They remain responsible for following up SAEs, or AEs, considered related to the study intervention or study procedures, or those that caused the participant to discontinue the study (see Section 7).

8.3.1 Time Period and Frequency for Collecting AE and SAE Information

All SAEs will be collected from the signing of the informed consent form (ICF until the safety follow-up visit (Section 1.3).

AEs, as described in the SoA, (ie, AEs leading to dose reduction, interruption/delay and discontinuation and any new CTCAE Ver 5.0 Grade 3 and 4 AEs, or Grade 2 AEs that affect vital organs (e.g. heart, liver) will be collected from the signing of the ICF until the safety follow up- visit

Any ongoing Grade 3 and 4 AEs, or Grade 2 AEs that affect vital organs (e.g. heart, liver) per feeder study protocol CTCAE version need to be reported as AEs in this rollover study. These events need to be re-graded by the investigator according to CTCAE Ver 5.0.

Medical important events, e.g. Grade 3/4 (S)AEs, since the start of treatment in the feeder study should be reported as medical history in this rollover study.

Medical occurrences that begin before the start of study intervention but after obtaining informed consent will be recorded on the AE section of the case report form (CRF).

Medical occurrences that started before but deteriorated after obtaining informed consent will be recorded as adverse events.

All SAEs will be recorded and reported to the sponsor or designee immediately and under no circumstance should this exceed 24 hours, as indicated in Appendix 3 (Section 10.3). The investigator will submit any updated SAE data to the sponsor within 24 hours of it being available.

Investigators are not obligated to actively seek AE or SAE after conclusion of the study participation. However, if the investigator learns of any SAE, including a death, at any time after a participant has been discharged from the study, and he/she considers the event to be reasonably related to the study intervention or study participation, the investigator must promptly notify the sponsor.

8.3.2 Method of Detecting AEs and SAEs

The method of recording, evaluating, and assessing causality of AE and SAE and the procedures for completing and transmitting SAE reports are provided in Appendix 3 (Section 10.3).

Care will be taken not to introduce bias when detecting AEs and/or SAEs. Open-ended and non-leading verbal questioning of the participant is the preferred method to inquire about AE occurrences.

8.3.3 Follow-up of AEs and SAEs

After the initial AE/SAE report, the investigator is required to proactively follow each participant at subsequent visits/contacts. All SAEs will be followed until resolution, stabilization, the event is otherwise explained, or the participant is lost to follow-up (as defined in Section 7.3). Further information on follow-up procedures is given in Appendix 3 (Section 10.3).

8.3.4 Regulatory Reporting Requirements for SAEs

- Prompt notification by the investigator to the sponsor of an SAE is essential so that legal obligations and ethical responsibilities towards the safety of participants and the safety of a study intervention under clinical investigation are met.

- The sponsor has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a study intervention under clinical investigation. The sponsor will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, Institutional Review Boards (IRB)/Independent Ethics Committees (IEC), and investigators.
- Investigator safety reports must be prepared for suspected unexpected serious adverse reactions (SUSAR) according to local regulatory requirements and sponsor policy and forwarded to investigators as necessary.
- An investigator who receives an investigator safety report describing an SAE or other specific safety information (eg, summary or listing of SAEs) from the sponsor will review and then file it along with the Investigator's Brochure and will notify the IRB/IEC, if appropriate according to local requirements.

8.3.5 Pregnancy

- Details of all pregnancies in female participants and, if indicated, female partners of male participants will be collected after the start of study intervention and until 2 months after discontinuation of intervention.
- If a pregnancy is reported, the investigator should inform the sponsor within 24 hours of learning of the pregnancy and should follow the procedures outlined in Appendix 4 (Section 10.4).
- Abnormal pregnancy outcomes (eg, spontaneous abortion, fetal death, stillbirth, congenital anomalies, ectopic pregnancy) are considered SAEs.

8.4 Treatment of Overdose

For this study, any dose of study intervention greater than **160 mg** within a **20**-hour time period will be considered an overdose.

In the event of an overdose, the investigator/treating physician should:

1. Closely monitor the participant for any AE/SAE and laboratory abnormalities until study intervention can no longer be detected systemically.
2. Obtain a plasma sample for PK analysis within 3 days from the date of the last dose of study intervention if requested by the Medical Monitor (determined on a case-by-case basis).
3. Any overdose or incorrect administration of study drug should be noted on the Study Drug Administration electronic Case Report Form (eCRF).
4. Adverse events associated with an overdose or incorrect administration of study drug should be recorded on the Adverse Event eCRF.

Decisions regarding dose interruptions or modifications will be made by the investigator in consultation with the Medical Monitor based on the clinical evaluation of the participant.

For detailed guidance on overdosing please refer to the most current version of the IB for regorafenib.

There is no specific treatment for regorafenib overdose. The highest dose of regorafenib studied clinically is 220 mg QD. The AEs observed at this dose were primarily dermatological events, hoarseness, diarrhea, mucositis, and nausea. In the event of suspected

overdose regorafenib should be immediately withheld and supportive care instituted under the supervision of a qualified health care professional.

There is no specific antidote for Stivarga® overdose. Subjects who have overdosed should be treated with symptomatic support. No additional data concerning management of overdose are available at this time.

8.5 Pharmacokinetics

PK parameters are not evaluated in this study.

8.6 Pharmacodynamics

Pharmacodynamic parameters are not evaluated in this study.

8.7 Genetics

Genetics are not evaluated in this study.

8.8 Biomarkers

Biomarkers are not evaluated in this study.

8.9 Medical Resource Utilization and Health Economics

Medical Resource Utilization and Health Economics are not evaluated in this study.

9. Statistical Considerations

Data from participant who are transferred to a rollover study may be pooled and analyzed together with the data from the study in which the participant was initially included.

Data will be analyzed using summary or frequency statistics or data listings.

9.1 Statistical Hypotheses

No confirmatory statistical hypothesis testing is planned. All safety analysis will be done in a descriptive manner only.

9.2 Sample Size Determination

No formal sample size estimation will be done.

Participants of on-going or future feeder studies will be enrolled in the study; therefore the number of participants is not predictable.

9.3 Populations for Analyses

For purposes of statistical analysis, the following analysis sets are defined:

Analysis set	Description
Enrolled	All participants who signed the ICF
Safety	All participants who take at least 1 dose of regorafenib within this rollover study.

9.4 Statistical Analyses

The statistical analysis plan will be developed and finalized before database lock and will describe the analysis sets and procedures for any missing imputation method, if applicable.

Descriptive analysis/listings of data collected e.g. demography, medical history, drug accountability, concomitant medication, adverse events (including serious), dose modifications and reasons for termination of treatment may be provided, as appropriate.

9.4.1 Efficacy Analyses

Not applicable for this rollover study as no efficacy analyses are planned.

9.4.2 Safety Analyses

All safety analyses will be performed on the Safety analysis set.

Serious adverse events and protocol-specified AEs will be analyzed descriptively by providing frequency tables of SAEs and AEs observed during the study.

Tolerability of the study drug will be evaluated by displaying the number of dose modifications in frequency tables.

Details will be given in the statistical analysis plan.

9.4.3 Other Analyses

Not applicable for this rollover study.

9.5 Interim Analyses

No formal interim analysis is planned.

10. Supporting Documentation and Operational Considerations

The focus of this rollover study is to provide regorafenib to patients and to collect safety information as specified in the SoA.

10.1 Appendix 1: Regulatory, Ethical, and Study Oversight Considerations

10.1.1 Regulatory and Ethical Considerations

This study will be conducted in accordance with the protocol and with the following:

- Consensus ethical principles derived from international guidelines including the Declaration of Helsinki and Council for International Organizations of Medical Sciences (CIOMS) International Ethical Guidelines
- Applicable ICH Good Clinical Practice (GCP) Guidelines
- Applicable laws and regulations

- The protocol, protocol amendments, ICF, Investigator Brochure, and other relevant documents (eg, advertisements) must be submitted to an IRB/IEC by the investigator and reviewed and approved by the IRB/IEC before the study is initiated.
- Any amendments to the protocol will require IRB/IEC approval before implementation of changes made to the study design, except for changes necessary to eliminate an immediate hazard to study participants.
- The investigator will be responsible for the following:

- Providing written summaries of the status of the study to the IRB/IEC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/IEC
- Notifying the IRB/IEC of SAEs or other significant safety findings as required by IRB/IEC procedures
- Providing oversight of the conduct of the study at the site and adherence to requirements of 21 CFR, ICH guidelines, the IRB/IEC, European regulation 536/2014 for clinical studies (if applicable), and all other applicable local regulations

10.1.2 Financial Disclosure

Investigators and sub-investigators will provide the sponsor with sufficient, accurate financial information as requested to allow the sponsor to submit complete and accurate financial certification or disclosure statements to the appropriate regulatory authorities. Investigators are responsible for providing information on financial interests during the course of the study and for 1 year after completion of the study.

10.1.3 Informed Consent Process

- The investigator or his/her representative will explain the nature of the study to the participant or his/her legally authorized representative and answer all questions regarding the study.
- Participants must be informed that their participation is voluntary. Participants or their legally authorized representative will be required to sign a statement of informed consent that meets the requirements of 21 CFR 50, local regulations, ICH guidelines, Health Insurance Portability and Accountability Act (HIPAA) requirements, where applicable, and the IRB/IEC or study center.
- The medical record must include a statement that written informed consent was obtained before the participant was enrolled in the study and the date the written consent was obtained. The authorized person obtaining the informed consent must also sign the ICF.
- Participants must be re-consented to the most current version of the ICF(s) during their participation in the study.
- A copy of the ICF(s) must be provided to the participant or the participant's legally authorized representative.

10.1.4 Data Protection

- Participants will be assigned a unique identifier by the sponsor. Any participant records or datasets that are transferred to the sponsor will contain the identifier only; participant names or any information which would make the participant identifiable will not be transferred.
- The participant must be informed that his/her personal study-related data will be used by the sponsor in accordance with local data protection law. The level of disclosure must also be explained to the participant.
- The participant must be informed that his/her medical records may be examined by Clinical Quality Assurance auditors or other authorized personnel appointed by the sponsor, by appropriate IRB/IEC members, and by inspectors from regulatory authorities.

10.1.5 Dissemination of Clinical Study Data

Result Summaries of Bayer's sponsored clinical trials in drug development phases 2, 3 and 4 and phase 1 trials in patients are provided in the Bayer Trial Finder application after marketing authorization approval in line with the position of the global pharmaceutical industry associations laid down in the "Joint Position on the Disclosure of Clinical Trial Information via Clinical Trial Registries and Databases". In addition results of clinical drug trials will be provided on the publicly funded website www.ClinicalTrials.gov and EU Clinical Trials Register in line with the applicable regulations.

Bayer commits to sharing upon request from qualified scientific and medical researchers patient-level clinical trial data, study-level clinical trial data, and protocols from clinical trials in patients for medicines and indications approved in the United States (US) and European Union (EU) on or after January 01, 2014 as necessary for conducting legitimate research.

All Bayer-sponsored clinical trials are considered for publication in the scientific literature irrespective of whether the results of the clinical trials are positive or negative.

10.1.6 Data Quality Assurance

- All participant data relating to the study will be recorded on printed or electronic CRF unless transmitted to the sponsor or designee electronically (eg, laboratory data). The investigator is responsible for verifying that data entries are accurate and correct by physically or electronically signing the CRF.
- The investigator must maintain accurate documentation (source data) that supports the information entered in the CRF.
- The investigator must permit study-related monitoring, audits, IRB/IEC review, and regulatory agency inspections and provide direct access to source data documents.
- Monitoring details describing strategy (eg, risk-based initiatives in operations and quality such as Risk Management and Mitigation Strategies and Analytical Risk-Based Monitoring), methods, responsibilities and requirements, including handling of noncompliance issues and monitoring techniques (central, remote, or on-site monitoring) are provided in the Monitoring Plan.
- The sponsor or designee is responsible for the data management of this study including quality checking of the data.
- The sponsor assumes accountability for actions delegated to other individuals (eg, Contract Research Organizations).
- Study monitors will perform ongoing source data verification to confirm that data entered into the CRF by authorized site personnel are accurate, complete, and verifiable from source documents; that the safety and rights of participants are being protected; and that the study is being conducted in accordance with the currently approved protocol and any other study agreements, ICH GCP, and all applicable regulatory requirements.
- Records and documents, including signed ICFs, pertaining to the conduct of this study must be retained by the investigator for 15 years after study completion unless local regulations or institutional policies require a longer retention period. No records may be destroyed during the retention period without the written approval of the sponsor. No records may be transferred to another location or party without written notification to the sponsor.

10.1.7 Source Documents

- Source documents provide evidence for the existence of the participant and substantiate the integrity of the data collected. Source documents are filed at the investigator's site.
- Data reported on the CRF or entered in the eCRF that are transcribed from source documents must be consistent with the source documents or the discrepancies must be explained. The investigator may need to request previous medical records or transfer records, depending on the study. Also, current medical records must be available.

10.1.8 Study and Site Closure

The sponsor designee reserves the right to close the study site or terminate the study at any time for any reason at the sole discretion of the sponsor. Study sites will be closed upon study completion. A study site is considered closed when all required documents and study supplies have been collected and a study-site closure visit has been performed.

The investigator may initiate study-site closure at any time, provided there is reasonable cause and sufficient notice is given in advance of the intended termination.

Reasons for the early closure of a study site by the sponsor or investigator may include but are not limited to:

- Failure of the investigator to comply with the protocol, the requirements of the IRB/IEC or local health authorities, the sponsor's procedures, or GCP guidelines

10.1.9 Publication Policy

Not applicable. It is not planned to publish data from this study, it might be that rollover study data will contribute to publications on feeder study data.

10.2 Appendix 2: Clinical Laboratory Tests

Not applicable as no blood samples will be taken in this rollover study.

10.3 Appendix 3: Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting

10.3.1 Definition of AE

AE Definition
• An AE is any untoward medical occurrence in a patient or clinical study participant, temporally associated with the use of study intervention, whether or not considered related to the study intervention. • NOTE: An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of study intervention.

Events <u>Meeting</u> the AE Definition
• Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments (eg, ECG, radiological scans, vital signs measurements),

Events Meeting the AE Definition
including those that worsen from baseline, considered clinically significant in the medical and scientific judgment of the investigator (ie, not related to progression of underlying disease). • Exacerbation of a chronic or intermittent pre-existing condition including either an increase in frequency and/or intensity of the condition. • New conditions detected or diagnosed after study intervention administration even though it may have been present before the start of the study. • Signs, symptoms, or the clinical sequelae of a suspected drug-drug interaction. • Signs, symptoms, or the clinical sequelae of a suspected overdose of either study intervention or a concomitant medication. Overdose per se will not be reported as an AE/SAE unless it is an intentional overdose taken with possible suicidal/self-harming intent. Such overdoses should be reported regardless of sequelae. • The signs, symptoms, and/or clinical sequelae resulting from lack of efficacy will be reported as AE or SAE if they fulfil the definition of an AE or SAE. Also, “lack of efficacy” or “failure of expected pharmacological action” also constitutes an AE or SAE.

Events NOT Meeting the AE Definition
• Any clinically significant abnormal laboratory findings or other abnormal safety assessments which are associated with the underlying disease, unless judged by the investigator to be more severe than expected for the participant’s condition. • The disease/disorder being studied or expected progression, signs, or symptoms of the disease/disorder being studied, unless more severe than expected for the participant’s condition. • Medical or surgical procedure (eg, endoscopy, appendectomy): the condition that leads to the procedure is the AE. • Situations in which an untoward medical occurrence did not occur (social and/or convenience admission to a hospital). • Anticipated day-to-day fluctuations of pre-existing disease(s) or condition(s) present or detected at the start of the study that do not worsen.

10.3.2 Definition of SAE

If an event is not an AE per definition above, then it cannot be an SAE even if serious conditions are met (eg, hospitalization for signs/symptoms of the disease under study, death due to progression of disease).

An SAE is defined as any untoward medical occurrence that, at any dose:
1. Results in death
Is life-threatening The term 'life-threatening' in the definition of 'serious' refers to an event in which the

participant was at risk of death at the time of the event. It does not refer to an event, which hypothetically might have caused death, if it were more severe.

Requires inpatient hospitalization or prolongation of existing hospitalization
In general, hospitalization signifies that the participant has been detained (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or outpatient setting. Complications that occur during hospitalization are AEs. If a complication prolongs hospitalization or fulfills any other serious criteria, the event is serious. When in doubt as to whether "hospitalization" occurred or was necessary, the AE should be considered serious. Hospitalization for elective treatment of a pre-existing condition that did not worsen from baseline is not considered an AE.

Results in persistent disability/incapacity

- The term disability means a substantial disruption of a person's ability to conduct normal life functions.
- This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (eg, sprained ankle) which may interfere with or prevent everyday life functions but do not constitute a substantial disruption.

Is a congenital anomaly/birth defect

Other situations:

- Medical or scientific judgment should be exercised in deciding whether SAE reporting is appropriate in other situations such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the participant or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These events should usually be considered serious.

  Examples of such events include invasive or malignant cancers, intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization, or development of drug dependency or drug abuse.

10.3.3 Recording and Follow-Up of AE and/or SAE

AE and SAE Recording

- When an AE/SAE occurs, it is the responsibility of the investigator to review all documentation (eg, hospital progress notes, laboratory reports, and diagnostics reports) related to the event.
- The investigator will then record all relevant AE (those AEs leading to dose reduction, interruption/delay and discontinuation and any new Any new CTCAE version 5.0 Grade 3 and 4 AEs, or Grade 2 AEs that affect vital organs [e.g. heart, liver]) and all SAE information in the CRF.
- It is **not** acceptable for the investigator to send photocopies of the participant's medical records to the medical monitor or Bayer's pharmacovigilance department in

lieu of completion of the completed/AE/SAE CRF page.

- There may be instances when copies of medical records for certain cases are requested by the medical monitor or Bayer's pharmacovigilance department. In this case, all participant identifiers, with the exception of the participant number, will be redacted on the copies of the medical records before submission to the medical monitor or Bayer's pharmacovigilance department.
- The investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. Whenever possible, the diagnosis (not the individual signs/symptoms) will be documented as the AE/SAE.

Assessment of Intensity

The investigator will make an assessment of intensity for each AE and SAE reported during the study and assign it as per CTCAE Ver 5.0.

Assessment of Causality

- The investigator is obligated to assess the relationship between study intervention and each occurrence of each AE/SAE.
- A "reasonable possibility" of a relationship conveys that there are facts, evidence, and/or arguments to suggest a causal relationship, rather than a relationship cannot be ruled out.
- The investigator will use clinical judgment to determine the relationship.
- Alternative causes, such as underlying disease(s), concomitant therapy, and other risk factors, as well as the temporal relationship of the event to study intervention administration will be considered and investigated.
- The investigator will also consult the Investigator's Brochure (IB) and/or Product Information, for marketed products, in his/her assessment.
- For each AE/SAE, the investigator **must** document in the medical notes that he/she has reviewed the AE/SAE and has provided an assessment of causality.
- There may be situations in which an SAE has occurred and the investigator has minimal information to include in the initial report to Bayer's pharmacovigilance department. However, **it is very important that the investigator always make an assessment of causality for every event before the initial transmission of the SAE data to Bayer's pharmacovigilance department.**
- The investigator may change his/her opinion of causality in light of follow-up information and send an SAE follow-up report with the updated causality assessment.
- The causality assessment is one of the criteria used when determining regulatory reporting requirements.

Follow-up of AEs and SAEs

- The investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as medically indicated or as requested by Bayer's pharmacovigilance department to elucidate the nature and/or causality of the AE or SAE as fully as possible. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other health care professionals.
- If a participant dies during participation in the study or during the safety follow-up period, the investigator will provide the medical monitor and/or Bayer's pharmacovigilance department with a copy of any post-mortem findings including histopathology, if applicable.
- New or updated information will be recorded in the originally completed CRF.
- The investigator will submit any updated SAE data to the Bayer's pharmacovigilance department within 24 hours of receipt of the information.

10.3.4 Reporting of SAEs

SAE Reporting to Bayer's pharmacovigilance department via an Electronic Data Collection Tool

- The primary mechanism for reporting an SAE to Bayer's pharmacovigilance department will be the electronic data collection tool.
- If the electronic system is unavailable, then the site will use the paper SAE data collection tool (see next section) in order to report the event within 24 hours.
- The site will enter the SAE data into the electronic system as soon as it becomes available.
- After the study is completed at a given site, the electronic data collection tool will be taken off-line to prevent the entry of new data or changes to existing data.
- If a site receives a report of a new SAE from a study participant or receives updated data on a previously reported SAE after the electronic data collection tool has been taken off-line, then the site can report this information on a paper SAE form (see next section).
- Contacts for SAE reporting can be found in in the SAE paper template.

SAE Reporting to Bayer's pharmacovigilance department via Paper CRF

- Facsimile transmission of the SAE paper CRF is the preferred method to transmit this information to the Bayer's pharmacovigilance department.
- In rare circumstances and in the absence of facsimile equipment, notification by telephone is acceptable with a copy of the SAE report sent by overnight mail or courier service.
- Initial notification via telephone does not replace the need for the investigator to complete and sign the SAE CRF pages within the designated reporting time frames.

SAE Reporting to Bayer's pharmacovigilance department via Paper CRF
• Contacts for SAE reporting can be found in the SAE paper template.

10.4 Appendix 4: Contraceptive Guidance and Collection of Pregnancy Information

Definitions:

Woman of Childbearing Potential (WOCBP)

A woman is considered fertile following menarche and until becoming post-menopausal unless permanently sterile (see below).

If fertility is unclear (eg, amenorrhea in adolescents or athletes) and a menstrual cycle cannot be confirmed before first dose of study intervention, additional evaluation should be considered.

Women in the following categories are not considered WOCBP

1. Premenarchal
2. Premenopausal female with 1 of the following:
   - Documented hysterectomy
   - Documented bilateral salpingectomy
   - Documented bilateral oophorectomy

   For individuals with permanent infertility due to an alternate medical cause other than the above, (eg, mullerian agenesis, androgen insensitivity), investigator discretion should be applied to determining study entry.

   Note: Documentation can come from the site personnel's: review of the participant's medical records, medical examination, or medical history interview.
3. Postmenopausal female
   - A postmenopausal state is defined as no menses for 12 months without an alternative medical cause.
     - A high follicle stimulating hormone (FSH) level in the postmenopausal range may be used to confirm a postmenopausal state in women not using hormonal contraception or hormonal replacement therapy (HRT). However, in the absence of 12 months of amenorrhea, confirmation with more than one FSH measurement is required.
   - Females on HRT and whose menopausal status is in doubt will be required to use one of the non-estrogen hormonal highly effective contraception methods if they wish to continue their HRT during the study. Otherwise, they must discontinue HRT to allow confirmation of postmenopausal status before study enrollment.

Collection of Pregnancy Information

Male participants with partners who become pregnant

- The investigator will attempt to collect pregnancy information on any male participant's female partner who becomes pregnant while the male participant is in this study. This applies only to male participants who receive regorafenib.
- After obtaining the necessary signed informed consent from the pregnant female partner directly, the investigator will record pregnancy information on the appropriate

form and submit it to the sponsor within 24 hours of learning of the partner's pregnancy. The female partner will also be followed to determine the outcome of the pregnancy. Information on the status of the mother and child will be forwarded to the sponsor. Generally, the follow-up will be no longer than 6 to 8 weeks following the estimated delivery date. Any termination of the pregnancy will be reported regardless of fetal status (presence or absence of anomalies) or indication for the procedure.

Female Participants who become pregnant

- The investigator will collect pregnancy information on any female participant who becomes pregnant while participating in this study. Information will be recorded on the appropriate form and submitted to the sponsor within 24 hours of learning of a participant's pregnancy.
- The participant will be followed to determine the outcome of the pregnancy. The investigator will collect follow-up information on the participant and the neonate, after obtaining the signed informed consent from both parents of the neonate, unless local law or specific circumstances of the respective case allow otherwise, and the information will be forwarded to the sponsor. Generally, follow-up will not be required for longer than 6 to 8 weeks beyond the estimated delivery date. Any termination of pregnancy will be reported, regardless of fetal status (presence or absence of anomalies) or indication for the procedure.
- While pregnancy itself is not considered to be an AE or SAE, any pregnancy complication or elective termination of a pregnancy will be reported as an AE or SAE. A spontaneous abortion is always considered to be an SAE and will be reported as such. Any post-study pregnancy related SAE considered reasonably related to the study intervention by the investigator will be reported to the sponsor as described in Section 8.3.4. While the investigator is not obligated to actively seek this information in former study participants, he or she may learn of an SAE through spontaneous reporting.

Any female participant who becomes pregnant while participating in the study will discontinue study intervention and will be withdrawn from the study.

10.5 Appendix 5: Abbreviations

AE	Adverse event
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
AUC	Area under the activity curve
BCRP	Breast cancer resistance protein
BP	blood pressure
CFR	Code of Federal Regulations
CIOMS	Council for International Organizations of Medical Sciences
C_{max}	Maximum observed plasma concentration
CONSORT	Consolidated Standards of Reporting Trials
CRC	Colorectal carcinoma
CRF	Case report form
CTCAE	Common terminology criteria for adverse events
CYP	Cytochrome P450
CYP3A4	Cytochrome P450 3A4
DNA	Deoxy-ribonucleic acid
ECG	electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic case report form
e.g.	For example
EoT	End of treatment
FSH	Follicle stimulating hormone
GCP	Good clinical practice
G-CSF	Granulocyte colony-stimulating factor
GIST	Gastrointestinal stroma
GMP	Good Manufacturing Process
HCC	Hepatocellular carcinoma
hCG	Human chorionic gonadotropin
HFSR	hand-foot-skin reaction
HRT	Hormonal replacement therapy
IB	Investigators brochure
IEC	Independent ethics committee
ICF	Informed consent form
ICH	International conference on harmonization
i.e.	id est; that is
IRB	Institutional review board
PI	Principal Investigator
PK	Pharmacokinetics
RCC	Renal cell carcinoma
SAE	Serious adverse event
SoA	Schedule of activities
SUSAR	Suspected unexpected serious adverse reactions
TEAE	Treatment-emergent adverse events
ULN	upper limit of normal
WOCBP	Women of childbearing potential

10.6 Appendix 6 CYP3A4 inducers and inhibitors

Table 10–1 presents an overview of CYP3A4 inducers and **strong** CYP3A4 inhibitors. CYP3A4 inducers and **strong** CYP3A4 inhibitors are NOT allowed due to drug-drug-interaction with regorafenib.

Table 10–1: An overview of CYP3A4 inducers and strong CYP3A4 inhibitors

STRONG CYP3A4 Inhibitors	CYP3A4 Inducers
Boceprevir	Avasimibe
Clarithromycin	Bosentan
Cobicistat, only available in the combination with elvitegravir, emtricitabine, tenofovir or disoproxil fumarate	Carbamazepine
Conivaptan	Efavirenz
Delavirdine	Enzalutamide
Idelalisib	Etravirine
Indinavir	Fosphenytoin
Itraconazole	Hypericum perforatum (St John's Wort)
Ketoconazole	Lersivirine
Lopinavir	Lumacaftor
Mibefradil	Methylphenobarbital
Miconazole	Mitotane
Nefazodone	Modafinil
Nelfinavir	Nafcillin
Posaconazole	Phenobarbital
Ritonavir	Phenytoin
Saquinavir	Primidone
Telaprevir	Rifabutin
Telithromycin	Rifampicin
Tipranavir	Rifamycin
Troleandomycin	Semagacestat
Voriconazole	Thioridazine

The CYP3A4 inducers and strong CYP3A4 inhibitors in Table 10–1 were identified using the Bayer-World Health Organization's Drug Dictionary (WHO-DD) and Bayer drug groupings for CYP3A4 inducers and CYP3A4 inhibitors.

11. References

Not applicable.