Non-interventional study information

Title	**RECORA- Re**gorafenib in patients with metastatic **co**lo**r**ectal cancer (mCRC) **a**fter failure of standard therapy
Protocol version identifier	3.0
Date of last version of protocol	06 April 2016
IMPACT study number	16665
Study type	☐ non-PASS ☒ PASS Joint PASS: ☐ YES ☒ NO
EU PAS register number	To be added after registration
Active substance	Proteine Kinase Inhibitors (L01XE21), regorafenib
Medicinal product	Stivarga®
Product reference	EMEA/H/C/002573
Procedure number	Not applicable
Marketing authorization holder(s)	Bayer Pharma AG, D-13342 Berlin, Germany
Research question and objectives	The evidence of regorafenib efficacy and safety in metastatic colorectal cancer patients was based on the multinational, multi-center Phase III CORRECT study, titled, "A randomized, double-blind, placebo-controlled phase III study of regorafenib plus BSC versus placebo plus BSC in patients with metastatic colorectal cancer who have progressed after standard therapy. The study met its primary endpoint of improving median overall survival from 5.0 months for the placebo group to 6.4 months for regorafenib. (HR=0.77; 95% CI 0.64-0.94, p=0.0052). The most common drug-related, treatment emergent adverse events (occurring in at least 25% of patients) included fatigue (47.4% vs. 28.1%), hand-foot-skin reaction (46.6% vs. 7.5%), diarrhea (33.8% vs. 8.3%), anorexia (30.4% vs. 15.4%), voice changes (29.4% vs. 5.5%), hypertension (27.8% vs. 5.9%), oral mucositis (27.2% vs. 3.6%), and rash/desquamation (26.0% vs. 4.0%) for patients receiving regorafenib compared to placebo. These data demonstrate that

	regorafenib can stabilize disease, even at an advanced stage, and prolong life in patients with metastatic colorectal cancer who have no other treatment options available. To date regorafenib is the only oral multikinase inhibitor as monotherapy that has demonstrated in a large Phase III trial the ability to improve clinical outcomes in patients with advanced refractory colorectal cancer Stivarga® is indicated for the treatment of patients with metastatic colorectal cancer who have been previously treated with, or are not considered candidates for, fluoropyrimidine-based chemotherapy, an anti-VEGF therapy, and an anti-EGFR therapy. The pivotal phase 3 CORRECT trial was conducted in a closely defined patient population according to strict inclusion and exclusion criteria. After approval of regorafenib patients with metastatic colorectal cancer receiving this drug are usually more heterogeneous with various comorbid conditions. Therefore, the aim of this non-interventional study is to characterize the effectiveness and safety of Stivarga® therapy under routine daily practice conditions in Germany. The primary objective of this non-interventional cohort field study is to investigate overall survival under current practice conditions. Secondary objectives are to determine: • progression free survival (either clinical progression and/or radiological progression) • time to progression (either clinical progression and/or radiological progression) • disease control rate • duration of Stivarga® treatment • tumor status at different visits • incidence of treatment emergent adverse events Additionally possible prognostic factors e.g. presence of severe comorbidities, metastatic sites, early relapse after adjuvant treatment, and KRAS mutation will be evaluated.
Country(-ies) of study	Germany
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Marketing authorization holder

Marketing authorization holder(s)	Bayer Pharma AG, D-13342 Berlin, Germany
MAH contact person	Markus Langen, Bayer HealthCare Germany, Medical Affairs, Bldg. K56, 51366 Leverkusen, Germany

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

ADR	Adverse Drug Reaction
AE	Adverse Event
AJCC	American Joint Committee on Cancer
ALT	Alanine Aminotransferase
AST	Aspartate Aminotransferase
BHC	Bayer HealthCare
CRC	Colorectal carcinoma
CI	Confidence interval
CRF	Case report form. Form containing data about patients filled out by the investigator.
CTCAE	Common Terminology Criteria for Adverse Events
DCR	Disease control rate
EC	Ethics Committee
ECOG	Eastern Cooperative Oncology Group
EDC	Electronic Data Capture
EFPIA	European Federation of Pharmaceutical Industries and Associations
EGFR	Epidermal Growth Factor Receptor
EMA	European Medicines Agency
ENCePP	European Network of Centres for Pharmacoepidemiology and Pharmacovigilance
EU	European Union
FDA	Food and Drug Administration
GCP	Good Clinical Practice
GPP	Good Publication Practice
GPV	Global Pharmacovigilance
HR	Hazard Ratio
IC_{50}	Half maximal inhibitory concentration
ICH	International Conference of Harmonization
IEC	Independent Ethics Committee
INN	International Nonproprietary Name
IRB	Institutional Review Board

ISO	International Organization for Standardization
KM	Kaplan-Meier
KRAS	GTPase KRas (Kirsten rat sarcoma viral oncogene homolog)
MAH	Marketing Authorization Holder
mCRC	Metastatic colorectal carcinoma
MedDRA	Medical Dictionary for Regulatory Activities
N/A	Not Applicable
NIS	Non-Interventional Study
OS	Overall Survival
PAS	Post-Authorization Study
PASS	Post-Authorization Safety Study
PFS	Progression-Free Survival
PSUR	Periodic Safety Update Report
PVCH	Pharmacovigilance Country Head
QPPV	Qualified Person responsible for PharmacoVigilance
QRP	Quality Review Plan
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SAS	Statistical Analysis System
SPC	Summary of Product Characteristics
STROBE	Strengthening the Reporting of Observational Studies in Epidemiology
TEAE	Treatment-Emergent Adverse Event
TTP	Time to Progression
VEGF	Vascular Endothelial Growth Factor
WHO DD	World Health Organization – Drug Dictionary

3. Responsible parties

3.1. Sponsor / MAH

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3.2. Collaborators / Committees

Contact details on the coordinating investigators, co-investigators and other site personnel and site participating in the study are listed in a stand-alone document (see Annex 1) which is available upon request.

4. Abstract

Title	**RECORA- Re**gorafenib in patients with metastatic **co**lo**r**ectal cancer (mCRC) **a**fter failure of standard therapy
Protocol version identifier	3.0
Date of last version of protocol	06 April 2016
IMPACT study number	16665
Study type	☐ non-PASS ☒ PASS Joint PASS: ☐ YES ☒ NO
Author	Ingo Bernard, Bayer HealthCare Germany, Medical Affairs, Bldg. K56, 51366 Leverkusen, Germany
Rationale and background	The evidence of regorafenib efficacy and safety in metastatic colorectal cancer patients was based on the multinational, multi-center Phase III CORRECT study, titled, "A randomized, double-blind, placebo-controlled phase III study of regorafenib plus BSC versus placebo plus BSC in patients with metastatic colorectal cancer who have progressed after standard therapy. The study met its primary endpoint of improving median overall survival from 5.0 months for the placebo group to 6.4 months for regorafenib. (HR=0.77; 95% CI 0.64-0.94, p=0.0052). The most common drug-related, treatment emergent adverse events (occurring in at least 25% of patients) included fatigue (47.4% vs. 28.1%), hand-foot-skin reaction (46.6% vs. 7.5%), diarrhea (33.8% vs. 8.3%), anorexia (30.4% vs. 15.4%), voice changes (29.4% vs. 5.5%), hypertension (27.8% vs. 5.9%), oral mucositis (27.2% vs. 3.6%), and rash/desquamation (26.0% vs. 4.0%) for patients receiving regorafenib compared to placebo. These data demonstrate that regorafenib can stabilize disease, even at an advanced stage, and prolong life in patients with metastatic colorectal cancer who have no other treatment options available. To date regorafenib is the only oral multikinase inhibitor as monotherapy that has demonstrated in a large Phase III trial the ability to improve clinical outcomes in patients with advanced refractory colorectal cancer The approval of regorafenib (Stivarga®) by the EMA is expected in Q3/2013. At time of writing of this study protocol Stivarga® is expected to be indicated for the

	treatment of patients with metastatic colorectal cancer who have been previously treated with, or are not considered candidates for, fluoropyrimidine-based chemotherapy, an anti-VEGF therapy, andan anti-EGFR therapy. The pivotal phase 3 CORRECT trial was conducted in a closely defined patient population according to strict inclusion and exclusion criteria. After approval of regorafenib patients with metastatic colorectal cancer receiving this drug are usually more heterogeneous with various comorbid conditions. Therefore, the aim of this non-interventional study is to characterize the effectiveness and safety of Stivarga® therapy under routine daily practice conditions in Germany.
Research question and objectives	The main objective of this non-interventional cohort field study is to investigate the effectiveness of Stivarga® under current practice conditions. Primary objective is to determine overall survival (OS). Secondary objectives are to determine: • progression free survival (PFS) (either clinical progression and/or radiological progression) • time to progression (TTP) (either clinical progression and/or radiological progression) • disease control rate (DCR) • duration of Stivarga® treatment • tumor status at different visits • incidence of treatment emergent adverse events Additionally possible prognostic factors e.g. presence of severe comorbidities, metastatic sites, early relapse after adjuvant treatment, and KRAS mutation will be evaluated.
Study design	Company-sponsored prospective, open-label, multi-center, single arm cohort non-interventional, post-authorization safety study.
Population	Female and male patients ≥ 18 years of age with a diagnosis of metastatic colorectal carcinoma (mCRC) will be enrolled in the sites during the enrollment period. All treatment decisions prior inclusion of a patient as well as during the observation must be made by the investigator based on his regular medical practice. Patients must give written informed consent prior to documentation.

Variables	Eligibility for the study, visit dates, demography, diagnosis, medical history/ comorbidities, prior medication/treatment, exposure/ treatment, concomitant medication/treatment, tumor assessment, response assessment to treatment, performance status, reason for ending the observation, adverse events (AE).
Data sources	Medical records, routine measurements (e.g. tumor assessment), patients, other physicians.
Study size	It is planned to enroll 500 patients.
Data analysis	Statistical analyses will be primarily of explorative and descriptive nature. All issues concerning patient validity, data consistency checks, permissible data modifications will be described in detail in the Data Management Plan. All statistical issues including calculated variables and proposed format and content of tables will be detailed in the Statistical Analysis Plan. Demographic data, baseline characteristics, diagnosis and prior treatment of CRC, concomitant diseases, and concomitant medication will be described with summary statistics such as mean, standard deviation, minimum, 1, 5, 25, 75, 95, 99 percent quantiles, median, maximum for continuous variables, and category counts and frequencies (percentages) for categorical variables. Concomitant medication will be coded using WHO's drug dictionary. Descriptive summaries of Kaplan-Meier (KM) estimates (including number of failed, number censored, 25th and 75th percentiles with respective 95% confidence interval and median with 95% confidence interval) and KM curves will be presented for time-to-event effectiveness variables (OS, TTP, PFS). Disease control rate and the corresponding 95% confidence interval will be calculated. Descriptive statistics will be calculated for the treatment duration. Adverse events will be summarized using the MedDRA and the CTCAE coding system. Event rates for single adverse events will be calculated based on the total number of patients valid for safety. Adverse events will be categorized according to relation, seriousness, CTCAE grade (version 4.03), discontinuation of therapy, action taken and outcome. Special attention will be paid to serious adverse events and unexpected or unlisted adverse drug reactions.

Milestones	First patient first visit:	Q4 2013
	Last patient first visit:	31 July 2016
	Last patient last visit:	Q1 2017
	End of data collection (clean database)	Q2 2017
	Final report of study results:	Q1 2018

5. Amendments and updates

- Amendment-01, Version 1.0, 2014-09-22, is available as standalone document.

Amendment-01 is integrated in this protocol. The study protocol was amended due to the medical review of the first 100 recruited patients in this trial. In accordance with current clinical practice guidelines regorafenib should be used as 3rd or 4th line standard option in pretreated patients. Therefore the second inclusion criterion of this study was amended. The recruitment period was extended by 3 months and the number of patients was reduced from 1,000 to 500 due to delays in enrolment.

- Amendment-02, Version 2.0, 2016-04-06, is available as standalone document.

Amendment-02 is integrated in this protocol. The study protocol was amended due to a slower recruitment than planned. The recruitment period was extended by 4 months and the planned date for a second interim analysis was added to the protocol. Additionally, the OS Team composition was updated and minor clarifications regarding the documentation of (S)AEs were made.

6. Milestones

Table 1 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.

Table 1: Milestones

Milestone	**Planned date**
Start of study	Q4 2013
Start of data collection	Q4 2013
Last patient first visit	31 July 2016
Interim analysis	Q2/2015 or if half the patients are enrolled (whatever is earlier) and a second interim analysis in July 2016
Last patient last visit	Q1 2017
End of data collection (clean database)	Q2 2017
Final report of study results	Q1 2018

7. Rationale and background

Colorectal cancer (CRC) is a disease in which malignant cancer cells form in the tissues of the colon or rectum. The majority of cancer occurring in the colon and rectum are adenocarcinomas, which account for more than 90% of all large bowel tumors. CRC is the fourth most common cancer worldwide, with over one million cases occurring every year. The mortality rate from CRC is approximately half of its global incidence. The five year survival incidence on average is 55%, but is highly variable dependent on the stage of the disease (from 74% for patients with Stage I disease to only 6% for Stage IV patients).

In the setting of recurrent or advanced colon cancer, location of the disease determines treatment. With locally recurrent and/or liver-only and/or lung-only metastatic disease, the only chance for curative treatment is surgical resection. A negative surgical resection margin is associated with 5-year survival rates of 25% to 40% in nonrandomized studies in cases of resectable liver metastases. Several drugs are currently approved for use in metastatic colorectal cancer: 5-fluorouracil (5-FU), capecitabine, irinotecan, oxaliplatin, bevacizumab, cetuximab, and panitumumab. Approximately equivalent outcomes have been demonstrated by multiple studies evaluating the safety and efficacy of several 5-FU-leucovorin regimens that employ varying schedules and dosages, all with a median survival time of about 12 months. In 3 randomized trials that compared 5-FU/leucovorin (FL) with the same combination and the addition of either irinotecan or oxaliplatin, there were improvements in progression free survival (PFS), overall survival (OS) and responses rates when one of these three agents was included.[1,2] An Intergroup study N9741 comparing irinotecan plus bolus 5-FU/leucovorin (IFL) with oxaliplatin, leucovorin, and 5-FU (FOLFOX4) as first-line therapy for metastatic colorectal cancer showed that those assigned to FOLFOX4 had a significant improvement in PFS (median, 6.9 months vs. 8.7 months; $P = .014$; HR = 0.74; as well as in OS (15.0 months vs. 19.5 months, $P = .001$; HR = 0.66). Two other trials evaluating FOLFOX vs. infusional folic acid/5-FU, and irinotecan (FOLFIRI) demonstrated that PFS and OS were not different between treatment arms.[3,4] Subsequent to this, either FOLFOX or FOLFIRI is considered acceptable for use as first-line therapy for metastatic colorectal cancer.

The use of bevacizumab in first-line treatment of metastatic CRC has been evaluated in several other studies. Hurwitz et al randomized patients to either IFL or IFL plus bevacizumab.[5] Those on the bevacizumab arm had a significant improvement in PFS (10.6 months compared with 6.2 months, HR for disease progression = 0.54; $P < .001$) and OS (20.3 months compared with 15.6 months, HR for death = 0.66; $P < .001$). Study E3200 by the Eastern Cooperative Oncology Group (ECOG) was a trial for patients who had failed 5-FU/irinotecan. Patients were randomized to receive FOLFOX or FOLFOX plus bevacizumab. A statistically significant improvement in PFS (7.3 vs. 4.7 months, $P <.0001$) and OS (12.9 vs. 10.8 months, $P = .0011$) was shown for patients treated with the combination FOLFOX4 plus bevacizumab vs. those treated with chemotherapy alone.[6] Based on these findings, bevacizumab can be added to FOLFIRI or FOLFOX in the treatment of metastatic CRC.

In the setting of second-line therapy of patients previously treated with 5-FU/leucovorin, irinotecan has shown an improvement in OS when compared to infusional 5-FU or best supportive care.[7,8] In a phase III study of patients who had failed irinotecan and 5-FU/leucovorin, Rothenberg et al randomized patients to be given infusional 5-FU, oxaliplatin, or FOLFOX4. The median time to progression (TTP) was longer for FOLFOX4 compared to the other arms (4.6 months vs. 2.7 months). In a phase II trial for patients who had failed an irinotecan-based regimen, Cunningham et al randomly

assigned patients to cetuximab or irinotecan plus cetuximab. Results demonstrated an improved median TTP for the combination of irinotecan plus cetuximab vs. cetuximab alone (4.2 vs. 1.5 months).[9] This led to the approval of cetuximab for metastatic CRC after progression with 5-FU and irinotecan. These results were further substantiated by another study by Jonker et al, which randomized 572 patients with epidermal growth factor receptor (EGFR)-positive CRC who had previously been treated with a fluoropyrimidine, irinotecan and oxaliplatin to either cetuximab plus best supportive care (BSC) or BSC alone.[10] The primary endpoint of the trial was OS. The cetuximab arm showed a significant improvement in OS (HR 0.77, p=0.005) and in PFS (HR 0.68, p<0.001). Median OS for the cetuximab group was 6.1 months compared to 4.6 months for BSC alone. In a phase III study of chemotherapy-refractory CRC, Van Cutsem et al randomized patients to panitumumab or best supportive care and demonstrated an improvement in PFS. No difference was observed in overall survival, which was confounded by similar activity of panitumumab after 76% of BSC patients entered the cross-over study.[11] Based on the data from this trial, the Food and Drug Administration (FDA) and European Medicines Agency (EMA) granted approval for panitumumab for chemotherapy-refractory CRC.

Regorafenib is a new oral multikinase inhibitor that inhibits tumor growth by inhibiting both the proliferation of tumor cells and the formation of new tumor vasculature. Regorafenib was selected based on its kinase inhibition profile, which includes angiogenic (VEGFR 2/3, Tie2), stromal (PDGFR-ß, FGFR) and oncogenic (c-KIT, RET and B-RAF) (receptor tyrosine) kinases. Those kinases are inhibited in biochemical and cell-based assays with inhibitory concentrations (IC_{50}) between 3 and about 300 nM. Regorafenib was also shown to potently inhibit the Raf/MEK/ERK pathway in vitro with IC_{50} between 20 and 400 nM. This pathway is an important mediator of responses to growth signals and angiogenic factors and is often aberrantly activated in human tumors due to the presence of activated RAS, mutant B-RAF, or constitutively activated growth factor receptors.[12] In CRC, mutated BRAF occurs with a frequency of 5% to 12% and activated RAS is found in approximately 38% of CRC patients.[13] Inhibition of this pathway may therefore be of clinical benefit in particular in CRC. Regorafenib inhibits the proliferation of a wide range of human tumor cell lines with IC_{50} between 40 and 5000 nM including the colon cancer cell lines SW620 and Colo-205, which are inhibited with about 1000 and 3300 nM, respectively. Anti-proliferative activity was demonstrated to be accompanied by induction of apoptosis in a hepatocellular cancer cell line. The compound potently inhibits also the growth factor dependent proliferation of vascular cells with IC_{50} of 3-150 nM, thereby mediating its antiangiogenic effects.

In vivo regorafenib inhibits tumor growth in a dose-dependent manner in multiple human xenografts growing subcutaneously in mice including the CRC models Colo-205 and HT-29 both carrying mutant $B\text{-}RAF^{V600E}$ and the models HCT-116 and HCT-15, which carry mutant $K\text{-}RAS^{G13D}$ and the latter being multidrug resistant and insensitive to taxol treatment. Furthermore, regorafenib was efficacious in oxaliplatin insensitive patient-derived human colon xenografts, where added benefit was observed with the combinatorial treatment of regorafenib and irinotecan in one case. Additionally, the compound revealed antimetastatic activity observed in a syngeneic orthotopic breast cancer model. In functional assays regorafenib exhibits antiproliferative and antiangiogneic effects in colon and breast xenografts as demonstrated by reduction in microvessel area and reduced Ki67 and pERK1/2 staining in tissue sections. The compound exerts further antiangiogenic effects by prolonging inhibition of extravasation in the tumor vasculature of a rat GS9L glioblastoma model, as shown by dynamic contrast enhanced magnetic resonance imaging (DCE-MRI).

M-2 (BAY 75-7495) and M-5 (BAY 81-8752), 2 major metabolites of regorafenib in human plasma, were analyzed and were shown to have similar activities in biochemical and cell-based assays *in vitro* compared to regorafenib. *In vivo* both metabolites inhibited the growth of colorectal HT-29 tumor xenografts and the VEGF induced vascular effects (e.g., extravasation and hypotension) with similar efficacy as regorafenib.

In summary, the results of these preclinical studies support the investigation in clinical trials of the potential of regorafenib to treat CRC patients.

The evidence of efficacy and safety in metastatic colorectal cancer patients was based on the multi-national, multi-center Phase III CORRECT study, titled, "A randomized, double-blind, placebo-controlled phase III study of regorafenib plus BSC versus placebo plus BSC in patients with metastatic colorectal cancer who have progressed after standard therapy". The study met its primary endpoint of significantly improving overall survival by 29% (HR=0.77, p=0.0052); a median OS of 6.4 months for regorafenib compared to 5.0 months for the placebo group. The trial also met two secondary efficacy endpoints, including a significant improvement in progression-free survival (PFS) (HR=0.49, p=0.000001), and a significant improvement in the disease control rate (DCR) (p<0.000001). The overall safety and tolerability profile for regorafenib was consistent with results from previous studies. The most common drug-related, treatment emergent adverse events (occurring in at least 25% of patients) included fatigue (47.4% vs. 28.1%), hand-foot-skin reaction (46.6% vs. 7.5%), diarrhea (33.8% vs. 8.3%), anorexia (30.4% vs. 15.4%), voice changes (29.4% vs. 5.5%), hypertension (27.8% vs. 5.9%), oral mucositis (27.2% vs. 3.6%), and rash/desquamation (26.0% vs. 4.0%) for patients receiving regorafenib compared to placebo. These data demonstrate that regorafenib can stabilize disease, even at an advanced stage, and prolong life in patients with metastatic colorectal cancer who have no other treatment options available. To date regorafenib is the only oral multi-kinase inhibitor as monotherapy that has demonstrated in a large Phase III trial the ability to improve clinical outcomes in patients with advanced refractory colorectal cancer.[14]

Abnormalities of liver function tests (alanine aminotransferase [ALT], aspartate aminotransferase [AST] and bilirubin) have been frequently observed in patients treated with regorafenib, also severe liver function test abnormalities (Grade 3 to 4) and hepatic dysfunction with clinical manifestations (including fatal outcomes) have been reported in a small proportion of patients. Therefore for patients with observed worsening of liver function tests considered related to treatment with regorafenib (i.e. where no alternative cause is evident, such as post-hepatic cholestasis or disease progression), the dose modification and monitoring advice in the Summary of Product Characteristics (SPC) should be followed. It is recommended in the SPC to perform liver function tests (ALT, AST and bilirubin) before initiation of treatment with Stivarga® and monitor closely (at least every 2 weeks) during the first 2 months of treatment. Thereafter, it is recommended to continue periodic monitoring at least monthly and as clinically indicated.

Stivarga® is indicated for the treatment of patients with metastatic colorectal cancer who have been previously treated with, or are not considered candidates for, fluoropyrimidine-based chemotherapy, an anti-VEGF therapy, and an anti-EGFR therapy.

The pivotal phase 3 CORRECT trial was conducted in a closely defined patient population according to strict inclusion and exclusion criteria. After approval of Stivarga® patients with metastatic colorectal cancer receiving this drug are usually more heterogeneous with various comorbid conditions. Therefore, the aim of this non-interventional study is to characterize the

effectiveness and safety of Stivarga® therapy under routine daily practice conditions in Germany.

8. Research questions and objectives

The pivotal phase 3 CORRECT trial was conducted in a closely defined patient population according to strict inclusion and exclusion criteria. After approval of regorafenib patients with metastatic colorectal cancer receiving this drug are usually more heterogeneous with various comorbid conditions. Therefore, the aim of this non-interventional study is to characterize the efficacy and safety of Stivarga® therapy under routine daily practice conditions in Germany.

8.1. Primary objective(s)

The primary objective is to investigate overall survival.

8.2. Secondary objective(s)

Secondary objectives are to determine:

- progression free survival (either clinical progression and/or radiological progression)
- time to progression (either clinical progression and/or radiological progression)
- disease control rate
- duration of Stivarga® treatment
- tumor status at different visits
- incidence of treatment emergent adverse events

Additionally possible prognostic factors e.g. presence of severe comorbidities, metastatic sites, early relapse after adjuvant treatment, and KRAS mutation will be evaluated.

9. Research methods

9.1. Study design

This study is a prospective, open-label, multi-center, single arm cohort non-interventional post-authorization safety study of patients with mCRC who are prescribed Stivarga®. The study will be conducted in Germany. The study will start after Stivarga® has been authorized and made commercially available in Germany. All patients for whom the selection criteria are fulfilled are eligible for enrollment into the study. Patient's clinical information will be documented at time of the initial visit and at time of follow-up visits which should be documented every 4 to 6 weeks.

The actual treatment duration will be determined solely by the physician. Patient data will be collected according to local clinical practice during personal or phone visits. The study ends 12 months after enrollment of the last patient. Serious adverse events will be followed up until resolution.

A prospective, non-interventional design was chosen as up to now no data are available on real-life treatment with Stivarga®.

9.1.1. Primary endpoint(s)

The primary endpoint is overall survival (OS). OS is defined as the time interval from start of Stivarga® therapy to the date of death due to any cause. Patients alive or lost to follow-up at the time of analysis will be censored at the last date known to be alive.

9.1.2. Secondary endpoint(s)

The secondary endpoints are:

- Progression free survival (PFS) is defined as the time interval measured from the day of start of Stivarga® treatment to diagnosed (radiological or clinical) progression or death, whichever comes first. Progression-free survival for patients without disease progression or death at the time of analysis will be censored at the last date of tumor evaluation.
- Time to progression (TTP) is defined as the time interval from start of Stivarga® therapy to the date of diagnosed (radiological or clinical) progression. Patients without tumor progression at the time of analysis will be censored at their last date of tumor evaluation.
- Disease control rate (DCR) is defined as percentage of patients, whose best response was not progressive disease (i.e. complete response, partial response or stable disease).
- Duration of Stivarga® treatment is defined as the time interval from start of Stivarga® therapy to the date of permanent discontinuation of Stivarga® therapy (regardless of the reason for discontinuation). It will be calculated as last dosing date - first dosing date + 1. A patient with only one dose of Stivarga® will be considered as having a treatment duration of one day.
- The tumor status at different visits will be evaluated according to the categories “complete response”, “partial response”, “stable disease”, “progressive disease by clinical judgment”, “progressive disease measurement proven”, “unknown” and “not applicable”. The best overall response will be analyzed providing absolute and relative frequencies of the tumor status categories.
- Incidence of treatment-emergent adverse events (TEAE) - patients will be monitored for TEAEs using the NCI-CTCAE Version 4.03. Detailed information collected for each TEAE will include: a description of the event, duration, whether the TEAE was serious, relationship to Stivarga®, action taken, clinical outcome. Summary tables will present the number of subjects observed with TEAEs and corresponding percentages. Additional subcategories will be based on event intensity and relationship to study drug.

9.1.3. Strengths of study design

The strength of the non-interventional study design is that is allows to observe diverse populations in a broad range of settings (natural environment) reflecting reality. 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 a sponsor or study protocol.

9.2. Setting

9.2.1. Eligibility

The study population will consist of patients with metastatic CRC for whom the decision has been taken by the investigator to treat with Stivarga® according to the local summary of product characteristics (SPC).

9.2.2. Inclusion criterion/criteria

- Male or female patients ≥ 18 years of age with metastatic CRC for whom the decision has been taken by the investigator to treat with Stivarga® as 3rd or 4th line treatment
- Patients must have signed an informed consent form

9.2.3. Exclusion criterion/criteria

Not applicable

9.2.4. Withdrawal

Each patient has the right to refuse further participation in the study at any time and without providing any reasons. A patient's participation is to be terminated immediately upon his/her request. The investigator should seek to obtain the reason and record this on the Case Report Form (CRF). In this non-interventional study, withdrawal from the study is independent of the underlying therapy. On the other hand, premature end of therapy does not automatically imply end of documentation: Follow-up continues at least 30 days after end of therapy.

9.2.5. Replacement

Patients will not be replaced after drop-out.

9.2.6. Representativeness

The investigators and the patients documented in the study should be selected only based on eligibility according to inclusion and exclusion criteria as outlined in Section 9.2.2. No further selection should be applied. A representative sample of sites will be included in the study, and investigators will be asked to sample consecutive patients whenever possible to avoid any selection bias and thus to increase likelihood representativeness.

9.2.7. Visits

The start of the study is the date from which information on the first study patient can be first recorded in the study dataset (first patient first visit). A visit is defined as any status assessment or new treatment decision the treating physician takes with the presence of the patient.

The investigator should document at least an initial visit, follow-up visits and a final visit for each patient in the case report form (CRF). Follow-up assessment should be documented every 4 to 6 weeks, although the patient's visit schedule itself will be at the treating physician's discretion. A certain number or frequency of visits is not requested by this protocol, however at least an initial visit and a final visit must be documented.

The observation period for each patient covers the period from start of Stivarga®-therapy to death. The median observation period per patient is estimated to be about 7 months, the study will end 12 months after last patient first visit (also see Section 9.5). The final data collection per patient is at patient's death, at end of study or at any time due to premature discontinuation of observation (whatever is earlier). If the documentation is stopped prematurely, the reasons for the end of observation have to be given. If a patient joins an interventional clinical study during the course of observation, at least the information on survival will still be collected up to the end of this study.

If a patient will still be alive at time of study closure, this will be documented at final observation.

The CRF is available upon request. The respective document is listed in Annex 1.

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.

Table 2: Tabulated overview on variables collected during the study

Schedule Procedure	Base-line	Initial visit	Follow-up	End of therapy	End of obser-vation	Follow-up after end of therapy
Visit date	X	X	X	X	X	X
Patient information and consent	X					
Demographic data	X					
Date of initial CRC diagnosis	X					
Medical history of CRC	X					
Previous treatment for CRC	X					
Concomitant diseases	X					
Weight and height		X				
Tumor status		X				
Performance status (ECOG)		X	X	X	X	
Start of Stivarga® treatment		X				
Initial dose of Stivarga ®		X				
Blood pressure		X*				
Laboratory values**		X	X	X	X	
Change of therapy since last visit			X	X	X	
Tumor status evaluation			X	X	X	
Concomitant radiotherapy			X	X	X	
Concurrent diagnostic and therapeutic procedures for mCRC			X	X	X	
Treatment (preventive or therapeutic) for hand foot skin reaction		X	X	X	X	
Concomitant medication		X	X	X	X	
Adverse Events			X	X	X	X***
Date of last Stivarga® dose				X	X	
Reason for discontinuation of treatment				X		
Reason for end of observation					X	
Survival assessment						X
Further treatment for mCRC						X

* weekly up to six weeks from start of therapy
** only documented if new information is available from regular practice. No additional diagnostics are required for the study.
*** for Stivarga®: up to 30 days after end of treatment

9.3.1. Variables to determine the primary endpoint(s)

- Overall survival

9.3.2. Variables to determine the secondary endpoint(s)

- Progression free survival
- Time to progression
- Disease control rate
- Duration of Stivarga® treatment
- Tumor status at different visits
- Incidence of treatment emergent adverse events

9.3.3. Demography

For demographic assessment, the following data will be recorded:

- Year of birth
- Sex
- Ethnicity

9.3.4. Co-morbidities (medical history, concomitant diseases)

9.3.4.1 Colon cancer classification

For the classification of colon cancer the following data will be recorded:

- Histology
- Stage (TNM classification)
- Grading (AJCC)
- Anatomical location
- KRAS mutation
- Date of most recent progression/relapse incl. type of assessment

9.3.4.2 Co-morbidities

Co-morbidities are any medical findings, whether or not they pertain to the study indication, that were present before start of therapy with Stivarga®, independent on whether or not they are still present.

The following co-morbidities are considered to be relevant to the study indication have to be documented:

- Hemorrhagic stroke
- Ischemic stroke
- Transient ischemic attack
- Myocardial infarction

- Angina pectoris
- Congestive cardiac failure including NYHA class
- Hypertension including CTC Grade
- Diabetes mellitus
- Renal insufficiency
- Liver insufficiency
- Leucocytopenia
- Thrombocytopenia
- Hand and foot skin reaction in the past
- Phlebitis in the past 12 months
- Pulmonary embolism in the past 12 months
- Deep vein thrombosis in the past 12 months
- Obesity
- Metabolic syndrome
- Other malignant neoplasm
- Other

9.3.4.3 Diagnosis and prior treatment for CRC

- Prior diagnosis and therapeutic procedures for CRC
- Prior systemic anticancer therapy (medication) with best response for each regimen
- Prior radiotherapy

9.3.5. Prior and concomitant medication

All medication taken in addition to the study drug for any indication (either initiated before study start or during the study) is termed concomitant medication.

9.3.5.1 Concomitant medication except preventive or therapeutic treatment of hand-foot-skin reaction

Information to be collected for concomitant medication includes: trade name or INN, start date, stop date/ongoing, dose, unit, frequency, and indication.

9.3.5.1 Preventive or therapeutic treatment of hand and foot skin reaction

Preventive or therapeutic treatment of hand foot skin reaction with skin cream will be documented on a separate form. Information to be collected includes type of treatment (non-urea based creams, keratolytic creams, topical corticosteroids, topical analgesics, oral analgesics), trade name, total daily dose (only in case of oral analgetics), indication (preventive or therapeutic), start and stop date (or continued)

9.3.6. Concurrent treatment

- Concurrent diagnostic and therapeutic procedures for mCRC

- Concurrent radiotherapy

9.3.7. Laboratory data

It is recommended in the SPC to perform liver function tests (ALT, AST and bilirubin) before initiation of treatment with Stivarga® and monitor closely (at least every 2 weeks) during the first 2 months of treatment. Thereafter, it is recommended to continue periodic monitoring at least monthly and as clinically indicated.

- Total bilirubin
- ALT
- AST

9.3.8. Exposure/treatment

9.3.8.1 At initial visit

Information on Stivarga®-treatment to be documented includes:

- Start date of therapy
- Dose, please specify other dose and reason for other dose
- Treatment time point

9.3.8.2 During follow-up visits

Each dose change and/or interruption of therapy during follow-up must be recorded in a study medication form. The following information must be documented: start/stop date of medication, treatment time point, new daily dose, reason for dose change/interruption.

9.3.9. Vital signs

The following vital signs will be recorded at initial visit:

- Weight (kg)
- Height (cm)
- Blood pressure (once per week up to six weeks from start of therapy)

9.3.10. Visit date(s)

Information on visit date(s) at initial visit and each documented follow-up visit includes:

- Date (day, month, year)

9.3.11. Tumor evaluation

9.3.11.1At initial visit

The following criteria will be assessed at initial visit:

- Status of tumor
    - Stage
    - Metastasis

- Date of tumor assessment
- Clinical status/radiological status

- ECOG

9.3.11.2At follow-up visits

The following criteria will be assessed at follow-up visits:

- Tumor status
  - Date of tumor assessment
  - Clinical status/radiological status
- ECOG

9.3.12. Survival status after end of therapy

Typical information to be collected at follow-up after end of therapy includes:

- Request for survival status performed
  - If no: reason for no assessment
  - If yes: survival status
- Documentation of AEs for up to 30 days after last Stivarga® intake
- Further anti-cancer therapy (medication) during follow-up
  - Any systemic treatment, if yes, please specify experimental drug or other

9.3.13. Adverse events

New adverse events occurring during the course of study will be documented from the first Stivarga® intake until 30 days after end of Stivarga® treatment (for further details refer to Section 11.2). Adverse events already documented will be updated with new information during the whole course of the study.

9.3.14. Reasons for choice of treatment

The treating physician will decide on the treatment of the patient based on his medical assessments in close relation to the patient's physical and psychological status. All treatment decisions will follow the real-life treatment behavior of the physician. As there can be expected a wide range of factors influencing treatment decisions over the entire observation period, this will not be captured on the CRF in detail. In any case reasons for stop of Stivarga®-treatment will be documented.

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, results of tumor assessments and other disease status information, also documented in the medical record, during visits that take place in routine practice. For any adverse events that occur, information is directly obtained from the patient. In case a patient is seen by more than one physician for his/her disease (e.g. the patient is monitored by a physician other than the initial investigator), the initial investigator should make every effort to

collect information on any visits (including results) that have taken place outside the investigator's site due to the patient's disease, for example by interviewing the respective physician or patient or by obtaining an accompanying letter with detailed information and results.

9.5. Study size

Assuming an exponentially distributed OS with a median of 6.4 months, approximately 73% of patients are expected to die within a 12 months observation period. It is aimed to enroll 500 patients in this study. With 500 patients and a loss-to-follow-up of 20% of patients approximately 292 deaths will be observed in a 12-months-time-period. This means that under these assumptions, the 95% confidence interval for the 1-year survival rate of 27% would be approximately (23%, 32%), i.e. of length 9 percentage points. This time frame and number of events seem to be reasonable to describe the Kaplan-Meier-curve for overall survival in the routine daily practice conditions adequately, in particular considering the fact that the pivotal phase III study CORRECT had similar patient numbers randomized to the regorafenib treatment arm (n=505 regorafenib patients valid for ITT analysis).

9.6. Data management

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.

The CRF is designed in the desktop publishing software, Quick Silver. 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. A Contract Research Organization (CRO) will be selected and assigned for EDC system development. Information on the EDC system is available upon request. The respective document is listed in Annex 1.

Each patient is identified by a unique central patient identification code. This code is only used for study purposes. The patient code consists of a combination of a country code, site number and patient number. For the duration of the study and afterwards, only the patient's investigator is able to identify the patient based on the patient identification code.

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 and maximum). Continuous variables will be described by absolute value and as change from baseline per analysis time point, if applicable.

Patients receiving at least one dose of Stivarga® will be included in the analysis. Whenever reasonable, data will be stratified by subgroups (e.g. primary site of disease, baseline ECOG, number of prior treatment lines, KRAS mutation at study entry, concomitant diseases of special interest, location of

metastases, age, sex). In particular, the stratification by the number of prior treatment lines (≤ 4 vs > 4) will be performed in order to account for the changed inclusion criteria.

Sample size and disposition information by analysis time point will be displayed in a frequency table.

All issues concerning patient validity, data consistency checks, permissible data modifications will be described in detail in the Data Management Plan. All statistical issues including derived variables for analysis, handling of missing data and proposed format and content of tables will be detailed in the Statistical Analysis Plan (SAP). The SAP will be finalized before study database lock.

It is planned to have two interim analyses: one analysis of the baseline and safety data approximately 1.5 years after start of study or after half the patients have been enrolled, whatever comes earlier, and a second analysis of efficacy and safety data in July 2016. The final analysis will be performed 12 months after last patient last visit.

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

Demographic data, baseline characteristics, diagnosis and prior treatment of CRC, concomitant diseases, and concomitant medication will be described with summary statistics such as mean, SD, minimum, 1, 5, 25, 75, 95, 99 percent quantiles, median, maximum, minimum for continuous variables, and category counts and frequencies (percentages) for categorical variables.. Concomitant medication will be coded using WHO's drug dictionary.

9.7.3. Analysis of treatment data

Descriptive statistics will be calculated for the treatment duration. The following frequencies will be calculated: the number of patients with dose reductions, number of patients with dose interruptions, total number of dose reductions and frequencies of reasons for reduction, total number of dose interruptions and frequencies of reasons for interruption.

9.7.4. Analysis of primary outcome(s)

Descriptive summaries of Kaplan-Meier (KM) estimates (including number of failed, number censored, 25^{th} and 75^{th} percentiles with respective 95% CI and median with 95% CI) and KM curves will be presented for OS.

9.7.5. Analysis of secondary outcome(s)

Descriptive summaries of KM estimates (including number of failed, number censored, 25^{th} and 75^{th} percentiles with respective 95% CI and median with 95% CI) and KM curves will be presented for time-to-event effectiveness variables (TTP, PFS). Summary statistics will be calculated for duration of Stivarga® treatment.

Disease control rate, defined as percentage of patients whose best response was not progressive disease (i.e. complete response, partial response or stable disease), and the corresponding 95% confidence interval will be calculated.

Category counts and frequencies (percentages) will be calculated for tumor status at different visits and best overall tumor response.

AEs will be summarized using the MedDRA and the CTCAE coding system. Event rates for single AEs will be calculated based on the total number of patients valid for safety. AEs will be categorized according to relation, seriousness, CTCAE grade (version 4.03), discontinuation of therapy, action taken and outcome. Special attention will be paid to SAEs and unexpected or unlisted ADRs.

The analyses described in this section will be performed on treatment-emergent AE. Events which are not treatment-emergent will be tabulated without further stratification. All patients will be presented with all details from the AE report form. Further details of the safety analysis will be described in the SAP.

Subgroup analyses stratified with prognostic/predictive factors collected at baseline may be explored.

9.7.6. Bias, confounding and effect-modifying factors

In general data collected in this study may suffer from biases (e.g. interviewer bias, either by systematic differences in data recording or different interpretation of information on exposure or outcome for different patients, reporting as well as selection bias). Besides, prospective studies are prone to bias from loss to follow-up or change in methods over time. To decrease the reporting bias source data verification will be performed in at least 10% of the sites. In order to reduce selection bias, a representative sample of sites will be included in the study. Sites will be selected according to several criteria, main criteria for site selection will be: availability of suitable patients, balanced proportion between clinics and private practices and an equal geographical distribution. Investigators should select patients to be documented in the study only based on eligibility according to inclusion and exclusion criteria, i.e. each patient diagnosed with mCRC and starting treatment for the disease with Stivarga® should be asked for participation in a consecutive manner. No further selection should be applied. Accordingly all patients with mCRC stage IV will be documented in a log file. If the decision has be taken by the physician to treat this patient with Stivarga® the reason for not enrolling the patient in the study has to be documented.

Primary and secondary outcome variables and safety data will be analyzed with regard to different baseline factors. However, unknown and unmeasured risk factors for the outcome variables will exist and might lead to confounding when comparing results in different subgroups and when comparing study results with historical results from clinical studies.

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 study protocol and the CRF.

A CRO will be selected and assigned for EDC system development, quality assurance, 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 permissible clarifications. The DMP is available upon request. The respective document is listed in Annex 1.

National and international data protection laws as well as regulations on observational non-interventional studies will be followed. Electronic records used for patient documentation will be validated according to 21 Code of Federal Regulations (CFR) Part 11 (FDA)[15]. The documentation is available upon request. The respective document is listed in Annex 1.

9.8.2. Quality review

In a subset of patients (at least 10% of all patients/sites) source data verification will be conducted. The purpose is to review the documented data for completeness and plausibility, adherence to the study protocol and verification with source documents. To accomplish this, monitors will access medical records on site for data verification. Detailed measures for quality reviews will be described in the Quality Review Plan (QRP). The QRP is available upon request. The respective document is listed in Annex 1.

9.8.3. Storage of records and archiving

The sponsor will make sure that all relevant documents of this post-authorization safety study including CRFs and other patient records will be stored after end or discontinuation of the study at least for 15 years. Other instructions for storage of medical records will remain unaffected.

The investigators participating in the study have 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 also 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 named TOSCA at the sponsor's site for at least 15 years.

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 this study might not generate unbiased estimates for incidence rates of adverse events and effectiveness variables. Results for secondary effectiveness variables PFS, TTP, DCR have to be interpreted carefully because of the uncontrolled setting: Time periods between follow-up visits are much more variable than in controlled clinical studies in which a fixed visit schedule has to be maintained, and the quality of the tumor status evaluation will differ from that in controlled clinical studies.

Comparison of outcomes after treatment with Stivarga® versus treatment with a comparator cannot be performed in this single arm study. Comparisons can only be performed with historical data from clinical studies, which is prone to bias and confounding.

9.10. Other aspects

Not applicable.

10. Protection of human subjects

10.1. Ethical conduct of the study

This study is a non-interventional study where Stivarga® is prescribed in the usual 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).[16] Recommendations given by other organizations will be followed as well (e.g. EFPIA)[17], ENCePP[18]). ICH-GCP guidelines will be followed whenever possible.

In addition, the guidelines on good pharmacovigilance practices will be followed; the relevant competent authorities of the EU member states will be notified according to Volume 9A.[19]

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

Documented approval from an appropriate IEC/IRB will be obtained for all participating sites prior to study start. When necessary, an extension, amendment or renewal of the IEC/IRB approval will be obtained and also forwarded to the sponsor. The IEC/IRB must supply to the sponsor, 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 in writing. 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 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. Study findings stored on a computer will be stored in accordance with local data protection laws.

All records identifying the patient will be kept confidential and will not be made publicly available. Patient names should not be provided either to the sponsor or to the CRO. If the patient name appears on any document, it must be obliterated before a copy of the document is supplied to the sponsor. 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. Definition

An adverse event (AE) is any untoward medical occurrence in a patient administered a medicinal product and which does not necessarily have to 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).

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
- An effect of the comparator drug
- An effect related to study procedure
- Any combination of one or more of these factors

- An effect related to lack of drug effect,
- Medication errors, drug abuse, drug misuse or drug dependency itself, as well any resulting event,
- An effect related to pre-existing condition improved (unexpected therapeutic benefits are observed)
- Drug exposure via mother/father (exposure during contraception, pregnancy, childbirth and breatfeeding).

As mentioned above no causal relationship with a study medication is implied by the use of the term "adverse event".

Hospitalizations will not be regarded as adverse events, if they:

- were planned before inclusion in the study
- are ambulant (shorter than 12 hours)
- are part of the normal treatment or monitoring of the studied disease i.e. they were not due to a worsening of the disease.

A drug related AE (called adverse reaction – AR) is any AE judged as having a reasonable suspected causal relationship to Stivarga®. An adverse reaction is defined as a response to medicinal product, which is noxious and unintended.

An AE is serious 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 patient 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 automatically considered as Serious, UNLESS at least one of the following exceptions is met:

- The admission results in a hospital stay of less than 12 hours, OR
- The admission is pre-planned (i.e., elective or scheduled surgery arranged prior to the start of the study), OR

- The admission is not associated with an adverse event (i.e. social hospitalization for purposes of respite care).

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 adverse event 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 administration of Stivarga®, all non-serious Adverse Events (AE) must be documented on the AE Report Form or to the CRF and forwarded to the sponsor within 7 calendar days of awareness. All serious AEs (SAE) must be documented and forwarded immediately (within 24 hours of awareness).

For each AE/SAE, the investigator must assess and document the seriousness, duration, causal relationship to study drug, action taken and outcome of the event.

If a pregnancy occurs during the study, although it is not a serious adverse event, it should be reported within the same time limits as a serious adverse event. The result of a pregnancy should be followed carefully and any abnormal result of the mother or baby should be reported.

Any AE/SAE occurring up to 30 days after the last intake of Stivarga® has to be documented. However, the documentation of any AE/SAE ends with the completion of the observation period of the patient.

As long as the patient has not received any Stivarga® AEs /SAEs do not need to be documented as such in this non-interventional study. However, they are part of the patient's medical history.

For any serious drug-related AE occurring more than 30 days after the last intake of Stivarga®, the standard procedures that are in place for spontaneous reporting have to be followed.

11.3. Management and reporting

Non-serious AEs

The outcome of all reported AEs (resolution, improvement etc.) 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

Non-serious ARs occurring under treatment with Stivarga® 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) and according to national regulations by the sponsor; however, all investigators must obey local legal requirements.

For non-serious ARs occurring under non-Bayer drugs 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 will be forwarded immediately (within 24 hours 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 sponsor for SAEs occurring under Stivarga®-treatment; however, all investigators must obey local legal requirements.

For SAEs that occurred while administering non-Bayer drugs 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.

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 with weekly listings (for information on collection, management and reporting of case reports, refer to section 11.2 and 11.3). If it is determined that a potential signal has arisen either from case reports or any other sources, the Core Safety Management Team (SOP BPD 037) may be initiated by the Global Safety Lead 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 the EMA PASS register (ENCEPP register). Results will be disclosed in a publicly available database within the standard timelines.

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

13. List of references

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Annex 1. List of stand-alone documents

Table 3: List of stand-alone documents

Number	Document reference number	Date	Title
1	SV1313_List of active physicians_final	Will be available at end of recruitment	List of all active physicians
2	SV1313_INV_CRF_draft	15 July 2013	CRF draft
3	SV1313_EDC_summary	Will be available at time of ready to enroll	EDC System description
4	SV1313_EDC_validation	Will be available at time of ready to enroll	EDC System Validation
5	SV1313_DAT_DMP	Will be available at time of ready to enroll	Data Management Plan
6	SV1313_ SAP	Will be available before study database lock	Statistical Analysis Plan
7	SV1313_DAT	Will be available at time of ready to enroll	Quality Review Plan

Annex 2. ENCePP checklist for study protocols

Section 1: Research question	**Yes**	**No**	**N/A**	**Page Number(s)**
1.1 Does the formulation of the research question clearly explain:				
1.1.1 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)	☒	☐	☐	17
1.1.2 The objectives of the study?	☒	☐	☐	18
1.2 Does the formulation of the research question specify:				
1.2.1 The target population? (i.e. population or subgroup to whom the study results are intended to be generalized)	☒	☐	☐	19
1.2.2 Which formal hypothesis(-es) is (are) to be tested?	☐	☐	☒	
1.2.3 If applicable, that there is no *a priori* hypothesis?	☒	☐	☐	26

Comments:

Section 2: Source and study populations	**Yes**	**No**	**N/A**	**Page Number(s)**
2.1 Is the source population described?	☒	☐	☐	17, 19
2.2 Is the planned study population defined in terms of:				
2.2.1 Study time period?	☒	☐	☐	14
2.2.2 Age and sex?	☒	☐	☐	19
2.2.3 Country of origin?	☒	☐	☐	17, 18
2.2.4 Disease/indication?	☒	☐	☐	19
2.2.5 Co-morbidity?	☐	☒	☐	
2.2.6 Seasonality?	☐	☐	☒	
2.3 Does the protocol define how the study population will be sampled from the source population? (e.g. event or inclusion/exclusion criteria)	☒	☐	☐	19

Comments:

Section 3: Study design	**Yes**	**No**	**N/A**	**Page Number(s)**
3.1 Does the protocol specify the primary and secondary (if applicable) endpoint(s) to be investigated?	☒	☐	☐	18, 19
3.2 Is the study design described? (e.g. cohort, case-control, randomized controlled trial, new or alternative design)	☒	☐	☐	18
3.3 Does the protocol describe the measure(s) of effect? (e.g. relative risk, odds ratio, deaths per 1000 person-years, absolute risk, excess risk, incidence rate ratio, hazard ratio, number needed to harm (NNH) per year)	☒	☐	☐	27
3.4 Is sample size considered?	☒	☐	☐	26
3.5 Is statistical power calculated?	☐	☐	☒	

Comments:

3.3 absolute risk will be calculated

Section 4: Data sources	**Yes**	**No**	**N/A**	**Page Number(s)**
4.1 Does the protocol describe the data source(s) used in the study for the ascertainment of:				
4.1.1 Exposure? (e.g. pharmacy dispensing, general practice prescribing, claims data, self-report, face-to-face interview, etc.)	☒	☐	☐	17, 18, 25
4.1.2 Endpoints? (e.g. clinical records, laboratory markers or values, claims data, self-report, patient interview including scales and questionnaires, vital statistics, etc.)	☒	☐	☐	18, 19
4.1.3 Covariates?	☒	☐	☐	22-26
4.2 Does the protocol describe the information available from the data source(s) on:				
4.2.1 Exposure? (e.g. date of dispensing, drug quantity, dose, number of days of supply prescription, daily dosage, prescriber)	☒	☐	☐	25
4.2.2 Endpoints? (e.g. date of occurrence, multiple event, severity measures related to event)	☒	☐	☐	25
4.2.3 Covariates? (e.g. age, sex, clinical and drug use history, co-morbidity, co-medications, life style, etc.)	☒	☐	☐	25
4.3 Is the coding system described for:				

Section 4: Data sources	**Yes**	**No**	**N/A**	**Page Number(s)**
4.3.1 Diseases? (e.g. International Classification of Diseases (ICD)-10)	☐	☒	☐	
4.3.2 Endpoints? (e.g. Medical Dictionary for Regulatory Activities(MedDRA) for adverse events)	☒	☐	☐	28
4.3.3 Exposure? (e.g. WHO Drug Dictionary, Anatomical Therapeutic Chemical (ATC)Classification System)	☒	☐	☐	28
4.4 Is the linkage method between data sources described? (e.g. based on a unique identifier or other)	☐	☐	☒	

Comments:

Section 5: Exposure definition and measurement	**Yes**	**No**	**N/A**	**Page Number(s)**
5.1 Does the protocol describe how exposure is defined and measured? (e.g. operational details for defining and categorizing exposure)	☒	☐	☐	1
5.2 Does the protocol discuss the validity of exposure measurement? (e.g. precision, accuracy, prospective ascertainment, exposure information recorded before the outcome occurred, use of validation sub-study)	☐	☐	☒	
5.3 Is exposure classified according to time windows? (e.g. current user, former user, non-use)	☐	☐	☒	
5.4 Is exposure classified based on biological mechanism of action?	☐	☐	☒	
5.5 Does the protocol specify whether a dose-dependent or duration-dependent response is measured?	☒	☐	☐	28

Comments:

Section 6: Endpoint definition and measurement	**Yes**	**No**	**N/A**	**Page Number(s)**

Section 6: Endpoint definition and measurement	**Yes**	**No**	**N/A**	**Page Number(s)**
6.1 Does the protocol describe how the endpoints are defined and measured?	☒	☐	☐	18, 19
6.2 Does the protocol discuss the validity of endpoint measurement? (e.g. precision, accuracy, sensitivity, specificity, positive predictive value, prospective or retrospective ascertainment, use of validation sub-study)	☐	☒	☐	

Comments:

Section 7: Biases and Effect modifiers	**Yes**	**No**	**N/A**	**Page Number(s)**
7.1 Does the protocol address:				
7.1.1 Selection biases?	☒	☐	☐	29
7.1.2 Information biases? (e.g. anticipated direction and magnitude of such biases, validation sub-study, use of validation and external data, analytical methods)	☒	☐	☐	29
7.2 Does the protocol address known confounders? (e.g. collection of data on known confounders, methods of controlling for known confounders)	☐	☒	☐	
7.3 Does the protocol address known effect modifiers? (e.g. collection of data on known effect modifiers, anticipated direction of effect)	☐	☐	☒	
7.4 Does the protocol address other limitations?	☒	☐	☐	30

Comments:

Section 8: Analysis plan	**Yes**	**No**	**N/A**	**Page Number(s)**
8.1 Does the plan include measurement of absolute effects?	☒	☐	☐	27, 28
8.2 Is the choice of statistical techniques described?	☒	☐	☐	27, 28
8.3 Are descriptive analyses included?	☒	☐	☐	27, 28

Section 8: Analysis plan	**Yes**	**No**	**N/A**	**Page Number(s)**
8.4 Are stratified analyses included?	☒	☐	☐	28
8.5 Does the plan describe the methods for identifying:				
8.5.1 Confounders?	☐	☐	☒	
8.5.2 Effect modifiers?	☐	☐	☒	
8.6 Does the plan describe how the analysis will address:				
8.6.1 Confounding?	☐	☐	☒	
8.6.2 Effect modification?	☐	☐	☒	

Comments:

Section 9: Quality assurance, feasibility and reporting	**Yes**	**No**	**N/A**	**Page Number(s)**
9.1 Does the protocol provide information on data storage? (e.g. software and IT environment, database maintenance and anti-fraud protection, archiving)	☒	☐	☐	30
9.2 Are methods of quality assurance described?	☒	☐	☐	29, 30
9.3 Does the protocol describe quality issues related to the data source(s)?	☐	☒	☐	
9.4 Does the protocol discuss study feasibility? (e.g. sample size, anticipated exposure, duration of follow-up in a cohort study, patient recruitment)	☐	☒	☐	
9.5 Does the protocol specify timelines for				
9.5.1 Study start?	☒	☐	☐	14
9.5.2 Study progress? (e.g. end of data collection, other milestones)	☒	☐	☐	14
9.5.3 Study completion?	☒	☐	☐	14
9.5.4 Reporting? (i.e. interim reports, final study report)	☒	☐	☐	14
9.6 Does the protocol include a section to document future amendments and deviations?	☒	☐	☐	14
9.7 Are communication methods to disseminate results described?	☒	☐	☐	35
9.8 Is there a system in place for independent review of study results?	☐	☒	☐	

Comments:

Section 10: Ethical issues	**Yes**	**No**	**N/A**	**Page Number(s)**
10.1 Have requirements of Ethics Committee/Institutional Review Board approval been described?	☒	☐	☐	31
10.2 Has any outcome of an ethical review procedure been addressed?	☐	☒	☐	
10.3 Have data protection requirements been described?	☒	☐	☐	29, 31, 32

Comments:

Name of the coordinating study entity[1]: _Bayer Vital GmbH_____

Date: 22/07/2013

Signature: _____

[1]*A legal person, institution or organization which takes responsibility for the design and/or the management of a study.*

Annex 3. Signature pages

Title	**RECORA- Re**gorafenib in patients with metastatic **co**lorectal cancer (mCRC) **a**fter failure of standard therapy
Protocol version identifier	3.0
Date of last version of protocol	06 April 2016
IMPACT study number	16665
Study type	☐ non-PASS ☒ PASS Joint PASS: ☐ YES ☒ NO
EU PAS register number	To be added after registration
Active substance (medicinal product)	Proteine Kinase Inhibitors (L01XE21), regorafenib
Marketing authorization holder(s)	Bayer Pharma AG, D-13342 Berlin, Germany
Function	Qualified Person Responsible for Pharmacovigilance
Name	Michael Kayser
Title	European Qualified Person Responsible for Pharmacovigilance
Address	Bayer Pharma AG, Aprather Weg 18a, 42096 Wuppertal, Germany

The undersigned confirms that s/he agrees to conduct the study under the conditions described in this protocol.

Date, Signature: April 22nd, 2016 M. Kayser

Title	**RECORA- Re**gorafenib in patients with metastatic **co**lorectal cancer (mCRC) **a**fter failure of standard therapy
Protocol version identifier	3.0
Date of last version of protocol	06 April 2016
IMPACT study number	16665
Study type	☐ non-PASS ☒ PASS Joint PASS: ☐ YES ☒ NO
EU PAS register number	To be added after registration
Active substance (medicinal product)	Proteine Kinase Inhibitors (L01XE21), regorafenib
Marketing authorization holder(s)	Bayer Pharma AG, D-13342 Berlin, Germany
Function	Study Medical Expert
Name	Ingo Bernard
Title	Medical Advisor
Address	Bayer HealthCare Germany, Bldg. K56, 51366 Leverkusen, Germany

The undersigned confirms that s/he agrees to conduct the study under the conditions described in this protocol.

Date, Signature: 25 April 2016, I. Bernard

Title	**RECORA- Re**gorafenib in patients with metastatic **co**lorectal cancer (mCRC) **a**fter failure of standard therapy
Protocol version identifier	3.0
Date of last version of protocol	06 April 2016
IMPACT study number	16665
Study type	☐ non-PASS ☒ PASS Joint PASS: ☐ YES ☒ NO
EU PAS register number	To be added after registration
Active substance (medicinal product)	Proteine Kinase Inhibitors (L01XE21), regorafenib
Marketing authorization holder(s)	Bayer Pharma AG, D-13342 Berlin, Germany
Function	Study Conduct Responsible
Name	Markus Langen
Title	Assistant Project Leader Leader Non-Interventional Studies
Address	Bayer HealthCare Germany, Bldg. K56, 51366 Leverkusen, Germany

The undersigned confirms that s/he agrees to conduct the study under the conditions described in this protocol.

Date, Signature: 2016-04-06, _____

Title	**RECORA- Re**gorafenib in patients with metastatic **co**lorectal cancer (mCRC) **a**fter failure of standard therapy
Protocol version identifier	3.0
Date of last version of protocol	06 April 2016
IMPACT study number	16665
Study type	☐ non-PASS ☒ PASS Joint PASS: ☐ YES ☒ NO
EU PAS register number	To be added after registration
Active substance (medicinal product)	Proteine Kinase Inhibitors (L01XE21), regorafenib
Marketing authorization holder(s)	Bayer Pharma AG, D-13342 Berlin, Germany
Function	Study Statistician
Name	Sabine Fiala-Buskies
Title	Global Integrated Analysis Statistician
Address	Bayer Pharma AG, Aprather Weg 18a, 42096 Wuppertal, Germany

The undersigned confirms that s/he agrees to conduct the study under the conditions described in this protocol.

Date, Signature: 12 April 2016, S. Fiala-Buskies

	colorectal cancer (mCRC) **a**fter failure of standard therapy
Protocol version identifier	3.0
Date of last version of protocol	06 April 2016
IMPACT study number	16665
Study type	☐ non-PASS ☒ PASS Joint PASS: ☐ YES ☒ NO
EU PAS register number	To be added after registration
Active substance (medicinal product)	Proteine Kinase Inhibitors (L01XE21), regorafenib
Marketing authorization holder(s)	Bayer Pharma AG, D-13342 Berlin, Germany
Function	Study Data Manager
Name	Dalila Lakbir
Title	Global Data Manager Non-Interventional Studies
Address	Bayer HealthCare, Bldg. K56, 51368 Leverkusen, Germany

The undersigned confirms that s/he agrees to conduct the study under the conditions described in this protocol.

Date, Signature: 19.4.16, D. Lakbir

Title	**RECORA- Re**gorafenib in patients with metastatic **co**lorectal cancer (mCRC) **a**fter failure of standard therapy
Protocol version identifier	3.0
Date of last version of protocol	06 April 2016
IMPACT study number	16665
Study type	☐ non-PASS ☒ PASS Joint PASS: ☐ YES ☒ NO
EU PAS register number	To be added after registration
Active substance (medicinal product)	Proteine Kinase Inhibitors (L01XE21), regorafenib
Marketing authorization holder(s)	Bayer Pharma AG, D-13342 Berlin, Germany
Function	Study Epidemiologist
Name	Jihong Zong
Title	Director Epidemiology MD
Address	Bayer HealthCare Pharmaceuticals, Hanover (Whippany, Cedar Knolls), NJ

The undersigned confirms that s/he agrees to conduct the study under the conditions described in this protocol.

Date, Signature: April 9, 2016 _____

Title	**RECORA- Re**gorafenib in patients with metastatic **co**lorectal cancer (mCRC) **a**fter failure of standard therapy
Protocol version identifier	3.0
Date of last version of protocol	06 April 2016
IMPACT study number	16665
Study type	☐ non-PASS ☒ PASS Joint PASS: ☐ YES ☒ NO
EU PAS register number	To be added after registration
Active substance (medicinal product)	Proteine Kinase Inhibitors (L01XE21), regorafenib
Marketing authorization holder(s)	Bayer Pharma AG, D-13342 Berlin, Germany
Function	Study Health Economics and Outcomes Research (HEOR) responsible person
Name	Brian Cuffel
Title	Head Global Health Economics and Outcomes Research (HEOR)
Address	Bayer HealthCare Pharmaceuticals Inc., 340 Changebridge Road, Pinebrook, NJ 07058-9714, United States

The undersigned confirms that s/he agrees to conduct the study under the conditions described in this protocol.

Date, Signature: 4/13/2016 , Brian Cuffel

Title	**RECORA- Re**gorafenib in patients with metastatic **co**lorectal cancer (mCRC) **a**fter failure of standard therapy
Protocol version identifier	3.0
Date of last version of protocol	06 April 2016
IMPACT study number	16665
Study type	☐ non-PASS ☒ PASS Joint PASS: ☐ YES ☒ NO
EU PAS register number	To be added after registration
Active substance (medicinal product)	Proteine Kinase Inhibitors (L01XE21), regorafenib
Marketing authorization holder(s)	Bayer Pharma AG, D-13342 Berlin, Germany
Function	Study Safety Lead
Name	Ashok Kumar Reddy Miriyala
Title	Global Safety Leader Regorafenib
Address	Bayer Pharma AG, Muellerstrasse 178, 13352 Berlin, Germany

The undersigned confirms that s/he agrees to conduct the study under the conditions described in this protocol.

Date, Signature: 25-APR-2016, M. Ashok Kumar Reddy

Title	**RECORA- Regorafenib in patients with metastatic colorectal cancer (mCRC) after failure of standard therapy**
Protocol version identifier	3.0
Date of last version of protocol	06 April 2016
IMPACT study number	16665
Study type	☐ non-PASS ☒ PASS Joint PASS: ☐ YES ☒ NO
EU PAS register number	To be added after registration
Active substance (medicinal product)	Proteine Kinase Inhibitors (L01XE21), regorafenib
Marketing authorization holder(s)	Bayer Pharma AG, D-13342 Berlin, Germany
Function	Head of Initiating Function
Name	Svetlana Kobina
Title	Head Global Medical Affairs TA Oncology
Address	Bayer HealthCare Pharmaceuticals Inc., 340 Changebridge Road, Pinebrook, NJ 07058-9714, United States

The undersigned confirms that s/he agrees to conduct the study under the conditions described in this protocol.

Date, Signature: April 25, 2016,