EU RISK MANAGEMENT PLAN (RMP)

STIVARGA®

BAY73-4506
(Regorafenib)

No. 7.3

Date of Report:
31 OCT 2025

EU Risk Management Plan for Stivarga (Regorafenib)

RMP Version to be assessed as part of this application:

RMP Version number: 7.3

Data lock point for this RMP: 30 SEP 2025

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Rationale for submitting an updated RMP:

The RMP has been updated to reflect the results of the paediatric clinical trials related to the paediatric investigation plan. The revised RMP documents paediatric exposure, study results and evaluates potential off-label use and risks. Inclusion of these data ensures transparency on the paediatric benefit–risk profile.

Summary of significant changes in this RMP:

- Part I: No changes.
- Part II-Module SI: No changes.
- Part II–Module SII: No changes.
- Part II–Module SIII: Clarification that clinical trial pools in the RMP do not include paediatric population.
- Part II–Module SIV: The RMP has been updated to reflect paediatric clinical trials.
- Part II–Module SV: Update of issues identified in paediatric investigation plan and off-label use in children
- Part II–Module SVI: No changes.
- Part II–Module SVII: No changes.
- Part II–Module SVIII: No changes.
- Part III: No changes.
- Part IV: No changes.
- Part V: No changes.
- Part VI: No changes.
- Part VII: No changes.

Other RMP versions under evaluation: None

Details of the currently approved RMP:

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QPPV signature:

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Table of content

Index of Tables

List of abbreviations

%	Percent
µmol/L	Micromoles per Litre
ACS	American Cancer Society
ADR	Adverse Drug Reaction
AE	Adverse Event
AFP	Alpha-Fetoprotein
ALT	Alanine Transaminase
AST	Aspartate Transaminase
AUC	Area Under the Curve
BCRP	Breast Cancer Resistance Protein
BRAF	V-Raf Murine Sarcoma Viral Oncogene Homolog B1
BSC	Best Supportive Care
CI	Confidence Interval
CMSAF	Controlled Monotherapy Safety Set
CONSIGN	Open-Label Phase IIIb Study of Regorafenib in Patients with Metastatic Colorectal Cancer Who Have Progressed After Standard Therapy
COPD	Chronic Obstructive Pulmonary Disease
CORRECT	Colorectal Cancer Treated with Regorafenib or Placebo After Failure of Standard Therapy
CR	Complete Response
CRC	Colorectal Cancer
CTCAE	Common Terminology Criteria for Adverse Events
CTD	Common Technical Document
CYP	Cytochrome

CYP2B6	Cytochrome P450 Family 2 Subfamily B Member 6
CYP2C19	Cytochrome P450 Family 2 Subfamily C Member 19
CYP2C8	Cytochrome P450 Family 2 Subfamily C Member 8
CYP2C9	Cytochrome P450 Family 2 Subfamily C Member 9
CYP3A4	Cytochrome P450 Family 3 Subfamily A Member 4
DILI	Drug-Induced Liver Injury
DLT	Dose-Limiting Toxicity
dMMR	Deficient Mismatch Repair
DNA	Deoxyribonucleic Acid
EAIR	Exposure-Adjusted Incidence Rate
ECG	Electrocardiogram
EFS	Event Free Survival
EGFR	Epidermal Growth Factor Receptor
eGFR	Estimated Glomerular Filtration Rate
EMA	European Medicines Agency
EMEA	European Medicines Evaluation Agency
EPAR	European Public Assessment Report
EU	European Union
FaR-RMS	Frontline and Relapsed Rhabdomyosarcoma (over-arching study for children and adults with newly diagnosed and relapsed rhabdomyosarcoma)
g/dL	Gram Per Decilitre
GFR	Glomerular Filtration Rate
GI	Gastrointestinal
GIST	Gastrointestinal Stromal Tumour

GLOBOCAN	Global Cancer Observatory
GPV	Global Pharmacovigilance
GRID	GIST Regorafenib In Progressive Disease
GVP	Guideline On Good Pharmacovigilance Practices
HBV	Hepatitis B Virus
HCC	Hepatocellular Carcinoma
HCV	Hepatitis C Virus
hERG K+	Human Ether-a-Go-Go Related Gene Potassium
HFSR	Hand-Foot Skin Reaction
HIV	Human Immunodeficiency Virus
HR	Hazard Ratio
HUS	Haemolytic Uremic Syndrome
i.e.,	*Id Est* (that is)
IARC	International Agency for Research on Cancer
IGFBP2	Insulin Like Growth Factor Binding Protein 2
IL	Interleukin
ILD	Interstitial Lung Disease
IR	Incidence Rate
KIT	Tyrosine-Protein Kinase Kit
KRAS	Kirsten Rat Sarcoma Gene
LVEF	Left Ventricular Ejection Fraction
M CSF	Macrophage Colony Stimulating Factor
MAA	Marketing Authorisation Application
MAD	Maximum Administered Dose

MAHA	Microangiopathic Haemolytic Anaemia
mCRC	Metastatic Colorectal Cancer
MDRD	Modification of Diet in Renal Disease
MedDRA	Medical Dictionary for Regulatory Activities
mg/m^2	Milligrams Per Body Surface Area
ml/min/1.73 m^2	Millilitres of Cleansed Blood Per Minute Per Body Surface
MLG	MedDRA Labelling Grouping
MSAF	Monotherapy Safety Set
MSI-H	Microsatellite Instability-High
MSS	Microsatellite Stable
MSSO	Maintenance and Support Services Organization
MTD	Maximum Tolerated Dose
n/N	Number
NAFLD	Non-Alcoholic Fatty Liver Disease
NASH	Non-Alcoholic Steatohepatitis
NCI	National Cancer Institute
OS	Overall Survival
PASS	Post-Authorisation Safety Study
PBMQ	Product-Specific Bayer MedDRA Query
PBRER	Periodic Benefit-Risk Evaluation Reports
PDGF	Platelet-Derived Growth Factor
PDGFR	Platelet-Derived Growth Factor Receptor
PDGFRA	Platelet-Derived Growth Factor Receptor A
PFS	Progression-Free Survival

P-gp	Permeability Glycoprotein
PIP	Paediatric Investigational Plan
PK	Pharmacokinetics
pMMR	Proficient Mismatch Repair
PPES	Palmar-Plantar Erythrodysaesthesia Syndrome
PR	Partial Response
PR interval	The Time from the Onset of the P Wave to the Start of the QRS Complex
PRES	Posterior Reversible Encephalopathy Syndrome
PSUR	Periodic Safety Update Reports
PT	Preferred Term
PV	Pharmacovigilance
QPPV	Qualified Person Responsible for Pharmacovigilance
QRS complex	Electrocardiographic Complex Consisting of the Q, R, And S Waves
RESORCE	Regorafenib in Patients with Hepatocellular Carcinoma (HCC) After Sorafenib
RMP	Risk Management Plan
RNA	Ribonucleic Acid
RP2D	Recommended Phase II Dose
RTK	Receptor Tyrosine Kinase
SAE	Serious Adverse Event
SAF	Safety Analysis Set
SCF	Stem Cell Factor
SCR	Serum Creatinine
SEER	Surveillance, Epidemiology and End Results

SJS	Steven-Johnson Syndrome
SmPC	Summary of Product Characteristics
SMQ	Standardised MedDRA Query
SRI	Severe Renal Impairment
SSAF	Sorafenib Treated Safety Analysis
STEC	Shiga Toxin-Producing *Escherichia Coli*
TEN	Toxic Epidermal Necrolysis
TKI	Tyrosine Kinase Inhibitor
TMA	Thrombotic Microangiopathy
TTP	Thrombotic Thrombocytopenic Purpura
UGT1A1	Uridine 5'-Diphospho-Glucuronosyltransferase Family 1 Member A1
UGT1A9	Uridine 5'-Diphospho-Glucuronosyltransferase Family 1 Member A9
uHCC	Unresectable Hepatocellular Carcinoma
UK	United Kingdom
ULN	Upper Limit of Normal
US	United States
USCS	US Cancer Statistics
VEGF	Vascular Endothelial Growth Factor
VEGFR	Vascular Endothelial Growth Factor Receptor
VIRR	Vincristine, Irinotecan and Regorafenib (experimental combination treatment in Study 17529)
VIRT	Vincristine, Irinotecan and Temozolomide (standard chemotherapy)
vs.	Versus
VWF	Von Willebrand Factor
µM	Micrometres

Part I: Product(s) overview

Table Part I-1: Product(s) overview

Active substance(s) (INN or common name)	Regorafenib
Pharmacotherapeutic group(s) (ATC Code)	L01EX05
Marketing Authorisation Holder	Bayer
Medicinal products to which this RMP refers	1
Invented name(s) in the European Economic Area (EEA)	Stivarga®
Marketing authorisation procedure	Centralised
Brief description of the product	Chemical class: The active ingredient of Stivarga is regorafenib. Regorafenib (BAY73-4506) is an oral multi-kinase inhibitor which targets angiogenic, stromal and oncogenic receptor tyrosine kinase (RTK). Regorafenib shows anti-angiogenic activity due to its dual targeted VEGFR2-TIE2 tyrosine kinase inhibition. Summary of mode of action: Regorafenib inhibits tumour growth, progression and metastasis by inhibiting the proliferation of tumour cells, the formation of new tumour vasculature and stromal signalling in the microenvironment of the tumour. Protein kinases inhibited include kinases involved in tumour angiogenesis (vascular endothelial growth factor receptor [VEGFR]1, 2, -3, TIE2), oncogenesis (KIT, RET, RAF-1, BRAF), metastasis (VEGFR3, PDGFR, FGFR) and tumour immunity (CSF1R). Important information about its composition: Each film-coated tablet contains 40 mg of regorafenib.
Hyperlink to the Product Information	Summary of Product Characteristics (SmPC)
Indication(s) in the EEA	Current: Stivarga is indicated as monotherapy for the treatment of adult patients with • metastatic colorectal cancer (CRC) who have been previously treated with, or are not considered candidates for, available therapies. These include fluoropyrimidine-based chemotherapy, an anti-VEGF therapy and an anti-EGFR therapy. • unresectable or metastatic gastrointestinal stromal tumours (GIST) who progressed on or are intolerant to prior treatment with imatinib and sunitinib.

Table Part I-1: Product(s) overview

	• hepatocellular carcinoma (HCC) who have been previously treated with sorafenib. Proposed: Not applicable
Dosage in the EEA	Current: Stivarga is available as 40 mg film-coated tablets for oral use. The recommended daily dose is 160 mg regorafenib (Four tablets Stivarga each containing 40 mg regorafenib), taken orally once daily for 3-weeks on therapy followed by 1-week off therapy to comprise a cycle of 4-weeks. Proposed: Not applicable
Pharmaceutical form(s) and strengths	Current: Film-coated tablet-40 mg Proposed: Not applicable
Is/will the product be subject to additional monitoring in the EU?	No

Part II: Safety specification

Part II: Module SI - Epidemiology of the indication(s) and target population(s)

SI.1 Indications

Stivarga is indicated as monotherapy for the treatment of adult patients with

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

SI.1.1 Metastatic Colorectal Cancer

Colorectal cancer (CRC) is the second most common cause of death from cancer worldwide. The 5-year prevalence of CRC worldwide for 2020 is estimated to be 101 per 100,000 persons. Metastatic CRC is associated with significant morbidity impacting the individual patient's life and is a serious, life-threatening condition. The 5-year relative survival for metastasised CRC is 14.7%.

Incidence:

The following data on CRC is based on an article that provides an update on the global cancer burden using the Global Cancer Observatory (GLOBOCAN) 2020 estimates of cancer incidence produced by the International Agency for Research on Cancer (IARC) (1):

More than 1.9 million new CRC (including anus) cases were estimated to occur in 2020, representing about one in 10 cancer cases. The CRC is the third most common cancer in men (10.6% of the total number of cancer cases) and the second in women (9.4% of the total number of cancer cases) worldwide.

There is an approximately 9-fold variation in colon cancer incidence rates (IRs) by world regions, with the highest age-standardised IR reported in Southern Europe (25.3 and 16.4 per 100,000 person-years in men and women respectively) and Northern Europe (23.2 and 18.8 per 100,000 person-years in men and women respectively). For rectal cancer, the highest age-standardised IR is reported in Eastern Europe (16.9 and 8.9 per 100,000 person-years in men and women respectively) and Northern Europe (15.1 and 8.4 per 100,000 person-years in men and women respectively).

Prevalence:

Based on 2020 GLOBOCAN CANCER TODAY estimates, the worldwide, 5-year prevalence of CRC (including anus) in 2020, for both sexes (ages ⩾20 years) is 101 per 100,000 (5,248,796 individuals) (2).

Epidemiological data from the United States (US) Surveillance, Epidemiology, and End Results (SEER) programme estimates that in 2021 there will be 149,500 new cases of CRC, representing 7.9% of all new cancer cases (3). In 2018, in Europe 500,000 new cases of CRC were diagnosed, representing 13.2% and 12.3% of all cancer cases in men and women (4).

Demographics of the population in the authorised indication and risk factors for the disease:

Data from SEER cancer statistics show that from 2014-2018, the median age at diagnosis for cancer of the colon was 67 years of age (3). Approximately 1.9% of cases were diagnosed between 20-34 years; 4.6% between 35-44 years; 15.1% between 45-54 years; 22.4% between 55-64 years; 24.8% between 65-74 years; 19.6% between 75-84 years; and 11.2% >84 years of age. The age-adjusted IR of new cases in the US (based on 2014-2018 cases) of CRC in men was 43.2 per 100,000 and 33.3 per 100,000 for women. Across different race/ethnicity (white, black, Asian/Pacific Islander, American Indian/Alaska Native, or Hispanic) CRC is more common in men compared to women.

Several risk factors are associated with the incidence of CRC (5). Age is a strong risk factor, where the likelihood of CRC diagnosis increases after the age of 40 years, rising sharply after the age of 50 years. In addition, a substantial number of environmental and lifestyle risk factors that include diet (e.g., red meat, processed meat, alcohol), obesity, smoking, and lack of physical activity may play an important role in the development of CRC. Inflammatory bowel disease, developing adenomas, or a family history of CRC or adenomatous polyps increase the risk of developing CRC. Approximately 5 to 10% of CRCs are a consequence of recognised hereditary conditions, the most common are familial adenomatous polyposis and hereditary non-polyposis CRC.

The main existing treatment options:

Chemotherapy agents for mCRC include capecitabine, irinotecan, oxaliplatin, and fluorouracil (5-FU) and can be combined with anti-angiogenic biologic agents (bevacizumab, [ziv] aflibercept, and ramucirumab) and epidermal growth factor receptor (EGFR) inhibitors (cetuximab and panitumumab) (6). In case of RAS-wt tumours anti-angiogenic biologic agents (bevacizumab, ziv-aflibercept, ramucirumab), EGFR inhibitors (cetuximab and panitumumab) in combination with chemotherapy are to be considered in patients with mCRC, since they improve significantly the outcome of mCRC (6). The recently approved immune checkpoint inhibitor (nivolumab or nivolumab combined with ipilimumab in the US; pembrolizumab) is indicated in mCRC patients with mismatch repair deficient (dMMR)/microsatellite instability-high (MSI-H), and encorafenib in combination with cetuximab is approved for mCRC patients with v-raf murine sarcoma viral oncogene homolog B1 (BRAF) mutation V600E who have already undergone at least one prior treatment regimen.

After failure of standard therapies, regorafenib and TAS-102 (trifluridin/tipiracil, Lonsurf) have shown to improve overall survival (OS) and progression-free survival (PFS) in a heavily pre-treated mCRC population. Since 2016, guidance of the European Society of Medical Oncology has formally recommended the use of regorafenib as third-line therapy for mCRC. In the National Comprehensive Cancer Network guidelines regorafenib is recommended for

use as third-line therapy in patients with a Kirsten rat sarcoma gene (KRAS) mutant tumour, and as third- or fourth-line therapy in patients with a KRAS wild type tumour.

Natural history of the indicated condition in the untreated population, including mortality and morbidity:

Based on GLOBOCAN 2020 estimates of cancer mortality, approximately 935,000 deaths from CRC were estimated to occur worldwide in the year 2020, accounting for 9.4% of all cancer deaths, making it the second most common cause of death from cancer (1).
The worldwide age-standardised mortality rate is lower in women compared to men for both colon (6.4 *vs.* 4.6 per 100,000 person-years) and rectal cancer (4.4 *vs.* 2.4 per 100,000 persons-years). In 2018, CRC led to 242,000 deaths in Europe, i.e., 12.0% and 13.2% of all cancer deaths in men and women, respectively (4).

Based on 2011-2017 data from SEER Cancer Statistics Review (3), 22% of patients present distant (metastasised) CRC at diagnosis. The 5-year relative survival of CRC is strongly related to the cancer stage at diagnosis (see Table Part II SI-1). The 5-year relative survival for metastasised CRC is 14.7%.

Table Part II SI-1: Stage distribution and 5-year relative survival by stage at diagnosis for 2011-2017, all races, both sexes

Stage at Diagnosis	Stage Distribution (%)	5-year Relative Survival (%)
Localised confined to primary site)	37	90.6
Regional (spread to regional lymph nodes)	36	72.2
Distant (cancer has metastasised)	22	14.7
Unknown (unstaged)	5	39.0

SEER 18 2011-2017, All Races, Both Sexes by SEER Summary Stage 2000

Important comorbidities

Comorbidities including hypertension, heart conditions, gastrointestinal (GI) conditions, arthritis and chronic obstructive pulmonary disease (COPD) are the most prominent conditions affecting >10% of colon cancer patients in a random sample of 1,610 patients (age >55 years) from the National Cancer Institute SEER registry (7).

According to the Eindhoven Cancer Registry in Europe, the most common comorbidities in CRC patients were COPD (25%), diabetes (32%), previous cancers (17%), hypertension (15%), and heart and vascular disease (22%) (8).

According to a study that analysed all CRC cases (1,061) diagnosed in Spain during 2011, the most common comorbidities were diabetes (23.6%), COPD (17.2%), and congestive heart failure (14.5%) (9). Age ≥75 years, obesity, male sex, being a current smoker, having surgery more than 60-days after cancer diagnosis, and not receiving surgical treatment were associated with a higher prevalence of CRC morbidity.

SI.1.2 Metastatic/unresectable GIST

Gastrointestinal stromal tumour (GIST) accounts for less than 1% of all GI tumours. The global IR of GIST is 1.0 per 100,000; a similar IR is reported for Europe. The growth of most GISTs is driven by oncogenic mutations in either of two receptor tyrosine kinases (RTK): KIT (75% of cases) or platelet-derived growth factor receptor A (PDGFRA) (10%). The GISTs are generally resistant to conventional chemotherapy with responses typically less than 10% and associated with significant toxicities.

Incidence:

Gastrointestinal stromal tumour accounts for less than 1% of all GI tumours (10). According to the 2021 Orphanet report, the global IR of GIST is 1.0 per 100,000; a similar IR is reported for Europe (11).

According to estimates from the American Cancer Society (ACS), there are approximately 4,000 to 6,000 GIST cases diagnosed every year in the US (12). Based on data from 34,257 patients obtained from the US Cancer Statistics (USCS), the overall incidence of GISTs from 2001-2015 was estimated to be 0.70 per 100,000 people per year (13).

Prevalence:

According to the 2021 Orphanet report, the prevalence of GIST in Europe was 13.0 per 100,000 (11). A study from Sweden of 288 patients with primary GIST diagnosed between 1983 and 2000 and using the risk-group stratification according to Fletcher *et al.* (14), the prevalence of all GIST risk groups was estimated to be 129 per million. For the various risk groups, prevalence was estimated as follows: 22.2 per million for very low risk, 51.9 per million for low risk, 24.2 for intermediate risk, 22.2 per million for high-risk group, 8.7 per million for the overtly malignant (a group that included all patients who had tumours with proven metastases at initial diagnosis) group (15).

Demographics of the population in the authorised indication and risk factors for the disease:

According to an analysis of 7,204 patients queried from the SEER database for GIST from 2002 to 2015, the age-adjusted IR (per 100,000) of GIST was reported as follows: 0.17 for patients younger than 45 years (11.1%); 0.77 or patients between 45-54 years (18.2%); 1.42 for patients between 55-64 years (25.4%); 2.24 patients between 65-74 years (24.0%); and 2.34 for patients 75 years and older (21.3%) (16). Gender-specific age-adjusted IR (per 100,000) was 0.85 and 0.67 for male (52.2%) and female (47.8%), respectively. There is no clear gender predominance. The age-adjusted IR among African-Americans (1.37 per 100,000) was more than double that of Whites (0.65 per 100,000) over the study period. The three most common GIST sites for the entire cohort were: stomach (58.4%), small intestine (27.6%), and oesophagus (0.50%).

There are very few known risk factors for GISTs including age(e.g., it occurs more common in people aged 50-80 years), having an inherited condition such as primary familial GIST syndrome, neurofibromatosis type-1, and Carney-Stratakis syndrome (17). The growth of

most GISTs is driven by oncogenic mutations in either of two receptor tyrosine kinases: KIT (75% of cases) or PDGFRA (10%) (18).

The main existing treatment options:

Surgery is usually the main treatment for GISTs that have not spread (17). Treatment options for unresectable GISTs (surgery or targeted therapy) depend on why they are unresectable and, if they have spread, how extensive the spread is. GISTs are generally resistant to conventional chemotherapy with responses typically less than 10% and associated with significant toxicities (19). The role of radiation therapy is generally considered limited.

Imatinib (Gleevec) is typically the preferred first treatment for most advanced GISTs (20), and is approved for the treatment of metastatic and/or unresectable advanced/metastatic GIST (21). Imatinib therapy is limited by primary resistance to the drug in approximately 15% of patients and over 80% of patients eventually exhibit disease progression driven by secondary resistance mutations located in additional KIT exons (22). Sunitinib (Sutent) is approved after progression on or intolerance to imatinib (23). Regorafenib has been approved for the treatment of patients with locally advanced, unresectable or metastatic GIST who have been previously treated with two tyrosine kinase inhibitors (TKIs). Avapritinib (Ayvakit) might be used for unresectable or metastatic GIST patients with PDGFRA exon 18-mutation (20). Further treatment option includes ripretinib for patients with advanced GIST that had progressed on three or more TKIs including imatinib.

Natural history of the indicated condition in the untreated population, including mortality and morbidity:

Metastatic GIST represents 15%-47% of diagnosed disease (24). The GISTs are most commonly present in the stomach (60%) and small intestine (25%), but they also arise in the colon, rectum, oesophagus, mesentery, and omentum (15% together) (18). Clinical symptoms associated with GISTs include fatigue, abdominal pain, dysphagia, satiety, and obstruction.

Risk of malignant progression in GISTs is often stratified into risk groups according to the consensus guidelines of the National Institute of Health, based on tumour size and mitotic rate (15). The reported survival times for GIST patients vary widely depending on stage of disease, the era reported and the landmark used for measuring survival (25).

In a retrospective study from the United Kingdom (UK), 185 patients with GIST were identified, of which 83% (153/185) underwent surgical resection and 17% (32/185) were not operated on due to reasons such as co-morbidity, metastatic disease or locally advanced disease (26). According to a consensus risk-group stratification system (low, intermediate, or high-risk) based on maximum GIST tumour size and mitotic count (14), 38/185 patients were assigned to the intermediate risk and 67/185 were assigned to the high-risk group (26). During a mean follow-up of 6.8 years, the GIST-specific mortality was 14.5% and the risk-category mortality was 5% and 37% in intermediate and high-risk groups, respectively.

In a study from Sweden of 288 patients with primary GIST diagnosed between 1983 and 2000, and using the risk-group stratification according to Fletcher *et al*. (14), 63% of patients in the high-risk group and 83% of patients with overtly malignant tumours (a group that included all patients who had tumours with proven metastases at initial

diagnosis) died due to GIST (15). The estimated median OS was 3.4 and 1.4 years for the high and overtly malignant risk group, respectively.

An analysis of the SEER database that identified 6,142 patients diagnosed with histologically confirmed GIST between 2001 and 2011 estimated a 5-year overall and GIST-specific survival rates of 65% and 79%, respectively (27). The 5-year OS rates for those with localised, regional, and metastatic disease at diagnosis were 77%, 64%, and 41%, respectively. Multivariate analysis showed that older age at diagnosis, males, black ethnicity/race, and advanced stage at diagnosis, were associated with increased mortality from GIST (27).

Important comorbidities:

Systematic data on comorbidities in the target population are limited. The co-morbidity of GIST with other tumours is usually reported in case reports and case analysis from single institution with the rate of 3%-33% (28) or 2.25%-41% (29) with lack of large sample statistics. The most common comorbidities associated with GIST are GI cancer, followed by lymphoma, prostate cancer, breast cancer, kidney cancer, lung cancer, female genital cancer, soft tissue and bone sarcoma, malignant melanoma and seminoma (30). A cohort study based on SEER registries from 1988-2016, that identified patients with GISTs after another malignancy (n = 851), reported that the most commonly diagnosed first primary malignancy was prostate cancer (27.7%, n = 236), followed by breast cancer (16.2%, n = 138), carcinoma of large intestine (12.2%, n = 104), and malignant tumour of urinary system (8.7%, n = 74) (31).

SI.1.3 Hepatocellular carcinoma

Hepatocellular carcinoma (HCC) is currently the tumour with the sixth highest number of new cases and the third leading cause of death worldwide. The estimated IR of HCC in Europe is 3.2 per 100,000 persons.

Most patients are diagnosed at advanced stages, when curative treatments, including resection, liver transplantation, and ablation, are no longer feasible. Sorafenib, a multi-kinase inhibitor, is indicated to treat advanced, unresectable HCC. For patients who experience disease progression following sorafenib treatment regorafenib represents an effective therapy.

Incidence:

Primary liver cancer includes HCC (comprising 75%-85% of cases) and intrahepatic cholangiocarcinoma (10%-15%), as well as other rare types (1). According to the 2021 Orphanet report, the estimated IR of HCC in Europe is 3.2 per 100,000 (11). In the US, the overall incidence of HCC was 7.7 per 100,000 during 1992-2015, increasing from 4.1 per 100,000 in 1992 to 9.5 per 100,000 in 2015 (32). According to GLOBOCAN estimates, HCC is currently the tumour with the sixth highest number of new cases in 2020 and the third leading cause of death worldwide (33).

Prevalence

According to the 2021 Orphanet report, the estimated prevalence rate of HCC in Europe is 15.0 per 100,000 (11).

Demographics of the population in the authorised indication and risk factors for the disease:

The major risk factors for the development of HCC are cirrhosis and chronic liver disease, regardless of aetiology (34). Specific risk factors include viral infections caused by hepatitis B (HBV) and/or hepatitis C (HCV), chronic alcohol consumption, particular comorbidities or other conditions such as non-alcoholic fatty liver disease (NAFLD), non-alcoholic steatohepatitis (NASH), genetic haemochromatosis, co-infection with HBV/HCV, and human immunodeficiency virus (HIV). HCC occurs more often in males than in females, with an overall male-to-female ratio of 3.6 (35).

A retrospective analysis of patients at liver transplantation centres in the US found that nearly 50% and about 15% of patients were infected with HBV or HCV, respectively, with approximately 5% of patients having markers of both infections (36). Data from large population-based studies have also identified high serum Deoxyribonucleic Acid (DNA) HBV and RNA HCV viral load as independent risk factors for developing HCC in patients with chronic infection (37-39).

The HCC differ according to the geographical distribution (40). In Africa and Southern Asia, the role of aflatoxin B1 and HBV infection-which is acquired at birth or early in life-is highly predominant. In these patients, HCC develops often at a young age and in the absence of cirrhosis. By contrast, in Japan, Egypt and in Southern Europe, HCV is the main cause of HCC which occurs in older patients, nearly all of them with advanced fibrosis or cirrhosis. In Northern and Central European countries, HCV infection and alcohol are the main causes of cirrhosis.

The incidence of HCC is increasing in the US, particular in the population infected by HCV. The annual IR among patients with HCV-related cirrhosis has been estimated to be between 2% and 8% (41). A meta-analysis including 68 studies with 27,854 patients with untreated HBV showed an annual HCC incidence 0.88 per 100 person-years, with an incidence of 3.16 per 100 person-years for patients with cirrhosis (42).

The main existing treatment options:

Most patients are diagnosed at advanced stages, when curative treatments, including resection, liver transplantation, and ablation, are no longer feasible (34).
Sorafenib significantly improved OS in these patients. For patients who experience disease progression following sorafenib treatment, regorafenib represents an effective therapy.

Other drugs that are available include: lenvatinib, combination of atezolizumab plus bevacizumab in the first-line treatment for unresectable HCC (43); ramucirumab in patients with high (≥400 ng/mL) alpha-fetoprotein (AFP) levels, carbozantinib, immune check inhibitors (pembrolizumab, nivolumab and combination of nivolumab/ipilimumab approved in the US) as second-line treatment (44-48).

Natural history of the indicated condition in the untreated population, including mortality and morbidity:

The HCC usually occurs in the setting of liver cirrhosis, because of chronic infections with HBV or HCV viruses, alcohol consumption, NASH, or diabetes (49).

A meta-analysis of survival rates of untreated patients in randomised clinical trials of HCC, reported that the 1-year and 2-year survival rate of untreated patients from 30 randomised controlled trials was 17.5% and 7.3%, respectively (50).

Data on age-adjusted mortality in 8,561 HCC patients in Austria suggest a median OS of 4.5 months for men and 3.2 months for women with 1-year/5-year survival rates of 33/11% and 28/10%, respectively (51, 52).

Important comorbidities

Characteristics of patients diagnosed with HCC were reported from a large health care claims database in the US for the time period 2002-2008 (53). Data at baseline (at HCC diagnosis) showed that three most frequent comorbidities in a cohort of 4,406 patients with HCC were mild diabetes (33.1%), various mild chronic liver diseases (29.3%), and COPD (20.8%). A matched cohort (44,060 controls matched for age, sex, region, and health plan type) showed frequencies of 19.2%, 0.5%, and 18.2% for the same specific concomitant conditions.

Part II: Module SII - Non-clinical part of the safety specification

A comprehensive toxicological program was performed to support clinical trials and marketing authorisation with orally administered regorafenib in patients with advanced cancer. Relevant non-clinical findings are summarised in the following sections below Table Part II SII-1.

Table Part II SII-1: Key safety findings from non-clinical studies and relevance to human usage

Key Safety findings (from non-clinical studies)	Relevance to human usage
Repeat-dose toxicity	
After repeated dosing to mice, rats and dogs, adverse effects were observed in a number of organs, primarily in the kidneys, liver, digestive tract, heart, lympho/haematopoietic system, endocrine system, thymus, reproductive system and skin. These effects occurred at systemic exposures in the range of or below the anticipated human exposure (based on area under the curve [AUC] comparison). Full or partial recovery within 4-weeks after end of treatment was demonstrated for most of the morphological changes. Alterations of teeth and bones were observed in young and growing rats and dogs.	The majority of findings observed in the non-clinical toxicology studies have potential relevance for patients with advanced cancer, which was confirmed already in clinical trials. Findings on teeth and bone in young and growing animals indicate a potential risk for children and adolescents.
Reproductive Toxicity	
Potential to impair fertility and to be embryo-foetotoxic. Specific studies on fertility have not been performed. However, a potential of regorafenib to adversely affect male and female reproduction has to be considered based on morphological changes in the testes, ovaries, and the uterus observed after repeated dosing in rats and dogs at exposures below the anticipated clinical exposure (based on AUC comparison). The observed changes were only partially reversible during a 4-week recovery period. A potential for effects of regorafenib on intrauterine development is expected based on the pharmacological mode of action (in particular, influence on neovascularization) and was confirmed in rabbits at exposures below the anticipated clinical exposure (based on AUC comparison). Main findings consisted	The Stivarga Summary of Product Characteristics (SmPC) (Section 4.6 “Pregnancy and Lactation”) states: Women of childbearing potential must be informed that regorafenib may cause foetal harm. Women of childbearing potential and men should ensure effective contraception during treatment and up to 8-weeks after completion of therapy. There are no data on the use of regorafenib in pregnant women. Based on its mechanism of action regorafenib is suspected to cause foetal harm when administered during pregnancy. Animal studies have shown reproductive toxicity (see Section "Preclinical safety data”). Stivarga should not be used during pregnancy unless clearly necessary and after careful consideration of the benefits for the mother and the risk to the foetus. It is unknown whether regorafenib/or its metabolites are excreted in human milk. In rats, regorafenib/or its metabolites

Table Part II SII-1: Key safety findings from non-clinical studies and relevance to human usage

Key Safety findings (from non-clinical studies)	Relevance to human usage
of malformations of the urinary system, the heart and major vessels, and the skeleton.	are excreted in milk. A risk to the breast-fed child cannot be excluded. Regorafenib could harm infant growth and development (see Section "Preclinical safety data"). Breast-feeding must be discontinued during treatment with Stivarga. There are no data on the effect of Stivarga on human fertility. Results from animal studies indicate that regorafenib can impair male and female fertility (see Section "Preclinical safety data").
Nephrotoxicity	
In the repeated dose toxicity studies in mice, rats and dogs the kidney was clearly identified as a target organ. An increase in absolute and relative kidney weight was observed. Clinical chemistry parameters measured in urine, like N-acetyl-D-glucosamine or Gamma-glutamyltransferase was slightly increased in individual animals. In some cases, an influence on excretion (decreased urinary volume, proteinuria) was noted. Microscopically glomerulopathy, tubular degeneration and dilation were observed, which were not fully reversible during a 4-week recovery period.	Findings regarding kidney toxicity observed in the non-clinical toxicology studies have potential relevance for patients with advanced cancer, which was confirmed already in clinical trials: "Proteinuria" has been included as adverse drug reactions (ADR) (frequency category: common) in proposed SmPC.
Hepatotoxicity	
In the repeated dose toxicity studies in mice, rats and dogs the liver was identified as target organ, most obviously by the increase in liver transaminases (primarily aspartate transaminase and alanine transaminase) in serum. In addition, the liver weight was slightly decreased. Clinical chemistry findings were usually slight but considered as indicative for a treatment-related effect on liver function. They were not accompanied by severe morphological findings.	Findings regarding liver toxicity observed in the non-clinical toxicology studies have potential relevance for patients with advanced cancer, which was confirmed already in clinical trials: "Increase in transaminases" (frequency category: common) and "Severe liver injury" (frequency category: uncommon) have been included as ADRs in proposed SmPC.
Genotoxicity	
There was no indication for a genotoxic potential of regorafenib tested in standard assays *in vitro* and *in vivo*. One major human active metabolite, M-2 (N-oxide), was positive in the chromosomal aberration assay.	Not relevant for patient population with advanced cancer.

Table Part II SII-1: Key safety findings from non-clinical studies and relevance to human usage

Key Safety findings (from non-clinical studies)	Relevance to human usage
An impurity and degradation product present in drug substance (< 0.1%) was tested positive in an *in vitro* bacterial cell assay.	
Carcinogenicity	
Studies on the carcinogenic potential of regorafenib have not been performed.	Not relevant for patient population with advanced cancer.
Studies in juvenile animals	
The daily oral administration of regorafenib to rats from post-natal Day-15 to Day-35 revealed severely impaired general condition and mortality at higher doses. The most prominent findings were reduced nutritional state, growth retardation together with delayed growth and atrophy of multiple organs such as the lymphatic system, the haematopoietic system, the gastrointestinal tract and the sexual organs. Haematological and clinical chemical parameters were only mildly affected, indicating only slight functional impairments of the organs. In addition, bones and teeth showed moderate to severe signs of growth disturbance due to the anti-angiogenic effect of the compound.	Alterations of teeth and bones observed in young, growing rats indicate a potential risk for children and adolescents.
General Safety Pharmacology	
Following single oral and intravenous administration in rats and dogs, regorafenib as well as its two major human plasma metabolites BAY75-7495 (M2) and BAY81-8752 (M5), were devoid of substantial adverse effects on cardiovascular, respiratory, and central nervous systemic function. At high concentrations, regorafenib (>12 µmol/L) as well as its metabolites M2 and M5 (<0.4 µmol/L) had the potential to delay cardiac repolarization *in vitro* by inhibition of the hERG K^+ current. Cardiovascular studies in dogs did not reveal effects on the electrocardiogram (ECG) at plasma concentrations similar or higher than those reached in humans with maximum oral doses of 220 mg (co-precipitate). Furthermore, a prolongation of the QT interval in the ECG is not expected at C_{max} levels in humans,	In line with non-clinical data no relevant changes in the mean QTc interval have been detected in a clinical study evaluating the effect of multiple doses of regorafenib (160 mg once daily for 21-days) on QTc interval.

Table Part II SII-1: Key safety findings from non-clinical studies and relevance to human usage

Key Safety findings (from non-clinical studies)	Relevance to human usage
because the threshold for inhibition of the hERG K^+ current, i.e. the IC_{20} concentrations, are ~250-fold (BAY73-4506), ~25-fold (BAY75-7495, M2), and ~88-fold (BAY81-8752, M5) higher than the respective $C_{max,u}$ levels.	
Mechanisms for drug interactions	
In vitro data indicate that regorafenib is metabolized by CYP3A4 and UGT1A9. *In vivo* data suggest that CYP3A4 inhibitors when co-administered with regorafenib had only a weak effect on the single dose pharmacokinetics (PK) of regorafenib. However, due to the nonlinear PK of the metabolites M-2 and M-5, the effects of CYP3A4 inhibition on steady-state PK are not known. *In vivo* data suggest that strong inducers of CYP3A4 activity (e.g., phenytoin, carbamazepine, and phenobarbital), when co-administered with regorafenib, may increase metabolism of regorafenib. Regorafenib exhibited no inductive potential on major CYP isoforms. *In vitro* studies with human liver microsomes demonstrated that regorafenib potently inhibited CYP2C8 (K_i = 0.6 µM) and also considerably affected CYP2C9 (K_i = 4.7 µM) and CYP2B6 (K_i = 5.2 µM). The inhibitory potency towards CYP3A4 (K_i = 11.1 µM) and CYP2C19 (Ki = 16.4 µM) was less pronounced. *In vivo* data suggest that regorafenib does not have an inhibitory effect on CYP2C8, CYP2C19 and CYP3A4, and that regorafenib may have a weak inhibitory effect on CYP2C9 mediated metabolism which is not considered clinically meaningful. Regorafenib as well as its active metabolites M-2 and M-5 inhibit glucuronidation mediated by UGT1A1 and UGT1A9 *in vitro. In vivo* data indicate that co-administration of regorafenib may increase systemic exposure to UGT1A1 and UGT1A9 substrates. Regorafenib and its metabolites M-2 and M-5 revealed no inhibitory potency on dihydropyrimidine dehydrogenase. Administration of regorafenib (160 mg for 14-days) prior to administration of a single	This data on potential drug-drug interactions is of relevance in human use and accordingly reflected in Section 4.5 “Interaction with other medicinal products and other forms of interaction” of proposed SmPC. In addition, several human interaction studies have been performed. It is recommended to avoid concomitant use of strong inhibitors of CYP3A4 activity (e.g., clarithromycin, grapefruit juice, itraconazole, ketoconazole, posaconazole, telithromycin and voriconazole) as their influence on the steady-state exposure of regorafenib and its metabolites (M-2 and M-5) has not been studied. Since a reduction in plasma regorafenib concentrations may result in a decreased efficacy, strong 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. Pharmacokinetic data indicate that regorafenib may be given concomitantly with substrates of CYP2C8, CYP2C9, CYP3A4, and CYP2C19 without a clinically meaningful drug interaction (see also Section “Special warnings and precautions for use”). Administration of regorafenib with a 5-days 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 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 of these findings is unknown.

Table Part II SII-1: Key safety findings from non-clinical studies and relevance to human usage

Key Safety findings (from non-clinical studies)	Relevance to human usage
dose of rosuvastatin (5 mg), a BCRP substrate, resulted in a 3.8-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. 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. The concentration-time profile indicates that regorafenib and its metabolites may undergo enterohepatic circulation (see Section 5.2). Co-administration with neomycin, a poorly absorbed antimicrobial agent used for eradicating the GI microflora (which may interfere with the enterohepatic circulation of regorafenib) had no effect on the regorafenib exposure, but there was an approximately 80% decrease in the exposure of the active metabolites M-2 and M-5 which showed *in vitro* and *in vivo* comparable pharmacological activity as regorafenib. The clinical significance of this neomycin interaction is unknown but may result in a decreased efficacy of regorafenib. Pharmacokinetic interactions of other antibiotics have not been studied.	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. 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. The concentration-time profile indicates that regorafenib and its metabolites may undergo enterohepatic circulation (see Section 'Pharmacokinetic properties'). Co-administration with neomycin, a poorly absorbed antimicrobial agent used for eradicating the GI microflora (which may interfere with the enterohepatic circulation of regorafenib) had no effect on the regorafenib exposure. There was a significant 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 Stivarga.
Other toxicity-related information or data	
Not applicable	

ADR: Adverse Drug Reactions, AUC: Area Under The Curve, BCRP: Breast Cancer Resistance Protein, CYP3A4: Cytochrome P450 Family 3 Subfamily A Member 4, CYP2B6: Cytochrome P450 Family 2 Subfamily B Member 6, CYP2C9: Cytochrome P450 Family 2 Subfamily C Member 9, CYP2C8: Cytochrome P450 Family 2 Subfamily C Member 8, CYP2C19: Cytochrome P450 Family 2 Subfamily C Member 19, mm: Micrometre, UGT1A1: Uridine 5'-Diphospho-Glucuronosyltransferase Family 1 Member A1, UGT1A9: Uridine 5'-Diphospho-Glucuronosyltransferase Family 1 Member A9, SmPC: Summary of Product Characteristics

Part II: Module SIII - Clinical trial exposure

For the purpose of exposure and event rate analyses, two pools are presented throughout the document. Pooled studies included in this RMP do not include paediatric population.

The first pool (referred to as "Phase III controlled trials population") comprises safety data from the randomised, double-blind, placebo-controlled Phase III studies 14387 (Colorectal cancer treated with regorafenib or placebo after failure of standard therapy [CORRECT]), Study No. 14874 (GIST Regorafenib in Progressive Disease [GRID]; placebo-controlled treatment phase), Study No. 15808 (Asian subjects with metastatic colorectal cancer treated with regorafenib or placebo after failure of standard therapy [CONCUR]), and Study No. 15982 (Regorafenib in patients with hepatocellular carcinoma (HCC) after sorafenib [RESORCE]). This pooled analysis uses data from each included study as of respective trial database cut-off date.

Rationale: These trials used a randomised controlled design, allowing direct analytical comparisons between the regorafenib and placebo arm.

The second pool (referred to as 'Phase I-III pooled monotherapy safety set') comprises safety data from cancer patients in all Phase I to III company-sponsored completed (i.e., final or interim clean database available) studies using the intermittent or continuous dosing schedule also including the CORRECT, GRID, CONCUR, and RESORCE trials; placebo-controlled + open-label regorafenib treatment phases, as well as study 15967 (open-label Phase IIIb study of regorafenib in patients with metastatic colorectal cancer who have progressed after standard therapy [CONSIGN]).

Rationale: These trials were all conducted with single agent regorafenib. Patient populations were comparable, in that they all had metastatic and/or unresectable solid tumours. The starting dose of regorafenib was 160 mg in these trials, with the exception of the dose escalation studies 11650 and 11651, in which regorafenib doses from 10 mg to 220 mg and 20 mg to 140 mg were administered, respectively. This pooled analysis uses data from each included study as of respective trial database cut-off date.

Table Part II SIII-1: Clinical trial exposure by treatment duration-controlled Phase III trials population CRC-/GIST/HCC

Treatment	Stivarga		Placebo	
Duration of exposure	**Persons**	**Person time[a]**	**Persons**	**Person time[a]**
<1 month	154	6.8	93	4.4
1 - <3 months	422	61.8	371	53.2
3 - <6 months	272	97.0	75	25.4
6 - <9 months	128	78.6	26	16.0
9 - <12 months	82	69.3	7	5.9

Table Part II SIII-1: Clinical trial exposure by treatment duration-controlled Phase III trials population CRC-/GIST/HCC

Treatment	Stivarga		Placebo	
Duration of exposure	**Persons**	**Person time[a]**	**Persons**	**Person time[a]**
≥12 months	84	128.3	8	13.5
Total	**1,142**	441.8	**580**	**118.5**

[a] In years
Note: For calculation, a month equals 30 days and a year equals 360 days.
Note: Duration of ongoing subjects is calculated by using the study specific cut-off date as day of last treatment.
Source: Tables for Risk Management Plan Controlled monotherapy safety set (CMSAF)–Table 2/4
Global Integrated Analysis: /by-sasp/patdb/ia/734506/stat/2021/prod_0625_rmp/pgms/t_cmsaf_durat.sas
25 JUN 2021

Table Part II SIII-2: Clinical trial exposure by treatment duration-controlled Phase III trial population-CRC

Treatment	Stivarga		Placebo	
Duration of exposure	**Persons**	**Person time[a]**	**Persons**	**Person time[a]**
<1 month	107	4.8	64	3.2
1 - <3 months	273	38.7	221	30.9
3 - <6 months	157	55.3	25	8.3
6 - <9 months	52	31.8	7	4.3
9 - <12 months	27	22.1	4	3.2
≥12 months	20	28.1	0	0.0
Total	**636**	**181.0**	**321**	**49.9**

[a] In years
Note: For calculation, a month equals 30 days and a year equals 360 days.
Note: Duration of ongoing subjects is calculated by using the study specific cut-off date as day of last treatment.
Source: Tables for Risk Management Plan Controlled monotherapy safety set (CMSAF)–Table 2/1
Global Integrated Analysis: /by-sasp/patdb/ia/734506/stat/2021/prod_0625_rmp/pgms/t_cmsaf_durat.sas
25 JUN 2021

Table Part II SIII-3: Clinical trial exposure by treatment duration-controlled Phase III trial population-GIST

Treatment	Stivarga		Placebo	
Duration of exposure	**Persons**	**Person time[a]**	**Persons**	**Person time[a]**
< 1 month	10	0.5	9	0.4
1 - <3 months	32	4.7	42	6.0
3 - <6 months	27	9.7	11	3.6

Table Part II SIII-3: Clinical trial exposure by treatment duration-controlled Phase III trial population-GIST

Treatment	Stivarga		Placebo	
Duration of exposure	**Persons**	**Person time[a]**	**Persons**	**Person time[a]**
6 - <9 months	32	20.3	4	2.6
9 - <12 months	26	22.1	0	0.0
≥12 months	5	5.4	0	0.0
Total	**132**	**62.6**	**66**	**12.5**

[a] In years
Note: For calculation, a month equals 30 days and a year equals 360 days.
Note: Duration of ongoing subjects is calculated by using the study specific cut-off date as day of last treatment.
Source: Tables for Risk Management Plan Controlled monotherapy safety set (CMSAF)–Table 2/2
Global Integrated Analysis: /by-sasp/patdb/ia/734506/stat/2021/prod_0625_rmp/pgms/t_cmsaf_durat.sas 25 JUN 2021

Table Part II SIII-4: Clinical trial exposure by treatment duration-controlled Phase III trial population-HCC

Treatment	Stivarga		Placebo	
Duration of exposure	**Persons**	**Person time[a]**	**Persons**	**Person time[a]**
<1 month	37	1.4	20	0.9
1 - <3 months	117	18.4	108	16.4
3 - <6 months	88	32.0	39	13.6
6 - <9 months	44	26.6	15	9.1
9 - <12 months	29	25.0	3	2.7
≥12 months	59	94.8	8	13.5
Total	**374**	**198.2**	**193**	**56.1**

[a] In years
Note: For calculation, a month equals 30 days and a year equals 360 days.
Note: Duration of ongoing subjects is calculated by using the study specific cut-off date as day of last treatment.
Source: Tables for Risk Management Plan Controlled monotherapy safety set (CMSAF)–Table 2/3
Global Integrated Analysis: /by-sasp/patdb/ia/734506/stat/2021/prod_0625_rmp/pgms/t_cmsaf_durat.sas 25 JUN 2021

Table Part II SIII-5: Clinical trial exposure by treatment duration-Phase I-III pooled monotherapy safety set-all cancer types

Treatment	Stivarga	
Duration of exposure	**Persons**	**Person time[a]**
<1 month	795	33.1

Table Part II SIII-5: Clinical trial exposure by treatment duration-Phase I-III pooled monotherapy safety set-all cancer types

Treatment	Stivarga	
Duration of exposure	**Persons**	**Person time[a]**
1 - <3 months	1,824	291.1
3 - <6 months	1,079	381.1
6 - <9 months	387	234.2
9 - <12 months	195	166.9
≥12 months	374	748.3
Total	**4,654**	**1,855.4**

[a] In years
Note: For calculation, a month equals 30 days and a year equals 360 days.
Note: Duration of ongoing patients is calculated by using the study specific cut-off date as day of last treatment.
Source: Tables for Risk Management Plan Monotherapy safety set (MSAF)–Table 2/1
Global Integrated Analysis: /by-sasp/patdb/ia/734506/stat/2021/prod_0625_rmp/pgms/t_cmsaf_durat.sas
25 JUN 2021

Table Part II SIII-6: Clinical trial exposure by actual dose - controlled Phase III trials population-CRC/GIST/HCC

Treatment	Stivarga		Placebo	
Daily dose of exposure	**Persons**	**Person time[a]**	**Persons**	**Person time[a]**
<80 mg	9	0.2	1	0.0
80 mg	252	65.6	14	1.9
120 mg	528	102.8	28	2.3
160 mg	1,141	272.8	579	114.2
>160 mg	1	0.0	1	0.0
80-160 mg	1,142	441.3	580	118.3
Total	**1,142**	**441.5**	**580**	**118.4**

[a] In years
Note: For calculation, a month equals 30 days and a year equals 360 days.
Note: Duration of ongoing subjects is calculated by using the study specific cut-off date as day of last treatment.
Note: Dose refers to actual dose, hence a subject may contribute to more than one dose.
Source: Tables for Risk Management Plan Controlled monotherapy safety set (CMSAF)–Table 2/8
Global Integrated Analysis: /by-sasp/patdb/ia/734506/stat/2021/prod_0625_rmp/pgms/t_cmsaf_dose.sas
25 JUN 2021

Table Part II SIII-7: Clinical trial exposure by actual dose - controlled Phase III trial population-CRC

Treatment	Stivarga		Placebo	
Daily dose of exposure	**Persons**	**Person time[a]**	**Persons**	**Person time[a]**
<80 mg	7	0.2	1	0.0
80 mg	108	20.5	1	0.1
120 mg	281	47.3	13	1.0
160 mg	636	112.6	321	48.6
>160 mg	0	0.0	1	0.0
80-160 mg	636	180.4	321	49.7
Total	**636**	**180.6**	**321**	**49.8**

[a] In years
Note: For calculation, a month equals 30 days and a year equals 360 days
Note: Duration of ongoing subjects is calculated by using the study specific cut-off date as day of last treatment
Note: Dose refers to actual dose, hence a subject may contribute to more than one dose
Source: Tables for Risk Management Plan Controlled monotherapy safety set (CMSAF)–Table 2/5
Global Integrated Analysis: /by-sasp/patdb/ia/734506/stat/2021/prod_0625_rmp/pgms/t_cmsaf_dose.sas
25 JUN 2021

Table Part II SIII-8: Clinical trial exposure by actual dose - controlled Phase III trials population-GIST

Treatment	Stivarga		Placebo	
Daily dose of exposure	**Persons**	**Person time[a]**	**Persons**	**Person time[a]**
<80 mg	2	0.0	0	0.0
80 mg	36	11.8	0	0.0
120 mg	74	16.8	2	0.1
160 mg	132	34.1	66	12.3
80-160 mg	132	62.6	66	12.5
Total	**132**	**62.6**	**66**	**12.5**

[a] In years
Note: For calculation, a month equals 30 days and a year equals 360 days.
Note: Duration of ongoing subjects is calculated by using the study specific cut-off date as day of last treatment.
Note: Dose refers to actual dose, hence a subject may contribute to more than one dose.
Source: Tables for Risk Management Plan Controlled monotherapy safety set (CMSAF)–Table 2/6
Global Integrated Analysis: /by-sasp/patdb/ia/734506/stat/2021/prod_0625_rmp/pgms/t_cmsaf_dose.sas
25 JUN 2021

Table Part II SIII-9:Clinical trial exposure by actual dose - controlled Phase III trials population-HCC

Treatment	Stivarga		Placebo	
Daily dose of exposure	**Persons**	**Person time[a]**	**Persons**	**Person time[a]**
80 mg	108	33.4	13	1.8
120 mg	173	38.8	13	1.1
160 mg	373	126.1	192	53.2
>160 mg	1	0.0	0	0.0
80-160 mg	374	198.2	193	56.1
Total	**374**	**198.2**	**193**	**56.1**

[a] In years
Note: For calculation, a month equals 30 days and a year equals 360 days.
Note: Duration of ongoing subjects is calculated by using the study specific cut-off date as day of last treatment.
Note: Dose refers to actual dose, hence a subject may contribute to more than one dose.
Source: Tables for Risk Management Plan Controlled monotherapy safety set (CMSAF)–Table 2/7

Table Part II SIII-10: Clinical trial exposure by actual dose–Phase I-III pooled monotherapy safety set-all cancer types

Treatment	Stivarga	
Daily dose of exposure	**Persons**	**Person time[a]**
Missing	2	0.0
< 60 mg	58	16.0
60-160 mg	4,631	1,836.3
> 160 mg	22	2.2
Total	**4,654**	**1,854.5**

[a] In years
Note: For calculation, a month equals 30 days and a year equals 360 days
Note: Duration of ongoing patients is calculated by using the study specific cut-off date as day of last treatment
Note: Dose refers to actual dose, hence a subject may contribute to more than one dose
Source: Tables for Risk Management Plan Monotherapy safety set (MSAF)–Table 2/2
Global Integrated Analysis: /by-sasp/patdb/ia/734506/stat/2021/prod_0625_rmp/pgms/t_msaf_dose.sas
25 JUN 2021

Table Part II SIII-11: Clinical trial exposure by age group and gender - controlled Phase III trials population-CRC/GIST/HCC

Treatment	Age group	Persons male	Persons female	Persons total	Person time[a] male	Person time[a] female	Person time[a] total
Stivarga	18-< 65 years	464	222	686	190.8	69.5	260.3
	65-< 75 years	250	94	344	106.9	31.3	138.3
	75-< 85 years	88	22	110	34.8	8.2	42.9
	≥85 years	2	0	2	0.3	0	0.3
	Missing	0	0	0	0	0	0
	Total	804	338	1,142	332.8	109	441.8
Placebo	18-<65 years	253	130	383	50.5	18.9	69.5
	65-<75 years	113	34	147	29.5	6	35.5
	75-<85 years	29	19	48	8.9	4.4	13.3
	≥85 years	2	0	2	0.2	0	0.2
	Missing	0	0	0	0	0	0
	Total	**397**	**183**	**580**	89.1	29.3	118.5

[a] In years
Note: For calculation, a month equals 30 days and a year equals 360 days.
Note: Duration of ongoing subjects is calculated by using the study specific cut-off date as day of last treatment.
Source: Tables for Risk Management Plan Controlled monotherapy safety set (CMSAF)–Table 2/12
Global Integrated Analysis: /by-sasp/patdb/ia/734506/stat/2021/prod_0625_rmp/pgms/t_cmsaf_agesex.sas 25 JUN 2021

Table Part II SIII-12: Clinical trial exposure by age group and gender-controlled Phase III trial population-CRC

Treatment	Age group	Persons male	Persons female	Persons total	Person time[a] male	Person time[a] female	Person time[a] total
Stivarga	18-< 65 years	237	165	402	72.8	39.6	112.4
	65-< 75 years	123	66	189	39.4	17.1	56.5
	75-< 85 years	32	13	45	7.5	4.5	12
	≥85 years	0	0	0	0	0	0
	Missing	0	0	0	0	0	0
	Total	392	244	636	119.7	61.3	181
Placebo	18-< 65 years	119	103	222	18	12.8	30.7
	65-< 75 years	53	24	77	11.8	3.7	15.6
	75-< 85 years	12	9	21	2.1	1.3	3.4
	≥85 years	1	0	1	0.2	0	0.2
	Missing	0	0	0	0	0	0
	Total	**185**	**136**	**321**	**32.1**	**17.8**	**49.9**

[a] In years
Note: For calculation, a month equals 30 days and a year equals 360 days.
Note: Duration of ongoing subjects is calculated by using the study specific cut-off date as day of last treatment.
Source: Tables for Risk Management Plan Controlled monotherapy safety set (CMSAF)–Table 2/9
Global Integrated Analysis: /by-sasp/patdb/ia/734506/stat/2021/prod_0625_rmp/pgms/t_cmsaf_agesex.sas 25 JUN 2021

Table Part II SIII-13: Clinical trial exposure by age group and gender-controlled Phase III trials population-GIST

Treatment	Age group	Persons male	Persons female	Persons total	Person time[a] male	Person time[a] female	Person time[a] total
Stivarga	18-< 65 years	58	31	89	26.2	16.6	42.8
	65-< 75 years	18	13	31	6.8	6.4	13.2
	75-< 85 years	8	4	12	4.9	1.7	6.6
	≥85 years	0	0	0	0	0	0
	Missing	0	0	0	0	0	0
	Total	84	48	132	37.9	24.7	62.6
Placebo	18-< 65 years	30	16	46	5.9	3.6	9.6
	65-< 75 years	9	4	13	1.3	0.6	2
	75-< 85 years	2	4	6	0.3	0.6	0.9
	≥85 years	1	0	1	0	0	0
	Missing	0	0	0	0	0	0
	Total	**42**	**24**	**66**	**7.6**	**4.9**	**12.5**

[a] In years
Note: For calculation, a month equals 30 days and a year equals 360 days.
Note: Duration of ongoing subjects is calculated by using the study specific cut-off date as day of last treatment.
Source: Tables for Risk Management Plan Controlled monotherapy safety set (CMSAF)–Table 2/10
Global Integrated Analysis: /by-sasp/patdb/ia/734506/stat/2021/prod_0625_rmp/pgms/t_cmsaf_agesex.sas 25 JUN 2021

Table Part II SIII-14: Clinical trial exposure by age group and gender - controlled Phase III trials population-HCC

Treatment	Age group	Persons male	Persons female	Persons total	Person time[a] male	Person time[a] female	Person time[a] total
Stivarga	18 - <65 years	169	26	195	91.8	13.3	105.1
	65 - <75 years	109	15	124	60.7	7.8	68.5
	75 - <85 years	48	5	53	22.3	1.9	24.3
	≥85 years	2	0	2	0.3	0	0.3
	Missing	0	0	0	0	0	0
	Total	328	46	374	175.2	23	198.2
Placebo	18 - <65 years	104	11	115	26.7	2.5	29.1
	65 - <75 years	51	6	57	16.3	1.7	18
	75 - <85 years	15	6	21	6.5	2.5	9
	≥85 years	0	0	0	0	0	0
	Missing	0	0	0	0	0	0
	Total	**170**	**23**	**193**	**49.5**	**6.7**	**56.1**

[a] In years
Note: For calculation, a month equals 30 days and a year equals 360 days.
Note: Duration of ongoing subjects is calculated by using the study specific cut-off date as day of last treatment.
Source: Tables for Risk Management Plan Controlled monotherapy safety set (CMSAF)–Table 2/11
Global Integrated Analysis: /by-sasp/patdb/ia/734506/stat/2021/prod_0625_rmp/pgms/t_cmsaf_agesex.sas 25 JUN 2021

Table Part II SIII-15: Clinical trial exposure by age group and gender–Phase I-III pooled monotherapy safety set-all cancer types

Treatment	Age group	Persons male	Persons female	Persons total	Person time[a] male	Person time[a] female	Person time[a] total
Stivarga	18 - <65 years	1,657	1,179	2,836	706.3	464.8	1,171.1
	65 - <75 years	924	479	1,403	369.6	159.0	528.6
	75 - <85 years	274	123	397	108.2	44.4	152.6
	≥85 years	14	4	18	2.6	0.5	3.1
	Missing	0	0	0	0.0	0.0	0.0
	Total	**2,869**	**1,785**	**4,654**	**1,186.7**	**668.6**	**1,855.4**

[a] In years
Note: For calculation, a month equals 30 days and a year equals 360 days.
Note: Duration of ongoing patients is calculated by using the study specific cut-off date as day of last treatment.
Source: Tables for Risk Management Plan Monotherapy safety set (MSAF)–Table 2/3
Global Integrated Analysis: /by-sasp/patdb/ia/734506/stat/2021/prod_0625_rmp/pgms/t_msaf_agesex.sas 25 JUN 2021

Table Part II SIII-16: Clinical trial exposure by ethnic origin-controlled Phase III trials population - CRC/GIST/HCC

Treatment	Stivarga		Placebo	
Exposure by demographic subgroup	**Persons**	**Person time[a]**	**Persons**	**Person time[a]**
White	613	227.8	313	64.5
Black or African American	12	3.3	11	1.6
Asian	399	159.0	196	32.8
American Indian or Alaska native	1	0.3	1	0.1
Not reported[b]	114	49.9	58	19.2
Multiple	3	1.5	1	0.1
Total	**1,142**	**441.8**	**580**	**118.5**

[a] In years [b] Due to local regulations in France, race was not collected in French patients.
Note: For calculation, a month equals 30 days and a year equals 360 days.
Note: Duration of ongoing subjects is calculated by using the study specific cut-off date as day of last treatment.
Source: Tables for Risk Management Plan Controlled monotherapy safety set (CMSAF) – Table 2/16
Global Integrated Analysis: /by-sasp/patdb/ia/734506/stat/2021/prod_0625_rmp/pgms/t_cmsaf_ethnic.sas
25 JUN 2021

Table Part II SIII-17: Clinical trial exposure by ethnic origin-controlled Phase III trial population - CRC

Treatment	Stivarga		Placebo	
Exposure by demographic subgroup	**Persons**	**Person time[a]**	**Persons**	**Person time[a]**
White	389	104.6	200	32.6
Black or African American	6	2.3	8	1.1
Asian	210	67.5	102	14.3
American Indian or Alaska native	1	0.3	1	0.1
Not reported[b]	29	6.2	10	1.7
Multiple	1	0.2	0	0.0
Total	**636**	**181.0**	**321**	**49.9**

[a] In years [b] Due to local regulations in France, race was not collected in French patients.
Note: For calculation, a month equals 30 days and a year equals 360 days.
Note: Duration of ongoing subjects is calculated by using the study specific cut-off date as day of last treatment.
Source: Tables for Risk Management Plan Controlled monotherapy safety set (CMSAF)–Table 2/13
Global Integrated Analysis: /by-sasp/patdb/ia/734506/stat/2021/prod_0625_rmp/pgms/t_cmsaf_ethnic.sas
25 JUN 2021

Table Part II SIII-18: Clinical trial exposure by ethnic origin - controlled Phase III trials population-GIST

Treatment	Stivarga		Placebo	
Exposure by demographic subgroup	**Persons**	**Person time[a]**	**Persons**	**Person time[a]**
White	89	44.4	45	8.5
Black or African American	0	0.0	1	0.2
Asian	34	14.2	16	3.0
Not reported[b]	9	4.0	4	0.8
Total	**132**	**62.6**	**66**	**12.5**

[a] In years [b] Due to local regulations in France, race was not collected in French patients.
Note: For calculation, a month equals 30 days and a year equals 360 days.
Note: Duration of ongoing subjects is calculated by using the study specific cut-off date as day of last treatment.
Source: Tables for Risk Management Plan Controlled monotherapy safety set (CMSAF)–Table 2/14
Global Integrated Analysis: /by-sasp/patdb/ia/734506/stat/2021/prod_0625_rmp/pgms/t_cmsaf_ethnic.sas
25 JUN 2021

Table Part II SIII-19: Clinical trial exposure by ethnic origin - controlled Phase III trials population-HCC

Treatment	Stivarga		Placebo	
Exposure by demographic subgroup	**Persons**	**Person time[a]**	**Persons**	**Person time[a]**
White	135	78.9	68	23.5
Black or African American	6	1.0	2	0.3
Asian	155	77.4	78	15.5
Not reported[b]	76	39.7	44	16.8
Multiple	2	1.3	1	0.1
Total	**374**	**198.2**	**193**	**56.1**

[a] In years [b] Due to local regulations in France, race was not collected in French patients.
Note: For calculation, a month equals 30 days and a year equals 360 days.
Note: Duration of ongoing subjects is calculated by using the study specific cut-off date as day of last treatment.
Source: Tables for Risk Management Plan Controlled monotherapy safety set (CMSAF) – Table 2/15
Global Integrated Analysis: /by-sasp/patdb/ia/734506/stat/2021/prod_0625_rmp/pgms/t_cmsaf_ethnic.sas
25 JUN 2021

Table Part II SIII-20: Clinical trial exposure by ethnic origin – Phase I-III pooled monotherapy safety set - all cancer types

Treatment	Stivarga	
Exposure by demographic subgroup	**Persons**	**Person time[a]**
White	3,474	1,855.4
Black or African American	70	18.3
Asian	542	267.4
American Indian or Alaska native	26	7.5
Native Hawaiian or other Pacific Islander	3	1.0
Not reported[b]	536	208.9
Multiple	3	3.5
Total	**4,654**	**1,855.4**

[a] In years [b] Due to local regulations in France, race was not collected in French patients.
Note: For calculation, a month equals 30 days and a year equals 360 days.
Note: Duration of ongoing patients is calculated by using the study specific cut-off date as day of last treatment.
Source: Tables for Risk Management Plan Monotherapy safety set (MSAF)–Table 2/4
Global Integrated Analysis: /by-sasp/patdb/ia/734506/stat/2021/prod_0625_rmp/pgms/t_msaf_ethnic.sas
25 JUN 2021

Table Part II SIII-21: Clinical trial exposure by special populations - controlled Phase III trials population - CRC/GIST/HCC

Treatment	Stivarga		Placebo	
Exposure by subgroup	**Persons**	**Person time[a]**	**Persons**	**Person time[a]**
Renal impairment: normal renal function baseline GFR ≥60 mL/min/1.73 m²	1,081	416.9	554	112.7
Renal impairment: impaired renal function baseline GFR <60 mL/min/1.73 m²	60	24.9	26	5.8
Renal impairment unknown	1	0.1	0	0.0
Hepatic impairment: normal baseline hepatic function (baseline maximum of ALT and AST ≤1.5×ULN)	913	347.5	468	92.8
Hepatic impairment: mildly impaired hepatic function (baseline maximum of ALT and AST >1.5×ULN - 3×ULN)	185	82.1	92	23.1
Hepatic impairment: moderately impaired hepatic function (baseline maximum of ALT and AST >3×ULN)	43	12.2	20	2.5
Hepatic impairment unknown	1	0.1	0	0.0
Total	**1,142**	**441.8**	**580**	**118.5**

ALT: Alanine transaminase, AST: Aspartate transaminase, eGFR: Estimated glomerular filtration rate, GFR: Glomerular filtration rate, MDRD: Modification of diet in renal disease, ULN: Upper limit normal.
[a] In years
Note: For calculation, a month equals 30 days and a year equals 360 days.
Note: Duration of ongoing subjects is calculated by using the study specific cut-off date as day of last treatment.
Note: eGFR was calculated according to the abbreviated MDRD formula: eGFR (ml/min/1.73m²) = k x 186 x SCR(-1.154) x age(-0.203),
Note: where k = 1 for men and k = 0.742 for women, SCR= serum creatinine measured in mg/dl.
Note: The result is multiplied by 1.210 for Blacks or African-Americans, by 0.881 for Japanese, by 1.227 for Chinese (mainland China. Hong Kong, Taiwan)
Normal renal function: eGFR >=60ml/min/1.73m², impaired renal function: eGFR <60ml/min/1.73m².
Source: Tables for Risk Management Plan Controlled monotherapy safety set (CMSAF) – Table 2/20
Global Integrated Analysis: /by-sasp/patdb/ia/734506/stat/2021/prod_0625_rmp/pgms/t_cmsaf_specialpop.sas 25 JUN 2021

Table Part II SIII-22: Clinical trial exposure by special populations - controlled Phase III trial population - CRC

Treatment	Stivarga		Placebo	
Exposure by subgroup	**Persons**	**Person time[a]**	**Persons**	**Person time[a]**
Renal impairment: normal renal function baseline GFR ≥60 mL/min/1.73 m²	610	173.5	311	48.6
Renal impairment: impaired renal function baseline GFR <60 mL/min/1.73 m²	25	7.4	10	1.3
Renal impairment unknown	1	0.1	0	0.0
Hepatic impairment: normal baseline hepatic function (baseline maximum of ALT and AST ≤1.5×ULN)	575	170.0	286	45.8
Hepatic impairment: mildly impaired hepatic function (baseline maximum of ALT and AST >1.5×ULN - 3×ULN)	55	10.0	31	3.7
Hepatic impairment: moderately impaired hepatic function (baseline maximum of ALT and AST >3×ULN)	5	0.8	4	0.4
Hepatic impairment unknown	1	0.1	0	0.0
Total	**636**	**181.0**	**321**	**49.9**

ALT: Alanine transaminase, AST: Aspartate transaminase, eGFR: Estimated glomerular filtration rate, GFR: Glomerular filtration rate, MDRD: Modification of diet in renal disease, ULN: Upper limit normal.
[a] In years
Note: For calculation, a month equals 30 days and a year equals 360 days.
Note: Duration of ongoing subjects is calculated by using the study specific cut-off date as day of last treatment.
Note: Person group allocation to special populations is based on pre-treatment assessment.
Note: eGFR was calculated according to the abbreviated MDRD formula: eGFR (ml/min/1.73m²) = k x 186 x SCR(-1.154) x age(-0.203),
Note: where k = 1 for men and k = 0.742 for women, SCR= serum creatinine measured in mg/dl.
Note: The result is multiplied by 1.210 for Blacks or African-Americans, by 0.881 for Japanese, by 1.227 for Chinese (mainland China. Hong Kong, Taiwan)
Normal renal function: eGFR > = 60ml/min/1.73m², impaired renal function: eGFR < 60 ml/min/1.73m².
Source: Tables for Risk Management Plan Controlled monotherapy safety set (CMSAF) – Table 2/17
Global Integrated Analysis: /by-sasp/patdb/ia/734506/stat/2021/prod_0625_rmp/pgms/t_cmsaf_specialpop.sas 25 JUN 2021

Table Part II SIII-23: Clinical trial exposure by special populations - controlled Phase III trials population - GIST

Treatment	Stivarga		Placebo	
Exposure by subgroup	**Persons**	**Person time[a]**	**Persons**	**Person time[a]**
Renal impairment: normal renal function baseline GFR ≥60 mL/min/1.73 m²	118	55.2	53	10.6
Renal impairment: impaired renal function baseline GFR <60 mL/min/1.73 m²	14	7.5	13	1.9
Hepatic impairment: normal baseline hepatic function (baseline maximum of ALT and AST ≤1.5×ULN)	123	59.8	59	11.6
Hepatic impairment: mildly impaired hepatic function (baseline maximum of ALT and AST >1.5×ULN - 3×ULN)	6	1.9	7	0.9
Hepatic impairment: moderately impaired hepatic function (baseline maximum of ALT and AST >3×ULN)	3	0.9	0	0.0
Total	**132**	**62.6**	**66**	**12.5**

ALT: Alanine transaminase, AST: Aspartate transaminase, eGFR: Estimated glomerular filtration rate, GFR: Glomerular filtration rate, MDRD: Modification of diet in renal disease, ULN: Upper limit normal.
[a] In years
Note: For calculation, a month equals 30 days and a year equals 360 days.
Note: Duration of ongoing subjects is calculated by using the study specific cut-off date as day of last treatment.
Note: Person group allocation to special populations is based on pre-treatment assessment.
Note: eGFR was calculated according to the abbreviated MDRD formula: eGFR (ml/min/1.73m²) = k x 186 x SCR(-1.154) x age(-0.203),
Note: where k = 1 for men and k = 0.742 for women, SCR= serum creatinine measured in mg/dl.
Note: The result is multiplied by 1.210 for Blacks or African-Americans, by 0.881 for Japanese, by 1.227 for Chinese (mainland China. Hong Kong, Taiwan)
Normal renal function: eGFR >=60ml/min/1.73m², impaired renal function: eGFR <60ml/min/1.73m².
Source: Tables for Risk Management Plan Controlled monotherapy safety set (CMSAF) – Table 2/18
Global Integrated Analysis: /by-sasp/patdb/ia/734506/stat/2021/prod_0625_rmp/pgms/t_cmsaf_specialpop.sas 25 JUN 2021

Table Part II SIII-24: Clinical trial exposure by special populations - controlled Phase III trials population - HCC

Treatment	Stivarga		Placebo	
Exposure by subgroup	**Persons**	**Person time[a]**	**Persons**	**Person time[a]**
Renal impairment: normal renal function baseline GFR ≥60 mL/min/1.73 m²	353	188.3	190	53.6
Renal impairment: impaired renal function baseline GFR <60 mL/min/1.73 m²	21	10.0	3	2.6
Hepatic impairment: normal baseline hepatic function (baseline maximum of ALT and AST ≤1.5×ULN)	215	117.7	123	35.5
Hepatic impairment: mildly impaired hepatic function (baseline maximum of ALT and AST >1.5×ULN - 3×ULN)	124	70.1	54	18.5
Hepatic impairment: moderately impaired hepatic function (baseline maximum of ALT and AST >3×ULN)	35	10.5	16	2.2
Total	**374**	**198.2**	**193**	**56.1**

ALT: Alanine transaminase, AST: Aspartate transaminase, eGFR: Estimated glomerular filtration rate, GFR: Glomerular filtration rate, MDRD: Modification of diet in renal disease, ULN: Upper limit normal.
[a] In years
Note: For calculation, a month equals 30 days and a year equals 360 days.
Note: Duration of ongoing subjects is calculated by using the study specific cut-off date as day of last treatment.
Note: Person group allocation to special populations is based on pre-treatment assessment.
Note: eGFR was calculated according to the abbreviated MDRD formula: eGFR (ml/min/1.73m²) = k x 186 x SCR(-1.154) x age(-0.203),
Note: where k = 1 for men and k = 0.742 for women, SCR= serum creatinine measured in mg/dl.
Note: The result is multiplied by 1.210 for Blacks or African-Americans, by 0.881 for Japanese, by 1.227 for Chinese (mainland China. Hong Kong, Taiwan).
Normal renal function: eGFR >=60ml/min/1.73m², impaired renal function: eGFR <60ml/min/1.73m².
Source: Tables for Risk Management Plan Controlled monotherapy safety set (CMSAF)–Table 2/19
Global Integrated Analysis: /by-sasp/patdb/ia/734506/stat/2021/prod_0625_rmp/pgms/t_cmsaf_specialpop.sas 25 JUN 2021

Table Part II SIII-25: Clinical trial exposure by special populations – Phase I-III pooled monotherapy safety set - all cancer types

Treatment	Stivarga	
Exposure by subgroup	**Persons**	**Person time[a]**
Renal impairment: normal renal function baseline GFR ≥60 mL/min/1.73 m²	3,950	1,566.2
Renal impairment: impaired renal function baseline GFR <60 mL/min/1.73 m²	351	188.7
Renal impairment unknown	353	100.5
Hepatic impairment: normal baseline hepatic function (baseline maximum of ALT and AST ≤1.5×ULN)	3,564	1,522.4
Hepatic impairment: mildly impaired hepatic function (baseline maximum of ALT and AST >1.5×ULN - 3×ULN)	614	202.3
Hepatic impairment: moderately impaired hepatic function (baseline maximum of ALT and AST >3×ULN)	127	31.1
Hepatic impairment unknown	349	99.5
Total	**4,654**	**1,855.4**

ALT: Alanine transaminase, AST: Aspartate transaminase, eGFR: Estimated glomerular filtration rate, GFR: Glomerular filtration rate, MDRD: Modification of diet in renal disease, ULN: Upper limit normal.
[a] In years
Note: For calculation, a month equals 30 days and a year equals 360 days.
Note: Duration of ongoing subjects is calculated by using the study specific cut-off date as day of last treatment.
Note: Person group allocation to special populations is based on pre-treatment assessment.
Note: eGFR was calculated according to the abbreviated MDRD formula: eGFR (ml/min/1.73m²) = k x 186 x SCR(-1.154) x age(-0.203),
Note: where k = 1 for men and k = 0.742 for women, SCR= serum creatinine measured in mg/dl.
Note: The result is multiplied by 1.210 for Blacks or African-Americans, by 0.881 for Japanese, by 1.227 for Chinese (mainland China. Hong Kong, Taiwan) Normal renal function: eGFR >=60ml/min/1.73m², impaired renal function: eGFR <60ml/min/1.73m².
Source: Tables for Risk Management Plan Monotherapy safety set (MSAF)–Table 2/5
Global Integrated Analysis: /by-sasp/patdb/ia/734506/stat/2021/prod_0625_rmp/pgms/t_msaf_specialpop.sas 25 JUN 2021

Table Part II SIII-26: Clinical trial exposure by indication - controlled Phase III trial population-CRC/GIST/HCC

Treatment	Stivarga		Placebo	
Exposure by indication	**Persons**	**Person time[a]**	**Persons**	**Person time[a]**
Colorectal cancer	636	181.0	321	49.9
Gastrointestinal stromal Tumour (GIST)	132	62.6	66	12.5
Hepatocellular cancer (HCC)	374	198.2	193	56.1
Total	**1,142**	**441.8**	**580**	**118.5**

[a] In years
Note: For calculation, a month equals 30 days and a year equals 360 days.
Note: Duration of ongoing subjects is calculated by using the study specific cut-off date as day of last treatment.
Source: Tables for Risk Management Plan Controlled monotherapy safety set (CMSAF)–Table 2/24
Global Integrated Analysis: /by-sasp/patdb/ia/734506/stat/2021/prod_0625_rmp/pgms/t_cmsaf_indicat.sas
25 JUN 2021

Table Part II SIII-27: Clinical trial exposure by indication - Phase I-III pooled monotherapy safety set - all cancer types

Treatment	Stivarga	
Exposure by indication	**Persons**	**Person time[a]**
Colorectal cancer	3,726	1,137.1
Gastrointestinal stromal tumour (GIST)	199	224.1
Hepatocellular cancer (HCC)	440	305.0
Other	289	189.2
Total	**4,654**	**1,855.4**

[a] In years
Note: For calculation, a month equals 30 days and a year equals 360 days.
Note: Duration of ongoing patients is calculated by using the study specific cut-off date as day of last treatment.
Source: Tables for Risk Management Plan Monotherapy safety set (MSAF)–Table 2/6
Global Integrated Analysis: /by-sasp/patdb/ia/734506/stat/2021/prod_0625_rmp/pgms/t_msaf_indicat.sas
25 JUN 2021

Part II: Module SIV - Populations not studied in clinical trials

SIV.1 Exclusion criteria in pivotal clinical studies within the development programme

The following table provides an overview of the safety-related eligibility criteria in the placebo-controlled pivotal Phase III registration studies for metastatic colorectal cancer (CRC) (14387-CORRECT, 15808 - CONCUR), metastatic and/or unresectable gastrointestinal stromal tumour (GIST) (14874-GRID) and in HCC second-line after sorafenib (15982-RESORCE).

Table Part II SIV-1: Exclusion criteria in the pivotal studies across the development program which are proposed/not proposed to be considered as missing information

Exclusion criteria	Reason for exclusion	Missing Information Yes/No	Rationale
Non-healing wound, ulcer, or bone fracture	Vascular endothelial growth factor (VEGF) antagonists may be associated with impaired wound healing	No	Addressed in SmPC Section 4.4 Special warnings and precautions for use-wound healing complications.
Pregnant or breast-feeding patients.	Toxicology data suggest a teratogenic potential of regorafenib	No	Addressed in SmPC Section 4.6 Fertility, pregnancy and lactation.
Congestive heart failure ≥ New York Heart Association Class-2. Left ventricular ejection fraction <50% or below the lower limit of normal for the institution (whichever is higher). *(In GRID)*	The VEGF antagonists have been associated with cardiovascular side effects. Patients with a recent history of cardiac disease may be at higher risk for such adverse events	Yes	Safety in patients with a cardiac history is considered a missing information.
Unstable angina (angina symptoms at rest), new-onset angina (begun within the last 3-months).	The VEGF antagonists have been associated with cardiovascular side effects. Patients with a recent history of cardiac ischaemic	No	Addressed in SmPC Section 4.4 Special warnings and precautions for use - Cardiac ischaemia and infarction.

Table Part II SIV-1: Exclusion criteria in the pivotal studies across the development program which are proposed/not proposed to be considered as missing information

Exclusion criteria	Reason for exclusion	Missing Information Yes/No	Rationale
Myocardial infarction less than 6-months before start of study drug.	events may be at higher risk for such adverse events.		
Uncontrolled hypertension. (Systolic blood pressure >150 *(in CORRECT)*/140 *(in GRID) mmHg* or diastolic pressure > 90 mmHg despite optimal medical management). Patients with phaeochromocytoma.	The VEGF antagonists are associated with blood pressure increases. Patients with phaeochromocytoma do have per se an increased risk of severe hypertension events	No	Addressed in SmPC Section 4.4 Special warnings and precautions for use - Arterial hypertension.
Patients with evidence or history of any bleeding diathesis, irrespective of severity. Any haemorrhage or bleeding event ≥ Common Terminology Criteria for Adverse Events (CTCAE) Grade III within 4-weeks prior to the start of study medication. 15982 HCC (RESORCE): Patients with large oesophageal varices at risk of bleeding that are not being treated with Conventional medical intervention: beta blockers or endoscopic treatment. Assessment of oesophageal varices for patients in whom conventional medical intervention for known oesophageal	The VEGF antagonists are associated with an increased bleeding risk.	No	Addressed in SmPC Section 4.4 Special warnings and precautions for use - Haemorrhage.

Table Part II SIV-1: Exclusion criteria in the pivotal studies across the development program which are proposed/not proposed to be considered as missing information

Exclusion criteria	Reason for exclusion	Missing Information Yes/No	Rationale
varices is already in place should be performed by endoscopy as per local standard of care			
Platelet count <100,000/mm3, Haemoglobin <9 g/dL, Absolute neutrophil count <1500/mm3	These laboratory-based exclusion criteria relate to ensuring patients are at a stable baseline bone marrow function before entering clinical studies.	No	The data do not suggest a severe effect of Stivarga on the bone marrow. Observed haematological abnormalities are considered to be adequately addressed in Tables 3 (“ADRs reported in clinical trials in patients treated with Stivarga”) and Table 4 (“Treatment emergent laboratory test abnormalities reported in placebo controlled Phase III trial in patients with metastatic CRC”), Table 5 (“Treatment-emergent laboratory test abnormalities reported in placebo-controlled Phase III trial (double-blind phase) in patients with GIST (GRID)”) and Table 6 (“Treatment emergent laboratory test abnormalities reported in placebo controlled Phase III trial in patients with HCC (RESORCE)”) of Section 4.8 (“Undesirable effects”) of the SmPC.
Total bilirubin >1.5 × ULN. Alanine transaminase (ALT) and aspartate aminotransferase (AST) >3 × ULN (>5 × ULN for patients with liver involvement of their cancer).	These laboratory-based exclusion criteria relate to ensuring patients are at a stable baseline hepatic function before entering clinical studies	Yes	Addressed in SmPC Section 4.2 Posology and method of administration and Section 4.4 Special warnings and precautions for use.
Serum creatinine >1.5 × ULN Inclusion criterion: Glomerular filtration rate (GFR) < 30 mL/min/1.73 m^2 according to	These laboratory-based exclusion criteria relate to ensuring patients are at a stable baseline renal	No	The data do not suggest a clinically severe effect of Stivarga on renal function. Observed mild/moderate proteinuria associated with Stivarga treatment is considered to be adequately addressed in Table 3 (“ADRs reported in clinical trials in patients

Table Part II SIV-1: Exclusion criteria in the pivotal studies across the development program which are proposed/not proposed to be considered as missing information

Exclusion criteria	Reason for exclusion	Missing Information Yes/No	Rationale
the modification of diet in renal disease (MDRD) abbreviated formula. These laboratory-based exclusion criteria relate to ensuring patients are at a stable baseline renal function before entering clinical studies	function before entering clinical studies		treated with Stivarga") and Table 4 ("Treatment emergent laboratory test abnormalities reported in placebo controlled Phase III trial in patients with metastatic CRC"), Table 5 ("Treatment-emergent laboratory test abnormalities reported in placebo-controlled Phase III trial (double-blind phase) in patients with GIST (GRID)") and Table 6 ("Treatment emergent laboratory test abnormalities reported in placebo controlled Phase III trial in patients with HCC (RESORCE)") of Section 4.8 ("Undesirable effects") of the SmPC. Renal impairment is considered to be adequately addressed in Section 4.2 of the SmPC: "In clinical studies, no relevant differences in exposure, safety or efficacy were observed between patients with mild (estimated Glomerular Filtration Rate [eGFR] 60-89 ml/min/1.73m²) renal impairment and patients with normal renal function. Limited pharmacokinetic data indicate no difference in exposure in patients with moderate renal impairment (eGFR 30-59 ml/min/1.73m²). No dose adjustment is required in patients with mild or moderate renal impairment. No clinical data are available in patients with severe renal impairment (eGFR <30 ml/min/1.73m²)."
Amylase (in CORRECT) and lipase >1.5 × ULN.	These laboratory-based exclusion criterion relate to ensuring patients are at a stable baseline pancreatic	No	Observed increases in amylase and lipase laboratory values are considered to be adequately addressed in Table 3 ("ADRs reported in clinical trials in patients treated with Stivarga") and Table 4 ("Treatment emergent laboratory test abnormalities reported in placebo

Table Part II SIV-1: Exclusion criteria in the pivotal studies across the development program which are proposed/not proposed to be considered as missing information

Exclusion criteria	Reason for exclusion	Missing Information Yes/No	Rationale
	function before entering clinical studies.		controlled Phase III trial in patients with metastatic CRC"), Table 5 ("Treatment-emergent laboratory test abnormalities reported in placebo-controlled Phase III trial (double-blind phase) in patients with GIST [GRID]") and Table 6 ("Treatment emergent laboratory test abnormalities reported in placebo controlled Phase III trial in patients with HCC [RESORCE]") of Section 4.8 ("Undesirable effects") of the SmPC. Biochemical and metabolic laboratory test abnormalities are also addressed in Section 4.4 "Special warnings and precautions for use" of the proposed SmPC: "Stivarga has been associated with an increased incidence of electrolyte abnormalities (including hypophosphatemia, hypocalcaemia, hyponatraemia and hypokalaemia) and metabolic abnormalities (including increases in thyroid stimulating hormone, lipase and amylase). The abnormalities are generally of mild to moderate severity, not associated with clinical manifestations, and do not usually require dose interruptions or reductions. It is recommended to monitor biochemical and metabolic parameters during Stivarga treatment and to institute appropriate replacement therapy according to standard clinical practice if required. Dose interruption or reduction, or permanent discontinuation of Stivarga should be considered in case of persistent or recurrent significant abnormalities."

Table Part II SIV-1: Exclusion criteria in the pivotal studies across the development program which are proposed/not proposed to be considered as missing information

Exclusion criteria	Reason for exclusion	Missing Information Yes/No	Rationale
Arterial or venous thrombotic or embolic events such as cerebrovascular accident (including transient ischaemic attacks), deep vein thrombosis or pulmonary embolism within the 6 months before start of study medication.	VEGF antagonists have been associated with cardiovascular side effects. Patients with a recent history of thromboembolic events may be at higher risk for such adverse events	No	The association of Stivarga with cardiac ischaemia and infarction is outlined further above. Otherwise, the data do not indicate an increase in venous thromboembolism, cerebrovascular or other arterial thrombosis events under Stivarga treatment.
Ongoing infection > Grade II National Cancer Institute CTCAE Known history of human immunodeficiency virus infection (HIV). Active hepatitis B or C, or chronic hepatitis B or C requiring treatment with antiviral therapy	In order to achieve interpretable study results, confounding factors such as significant co-morbidity were minimised.	No	The increased risk of infection associated with Stivarga treatment is considered to be adequately addressed in Table 3 (“ADRs reported in clinical trials in patients treated with Stivarga”) and respective paragraph within “Description of selected adverse reactions” (“In the placebo-controlled Phase III trials, infections were more often observed in patients treated with Stivarga as compared to patients receiving placebo (all grades: 31.6% *vs.* 17.2%). Most infections in patients treated with Stivarga were mild to moderate in severity (Grades I and II: 23.0%), and included urinary tract infections (5.7%), nasopharyngitis (4.0%), mucocutaneous and systemic fungal infections (3.3%) as well as pneumonia (2.6%). Fatal outcomes associated with infection were more often observed in patients treated with Stivarga (1.0%) as compared to patients receiving placebo (0.3%) and were mainly respiratory events”) of Section 4.8 (“Undesirable effects”) of the SmPC. Patients with HIV and hepatitis are often excluded from clinical studies to reduce risks of tissue and blood sample handling. It is not anticipated that patients with either of

Table Part II SIV-1: Exclusion criteria in the pivotal studies across the development program which are proposed/not proposed to be considered as missing information

Exclusion criteria	Reason for exclusion	Missing Information Yes/No	Rationale
			these conditions will have any additional risk when dosed with Stivarga.
Renal failure requiring haemo or peritoneal dialysis. Dehydration NCI CTC Grade ≥I. History of organ allograft	In order to achieve interpretable study results, confounding factors such as significant co-morbidity were minimised	No	The data do not suggest a clinically severe effect of Stivarga on renal function. No increase in dehydration events in Stivarga-treated patients compared to patients in placebo arms within pivotal Phase III trials was observed. Renal impairment is considered to be adequately addressed in Section 4.2 of SmPC: "Available clinical data indicate similar exposure of regorafenib and its metabolites M-2 and M-5 in patients with mild, moderate or severe renal impairment compared to patients with normal renal function. No dose adjustment is required in patients with mild, moderate or severe renal impairment." Patients with a history of organ allograft are often excluded from clinical studies to reduce confounding factors. It is not anticipated that such patients will have any additional risk when dosed with Stivarga.
Patients with seizure disorder requiring medication	Strong CYP3A4 inducers may decrease the exposure to regorafenib.	No	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 area under the curve 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 strong CYP3A4 inducers (e.g., phenytoin, carbamazepine, phenobarbital) may also increase metabolism of regorafenib. Since a reduction in plasma regorafenib concentrations may result in a decreased

Table Part II SIV-1: Exclusion criteria in the pivotal studies across the development program which are proposed/not proposed to be considered as missing information

Exclusion criteria	Reason for exclusion	Missing Information Yes/No	Rationale
			efficacy, strong 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.
Any history of or currently known brain metastases	To reduce the risk of cerebral haemorrhage	No	Patients with brain metastases are allowed to participate in the Phase IIIb CRC study (15967-CONSIGN) and the 16339-EAP and 16040-MAP in GIST. So far, the data do not indicate an increased risk for cerebral haemorrhage in patients with brain metastasis
Interstitial lung disease (ILD) with ongoing signs and symptoms at the time of informed consent	Tyrosine kinase inhibitors may be associated with an increased risk of ILD	No	After many years of monitoring ILD as important potential risk, no association between regorafenib and ILD is confirmed.
Uncontrolled ascites (defined as not easily controlled with diuretic or paracentesis treatment).	In order to achieve interpretable study results, confounding factors such as significant co-morbidity were minimised.	No	Patients with a history of uncontrolled ascites and/or pleural effusion that causes respiratory compromise are often excluded from clinical studies to reduce confounding factors. It is not anticipated that such patients will have any additional risk when dosed with Stivarga
Pleural effusion or ascites that causes respiratory compromise (NCI-CTCAE Version 4.0 Grade ≥2 dyspnoea).	Stivarga has been associated with development of proteinuria events. Patients with a recent history of persistent Grade 3 or higher proteinuria events may be at higher risk for such events.	No	The data do not suggest a clinically severe effect of Stivarga on renal function. Observed mild/moderate proteinuria associated with Stivarga treatment is considered to be adequately addressed in Table 3 (“Adverse drug reactions reported in clinical trials in patients treated with Stivarga”), Table 4 (“Treatment emergent laboratory test abnormalities reported in placebo controlled Phase III trial in patients with metastatic CRC [CORRECT]”), Table 5 (“Treatment-

Table Part II SIV-1: Exclusion criteria in the pivotal studies across the development program which are proposed/not proposed to be considered as missing information

Exclusion criteria	Reason for exclusion	Missing Information Yes/No	Rationale
			emergent laboratory test abnormalities reported in placebo-controlled Phase III trial [double-blind phase] in patients with GIST [GRID]") and Table 6 ("Treatment emergent laboratory test abnormalities reported in placebo controlled Phase III trial in patients with HCC (RESORCE)") of Section 4.8 ("Undesirable effects") of the SmPC.

ADR: Adverse Drug Reactions, CRC: Colorectal Cancer, CTCAE: Common Terminology Criteria for Adverse Events, eGFR: Estimated Glomerular Filtration Rate, GIST: Gastrointestinal Stromal Tumour, ILD: Interstitial lung disease, SmPC: Summary of Product Characteristics

SIV.2 Limitations to detect adverse reactions in clinical trial development programmes

The clinical development programme is unlikely to detect certain types of adverse reactions such as rare adverse reactions, adverse reactions with a long latency, or those caused by prolonged or cumulative exposure.

Table Part II SIV-2: Limitations to detect adverse reactions in clinical trial development programmes

Ability to detect adverse reaction	Limitation of trial program	Discussion of implications for target population
Which are rare	So far more than 5,000 cancer patients were treated with Stivarga in company-sponsored clinical trials in the development program. Hence, the upper limit of the 95% CI of an undetected adverse reaction is not higher than 3/5,000 (0.06%).	The ADRs with a frequency of around one in 1,000 could be detected if there were no background incidence. It is unlikely that a rare adverse reaction will impact the benefit/risk balance of Stivarga in a target population with a life-threatening disease.
Due to prolonged exposure	So far more than 956 patients have been treated with Stivarga for at least 6-months (see RMP Table Part II SIII-5). Stivarga was evaluated in a single dose of up to 220 mg.	At present there is no data indicating that prolonged and high cumulative exposure may result in delayed and/or unexpected toxicities. Considering the reduced life expectancy of the target population the implications are limited.
Due to cumulative effects		
Which have a long latency		

ADR: Adverse Drug Reaction, CI: Confidence Interval, mg: Milligram

SIV.3 Limitations in respect to populations typically under-represented in clinical trial development programmes.

Table Part II SIV-3: Exposure of special populations included or not in clinical trial development programmes

Type of special population	Exposure
Pregnant women	Based on its mechanism of action regorafenib is suspected to cause congenital malformations when administered during pregnancy. Section 4.6 of the SmPC states: "Women of childbearing potential/Contraception in males and females: Women of childbearing potential must be informed that regorafenib may cause foetal harm. Women of childbearing potential and men should ensure effective contraception during treatment and up to 8-weeks after completion of therapy. Pregnancy: There are no data on the use of regorafenib in pregnant women. Based on its mechanism of action regorafenib is suspected to cause foetal harm when administered during pregnancy. Animal studies have shown reproductive toxicity. Stivarga should not be used during pregnancy unless clearly necessary and after careful consideration of the benefits for the mother and the risk to the foetus."
Breastfeeding women	It is unknown whether regorafenib or its metabolites are excreted in human milk. In rats, regorafenib or its metabolites are excreted in milk. A risk to the breast-fed child cannot be excluded. Regorafenib could harm infant growth and development. Breast-feeding must be discontinued during treatment with Stivarga
Fertility	There are no data on the effect of Stivarga on human fertility. Results from animal studies indicate that regorafenib can impair male and female fertility
Patients with relevant comorbidities	
• Patients with hepatic impairment	Patients with severe hepatic impairment were excluded from Stivarga clinical trials. For the definitions used for hepatic impairment in non-PK clinical studies see Part II: Module SIII - Clinical trial exposure and Table Part II SIII-21 to Table Part II SIII-25. The pharmacokinetics of regorafenib were studied in patients with hepatocellular carcinoma and other solid tumours who had either normal hepatic function or pre-existing mild or moderate hepatic impairment according to the Child-Pugh classification. Section 4.2 of the SmPC states: "Regorafenib is eliminated mainly *via* the hepatic route. In clinical studies, no relevant differences in exposure, safety or efficacy were observed between patients with mild hepatic impairment (Child-Pugh A) and normal hepatic function. No dose adjustment is required in patients with mild hepatic impairment. Since only limited data are available for patients with moderate hepatic impairment (Child-Pugh B), no dose recommendation can be provided. Close

Table Part II SIV-3: Exposure of special populations included or not in clinical trial development programmes

Type of special population	Exposure
	monitoring of overall safety is recommended in these patients (see Sections 4.4 and 5.2). Stivarga is not recommended for use in patients with severe hepatic impairment (Child Pugh C) as Stivarga has not been studied in this population."
• Patients with renal impairment	Patients with normal or mild to moderate renal impairment (MDRD eGFR ≥30 ml/min/1.73 m^2) were included in Stivarga clinical studies. The pharmacokinetics (PK) of regorafenib was studied in patients with solid tumours who had normal renal function or pre-existing mild or moderate renal impairment. Patients received 160 mg regorafenib once daily. The steady-state exposure of regorafenib is comparable in patients with mild renal impairment and patients with normal renal function. Limited data from Phase I and II studies indicate that the range of exposure in patients with moderate renal impairment is comparable to that seen in patients with normal renal function. The population pharmacokinetic analysis of the study 14387 confirmed that eGFR is not correlated with exposure in the studied exposure range. A Phase-I, multi-centre, non-randomized, open-label, parallel-group study was performed to evaluate the effect of severe renal impairment (SRI) on the pharmacokinetics and safety of regorafenib and its two pharmacologically active metabolites M-2 and M-5 after single and repeated dosing in patients with advanced solid malignant Tumours: Severe renal impairment had no clinically relevant effect on the pharmacokinetics of regorafenib following single and multiple dose administration compared to a control group of patients with normal or mildly impaired renal function. M-2 exposure was approximately 30% lower in the SRI group after single and multiple dose administration compared to the control group, which is regarded as not clinically relevant. M-5 exposure was approximately 55% and 30% lower in the SRI group after single and multiple dose administration, respectively, compared to the control group. However, this effect is not considered clinically relevant. In conclusion, the pharmacokinetics of 160 mg regorafenib was not affected by severe renal impairment. Section 4.2 of the proposed SmPC states: "Available clinical data indicate similar exposure of regorafenib and its metabolites M-2 and M-5 in patients with mild, moderate or severe renal impairment compared to patients with normal renal function. No dose adjustment is required in patients with mild, moderate or severe renal impairment."
• Patients with other relevant co-morbidities	Not applicable
• Patients with a disease severity different from	• CRC: As all patients with metastatic CRC refractory to all available approved therapies were potentially eligible, there is no patient

Table Part II SIV-3: Exposure of special populations included or not in clinical trial development programmes

Type of special population	Exposure
inclusion criteria in clinical trials	population with a higher disease severity than that of metastatic CRC studied in the registration trial. • GIST: As all patients with metastatic and/or unresectable GIST whose disease has progressed despite prior treatments with approved standard therapies (imatinib and sunitinib) were potentially eligible, there is no patient population with a higher disease severity than that of metastatic and/or unresectable GIST studied in the registration trial. • HCC: As all patients with advanced HCC whose disease has progressed despite prior treatments with approved standard therapies (sorafenib), were potentially eligible, there is no patient population with a higher disease severity than that of advanced HCC studied in the registration trial. • Patients with a poor performance status (Eastern Cooperative Oncology Group Performance Status > 1) and those with very short life expectancy (<3-months) were not included in clinical trials. An individual risk-benefit evaluation is necessary for these patients with poor prognosis. Section 4.2 of the SmPC states: "Patients with performance status (PS) 2 or higher were excluded from clinical studies. There is limited data in patients with PS ≥2."
Population with relevant different ethnic origin	In clinical studies included in the safety pool for this RMP, 3,474 of 4,654 (74.6%) of patients treated with Stivarga were Caucasians, 542 (11.6%) Asians, and 70 (1.5%) Black or African-Americans and 26 (0.61%) American Indian or Alaska native and 3 native Hawaiian or other Pacific Islander (0.07%). Ethnicity was not reported in 536 patients. The exposure of Stivarga observed in several Phase I and Phase II studies in various Asian populations (Chinese, Japanese, Korean) was within the same range as seen in Caucasians. This is further substantiated by the population PK analysis of the pivotal study 14387, which did not indicate any relevant differences in the pharmacokinetics of regorafenib, M-2 or M-5 in Asian compared to Caucasian patients. Section 4.2 of the SmPC states: "In clinical studies, no relevant differences in exposure, or efficacy were observed between patients of different ethnic groups. A higher incidence of hand-foot skin reaction (HFSR)/palmar-plantar erythrodysaesthesia syndrome, severe liver function test abnormalities and hepatic dysfunction was observed in Asian (in particular Japanese) patients treated with Stivarga compared with Caucasians. The Asian patients treated with Stivarga in clinical studies were primarily from East Asia (~90%). There is limited data on regorafenib in the black patient population. No dose adjustment is necessary based on ethnicity (see Section 5.2)."

Table Part II SIV-3: Exposure of special populations included or not in clinical trial development programmes

Type of special population	Exposure
Subpopulations carrying relevant genetic polymorphisms	Regorafenib is a UGT1A1 inhibitor. Patients with genetic polymorphism for the hepatic UGT1A1 isoenzyme resulting in impaired glucuronidation capacity (Gilbert's syndrome) may develop subclinical or overt unconjugated hyperbilirubinemia after starting treatment. The hyperbilirubinemia is generally mild and does not usually result in clinical complications. Section 4.4 of the SmPC states: "Regorafenib is a uridine diphosphate glucuronosyl transferase (UGT) 1A1 inhibitor. Mild, indirect (unconjugated) hyperbilirubinemia may occur in patients with Gilbert's syndrome."
Children	The clinical efficacy and safety of regorafenib have not been extensively studied in children. Overall, 146 children with age ranging from 1.5 to 17 years have been treated in two clinical trials related to the paediatric investigational plan (Study 15906 and Study 17529). Study 15906 was a prospective, open-label, multi-centre, nonrandomized, Phase I dose escalation trial conducted to evaluate PK, pharmacodynamics, tolerability, safety and tumour activity of regorafenib in paediatric subjects with solid malignant tumours recurrent or refractory to standard therapy. This study was completed on 26 AUG 2024. A total of 62 participants were treated in this study with the median age of 13 years in the escalation phase and 10 years in the expansion phase. In the dose escalation phase, 41 participants received regorafenib monotherapy at increasing dose levels (60, 72, 82, and 93 mg/m²). The median overall duration of treatment with regorafenib was 2 cycles (range: 1 to 30 cycles). None of the 39 participants evaluable for efficacy achieved a complete response (CR); one participant achieved a partial response (PR), and 15 participants had stable disease. In the expansion phase, 21 participants received treatment. The median overall duration of treatment with regorafenib was 4 cycles (range: 1 to 85 cycles). The best response assessments were available for 20 participants with the overall response rate (CR and PR) of 47.6%. The median overall survival time for participants in the expansion phase was 12.85 months (range 42 days to 63.74 months) and the median progression-free survival (PFS) was 6.97 months (range 19 days to 59.96 months). Regorafenib demonstrated tolerability at doses up to 82 mg/m^2 in pediatric patients with recurrent or refractory solid malignant tumors. An increased incidence of Grades 3-4 haematological events was observed, and it appears that participants with a prior history of myelosuppressive therapies such as high dose chemotherapy with stem cell rescue or craniospinal irradiation may be at a higher risk. Haematological toxicities were mostly transient and manageable by dose modifications. No new safety concern was identified in this study Pharmacokinetic evaluations showed that regorafenib exposure when administered in combination with vincristine and irinotecan was consistent with the exposure observed in the dose escalation phase

Table Part II SIV-3: Exposure of special populations included or not in clinical trial development programmes

Type of special population	Exposure
	and comparable to adult populations receiving regorafenib at a dose of 160 mg daily. PK and safety data obtained in the dose expansion phase of this study did not demonstrate a dose dependent relationship to the types or severity of toxicities observed. The study has completed and, given the data from the dose escalation phase (similar efficacy, safety and PK data) and the overall results of the dose expansion phase, the recommended Phase II dose (RP2D) of regorafenib will be 82 mg/m^2 when sequentially administered to a vincristine/irinotecan backbone chemotherapy in a 3-week schedule. Study 17529 is a Phase II study that is part of an overarching study for children and adults with newly diagnosed and relapsed rhabdomyosarcoma titled Frontline and Relapsed Rhabdomyosarcoma (FaR-RMS). Within study 17529, the CT3 portion investigated the efficacy and safety of regorafenib in combination with vincristine and irinotecan (VIRR) in patients with relapsed rhabdomyosarcoma compared to standard therapy of vincristine, irinotecan and temozolomide (VIRT). The primary endpoint was 1-year event free survival (EFS). Initially, CT3 was to enroll at least 260 patients of which at least 70% were paediatric patients from 6 months to less than 18 years old. Due to the recruitment stop after futility, the intention to treat population consisted of 103 patients (51 for VIRR and 52 for VIRT). Of the 103 randomised patients, 84 were paediatric age group (44 for VIRR and 40 for VIRT). The interim analysis to assess futility (stage 1), conducted with a cut-off date of 23 June 2025, indicated that the 1-year EFS rate for the VIRT arm was 29% (95% CI: 14, 46) compared to 19% (95% CI: 7, 37) for the VIRR arm. The adjusted hazard ratio (HR) was 1.36, while the unadjusted HR was 1.27, both derived from a Cox proportional hazards model. The safety population comprised 47 patients in each treatment arm. The safety profiles of the combination treatments were consistent with that of the individual components. The incidence of adverse events was similar across both treatment arms (48.7% in VIRT and 51.3% in VIRR). Most of the TEAEs were grade 1 or 2 (80.2%), indicating that the treatments were tolerated. No new safety concern was identified. Although the main study FaR-RMS is still ongoing, randomisation has been closed for CT3 portion. The planned Stage 1 Futility assessment was performed and the Data Monitoring Committee (DMC) recommended to close the CT3 randomisation based on the surpassing of the trial futility boundary and the assessment that the probability of the trial showing the protocol predefined 15% superiority of the experimental arm VIRR over VIRT, is extremely low. In both paediatric studies, the safety profile of regorafenib was consistent with its established safety profile in adults. Due to limited sample size and the short duration of regorafenib treatment in children, the efficacy and safety of regorafenib is not fully established.

Table Part II SIV-3: Exposure of special populations included or not in clinical trial development programmes

Type of special population	Exposure
	Additionally, data on long-term treatment with regorafenib in the paediatric population is not available. As the safety and efficacy have not been established, the treatment of children or adolescents for relapsed RMS with Stivarga is not recommended.
Elderly	Around 1,818 out of 4,654 (39.06%) of patients treated with Stivarga in the studies included in the safety pools for this RMP were aged 65-years and above. In the placebo-controlled Phase III trials, 234 out of 636 (36.8%) CRC patients, 43 out of 132 (32.6%) GIST patients and 179 out of the 374 (47.9%) HCC patients treated with Stivarga were aged 65 years and above. The exposure and safety of Stivarga in this age group was not different compared to younger age groups. Section 4.2 of the SmPC states: “In clinical studies, no relevant differences in exposure, safety or efficacy were observed between elderly (aged 65 years and above) and younger patients.”

CRC: Colorectal Cancer, DLT: Dose-Limiting Toxicity, GIST: Gastrointestinal Stromal Tumours, HCC: Hepatocellular Carcinoma, mg/m^2: Milligrams Per Body Surface Area, RP2D: Recommended Phase II dose, SmPC: Summary of Product Characteristics, SRI: Severe Renal Impairment

Part II: Module SV - Post-authorisation experience

SV.1 Post-authorisation exposure

SV.1.1 Method used to calculate exposure

1. Based on current sales data, at present around 65% of commercial regorafenib (Stivarga) formulation is used for CRC, around 10% for GIST and around 25% for HCC.
2. Mean treatment (excluding time off drug/interruption) duration in the regorafenib arm of the pivotal Phase III studies in CRC (14387-CORRECT), GIST (14874-GRID) and HCC (15982-RESORCE) were 8.9 weeks (ca. 62-days), 15.0 weeks (ca. 105-days), and 18.6 weeks (ca. 130-days), respectively.
3. Four tablets (40 mg each) per day are used as basis as regorafenib standard daily dose is 160 mg once daily. Thus, in 62 days a CRC patient received 248 tablets and in 105 days a GIST patient received 420 tablets and in 130-days a HCC patient received 520 tablets.
4. Regorafenib-treated patients in studies 14387 (CORRECT), 14874 (GRID) and 15982 (RESORCE) received on average nearly 80% of planned dose, i.e., 0.8 has to be used as correction factor for all three studies. Thus, 248 tablets × 0.8 = 198 tablets per CRC patient, 420 tablets × 0.8 = 336 tablets per GIST patient and 520 tablets × 0.8 = 416 tablets per HCC patient.

SV.1.2 Exposure

The distributed volume of regorafenib from 01 SEP 2012 through 26 SEP 2023 was **116,060,763** tablets of Stivarga.

Based on an estimated use of 198 tablets per patient for a 62-day course of treatment in CRC, 336 tablets per patient for a 105-day course for GIST and 416 tablets per patient for a 130-day course for HCC, approximately **485,298** patients worldwide were treated cumulatively until 26 SEP 2023.

Cumulative patient exposure by indication is provided below:

Table Part II SV-1: Cumulative patient exposure by indication

Indications	Number of estimated patients cumulative
CRC patients	381,008
GIST patients	34,542
HCC patients	69,748
Total	**485,298**

CRC: Colorectal Cancer, GIST: Gastrointestinal Stromal Tumour, HCC: Hepatocellular Carcinoma

SV.1.2.1 Post-authorisation use in populations not studied in clinical trials

There is no specific exposure data on post-authorisation use in pregnant or breast-feeding women, patients with hepatic or renal impairment. Use of Stivarga in children was explored in two clinical trials and limited post-authorisation exposure information in children is presented in this section.

SV.1.2.1.1 Specific paediatric issues

SV.1.2.1.1.1 Issues identified in paediatric investigation plans

In study 15906, haematological toxicities were higher in participants with a prior history of myelosuppressive therapies such as high dose chemotherapy with stem cell rescue or craniospinal irradiation and were manageable through dose modifications. Three patients were reported by investigator to have advanced bone age. The safety signal of "advanced bone age" was formally assessed and the signal was refuted. An additional independent review by external experts of the hand-wrist X-rays of the three participants with reported abnormalities concluded that these were normal variants. It was planned to obtain additional evidence in study 17529, however the interim analysis resulted in the closure of randomization, hence no further clinical trial information is expected. As seen in Study 15906, most toxicities were transient and manageable by dose modifications indicating that the treatment was generally well tolerated.

Due to limitations in the number of patients, treatment duration and long term follow up, the efficacy and safety of regorafenib in the paediatric population have not yet been fully established.

SV.1.2.1.1.2 Potential for paediatric off-label use

The CRC and HCC are exceedingly rare in the paediatric population, however, there is a theoretical potential for off-label use in paediatric oncology for other tumours including children with GIST. Epidemiological data on paediatric GIST from the UK National Registry of Childhood Tumours show an annual incidence of 0.02 per million children below the age of 14 years (54).

Based on preliminary efficacy signals in relapsed or refractory rhabdomyosarcoma and other solid tumours including Ewings Sarcoma (55), there is a potential for off-label use of regorafenib in children, particularly in combination with standard chemotherapy treatments. However, the efficacy and safety of regorafenib in the paediatric population are considered not yet been fully established.

SV.1.2.2 Post-authorisation off-label use

There is no exposure data on post-authorisation off-label use.

Information in Bayer's safety database indicates that there have been case reports describing off-label use of Stivarga in a variety of indications including hepatocellular cancer, soft tissue sarcoma, lip and/or oral cavity cancer, gastric cancer, malignant melanoma, lung neoplasm malignant, breast cancer, prostate cancer, oesophageal adenocarcinoma, bladder cancer,

thyroid cancer. The reported events are overall in line with the known regorafenib safety profile and as expected in these patients with advanced/refractory underlying malignancies.

As of 30 SEP 2025, Bayer has received 513 adverse event case reports related to off-label use of regorafenib in the paediatric population: 341 cases in adolescents (13-17 years), 166 cases in children (2-12 years), four cases in infants (1 month to under 2 years) and two cases in neonates (under 1 month). Treatment indications were mostly sarcomas and rhabdomyosarcoma. At least half of the cases (n = 255) reported serious adverse events. This limited information suggests that the safety profile is consistent with the known safety profile of regorafenib in the adult population.

While no new safety issue has been identified from these case reports, off-label use will continue to be closely monitored.

SV.1.2.3 Epidemiological study exposure

Not applicable

SV.1.2.4 Observational study exposure

REFINE PASS Study (Study 19244):

This is an international, prospective, open-label, multi-centre, observational study. Patients with unresectable hepatocellular carcinoma (uHCC) and for whom a decision to treat with regorafenib had been made (by the treating physician) were eligible for enrolment into the study.

The purpose was to evaluate, under real-world practice conditions, the safety and effectiveness of regorafenib in patients with uHCC for whom a decision to treat with regorafenib had been made before study enrolment. The study also evaluated regorafenib treatment in a variety of HCC patient subsets that were not addressed in the RESORCE study, as well as provided information on treatment patterns and outcomes in the real-world setting.

Overall, 1,005 patients were included in the safety analysis set (SAF) (patients with a diagnosis of uHCC who had received at least one regorafenib dose and signed an informed consent form). Around, 965 (93.9%) patients were valid for sorafenib treated safety analysis (SSAF), including a subset of sorafenib intolerant patients (N = 91).

Part II: Module SVI - Additional EU requirements for the safety specification

SVI.1 Potential for misuse for illegal purposes

There is no potential for misuse for illegal purposes with the Stivarga.

Part II: Module SVII - Identified and potential risks

SVII.1 Identification of safety concerns in the initial RMP submission

Not applicable. According to the European Medicines Agency's (EMA) guidance on the format of the Risk Management Plan (RMP) in the European Union (EU) Good Pharmacovigilance Practices (GVP), Module V, Rev.2, effective since 31 MAR 2017, Section 1 of Module SVII is expected to be submitted only for initial marketing authorisation applications.

SVII.2 New safety concerns and reclassification with a submission of an updated RMP

The safety concerns were reanalysed to evaluate whether or not they meet the new definition of important potential/identified risks as per GVP Module V, Rev. 2 by specifying if the risk negatively affects the benefit-risk balance of Stivarga, whether additional pharmacovigilance (PV) activities or additional risk minimisation activities are required, and whether the EU SmPC includes labelling language recommending specific clinical actions as routine risk minimisation activity for each of the safety concerns.

The risks that no longer meet the criteria for important risks (safety concerns) were removed for the following reasons:

- No additional activities beyond routine risk minimisation measures are in place.
- The risk minimisation messages in the product information (SmPC) provide detailed, adequate, and sufficient information and guidance on these risks.
- The routine risk minimisation activities recommending clinical measures to address a risk are fully integrated into standard clinical practice
- The risks are therefore adequately managed by current labelling information.
- There is no reasonable expectation that any additional PV activities can further characterise the risk.
- The risks are followed-up *via* routine pharmacovigilance, namely through signal detection and adverse event reporting.
- Most risks are class effects of multikinase inhibitors and as such are sufficiently characterised and well known by prescribers.

Table Part II SVII-1: Reasons for removal of important identified risks and important potential risks from the list of safety concerns

Safety concern	Reason for removal
Previously classified as important identified risks	
Severe drug-induced liver injury (DILI)	Considering the time on the market and the extensive exposure to Stivarga, this risk is now considered adequately characterised in the SmPC. Detailed guidance on monitoring of liver values,

Table Part II SVII-1: Reasons for removal of important identified risks and important potential risks from the list of safety concerns

Safety concern	Reason for removal
	and dose modification and clinical action is provided in the SmPC. No additional pharmacovigilance (PV) activities and risk minimisation measures are in place.
Cardiac ischemic events	Considering the time on the market and the extensive exposure to Stivarga, this risk is now considered adequately characterised in the SmPC. Targeted guidance for clinical action is included in the SmPC. No additional PV activities and risk minimisation measures are in place.
Hypertension and hypertensive crisis	Considering the time on the market and the extensive exposure to Stivarga, this risk is now considered adequately characterised in the SmPC. Targeted guidance for clinical action is included in the SmPC. No additional PV activities and risk minimisation measures are in place.
Haemorrhage	Considering the time on the market and the extensive exposure to Stivarga, this risk is now considered adequately characterised in the SmPC. Targeted guidance for clinical action is included in the SmPC. No additional PV activities and risk minimisation measures are in place.
Hand-foot skin reaction (HFSR)	Considering the time on the market and the extensive exposure to Stivarga, this risk is now considered adequately characterised in the SmPC. Detailed guidance on monitoring of skin symptoms, dose modification and clinical action is included in the SmPC. No additional PV activities and risk minimisation measures are in place.
Gastrointestinal perforation and fistulae	Considering the time on the market and the extensive exposure to Stivarga, this risk is now considered adequately characterised in the SmPC. Targeted guidance for clinical action is included in the SmPC. No additional PV activities and risk minimisation measures are in place.
Stevens-Johnson syndrome (SJS) /Toxic epidermal necrolysis (TEN)	Considering the time on the market and the extensive exposure to Stivarga, this risk is now considered adequately characterised in the SmPC. Clinical management is considered common medical knowledge, which includes early recognition and removal of the offending drug to prevent progression to severe complications. No additional PV activities and risk minimisation measures are in place.
Infection	Considering the time on the market and the extensive exposure to Stivarga, this risk is now considered adequately characterised in the SmPC. Early recognition of infection events and adequate management according to standard of care are the most effective measures to prevent worsening of these events.

Table Part II SVII-1: Reasons for removal of important identified risks and important potential risks from the list of safety concerns

Safety concern	Reason for removal
	Targeted guidance for clinical action is included in the SmPC. No additional PV activities and risk minimisation measures are in place.
Posterior reversible encephalopathy syndrome (PRES)	Considering the time on the market and the extensive exposure to Stivarga, this risk is now considered adequately characterised and to have no impact on B-R balance. No additional PV activities and risk minimisation measures are in place.
Thrombotic microangiopathies (TMA)	Considering the time on the market and the extensive exposure to Stivarga, this risk is now considered adequately characterised and to have no impact on B-R balance. No additional PV activities and risk minimisation measures are in place.
Previously classified as important potential risks	
Wound healing complications	Considering the time on the market and the extensive exposure to Stivarga, this risk is now considered adequately addressed in the SmPC. No additional PV activities and risk minimisation measures are in place.

ILD: Interstitial lung disease; GI: gastrointestinal; HFSR: Hand-foot skin reaction; PV: Pharmacovigilance; SJS: Stevens-Johnson syndrome; SmPC: Summary of Product Characteristics; TEN: Toxic epidermal necrolysis

SVII.3 Details of important identified risks, important potential risks, and missing information

In the following, important identified risks are defined as the most important identified adverse events (AEs)/adverse reactions that are serious or frequent and that might have an impact on the balance of benefits and risks of the product, and for which there is a high level of evidence for a causal association to the product. Important potential risks are defined as those important AEs/adverse reactions that are serious or frequent and that also might have an impact on the balance of benefits and risks of the product, and for which a causal association cannot be excluded, although an integrated view of the available data does not strongly suggest causation.

SVII.3.1 Presentation of important identified risks and important potential risks

Data from the completed Category 3 study REFINE (19244) have been added below and to Section SVII.3.1.1 and Section SVII.3.1.2.

In addition, the updated results of monotherapy populations studies are presented.

Clinical Studies:

Unless stated otherwise, AE frequencies from clinical trials are based on data which were available at Global Integrated Analyses by 25 JUN 2021, comprising the Phase III

double-blind placebo-controlled pivotal trial in mCRC (study 14387, Colorectal cancer treated with Stivarga or placebo after failure of standard therapy [CORRECT] and study 15808, Asian subjects with metastatic colorectal cancer treated with regorafenib or placebo after failure of standard therapy [CONCUR]), as well as in metastatic and/or unresectable gastrointestinal stoma tumour (GIST) (study 14874, GIST Regorafenib in Progressive Disease [GRID]) and in hepatocellular carcinoma (HCC) second-line after sorafenib (study 15982, RESORCE), and clinical pooled data from all Phase I-III clinical studies in which Stivarga was administered as monotherapy to patients with cancer including study 15967 (open-label Phase IIIb study of regorafenib in patients with metastatic colorectal cancer who have progressed after standard therapy [CONSIGN]).

All results are displayed for patients valid for safety:

- For the Phase III studies, CORRECT, GRID, CONCUR and RESORCE (referred to as "Phase III controlled trials population"): Stivarga, N = 1,142 (636 CRC + 132GIST + 374 HCC); placebo: N = 580 (321 CRC + 66 GIST + 193 HCC)
- For the pooled Phase I-III studies, also including CORRECT, GRID, RESORCE, CONSIGN and CONCUR (referred to as "Phase I-III pooled monotherapy safety set): Stivarga, N = 4,654

The Global Integrated Analyses pool includes only completed company-sponsored studies for which a clean clinical database is available. For risks also identified from studies not included in the pools (e.g., ongoing trials), the Global Pharmacovigilance (GPV) safety database, which includes all serious adverse events (SAEs) from completed and ongoing studies and early access programs as well as SAEs reported within an ongoing patient support program and spontaneous reports, was used for the evaluation, with a data cut-off of 25 JUN 2021. At this date, approximately more than 5,000 patients have been exposed to Stivarga within completed and ongoing company-sponsored clinical trials.

Study 19244 (REFINE):

- REFINE (Regorafenib observational study in hepatocellular Carcinoma) PASS study safety analysis set, patients who did not tolerate sorafenib (Study 19244) with the study completion date of 21 JUN 2022.
- This was an international, prospective, open-label, multi-centre, observational study (EU PAS register number: EUPAS20981). The primary objective of this international observational study was to evaluate the safety of regorafenib in patients with uHCC, including incidences of all treatment-emergent adverse events (TEAEs) and dose modifications due to TEAEs in real-world practice conditions.

Post-marketing experience:

The global safety database was searched by DLP 26 SEP 2023, per specified search criteria for each risk.

Unless otherwise specified, all safety data in this risk management plan (RMP) are coded by Medical Dictionary for Regulatory Activities (MedDRA) terms. Because the complexity of

the dictionary calls for aggregation of the safety information into medically meaningful groupings of MedDRA preferred terms (PTs), three types of MedDRA groupings are used in this RMP:

- Maintenance and Support Services Organization (MSSO) Standardised MedDRA Queries (SMQs).
- Product-specific Bayer MedDRA Queries (PBMQ): This concept follows the same principle as MSSO SMQs, and is used for medical concepts for which no MSSO SMQ currently exists (e.g., wound healing impairment).
- MedDRA Labelling Grouping (MLG): The standardised MedDRA Term Groupings developed at Bayer Pharma for labelling purposes are called "MedDRA Labelling Groupings" (MLGs). MLGs consist of two parts: the "name" of the MLG in a concise and understandable medical terminology, e.g., "Myocardial infarction" and a list of MedDRA PTs representing a clinical diagnosis with related specific, pathognomonic signs and symptoms, isolated defined signs, symptoms or specific test results and a similar degree of severity. To allow for calculation of incidences, the concept of MLGs requires that selected PTs can only be linked to one MLG.

SVII.3.1.1 Important identified risks

Not applicable

SVII.3.1.2 Important potential risks

SVII.3.1.2.1 Interstitial lung disease (ILD)

MedDRA terms:

MedDRA search strategy:

SMQ: Interstitial lung disease

Potential mechanisms:

Mechanisms of ILD are currently unknown. Pathology features in drug associated ILD include diffuse alveolar damage, hyaline membrane formation, epithelial desquamation, fibroblastic proliferation of the alveolar walls, and neutrophil influx into the alveolar space. This is thought to be due to a cytokine-mediated inflammatory reaction with mixed exudative and fibrotic response that affects the alveolar capillary wall, creating abnormal permeability of the alveolar membrane (56).

Evidence source(s) and strength of evidence:

CTD Module 2.7.4, Section 2.1.5

Tables for Risk Management Plan Controlled monotherapy safety set (CMSAF) – EU: Table 3/53, 3/54, 3/55, 3/56, and 3/69

Tables for Risk Management Plan Monotherapy safety set (MSAF) – EU: Table 3/14, 3/18

Tables for Risk Management Plan Monotherapy safety set (MSAF) – EU - CONSIGN (15967): Table 3/14

REFINE safety analysis set, patients who did not tolerate sorafenib: Table 14.2.1/13

Characterisation of the risk:

Frequency

Phase III clinical trials

- *Controlled Phase III trial population*

In the **CRC/GIST/HCC population**, the SMQ "Interstitial Lung Disease" (ILD) yielded eight events in the Stivarga group corresponding to an incidence of 0.70% (95% CI [0.30; 1.38]), whereas two results were found in the placebo group corresponding to an incidence of 0.34% (95% CI [0.04; 1.24]).

The EAIR per 100 subject-years for the Stivarga group was calculated to be 1.54 (95% CI [0.67; 3.04]) and 1.26 (95% CI [0.15; 4.55]) for the placebo group.

In the **CRC population**, the SMQ "Interstitial Lung Disease" yielded three events (one case of acute respiratory distress syndrome, one case of lung infiltration and one case of pneumonitis, each with an incidence of 0.16%) in the Stivarga group corresponding to an incidence of 0.47% (95% CI [0.10; 1.37]), whereas two results (pneumonitis) were found in the placebo group corresponding to an incidence of 0.62% (95% CI [0.08; 2.23]).

The EAIR per 100 subject-years for the Stivarga group was calculated to be 1.32 (95% CI [0.27; 3.85]) and 2.69 (95% CI [0.33; 9.71]) for the placebo group.

In the **GIST population**, no events included in the SMQ "ILD" were reported in the Stivarga and in the placebo group.

In the **HCC population**, the SMQ "Interstitial Lung Disease" (ILD) yielded five events in the Stivarga group corresponding to an incidence of 1.34% (95% CI [0.44; 3.09]), whereas no results were found in the placebo group.

The EAIR per 100 subject-years for the Stivarga group was calculated to be 2.24 (95% CI [0.28; 4.21]).

- *Phase I-III pooled monotherapy safety set*

The SMQ "Interstitial Lung Disease" yielded 22 events corresponding to an incidence of 0.47% (95% CI [0.30; 0.71]). The 22 reported events were cases of acute respiratory distress syndrome, alveolitis, granulomatous pneumonitis, interstitial lung disease, lung infiltration, pneumonitis and radiation pneumonitis.

The EAIR per 100 subject-years was calculated to be 1.00 (95% CI [0.62; 1.51]).

Noteworthy, 2,864 of the 4,654 patients included in Phase I-III pooled monotherapy safety set are patients with metastatic CRC treated with regorafenib in the Phase IIIb 15967-CONSIGN trial. This CONSIGN population is overall consistent with the patient population treated within the placebo-controlled Phase III CRC trials 14387-CORRECT and 15808-CONCUR.

Incidence rates of treatment-emergent events of interest – using SMQ "Interstitial Lung Disease" - were 0.24 (95% CI [0.10; 0.50]) in CONSIGN and 0.47 (95% CI [0.10; 1.37]) for regorafenib-treated patients in CORRECT + CONCUR.

Observational study:

- *The REFINE PASS study safety analysis set (SAF, subgroup of sorafenib intolerant)*

In the REFINE PASS study-subgroup of sorafenib intolerant patients, there was one Grade II event reported for Interstitial lung disease, corresponding to an incidence of 1.1% (95% CI [0.0, 6.0]).

Post-marketing data:

Bayer's global safety database was queried for cases as of DLP 26 SEP 2022 reporting at least one or more adverse events from the SMQ: Interstitial Lung Disease. Table Part II SVII-2 summarizes the sources of case reports with terms matching the search criteria received for Stivarga since 27 SEP 2012.

Table Part II SVII-2: Sources of cumulative cases with terms matching the SMQ: Interstitial Lung Disease in Stivarga cases reported since 27 SEP 2012

Source	N	%
Spontaneous	63	48
Study/observational study	34	26
Study/interventional study	28	21
Study/compassionate use	4	3
Literature	2	2
Grand Total	**131**	**100**

SMQ: Standardised MedDRA Query

Countries from which ≥5% (n = 7) cases were reported included Japan (n = 57 [44%], US (n = 20 [15%], China (n = 12 [9%]), and France (n = 8 [6%]).

Patient age was reported in 113 (86%) cases and ranged from 30 years to 84 years. Patient's gender was reported in 122 (93%) cases, including 88 (67%) males and 34 (26%) females. The indication for Stivarga use was CRC in 43 (33%) cases, HCC in 23 (18%) cases, and GIST in seven (5%) cases.

A total of 131 cases with terms matching the SMQ: Interstitial Lung Disease criteria were reported. Of these cases, 118 (90%) were medically confirmed, and 13 (10%) were non-medically confirmed. Of the 131 cases, 127 (97%) were serious and four (3%) were non-serious.

There were 140 events matching the search criteria from 131 cases. Fatal outcome occurred in 20 cases (15%) with a matching event. The reporting frequency percentage for these 20 deaths calculated based on the number of exposed cases according to sales data (N = 372,812, See Section SV.1.2) was 0.01%. Among the 20 cases with a fatal event matching the search

criteria, three had a matching search term that was considered related in the reporter/company assessment.

The reported cases describe a range of pulmonary events and findings, and the exact nature of the event is unclear in most cases. In all cases with sufficient information for meaningful assessment, alternative causes such as pulmonary infection or metastatic disease, and/or important confounders such as concurrent or recent treatment with drugs known to be associated with an increased risk for ILD such as nivolumab are apparent. There were three cases in which a term matching the search criteria was fatal and assessed as related by the reporter/company assessment. The assessment of cases with fatal outcome was conservative in nature, generally due to temporal relationship between event and Stivarga use. However, an alternative explanation like disease progression including pulmonary metastasis or intercurrent conditions which are known to be associated with fatal outcome, historical treatments known to cause interstitial lung disease, smoking status of patient serve as contributory risk factors or in some cases there is insufficient information for adequate assessment. The evaluation of the risk remains consistent from the previous information from clinical studies. The risk will continue to be monitored.

Seriousness/outcomes

Phase III clinical trials

- *Controlled Phase III trial population*

In the **CRC/GIST/HCC population**, six serious events included in the SMQ "ILD" were reported in the Stivarga group. four of these serious events led to hospitalisation and one had a fatal outcome. In the placebo group, one of two events were reported serious.

In the **CRC population**, all three cases with events included in the MedDRA SMQ ILD that occurred in the Stivarga treatment group were considered serious. One of these events (acute respiratory distress syndrome) resulted in a fatal outcome that occurred later than 30 days after the last dose of study drug (non-treatment emergent death). The reporting investigator considered the event as unrelated to Stivarga. The second event (lung infiltration) related to a single pulmonary infiltrate in a patient with sputum positive for fungal organisms (aspergillus, candida). The investigator considered the event related to Stivarga. The outcome was 'not resolved'. The third event (lung infection) is considered related to the concomitant lung metastases (obstructive pneumonitis) and therefore assessed as unrelated to the treatment with regorafenib by the investigator.

In the **GIST population**, no serious events included in the SMQ "ILD" were reported in the Stivarga and in the placebo group.

In the **HCC population**, three serious events included in the SMQ "ILD" were reported in the Stivarga group. All of these serious events led to hospitalisation, and none had a fatal outcome. In the placebo group, no events were reported serious.

- *Phase I-III pooled monotherapy safety set*

Of the 22 cases with events included in the MedDRA SMQ ILD, eight were considered serious, amounting to an incidence of 0.17% of all patients (95% CI [0.07; 0.34]). There was a

fatal outcome in one case and six patients needed to be hospitalized. Nine out of 22 events were recovered/resolved.

Observational study:

- *The REFINE PASS study safety analysis set (SAF, subgroup of sorafenib intolerant)*

No serious cases reported related to thrombotic microangiopathy in the REFINE PASS study-subgroup of sorafenib intolerant patients.

Post-marketing data:

Of the 140 events matching the search criteria, 97 (74%) had a reported outcome. Of the reported events, 28 (21%) were 'recovered/resolved', 14 (11%) were 'not recovered/not resolved', 27 (21%) were 'recovering/resolving', 4 (3%) were 'recovered/resolved with sequelae', and outcome was 'unknown' in 43 (33%). There were three events (2%) with a matching term that had a fatal outcome.

Severity and nature of risk*:*

While one of the 22 cases that occurred in the Phase I-III pooled MSAF had a fatal outcome (CTCAE Grade V), the other 18 cases were of Grade I-III severity, except for two cases of Grade IV severity and for one case, which was missing. Of these 22 cases, 13 were reported as not recovered, two as recovered with sequelae, three as recovered and one had a fatal outcome.

The ILD are a heterogeneous group of parenchymal infiltrations that can progress to alveolar wall fibrosis, pulmonary hypertension, and congestive heart failure. Clinical features are non-specific, but most often include dyspnoea, cough, and fever. Causes of ILD include infection, lymphangitic carcinomatosis, radiation therapy, pulmonary oedema, haemorrhage, environmental/occupational lung disease, aspiration pneumonia, non-specific (idiopathic) forms of ILD, and drug-related ILD (57, 58).

A wide variety of drugs (as many as 150) have been implicated among causes of ILD, including epidermal growth factor receptor (EGFR)-targeting and (less frequently) VEGFR-targeting TKIs. The diagnosis of drug-associated ILD is made based upon the exclusion of alternative aetiologies in the presence of suggestive imaging and histological features (56, 58).

There were no confirmed cases of true ILD in Stivarga-treated patients, and the events identified by the broad SMQ search were compatible with infective events (fungal infiltrate, pneumonia-related sepsis) and hence clearly attributable to alternative causes.

Post-marketing data:

From the global safety data, a total of 140 terms matching the search criteria occurred in 131 cases. Interstitial lung disease (n = 52, 37% of matching terms), Pneumonitis (n = 44, 31%), Lung infiltration (n = 14, 10%), and acute respiratory distress syndrome (n = 8, 6%), accounted for ≥ 5% (n = 7) of these events. Table Part II SVII-3 shows all terms identified by the search query.

Table Part II SVII-3: Events in the "SMQ: Interstitial Lung Disease" identified in the search query

MedDRA PT	Total	% of events matching the search criteria
Interstitial lung disease	52	37
Pneumonitis	44	31
Lung infiltration	14	10
Acute respiratory distress syndrome	8	6
Pulmonary fibrosis	4	3
Cystic lung disease	3	2
Lung opacity	3	2
Acute interstitial pneumonitis	2	1
Pulmonary toxicity	2	1
Bronchiolitis	2	1
Pulmonary necrosis	1	1
Radiation pneumonitis	1	1
Alveolitis	1	1
Pulmonary alveolar haemorrhage	1	1
Acute lung injury	1	1
Organising pneumonia	1	1
Grand Total	**140**	**100%**

PT: Preferred term, SMQ: Standardised MedDRA Queries

Background incidence/prevalence*:*

There are no published epidemiological studies available investigating the incidence of ILD specifically in patients with metastatic CRC, metastatic/unresectable GIST or HCC. For this rare event, the background risk in these patients unexposed to Stivarga cannot be currently estimated from clinical data.

Background prevalence of the various forms of ILD in the general population has been estimated at four to 98 events per 100,000 person-years (59-61).

Among cancer patients receiving older chemotherapeutic agents, it is estimated that up to 10% develop pulmonary toxicity (62). Chemotherapeutic drugs most commonly considered as causing ILD in cancer patients include paclitaxel, docetaxel, and gemcitabine (58). Danson *et al.* (57) have reported that pulmonary toxicity occurs in up to 5% of patients receiving gemcitabine. Among newer agents, the epidermal growth factor receptor (EGFR) tyrosine kinase inhibitor (TKI) gefitinib has recently been reported to cause ILD in up to 3.5% of

Japanese patients treated for NSCLC, usually with onset within the first three months of therapy (63).

Risk factors and risk groups

Smoking is thought to be a risk factor, as are pre-existing pulmonary pathologies including lung cancer. The incidence also seems to be higher in Japanese patients. The reason for the increased incidence in Japanese patients is currently unknown but may be because of ethnic, environmental or clinical practice differences (57).

Preventability

It is unknown if drug induced ILD may be prevented. No specific measures to prevent ILD are required for Stivarga since there are no confirmed cases.

Impact on the risk-benefit balance of the product:

Impact on individual patient

In general, fatigue, dyspnoea and cough are the main symptoms in ILD. These symptoms are disabling for the patient and can cause an impaired quality of life (QOL). ILD could be life-threatening or fatal.

Public health impact:

Since no confirmed cases have been reported, it is considered that there is currently no evidence that Stivarga increases the risk of ILD, hence, this potential risk is not of any relevance to public health.

SVII.3.1.2.2 Atrial fibrillation

MedDRA terms:

MedDRA search strategy:

PT: Atrial fibrillation

Potential mechanisms:

There is no known mechanism by which Stivarga may cause AF.

In animal studies, Stivarga and its active metabolites M-2 and M-5 were devoid of substantial adverse effects on cardiovascular function (See Part II: Module SII - Non-clinical part of the safety specification).

Evidence source(s) and strength of evidence:

Regorafenib study reports PH-33963, PH-35619, PH-34500

Tables for Risk Management Plan Controlled monotherapy safety set (CMSAF) – EU: Table 3/65, 3/66, 3/67, and 3/68

Tables for Risk Management Plan Monotherapy safety set (MSAF) – EU: Table 3/17

REFINE safety analysis set, patients who did not tolerate sorafenib: Table 14.2.1/14

Characterisation of the risk:

Frequency

Phase III clinical trials

- *Controlled Phase III trial population*

In the **CRC/GIST/HCC population**, 15 events of atrial fibrillation (AF) were reported in patients treated with Stivarga, corresponding to an incidence of 1.31% (95% CI [0.74; 2.16]) (See Table Part II SVII-4). Adjusted for exposure, the incidence rate per 100 subject-years was 2.93 (95% CI [1.64; 4.83]). There were no cases of AF in the placebo group.

Table Part II SVII-4: Incidence rates of treatment emergent medical event "atrial fibrillation" by MedDRA Version 24.0 PT "atrial fibrillation", worst CTCAE grade and treatment group – controlled Phase III trial population – CRC/GIST/HCC

MedDRA search strategy		Stivarga (N = 1,142) N (%)	Placebo (N = 580) N (%)
Atrial fibrillation (PT)	**Worst CTCAE Grade**	**Incidence Rate**	**Incidence Rate**
	Grade I	3 (0.26)	0 (0.00)
	Grade II	8 (0.70)	0 (0.00)
	Grade III	4 (0.35)	0 (0.00)
	Grade IV	0 (0.00)	0 (0.00)
	Grade V	0 (0.00)	0 (0.00)
	All [95% CI for rate (%)]	15 (1.31) [0.74; 2.16]	0 (0.00) [0.00; 0.63]
	Risk ratio [95% CI]	6.67 [1.16; 38.36]	
	EAIR[a,b] [95% CI]	2.93 [1.64; 4.83]	0.00 [0.00; 2.32]
	EAIR difference [95% CI]	3.02 [1.48; 4.56]	

CI = Confidence Interval, EAIR = Exposure-adjusted incidence rate
[a] Per 100 subject-years, [b] EAIR = Number of subjects with the event/sum of exposure times, where exposure time = time to first occurrence if an event occurred or
= treatment duration + time at risk after treatment end if no event occurred, where time at risk = 30 days if patient did not start open label treatment or
= time until start of open label treatment if patient started open label treatment
Source: Tables for Risk Management Plan controlled monotherapy safety set (CMSAF), Table 3/68

In the Stivarga group of the **CRC population**, nine events of AF were reported corresponding to an incidence of 1.42% (95% CI [0.65; 2.67]), whereas no events were reported in the placebo group (See Table Part II SVII-5). Correspondingly, the EAIR per 100 subject-years

for the Stivarga group was calculated to be 4.02 (95% CI [1.84; 7.64]). In the placebo controlled Phase III study CONCUR in metastatic CRC, there were two AF events (1.5%) reported in the regorafenib treatment arm (n = 136) and none in the placebo arm (n = 68).

Table Part II SVII-5: Incidence rates of treatment emergent medical event "atrial fibrillation" by MedDRA Version 24.0 PT "atrial fibrillation", worst CTCAE grade and treatment group – controlled Phase III trial population – CRC

MedDRA search strategy		Stivarga (N = 636) N (%)	Placebo (N = 321) N (%)
Atrial fibrillation (PT)	**Worst CTCAE Grade**	**Incidence Rate**	**Incidence Rate**
	Grade I	2 (0.31)	0 (0.00)
	Grade II	5 (0.79)	0 (0.00)
	Grade III	2 (0.31)	0 (0.00)
	Grade IV	0 (0.00)	0 (0.00)
	Grade V	0 (0.00)	0 (0.00)
	All [95% CI for rate (%)]	9 (1.42) [0.65; 2.67]	0 (0.00) [0.00; 1.14]
	Risk ratio [95% CI]	7.78 [0.66; 91.68]	
	EAIR[a,b] [95% CI]	4.02 [1.84; 7.64]	0.00 [0.00; 4.95]
	EAIR difference [95% CI]	4.07 [1.39; 6.74]	

CI = Confidence Interval, EAIR = Exposure-adjusted incidence rate
[a] Per 100 subject-years, [b] EAIR = Number of subjects with the event/sum of exposure times, where exposure time = time to first occurrence if an event occurred or
= treatment duration + time at risk after treatment end if no event occurred, where time at risk = 30 days if patient did not start open label treatment or
= time until start of open label treatment if patient started open label treatment
Source: Tables for Risk Management Plan controlled monotherapy safety set (CMSAF), Table 3/65

In the **GIST population**, one event of Grade II AF was reported at an incidence of 0.76% (95% CI [0.02; 4.15]) and an EAIR of 1.49 (95% CI [0.04; 8.30]) per 100 subject-years, respectively, in the Stivarga group. No events were reported in the placebo group.

In the Stivarga group of the **HCC population**, five events of AF were reported corresponding to an incidence of 1.34% (95% CI [0.44; 3.09]), whereas no events were reported in the placebo group (See Table Part II SVII-6). Correspondingly, the EAIR per 100 subject-years for the Stivarga group was calculated to be 2.26 (95% CI [0.73; 5.28]).

Table Part II SVII-6: Incidence rates of treatment emergent medical event "atrial fibrillation" by MedDRA Version 24.0 PT "atrial fibrillation", worst CTCAE grade and treatment group – controlled Phase III trial population – HCC

MedDRA search strategy		Stivarga (N = 374) N (%)	Placebo (N = 193) N (%)
Atrial fibrillation (PT)	**Worst CTCAE Grade**	**Incidence Rate**	**Incidence Rate**
	Grade I	1 (0.27)	0 (0.00)
	Grade II	2 (0.53)	0 (0.00)
	Grade III	2 (0.53)	0 (0.00)
	Grade IV	0 (0.00)	0 (0.00)
	Grade V	0 (0.00)	0 (0.00)
	All [95% CI for rate (%)]	5 (1.34) [0.44; 3.09]	0 (0.00) [0.00; 1.89]
	Risk ratio [95% CI]	8.58 [0.27; 271.52]	
	EAIR[a,b] [95% CI]	2.26 [0.73; 5.28]	0.00 [0.00; 5.24]
	EAIR difference [95% CI]	2.26 [0.28; 4.24]	

CI: Confidence Interval, EAIR: Exposure-adjusted incidence rate
[a] Per 100 subject-years, [b] EAIR = Number of subjects with the event/sum of exposure times, where exposure time = time to first occurrence if an event occurred or
= treatment duration + time at risk after treatment end if no event occurred, where time at risk = 30 days if patient did not start open label treatment or
= time until start of open label treatment if patient started open label treatment
Source: Tables for Risk Management Plan controlled monotherapy safety set (CMSAF), Table 3/67

- *Phase I-III pooled monotherapy safety set*

Around 49 cases of AF were reported corresponding to an incidence of 1.05% (95% CI [0.78; 1.39]). The EAIR per 100 subject-years was 2.23 (95% CI [1.65; 2.95])
(See Table Part II SVII-7).

Table Part II SVII-7: Incidence rates of treatment emergent medical event "atrial fibrillation" by MedDRA Version 24.0 PT "atrial fibrillation" and worst CTCAE grade – Phase I-III pooled monotherapy safety set – all cancer types

MedDRA search strategy		Stivarga (N = 4,654) N (%)
Atrial fibrillation (PT)	**Worst CTCAE Grade**	**Incidence Rate**
	Grade 1	10 (0.21)
	Grade 2	26 (0.56)
	Grade 3	13 (0.28)
	Grade 4	0 (0.00)
	Grade 5	0 (0.00)
	All [95% CI for rate (%)]	49 (1.05) [0.78; 1.39]
	EAIR[a,b] [95% CI]	2.23 [1.65; 2.95]

CI = Confidence Interval, EAIR = Exposure-adjusted incidence rate
[a] Per 100 subject-years, [b] EAIR = Number of subjects with the event/sum of exposure times, where exposure time = time to first occurrence if an event occurred or
= treatment duration + time window of 30 days
Source: Tables for Risk Management Plan monotherapy safety set (MSAF), Table 3/17

Observational study:

- *The REFINE PASS study safety analysis set (SAF, subgroup of sorafenib intolerant)*

In the REFINE PASS study-subgroup of sorafenib intolerant patients, there were no cases reported for atrial fibrillation.

Post-marketing data:

Bayer's global safety database was queried for cases as of DLP 26 SEP 2022 reporting PT: Atrial fibrillation. Table Part II SVII-8 summarizes the sources of case reports with terms matching the search criteria received for Stivarga since 27 SEP 2012.

Table Part II SVII-8: Sources of cumulative cases with PT: Atrial fibrillation in Stivarga cases reported since 27 SEP 2012

Source	N	%
Study/observational study	76	56
Study/interventional study	38	28
Spontaneous	18	13
Literature	3	2
Study/compassionate use	1	1
Grand Total	**136**	**100**

Countries from which ≥5% (n = 6) cases were reported included the US (n = 67 [49%]), France (n = 13[10%]), Japan (n = 11 [8%]), and Italy (n = 8 [6%]).

Patient age was reported in 133 (98%) cases and ranged from 50 years to 91 years. Patient's gender was reported in 133 (98%) cases, including 90 (68%) males and 43 (32%) females. The indication for Stivarga use was CRC in 52 (38%) cases, HCC in 17 (13%) cases, and GIST in 16 (12%) cases.

A total of 136 cases with terms matching the PT: Atrial fibrillation were reported. Of these cases, 87 (63%) were medically confirmed, and 37 (27%) were non-medically confirmed. Of the 136 cases, 134 (99%) were serious and two (1%) were non-serious.

There were 143 events matching the search criteria from 136 cases. Fatal outcome occurred in one case report. In this case the patient was in septic shock. The reporting frequency percentage for death calculated based on the number of exposed cases according to sales data (N = 372,812, See Section SV.1.2) was 0.0003%. The event was considered unrelated in the company assessment.

The cases mostly describe recurrence of paroxysmal atrial fibrillation and/or plausible alternative triggers for onset of atrial fibrillation such as infection, or are too poorly documented for in-depth assessment. Confounding factors (cardiovascular disease or risk factors additional to the underlying malignancy or co-suspect drugs) were also reported in a number of cases. None of the cases provide sufficient evidence to assume regorafenib-induced atrial fibrillation. There was one case in which a term matching the search criteria was fatal and assessed as unrelated by the company assessment. The evaluation of the risk remains consistent from the previous information from clinical studies. The risk will continue to be monitored.

Seriousness/outcomes

Phase III clinical trials

- *Controlled Phase III trial population*

In the **CRC/GIST/HCC population**, five of the 15 reported events were considered to be serious, amounting to an incidence of 0.44% of the total trial population. All of these events led to hospitalization. There was no fatal outcome. The event was resolved in 12 cases, among

them four serious cases. The dose needed to be reduced in one case. Permanent study drug discontinuation did not become necessary.

The three serious cases were reported in the **CRC population**, where they amounted to an incidence of 0.47% of the trial population. Atrial fibrillation was resolved in six cases, among them two serious cases.

The one event of AF reported in the **GIST population** was considered to be non-serious and was resolved.

In the **HCC population**, two of the five reported events were considered to be serious, amounting to an incidence of 0.53% of the total trial population. Both serious events led to hospitalization. There was not fatal outcome. The AF was resolved in all five cases. The dose needed to be reduced in one case. Permanent study drug discontinuation did not become necessary.

- *Phase I-III pooled monotherapy safety set*

Atrial fibrillation was considered to be serious in 17 cases (0.38%). In 16 of these cases, hospitalization became necessary. There was no fatal outcome. In29 cases, the event was resolved, among them 15 serious cases. In five cases, the AE led to permanent study drug discontinuation. The dose needed to be reduced in two cases.

Observational study:

- *The REFINE PASS study safety analysis set (SAF, subgroup of sorafenib intolerant)*

In the REFINE PASS study-subgroup of sorafenib intolerant patients, there were no serious cases reported for atrial fibrillation.

Post-marketing data:

Of the 143 events matching the search criteria, 102 (72%) had a reported outcome. Of the reported events, 48 (47%) were ‘recovered/resolved’, 27 (27%) were ‘not recovered/not resolved’, 17 (16%) were ‘recovering/resolving’, two (2%) were ‘recovered/resolved with sequelae’ and outcome was ‘unknown’ in seven (7%). One event (1%) had a fatal outcome.

Severity and nature of risk*:*

Atrial fibrillation is of Grade I-II severity in the majority of patients (36 out of 49 cases in the Phase I-III MSAF). Grade III AF was reported in 13 out of 49 cases. No Grade IV or Grade V events of AF occurred (See Table Part II SVII-7).

Post-marketing data:

From the global safety data, a total of 143 terms matching the search criteria occurred in 136 cases. The reported PT was Atrial fibrillation [n = 143 (100%)].

Background incidence/prevalence*:*

There are no published epidemiological studies available investigating the incidence of atrial fibrillation specifically in patients with metastatic CRC. For this event, the background risk in patients unexposed to Stivarga can currently be best estimated from clinical trial data. In the

placebo-controlled Phase III study CORRECT in metastatic CRC, the prevalence of AF at baseline among the safety population (N = 753) was 2.6% overall (3.2% in the Stivarga arm and 1.6% in the placebo arm).

There is some limited evidence available from a hospital-based case-control study indicating a approx. two times higher prevalence of AF in patients at first diagnosis of colorectal cancer (metastatic and non-metastatic) compared to age-matched controls (64). The reason for this is unclear, the authors speculate about autonomic, endocrine, coagulation and inflammatory alterations as possible physiopathological basis for this observation.

In a population based case-control study using medical databases from Northern Denmark, persons with new diagnosis of atrial fibrillation and atrial flutter were more than 11 times more likely to have been diagnosed with colorectal cancer within 90 days prior to atrial fibrillation or atrial flutter diagnosis, irrespective of the stage of cancer diagnosis (adjusted odds ratio = 11.8; 95% CI: 9.3, 14.9) (65). Within 30 days prior to diagnosis with atrial fibrillation or atrial flutter, there was an even stronger association between colorectal cancer and atrial fibrillation or atrial flutter (unadjusted odds ratio = 24.6; 95% CI: 18.0, 33.7). There was no association between atrial fibrillation or atrial flutter and colorectal cancer diagnosed greater than 90 days before a new diagnosis of atrial fibrillation or atrial flutter. In a population-based cohort study also from Denmark, the standardised incidence ratio for colon cancer in patients with atrial flutter was 7.59 (95% CI: 7.10-8.11) (66).

No published epidemiological studies on the incidence of AF in GIST and HCC patients are available.

Risk factors and risk groups:

Risk factors for AF that are well established include advancing age, male sex, diabetes mellitus, hypertension, valvular disease, myocardial infarction, heart failure, obesity, elevated inflammatory marker concentrations, and PR interval prolongation (67). Many of these are prevalent in the population of patients with metastatic CRC.

Recent studies have also demonstrated a role of early life antecedents (e.g., low birth weight), lack of physical activity and chronic kidney disease as additional risk factors for atrial fibrillation (67).

Preventability

Proven interventions to reduce the risk specifically in the target population of patients with metastatic CRC are currently not known.

Addressing modifiable risk factors (e.g. control of hypertension, good glycaemic management in patients with diabetes) according to standard clinical practice may be expected to minimize the risk.

Impact on the risk-benefit balance of the product:

Impact on individual patient

Atrial fibrillation is a common, age-related arrhythmia that adversely affects quality of life and causes considerable morbidity and mortality.

Public health impact

Since the overall incidence in the Stivarga clinical trial was low and the majority of cases were non-serious, and since it is unclear if there is a true increase in risk relative to background risk in the studied patient population with Stivarga, the public health impact, if any, is likely to be limited.

SVII.3.1.2.3 Reproductive and developmental toxicity

MedDRA terms

MedDRA search strategy:

SMQ: Pregnancy and neonatal topics

Potential mechanisms:

A potential for effects of Stivarga on intrauterine development is expected based on the pharmacological mode of action (in particular, influence on neovascularization) and was confirmed in rabbits at exposures below the anticipated clinical exposure (based on AUC comparison). Main findings consisted of malformations of the urinary system, the heart and major vessels, and the skeleton.

Evidence source(s) and strength of evidence

Regorafenib study report PH-36036

Tables for Risk Management Plan Controlled monotherapy safety set (CMSAF)–EU: Table 3/61, 3/62, 3/63, and 3/64

Tables for Risk Management Plan Monotherapy safety set (MSAF)–EU: Table 3/16, and 3/18

Tables for Risk Management Plan Monotherapy safety set (MSAF)–EU-CONSIGN (15967): Table 3/16

REFINE safety analysis set, patients who did not tolerate sorafenib: Table 14.2.1/15

Characterisation of the risk

Frequency

Phase III clinical trials

- *Controlled Phase III trial population*

In the **CRC/GIST/HCC population**, there were four cases pertaining to reproductive and developmental toxicity (PT Gilbert syndrome, PT Pyloric stenosis; considered unrelated) reported in the Stivarga treatment arm. Three cases were reported in placebo-treated patients. This corresponded to an incidence of 0.35% (95% CI [0.10; 0.89]) for patients treated with Stivarga, and 0.52% (95% CI [0.11; 1.50]) of the placebo-treated patients. The EAIR per 100 subject-years was 0.77 (95% CI [0.21; 1.97)] in the Stivarga group and 1.89 (95% CI [0.39; 5.53]) in the placebo group.

In the **CRC population**, one case reported in the Stivarga treatment arm, two cases were reported in placebo-treated patients. In the Stivarga group, this corresponded to an incidence of 0.16% (95% CI [0.00; 0.87]), while the incidence was 0.62% (95% CI [0.08; 2.23]) in the placebo group. The EAIR per 100 subject-years was 0.44 (95% CI [0.01; 2.45]) for patients treated with Stivarga and 2.70 (95% CI [0.33; 9.74]) for those receiving placebo.

In the **GIST population**, there have been no cases of pregnancy or exposure *via* parent reported in the Stivarga Phase III clinical trial.

In the **HCC population**, the three events were reported in the Stivarga group corresponding to an incidence of 0.80% (95% CI [0.17; 2.33]), whereas one result were found in the placebo group corresponding to an incidence of 0.52% (95% CI [0.01; 2.85]).

- *Phase I-III pooled monotherapy safety set*

Seventeen cases were reported pertaining to reproductive and developmental toxicity (none of these cases were related to any pregnancy or outcome of pregnancy), corresponding to an incidence of 0.37% (95% CI [0.21; 0.58]). The EAIR per 100 subject-years was 0.77 (95% CI [0.45; 1.23]).

Noteworthy, 2,864 of the 4,654 patients included in Phase I-III pooled monotherapy safety set are patients with metastatic CRC treated with regorafenib in the Phase IIIb 15967-CONSIGN trial. This CONSIGN population is overall consistent with the patient population treated within the placebo-controlled Phase III CRC trials 14387-CORRECT and 15808-CONCUR. Incidence rates of treatment-emergent events of interest – using SMQ "Pregnancy and neonatal topics" - were 0.24 (95% CI [0.10; 0.50]) in CONSIGN and 0.31 (95% CI [0.04; 1.13]) for regorafenib-treated patients in CORRECT + CONCUR.

Observational study:

- *The REFINE PASS study safety analysis set (SAF, subgroup of sorafenib intolerant)*

In the REFINE PASS study-subgroup of sorafenib intolerant patients, there was one Grade II event reported pertaining to Reproductive and developmental toxicity, corresponding to an incidence of 1.1% (95% CI [0.0, 6.0]).

Post-marketing data:

Bayer's global safety database was queried for cases as of DLP 26 SEP 2022 reporting at least one or more adverse events from the SMQ: Pregnancy and neonatal topics (SMQ).
Table Part II SVII-9 summarizes the sources of case reports with terms matching the search criteria received for Stivarga since 27 SEP 2012.

Table Part II SVII-9: Sources of cumulative cases with terms matching SMQ: Pregnancy and neonatal topics (SMQ) in Stivarga cases reported since 27 SEP 2012

Source	N	%
Study/observational study	98	56
Spontaneous	58	33

Table Part II SVII-9: Sources of cumulative cases with terms matching SMQ: Pregnancy and neonatal topics (SMQ) in Stivarga cases reported since 27 SEP 2012

Source	N	%
Study/interventional study	15	9
Literature	4	2
Grand Total	**175**	**100**

Countries from which ≥ 5% (n = 9) cases were reported included the US (n = 55 [31%]), China (n = 30 [17%]), Japan (n = 19 [11%]), and France (n = 9 [5%]).

Patient age was reported in 152 (93%) cases and ranged from 24 years to 89 years. Patient's gender was reported in 164 (94%) cases, including 116 (71%) males and 48 (29%) females. The indication for Stivarga use was HCC in 66 (40%) cases, CRC in 19 (11%) cases, and GIST in three (2%) cases.

A total of 175 cases with terms matching the SMQ: Pregnancy and neonatal topics (SMQ) were reported. Of these cases, 102 (58%) were medically confirmed, and 73 (42%) were non-medically confirmed. Of the 175 cases, 138 (79%) were serious and 37 (21%) were non-serious.

There were 196 matching the search criteria from 175 cases. Fatal outcome occurred in six cases (3%) with a matching event. The reporting frequency percentage for these six deaths calculated based on the number of exposed cases according to sales data (N = 372,812, See Section SV.1.2) was 0.002%. Among the six cases with a fatal event matching the search criteria, none had a matching search term that was considered related in the reporter or company assessment.

A lot of cases describe an increase in the Tumour marker alpha 1 fetoprotein and the remaining also describe findings in adult patients unrelated to reproductive or developmental toxicity ("Failure to thrive" and "Choledochal cyst", respectively). Overall, the cases received do not provide meaningful information on regorafenib-induced reproductive and developmental toxicity. The evaluation of the risk remains consistent from the previous information from clinical studies. The risk will continue to be monitored.

Seriousness/outcomes

Phase III clinical trials

- *Controlled Phase III trial population*

In the **CRC/GIST/HCC population**, no event pertaining to reproductive and developmental toxicity (SMQ: Pregnancy and neonatal topics) was considered serious and led to hospitalization in the Stivarga treatment group. In the placebo group, all three events were considered non-serious. The reported terms retrieved via SMQ within the regorafenib treatment arm were "worsening of Gilbert syndrome" and "pyloric digestive obstruction", both not related to pregnancy and related outcomes.

In the **CRC population**, no serious event was reported.

As described above, there have been no cases of pregnancy or exposure *via* parent reported in the **GIST population**.

In the **HCC population** no serious event was reported.

- *Phase I-III pooled monotherapy safety set*

Four of the 17 events were considered to be serious, corresponding to an overall incidence of 0.09%. Two events resulted in a fatal outcome (PT "Failure to thrive" and PT "Neurofibromatosis") and two events required hospitalization. Dose reduction of the study drug became necessary in one case, while two events led to permanent study drug discontinuation. In four non-serious cases, the event was considered to have resolved.

Observational study:

- *The REFINE PASS study safety analysis set (SAF, subgroup of sorafenib intolerant)*

There were no serious events reported in the REFINE PASS study-subgroup of sorafenib intolerant patients.

Post-marketing data:

Of the 196 events matching the search criteria, 83 (42%) had a reported outcome. Of the reported events, ten (11%) were 'recovered/resolved', 37 (46%) were 'not recovered/not resolved', 15 (18%) were 'recovering/resolving', one (1%) was 'recovered/resolved with sequelae' and outcome was 'unknown' in 14 (17%). There were six events (7%) with a matching term that had a fatal outcome.

Severity and nature of risk*:*

Except for two fatal outcomes (Grade V severity; PT "Failure to thrive", unrelated; and PT "Neurofibromatosis"), all events of reproductive and developmental toxicity were of Grade I-III severity in the Phase I-III MSAF.

A potential of Stivarga to adversely affect male and female reproduction has to be considered based on morphological changes in the testes, ovaries, and the uterus observed after repeated dosing in rats and dogs at exposures below the anticipated clinical exposure (based on area under the curve (AUC) comparison). The observed changes were only partially reversible during a 4-week recovery period.

The influence of Stivarga on embryo foetal development was investigated in a pivotal good laboratory practice study in rabbits (PH-36036).

In this study, signs of maternal toxicity were observed at the dose of 1.6 mg/kg/day including a marginal to slight body weight loss, total resorptions and thus a decreased gestation rate. Post-implantation loss was severely increased at this dose level. Therefore, based on the results of this study a no-observed adverse effects level (NOAEL) of 0.8 mg/kg/day could be derived for systemic maternal toxicity.

A treatment related effect on malformations was clearly observed at 1.6 mg/kg/day (mainly findings of the urinary system, the heart, and the axial skeleton) and at 0.8 mg/kg/day (mainly malposition of forelimb(s) or hind limb(s), findings of the heart and major vessels, urinary

system, and skeleton [skull bones, caudal vertebral bodies]). A treatment related effect on external and visceral deviations is assumed for findings of the urinary system at 1.6 mg/kg/day and 0.8 mg/kg/day. Foetal examinations for skeletal retardations and variations revealed increased incidences of fused sternebrae and 7th cervical ribs at 0.8 mg/kg/day and 1.6 mg/kg/day. Therefore, based on these results a NOAEL of 0.4 mg/kg/day for embryo-foetal development could be derived in this study.

Toxicokinetic investigations in steady state conditions on day 20 p.c. showed a dose-linear increase of Stivarga in terms of AUC (0-24) (3.9, 8.8, and 19 mg × h/L) and C_{max} (0.21, 0.53, and 0.99 mg/L) exposure for 0.4, 0.8, and 1.6 mg/kg/day, respectively. The contribution of the metabolites M-2 and M-5 was minor (equal or less than about 2-fold) and independent of the administered dose.

Post-marketing data:

From the global safety data, a total of 196 terms matching the search criteria occurred in 175 cases. Alpha-1-foetoprotein increased (n = 117, 60% of matching terms), Failure to thrive (n = 25, 13%), Alpha-1-foetoprotein decreased (n = 14, 7%), Alpha-1-foetoprotein abnormal (n = 4, 2%), and Maternal exposure during pregnancy (n = 3, 2%), accounted for ≥ 5% (n = 9) of these events. Table Part II SVII-10 below shows terms identified by the search query.

Table Part II SVII-10: Events in the SMQ: Pregnancy and neonatal topics (SMQ) were reported identified in the search query

MedDRA PT	Total	% of events matching the search criteria
Alpha-1-foetoprotein increased	117	60
Failure to thrive	25	13
Alpha-1-foetoprotein decreased	14	7
Alpha-1-foetoprotein abnormal	4	2
Maternal exposure during pregnancy	3	2
Pregnancy of partner	3	2

PT: Preferred term, SMQ: Standardised MedDRA Query

Background incidence/prevalence:

No published articles one the occurrence of reproductive and developmental toxicity are available in patients with metastatic CRC, GIST, or HCC.

It is estimated that approximately only one in 1,000 women are diagnosed with cancer during pregnancy (68), therefore reliable data on the background incidence of intra-uterine and perinatal complications are not available. Of note is also the typical age-distribution of colon cancer, (See Part II: Module SI - Epidemiology of the indication(s) and target population(s)) with the large majority of patients in age-groups > 45 years of age.

A recent registry-based review of 201 pregnancies (including 157 exposed to chemotherapy during pregnancy) reported the rate of congenital malformations in the patients exposed to chemotherapy to be 3.8%, and that this is not higher than in the general population (68).

Risk factors and risk groups

Women of child-bearing potential, their male partners, and the unborn child (if exposed via parent) are the risk groups. However, it should be considered that most of the female patients treated with regorafenib for CRC or GIST are post-menopausal since the disease is rather a disease in the elderly population.

Preventability

To prevent the risk, pregnancy testing in women of child-bearing potential prior to initiation of therapy, and use of effective contraception by female and male patients for the duration of treatment and up to two months after discontinuation of therapy (i.e., at least five times the half-life of the longest-lived Stivarga metabolite M-5, plus a safety margin) is recommended.

Impact on the risk-benefit balance of the product:

Impact on individual patient

This may have life-threatening or fatal consequences for the unborn child. No data in humans are available.

Public health impact

Considering the rare occurrence of cancer during pregnancy, and that there are effective methods to prevent the risk, a public health impact is not anticipated.

SVII.3.2 Presentation of the missing information

SVII.3.2.1 Safety in patients with a cardiac history

Evidence source:

Patient population has not been studied.

Population in need of further characterisation:

No data are available and thus the safety profile will be derived from routine pharmacovigilance activities.

Anticipated risk/consequence of the missing information:

Increased risk of AEs.

Part II: Module SVIII - Summary of the safety concerns

Table Part II SVIII-1: Summary of safety concerns

Important identified risks	• None
Important potential risks	• Interstitial lung disease (ILD) • Atrial fibrillation • Reproductive and developmental toxicity
Missing information	• Safety in patients with a cardiac history

PRES: Posterior reversible encephalopathy syndrome, TMA: Thrombotic microangiopathies

Part III: Pharmacovigilance plan (including post-authorisation safety studies)

III.1 Routine pharmacovigilance activities

Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:

Routine pharmacovigilance was and will be conducted for Stivarga as detailed in corresponding pharmacovigilance procedures that are in place at Bayer. These routine activities include the collection, follow-up, evaluation, and expedited reporting of individual case reports from all respective sources, ongoing monitoring and signal detection activities, preparation of Periodic Benefit-Risk Evaluation Reports (PBRER)/Periodic Safety Update Reports (PSUR), and initiation of label changes as required, and are described in applicable Standard Operating Procedures.

No other routine pharmacovigilance activities beyond adverse reactions reporting and signal detection are currently planned for the safety concerns listed for Stivarga.

III.1.1 Specific adverse reaction follow-up questionnaires for safety concerns

Not applicable

III.1.2 Other forms of routine pharmacovigilance activities for safety concerns

Not applicable for this RMP as there are no other forms of routine PV activities for any of the safety concerns included in this RMP.

III.2 Additional pharmacovigilance activities

No additional pharmacovigilance activities are in place.

A tabulated summary of the completed pharmacovigilance study programme is provided in Annex 2

III.3 Summary table of additional pharmacovigilance activities

Not applicable

Part IV: Plans for post-authorisation efficacy studies

No post-authorisation efficacy studies are ongoing or planned, as it is not warranted.

Part V: Risk minimisation measures (including evaluation of the effectiveness of risk minimisation activities)

V.1 Routine risk minimisation measures

Table Part V-1: Description of routine risk minimisation measures by safety concern

Safety concern	Routine risk minimisation activities
Important identified risks	
None	• None
Important potential risks	
Interstitial lung disease (ILD)	**Routine risk communication:** SmPC: • None **Routine risk minimisation activities recommending specific clinical measures to address the risk:** • None **Other routine risk minimisation measures beyond the Product Information:** • Prescription only medicine
Atrial fibrillation	**Routine risk communication:** SmPC: • None **Routine risk minimisation activities recommending specific clinical measures to address the risk:** • None **Other routine risk minimisation measures beyond the Product Information:** Prescription only medicine
Reproductive and developmental toxicity	**Routine risk communication:** SmPC: • Section 4.6 Fertility, pregnancy and lactation **Routine risk minimisation activities recommending specific clinical measures to address the risk:** • None **Other routine risk minimisation measures beyond the Product Information:**

Table Part V-1: Description of routine risk minimisation measures by safety concern

Safety concern	Routine risk minimisation activities
	• Prescription only medicine
Missing information	
Safety in patients with a cardiac history	**Routine risk communication:** SmPC: • Section 4.4 Special warnings and precautions for use **Routine risk minimisation activities recommending specific clinical measures to address the risk:** • None **Other routine risk minimisation measures beyond the Product Information:** • Prescription only medicine

V.2 Additional risk minimisation measures

No additional risk minimisation activities are considered necessary at this time.

Routine risk minimisation activities as described in Part V.1 are sufficient to manage the safety concerns of the medicinal product.

V.3 Summary of risk minimisation measures

No safety concerns were identified for Stivarga that require additional risk minimisation activities beyond the information provided to healthcare professional and patients in the proposed labelling materials.

Table Part V-2: Summary table of pharmacovigilance activities and risk minimisation activities by safety concern

Safety concern	Risk minimisation measures	Pharmacovigilance activities
Important identified risks		
None	None	**None**
Important potential risks		
Interstitial lung disease (ILD)	**Routine risk minimisation measures:** None **Additional risk minimisation measures:** None	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** None **Additional pharmacovigilance activities:**

Table Part V-2: Summary table of pharmacovigilance activities and risk minimisation activities by safety concern

Safety concern	Risk minimisation measures	Pharmacovigilance activities
		None
Atrial fibrillation	**Routine risk minimisation measures:** None **Additional risk minimisation measures:** None	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** None **Additional pharmacovigilance activities:** None
Reproductive and developmental toxicity	**Routine risk minimisation measures:** • Section 4.6 Fertility, pregnancy and lactation **Additional risk minimisation measures:** None	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** None **Additional pharmacovigilance activities:** None
Missing information		
Safety in patients with a cardiac history	**Routine risk minimisation measures:** • SmPC Section 4.4 Special warnings and precautions for use **Additional risk minimisation measures**: None	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** None **Additional pharmacovigilance activities**: None

PRES: Posterior Reversible Encephalopathy Syndrome, SmPC: Summary of Product Characteristics, TMA: Thrombotic Microangiopathies

Part VI: Summary of the risk management plan

Summary of risk management plan for Stivarga (Regorafenib)

This is a summary of the RMP for Stivarga. The RMP details important risks of Stivarga, how these risks can be minimised, and how more information will be obtained about these risks and uncertainties (missing information).

Stivarga's SmPC and its package leaflet give essential information to healthcare professionals and patients on how Stivarga should be used.

This summary of the RMP for Stivarga should be read in the context of all this information including the assessment report of the evaluation and its plain-language summary, all which is part of the European Public Assessment Report (EPAR).

Important new concerns or changes to the current ones will be included in updates of Stivarga's RMP.

I. The medicine and what it is used for

Stivarga is authorised for

- metastatic colorectal cancer (CRC) who have been previously treated with, or are not considered candidates for, available therapies. These include fluoropyrimidine-based chemotherapy, an anti-VEGF therapy and an anti-EGFR therapy.
- unresectable or metastatic gastrointestinal stromal tumours (GIST) who progressed on or are intolerant to prior treatment with imatinib and sunitinib.
- Hepatocellular carcinoma (HCC) who have been previously treated with sorafenib. (See SmPC for the full indication).

It contains Regorafenib as the active substance and it is given by oral route of administration.

Further information about the evaluation of Stivarga's benefits can be found in Stivarga's EPAR, including in its plain-language summary, available on the EMA website, under the medicine's webpage.

II. Risks associated with the medicine and activities to minimise or further characterise the risks

Important risks of Stivarga, together with measures to minimise such risks and the proposed studies for learning more about Stivarga's risks, are outlined below.

Measures to minimise the risks identified for medicinal products can be:

- Specific information, such as warnings, precautions, and advice on correct use, in the package leaflet and SmPC addressed to patients and healthcare professionals;
- Important advice on the medicine's packaging;
- The authorised pack size — the amount of medicine in a pack is chosen so to ensure that the medicine is used correctly;

- The medicine's legal status — the way a medicine is supplied to the patient (e.g. with or without prescription) can help to minimise its risks.

Together, these measures constitute *routine risk minimisation* measures.

In addition to these measures, information about adverse reactions is collected continuously and regularly analysed, including PBRER/PSUR assessment so that immediate action can be taken as necessary. These measures constitute *routine pharmacovigilance activities*.

If important information that may affect the safe use of Stivarga is not yet available, it is listed under 'missing information' below.

II.A List of important risks and missing information

Important risks of Stivarga are risks that need special risk management activities to further investigate or minimise the risk, so that the medicinal product can be safely taken. Important risks can be regarded as identified or potential. Identified risks are concerns for which there is sufficient proof of a link with the use of Stivarga. Potential risks are concerns for which an association with the use of this medicine is possible based on available data, but this association has not been established yet and needs further evaluation. Missing information refers to information on the safety of the medicinal product that is currently missing and needs to be collected (e.g., on the long-term use of the medicine).

Table Part VI-1: Summary of safety concerns

Important identified risks	• None
Important potential risks	• Interstitial lung disease (ILD) • Atrial fibrillation • Reproductive and developmental toxicity
Missing information	• Safety in patients with a cardiac history

PRES: Posterior reversible encephalopathy syndrome, TMA: Thrombotic microangiopathies

II.B Summary of important risks

Table Part VI-2: Important identified risks, potential risks and missing information

Important identified risk: Not applicable	
Important potential risk: Interstitial lung disease	
Evidence for linking the risk to the medicine	• CTD Module 2.7.4, Section 2.1.5 • Tables for Risk Management Plan Controlled monotherapy safety set (CMSAF) – EU: Table 3/53, 3/54, 3/55, 3/56, and 3/69 • Tables for Risk Management Plan Monotherapy safety set (MSAF)–EU: Table 3/14, 3/18 • Tables for Risk Management Plan Monotherapy safety set (MSAF)–EU - CONSIGN (15967): Table 3/14 • REFINE safety analysis set, patients who did not tolerate sorafenib: Table 14.2.1/13.

Table Part VI-2: Important identified risks, potential risks and missing information

Risk factors and risk groups	Smoking is thought to be a risk factor, as are pre-existing pulmonary pathologies including lung cancer. The incidence also seems to be higher in Japanese patients probably due to ethnic, environmental or clinical practice differences
Risk minimisation measures	None
Important potential risk: Atrial fibrillation	
Evidence for linking the risk to the medicine	• Regorafenib study reports PH-33963, PH-35619, PH-34500 • Tables for Risk Management Plan Controlled monotherapy safety set (CMSAF) – EU: Table 3/65, 3/66, 3/67, and 3/68 • Tables for Risk Management Plan Monotherapy safety set (MSAF)– EU: Table 3/17 • REFINE safety analysis set, patients who did not tolerate sorafenib: Table 14.2.1/14
Risk factors and risk groups	Risk factors for AF that are well established include advancing age, male sex, diabetes mellitus, hypertension, valvular, disease, myocardial infarction, heart failure, obesity, elevated inflammatory marker concentrations, and PR interval prolongation (119).
Risk minimisation measures	None
Important potential risk: Reproductive and developmental toxicity	
Evidence for linking the risk to the medicine	• Regorafenib study report PH-36036 • Tables for Risk Management Plan Controlled monotherapy safety set (CMSAF)–EU: Table 3/61, 3/62, 3/63, and 3/64 • Tables for Risk Management Plan Monotherapy safety set (MSAF)– EU: Table 3/16, and 3/18 • Tables for Risk Management Plan Monotherapy safety set (MSAF)– EU-CONSIGN (15967): Table 3/16 • REFINE safety analysis set, patients who did not tolerate sorafenib: Table 14.2.1/15.
Risk factors and risk groups	Women of child-bearing potential, their male partners, and the unborn child (if exposed via parent) are the risk groups
Risk minimisation measures	Routine risk minimisation measures: • SmPC Section 4.6 Fertility, pregnancy and lactation Additional risk minimisation measures: • None

Table Part VI-2: Important identified risks, potential risks and missing information

Missing information: Safety in patients with a cardiac history	
Risk minimisation measures	Routine risk minimisation measures: • SmPC Section 4.4 Special warnings and precautions for use Additional risk minimisation measures: • None

SmPC: Summary of Product Characteristics, TMA: Thrombotic Microangiopathy, TTP: Thrombocytopenic Purpura, VEGF: Vascular Endothelial Growth Factor.

II.C Post-authorisation development plan

II.C.1 Studies which are conditions of the marketing authorisation

There are no studies which are conditions of the marketing authorisation or specific obligation of Stivarga.

II.C.2 Other studies in post-authorisation development plan

Not applicable

Part VII: Annexes

Table of Contents

Annex 4 - Specific adverse drug reaction follow-up forms

Not applicable

Annex 6 - Details of proposed additional risk minimisation activities (if applicable)

Not applicable