1. NAME OF THE MEDICINAL PRODUCT
Stivarga 40 mg film-coated tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION
Each film-coated tablet contains 40 mg of regorafenib (as monohydrate).

3. PHARMACEUTICAL FORM
Film-coated tablet, as light pink oval shaped tablet.

4. CLINICAL PARTICULARS
4.1 Indication(s)

Colorectal Cancer
Stivarga is indicated for the treatment of patients with metastatic colorectal cancer (CRC) who have been previously treated with fluoropyrimidine-, oxaliplatin- and irinotecan-based chemotherapy, an anti-VEGF therapy, and, if RAS wild type, an anti-EGFR therapy.

Gastrointestinal Stromal Tumors
Stivarga is indicated for the treatment of patients with locally advanced, unresectable or metastatic gastrointestinal stromal tumor (GIST) who have been previously treated with imatinib mesylate and sunitinib malate.

Hepatocellular Carcinoma
Stivarga is indicated for the treatment of patients with hepatocellular carcinoma (HCC) who have been previously treated with sorafenib.

4.2 Dosage and method of administration
4.2.1 Method of administration
For oral use.

4.2.2 Dosage regimen
The recommended dose is 160 mg regorafenib (4 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.

Stivarga should be taken at the same time each day. The tablets should be swallowed whole with water after a light meal. If a dose of Stivarga is missed, then it should be taken on the same day as soon as the patient remembers. The patient should not take two doses on the same day to make up for a missed dose.

Treatment should continue until disease progression or unacceptable toxicity occurs (see section ‘Special warnings and precautions for use’).

4.2.3 Dose modification

If dose modifications are required, reduce the dose in 40 mg (one tablet) increments; the lowest recommended daily dose of STIVARGA is 80 mg daily.

Interrupt Stivarga for the following:

- Grade 2 hand-foot skin reaction (HFSR) [palmar-plantar erythrodysesthesia syndrome (PPES)] that is recurrent or does not improve within 7 days despite dose reduction; interrupt therapy for a minimum of 7 days for Grade 3 HFSR

- Symptomatic Grade 2 hypertension
- Any Grade 3 or 4 adverse reaction
- Worsening infection of any grade

Reduce the dose of Stivarga to 120 mg:

- For the first occurrence of Grade 2 HFSR of any duration
- After recovery of any Grade 3 or 4 adverse reaction except infection
- For Grade 3 aspartate aminotransferase (AST)/ alanine aminotransferase (ALT) elevation; only resume if the potential benefit outweighs the risk of hepatotoxicity

Reduce the dose of Stivarga to 80 mg:

- For re-occurrence of Grade 2 HFSR at the 120 mg dose
- After recovery of any Grade 3 or 4 adverse reaction at the 120 mg dose (except hepatotoxicity or infection)

Discontinue Stivarga permanently for the following:

- Failure to tolerate 80 mg dose
- Any occurrence of AST or ALT more than 20 times the upper limit of normal (ULN)
- Any occurrence of AST or ALT more than 3 times ULN with concurrent bilirubin more than 2 times ULN
- Re-occurrence of AST or ALT more than 5 times ULN despite dose reduction to 120 mg
- For any Grade 4 adverse reaction; only resume if the potential benefit outweighs the risks

4.2.4 Additional information on special populations

4.2.4.1 Patients with hepatic impairment
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 monitoring of overall safety is recommended in these patients (see also sections ‘Special warnings and precautions for use’ and ‘Pharmacokinetic properties’).

Stivarga is not recommended for use in patients with severe hepatic impairment (Child-Pugh C) as Stivarga has not been studied in this population.

4.2.4.2 Patients with renal impairment
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. (see also section ‘Pharmacokinetic properties’).

4.2.4.3 Pediatric patients
The safety and efficacy of Stivarga in children and adolescents below 18 years of age have not been established.

4.2.4.4 Geriatric patients
In clinical studies, no relevant differences in exposure, safety or efficacy were observed between elderly (aged 65 years and above) and younger patients. No dose adjustment is necessary in elderly patients (see also section ‘Pharmacokinetic properties’).

4.2.4.5 Gender
In clinical studies, no relevant differences in exposure, safety or efficacy were observed between male and female patients. No dose adjustment is necessary based on gender (see also section ‘Pharmacokinetic properties’).

4.2.4.6 Ethnic differences
In clinical studies, no relevant differences in exposure or efficacy were observed between patients of different ethnic groups. No dose adjustment is necessary based on ethnicity. A higher incidence of hand foot skin reaction (HFSR), severe liver function test abnormalities and hepatic dysfunction was observed in Asian (in particular Japanese) patients treated with Stivarga as compared with Caucasians. The Asian patients treated with Stivarga in clinical studies were primarily from East Asia (~90%).

4.3 Contraindications
There is no contraindication to the use of Stivarga.

4.4 Special warnings and precautions for use
4.4.1 Hepatic effects

Severe drug induced liver injury with fatal outcome occurred in Stivarga-treated patients in clinical trials. In most cases, liver dysfunction occurred within the first 2 months of therapy and was characterized by a hepatocellular pattern of injury.

In the CORRECT study, fatal hepatic failure occurred in 1.6% of patients in the regorafenib arm and in 0.4% of patients in the placebo arm. In the GRID study, fatal hepatic failure occurred in 0.8% of patients in the regorafenib arm. In the RESORCE study, there was no increase in the incidence of fatal hepatic failure as compared to placebo (see section Undesirable effects).

Obtain liver function tests (ALT, AST, and bilirubin) before initiation of Stivarga and monitor at least every two weeks during the first 2 months of treatment. Thereafter, monitor monthly or more frequently as clinically indicated. Monitor liver function tests weekly in patients experiencing elevated liver function tests until improvement to less than 3 times the ULN or baseline.

Temporarily hold and then reduce or permanently discontinue Stivarga depending on the severity and persistence of hepatotoxicity as manifested by elevated liver function tests or hepatocellular necrosis (see section Dosage and method of administration).

4.4.2 Infections

Stivarga has been associated with an increased incidence of infection events, some of which were fatal (see section ‘Undesirable effects’).
In cases of worsening infection events, interruption of Stivarga treatment should be considered.

4.4.3 Hemorrhage

Stivarga caused an increased incidence of hemorrhage. The overall incidence (Grades 1-5) was 18.2% in 1142 patients treated with Stivarga and 9.5% in patients receiving placebo in randomized, placebo-controlled trials. The incidence of grade 3 or greater hemorrhage in patients treated with Stivarga was 3.0%. The incidence of fatal hemorrhagic events was 0.7% involving the central nervous system or the respiratory, gastrointestinal, or genitourinary tracts.

Permanently discontinue Stivarga in patients with severe or life-threatening hemorrhage. Monitor INR levels more frequently in patients receiving warfarin (see Pharmacological properties).

4.4.4 Gastrointestinal perforation and fistula
Gastrointestinal perforation (including fatal outcomes) and fistulae have been reported in patients treated with Stivarga (see section 'Undesirable effects'). These events are also known to be common disease-related complications in patients with intra-abdominal malignancies. Discontinuation of Stivarga is recommended in patients developing gastrointestinal perforation or fistula. The safety of reinitiating Stivarga therapy following gastrointestinal perforation or fistula is not known.

4.4.5 Cardiac ischemia and infarction

Stivarga increased the incidence of myocardial ischemia and infarction (0.9% versus. 0.2%) in randomized placebo-controlled trials (see section Undesirable effects).
Withhold Stivarga in patients who develop new or acute onset cardiac ischemia or infarction. Resume Stivarga only after resolution of acute cardiac ischemic events if the potential benefits outweigh the risks of further cardiac ischemia.

4.4.6 Reversible Posterior Leukoencephalopathy Syndrome

Reversible Posterior Leukoencephalopathy Syndrome (RPLS), a syndrome of subcortical vasogenic edema diagnosed by characteristic finding on MRI, occurred in one of 4800 Stivarga-treated patients across all clinical trials. Perform an evaluation for RPLS in any patient presenting with seizures, severe headache, visual disturbances, confusion or altered mental function. Discontinue Stivarga in patients who develop RPLS.

4.4.7 Arterial hypertension
In randomized, placebo-controlled trials, hypertensive crisis occurred in 0.2% of patients in the regorafenib arms and in none of the patients in the placebo arms. Stivarga caused an increased incidence of hypertension (30% versus 8% in CORRECT, 61% versus 26% in GRID, and 31% versus 6% in RESORCE) (see section Undesirable effects). The onset of hypertension occurred during the first cycle of treatment in most patients who developed hypertension (67% in randomized, placebo-controlled trials). Do not initiate Stivarga unless blood pressure is adequately controlled. Monitor blood pressure weekly for the first 6 weeks of treatment and then every cycle, or more frequently, as clinically indicated. Temporarily or permanently withhold Stivarga for severe or uncontrolled hypertension (see section Dosage and method of administration).

4.4.8 Aneurysms and artery dissections
The use of VEGF pathway inhibitors in patients with or without hypertension may promote the formation of aneurysms and/or artery dissections. Before initiating Stivarga, this risk should be carefully considered in patients with risk factors such as hypertension or history of aneurysm.

4.4.9 Wound healing complications

No formal studies of the effect of regorafenib on wound healing have been conducted. Since vascular endothelial growth factor receptor (VEGFR) inhibitors such as regorafenib can impair wound healing, treatment with regorafenib should be stopped at least 2 weeks prior to scheduled surgery. The decision to resume regorafenib after surgery should be based on clinical judgment of adequate wound healing. Regorafenib should be discontinued in patients with wound dehiscence.

4.4.10 Dermatological toxicity
In randomized, placebo-controlled trials, adverse skin reactions occurred in 71.9% of patients in the regorafenib arm and in 25.5% of patients in the placebo arm, including hand-foot skin reaction (HFSR) also known as palmar-plantar erythrodysesthesia syndrome (PPES), and severe rash requiring dose modification.

In the randomized, placebo-controlled trials, the overall incidence of HFSR was higher in 1142 Stivarga-treated patients (53%)than in the placebo-treated patients (8%). Most cases of HFSR in Stivarga-treated patients appeared during the first cycle of treatment. The incidences of Grade 3 HFSR (16% versus <1%), Grade 3 rash (3% versus <1%), serious adverse reactions of erythema multiforme (<0.1% vs. 0%) and Stevens-Johnson Syndrome (<0.1% vs. 0%) were also higher in Stivarga treated patients (see section Undesirable effects). Across all trials, a higher incidence of HFSR was observed in Asian patients treated with Stivarga (all grades: 72%; Grade 3: 18%).

Toxic epidermal necrolysis occurred in 0.02%of 4518 Stivarga-treated patients across all clinical trials of Stivarga administered as a single agent.

Withhold Stivarga, reduce the dose or permanently discontinue Stivarga depending on the severity and persistence of dermatologic toxicity (see section Dosage and method of administration). Institute supportive measures for symptomatic relief.

4.4.11 Biochemical and metabolic laboratory test abnormalities
Stivarga has been associated with an increased incidence of electrolyte abnormalities (including hypophosphatemia, hypocalcemia, hyponatremia and hypokalemia) 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 (see section ‘Dosage and method of administration’ – subsection ‘Dose modification’).

4.4.12 Disease-specific precautions – Hepatocellular carcinoma (HCC)
In the pivotal placebo-controlled phase III study, patients received prior therapy with sorafenib.
There is insufficient data on patients who discontinued sorafenib therapy due to sorafenib-related toxicity or only tolerated a low dose (< 400 mg daily) of sorafenib. The tolerability of Stivarga in these patients has not been established.

4.5 Interaction with other medicinal products and other forms of interaction
4.5.1 Inhibitors / inducers of CYP3A4

Effect of Strong CYP3A4 Inducers on Regorafenib:
Co-administration of a strong CYP3A4 inducer (rifampin) with a single 160 mg dose of Stivarga decreased the mean exposure of regorafenib, increased the mean exposure of the active metabolite M-5, and resulted in no change in the mean exposure of the active metabolite M-2. Avoid concomitant use of strong CYP3A4 inducers (e.g. rifampin, phenytoin, carbamazepine, phenobarbital, and St. John's Wort) [see Pharmacological properties].

Effect of Strong CYP3A4 Inhibitors on Regorafenib:
Co-administration of a strong CYP3A4 inhibitor (ketoconazole) with a single 160 mg dose of Stivarga increased the mean exposure of regorafenib and decreased the mean exposure of the active metabolites M-2 and M-5. Avoid concomitant use of strong inhibitors of CYP3A4 activity (e.g. clarithromycin, grapefruit juice, itraconazole, ketoconazole, posaconazole, telithromycin, and voriconazole) [see Pharmacological properties].

4.5.2 Inhibitors / inducers of Breast cancer resistance protein (BCRP) and P-glycoprotein
In vitro data indicate that the active metabolites M-2 and M-5 are substrates for BCRP and P-glycoprotein. Inhibitors and inducers of BRCP and P-glycoprotein may interfere with the exposure of M-2 and M-5. The clinical significance of these findings is unknown.

4.5.3 UGT1A1 and UGT1A9 substrates
In vitro data indicate that regorafenib as well as its active metabolite M-2 inhibit glucuronidation mediated by uridine diphosphate glucuronosyl transferases UGT1A1 and UGT1A9, whereas M-5 only inhibits UGT1A1 at concentrations which are achieved *in vivo* at steady state.

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

4.5.4 Breast cancer resistant protein (BCRP) and P-glycoprotein substrates

Administration of regorafenib (160 mg for 14 days) prior to administration of a single 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.

4.5.5 CYP isoform-selective substrates
In vitro data indicate that regorafenib is a competitive inhibitor of the cytochromes CYP2C8, CYP2C9, CYP2B6 at concentrations which are achieved *in vivo* at steady state (peak plasma concentration of 8.1 micromolar). The *in vitro* inhibitory potency towards CYP3A4 and CYP2C19 was less pronounced.
A clinical probe substrate study was performed to evaluate the effect of 14 days of dosing with 160 mg regorafenib on the pharmacokinetics of probe substrates of CYP2C8 (rosiglitazone), CYP2C9 (S-warfarin), CYP 2C19 (omeprazole) and CYP3A4 (midazolam).
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').

4.5.6 Antibiotics

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 gastrointestinal 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.

4.6 Fertility, pregnancy and lactation
4.6.1 Pregnancy

Risk Summary
Based on its mechanism of action, Stivarga can cause fetal harm when administered to a pregnant woman. There are no adequate and well-controlled studies with Stivarga in pregnant women. Regorafenib was embryolethal and teratogenic in rats and rabbits at exposures lower than human exposures at the recommended dose, with increased incidences of cardiovascular, genitourinary, and skeletal malformations. If this drug is used during pregnancy or if the patient becomes pregnant while taking this drug, the patient should be apprised of the potential hazard to a fetus.

Animal Data
In embryo-fetal development studies, a total loss of pregnancy (100% resorption of litter) was observed in rats at doses as low as 1 mg/kg (approximately 6% of the recommended human dose, based on body surface area) and in rabbits at doses as low as 1.6 mg/kg (approximately 25% of the human exposure at the clinically recommended dose measured by AUC).

In a single dose distribution study in pregnant rats, there was increased penetration of regorafenib across the blood-brain barrier in fetuses compared to dams. In a repeat dose study with daily administration of regorafenib to pregnant rats during organogenesis, findings included delayed ossification in fetuses at doses ≥ 0.8 mg/kg (approximately 5% of the recommended human dose based on body surface area) with dose-dependent increases in skeletal malformations including cleft palate and enlarged fontanelle at doses ≥ 1 mg/kg (approximately 10% of the clinical exposure based on AUC). At doses ≥ 1.6 mg/kg (approximately 11% of the recommended human dose based on body surface area), there were dose dependent increases in the incidence of cardiovascular malformations, external abnormalities, diaphragmatic hernia, and dilation of the renal pelvis.

In pregnant rabbits administered regorafenib daily during organogenesis, there were findings of ventricular septal defects evident at the lowest tested dose of 0.4 mg/kg (approximately 7% of the AUC in patients at the recommended dose). At doses of ≥ 0.8 mg/kg (approximately 15% of the human exposure at the recommended human dose based on AUC), administration of regorafenib resulted in dose-dependent increases in the incidence of additional cardiovascular malformations and skeletal anomalies as well as significant adverse effects on the urinary system including missing kidney/ureter; small, deformed and malpositioned kidney; and hydronephrosis. The proportion of viable fetuses that were male decreased with increasing dose in two rabbit embryo-fetal toxicity studies.

4.6.2 Lactation

It is unknown whether regorafenib or its metabolites are excreted in human milk. In rats, regorafenib and its metabolites are excreted in milk. Because many drugs are excreted in human milk and because of the potential for serious adverse reactions in nursing infants from Stivarga, a decision should be made whether to discontinue nursing or discontinue the drug, taking into account the importance of the drug to the mother.

4.6.3 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 (see section 'Preclinical safety data').

4.6.4 Women of childbearing potential / Contraception
Women of childbearing potential must be informed that regorafenib may cause fetal harm.
Women of childbearing potential and men should ensure effective contraception during treatment and up to 8 weeks after completion of therapy.

4.7 Effects on ability to drive or use machines
No studies on the effects of Stivarga on the ability to drive or use machines have been performed.

4.8 Undesirable effects
Clinical Trials Experience
Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rate observed in practice.

The data described in the WARNINGS AND PRECAUTIONS section reflect exposure to STIVARGA in more than 4800 patients who were enrolled in four randomized, placebo-controlled trials (n=1142), an expanded access program (CONSIGN, n=2864), or single arm clinical trials (single agent or in combination with other agents). There were 4518 patients who received STIVARGA as a single agent; the distribution of underlying malignancies was 80% CRC, 4% GIST, 10% HCC, 6% other solid tumors; and 74% were White, 11% Asian, and 15% race not known. Among these 4518 patients, 83% received STIVARGA for at least 21 days and 20% received STIVARGA for 6 months or longer.

In randomized placebo-controlled trials (CORRECT, GRID, RESORCE and CONCUR), the most frequently observed adverse drug reactions (≥20%) in patients receiving Stivarga are pain (including gastrointestinal and abdominal pain), HFSR, asthenia/fatigue, HFSR, diarrhea, decreased appetite/food intake, hypertension, infection, dysphonia, hyperbilirubinemia, fever, mucositis, weight loss, rash, and nausea.

Colorectal Cancer
The safety data described below, except where noted, are derived from a randomized (2:1), double-blind, placebo-controlled trial (CORRECT) in which 500 patients (median age 61 years; 61% men) with previously-treated metastatic colorectal cancer (CRC) received Stivarga as a single agent at the dose of 160 mg daily for the first 3 weeks of each 4 week treatment cycle and 253 patients (median age 61 years; 60% men) received placebo. The median duration of therapy was 1.7 months (range 2 days, 10.8 months) for patients receiving Stivarga. Due to adverse reactions, 61% of the patients receiving Stivarga required a dose interruption and 38% of the patients had their dose reduced. Adverse reactions that resulted in treatment discontinuation occurred in 8.2% of Stivarga-treated patients compared to 1.2% of patients who received placebo. Hand-foot skin reaction (HFSR) and rash were the most common reasons for permanent discontinuation of Stivarga.

Table 1 provides the incidence of adverse reactions (≥10%) in patients in CORRECT.

Table 1: Adverse drug reactions reported in ≥10% of patients treated with Stivarga in CORRECT and reported more commonly than in patients receiving placebo[a].

Adverse Reactions	**Stivarga (N=500)**		**Placebo (N=253)**	
	Grade		**Grade**	
	All %	**≥ 3 %**	**All %**	**≥ 3 %**
General disorders and administration site conditions				
Asthenia/ fatigue	64	15	46	9
Pain	59	9	48	7
Fever	28	2	15	0

Metabolism and nutrition disorders				
Decreased appetite and food intake	47	5	28	4
Skin and subcutaneous tissue disorders				
HFSR/PPES	45	17	7	0
Rash [b]	26	6	4	<1
Gastrointestinal disorders				
Diarrhea	43	8	17	2
Mucositis	33	4	5	0
Investigations				
Weight loss	32	<1	10	0
Infections and infestations				
Infection [c]	31	9	17	6
Vascular disorders				
Hypertension	30	8	8	<1
Hemorrhage [c]	21	2	8	<1
Respiratory, thoracic and mediastinal disorders				
Dysphonia	30	0	6	0
Nervous system disorders				
Headache	10	<1	7	0

[a] Adverse reactions graded according to National Cancer Institute Common Toxicity for Adverse Events version 3.0 (NCI CTCAE v3.0).

[b] [a]The term rash represents reports of events of drug eruption, rash, erythematous rash, generalized rash, macular rash, maculo-papular rash, papular rash, and pruritic rash.

[c]Fatal outcomes observed

Gastrointestinal Stromal Tumors

The safety data described below are derived from a randomized (2:1), double-blind, placebo-controlled trial (GRID) in which 132 patients (median age 60 years; 64% men) with previously treated GIST received Stivarga as a single agent at a dose of 160 mg daily for the first 3 weeks of each 4 week treatment cycle and 66 patients (median age 61 years; 64% men) received placebo. The median duration of therapy was 5.7 months (range 1 day, 11.7 months) for patients receiving Stivarga. Dose interruptions for adverse events were required in 58% of patients receiving Stivarga and 50% of patients had their dose reduced. Adverse reactions that resulted in treatment discontinuation were reported in 2.3% of Stivarga-treated patients compared to 1.5% of patients who received placebo.

Table 2 provides the incidence of adverse reactions (≥10%) in patients in GRID.

Table 2 Adverse reactions reported in ≥10% of patients treated with Stivarga in GRID and reported more commonly than in patients receiving placebo[a]

Adverse Reactions	**Stivarga (N=132)**		**Placebo (N=66)**	
	Grade		**Grade**	
	All %	**≥ 3 %**	**All %**	**≥ 3 %**
Skin and subcutaneous tissue disorders				
HFSR/PPE	67	22	12	2
Rash [b]	30	7	3	0
Alopecia	24	2	2	0
General disorders and administration site conditions				
Asthenia/Fatigue	52	4	39	2

Fever	21	0	11	2
Vascular disorders				
Hypertension	61	29	26	5
Hemorrhage	11	4	3	0
Gastrointestinal disorders				
Pain	60	8	55	14
Diarrhea	47	8	9	0
Mucositis	40	2	8	2
Nausea	20	2	12	2
Vomiting	17	<1	8	0
Respiratory, thoracic and mediastinal disorders				
Dysphonia	39	0	9	0
Infections and infestations				
Infection [c]	32	5	5	0
Metabolism and nutrition disorders				
Decreased appetite and food intake	31	<1	21	3
Hypothyroidism [d]	18	0	6	0
Nervous system disorders				
Headache	16	0	9	0
Investigations				
Weight loss	14	0	8	0
Musculoskeletal and connective tissue disorders				
Muscle spasms	14	0	3	0

[a] Adverse reactions graded according to NCI CTCAE v4.0.
[b]a The term rash represents reports of events of rash, erythematous rash, macular rash, maculo-papular rash, papular rash and pruritic rash.
[c] Fatal outcomes observed.
[d]Hypothyroidism incidence based on subset of patients with normal TSH and no thyroid supplementation at baseline.

Hepatocellular Carcinoma

The safety data described below are derived from a randomized (2:1), double-blind, placebo-controlled trial (RESORCE) in which patients with previously-treated HCC received either STIVARGA (n=374) 160 mg orally on days 1-21 of each 4 week treatment cycle or placebo (n=193). The median age was 63 years, 88% were men, 98% had Child-Pugh A cirrhosis, 66% had an ECOG performance status (PS) of 0 and 34% had PS of 1. The median duration of therapy was 3.5 months (range 1 day to 29.4 months) for patients receiving STIVARGA. Of the patients receiving STIVARGA, 33% were exposed to STIVARGA for greater than or equal to 6 months and 14% were exposed to STIVARGA for greater than or equal to 12 months. Dose interruptions for adverse events were required in 58.3% of patients receiving STIVARGA and 48% of patients had their dose reduced. The most common adverse reactions requiring dose modification (interruption or dose reduction) were HFSR/PPES (20.6%), blood bilirubin increase (5.9%), fatigue (5.1%) and diarrhea (5.3%). Adverse reactions that resulted in treatment discontinuation were reported in 10.4% of STIVARGA-treated patients compared to 3.6% of patients who received placebo; the most common adverse reactions requiring discontinuation of STIVARGA were HFSR/PPES (1.9%) and AST increased (1.6%).

Table 3 provides the incidence of adverse reactions (≥10%) in patients in RESORCE.

Table 3: Adverse reactions reported in ≥10% of patients treated with STIVARGA in RESORCE and reported more commonly than in patients receiving placebo [a]

Adverse Reactions	STIVARGA (N=374)		Placebo (N=193)	
	Grade		Grade	
	All %	≥ 3 %	All %	≥ 3 %
Skin and subcutaneous tissue disorders				
HFSR/PPE	52	12	7	<1
General disorders and administration site conditions				
Pain	56	9	44	8
Asthenia/Fatigue	42	10	33	5
Fever	20	0	7	0
Vascular disorders				
Hypertension	31	15	6	5
Hemorrhage [b]	18	5	16	8
Gastrointestinal disorders				
Diarrhea	42	3	15	0
Nausea	18	<1	13	0
Vomiting	13	<1	7	<1
Mucositis	13	1	2	≤1
Respiratory, thoracic and mediastinal disorders				
Dysphonia	18	0	2	0
Infections and infestations				
Infection [b]	31	8	18	6
Metabolism and nutrition disorders				
Decreased appetite and food intake	31	3	15	2
Investigations				
Weight loss	14	2	4	0
Musculoskeletal and connective tissue disorders				
Muscle spasms	10	0	2	0

[a] Adverse reactions graded according to NCI CTCAE v4.0.
[b] Fatal outcomes observed.

Other clinically significant adverse reactions observed in less than 10% of STIVARGA-treated patients were: alopecia (7%), hypothyroidism (6.7%), pancreatitis (1.6%), exfoliative rash (1.3%), tremor (1.3%), erythema multiforme (0.8%), myocardial ischemia (0.8%), gastrointestinal fistula (0.3%), and myocardial infarction (0.3%).

4.8.3 Description of selected adverse reactions

4.8.3.1 Hemorrhage

In the two placebo-controlled phase III trials, the overall incidence of hemorrhage was 18.2% in patients treated with Stivarga and 9.5% in patients receiving placebo. Most cases of bleeding events in patients treated with Stivarga were mild to moderate in severity (Grades 1 and 2: 15.2%), most notably epistaxis

(6.1%). Fatal outcome in patients treated with Stivarga was uncommon (0.7%), and included cerebral respiratory, gastrointestinal and genitourinary events.

4.8.3.2 Infections
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 1 and 2: 23.0%), and included urinary tract infections (5.7%), nasopharyngitis (4.0%), mucocutaneous and systemic fungal infections (3.3%) as well as pneumonia (2.6%). Fatal outcomes associated with infection were observed more often in patients treated with Stivarga (1.0%) as compared to patients receiving placebo (0.3%), and were mainly respiratory events.

4.8.3.3 Hand-foot skin reaction
In the placebo-controlled phase III trials, hand-foot skin reaction (HFSR) were more often observed in patients treated with Stivarga as compared to patients receiving placebo (all grades: 51.4% vs 6.5% CRC, 66.7% vs. 15.2% GIST and 51.6% vs. 7.3% HCC). Most cases of HFSR in patients treated with Stivarga appeared during the first cycle of treatment and were mild to moderate in severity (Grades 1 and 2: 34.3% CRC, 44.7%, GIST and 39.3% HCC). The incidence of Grade 3 HFSR was 17.1% (CRC), 22.0% (GIST) and 12.3% (HCC). A higher incidence of HFSR was observed in Stivarga-treated Asian patients (all grades: 74.8% CRC, 88.2%, GIST and 67.1% HCC and Grade 3: 20.5% CRC, 23.5% GIST and 13.5% HCC) (see also section 'Dosage and method of administration' – subsection 'Additional information on special populations').

4.8.3.4 Hypertension
In the placebo-controlled phase III trials, the overall incidence of hypertension was higher in patients treated with Stivarga as compared to patients receiving placebo (29.6% vs. 7.5% CRC, 60.6% vs. 25.8% GIST and 31.0% vs. 6.2% HCC).Most cases of hypertension in patients treated with Stivarga appeared during the first cycle of treatment and were mild to moderate in severity (Grades 1 and 2: 20.9%, CRC, 31.8% GIST and 15.8% HCC). The incidence of Grade 3 hypertension was 8.7% (CRC), 28.0% (GIST) and 15.2% (HCC). One case of Grade 4 hypertension was reported in the GIST trial.

4.8.3.5 Severe liver injury
In most cases of severe liver injury, liver dysfunction had an onset within the first 2 months of therapy, and was characterized by a hepatocellular pattern of injury with transaminase elevations >20xULN, followed by bilirubin increase. In clinical trials, a higher incidence of severe liver injury with fatal outcome was observed in Japanese patients (~1.5%) treated with Stivarga compared with non-Japanese patients(<0.1%).

4.8.4 Laboratory test abnormalities
Laboratory Abnormalities
Table 4 provides laboratory abnormalities observed in CORRECT.

Table 4: Laboratory test abnormalities reported in CORRECT

Laboratory Parameter	Stivarga (N=500[a])			Placebo (N=253[a])		
	Grade [b]			Grade [b]		
	All %	3 %	4 %	All %	3 %	4 %
Blood and lymphatic system disorders						
Anemia	79	5	1	66	3	0
Thrombocytopenia	41	2	<1	17	<1	0
Neutropenia	3	1	0	0	0	0
Lymphopenia	54	9	0	35	4	<1

Metabolism and nutrition disorders						
Hypocalcemia	59	1	<1	18	1	0
Hypokalemia	26	4	0	8	<1	0
Hyponatremia	30	7	1	22	4	0
Hypophosphatemia	57	31	1	11	4	0
Hepatobiliary disorders						
Hyperbilirubinemia	45	10	3	17	5	3
Increased AST	65	5	1	46	4	1
Increased ALT	45	5	1	30	3	<1
Renal and urinary disorders						
Proteinuria [c]	84	2	0	61	1	0
Investigations						
Increased INR [d]	24	4	N/A	17	2	N/A
Increased Lipase	46	9	2	19	3	2
Increase Amylase	26	2	<1	17	2	<1

[a] % based on number of patients with post-baseline samples which may be less than 500 (regorafenib) or 253 (placebo)
[b] NCI CTCAE v3.0
[c] Based on urine protein-creatinine ratio data
[d]International normalized ratio: No Grade 4 denoted in NCI CTCAE, v3.0

Compared to the global phase III CRC trial (CORRECT) with predominantly (~80%) Caucasian patients enrolled, a higher incidence of liver enzyme increases was observed in Stivarga treated patients in the Asian phase III CRC trial (CONCUR) with predominantly (>90%) East Asian patients enrolled:

Table 4a: Treatment emergent liver enzyme test abnormalities reported in placebo-controlled phase III trial in Asian patients with metastatic CRC (CONCUR)

Laboratory parameter, (in % of samples investigated)	**Stivarga plus BSC§ (N=136)**			**Placebo plus BSC§ (N=68)**		
	All Grades*	Grade 3*	Grade 4*	All Grades*	Grade 3*	Grade 4*
Bilirubin increased	66.7	7.4	4.4	32.8	4.5	0.0
AST increased	69.6	10.4	0.7	47.8	3.0	0.0
ALT increased	54.1	8.9	0.0	29.9	1.5	0.0

§ Best Supportive Care

* Common Terminology Criteria for Adverse Events (CTCAE), Version 4.0

Table 5 provides laboratory abnormalities observed in GRID.

Table 5 Laboratory test abnormalities reported in GRID

Laboratory Parameter	**Stivarga**	**Placebo**

	(N=132[a])			(N=66[a])		
	Grade [b]			Grade [b]		
	All %	**3 %**	**4 %**	**All %**	**3 %**	**4 %**
Blood and lymphatic system disorders						
Thrombocytopenia	13	1	0	2	0	2
Neutropenia	16	2	1	12	3	0
Lymphopenia	30	8	0	24	3	0
Metabolism and nutrition disorders						
Hypocalcemia	17	2	0	5	0	0
Hypokalemia	21	3	0	3	0	0
Hypophosphatemia	55	20	2	3	2	0
Hepatobiliary disorders						
Hyperbilirubinemia	33	3	1	12	2	0
Increased AST	58	3	1	47	3	0
Increased ALT	39	4	1	39	2	0
Renal and urinary disorders						
Proteinuria[c]	59	3	-[d]	53	3	-[d]
Investigations						
Increased Lipase	14	0	1	5	0	0

[a]% based on number of patients with post-baseline samples which may be less than 132 (regorafenib) or 66 (placebo).
[b]NCI CTCAE, v4.0.
[c] Based on urine protein-creatinine ratio data.
[d] No Grade 4 denoted in NCI CTCAE, v4.0.

Table 6 provides laboratory abnormalities observed in RESORCE.

Table 6: Laboratory test abnormalities reported in RESORCE

Laboratory Parameter	STIVARGA (N=374 [a])			Placebo (N=193 [a])		
	Grade [b]			Grade [b]		
	All %	3 %	4 %	All %	3 %	4 %
Blood and lymphatic system disorders						
Thrombocytopenia	63	5	<1	50	0	0
Neutropenia	14	3	0	15	<1	<1
Lymphopenia	68	16	2	59	11	<1
Metabolism and nutrition disorders						
Hypocalcemia	23	<1	0	10	0	0
Hypokalemia	31	4	<1	9	2	0
Hypophosphatemia	70	32	2	31	7	0
Hepatobiliary disorders						
Hyperbilirubinemia	78	13	3	55	11	5
Increased AST	93	16	2	84	17	3
Increased ALT	70	6	<1	59	5	0
Renal and urinary disorders						
Proteinuria [c]	51	17	- [d]	37	3	- [d]
Investigations						
Increased INR	44	<1	- [d]	35	2	- [d]
Increased Lipase	41	11	3	27	8	1
Increased Amylase	23	3	<1	19	2	<1

§ Best Supportive Care
[a] Percent based on number of patients with post-baseline samples which may be less than 374 (regorafenib) or 193 (placebo).
[b] NCI CTCAE v4.0.
[c] Based on dipstick data.
[d] No Grade 4 denoted in NCI CTCAE v4.0.

Postmarketing Experience
The following adverse reaction has been identified during postapproval use of Stivarga. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure:

- hypersensitivity reaction

4.9 Overdose
The highest dose of Stivarga studied clinically was 220 mg per day. The most frequently observed adverse drug reactions at this dose were dermatological events, dysphonia, diarrhea, mucosal inflammation, dry mouth, decreased appetite, hypertension, and fatigue.
There is no specific antidote for Stivarga overdose. In the event of suspected overdose, interrupt Stivarga, institute supportive care, and observe until clinical stabilization.

5. PHARMACOLOGICAL PROPERTIES
5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antineoplastic agents, Protein kinase inhibitor
ATC Code: L01XE21

5.1.1 Mechanism of action and pharmacodynamic effects
Regorafenib is an oral tumor deactivation agent that potently blocks multiple protein kinases, including kinases involved in tumor angiogenesis (VEGFR1, -2, -3, TIE2), oncogenesis (KIT, RET, RAF-1, BRAF, BRAFV600E), metastasis (VEGFR3, PDGFR, FGFR) and tumor immunity (CSF1R). In particular, regorafenib inhibits mutated KIT, a major oncogenic driver in gastrointestinal stromal tumors, and thereby blocks tumor cell proliferation. In preclinical studies regorafenib has demonstrated potent antitumor activity in a broad spectrum of tumor models including colorectal, gastrointestinal stromal and hepatocellular tumor models which is likely mediated by its antiangiogenic and antiproliferative effects. In addition, regorafenib reduced the level of tumor associated macrophages and has shown anti-metastatic effects *in vivo*. Major human metabolites (M-2 and M-5) exhibited similar efficacies compared to regorafenib in *in vitro* and *in vivo* models.

5.1.2 Clinical efficacy and safety

5.1.2.1 <u>Metastatic colorectal cancer (CRC)</u>
The clinical efficacy and safety of Stivarga have been evaluated in an international, multi-center, randomized, double-blind, placebo-controlled phase III study (CORRECT) in heavily pre-treated patients with metastatic colorectal cancer who have progressed after failure of standard therapy.
The primary efficacy endpoint was Overall Survival (OS). Secondary endpoints were Progression-Free Survival (PFS), objective tumor response rate and disease control rate.
In total, 760 patients were randomized 2:1 to receive 160 mg regorafenib (4 tablets Stivarga each containing 40 mg regorafenib) orally once daily (N=505) plus Best Supportive Care (BSC) or matching placebo (N=255) plus BSC for 3 weeks on therapy followed by 1 week off therapy. The mean daily regorafenib dose received was 147 mg.
Patients continued therapy until disease progression or unacceptable toxicity. A pre-planned interim analysis for efficacy was performed when 432 deaths had occurred. The study was un-blinded after this planned interim analysis of OS had crossed the pre-specified efficacy boundary, showing evidence of prolonged survival with Stivarga plus BSC compared to placebo plus BSC.
Of the 760 randomized patients, the median age was 61 years, 61% were male, 78% were Caucasian, and all patients had baseline ECOG Performance Status (PS) of 0 or 1. PS2 patients and patients with baseline dehydration ≥ 1 were excluded from the pivotal trial. The primary site of disease was colon (65%), rectum (29%), or both (6%). A KRAS mutation was reported in 57% of patients at study entry. Most patients received 3 or fewer previous lines of treatment for metastatic disease. Therapies included treatment with fluoropyrimidine-based chemotherapy, an anti-VEGF therapy, and, if the patient was KRAS wild type, an anti-EGFR therapy.
The addition of Stivarga to BSC resulted in significantly longer survival as compared to placebo plus BSC with a p-value of 0.005178 from stratified log rank test, a hazard ratio of 0.774 [95% CI 0.636, 0.942] and a median OS of 6.4 months vs. 5.0 months (see Table 7and Figure 1). PFS was significantly longer in patients receiving Stivarga plus BSC (hazard ratioHR: 0.494, p<0.000001, see Table 7 and Figure 2).
*the 1-sided p-value for the CORRECT study was 0.005178

Table 7: Efficacy Results from the CORRECT study

Efficacy parameter	Hazard Ratio* (95% CI)	P-value (one-sided)	Median (95% CI)	
			Stivarga plus BSC§ (N=505)	Placebo plus BSC§ (N=255)
Overall Survival	0.774	0.005178	6.4 months	5.0 months

	(0.636, 0.942)		(5.9, 7.3)	(4.4, 5.8)
Progression-Free Survival**	0.494 (0.419, 0.582)	<0.000001	1.9 months (1.9, 2.1)	1.7 months (1.7, 1.7)

§Best Supportive Care
*** Hazard ratio < 1 favors Stivarga**
**** based on investigator's assessment of tumor response**

Figure 1: Kaplan-Meier curves of Overall Survival

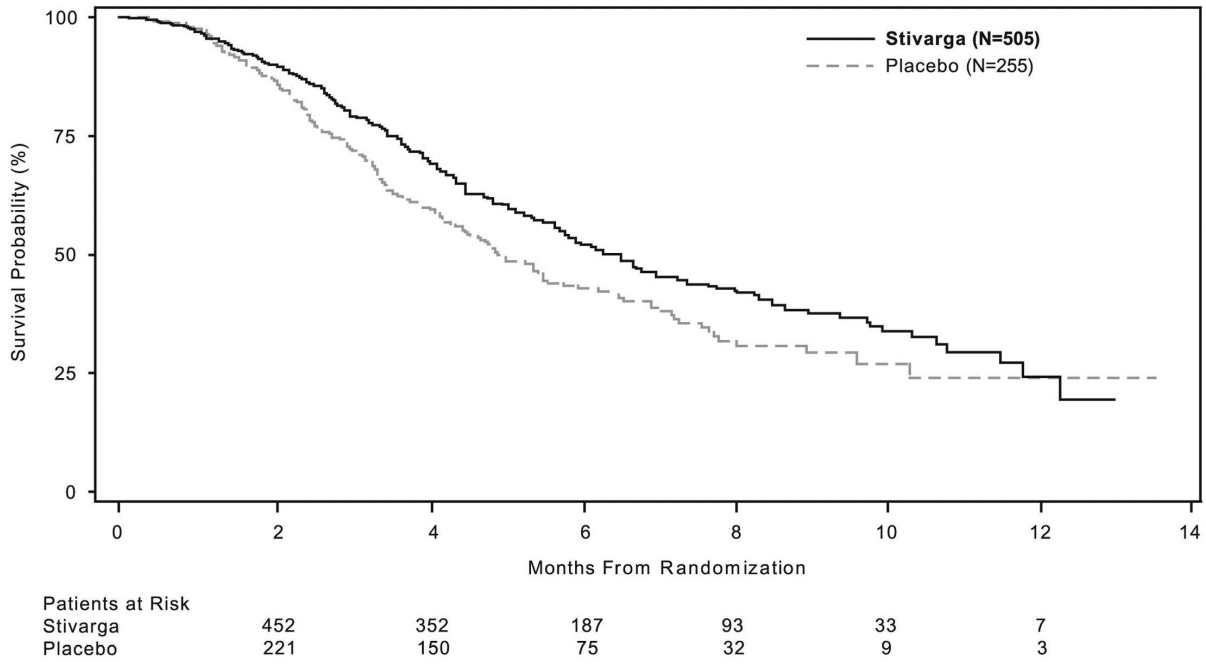
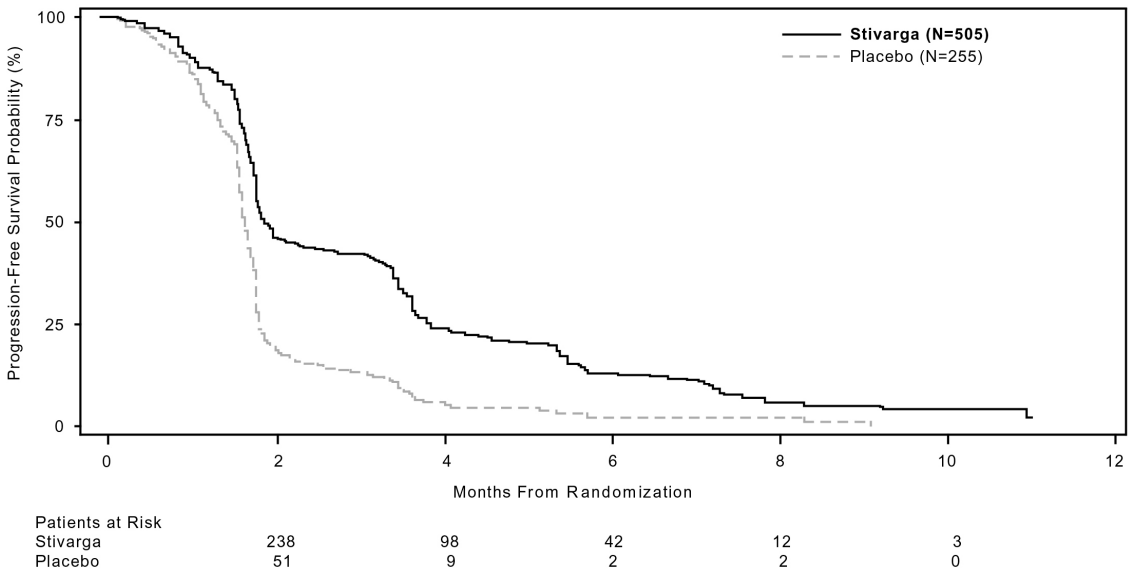


Figure 2: Kaplan-Meier curves of Progression-Free Survival



The OS and PFS benefit were consistently independent of age, KRAS mutation status, and number of previous treatment lines. The response rate (complete response or partial response) was 1% and 0.4% for Stivarga and placebo treated patients, respectively (p=0.188432, 1-sided). No complete responses were observed. The disease control rate (complete response or partial response or stable disease) was significantly higher in patients treated with Stivarga (41.0% vs 14.9%, p<0.000001, 1-sided).

A second phase III, international, multi-center, randomized, double-blind, placebo-controlled study (CONCUR) evaluated the efficacy and safety of Stivarga in 204 pre-treated Asian patients (> 90% East Asian) with metastatic colorectal cancer who have progressed after failure of fluoropyrimidine-based chemotherapy. One hundred twenty-two patients in CONCUR were also previously treated with VEGF- or EGFR-targeted agents.

The primary efficacy endpoint was OS. The addition of Stivarga to BSC resulted in a significantly longer survival, as compared to placebo plus BSC with a hazard ratio of 0.550 (p = 0.000159 stratified log rank test) and a median OS of 8.8 months vs. 6.3 months [95% CI 0.395, 0.765]. PFS was also significantly longer in patients receiving Stivarga plus BSC (hazard ratio: 0.311, p<0.000001).

The safety profile of Stivarga plus BSC in the CONCUR study was consistent with the safety profile observed in the CORRECT study.

A third, prospective, open-label, single-arm, multicenter, phase III B study (CONSIGN) was conducted in patients with metastatic colorectal cancer whose disease had progressed after treatment with standard therapies to confirm the safety of Stivarga in a large cohort of patients (n = 2872).

Inclusion criteria were the same as in the CORRECT study. The safety profile of Stivarga in the CONSIGN study was consistent with the safety profile observed in the CORRECT and CONCUR studies.

The median PFS, assessed by investigators, was 2.7 months (95% CI 2.6, 2.7) which was comparable to the efficacy observed in the previous phase III studies.

5.1.2.2 Gastrointestinal stromal tumors (GIST)
The clinical efficacy and safety of regorafenib have been evaluated in an international, multi-center, randomized, double-blind, placebo-controlled phase III (GRID) study in patients with gastrointestinal stromal tumors (GIST) previously treated with 2 tyrosine kinase inhibitors (imatinib and sunitinib).

The analysis of the primary efficacy endpoint Progression-Free Survival (PFS) was conducted after 144 PFS events (central blinded assessment). Secondary endpoints including Time To Progression (TTP) and Overall Survival (OS) (interim analysis) were also assessed.

In total, 199 patients with GIST were randomized 2:1 to receive either 160 mg regorafenib plus Best Supportive Care (BSC; n=133) orally once daily or matching placebo plus BSC (n=66) for 3 weeks on therapy followed by 1 week off therapy. The mean daily regorafenib dose received was 140 mg.

Patients continued therapy until disease progression or unacceptable toxicity. Patients receiving placebo who experienced disease progression were offered open-label regorafenib (cross-over option). Patients receiving regorafenib who experienced disease progression and for whom in the investigator's opinion, treatment with regorafenib was providing clinical benefit, were offered the opportunity to continue open-label regorafenib.

Of the 199 randomized patients, the mean age was 58 years, 64% were male, 68% were Caucasian, and all patients had baseline ECOG Performance Status of 0 or 1. The overall median time since most recent progression or relapse to randomization was 6 weeks.

Regorafenib plus BSC resulted in significantly longer PFS as compared to placebo plus BSC with a hazard ratio of 0.268 [95% CI 0.185, 0.388] and a median PFS of 4.8 months vs. 0.9 months ($p < 0.000001$). The relative risk of disease progression or death was reduced by approximately 73.2% in regorafenib-treated patients compared to placebo treated patients (see Table 8, Figure 3).The increase in PFS was consistent independent of age, sex, geographic region, prior lines of treatment, ECOG performance status.

TTP was significantly longer in the patients receiving regorafenib plus BSC than in patients receiving placebo plus BSC with a hazard ratio of 0.248 [95% CI 0.170, 0.364], and a median TTP of 5.4 months vs. 0.9 months ($p<0.000001$) (see Table 8).

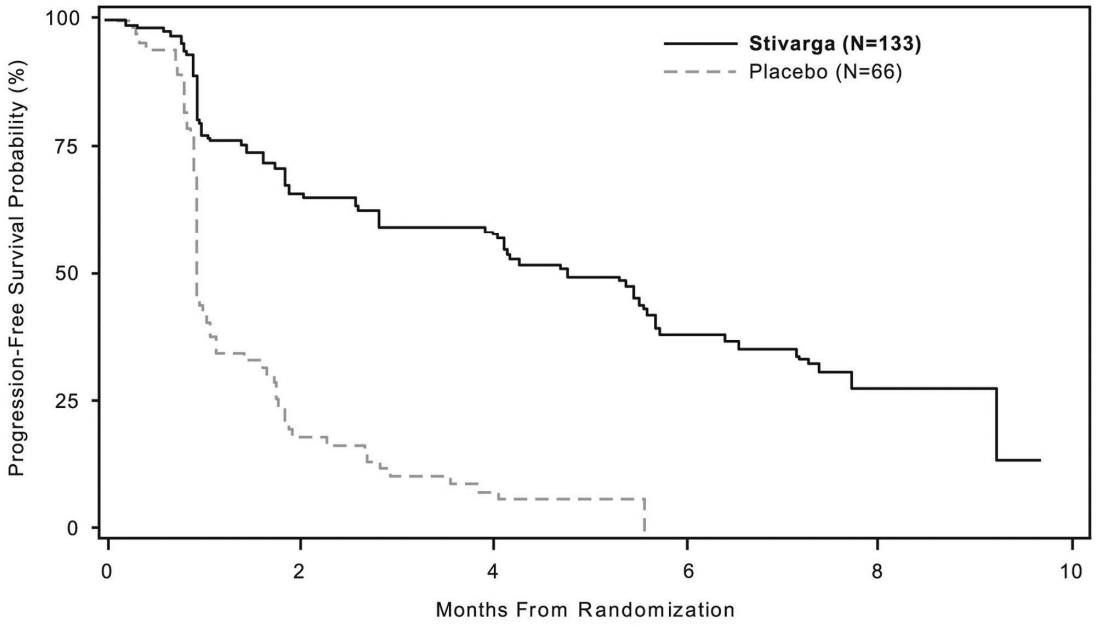
The HR of the OS analysis indicated a trend towards a positive treatment effect (HR = 0.772 [95% CI, 0.423, 1.408]; p = 0.199; median OS not reached in either arm) despite the post-progression cross-over of 85% of patients initially randomized to the placebo arm (see Table 8, Figure 4).

Table 8: Efficacy Results from the GRID study

Efficacy parameter	Hazard Ratio* (95% CI)	P-value (one-sided)	Median (95% CI)	
			Stivarga plus BSC§ (N=133)	Placebo plus BSC§ (N=66)
Progression-Free Survival	0.268 (0.185, 0.388)	<0.000001	4.8 months (4.0, 5.7)	0.9 months (0.9, 1.1)
Time To Progression	0.248 (0.170,0.364)	<0.000001	5.4 months (4.1, 5.7)	0.9 months (0.9, 1.1)
Overall Survival	0.772 (0.423, 1.408)	0.199	NR**	NR**

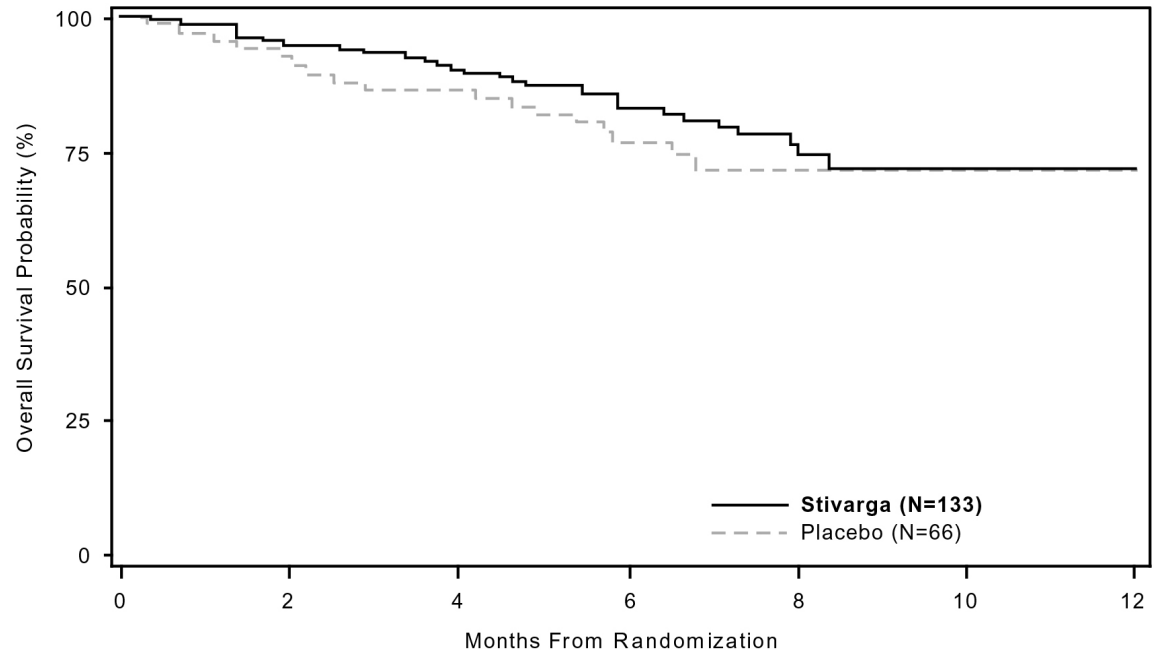
§Best Supportive Care
* Hazard ratio < 1 favors Stivarga
** NR: not reached

Figure 3: Kaplan-Meier curves of Progression-Free Survival



Patients at Risk				
Stivarga	82	72	27	9
Placebo	12	5	0	0

Figure 4: Kaplan-Meier curves of Overall Survival



Patients at Risk						
Stivarga	126	119	94	39	10	1
Placebo	61	57	41	16	3	1

In addition, 56 placebo plus BSC patients received open-label Stivarga after cross-over following disease progression and a total of 41 Stivarga plus BSC patients continued Stivarga treatment after disease progression. The median secondary PFS (as measured by the investigator's assessment) were 5.0 and 4.5 months, respectively.

5.1.2.3. Hepatocellular carcinoma (HCC)

The clinical efficacy and safety of Stivarga have been evaluated in an international, multi-center, randomized, double-blind, placebo-controlled phase III study (RESORCE) in patients with hepatocellular carcinoma who have been previously treated with sorafenib.

The primary efficacy endpoint was Overall Survival (OS). Secondary endpoints were Progression-Free Survival (PFS), Time To Progression (TTP), Objective Tumor Response Rate (ORR) and Disease Control Rate (DCR).

In total, 573 patients with HCC were randomized 2:1 to receive either 160 mg regorafenib orally once daily (n=379) plus Best Supportive Care (BSC) or matching placebo (n=194) plus BSC for 3 weeks on therapy followed by 1 week off therapy. The mean daily regorafenib dose received was 144 mg. Patients were eligible to participate in the study if they experienced radiological disease progression during treatment with sorafenib and if they had a liver function status of Child-Pugh class A. Patients who permanently discontinued sorafenib therapy due to sorafenib-related toxicity or who tolerated less than 400 mg sorafenib once daily prior to withdrawal were excluded from the study. Randomization was performed within 10 weeks after the last treatment with sorafenib. Patients continued therapy with Stivarga until clinical or radiological disease progression or unacceptable toxicity. However, patients could continue Stivarga therapy past progression at the discretion of the investigator.

Demographics and baseline disease characteristics were similar between the Stivarga- and placebo-treated groups and are shown below for all 573 randomized patients:

- Median age: 63 years
- Male: 88%
- Caucasian: 36%, Asian: 41%
- ECOG performance status of 0: 66%, ECOG performance status of 1: 34%
- Child-Pugh A: 98%, Child-Pugh B: 2%
- Etiology included Hepatitis B (38%), Hepatitis C (21%), Non-Alcoholic Steato Hepatitis (NASH, 7%)
- Absence of both macroscopic vascular invasion and extra-hepatic tumor spread: 19%
- Barcelona Clinic Liver Cancer (BCLC) stage B: 13%; BCLC stage C: 87%
- Loco-regional transarterial embolization or chemoinfusion procedures: 61%
- Radiotherapy prior to regorafenib treatment: 15%
- Median duration of sorafenib treatment: 7.8 months

The median duration of treatment was 3.6 months on Stivarga and 1.9 months on placebo.

The addition of Stivarga to BSC resulted in a significantly better overall survival as compared to placebo plus BSC with a hazard ratio of 0.624 [95% CI 0.498, 0.782], p=0.000017 stratified log rank test, and a median OS of 10.6 months vs. 7.8 months (see Table 9 and Figure 5).

The median OS from start of sorafenib in the Stivarga treatment arm was 26.0 months [95% CI 22.6, 28.1] and 19.2 months [95% CI 16.0, 22.8] in the placebo arm.

PFS was significantly better in patients receiving Stivarga plus BSC, than in patients receiving placebo plus BSC with a hazard ratio of 0.453 [95% CI 0.369, 0.555], p<0.000001 stratified log rank test, and a median PFS of 3.1 months vs. 1.5 months (see Table 9 and Figure 6).

TTP was significantly better in patients receiving Stivarga plus BSC, than in patients receiving placebo plus BSC with a hazard ratio of 0.439 [95% CI 0.355,0.542], p<0.000001 stratified log rank test, and a median TTP of 3.2 months vs. 1.5 months (see Table 9).

OS, PFS and TTP advantages were consistent across all subsets analyzed.

The response rate (complete response or partial response) was 11% for Stivarga and 4% for placebo treated patients (p=0.003650). The disease control rate (complete response, partial response and stable disease maintained for 6 weeks) was significantly higher in patients treated with Stivarga (65% vs. 36%, p<0.000001). Patients' health-related quality-of-life and health utility values were measured with FACT-Hepatobiliary (FACT-HEP) and EQ-5D questionnaires, respectively. There was no clinically meaningful difference between Stivarga and placebo as measured by FACT-HEP total score, EQ-5D index score and EQ-5D VAS.

Table 9: Efficacy Results from the RESORCE study

Efficacy parameter	Hazard Ratio* (95% CI)	P-value (one-sided)	Median (95% CI)	
			Stivarga plus BSC§ (N=379)	Placebo plus BSC§ (N=194)
Overall Survival	0.624 (0.498, 0.782)	0.000017	10.6 months (9.1, 12.1)	7.8 months (6.3, 8.8)
Progression-Free Survival **	0.453 (0.369, 0.555)	<0.000001	3.1 months (2.8, 4.2)	1.5 months (1.4, 1.6)
Time To Progression **	0.439 (0.355,0.542)	<0.000001	3.2 months (2.9, 4.2)	1.5 months (1.4, 1.6)

§ Best Supportive Care

* Hazard ratio < 1 favors Stivarga

** based on investigator's assessment of tumor response by modified RECIST

Figure 5: Kaplan-Meier curve of Overall Survival

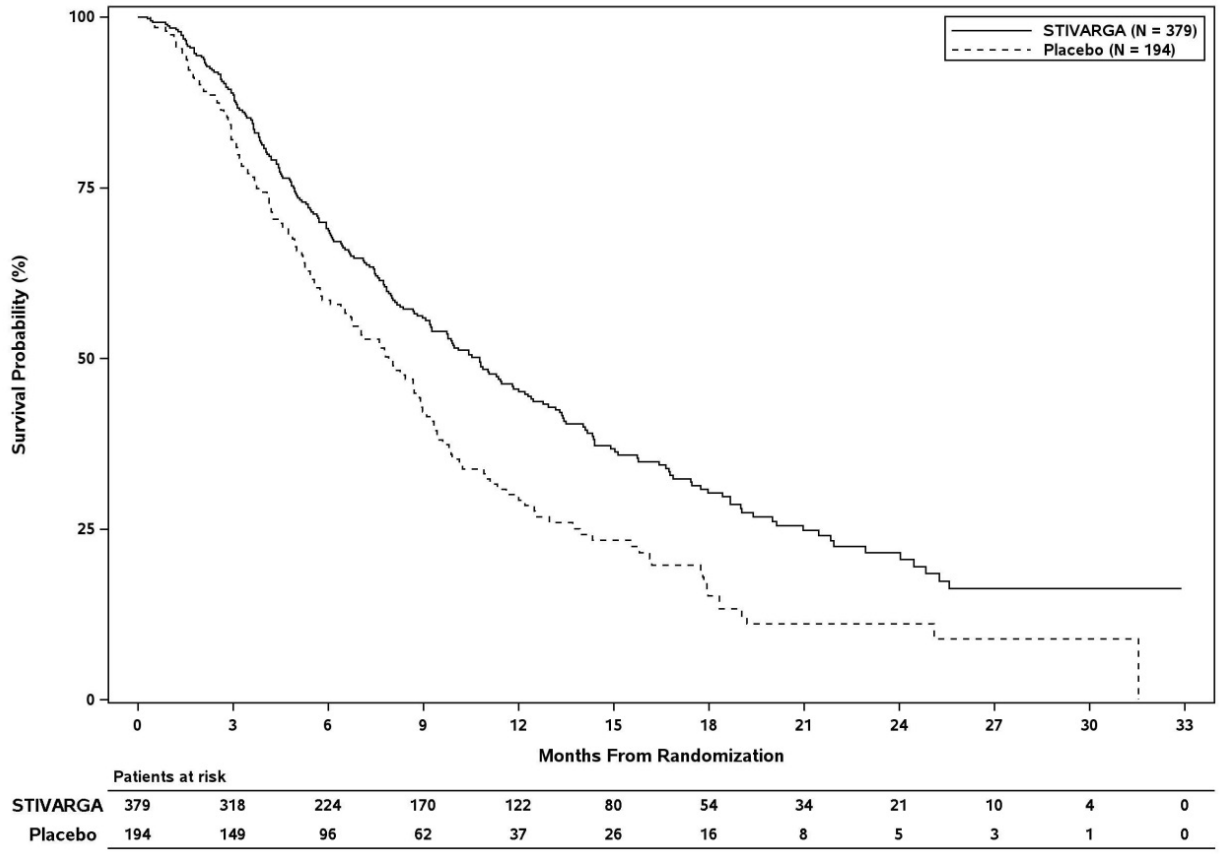
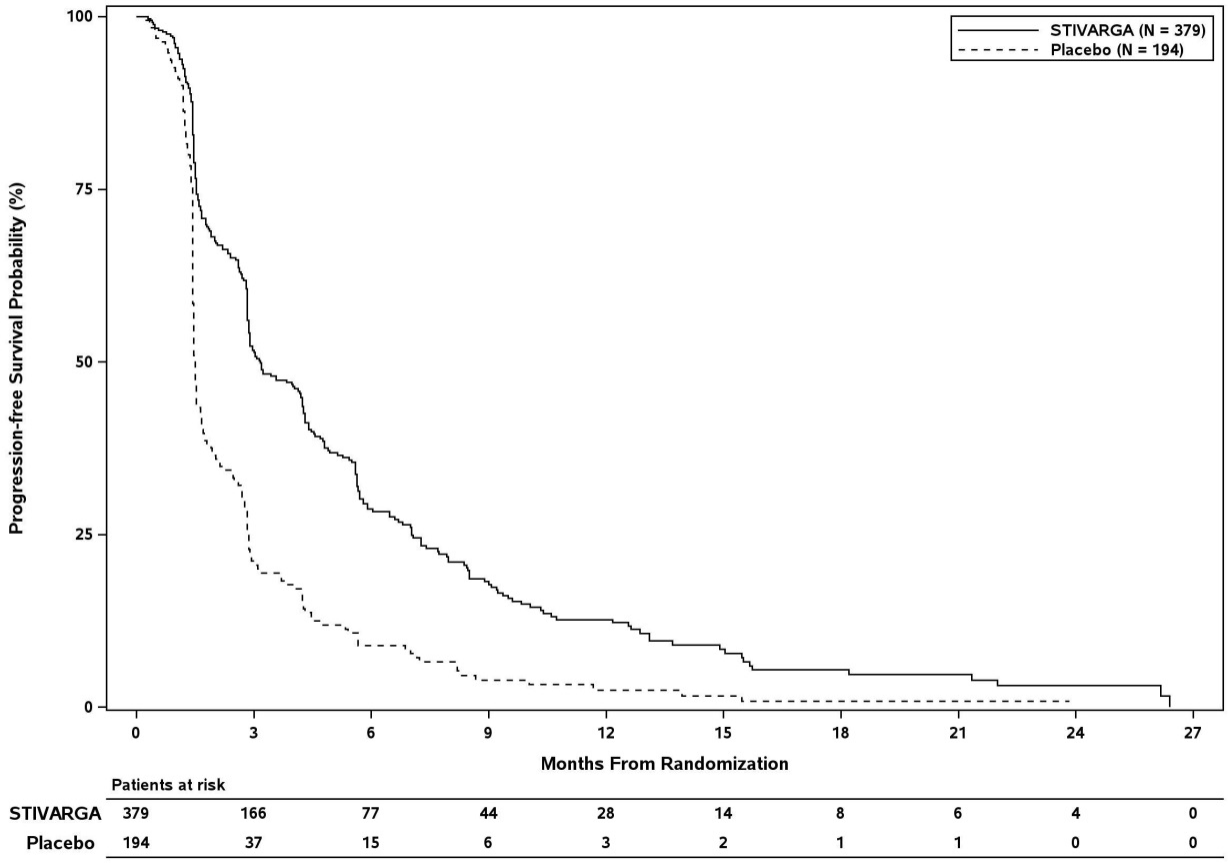


Figure 6: Kaplan-Meier curve of Progression-Free Survival (mRECIST)



5.2 Pharmacokinetic properties

5.2.1 Absorption

Regorafenib reaches mean peak plasma levels of about 2.5 mg/L at about 3 to 4 hours after single oral dose of 160 mg regorafenib given as 4 tablets each containing 40 mg. The mean relative bioavailability of tablets compared to an oral solution is 69-83%.

The concentrations of regorafenib and its major pharmacologically active metabolites M-2 (N-oxide) and M-5 (N-oxide and N-desmethyl) were highest when given after a low-fat (light) breakfast as compared to either a high-fat breakfast or fasting condition. The exposure for regorafenib was increased by 48% when administered with high-fat breakfast, and 36% when administered with a low fat breakfast, compared to fasting. The exposures of metabolite M-2 and M-5 are higher when regorafenib is given with low fat breakfast as compared to fasting condition and lower when given with a high fat meal as compared to fasting condition.

5.2.2 Distribution

Plasma concentration-time profiles for regorafenib as well as for the major circulating metabolites showed multiple peaks across the 24-hour dosing interval, which are attributed to enterohepatic circulation. *In vitro* protein binding of regorafenib to human plasma proteins is high (99.5%).

5.2.3 Metabolism / Biotransformation

Regorafenib is metabolized primarily in the liver by oxidative metabolism mediated by CYP3A4, as well as by glucuronidation mediated by UGT1A9. Two major and six minor metabolites of regorafenib have been identified in plasma. The main circulating metabolites of regorafenib in human plasma are M-2 (N-oxide) and M-5 (N-oxide and N-desmethyl), which are pharmacologically active and have similar concentrations as regorafenib at steady state.

- *In vitro* protein binding of M-2 and M-5 is higher (99.8% and 99.95%, respectively) than that of regorafenib (99.5%).

Metabolites may be reduced or hydrolyzed in the gastrointestinal tract by microbial flora, allowing reabsorption of the unconjugated drug and metabolites (enterohepatic circulation). Co-administration of a single dose of regorafenib after pre-treatment with neomycin (a poorly absorbed antimicrobial agent that eradicates the gastrointestinal microflora) had no significant effect on the exposure of regorafenib. There was a decrease in the exposure of M-2 and M-5 by 76% and 86%, respectively.

5.2.4 Elimination

Following a single 160 mg oral dose of Stivarga, the geometric mean (range) elimination half-lives for regorafenib and the M-2 metabolite in plasma are 28 hours (14 to 58 hours) and 25 hours (14 to 32 hours), respectively. M-5 has a longer mean (range) elimination half-life of 51 hours (32 to 70 hours). Approximately 71% of a radiolabeled dose was excreted in feces (47% as parent compound, 24% as metabolites) and 19% of the dose was excreted in urine (17% as glucuronides) within 12 days after administration of a radiolabeled oral solution at a dose of 120 mg.

5.2.5 Linearity/non-linearity
Systemic exposure of regorafenib at steady-state increases dose proportionally up to 60 mg and less than proportionally at doses greater than 60 mg. Accumulation of regorafenib at steady state results in about a 2-fold increase in plasma concentrations, which is consistent with the elimination half-life and dosing frequency. At steady state, regorafenib reaches mean peak plasma levels of about 3.9 mg/L (8.1 micromolar) after oral administration of 160 mg regorafenib and the peak-to-trough ratio of mean plasma concentrations is less than 2.

Both metabolites, M-2 and M-5, exhibit non-linear accumulation. Whereas plasma concentrations of M-2 and M-5 after a single dose of regorafenib are much lower than those of parent compound, steady-state plasma concentrations of M-2 and M-5 are comparable to those of regorafenib.

5.2.6 Additional information on special populations
5.2.6.1 Patients with hepatic impairment
The pharmacokinetics of Stivarga in Child-Pugh A and B (mild to moderate) hepatically impaired patients were similar to the pharmacokinetics in patients with normal hepatic function. There are no data for patients with Child-Pugh C (severe) hepatic impairment. Regorafenib is mainly eliminated via the liver, and exposure might be increased in this patient population.

5.2.6.2 Patients with renal impairment
Available clinical data and physiology-based pharmacokinetic modeling indicate similar steady-state 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.
The pharmacokinetics of regorafenib has not been studied in patients with end-stage renal disease. However, physiology-based pharmacokinetic modeling does not predict any relevant change in exposure in these patients.

5.2.7 Cardiac Electrophysiology/QT prolongation
No QTc prolonging effects were observed after administration of 160 mg regorafenib at steady state in a dedicated QT study in male and female cancer patients.

5.2.8 Drug-drug interactions
In vitro screening on cytochrome P450 enzymes: In vitro studies with human hepatic microsomes or recombinant enzymes showed that regorafenib competitively inhibits CYP2C8, CYP2C9, CYP2B6, CYP3A4, and CYP2C19 with R1 values > 1.1; M-2 inhibits CYP2C9, CYP2C8, CYP3A4, and CYP2D6 with R1 values > 1.1 and M-5 inhibits CYP2C8 with a R1 value > 1.1. In vitro studies with primary human

hepatocytes showed that regorafenib is not expected to induce CYP1A2, CYP2B6, CYP2C19, and CYP3A4 enzyme activity.

In vitro screening on uridine diphosphate glucuronosyltransferases: In vitro studies with human hepatic microsomes showed that regorafenib, M-2, and M-5 competitively inhibits UGT1A9 and UGT1A1 at therapeutically relevant concentrations.

In vitro screening on transporters: In vitro data showed that regorafenib is an inhibitor of ABCG2 (Breast Cancer Resistance Protein) and ABCB1 (P-glycoprotein).

Effect of CYP3A4 Strong Inducers on Regorafenib: Twenty-two healthy men received a single 160 mg dose of Stivarga alone and then 7 days after starting rifampin. Rifampin, a strong CYP3A4 inducer, was administered at a dose of 600 mg daily for 9 days. The mean AUC of regorafenib decreased by 50% and mean AUC of M-5 increased by 264%. No change in the mean AUC of M-2 was observed [see Interaction with other medicinal products and other forms of interaction].

Effect of CYP3A4 Strong Inhibitors on Regorafenib: Eighteen healthy men received a single 160 mg dose of Stivarga alone and then 5 days after starting ketoconazole. Ketoconazole, a strong CYP3A4 inhibitor, was administered at a dose of 400 mg daily for 18 days. The mean AUC of regorafenib increased by 33% and the mean AUC of M-2 and M-5 both decreased by 93%.

Effect of regorafenib on a substrate of UGT1A1 substrates: Eleven patients received irinotecan-containing combination chemotherapy with Stivarga at a dose of 160 mg. The mean AUC of irinotecan increased 28% and the mean AUC of SN-38 increased by 44% when irinotecan was administered 5 days after the last of 7 daily doses of Stivarga.

5.3 Preclinical safety data

5.3.1 Systemic 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, thyroid gland, lympho-/hematopoietic system, endocrine system, reproductive system and skin. These effects occurred at systemic exposures in the range of or below the anticipated human exposure (based on AUC comparison).
Alterations of teeth and bones and adverse effects in the reproductive system were more pronounced in young and growing animals as well as in juvenile rats and indicate a potential risk for children and adolescents.

5.3.2 Genotoxicity and carcinogenicity

Studies on the carcinogenic potential of regorafenib have not been performed.

There was no indication for a genotoxic potential of regorafenib tested in standard assays in vitro and in vivo in mice.

5.3.3 Reproductive and developmental toxicity

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 human exposure (based on AUC comparison). The observed changes were only partially reversible.
An effect of regorafenib on intrauterine development was shown in rabbits at exposures below the anticipated human exposure (based on AUC comparison). Main findings consisted of malformations of the urinary system, the heart and major vessels, and the skeleton.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet core:
Cellulose microcrystalline
Croscarmellose sodium
Magnesium stearate
Povidone
Silica, colloidal anhydrous

Film coat:
Iron oxide red
Iron oxide yellow
Lecithin (derived from soy)
Macrogol
Polyvinyl alcohol, partially hydrolyzed
Talc
Titanium dioxide

6.2 Incompatibilities
Not applicable.

6.3 Shelf life
Please refer to labels.

Keep the bottle tightly closed after first opening. Once the bottle is opened the medicinal product has shown to be stable for 7 weeks. Thereafter, the product is to be discarded.

6.4 Special precautions for storage
Store below 30°C. Store in the original package in order to protect from moisture.
Keep the desiccant in the bottle.

6.5 Nature and contents of container
Bottle of 28 tablets
Single bottle pack and pack of 3 bottles per package with a desiccant.
Not all pack sizes may be marketed.

6.6 Instructions for use/handling
Press down the closure according to instructions on the cap while turning to the left. Keep the bottle tightly closed after first opening. The desiccant capsule must not be consumed.
Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

Product Registrant:
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Date of revision: March 2020