Product Monograph

Including Patient Medication Information

PrSTIVARGA®

regorafenib tablets

For oral use

40 mg

Multikinase Inhibitor – Antineoplastic

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Mississauga, Ontario
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Recent Major Label Changes

Not applicable

Table of Contents

Sections or subsections that are not applicable at the time of authorization are not listed.

Part 1: Healthcare Professional Information

1 Indications

STIVARGA (regorafenib) is indicated for:

- Treatment of patients with metastatic colorectal cancer (CRC) who have been previously treated with fluoropyrimidine-based chemotherapy, oxaliplatin, irinotecan, an anti-VEGF therapy, and, if *RAS* wild type, an anti-EGFR therapy.
- Treatment of adult patients with metastatic and/or unresectable gastrointestinal stromal tumors (GIST) who have had disease progression on or intolerance to imatinib mesylate and sunitinib malate treatment. Approval of STIVARGA is based on Progression Free Survival (PFS) (see 14 Clinical Trials).
- Treatment of patients with hepatocellular carcinoma (HCC) who have been previously treated with sorafenib.

1.1 Pediatrics

Pediatrics (<18 years of age): The safety and efficacy of regorafenib in pediatric patients has not been established; therefore, Health Canada has not authorized an indication for pediatric use (see 7.1.3 Pediatrics).

1.2 Geriatrics

Geriatrics (≥65 years of age): No differences in safety or efficacy were observed between older and younger patients (see 14 Clinical Trials).

2 Contraindications

STIVARGA is contraindicated in patients who are hypersensitive to regorafenib or sorafenib or any ingredient in the formulation, including any non-medicinal ingredient, or component of the container. For a complete listing, see 6 Dosage Forms, Strengths, Composition and Packaging.

3 Serious Warnings and Precautions Box

STIVARGA should be prescribed by a qualified healthcare professional who is experienced in the use of antineoplastic therapy.
STIVARGA has not been studied in patients with severe hepatic impairment.
The following are clinically significant adverse events:

- Hepatotoxicity including fatal cases (see 7 Warnings and Precautions – Hepatic/Biliary/Pancreatic)
- Hemorrhage (including gastrointestinal and respiratory tracts) including fatal cases (see 7 Warnings and Precautions – Hematologic)
- Cardiac ischemia and infarction (see 7 Warnings and Precautions – Cardiovascular)
- Reversible Posterior Leukoencephalopathy Syndrome (see 7 Warnings and Precautions – Neurologic)
- Gastrointestinal perforation and fistula including fatal cases (see 7 Warnings and Precautions – Gastrointestinal)
- Arterial hypertension (see 7 Warnings and Precautions – Cardiovascular)
- Hand-Foot Skin Reaction (see 7 Warnings and Precautions – Skin)
- Infections including fatal cases (see 7 Warnings and Precautions - Infections)

4 Dosage and Administration

4.2 Recommended Dose and Dosage Adjustment

The recommended dose of STIVARGA is 160 mg (4 tablets, 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.

Treatment should continue as long as benefit is observed or until unacceptable toxicity occurs (see 7 Warnings and Precautions).

Dose modification

Interrupt STIVARGA for the following:

- NCI CTCAE Version 3.0 (v3.0) Grade 2 hand-foot skin reaction (HFSR) [palmar-plantar erythrodysesthesia (PPE)] 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 NCI CTCAE v3.0 Grade 3 or 4 adverse reaction

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
- 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)

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

Patients with Hepatic Impairment

Regorafenib is eliminated mainly via the hepatic route.

No clinically important differences in the mean exposure of regorafenib or the active metabolites M-2 and M-5 were observed in patients with hepatocellular carcinoma and mild (Child-Pugh A) hepatic impairment compared to patients with normal hepatic function. No dose adjustment is required in patients with mild (Child-Pugh A) hepatic impairment. Limited data are available for patients with moderate hepatic impairment (Child-Pugh B). Regorafenib has not been studied in patients with severe hepatic impairment (Child-Pugh C). Administration of regorafenib should be avoided in patients with

severe hepatic impairment. Closely monitor patients with hepatic impairment for adverse reactions (see 7 Warnings and Precautions - Monitoring and Laboratory Tests).

Patients with Renal Impairment

Clinical data indicate similar exposure of regorafenib and its active 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 renal impairment, moderate renal impairment, or severe renal impairment (see 10.3 Pharmacokinetics). No data are available for patients with end-stage renal disease.

Ethnic Differences

In clinical studies, no relevant differences in exposure were observed between patients of different ethnic groups. No dose adjustment is necessary based on ethnicity (see 10.3 Pharmacokinetics).

4.4 Administration

STIVARGA should be taken at the same time each day after a light, low-fat, low-calorie meal (<30% fat, ~300-550 calories). An example of a low-fat, low-calorie meal is two slices of white toast with 1 tablespoon of low-fat margarine and 1 tablespoon of jelly and 8 ounces of skim milk (approximately 319 calories and 8.2 grams of fat). The tablets should be swallowed whole with water.

4.5 Missed Dose

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.

5 Overdose

The highest dose of STIVARGA studied clinically is 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, STIVARGA should be withheld immediately, with best supportive care initiated by a medical professional, and the patient should be observed until clinical stabilization.

For the most recent information in the management of a suspected drug overdose, contact your regional poison control centre or Health Canada's toll-free number, 1-844 POISON-X (1-844-764-7669).

6 Dosage Forms, Strengths, Composition and Packaging

Table 1: Dosage Forms, Strengths and Composition

Route of Administration	Dosage Form / Strength/Composition	Non-Medicinal Ingredients
oral	tablet, 40 mg	cellulose microcrystalline, croscarmellose sodium, iron oxide red, iron oxide yellow, lecithin (soy), macrogol, magnesium stearate, polyvinyl alcohol (partially hydrolysed), povidone, silica colloidal anhydrous, talc, titanium dioxide

Description

STIVARGA (regorafenib tablets) is supplied as oval shaped, light pink, film-coated tablets containing 40 mg of regorafenib. Tablets are debossed with 'BAYER' on one side and '40' on the other side. The product is supplied in 45 mL bottles of 28 tablets with a desiccant.

7 Warnings and Precautions

See 3 Serious Warnings and Precautions Box.

General

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.

Wound Healing Complications

No formal studies of the effect of STIVARGA on wound healing have been conducted. Since drugs with anti-angiogenic properties may suppress 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.

Carcinogenesis and Genotoxicity

Studies on the carcinogenic potential of regorafenib have not been performed. There was no indication for a genotoxic potential of regorafenib after testing in standard in vitro and in vivo assays in mice. However, M-2, the active metabolite of regorafenib in humans, was positive for clastogenicity, causing chromosome aberration in Chinese hamster V79 cells.

Cardiovascular

In the placebo-controlled Phase III studies (CRC + GIST + HCC), the overall incidence of cardiac adverse events was higher in the regorafenib-treated patients compared to placebo-treated patients (8.1% vs 4.5%). The incidence of severe (Grade 3/4) cardiac arrhythmia events was higher in regorafenib-treated patients (0.6% vs 0.4%) and was comprised of four cases of atrial fibrillation, one case of

electrocardiogram QT prolonged, one case of supraventricular, and one case of ventricular extrasystoles in the regorafenib arm (see 8.2 Clinical Trial Adverse Drug Reactions).

Decreased Heart Rate

STIVARGA may decrease heart rate (see 10 Clinical Pharmacology). Caution should be observed in patients with a low heart rate at baseline (< 60 beats per minute), a history of syncope or arrhythmia, sick sinus syndrome, sinoatrial block, atrioventricular (AV) block, ischemic heart disease, or congestive heart failure. Concomitant medications that result in a decrease in heart rate should be avoided to the extent possible during treatment with STIVARGA (see 9 Drug Interactions).

Arterial Hypertension

In the placebo-controlled Phase III studies, the overall incidence of hypertension was higher in patients treated with STIVARGA as compared to patients receiving placebo. In the Phase III CRC pivotal study, a 3-fold higher incidence of arterial hypertension (30% vs 8%; Grade 3: 8% vs 1%) was observed in regorafenib-treated patients compared to placebo-treated patients. In the Phase III GIST study, a 2-fold higher incidence of arterial hypertension (61% vs 26%; Grade 3: 28% vs 5%; Grade 4: 1% vs 0%) was observed in regorafenib-treated patients compared to placebo-treated patients with a 10% higher incidence of Grade 3/4 hypertensive events in the population ≥65 years of age. In the Phase III HCC study, higher incidence of arterial hypertension (31% vs 6%; Grade 3: 15% vs 5%) was observed in regorafenib-treated patients compared to placebo-treated patients. The onset of hypertension occurred during the first cycle of treatment in most patients. Blood pressure should be controlled prior to initiation of treatment with regorafenib. It is recommended to monitor blood pressure weekly for the first 6 weeks of treatment and then prior to every cycle, or more frequently if required (see 7 Warnings and Precautions – Monitoring and Laboratory Tests). In cases of severe or persistent hypertension, despite adequate medical management, regorafenib should be temporarily or permanently withheld (see 4.2 Recommended Dose and Dosage Adjustment).

Hypertensive crisis occurred in eight of 4800 (0.17%) patients treated with regorafenib across company-sponsored clinical trials with regorafenib. In case of hypertensive crisis, regorafenib should be discontinued.

Serious cases of artery dissection have been reported in patients using VEGFR TKIs, including STIVARGA, with or without hypertension.

Cardiac Ischemia and/or Infarction

Regorafenib has been associated with an increased incidence of myocardial ischemia and infarction (see 8 Adverse Reactions). In the placebo-controlled Phase III studies (CRC + GIST + HCC), the incidence of myocardial ischemia and infarction was higher for regorafenib-treated patients (ischemia 0.61%; infarction 0.26%) compared to placebo-treated patients (ischemia 0.17%; infarction 0%).

Patients with a history of ischemic heart disease should be monitored for clinical signs and symptoms of myocardial ischemia. In patients who develop new or acute onset cardiac ischemia and/or infarction regorafenib should be withheld until resolution. The decision to re-initiate regorafenib therapy should be based on careful consideration of the potential benefits and risks of the individual patient. Regorafenib should be permanently discontinued if there is no resolution.

Endocrine and Metabolism

STIVARGA increased the incidence of hypothyroidism (7% vs 0.5%) compared to placebo in placebo-controlled Phase III studies (CRC + GIST + HCC).

Gastrointestinal

Gastrointestinal Perforation or Fistula

Gastrointestinal perforation and fistula are serious adverse reactions and have been reported in patients treated with STIVARGA in clinical trials. In placebo-controlled Phase III studies (CRC + GIST + HCC), STIVARGA increased the incidence of gastrointestinal fistula (0.8% in regorafenib-treated patients vs 0.2% in placebo-treated patients). There were 2 fatal intestinal perforations reported in the Phase III GIST trial and one in the Phase III HCC trial (see 8 Adverse Reactions). Regorafenib should be permanently discontinued in patients who develop gastrointestinal perforation or fistula.

Hematologic

The overall incidence of hemorrhage was 18% in regorafenib-treated patients compared to 10% in placebo-treated patients in placebo-controlled Phase III studies (CRC + GIST + HCC). Most cases of bleeding events in regorafenib-treated patients were mild to moderate in severity (Grade 1 and 2: 15%), most notably epistaxis (6%). The incidence of Grade 3 to 5 bleeding events in regorafenib-treated patients was 3%; The incidence of fatal outcome in regorafenib-treated patients was 0.7%, and involved cerebral, respiratory, genitourinary and gastrointestinal events. Treatment with regorafenib should be stopped in patients with severe or life threatening hemorrhage. Patients receiving warfarin should be closely monitored (see 7 Warnings and Precautions – Monitoring and Laboratory Tests).

Hepatic/Biliary/Pancreatic

In the Phase III CRC pivotal study, the incidence of hepatobiliary disorders by MedDRA SOC was higher in regorafenib-treated patients (20% vs 12%) compared to placebo-treated patients. Fatal events of hepatic dysfunction were reported in 10/500 (2%) of regorafenib-treated patients compared to 4 (1.6%) of placebo-treated patients. Adverse events of hepatic dysfunction led to the treatment cessation in 7 (1.4%) regorafenib-treated patients and 3 (1.2%) placebo treated patients.

In the Phase III GIST study, the incidence of hepatobiliary disorders was higher in regorafenib-treated patients (6% vs 3%) compared to placebo-treated patients. Fatal events of hepatobiliary disorders (case of acute hepatic failure) were reported in 1/132 (1%) of regorafenib-treated patients compared to none of 66 placebo-treated patients. Adverse events of hepatobiliary disorders led to the treatment cessation in one (0.8%) of 132 regorafenib-treated patients and one (1.5%) of 66 placebo treated patients.

In the Phase III HCC study, the incidence of hepatobiliary disorders was comparable in regorafenib-treated patients (15% vs 16 %) compared to placebo-treated patients. Incidence of fatal events of hepatobiliary disorders was not higher in regorafenib-treated patients compared to placebo treated patients. Adverse events of hepatobiliary disorders that led to treatment cessation was not higher in regorafenib-treated patients compared to placebo treated patients.

Hepatic Injury

Severe drug-induced liver injury with fatal outcome was reported in patients treated with regorafenib in company-sponsored clinical trials. In most cases of severe liver injury, liver dysfunction occurred within the first 2 months of therapy, and was characterized by a hepatocellular pattern of injury with transaminase elevations >20xULN, followed by bilirubin increase and hepatocellular necrosis. Regorafenib-induced severe liver injury with fatal outcome was observed in 0.2% of regorafenib-treated patients in the Phase III CRC pivotal study and in 0.8% of regorafenib-treated patients in the Phase III GIST study. Incidence of fatal hepatic events in the Phase III HCC study was not higher in regorafenib-treated patients compared to placebo treated patients. In clinical trials, a higher incidence of severe liver function test abnormalities and hepatic dysfunction was observed in Asian (in particular Japanese) patients treated with STIVARGA as compared with Caucasians (see 10.3 Pharmacokinetics). It was also reported that 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%).

In the placebo-controlled Phase III studies (CRC + GIST + HCC), hepatic injury/failure adverse events were reported in 136/1142 (12%) of regorafenib-treated patients compared to 56/580 (10%) placebo-treated patients. Abnormalities of liver function tests (alanine aminotransferase (ALT), aspartate aminotransferase (AST) and bilirubin) have been frequently observed in patients treated with STIVARGA. Severe liver function test abnormalities (Grade 3 to 4) and hepatic dysfunction with clinical manifestations (including fatal outcomes) have been reported (see 8 Adverse Reactions).

It is recommended to perform liver function tests (ALT, AST and bilirubin) before initiation of treatment with regorafenib and monitor closely (at least every two weeks) during the first 2 months of treatment. Thereafter, periodic monitoring should be continued at least monthly and as clinically indicated. For patients with observed worsening of liver function tests, dose modification (interruption, reduction) or discontinuation of regorafenib is recommended (see 7 Warnings and Precautions – Monitoring and Laboratory Tests).

Mild, indirect (unconjugated) hyperbilirubinemia may occur in patients with Gilbert's syndrome; however there is no supporting clinical data.

Infections

STIVARGA has been associated with an increased incidence of infection events, some of which were fatal (see 8 Adverse Reactions).

In cases of worsening infection events, interruption of STIVARGA treatment should be considered.

In the placebo-controlled Phase III studies, infections were more often observed in patients treated with regorafenib 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%), and pneumonia (2.6%). Fatal outcomes associated with infection were observed more often in patients treated with regorafenib (1.0%) as compared to patients receiving placebo (0.3%), and were mainly respiratory events.

Immune

Severe drug hypersensitivity reactions including severe skin eruption, fever, dyspnea, hematological abnormalities (eosinophilia, thrombocytopenia) and internal organ involvement eg, liver) have occurred in association with STIVARGA.

Stevens - Johnson syndrome (SJS) and Toxic Epidermal Necrolysis (TEN) have been reported in clinical studies as rare events and in the post-market setting. In patients who experience a severe dermatologic reaction, STIVARGA treatment should be permanently discontinued.

Monitoring and Laboratory Tests

Liver function

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.

Metabolic/electrolytes

Regorafenib 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 regorafenib treatment and to institute appropriate replacement therapy according to standard clinical practice if required. Dose interruption or reduction, or permanent discontinuation of regorafenib should be considered in case of persistent or recurrent significant abnormalities (see 4.2 Recommended Dose and Dosage Adjustment).

Monitor INR levels more frequently in patients receiving warfarin.

Blood pressure

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 (see 4.2 Recommended Dose and Dosage Adjustment).

Neurologic

Reversible Posterior Leukoencephalopathy Syndrome

Reversible Posterior Leukoencephalopathy Syndrome (RPLS) has been reported rarely in association with STIVARGA treatment (see 8 Adverse Reactions).

Signs and symptoms of RPLS include seizures, headache, altered mental status, visual disturbance or cortical blindness, with or without associated hypertension. A diagnosis of RPLS requires confirmation by brain imaging. In patients developing RPLS, discontinuation of regorafenib, along with control of hypertension and supportive medical management of other symptoms is recommended. The safety of re-initiating regorafenib therapy in patients previously experiencing RPLS is not known.

Reproductive Health

- **Fertility**

  There are no data on the effect of regorafenib on human fertility. Histological findings in rat and dog studies indicate that regorafenib can impair male and female fertility at doses/exposures at or below those in humans. These findings suggest that regorafenib may adversely affect fertility in humans (see 16 Non-Clinical Toxicology).

- **Males**

It is not known if regorafenib or its metabolites are present in semen. Male patients must take appropriate precautions to avoid fathering a child during STIVARGA treatment.

Respiratory

In case of unexplained respiratory symptoms such as non-productive cough, dyspnea, crackles, or radiological pulmonary infiltrates, STIVARGA should be discontinued until further pulmonary investigation excludes interstitial lung disease and pneumonitis.

Skin

Dermatological toxicity

Regorafenib caused increased incidences of adverse reactions involving the skin and subcutaneous tissues (72% versus 24% in the Phase III CRC pivotal study, 78% versus 24% in the Phase III GIST study, and 66% versus 31% in Phase III HCC), including hand-foot skin reaction (HFSR) also known as palmar-plantar erythrodysesthesia (PPE), and severe rash. Both reactions required dose modifications.

In the Phase III CRC studies, the overall incidence of hand-foot skin reaction (HFSR/palmar-plantar erythrodysesthesia syndrome) (51% vs 7%) and Grade 3 HFSR (17% vs 0%) was increased in regorafenib-treated patients. The overall incidence of rash (25% vs 4%) and Grade 3 rash (6% vs <1%) were higher in regorafenib treated patients compared to placebo. The incidence of serious adverse events of erythema multiforme (0.2% vs 0%) was also higher in regorafenib-treated patients.

In the Phase III GIST study, the overall incidence of HFSR (66% vs 15%), Grade 3 HFSR (22% vs 2%) and Grade 3 rash (5% vs 0%) were increased in regorafenib-treated patients.

In the Phase III HCC study, the overall incidence of HFSR (52% vs 7%), Grade 3 HFSR (12% vs <1%), Grade 3 rash (<1% vs 0%) were increased in regorafenib-treated patients.

Hand-foot skin reaction (HFSR / palmar-plantar erythrodysesthesia syndrome) and rash were the most frequently observed dermatological adverse drug reactions with STIVARGA (see 8 Adverse Reactions). A higher incidence of HFSR events have been reported in Asian patients (all Grades: 78% [CRC], 88% [GIST], and 67% [HCC] and Grade 3: 28% [CRC], 24% [GIST], and 14% [HCC]) as compared to non-Asian patients (all Grades: 38% [CRC], 60% [GIST], and 42% [HCC; Caucasians only] and Grade 3: 13% [CRC], 21% [GIST], and 8% [HCC; Caucasians only]) (see 10.3 Pharmacokinetics). Measures for the prevention of HFSR include control of calluses and use of shoe cushions and gloves to prevent pressure stress to soles and palms. Management of HFSR may include the use of keratolytic creams (eg, urea, salicylic acid, or alpha hydroxyl acid-based creams applied sparingly only on affected areas) and moisturizing creams (applied liberally) for symptomatic relief. Dose reduction and/or temporary interruption of regorafenib, or in severe or persistent cases, permanent discontinuation of regorafenib should be considered (see 4.2 Recommended Dose and Dosage Adjustment).

7.1 Special Populations

7.1.1 Pregnancy

There are no adequate and well-controlled studies in pregnant women using regorafenib. Animal studies have shown reproductive toxicity. Based on its mechanism of action, STIVARGA can cause fetal harm when administered to a pregnant woman. Regorafenib was embryolethal and teratogenic in rats and rabbits at doses/exposures lower than in humans, with increased incidences of cardiovascular, genitourinary, and skeletal malformations (see 16 Non-Clinical Toxicology).

Regorafenib should not be used during pregnancy or in any woman not employing adequate contraception (see 16 Non-Clinical Toxicology). Adequate contraception should be used during therapy

and for at least 8 weeks after completion of therapy. Women of childbearing potential must be apprised of the potential hazard to the fetus, which includes severe malformation (teratogenicity), failure to thrive, and fetal death (embryotoxicity).

7.1.2 Breastfeeding

It is not known whether regorafenib is excreted in human milk. In rats, regorafenib and/or its metabolites were excreted in milk. Because of the potential harm to the infant, mothers should be advised against breastfeeding while receiving regorafenib.

7.1.3 Pediatrics

Pediatrics (<18 years of age): The safety and effectiveness of regorafenib in pediatric patients has not been established. Toxicology studies in rodents showed hypertrophy of epiphyseal growth plates and abnormalities in growing incisors. Alterations of teeth and bones/cartilage and adverse effects in the reproductive system were more pronounced in juvenile animals, indicating a potential risk for children and adolescents (see 16 Non-Clinical Toxicology and 10.3 Pharmacokinetics). Regorafenib is not recommended for use in children and adolescents.

7.1.4 Geriatrics

Geriatrics (≥65 years of age): In the Phase III pivotal study in patients with metastatic CRC, 38% (n=285) were older than 65 years of age. In the Phase III study in patients with GIST, 32% (n=63) were older than 65 years of age. In the Phase III study in patients with HCC, 45% (n=258) were older than 65 years of age. Analyses of data by age demographics suggest that no dose adjustment is required on the basis of patient age (65 years or older). No differences in safety or efficacy were observed between older and younger patients (see 14 Clinical Trials).

8 Adverse Reactions

8.1 Adverse Reaction Overview

The data described in this section reflect exposure to regorafenib in 4,800 patients including 636 patients with metastatic CRC (Phase III CRC pivotal study [CORRECT] and a study conducted in East Asia [CONCUR]), 132 patients with gastrointestinal stromal tumors (GIST), and 374 patients with hepatocellular carcinoma (HCC) in placebo-controlled phase III trials.

The most frequently observed adverse drug reactions (≥30%) in patients receiving regorafenib are pain, hand-foot skin reaction, asthenia/fatigue, diarrhea, decreased appetite and food intake, hypertension, and infection.

The most serious adverse drug reactions in patients receiving regorafenib are severe liver injury, hemorrhage, cardiac ischemia/infarction, hypertension, reversible posterior leukoencephalopathy syndrome (RPLS), Stevens-Johnson syndrome/toxic epidermal necrolysis, gastrointestinal perforation or fistula, and infection (see 7 Warnings and Precautions). Of these, hypertension, infection, and hemorrhage have been observed most frequently.

8.2 Clinical Trial Adverse Reactions

Clinical trials are conducted under very specific conditions. Therefore, the frequencies of adverse reactions observed in the clinical trials may not reflect frequencies observed in clinical practice and should not be compared to frequencies reported in clinical trials of another drug.

Phase III CRC pivotal trial (CORRECT): Randomized, double-blind placebo-controlled clinical study in patients with metastatic colorectal cancer who failed at least 2 lines of prior therapy

The safety data for patients with metastatic CRC reflects the safety of regorafenib administered as a single agent at the recommended dose of 160 mg daily for 3 weeks on therapy and 1 week off therapy. The median duration of therapy was 7 weeks. The period of observation for adverse events was less than 3 months (median time) in both treatment groups. Of the 753 patients in the safety population, 500 patients received regorafenib and 253 patients received placebo.

A dose modification due to adverse reactions occurred in 67% and 22% of patients in the regorafenib and placebo group, respectively. The rates of dose reductions were also higher with regorafenib (38% vs 3%) as were the rates of dose interruptions (61% vs 22%) and treatment cessations (18% vs 13%) compared to placebo.

The rate of death due to adverse events not associated with disease progression was slightly higher with regorafenib (1.6% vs 1.2%). Five deaths were considered to be regorafenib-related: 1 case each of liver dysfunction; sudden death; cerebrovascular incident; pulmonary hemorrhage, bronchus; hemorrhage, GI, anus and hemorrhage, GU, vagina (the last two occurred in one patient) (see 7 Warnings and Precautions – 3 Serious Warnings and Precautions Box).

The rates of serious adverse events were similar between the treatment groups (44% vs 40%). The most common SAEs were (regorafenib vs placebo): physical health deterioration (7.2% vs 9.5%), pyrexia (2.8% vs 0.4%), abdominal pain (2.4% vs 0.8%), pneumonia (2.0% vs 1.6%), dyspnea (2.0% vs 1.2%), diarrhea (1.6% vs 0%), hepatic failure (1.4% vs 0.8%), atrial fibrillation (0.6% vs 0%), myocardial ischemia (0.6% vs 0%), rectal hemorrhage (0.6% vs 0%), pulmonary hemorrhage (0.4% vs 0%), and disseminated intravascular coagulation (0.4% vs 0%).

In female patients, the overall incidence of serious adverse events was higher compared to male patients (50.3% vs 39.7%), as was the incidence of drug related SAEs (14.0% vs 10.4%). Drug-related SAE in female patients treated with regorafenib was higher (14% vs 0%) as compared to placebo-treated females. There were 2 cases of disseminated intravascular coagulation Grade 3 events, both serious.

In patients with mild and moderate hepatic impairment the incidence of adverse events was higher (100% vs 62%) as compared to patients with normal hepatic function at baseline (see 7.1 Special Populations).

Hepatobiliary disorders reported more frequently in regorafenib-treated patients as compared to placebo-treated patients included: hyperbilirubinemia (19% vs 9%); increase in transaminases (7.6% vs 4.4%); hepatic function abnormal (2% vs 1.6%); hepatic pain (1.6% vs 0.8%); jaundice (1.2% vs 0.4%); jaundice cholestatic (0.6% vs 0.4%) ; cholecystitis acute (0.4% vs 0%); and liver disorder (0.4% vs 0%) (see 7 Warnings and Precautions – Hepatic/Biliary/Pancreatic).

A hemorrhage/bleeding event (any grade) occurred in 107 (21%) regorafenib-treated patients and in 19 (8%) placebo-treated patients. The most common bleeding events (any grade) in both treatment groups were (regorafenib vs placebo): hemorrhage pulmonary, nose bleed (8.8% vs 2.4%); hemorrhage, GI, anus (3.2% vs 0.4%); hemorrhage, GU, urinary NOS (2.6% vs 1.2%); hemorrhage - other (2.0% vs 0%), and hemorrhage, GI, rectum (1.2% vs 0%). The incidence of serious bleeding was higher with regorafenib (2.0% vs 0.8%). Five Grade 5 events in 4 regorafenib-treated patients (0.8%) resulted in death including hemorrhage GI, abdomen; GI, anus; GU, vagina; tumor; and pulmonary, bronchus. No patients in the placebo group had a Grade 5 (fatal) hemorrhage event (see 7 Warnings and Precautions – Hematologic).

Serious events of cardiac disorders SOC were reported for 9 regorafenib (1.8%); and 2 placebo (0.8%) patients; the most common were atrial fibrillation (0.6% vs 0%) and myocardial ischemia (0.6% vs 0%). The rates of congestive heart failure events (all grades) were higher with regorafenib compared to placebo (9.8% vs 7.1%) as were the rates of cardiac ischemia (1.2% vs 0.4%) and cardiac arrhythmia (3.0% vs 0.8%) (see 7 Warnings and Precautions – Cardiovascular).

The incidence of MedDRA preferred terms truly reflective of GI fistula was low and similar between regorafenib (0.8%) and placebo (0.4%), and there were no cases of GI perforation in the regorafenib arm, compared to one case in the placebo arm (see 7 Warnings and Precautions – Gastrointestinal).

There was an increased incidence of renal and urinary adverse events in the regorafenib-treated patients (16.4% vs 8.7%) compared with placebo-treated patients; mainly due to the higher incidence of proteinuria (7.4% vs 2.4%), and hematuria (2.8% vs 1.2%). Serious renal and urinary AEs were reported more frequently in placebo-treated patients (2.8% vs 1.4%) and Grade 3 /4 events of renal failure were reported in 2.4% of patients in the placebo group and 1.8 % of patients in the regorafenib group. The rate of acute renal failure was higher in regorafenib-treated patients (1% vs 0.4%) compared to placebo-treated patients.

The most frequently observed adverse drug reactions (≥30%) in patients receiving regorafenib are asthenia/fatigue, decreased appetite and food intake, HFSR, diarrhea, weight loss, infection, hypertension and dysphonia.

Table 2 compares the incidence of adverse reactions (≥10%) in patients receiving regorafenib and reported more commonly than in patients receiving placebo in the phase III study. They are classified according to organ system with the most appropriate medical term used to describe a certain reaction and its synonyms and related conditions.

Table 2: Adverse drug reactions (≥10%) by MedDRA reported in patients treated with regorafenib and reported more commonly than in patients receiving placebo in CORRECT

Adverse Reactions	Regorafenib (n=500)			Placebo (n=253)		
	Grade			Grade		
	All %	3 %	4 %	All %	3 %	4 %
Infections and infestations						
Infection[a]	31	7	2	17	5	<1
Blood and lymphatic system disorders						
Thrombocytopenia	15	3	<1	2	<1	0
Anemia	14	5	<1	12	3	<1
Metabolism and nutrition disorders						
Decreased appetite and food intake	47	5	0	28	4	0
Nervous system disorders						
Headache	10	<1	0	7	0	0
Vascular disorders						
Hemorrhage[a]	21	1	0	8	1	0
Hypertension	30	8	0	8	1	0

Adverse Reactions	Regorafenib (n=500)			Placebo (n=253)		
	Grade			Grade		
	All %	3 %	4 %	All %	3 %	4 %
Respiratory, thoracic and mediastinal disorders						
Dysphonia (voice changes)	30	0	0	6	0	0
Gastrointestinal disorders						
Diarrhea	43	8	<1	17	2	0
Stomatitis	18	2	0	4	0	0
Hepatobiliary disorders						
Hyperbilirubinemia	19	6	1	9	4	2
Skin and subcutaneous tissue disorders						
HFSR	47	17	-[b]	7	0	-[b]
Rash	26	6	0	4	<1	0
General disorders and administration site conditions						
Asthenia/fatigue	64	15	<1	46	9	2
Pain[c]	59	9	<1	48	6	<1
Fever	28	2	<1	15	0	0
Mucosal inflammation	16	2	0	2	0	0
Investigations						
Weight loss	32	<1	0	10	0	0

a fatal outcome has been observed
b No Grade 4 denoted in CTCAE, Version 3.0
c Summarizes reported pain-related events across all system organ classes

Other adverse reactions observed in less than 10% of patients treated with regorafenib and at a higher incidence than patients treated with placebo were: dry skin (8.8% vs 3.2%), proteinuria (8.6% vs 2.4%), alopecia (7.6% vs 1.6%), hypokalemia (7.6% vs 1.9%), taste disorder (7.6% vs 2.4%), increase in transaminases (7.6% vs 4.4%), hypophosphatemia (6.4% vs 0.8%), increase in lipase (6.2% vs 1.2%), hypocalcemia (5.8% vs 0.4%), hyponatremia (5.8% vs 2.4%), muscle spasms (5.4% vs 2.0%), dry mouth (4.8% vs 2.0%), leukopenia (4.2% vs 0.8%), hypothyroidism (4.2% vs 0.4%), increase in amylase (3.0% vs 0.4%), abnormal international normalized ratio (INR) (2.4% vs 0.8%), hypomagnesemia (2.2% vs 0.4%), tremor (2.0% vs 0%), gastroesophageal reflux (1.4% vs 0%), atrial fibrillation (1.2% vs 0%), hyperuricemia (1.2% vs 0%), gastroenteritis (1.2% vs 0.4%), nail disorder (1.0% vs 0%), gastrointestinal fistula (0.8% vs 0.4%), myocardial ischemia (0.6% vs 0.4%), QT-prolongation (0.6% vs 0%), sinus bradycardia (0.6% vs 0%), myocardial infarction (0.4% vs 0%), ventricular extrasystoles (0.4% vs 0%).

Phase III GIST pivotal trial: Randomized, double-blind placebo-controlled clinical study in adult patients with metastatic and/or unresectable GIST who have had disease progression on or intolerance to imatinib mesylate, and disease progression on sunitinib malate treatment

The safety data for patients with advanced GIST reflects the safety of regorafenib administered as a single agent at the recommended dose of 160 mg daily for 3 weeks on therapy and 1 week off therapy. The mean daily regorafenib dose received was 140 mg. In this study, the mean duration of therapy was 20 weeks for patients randomized to the regorafenib arm and 9 weeks for patients randomized to the

placebo arm. Of the 198 patients in the safety population, 132 received regorafenib and 66 received placebo.

Due to adverse reactions, 58% of the patients receiving regorafenib required a dose interruption and 50% of the patients had their dose reduced. Drug-related adverse reactions that resulted in treatment discontinuation were reported in 2.3% of regorafenib treated patients compared to 1.5% of placebo-treated patients. The median number of days to the first dose modification was 19 in regorafenib treated patients.

In the placebo-controlled treatment phase, the rate of death due to adverse events not associated with disease progression was higher with regorafenib (1.5%, n=2 vs 0%). Both deaths were considered to be regorafenib-related: 1 case each of acute hepatic failure and cardiac arrest (see 7 Warnings and Precautions – 3 Serious Warnings and Precautions Box). During the open-label treatment phase, there were 2 deaths considered to be regorafenib related: 1 case each of acute kidney injury and acute respiratory distress syndrome.

The most frequently observed adverse drug reactions (≥30%) were (regorafenib vs placebo): hand-foot skin reaction (HFSR/palmar-plantar erythrodysesthesia syndrome; 67% vs 15%), hypertension (59% vs 27%), asthenia/fatigue (52% vs 39%), diarrhea (47% vs 9%), dysphonia (39% vs 9%), infection (32% vs 5%), decreased appetite and food intake (31% vs 21%) and rash (30% vs 3%).

The rate of serious adverse events was higher in the regorafenib treatment group (28.8% vs 21.2%). Most serious adverse events were associated with the gastrointestinal system (12.1% vs 6.1%), with abdominal pain and ascites reported most frequently.

Hepatobiliary disorders reported more frequently in regorafenib-treated patients as compared to placebo-treated patients included: increase in transaminases (11% vs 5%); hyperbilirubinemia (9.9% vs 3.0%); cholecystitis (1.5% vs 0%); hepatic cyst (1.5% vs 0%); acute hepatic failure (0.8% vs 0%); and cytolytic hepatitis (0.8% vs 0%) (see 7 Warnings and Precautions – Hepatic/Biliary/Pancreatic).

A hemorrhage/bleeding event (any grade) occurred in 15 (11%) regorafenib-treated patients and in 2 (3%) placebo-treated patients. The most common bleeding events (any grade) that occurred more frequently in the regorafenib arm were (regorafenib vs placebo): epistaxis (2.3% vs 0%); lower GI hemorrhage (2.3% vs 0%); gingival bleeding (1.5% vs 0%); and tumor hemorrhage (1.5% vs 0%). No patient had a Grade 5 (fatal) hemorrhage event (see 7 Warnings and Precautions – Hematologic).

Serious events of cardiac disorders were reported for 2 regorafenib (1.5%) and no placebo patients; in one patient cardiac arrest and in another acute coronary syndrome/ arteriosclerotic heart disease were reported. No congestive heart failure events were reported (see 7 Warnings and Precautions – Cardiovascular).

The incidence of GI fistula was 1.5% in regorafenib arm and 0% in placebo arm. There were two cases of GI perforation (with fatal outcome) in regorafenib-treated patients and no cases in the placebo arm (see 7 Warnings and Precautions – Gastrointestinal).

There was an increased incidence of renal and urinary adverse events in the regorafenib-treated patients (16.7% vs 4.5%) compared with placebo-treated patients, mainly due to the higher incidence of proteinuria (6.8% vs 1.5%). Serious renal and urinary AEs were reported more frequently in regorafenib-treated patients (3.0% vs 0%). The rate of acute renal failure was higher in regorafenib-treated patients (1.5% vs 0%) compared to placebo-treated patients.

Table 3 compares the incidence of adverse reactions (≥10%) in patients receiving regorafenib plus best supportive care (BSC) and reported more commonly than in patients receiving placebo in the phase III

study. They are classified according to organ system with the most appropriate medical term used to describe a certain reaction and its synonyms and related conditions.

Table 3: Adverse drug reactions reported in ≥10% of patients treated with regorafenib and more commonly reported than in patients given placebo in the controlled phase III trial (double-blind phase) in patients with GIST (GRID)

Adverse Reaction	Regorafenib (n=132)			Placebo (n=66)		
	Grade			Grade		
	All %	3 %	4 %	All %	3 %	4 %
Infections and infestations						
Infection[a]	32	4	1	5	0	0
Blood and lymphatic system disorders						
Anemia	11	2	0	8	2	0
Metabolism and nutrition disorders						
Decreased appetite and food intake	31	<1	0	21	3	0
Hypothyroidism	13	0	0	3	0	0
Nervous system disorders						
Headache	16	0	0	9	0	0
Vascular disorders						
Hemorrhage	11	2	2	3	0	0
Hypertension	61	28	1	26	5	0
Respiratory, thoracic and mediastinal disorders						
Dysphonia	39	0	0	9	0	0
Gastrointestinal disorders						
Diarrhea	47	8	0	9	0	0
Stomatitis	25	0	0	6	2	0
Nausea	20	2	0	12	2	0
Vomiting	17	<1	0	8	0	0
Hepatobiliary disorders						
Increase in transaminases	11	3	0	5	2	0
Skin and subcutaneous tissue disorders						
HFSR	67	22	-[b]	15	2	-[b]
Rash	30	7	0	3	0	0
Alopecia	24	2	0	2	0	0
Musculoskeletal and connective tissue disorders						
Muscle spasms	14	0	0	3	0	0
General disorders and administration site conditions						
Asthenia/Fatigue	52	4	0	39	2	0
Mucosal inflammation	17	2	0	2	0	0
Pain[c]	60	8	0	55	14	0
Fever	21	0	0	11	2	0

Adverse Reaction	Regorafenib (n=132)			Placebo (n=66)		
	Grade			Grade		
	All %	3 %	4 %	All %	3 %	4 %
Investigations						
Weight loss	14	0	0	8	0	0

a fatal outcome has been observed
b No Grade 4 denoted in CTCAE, Version 4.0
c Summarizes reported pain-related events across all system organ classes

Other adverse reactions, observed in less than 10% of patients treated with regorafenib and at a higher incidence than patients treated with placebo were: hyperbilirubinemia (9.9% vs 3.0%), taste disorders (9.9% vs 3.0%), leukopenia (8.3% vs 7.6%), proteinuria (7.6% vs 1.5%), thrombocytopenia (6.1% vs 0%), dry mouth (6.1% vs 4.6%), hypophosphatemia (5.3% vs 0%), dry skin (4.6% vs 0%), hypokalemia (3.8% vs 3.0%), gastroenteritis (1.5% vs 0%), gastrointestinal fistula (1.5% vs 0%), hypocalcemia (1.5% vs 0%), increase in lipase (1.5% vs 0%), abnormal international normalized ratio (INR) (0.8% vs 0%), tremor (0.8% vs 0%).

Phase III HCC pivotal trial: Randomized, double-blind placebo-controlled clinical study in adult patients with hepatocellular carcinoma who have been previously treated with sorafenib

The safety data for patients with HCC reflects the safety of regorafenib administered as a single agent at the recommended dose of 160 mg daily for 3 weeks on therapy and 1 week off therapy. The mean daily regorafenib dose received was 144 mg. In this study, the median duration of therapy was 3.6 months for patients randomized to the regorafenib arm and 1.9 months for patients randomized to the placebo arm. Of the 563 patients in the safety population, 374 received regorafenib and 193 received placebo.

Table 4 compares the incidence of adverse reactions (≥10%) in patients receiving regorafenib and reported more commonly than in patients receiving placebo in the phase III study. They are classified according to organ system with the most appropriate medical term used to describe a certain reaction and its synonyms and related conditions. Dose interruptions for adverse events were required in 58.3% of patients receiving regorafenib and 47.9% of patients had their dose reduced.

Table 4: Adverse drug reactions reported in ≥10% of patients treated with regorafenib and more commonly reported than in patients given placebo in the controlled phase III trial (double-blind phase) in patients with HCC (RESORCE)

Adverse Reaction	regorafenib (n=374)			Placebo (n=193)		
	Grade			Grade		
	All %	3 %	4 %	All %	3 %	4 %
Infections and infestations						
Infection[a]	31	6	<1	18	5	<1
Blood and lymphatic system disorders						
Thrombocytopenia	10	4	<1	3	0	0
Anemia	16	4	<1	11	6	0
Metabolism and nutrition disorders						
Decreased appetite and food intake	31	3	0	15	2	0
Vascular disorders						
Hypertension	31	15	0	6	5	0
Hemorrhage[a]	18	2	1	16	3	2
Respiratory, thoracic and mediastinal disorders						
Dysphonia	18	0	0	2	0	0
Gastrointestinal disorders						
Diarrhea	42	3	0	15	0	0
Vomiting	13	<1	0	7	<1	0
Nausea	18	<1	0	13	0	0
Hepatobiliary disorders						
Hyperbilirubinemia	29	10	<1	18	8	3
Increase in transaminases	27	11	1	22	10	2
Skin and subcutaneous tissue disorders						
Hand-foot skin reaction/ Palmar-plantar erythrodysesthesia syndrome	52	12	-[b]	7	<1	-[b]
Muscoloskeletal and connective tissue disorders						
Muscle spasms	10	0	0	2	0	0
General disorders and administration site conditions						
Asthenia/fatigue	42	10	0	33	5	0
Pain[c]	56	9	<1	44	8	0
Fever	20	0	0	7	0	0
Investigations						
Weight loss	14	2	0	4	0	0

a fatal outcome has been observed
b No Grade 4 denoted in CTCAE, Version 4.0
c Summarizes reported pain-related events across all system organ classes

Other adverse reactions observed in less than 10% of patients treated with regorafenib and at a higher incidence than patients treated with placebo were: hypophosphatemia (9.9% vs 2.1%), leukopenia (8.8% vs 3.6%), proteinuria (8.8% vs 1.6%), rash (8.6% vs 8.3%), stomatitis (8.3% vs 2.1%), increase in lipase (7.2% vs 3.1%), alopecia (7.0% vs 2.6%), hypokalemia (7.0% vs 2.6%), hypothyroidism (6.7% vs 0.0%), headache (6.4% vs 6.2%), hyponatremia (5.9% vs 3.1%), dry mouth (5.9% vs 4.7%), hypomagnesemia (3.2% vs 0.0%), taste disorder (3.2% vs 1.0%), increase in amylase (2.9% vs 0.0%), mucosal inflammation (2.9% vs 0.0%), hypocalcemia (2.4% vs 0.0%), pancreatitis (1.6% vs 0.0%), exfoliative rash (1.3% vs 0.0%), tremor (1.3% vs 0.0%), hyperuricemia (1.1% vs 1.0%), erythema multiforme (0.8% vs 0.0%), myocardial ischemia (0.8% vs 0.0%), gastroenteritis (0.5% vs 0.0%), gastrointestinal fistula (0.3% vs 0.0%), myocardial infarction (0.3% vs 0.0%), nail disorder (0.3% vs 0.0%).

8.4 Abnormal Laboratory Findings: Hematologic, Clinical Chemistry and Other Quantitative Data

Clinical Trial Findings

Laboratory abnormalities observed in the Phase III CRC Studies are shown in Table 5 and Table 6.

Table 5: Laboratory test abnormalities reported in Study 14387

Laboratory Parameter	STIVARGA plus BSC (n=500[a])			Placebo plus BSC (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	84	2	0	61	<1	0
Investigations						
Increased INR[c]	24	4	N/A	17	2	N/A
Increased Lipase	46	9	2	19	3	2
Increased 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 Common Terminology Criteria for Adverse Events (CTCAE), v3.0
c International normalized ratio: No Grade 4 denoted in CTCAE, v3.0
BSC = best supportive care

Compared to the global Phase III CRC Study (Study 14387) with predominately (~80%) Caucasian patients enrolled, a higher incidence of liver enzyme increases was observed in regorafenib-treated patients in the Asian Phase III CRC trial (Study 15808) with predominantly (>90%) East Asian patients enrolled:

Table 6: Laboratory test abnormalities reported in Study 15808

Laboratory Parameter	STIVARGA plus BSC (n=136)			Placebo plus BSC (n=68)		
	Grade[a]			Grade[a]		
	All %	3 %	4 %	All %	3 %	4 %
Hepatobiliary disorders						
Hyperbilirubinemia	67	7	4	33	5	0
Increased AST	70	10	1	48	3	0
Increased ALT	54	9	0	30	2	0

a Common Terminology Criteria for Adverse Events (CTCAE), v4.0
BSC = best supportive care

Laboratory abnormalities observed in the Phase III GIST Study are shown in Table 7.

Table 7: Laboratory test abnormalities reported in Study 14874

Laboratory Parameter	STIVARGA plus BSC (n=132[a])			Placebo plus BSC (n=66[a])		
	Grade[b]			Grade[b]		
	All %	3 %	4 %	All %	3 %	4 %
Blood and lymphatic system disorders						
Anemia	75	3	-[c]	73	2	-[c]
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	59	3	-[c]	53	3	-[c]
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 CTCAE, v4.0
c No Grade 4 (laboratory threshold value) denoted in CTCAE, v4.0.
BSC=best supportive care

Laboratory abnormalities observed in the Phase III HCC Study are shown in Table 8.

Table 8: Laboratory test abnormalities reported in Study 15982

Laboratory Parameter	STIVARGA plus BSC (n=374)			Placebo plus BSC (n=193)		
	Grade[a]			Grade[a]		
	All %	3 %	4 %	All %	3 %	4 %
Blood and lymphatic system disorders						
Anemia	73	6	-[b]	71	5	-[b]
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	51	17	-[b]	37	3	-[b]
Investigations						
Increased INR[c]	44	<1	-[b]	35	2	-[b]
Increased Lipase	41	11	3	27	8	1
Increased Amylase	23	3	<1	19	2	<1

a CTCAE, v4.0
b No Grade 4 (laboratory threshold value) denoted in CTCAE, v4.0.
c International normalized ratio
BSC=best supportive care

8.5 Post-Market Adverse Reactions

Events included in this section have been identified post-approval, which includes spontaneous case reports as well as adverse events from ongoing or completed clinical studies.

Immune system disorders: erythema multiforme, hypersensitivity reaction, Stevens-Johnson syndrome, toxic epidermal necrolysis

Neoplasms benign, malignant and unspecified (Including cysts and polyps):
Keratoacanthoma/squamous cell carcinoma of the skin

Vascular disorders: Artery dissection and artery aneurysm (including rupture) have been reported in association with the use VEGFR TKIs, including STIVARGA

Blood and lymphatic system disorders: Thrombotic microangiopathy

Thrombotic Microangiopathy

Thrombotic Microangiopathy (TMA) (including cases identified as thrombotic thrombocytopenic purpura [TTP] and renal-limited TMA), has been reported in post-marketing experience in association with the use of STIVARGA. STIVARGA therapy should be discontinued if TMA is diagnosed, and prompt treatment is required. Reversal of the effects of TMA has been observed after STIVARGA therapy was discontinued.

9 Drug Interactions

9.2 Drug Interactions Overview

Regorafenib is metabolized in the liver by oxidative metabolism mediated by CYP3A4 and by glucuronidation mediated by UGT1A9.

9.3 Drug-Behaviour Interactions

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

9.4 Drug-Drug Interactions

CYP3A4 Inhibitors

Administration of ketoconazole (400 mg for 18 days), a strong CYP3A4 inhibitor, with a single dose of regorafenib (160 mg on day 5) resulted in an increase in mean regorafenib exposure (AUC) of approximately 33%, and a decrease in mean exposure of the active metabolites, M-2 (N-oxide) and M-5 (N-oxide and N-desmethyl), of 94% and 93%, respectively. Avoid concomitant administration of regorafenib with strong CYP3A4 inhibitors.

CYP3A4 Inducers

Administration of rifampin (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 mean regorafenib exposure (AUC) 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 inducers of CYP3A4 activity (eg, phenytoin, carbamazepine phenobarbital and St. John's Wort) may also increase metabolism of regorafenib. Avoid concomitant administration of regorafenib with strong CYP3A4 inducers.

UGT1A1 and UGT1A9 substrates

In vitro data indicate that regorafenib as well as its active metabolites M-2 inhibits glucuronidation mediated by uridine diphosphate glucuronosyl transferases UGT1A1 (Ki values of 0.6 to 3.1 µM) and UGT1A9 (Ki values of 2.1 to 4.3 µM) whereas M-5 only inhibits UGT1A1 (Ki value of 1.1 µM) at concentrations which are achieved in vivo at steady state. Administration of regorafenib with a 5-day break prior to administration of irinotecan resulted in an increase of approximately 44% in mean exposure (AUC) to SN-38, a substrate of UGT1A1 and an active metabolite of irinotecan. An increase in mean exposure to 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.

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 Breast Cancer Resistance Protein (BCRP) substrate, resulted in a 3.8-fold increase in mean exposure (AUC) of rosuvastatin and a 4.6-fold increase in Cmax.

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 toxicity 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.

CYP isoform-selective substrates

In vitro data indicate that regorafenib is a competitive inhibitor of the cytochromes CYP2C8 (Ki value of 0.6 μM), CYP2C9 (Ki value of 4.7 μM), CYP2B6 (Ki value of 5.2 μM) at concentrations which are achieved in vivo at steady state (peak plasma concentration of 8.1 μM). The in vitro inhibitory potency towards CYP3A4 (Ki value of 11.1 μM) and CYP2C19 (Ki value of 16.4 μM) 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), CYP2C19 (omeprazole) and CYP3A4 (midazolam). Pharmacokinetic data indicate that concomitant administration of regorafenib with substrates of CYP2C8, CYP2C9, CYP3A4, and CYP2C19 is unlikely to result in a clinically meaningful drug interaction.

Co-administration of rosiglitazone (a substrate of CYP2C8) with regorafenib resulted in almost no change in exposure for both rosiglitazone and its CYP2C8 metabolite N-desmethyl rosiglitazone, suggesting no inhibition of CYP2C8.

Co-administration of regorafenib with warfarin (a substrate of CYP2C9) resulted in a mean increase of 25% in AUC, and 26% in the Cmax of S-warfarin as compared to warfarin alone. These data suggest that regorafenib may have a weak inhibitory effect on the CYP2C9 mediated metabolism of S-warfarin which is not likely to be clinically meaningful.

Co-administration of midazolam (a substrate of CYP3A4) with regorafenib resulted in a mean increase of 12% in AUC and a mean increase of 28% in Cmax of midazolam as compared to midazolam alone. The observed increase in midazolam exposure upon concomitant administration with regorafenib is not likely to be clinically meaningful.

The 6 hour post-dose omeprazole (CYP2C19 substrate) and 5-OH omeprazole data indicate a comparable metabolite to parent ratio, suggesting no inhibition of CYP2C19.

Antibiotics

Regorafenib and its metabolites undergo enterohepatic circulation. Co-administration of antibiotics that affect the flora of the gastrointestinal tract may interfere with the enterohepatic circulation of regorafenib and may result in changes to regorafenib exposure. The clinical significance of these potential interactions is unknown, since there is no supporting clinical data.

9.5 Drug-Food Interactions

The concentrations of regorafenib and its major metabolites were highest when given after a low-fat, low-calorie (<30% fat, ~300-550 calories) breakfast as compared to either a high-fat, high-calorie (~50% fat, ~1000 calories,) breakfast or fasting conditions. The exposure of regorafenib was increased by 48% when administered with a high-fat breakfast, and 36% when administered with a low fat breakfast, compared to fasting.

The exposures of the metabolites M-2 and M-5 were increased by 40% and 23%, respectively, when regorafenib was given with a low fat breakfast as compared to fasting conditions. The exposures of the metabolites M-2 and M-5 were decreased by 20% and 51%, respectively, when regorafenib was given with a high-fat breakfast as compared to fasting conditions.

9.6 Drug-Herb Interactions

Interactions with herbal products have not been established. Avoid concomitant use of regorafenib with St. John's Wort, a strong inducer of CYP3A4 activity.

9.7 Drug-Laboratory Test Interactions

Interactions with laboratory tests have not been established.

10 Clinical Pharmacology

10.1 Mechanism of Action

Regorafenib is an inhibitor of multiple protein kinases (IC50s <300 nM), 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). Major human metabolites (M-2 and M-5) exhibited similar efficacies compared to regorafenib.

Regorafenib has demonstrated inhibition of mutated KIT, a major oncogenic driver in gastrointestinal stromal tumors, and inhibition of gastrointestinal stromal tumor cell proliferation.

10.2 Pharmacodynamics

n preclinical studies, regorafenib has demonstrated anti-angiogenic activity in a rat tumor model, and inhibition of tumor growth as well as anti-metastatic activity in several mouse xenograft models including some for human colorectal carcinoma.

Electrocardiography: An open-label, non-randomized study was performed to assess the electrophysiological effects of STIVARGA 160 mg administered once daily to cancer patients (N=25 receiving target dose). STIVARGA was administered for 21 consecutive days followed by a 7 day break. Time-matched ECG data were collected at 8 time points at baseline and on day 21 of the first cycle. A statistically significant decrease from baseline in heart rate was observed on day 21 from 4-10 hours post-dosing, with a maximum mean decrease of 8.2 bpm (90% CI 11.6, -4.7). 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.

10.3 Pharmacokinetics

Absorption

Regorafenib reaches mean peak plasma levels (Cmax) of 2.5 mg/L at about 3 to 4 hours, with a mean exposure ((AUC(0-tlast)) of 47.1 mg.h/L and with an exposure (AUC) of 70.5 mg.h/L after a single oral dose of 160 mg regorafenib (4 tablets each containing 40 mg).

The mean relative bioavailability of tablets compared to an oral solution is approximately 70-83%.

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 (20-30h) and dosing frequency. At steady state, regorafenib reaches mean Cmax of about 3.9 mg/L (8.1 µM) at median tmax,ss of 5h (0.6-8.8h) and with a mean exposure (AUCss) of 58.3 mg.h/L.

Regorafenib pharmacokinetics exhibited a high inter-patient variability in exposures as demonstrated by a mean percent coefficient of variation (%CV) of approximately 43% for both AUC and Cmax at steady-state. Inter-subject variability in pharmacokinetics of the metabolites M-2 and M-5 was greater than that of the parent drug.

Pharmacokinetic parameters of regorafenib and metabolites M-2 and M-5 following single (Day 1) and multiple (Day 21) doses of 160 mg regorafenib daily for 21 days in cancer patients (Study 11650) are presented in Table 9.

Table 9: Pharmacokinetic parameters of regorafenib and metabolites M-2 and M-5 following single and multiple doses of 160 mg regorafenib daily for 21 days in cancer patients (geometric mean/%CV)

	Day 1			Day 21		
	$AUC_{(0\text{-}tlast)}$ mg·h/L	**C_{max} mg/L**	**t½ h**	**$AUC(0\text{-}24)_{ss}$ mg·h/L**	**$C_{max,ss}$ mg/L**	**t½ h**
Regorafenib	47.1 / 41%	2.53 / 43%	28.4/58%	58.3 / 43%	3.90 / 44%	22.2 / 45%
M-2	17.0/61%	0.83/64%	21.5 / 55%	53.7/69%	3.3 / 78%	21.0 / 28%
M-5	2.09 / 96%	0.08 / 88%	n.c.	48.7/83%	2.9 / 89%	n.c.

n.c. not calculated due to insufficient data

The food effect (fasted state, high-fat and low-fat diets) after a single 160 mg dose of regorafenib was studied in 24 healthy male volunteers. The exposure of regorafenib and its major metabolites was highest when given after a low-fat (<30% fat) breakfast as compared to either a high-fat (~50% fat) breakfast or fasting condition. The mean AUC for regorafenib was increased by 48% when administered with a high-fat breakfast, and 36% when administered with a low fat breakfast, compared to fasting. The mean AUC of the metabolites M-2 and M-5 were increased by 40% and 23%, respectively, when regorafenib was given with a low fat breakfast as compared to fasting conditions. The mean AUC of the metabolites M-2 and M-5 were decreased by 20% and 51%, respectively, when regorafenib was given with a high-fat breakfast as compared to fasting conditions.

Distribution

Plasma concentration-time profiles for regorafenib as well as for the major circulating metabolites showed multiple peaks across the 24-hour dosing interval, generally occurring approximately 4, 8 and 24 hours post-dose, which are attributed to enterohepatic circulation. Regorafenib is highly bound (99.5%) to human plasma proteins. Mean apparent volume of distribution at steady state (Vss/f) is 88 L (CV 60%).

Metabolism

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 have similar pharmacologic activity and steady-

state total plasma concentrations as regorafenib. Protein binding of M-2 and M-5 is 99.8% and 99.95%, respectively.

Regorafenib and its metabolites may undergo enterohepatic circulation. Primary metabolites may be reduced or hydrolyzed in the gastrointestinal tract by microbial flora, allowing reabsorption of the unconjugated drug and metabolites (enterohepatic circulation).

Elimination

Following single and multiple oral administration of 160 mg, mean elimination half-life for regorafenib and its metabolite M-2 in plasma ranges from 20 to 30 hours in different studies. The mean elimination half-life for the metabolite M-5 is approximately 60 hours (range from 40 to 100 hours).

Approximately 90% of the radioactive dose was recovered within 12 days after administration, with about 71% of the dose excreted in feces (47% as parent compound, 24% as metabolites), and about 19% of the dose excreted in urine as glucuronides. Urinary excretion of radioactivity was almost complete by 72 hours post-dose, whereas excretion via feces continued until 144 hours post-dose, after which the rate of excretion exhibited a near plateau. Parent compound found in feces could be derived from intestinal breakdown of conjugated metabolites, as well as unabsorbed drug.

Special populations and conditions

- **Pediatrics:** The pharmacokinetics of regorafenib were investigated in an ongoing Phase I study in 41 pediatric patients (range: 3 to 17 years of age) with solid malignant tumors that are recurrent or refractory to standard therapy. Dose levels evaluated ranged from 60 to 93 mg/m^2 administered once daily. The efficacy of regorafenib in this pediatric population has not been established.
- **Ethnic origin:** The exposure of regorafenib observed in several phase I and II studies in various Asian populations (Chinese, Japanese, Korean) is within the same range as seen in Caucasians. In clinical studies, no relevant differences in exposure were observed between patients of different ethnic groups. 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%).
- **Hepatic Insufficiency:** A single 100 mg dose of regorafenib was evaluated in patients with hepatocellular carcinoma (HCC) and with mild hepatic impairment (Child-Pugh A, n=14), moderate hepatic impairment (Child-Pugh B, n=4) and with normal hepatic function (n=10). The exposure of Korean HCC patients with mild hepatic impairment (Child-Pugh A, n=8) receiving multiple doses of 160 mg regorafenib was also evaluated. The exposure parameters (AUC and Cmax) of regorafenib and its metabolites M-2 and M-5 were comparable in the HCC patients with mild hepatic impairment and patients with normal hepatic function.

  The limited data for patients with moderate hepatic impairment indicated similar exposure when compared to patients with normal hepatic function.

  The pharmacokinetics of regorafenib has not been studied in patients with severe hepatic impairment (Child-Pugh C).
- **Renal Insufficiency:** 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.

A daily dose of 160 mg regorafenib administered for 21 days was evaluated in patients with normal renal function (eGFR ≥ 90 mL/min, n=18), mild renal impairment (60 mL/min ≤ eGFR < 90 mL/min, n=10), or moderate renal impairment (30 mL/min ≤ eGFR < 60 mL/min, n=1).

Patients with severe renal impairment (15 mL/min ≤ CLCR < 30 mL/min, n=6) were compared to patients with normal or mildly impaired renal function (CLCR ≥ 60 mL/min, n=18) in two stages (Stage 1: a single dose of 160 mg regorafenib, followed by wash-out of at least 5 days, and Stage 2: daily dose of 160 mg administered for 21 days).

11 Storage, Stability and Disposal

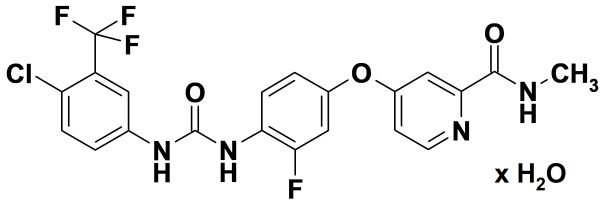
Store STIVARGA tablets in the original container at 15–30°C. Protect from moisture. Keep the desiccant in the bottle. Keep the bottle tightly closed after first opening.

Once the bottle is opened the product is to be discarded after 7 weeks.

Part 2: Scientific Information

13 Pharmaceutical Information

Drug Substance

Non-proprietary name of the drug substance:	Regorafenib monohydrate
Chemical name:	4-[4-({[4-chloro-3-(trifluoromethyl)phenyl]carbamoyl} amino)-3-fluorophenoxy]-*N*-methylpyridine-2-carboxamide monohydrate
Molecular formula and molecular mass:	$C_{21}H_{15}ClF_4N_4O_3$ * H_2O 500.83
Structural formula:	
Physicochemical properties:	Regorafenib monohydrate is a white to pink or brownish solid substance and practically insoluble in water. Regorafenib crystallizes in three modifications with melting points at 206 °C (Mod. I, under decomposition), 181 °C (Mod. II, under decomposition) and 141 °C (Mod. III). In addition, one pseudopolymorph has been found, a monohydrate (water content 3.6 %). The amorphous form can exist at room temperature.

14 Clinical Trials

14.1 Clinical Trials by Indication

Metastatic colorectal cancer (CRC)

Table 10: Summary of patient demographics for Phase III trial in metastatic colorectal cancer

Study #	Study design	Dosage, route of administration and duration	Study subjects (n)	Age (range)	Sex
14387	Phase III, randomized, double-blind, placebo-controlled	160 mg regorafenib orally once daily + BSC or matching placebo + BSC for 3 weeks followed by 1 week off therapy until disease progression or unacceptable toxicity	N=760 (n=505 for regorafenib + BSC group; n=255 for placebo + BSC group)	60.7 (22 to 82) for regorafenib + BSC group, 60.1 (25 to 85) for placebo+ BSC group	194/311 for regorafenib + BSC group, 102/153 for placebo + BSC group

The clinical efficacy and safety of STIVARGA (regorafenib) was evaluated in an international, multi-center, randomized, double-blind, placebo-controlled phase III study (CORRECT) in patients with metastatic colorectal cancer who had progressed after failure of standard therapy (including fluoropyrimidine-based chemotherapy, an anti-VEGF therapy and an anti-EGFR therapy [if KRAS Wild Type (WT)]).

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

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. Patients continued therapy until disease progression or unacceptable toxicity.

Demographics and baseline disease characteristics were comparable between the regorafenib and placebo groups with regard to age (mean age of 60.7 in regorafenib group and 60.1 in placebo group), gender (61.6% male, 38.4% female vs 60% male, 40% female) and ECOG performance status (52.5% ECOG PS 0 vs 57.3% ECOG PS 0). Primary site of disease was colon (64% vs 67.5%), rectum (29.9% vs 27.1%) or colon and rectum (5.9% vs 5.5%). KRAS mutation was reported in 54.1% of regorafenib group vs 61.6% of placebo group. All patients had received prior treatment with fluoropyrimidine, oxaliplatin, irinotecan and bevacizumab. Of the patients with a KRAS WT tumor, 99.5% in the regorafenib group and 100% in the placebo group had received prior treatment with cetuximab and/or panitumumab.

A pre-planned interim analysis for efficacy was performed when 432 deaths had occurred. The study was unblinded 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.

Table 11: Efficacy results from study 14387

Efficacy parameter	Hazard Ratio[a] (95% CI)	P-value (two-sided)	Median (95% CI)	
			STIVARGA plus BSC (N=505)	Placebo plus BSC (N=255)
Overall Survival	0.77 (0.64, 0.94)	0.010356	6.4 months (5.9, 7.3)	5.0 months (4.4, 5.8)
Progression-Free Survival	0.49 (0.42, 0.58)	<0.000001	1.9 months (1.9, 2.1)	1.7 months (1.7, 1.7)

a Hazard ratio < 1 favors STIVARGA

BSC = Best Supportive Care; CI= Confidence interval

Figure 1: Kaplan-Meier curves of Overall Survival (Study 14387)

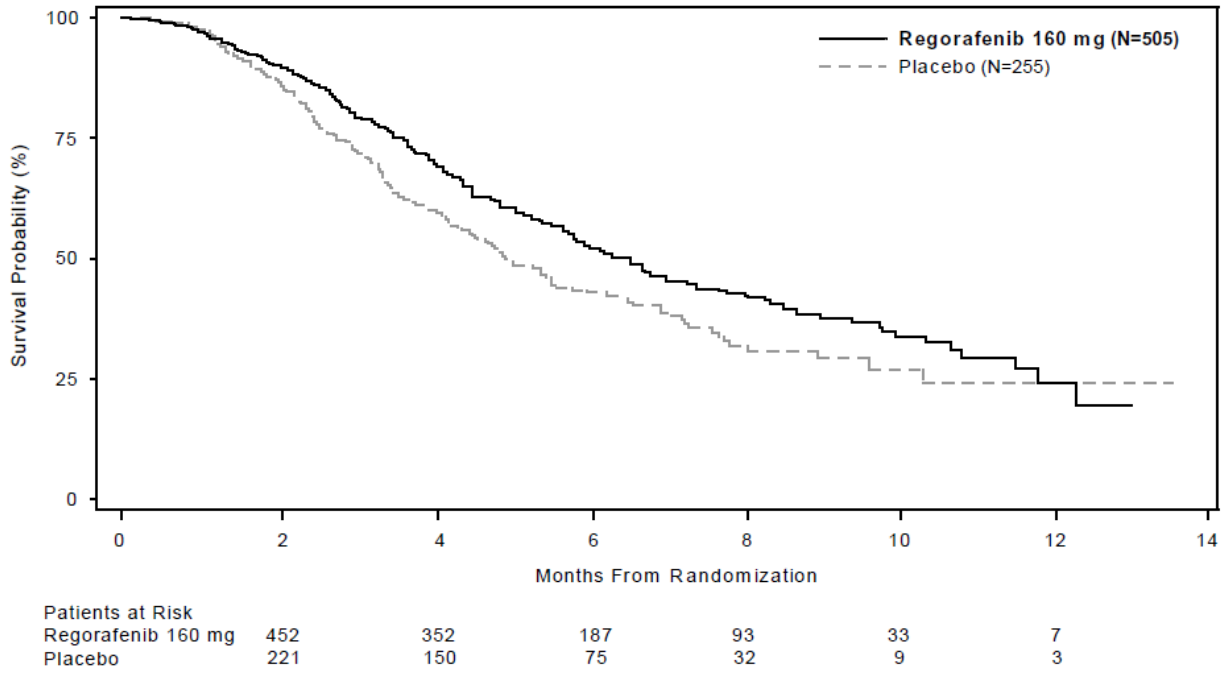
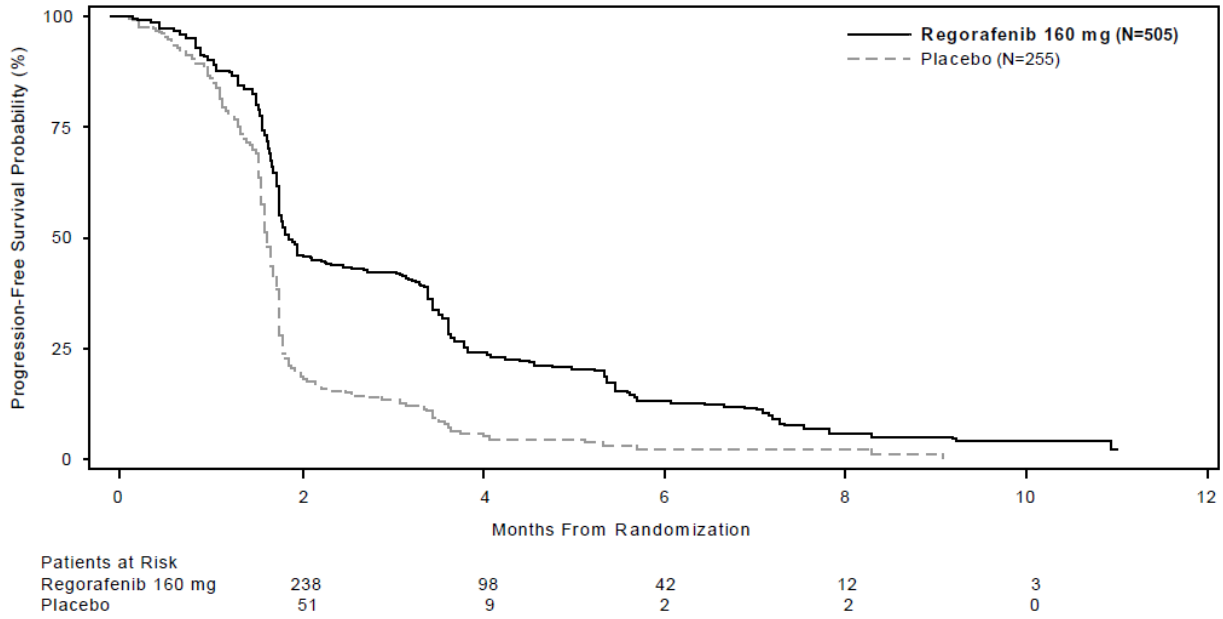


Figure 2: Kaplan-Meier curves of Progression-Free Survival (Study 14387)



There was no difference in the objective tumor response rate between the two groups. Based on RECIST criteria, there were no complete responses to regorafenib treatment in metastatic CRC patients. The partial response rate was 1.0% (5 patients) in the regorafenib plus BSC group vs 0.4% (1 patient) in the placebo plus BSC group; 42.8% (216 patients) in the regorafenib plus BSC group and 14.5% (37 patients) in the placebo plus BSC group had stable disease.

The results of subgroup analyses were supportive of the primary analyses of OS and PFS, demonstrating a trend to improvement in regorafenib-treated patients as compared to placebo-treated patients. Subgroup analysis results by historical KRAS mutational status demonstrated a stronger trend for OS in favor of regorafenib over placebo for KRAS WT patients than in KRAS mutated patients; trends for PFS favoring regorafenib were observed regardless of KRAS mutational status.

Study 15808

A second phase III, international, multi-center, randomized, double-blind, placebo-controlled study (CONCUR) evaluated 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 safety profile of STIVARGA plus BSC in the CONCUR study was consistent with the safety profile observed in the CORRECT study.

Gastrointestinal Stromal Tumors (GIST)

Table 12: Summary of patient demographics for GRID study

Study #	Study design	Dosage, route of administration and duration	Study subjects (n)	Age (range)	Sex
GRID Study (14874)	Phase III, multi-centre randomized, double-blind, placebo-controlled study	**Regorafenib group:** 160 mg regorafenib once daily (od), 3 weeks on/1 week off Plus BSC Route of administration: oral Duration: until progression as per blinded central review, unblinded then option to continue regorafenib as per discretion of the investigator **Placebo group:** Once daily (od), 3 weeks on/1 week off Plus BSC Route of administration: oral Duration: until progression as per blinded central review, unblinded, then option to be treated with regorafenib until second progression	**Study total:** N = 199 **Regorafenib group:** N = 133 **Placebo group:** N = 66	**Regorafenib group:** 58.2 (18-82) **Placebo group:** 58.1 (25-87)	**Regorafenib group:** 48/85 **Placebo group:** 24/42

Abbreviations: BSC= best supportive care

The clinical efficacy and safety of regorafenib was evaluated in the Phase III Study entitled GRID (GIST – Regorafenib In Progressive Disease) a multicenter randomized, double-blind, placebo-controlled, study to assess the safety and efficacy of regorafenib + best supportive care (BSC) compared with placebo + BSC in patients with metastatic and/or unresectable GIST with at least imatinib mesylate and sunitinib

malate as prior treatment regimens, with objective disease progression or intolerance to imatinib mesylate, as well as disease progression while on sunitinib malate therapy.

The primary efficacy endpoint was Progression Free Survival (PFS) based on disease assessment by independent radiological review using modified RECIST 1.1 criteria. Lymph nodes and bone lesions were not target lesions and a progressively growing new tumor nodule within a pre-existing tumor mass was progression. The key secondary outcome measure was overall survival.

One hundred and ninety-nine patients with metastatic and/or unresectable GIST were randomized (in a 2:1 ratio) to receive either regorafenib 160 mg once daily orally 3 weeks on / 1 week off + BSC (N=133) or matching placebo + BSC (N=66) in the double blind period of the study. The most common location of the primary tumor site at diagnosis was the stomach (36.7%), followed by the jejunum (16.1%). Of patients with historical biomarker data, 53.1% (51/96) had GIST with an initial pre-study baseline mutation in KIT exon 11, and 16% (15/96) had GIST harboring an initial pre-study baseline mutation in KIT exon 9. Eight patients (8.3%) were wild type (no KIT and no PDGFRα mutation).

The analysis for PFS was performed when 144 of the 199 patients had an event qualifying as progression (first observed radiological progression, according to blinded central radiology review using modified RECIST version 1.1 criteria, or death).

The results of the primary analysis showed a statistically significant advantage for regorafenib over placebo for PFS. Median PFS time was longer in the regorafenib group at 147 days (4.8 months), compared to 28 days (0.9 months) in the placebo group (Hazard Ratio: 0.27); 95% CI 0.19, 0.39: p<0.0001) (see Table 13).

An interim analysis of overall survival was conducted at the time of the final PFS analysis. At that time, 85% of placebo group patients had crossed over to open-label regorafenib treatment and a total of 46 events had occurred; 29 events (21.8% of patients) in the regorafenib group and 17 events (25.8%) in the placebo group. There was a positive trend towards overall survival with a Hazard Ratio of 0.77 (95% CI: 0.42 to 1.408; p =0.20) at the time of the interim analysis based on 29% of the total events for the final analysis (see Table 13).

Table 13: GRID efficacy results

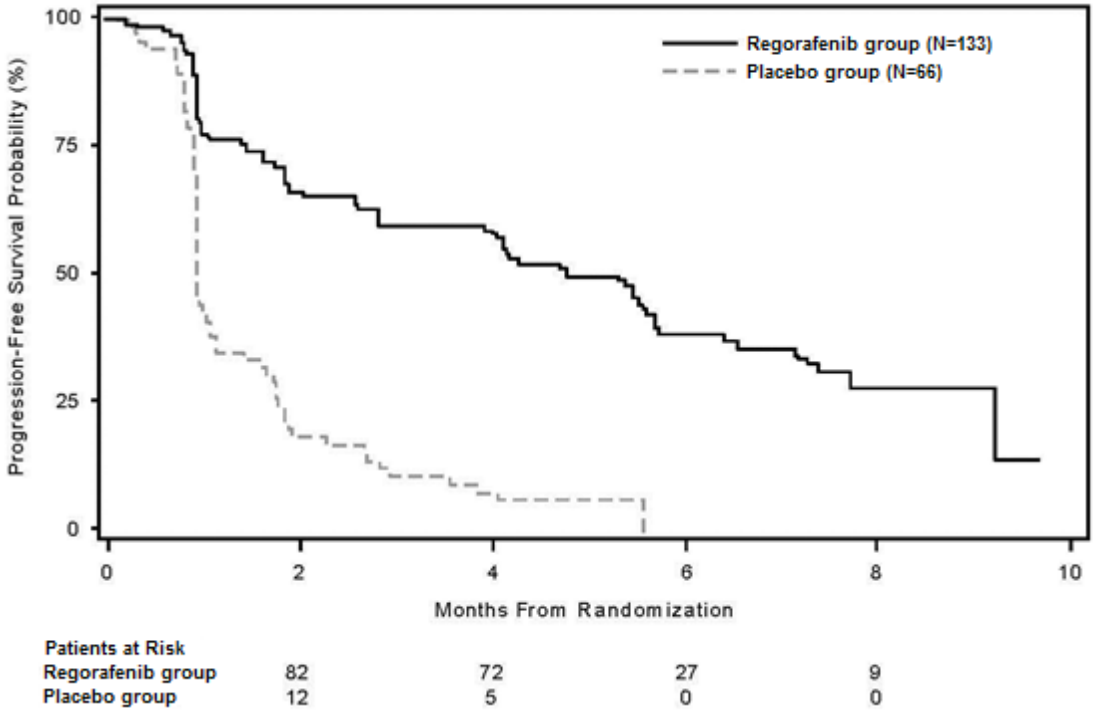
Efficacy parameter	Hazard Ratio (95% CI)	P-Value (two- sided)	Median (95% CI)	
			Placebo + BSC (n = 66)	Regorafenib + BSC (n = 133)
PFS	0.27 (0.19, 0.39)	<0.0001	0.9 months (0.9, 1.1)	4.8 months (4.0, 5.7)
OS	0.77 (0.42, 1.41)	0.20	NA[a]	NA[a]

Abbreviations: CI = confidence interval; HR = hazard ratio; NA = not assessable; PFS = progression-free survival

a Value cannot be estimated due to censored data

Kaplan-Meier curves for PFS by treatment group are shown in Figure 3. The estimated Kaplan-Meier PFS rate was consistently higher in the regorafenib group than in the placebo group at all timepoints.

Figure 3: Kaplan-Meier curve of Progression-Free Survival, central assessment, 144 events (GRID Study)



Based on RECIST criteria by central assessment, there were no complete responses to regorafenib treatment in GIST patients. The partial response rate was 4.5% (6 patients) in the regorafenib plus BSC group vs 1.5% (1 patient) in the placebo plus BSC group; 71.4% (95 patients) in the regorafenib plus BSC group and 33.3% (22 patients) in the placebo plus BSC group had stable disease.

Hepatocellular Carcinoma (HCC)

Table 14: Summary of patient demographics for RESOURCE study

Study #	Study design	Dosage, route of administration and duration	Study subjects (n)	Age (range)	Sex
RESORCE Study (15982)	Phase III, multi-centre randomized, double-blind, placebo-controlled study	**Regorafenib group:** 160 mg regorafenib once daily (od), 3 weeks on/1 week off Plus BSC Route of administration: oral Duration: until clinical or radiological disease progression, option to continue regorafenib as per discretion of the investigator **Placebo group:** Once daily (od), 3 weeks on/1 week off Plus BSC Route of administration: oral Duration: until clinical or radiological disease progression	**Study total:** N = 573 **Regorafenib group:** N = 379 **Placebo group:** N = 194	**Regorafenib group:** 61.8 (19-85) **Placebo group:** 61.1 (23-83)	**Regorafenib group:** 46/333 **Placebo group:** 23/171

Abbreviations: BSC= best supportive care

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 regorafenib 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 regorafenib- and placebo-treated groups and are shown below for all 573 randomized patients:

- Caucasian: 36%, Asian: 41%
- ECOG PS of 0: 66%, ECOG PS 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 addition of STIVARGA to BSC as compared to placebo plus BSC resulted in a hazard ratio (HR) 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 15 and Figure 4).

PFS in patients receiving STIVARGA plus BSC as compared to placebo plus BSC resulted in a HR 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 15 and Figure 5) based on modified RECIST and a HR of 0.427 (95% CI 0.348, 0.524), p<0.000001 stratified log rank test based on RECIST 1.1.

TTP in patients receiving STIVARGA plus BSC as compared to placebo plus BSC resulted in a HR 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 15).

The results for OS are shown in Figure 6. The effect of STIVARGA on OS was consistent across these subgroups, including survival benefit for treatment with STIVARGA independent of geographic region, ECOG PS, alpha-fetoprotein (AFP) level, presence of extrahepatic disease, and presence of macrovascular invasion.

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 65% vs 36%, p<0.000001 in patients treated with STIVARGA vs placebo. 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 15: RESORCE efficacy results

Efficacy parameter	Hazard Ratio[a] (95% CI)	P-value (one-sided)	Median (95% CI)	
			STIVARGA plus BSC (N=379)	Placebo plus BSC (N=194)
OS	0.624 (0.498,0.782)	0.000017	10.6 months (9.1, 12.1)	7.8 months (6.3, 8.8)
PFS[b]	0.453 (0.369, 0.555)	<0.000001	3.1 months (2.8, 4.2)	1.5 months (1.4, 1.6)
TTP[b]	0.439 (0.355,0.542)	<0.000001	3.2 months (2.9, 4.2)	1.5 months (1.4, 1.6)

Abbreviations: BSC = best supportive care; CI = confidence interval; HR = hazard ratio; NA = not assessable; OS = overall survival; PFS = progression-free survival; TTP = time to progression

a Hazard ratio < 1 favors STIVARGA

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

Figure 4: Kaplan-Meier Curve of Overall Survival (RESORCE Study)

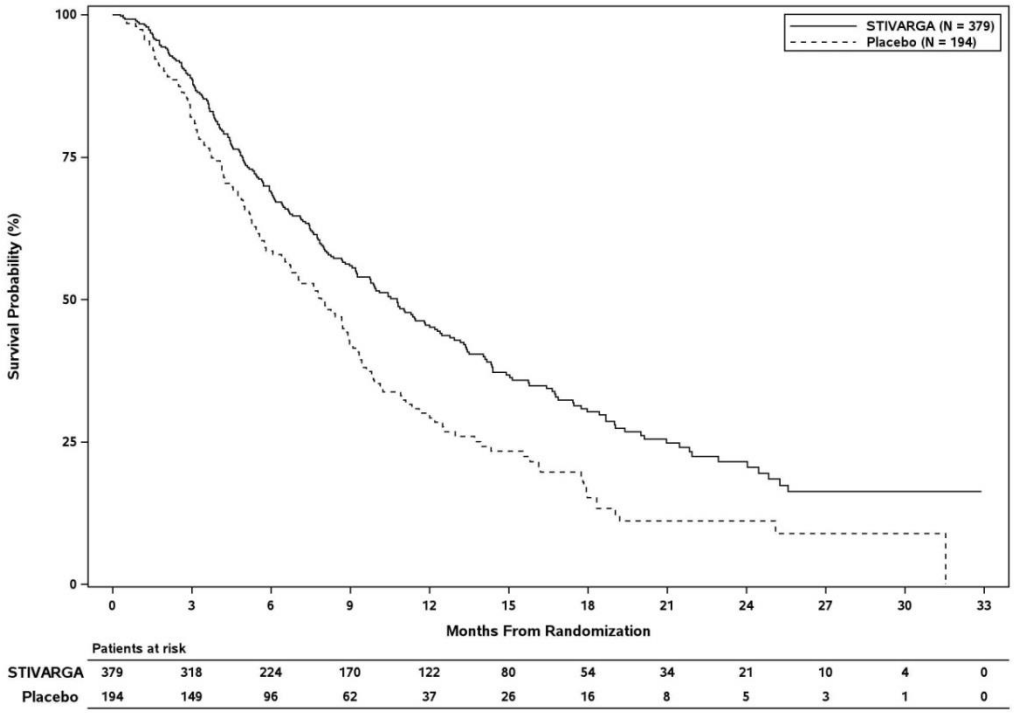


Figure 5: Kaplan-Meier Curve of Progression-Fee Survival (mRECIST) (RESORCE Study)

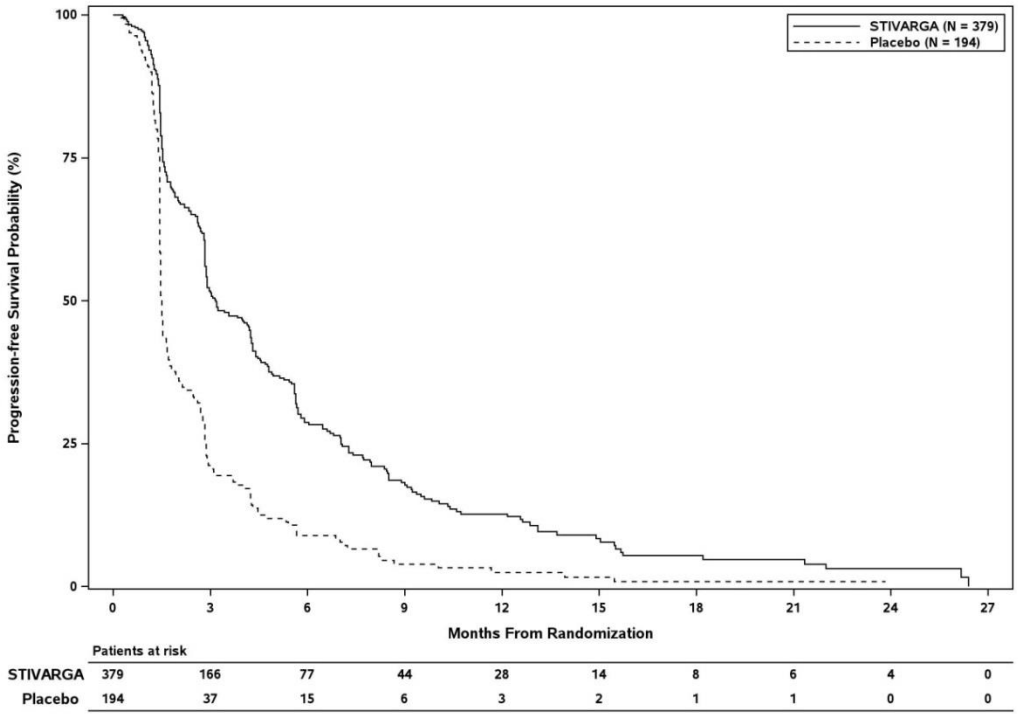
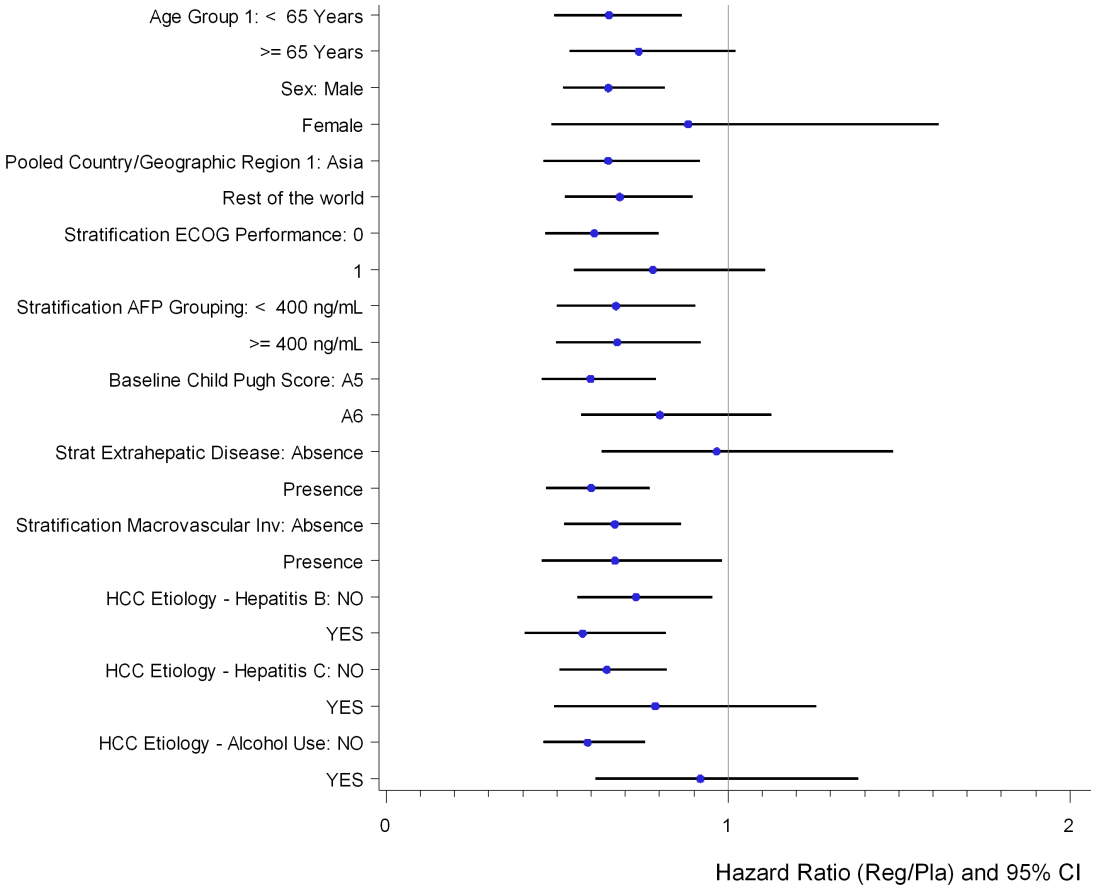


Figure 6: Overall Survival Subgroups (Hazard Ratio and 95% CI for STIVARGA: Placebo) – Study 15982



16 Non-Clinical Toxicology

This section includes animal data on regorafenib pharmacology not derived from human studies.

Nonclinical Pharmacology

M-2 and M-5 were shown to have similar pharmacological activities compared to regorafenib in biochemical and cell-based assays in vitro and in tumor growth inhibition studies in mice. Regorafenib, M-2 and M-5 antagonized VEGF induced hypotension in rats and prolonged inhibition of extravasation in the tumor vasculature of a rat GS9L glioblastoma model. In cellular assays, M-2 and M-5 inhibited key targets such as VEGFR2, TIE-2, mutant and wild-type KIT and mutant BRAF with IC50 values between 4 and 180 nM very similar to regorafenib (17 to 69 nM). M-2 and M-5 dosed orally at 10 mg/kg/day exhibited significant tumor growth inhibition in preclinical human HT-29 colorectal and MDA-MB-231 breast cancer xenografts growing subcutaneously in mice with a TGI of 60%/58% and 54%/50%, respectively. Both metabolites most likely contribute to the clinical antitumor activity of regorafenib in humans.

Nonclinical Pharmacokinetics

Regorafenib oral bioavailability was high (89%) in the rat and moderate in dogs (29 - 70%) with no indication of enterohepatic circulation. Regorafenib is metabolized in all species but with significant species differences. In plasma, M-2 and M-5 (glucuronide conjugate of regorafenib) were major or detectable in humans while they were either minor or not detectable in mouse, rat and dog plasma. The enterohepatic circulation noted in humans may be related to the metabolites formed. Mean plasma clearance in rats (0.15 L/kg•h) was lower than in dogs (0.24 L/kg•h). The volume of distribution was moderate in rats (0.9 L/kg) and high in dogs (1.8 L/kg). The plasma elimination half-lives of regorafenib were 4.1 to 7.3 hours in rats, 5.3 to 8.1 hours in dogs and 4 hours in mice. After administration of ^{14}C-regorafenib, the majority of radioactivity was excreted via the biliary/fecal route. In rats and dogs ~85% of the radioactivity was recovered in feces and ~71% of the dose was recovered in feces in humans. The urinary excretion was low in rat (about 6 % of the dose) and minimal in dog (<1%) while in humans renal excretion was higher (~19%). 14C-Regorafenib related radioactivity was secreted markedly into the milk of lactating rats, with approximately 50% of the dose in the milk within 48 hours. The milk/plasma ratio for AUC and Cmax was ~6. Since M-2 and M-5 were not formed to a significant degree in preclinical species, dedicated toxicology studies were performed on the two metabolites (see 16 Non-Clinical Toxicology).

General toxicology

Single oral dose administration at the highest feasible dose of 250 mg/kg did not result in mortality or treatment-related clinical signs in female mice and rats.

Clinical laboratory alterations in repeat-dose oral toxicology studies included mild shortening of thromboplastin time in rats, and increases in transaminases, total bilirubin, and TSH, and proteinuria in rats and/or dogs. After repeated oral dosing in studies up to 5 weeks, 26 weeks and 52 weeks duration in mice, rats and dogs, respectively, adverse effects were observed in a number of organs, primarily in the kidneys, liver, digestive tract, heart, lympho-/hematopoietic system, endocrine system, reproductive system and skin.

Pathologic changes in rodents and/or dogs included the following:

Glomerulopathy and tubular degeneration/regeneration were present in kidneys in mice, rats and dogs; and bile duct proliferation, pigment deposition (rats and dogs), increased microgranuloma, and centrilobular hypertrophy (dogs) were present in liver.

Gastrointestinal changes in rats included hypertrophy of stomach pylorus and of duodenum, and degeneration and inflammation of duodenum and choleduodenal junction.

In the chronic 26-week study in rats there was an increased incidence and severity of thickening of atrioventricular valves. Perivascular and/or interstitial myocardial edema was present in 4- and 13-week rat studies.

There was lymphoid atrophy or necrosis of lymphoid tissues in rats and dogs; and hypocellularity of bone marrow in mice, rats and dogs.

Necrosis/degeneration of adrenal zona fasciculata and thyroid follicular cell atrophy occurred in rodents and dogs.

Changes in reproductive organs were present in male and female rodents and dogs including: atrophy/degeneration of seminiferous tubules in testes and oligospermia or aspermia; and decreased numbers of copora lutea and increased cystic corpora lutea, decreased number of developing follicles and increased atretic follicles in ovaries. Findings in uterus and vagina of rodents accompanied the ovarian changes.

Pathologic changes were manifest in skin, particularly in dogs, but also in rats. Hair growth arrest with complete alopecia and inflammatory changes in skin occurred in dogs.

Effects in animals occurred at systemic exposures in the range of or below the anticipated human exposure (based on AUC comparison). Most treatment-related findings appeared reversible in dogs although reversibility was not clearly demonstrated in rats. Assessment of reversibility in rats was impacted by the lasting effect of damaged/broken teeth caused by regorafenib on food consumption and general body condition during the treatment-free recovery period.

Alterations of teeth and bones/cartilage and adverse effects in the reproductive system were more pronounced in young and growing rats and dogs and indicate a potential risk for children and adolescents.

Alterations with regard to increased growth of teeth (histologically associated with dentin and ameloblast degeneration) and bones/cartilage (thickening of growth plate, chondrodystrophy) are considered not to present a potential risk for adult humans, as in adults these organs are not subject to growth.

Results of 4-week repeat dose oral toxicity studies in mice with each of M-2 and M-5 (major metabolites in humans) indicated that these metabolites evoked less toxicity in mice than did regorafenib.

Genotoxicity

There was no indication for a genotoxic potential of regorafenib tested in standard assays in vitro and in vivo in mice. The metabolites M-2 and M-5 were not mutagenic in bacterial assays. M-2 but not M-5, revealed a statistically significant increase in the ratio of aberrant metaphases in an in vitro chromosome aberration assay in Chinese hamster V79 cells.

One intermediate in the manufacturing process, which is also present in the final drug substance (<0.1%), was positive for mutagenesis in an in vitro bacterial cell assay (Ames test). Genotoxicity was evaluated in the rat and the intermediate did not increase the micronucleus frequency in bone marrow. In the liver Comet Assay, the intermediate induced primary DNA damage with a no-observed-effect-level (NOEL) of 60 mg/kg which is approximately 22,000 times higher than the estimated maximal AFP-PMA body burden of 0.0027 mg/kg/day or approximately 3600 times higher based on mg/m2 body

surface area (a common approach for interspecies scaling) for a cancer patient under regorafenib therapy.

Carcinogenicity

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

Reproductive and developmental toxicology

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 (see 16 Non-Clinical Toxicology - General toxicology).

In pregnant rabbits administered regorafenib daily during organogenesis, there were compound-related findings of ventricular septal defects evident 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. At 1.6 mg/kg, regorafenib was embryolethal with total resorption in ~20% of the rabbits. The embryo-fetal development study in rats was more limited in terms of number of animals but in rats as well as rabbits, regorafenib treatment was associated with developmental toxicity, teratogenicity and pregnancy loss at subtherapeutic doses.

Juvenile toxicity

In a repeat-dose toxicity study in juvenile rats, the most prominent findings were a reduced nutritional status and growth retardation together with delayed growth and atrophy of multiple organs such as the lymphatic system, hematopoietic system, gastrointestinal tract and sexual organs. In addition, bone and teeth showed moderate to severe signs of growth disturbance.

Patient Medication Information

READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE

[Pr]STIVARGA®

regorafenib tablets

This patient medication information is written for the person who will be taking **STIVARGA**. This may be you or a person you are caring for. Read this information carefully. Keep it as you may need to read it again.

This patient medication information is a summary. It will not tell you everything about this medication. If you have more questions about this medication or want more information about **STIVARGA**, talk to a healthcare professional.

Serious warnings and precautions box

This drug should be prescribed only by a healthcare professional experienced in anticancer drugs. You may experience the following serious side effects when taking STIVARGA:

- Liver problems which may cause death.
- Bleeding problems which may cause death.
- Chest pain or heart problems.
- Brain disorder that can cause headache, confusion, seizures and visual loss.
- Severe bowel problems (a tear developing in the stomach or a bowel) which may cause death.
- High blood pressure.
- Hand-Foot Skin Reaction that can cause redness, pain, swelling, or blisters on the palms of your hands and soles of your feet.
- Infections which may cause death.

What STIVARGA is used for:

STIVARGA is used in adults to treat:

- colon or rectal cancer that has spread to other parts of the body. STIVARGA is used in patients who already received other treatments (fluoropyrimidine-based chemotherapy, oxaliplatin, irinotecan, anti-VEGF therapy, and anti-EGFR therapy).
- gastrointestinal stromal tumors that have spread to other parts of the body or cannot be removed by surgery. STIVARGA is used in patients who already received treatment with anticancer drugs imatinib and sunitinib.
- liver cancer in patients who have been previously treated with another anticancer medicine, sorafenib.

How STIVARGA works:

STIVARGA is a multikinase inhibitor. It works by:

- slowing down the growth and spread of cancer cells

- stopping/cutting off the development of new blood vessels that supply the tumors

The ingredients in STIVARGA are:

Medicinal ingredient(s): regorafenib

Non-medicinal ingredients: cellulose microcrystalline, croscarmellose sodium, iron oxide red, iron oxide yellow, lecithin (soy), macrogol, magnesium stearate, polyvinyl alcohol (partially hydrolyzed), povidone, silica colloidal anhydrous, talc and titanium dioxide

STIVARGA comes in the following dosage form(s):

Tablet (film-coated); 40 mg

Do not use STIVARGA if:

- you are allergic to regorafenib, sorafenib or any of the other ingredients of STIVARGA.

To help avoid side effects and ensure proper use, talk to your healthcare professional before you take STIVARGA. Talk about any health conditions or problems you may have, including if you:

- have liver problems including Gilbert's syndrome. Treatment with STIVARGA may lead to a higher risk of liver problems.
- have any bleeding problems or if you are taking warfarin or a medicine that thins the blood to prevent blood clots. Treatment with STIVARGA may lead to a higher risk of bleeding.
- have heart problems.
- have or have had high blood pressure and its complications, including separation of the layers of the arterial wall (artery dissection).
- have an upcoming surgery. STIVARGA might affect the way your wounds heal and treatment may need to be stopped until your wound heals.

Other warnings you should know about:

Check-ups and testing: Before starting treatment and periodically during your treatment, your healthcare professional will perform or check:

- Blood tests for:
    - electrolyte levels (including potassium, calcium, phosphorus and sodium).
    - liver function
    - thyroid stimulating hormone
- Digestive enzymes.
- How well your heart is working.
- Your blood pressure.

Pregnancy, contraception and breastfeeding:

- Avoid becoming pregnant while taking STIVARGA. It may harm your unborn baby.
- If you are pregnant, able to get pregnant, or think you are pregnant, there are specific risks you must discuss with your healthcare professional.

- Reliable birth control should be used by both males and females during treatment and for 8 weeks after the last dose of STIVARGA.
- It is not known if STIVARGA passes into breast milk. Do not breastfeed during treatment with STIVARGA.

Fertility: Treatment with STIVARGA may affect the ability in both men and women to have children.

Skin problems:

STIVARGA can cause hand-foot skin reaction. Use shoe cushions and gloves to reduce the risk of developing this skin condition. To manage your symptoms, your healthcare professional may recommend the use of creams. If you experience this side effect, your healthcare professional may change your dose or temporarily stop your treatment until this skin condition improves.

Tell your healthcare professional about all the medicines you take, including any drugs, vitamins, minerals, natural supplements or alternative medicines.

STIVARGA may affect the way other medicines work, and other medicines may affect how STIVARGA works. You may need to change the dosage or stop taking one of the medicines.

The following may interact with STIVARGA:

- Medicines to treat fungal infections (e.g. ketoconazole)
- Medicines to treat bacterial infections (e.g. rifampin)
- Medicines to treat epilepsy (e.g. phenytoin, carbamazepine, phenobarbital)
- Methotrexate, a medicine used to treat cancer
- Medicines used to treat high cholesterol (e.g. rosuvastatin, fluvastatin, atorvastatin)
- St. John's wort

How to take STIVARGA:

- Take exactly as your healthcare professional has told you. Speak with your doctor or pharmacist if you are not sure.
- Swallow tablets whole with water.
- STIVARGA is taken in a four week cycle. You take STIVARGA for three weeks followed by one week off. Your doctor may change, reduce, interrupt or stop your treatment if necessary.
- STIVARGA should be taken at the same time each day after a light (low fat) meal. An example of a low-fat, low-calorie meal is two slices of white toast with 1 tablespoon of low-fat margarine and 1 tablespoon of jelly and 8 ounces of skim milk (approximately 319 calories and 8.2 grams of fat).

Usual dose:

Take 4 tablets (160 mg of regorafenib) once a day for three weeks. Do NOT take any pills in week four.

Overdose:

If you think you, or a person you are caring for, have taken too much STIVARGA, contact a healthcare professional, hospital emergency department, regional poison control centre or Health Canada's toll-free number, 1-844 POISON-X (1-844-764-7669) immediately, even if there are no signs or symptoms.

Missed dose:

If you miss a dose, take it as soon as you remember on that day. Do not take two doses of STIVARGA on the same day to make up for a missed dose from the previous day. Tell your healthcare professional about any missed dose.

Possible side effects from using STIVARGA:

These are not all the possible side effects you may have when taking STIVARGA. If you experience any side effects not listed here, tell your healthcare professional.

The side effects of STIVARGA may include:

- pain
- rash, itching or peeling of your skin
- tiredness, fatigue
- diarrhea (frequent or loose bowel movements)
- loss of appetite

Serious side effects and what to do about them

Frequency/Side Effect/Symptom	**Talk to your healthcare professional**		**Stop taking the/this drug (if applicable) and get immediate medical help**
	Only if severe	**In all cases**	
Common			
Bleeding problems: blood in the stools or black stools, blood in the urine, stomach pain, coughing / vomiting up blood, menstrual bleeding that is heavier than normal, unusual vaginal bleeding, frequent nose bleeds			✓
High blood pressure: severe and persistent headache, visual disturbances			✓
Hand-foot skin reaction: redness, pain, swelling, or blisters on the palms of your hands or sole of your feet		✓	
Infection: high fever, severe cough with or without an increase in mucus (sputum) production, severe sore throat, shortness of breath, burning or pain when urinating, unusual vaginal discharge or irritation, redness, swelling and/or pain in any part of		✓	

Frequency/Side Effect/Symptom	Talk to your healthcare professional		Stop taking the/this drug (if applicable) and get immediate medical help
	Only if severe	In all cases	
the body			
Wound healing problems		✓	
Rare			
Serious liver problems: yellowish discoloration of the skin and the whites of the eyes (jaundice), dark urine, confusion and/or disorientation, nausea or vomiting			✓
Decreased blood flow to the heart and heart attack: chest discomfort or pain which may spread beyond your chest to your shoulders, arms, back, neck, teeth, jaw or stomach and may come and go, shortness of breath, sudden outbreak into a sweat with cold, clammy skin, feeling dizzy or fainting			✓
Severe stomach and bowel problems: severe stomach (abdominal) pain or stomach pain that does not go away, vomiting blood, red or black stools			✓
Severe drug allergic reaction: skin eruption, fever, shortness of breath, liver problems			✓
Very rare			
Artery Dissection (a tear forms in a wall of an artery): sudden severe pain in the back, chest or abdomen			✓
Artery Aneurysm (a bulge in the wall of any artery including in the chest, arms, legs, heart and brain): symptoms will differ by the site. They can be cough, coughing up blood. Strong pain high in your neck or in your back when you didn't hurt yourself. Problems swallowing. Hoarse voice. Unusual pulsing in your chest or abdomen			✓
Unknown			

Frequency/Side Effect/Symptom	Talk to your healthcare professional		Stop taking the/this drug (if applicable) and get immediate medical help
	Only if severe	In all cases	
Thrombotic Microangiopathies (blood clots in small blood vessels): bleeding, bruising, weakness, confusion, fever, chills, nausea, vomiting, diarrhea, low or no urine output			✓

If you have a troublesome symptom or side effect that is not listed here or becomes bad enough to interfere with your daily activities, tell your healthcare professional.

Reporting side effects

You can report any suspected side effects associated with the use of health products to Health Canada by:

- Visiting the Web page on Adverse Reaction Reporting (canada.ca/drug-device-reporting) for information on how to report online, by mail or by fax; or
- Calling toll-free at 1-866-234-2345.

NOTE: Contact your healthcare professional if you need information about how to manage your side effects. The Canada Vigilance Program does not provide medical advice.

Storage:

Keep out of the reach and sight of children.

Do not use the tablets after the expiry date which is stated on the label after EXP. The expiry date refers to the last day of that month.

Store STIVARGA at 15- 30°C in the original package to protect it from moisture.

Keep the bottle tightly closed after first opening and keep the desiccant in the bottle.

Once the bottle is opened the medicine is to be discarded after 7 weeks.

Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help to protect the environment.

If you want more information about STIVARGA:

- Talk to your healthcare professional
- Find the full product monograph that is prepared for healthcare professionals and includes the Patient Medication Information by visiting the Health Canada Drug Product Database website (https://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/drug-product-database.html); the manufacturer's website http://www.bayer.ca or by calling Bayer Medical Information at 1-800-265-7382 or emailing canada.medinfo@bayer.com.

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