27 June 2013
EMA/CHMP/403683/2013
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Stivarga

International non-proprietary name: REGORAFENIB

Procedure No. EMEA/H/C/002573/0000

Note

Assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

Table of contents

List of abbreviations

ADH	alcohol dehydrogenase
ADR	adverse drug reaction
AE	adverse event
AESI	adverse event of special interest
ALP	alkaline phosphatase
ALT	alanine aminotransferase
AST	aspartate aminotransferase
AUC	area under the curve
BCRP	Breast Cancer Resistant Protein
BCS	Biopharmaceutical Classification System
BRAF	virus-induced Rapidly Accelerated Fibrosarcoma (v-raf) B1 homologue
BSC	best supportive care
BUN	blood urea nitrogen
BW	body weight
CNS	central nervous system
CI	confidence interval
CR	complete response
CTCAE	common terminology criteria for adverse events
CAPIRI	capecitabine, irinotecan
CAPOX	capecitabine, oxaliplatin
CMH	Cochran-Mantel-Haenszel
CRC	colorectal cancer
CYP	cytochrome P450
DCE-MRI	Dynamic contrast enhanced MRI (magnetic resonance imaging)
DILI	drug-induced liver injury
DPD	dihydro-pyrimidine dehydrogenase
ECG	electrocardiogram
ECOG	Eastern Cooperative Oncology Group
EGFR	epidermal growth factor receptor
FACS	fluorescence activated cell sorter
FOLFIRI	folinic acid (leucovorin), 5-fluorouracil, irinotecan
FOLFOX	folinic acid (leucovorin), 5-fluorouracil, oxaliplatin
GGT	gamma glutamyl transferase
HB	haemoglobin
HCC	hepatocellular carcinoma
HCT	haematocrit
HFSR	Hand-foot skin reaction
HPLC	high performance liquid chromatography
HR	hazard ratio
KRAS	Kirsten rat sarcoma 2 viral oncogene homologue
LDH	lactate dehydrogenase
LVEF	left ventricular ejection fraction
MCH	mean corpuscular haemoglobin

MCHC	mean corpuscular haemoglobin concentration
mCRC	metastatic colorectal cancer
MCV	mean corpuscular volume
MRP	multidrug resistance-associated protein
MTD	maximum tolerated dose
NSCLC	non-small cell lung cancer
NOAEL	no observed adverse effect level
OATP	Organic anion-transporting polypeptide
ORR	objective response rate
OS	overall survival
OVAT	One Variable At a Time
PK	pharmacokinetics
PFS	progression free survival
PR	partial response
RECIST	response evaluation criteria in solid tumours
RPES	Posterior reversible encephalopathy syndrome
SAE	serious adverse event
SD	stable disease
SJS	Stevens-Johnson-Syndrome
TEN	Toxic epidermal necrolysis
TG	triglycerides
TKI	tyrosine kinase inhibitor
TSH	thyroid stimulating hormone
UGT	Uridine 5'-diphospho-glucuronosyltransferase
ULN	upper limit of normal
VEGF	vascular endothelial growth factor
VEGFR	vascular endothelial growth factor receptor

1. Background information on the procedure

1.1. Submission of the dossier

The applicant Bayer Pharma AG submitted on 3 May 2012 an application for Marketing Authorisation to the European Medicines Agency (EMA) for Stivarga, through the centralised procedure falling within the Article 3(1) and point 3 of Annex of Regulation (EC) No 726/2004. The eligibility to the centralised procedure was agreed upon by the EMA/CHMP on 21 July 2011.

The applicant applied for the following indication: Stivarga is indicated for the treatment of adult patients with metastatic colorectal cancer (CRC) who have been previously treated with, or are not considered candidates for, available therapies. These include fluoropyrimidine-based chemotherapy, an anti-VEGF therapy, and, in case of KRAS wild type CRC, an anti-EGFR therapy.

The legal basis for this application refers to:

Article 8.3 of Directive 2001/83/EC - complete and independent application

The application submitted is composed of administrative information, complete quality data, non-clinical and clinical data based on applicants' own tests and studies and/or bibliographic literature substituting/supporting certain tests or studies.

Information on Paediatric requirements

Pursuant to Article 7 (EC) No 1901/2006, the application included an EMA Decision CW/1/2011 on the granting of a class waiver.

Information relating to orphan market exclusivity

Similarity

Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the applicant did not submit a critical report addressing the possible similarity with authorised orphan medicinal products because there is no authorised orphan medicinal product for a condition related to the proposed indication.

New active Substance status

The applicant requested the active substance regorafenib contained in the above medicinal product to be considered as a new active substance in itself, as the applicant claims that it is not a constituent of a product previously authorised within the Union.

Scientific Advice

The applicant did not seek Scientific Advice at the CHMP for the colorectal cancer indication.

Licensing status

The product was not licensed in any country at the time of submission of the application.

1.2. Manufacturers

Manufacturer responsible for batch release

Bayer Pharma AG
51368 Leverkusen
Germany

1.3. Steps taken for the assessment of the product

The Rapporteur and Co-Rapporteur appointed by the CHMP were:

Rapporteur: Barbara van Zwieten-Boot Co-Rapporteur: Daniela Melchiorri

- The application was received by the EMA on 3 May 2012.
- Accelerated Assessment procedure was agreed-upon by CHMP on 19 April 2012
- The procedure started on 23 May 2012.
- The Rapporteur's first Assessment Report was circulated to all CHMP members on 10 August 2012. The Co-Rapporteur's first Assessment Report was circulated to all CHMP members on 10 August 2012
- During the meeting on 20 September 2012, the CHMP agreed on the consolidated List of Questions to be sent to the applicant. The final consolidated List of Questions was sent to the applicant on 20 September 2012
- The applicant submitted the responses to the CHMP consolidated List of Questions on 15 November 2012.
- The Rapporteurs circulated the Joint Assessment Report on the applicant’s responses to the List of Questions to all CHMP members on 19 December 2012
- During the PRAC meeting on 10 January 2013, the PRAC adopted an RMP Advice and assessment overview
- During the CHMP meeting on 17 January 2013, the CHMP agreed on a list of outstanding issues to be addressed in writing by the applicant
- The applicant submitted the responses to the CHMP List of Outstanding Issues on 18 February 2013.
- During the PRAC meeting on 7 March 2013, the PRAC adopted an RMP Advice and assessment overview
- During a meeting of a SAG Oncology on 7 March 2013, experts were convened to address questions raised by the CHMP
- The Rapporteurs circulated the Joint Assessment Report on the applicant’s responses to the

list of outstanding issues to all CHMP members on 13 March 2013 During the CHMP meeting on 21 March 2013, the CHMP agreed on a 2nd list of outstanding issues to be addressed in writing by the applicant

- The applicant submitted the responses to the CHMP List of Outstanding Issues on 27 May 2013.
- The Rapporteurs circulated the Joint Assessment Report on the applicant's responses to the 2nd list of outstanding issues to all CHMP members on 7 June 2013
- During the PRAC meeting on 13 June 2013, the PRAC adopted an RMP Advice and assessment overview
- The Rapporteurs circulated an updated Joint Assessment Report on the applicant's responses to the 2nd list of outstanding issues to all CHMP members on 21 June 2013
- During the meeting on 27 June 2013, the CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a positive opinion for granting a Marketing Authorisation to Stivarga.

2. Scientific discussion

2.1. Introduction

Colorectal cancer (CRC) is the third most common cancer in men and the second most common cancer in women worldwide. In Europe, CRC is the most frequently diagnosed cancer and the second leading cause of cancer death (Ferlay J, Parkin DM, Steliarova-Foucher E (2010). 'Estimates of cancer incidence and mortality in Europe in 2008' Eur J Cancer; 46(4):765-81). The stage of disease at the time of diagnosis represents the most relevant prognostic factor. Five-year survival rates range from 93% for stage I disease to less than 10% for stage IV. In approximately 60% of cases the initial diagnosis is carried out at late stages of disease which are characterised by poor prognosis.

Surgery, followed by adjuvant chemotherapy in certain cases, represents the standard therapeutic approach for patients with loco-regional disease. However, around 25% of patients will subsequently develop distant metastases. Besides this, approximately 25% of patients present with metastatic disease at initial diagnosis.

At present, there is no curative treatment for patients with metastatic CRC (mCRC). When left untreated, these patients have a poor prognosis, with a median survival of about 6 months. With the exception of few selected patients where resection of metastases is indicated, the standard treatment for patients with metastatic disease is represented by systemic chemotherapy, which has demonstrated to significantly improve overall survival to an average of 20 months. The currently available systemic chemotherapeutic options for patients with mCRC consist essentially of fluoropyrimidine-based regimens alone or in combination with oxaliplatin (FOLFOX, CAPOX) or irinotecan (FOLFIRI, CAPIRI). Fluoropyrimidine-based regimens have demonstrated similar activity when given as first or second line therapy (Tournigand C, André T, Achille E, Lledo G, Flesh M, Mery-Mignard D, Quinaux E, Couteau C, Buyse M, Ganem G, Landi B, Colin P, Louvet C, de Gramont A (2004). 'FOLFIRI followed by FOLFOX6 or the reverse sequence in advanced

colorectal cancer: a randomized GERCOR study' J Clin Oncol; 22(2):229-37). Addition of the anti-VEGF monoclonal antibody bevacizumab to the above mentioned first or second line chemotherapies has demonstrated to modestly improve survival and delay disease progression. In patients carrying tumours with a wild type form of the Kirsten rat sarcoma (KRAS) gene, the anti-epidermal growth factor receptor (EGFR) monoclonal antibodies cetuximab or panitumumab can also be administered as monotherapy or in combination with fluoropyrimidine-based regimens. Finally, the anti-VEGF fusion protein aflibercept has recently been approved in combination with FOLFIRI as second line treatment of patients with mCRC.

Regorafenib is low molecular weight, orally available, inhibitor of multiple protein kinases, including kinases involved in tumour angiogenesis (VEGFR1, -2, -3, TIE2), oncogenesis (KIT, RET, RAF-1, BRAF, BRAFV600E), and the tumour microenvironment (PDGFR, FGFR). In preclinical studies regorafenib has demonstrated antitumour activity in a broad spectrum of tumour models including colorectal tumour models which is mediated both by its antiangiogenic and antiproliferative effects. Major human metabolites (M-2 and M-5) exhibited similar efficacies compared to regorafenib both *in vitro* and *in vivo* models.

The indication sought for regorafenib is the following: Stivarga is indicated for the treatment of adult patients with metastatic colorectal cancer (CRC) who have been previously treated with, or are not considered candidates for, available therapies. These include fluoropyrimidine-based chemotherapy, an anti-VEGF therapy, and, in case of KRAS wild type CRC, an anti-EGFR therapy.

The finally approved indication is the following: Stivarga is indicated for the treatment of adult patients with metastatic colorectal cancer (CRC) who have been previously treated with, or are not considered candidates for, available therapies. These include fluoropyrimidine-based chemotherapy, an anti-VEGF therapy and an anti-EGFR therapy.

The recommended dose is 160 mg once daily (four 40 mg tablets OD) for 3 weeks on therapy followed by 1 week off therapy to comprise a cycle of 4 weeks. Regorafenib should be taken at the same time each day after a light meal.

2.2. Quality aspects

2.2.1. Introduction

The finished product is presented as film-coated tablets containing 40 mg of regorafenib as the active substance. The excipients used in the formulation of Stivarga are povidone, croscarmellose sodium, microcrystalline cellulose, silica colloidal anhydrous and magnesium stearate.

The product is available in white opaque HDPE bottle closed with a PP/PP screw cap with sealing insert and a molecular sieve desiccant. Each bottle contains 28 film-coated tablets.

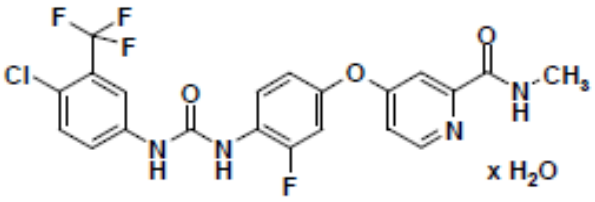
2.2.2. Active Substance

Regorafenib monohydrate is a white to slightly pink or slightly brownish solid substance, practically insoluble in water, dilute alkaline solution, dilute acid solution, n-heptane, glycerine and toluene. It is slightly soluble in acetonitrile, dichloromethane, propylene glycol, methanol, 2-

propanol, ethanol and ethyl acetate. It is sparingly soluble in acetone and soluble in PEG 400 (macrogol). Regorafenib is not hygroscopic.

The chemical name is 4-[4-({[4-chloro-3-(trifluoromethyl)phenyl]carbamoyl} amino)-3-fluorophenoxy]-Nmethylpyridine-2-carboxamide (monohydrate) and has the following structural formula:

Figure 1: chemical structure of regorafenib



Regorafenib crystallizes in three modifications with melting points at 206 °C (Mod. I), at 181 °C (Mod. II,) and at 141 °C (Mod. III). In addition, one pseudo-polymorph has been found, a monohydrate (water content of 3.6 %). Solid state form characterisation has been performed by XRD, IR, Raman, NIR, FIR, 13C-solid state-NMR, DSC and TGA. Regorafenib monohydrate was selected as stable active substance which can be manufactured reproducibly and is used in crystalline, non-micronized form for the production of Regorafenib tablets.

The structure of regorafenib monohydrate has been elucidated using IR and Raman spectroscopy, UV-VIS, NMR (1H and 13C), MS, elemental analysis and X-Ray structural analysis. The analysis was performed on one batch of the active substance.

Manufacture

Regorafenib is synthesized in three main steps using well defined starting materials with acceptable specification.

Adequate in-process controls are applied during the synthesis. The specifications and control methods for intermediate products, starting materials and reagents have been presented.

The manufacturing process has been developed using elements of Quality by Design such as risk-assessment, OVAT (One Variable At a Time) experiments, design of experiments and spiking experiments. The results of these studies were used to define proven acceptable ranges for the different steps of the regorafenib manufacturing process. For each stage of the synthesis an experimental model was established taking potential scale effects into consideration. The models used were shown to be scientifically justified and therefore enable a prediction of quality. This supports the extrapolation of operating conditions and amounts of reacting materials across multiple scales and equipment.

The characterisation of the active substance and its impurities are in accordance with the EU guideline on chemistry of new active substances. Potential and actual impurities were well discussed with regards to their origin and characterised.

Impurities present at higher than the qualification threshold according to ICH Q3A were qualified by toxicological and clinical studies and appropriate specifications have been set.

Batch analysis data is provided on three commercial scale batches produced with the proposed synthetic route, and the batch analysis data show that the active ingredient can be manufactured reproducibly.

The active substance is packed in polypropylene or polyethylene bags. The secondary packaging is a closed container for mechanical protection.

Specification

The active substance specification includes tests for: appearance (visual examination), identity (IR, HPLC), assay (HPLC) impurities (HPLC), residual solvents (GC) and water content (Karl Fisher).

The analytical methods used have been adequately described and (non-compendial methods) appropriately validated in accordance with the ICH guidelines.

Batch analysis data on three production scale batches of the active substance are provided. The results are within the specifications and consistent from batch to batch.

Stability

Three pilot scale batches of the active substance packed in the intended commercial package from the proposed manufacturer were put on stability testing as per ICH conditions: under long term (25°C/60%RH) for up 24 months, and accelerated (40°C/75%RH) for up 12 months. Results on stress conditions (thermal, oxidative, and hydrolytic stress) show that regorafenib is chemically extremely stable to thermal stress, has good stability towards hydrolytic stress and is quite stable to oxidative stress. Photostability studies were also performed on one batch. The results showed that in the solid state regorafenib is not sensitive to light, when irradiated according to ICH Q1B.

The following parameters were tested: appearance, organic impurities, assay and water. The stability results justify the proposed retest period in the proposed container.

2.2.3. Finished Medicinal Product

Pharmaceutical Development

The objective of the pharmaceutical development was to provide an immediate release solid dosage form of regorafenib with high oral bioavailability and high patient compliance.

A solid solution (co-precipitate) tablet formulation was selected as dosage form, in order to transfer the active substance, which is characterized by an extremely low solubility in aqueous media, into the amorphous form. Upon contact with the dissolution medium the tablets disintegrate and the solid solution dissolves forming a supersaturated solution with a significantly higher concentration of regorafenib in solution than expected based on the solubility of the crystalline active substance. Consequently, higher oral bioavailability is achieved when

administering regorafenib as a solid solution tablet compared to a conventional tablet comprising the active substance in crystalline micronized form.

The excipients used in the formulation of regorafenib tablets are common ingredients for a solid oral dosage form. The excipients have been chosen based on preliminary formulation development experience and compatibility studies. Regorafenib tablets are film-coated in order to provide a homogeneous appearance, to add a colour for product identification, to reduce dusting during handling of the tablets and to facilitate swallowing. The coating system comprises PVA, ferric oxide red, ferric oxide yellow and titanium dioxide, lecithin, macrogol and talc.

The pharmaceutical development of the finished product contains QbD elements.

A comprehensive risk analysis was performed using the failure mode effect analysis (FMEA) method in order to define critical process steps and process parameters that may have an influence on specified finished product attributes. The risk identification was based on the prior knowledge of products with similar formulations and manufacturing processes as well as on the experience from formulation development, process design and scale-up studies with regorafenib tablets. The critical process parameters were monitored carefully during validation and the critical quality attributes were evaluated intensively during process validation and stability tests.

In addition, further studies were conducted to define adequate operating ranges for these process parameters to ensure a robust and reproducible manufacturing process. Furthermore, development studies enabled the identification of appropriate in-process controls and product specifications to ensure the intended quality, safety, efficacy and performance of the product through traditional final product release testing.

The dissolution method has been adequately developed and its discriminating capability demonstrated. The use of surfactant and the dissolution medium was justified. Sink conditions were confirmed. The dissolution test was shown to be sufficiently discriminative in detecting relevant changes to the solid solution granules.

The formulation used during clinical studies is the same as that used for marketing.

The primary packaging proposed is white opaque HDPE bottle closed with a PP/PP screw cap with sealing insert and a molecular sieve desiccant. The material complies with Ph.Eur. requirements and it is adequate to support the stability and use of the product.

Adventitious agents

No excipients derived from animal or human origin have been used.

Manufacture of the product

The manufacture of the finished product involves conventional processes including (1) mixing, (2) granulation, (3) roller compaction, (4) blending, (5) post-blending, (6) tableting, (7) coating and (8) drying. The process is considered to be a standard manufacturing process.

The manufacturing process has been validated by a number of studies for the major steps of the manufacturing process and has been demonstrated to be capable to reproducibly produce

finished product of the intended quality. The in process controls are adequate for this film coated tablet preparation.

The batch analysis data on five full scale batches shows that the tablets can be manufactured reproducibly according to the agreed finished product specification, which is suitable for control of this oral preparation.

Product specification

The finished product release specifications include appropriate tests for appearance (visual examination), identity (HPLC and TLC or NIR), uniformity of dosage units (Ph.Eur.), degradation products (HPLC), assay (HPLC), dissolution (Ph.Eur.), absence of crystalline regorafenib (XRPD), water content (Karl Fisher), residual solvents (GC) and microbiological contamination (Ph.Eur).

Batch analysis results of five production scale batches confirm consistency and uniformity of manufacture and indicate that the process is capable and under control.

The specification is acceptable, ensures batch-to-batch consistency and provides an adequate control of the solid state form. The analytical methods have been adequately described and validated.

Stability of the product

Stability data on three pilot scale batches stored under long term conditions for 36 months at 25ºC/60%RH and at 30°C/76% RH, and for up to 6 months under accelerated conditions at 40ºC/75%RH according to ICH guidelines were provided. The batches of regorafenib film-coated tablets are identical to those proposed for marketing and were packed in the primary packaging proposed for marketing.

Samples were tested for appearance, dissolution, degradation products, assay, water content, breaking load, disintegration and microbial purity. The analytical procedures used were stability indicating.

Photostability testing as defined in the ICH Guideline on Photostability Testing of New Drug Substances and Products was performed. No significant differences were seen and no light storage restrictions are needed.

Stability data has been provided demonstrating that the product remains stable following first opening of the container, when stored at 30°C/75% RH. The in-use stability data provided justify the claimed maximum in-use shelf-life of 7 weeks.

The finished product is sensitive to moisture. For this reason the tablets are packed and stored in tightly closed HDPE bottles with a desiccant capsule inside.

Based on available stability data, the proposed shelf-life and storage conditions as stated in the SmPC are acceptable.

2.2.4. Discussion on chemical, pharmaceutical and biological aspects

Information on development, manufacture and control of the active substance and finished product has been presented in a satisfactory manner. The finished product is formulated as an amorphous solid solution dosage form, in the presence of a precipitation inhibitor. This leads to an increase in solubility of the active substance. The presence of the precipitation inhibitor helps maintain supersaturation levels, thereby improving bioavailability. Quality by Design principles have been used in this application during the pharmaceutical development but a Design Space was not claimed for the manufacturing process of the active substance neither for the finished product. Risk assessment was performed to optimise the manufacturing conditions of the active substance. For the finished product, the Quality by Design approach was used for the development of the manufacturing process. The control strategy and process validation follow the traditional approach. The results of tests carried out indicate consistency and uniformity of important product quality characteristics, and these in turn lead to the conclusion that the product should have a satisfactory and uniform performance in the clinic.

2.2.5. Conclusions on the chemical, pharmaceutical and biological aspects

The quality of this product is considered to be acceptable when used in accordance with the conditions defined in the SmPC. Physicochemical and biological aspects relevant to the uniform clinical performance of the product have been investigated and are controlled in a satisfactory way.

2.3. Non-clinical aspects

2.3.1. Introduction

In vivo studies were performed in mouse, rat, rabbit, dog and monkey. All pivotal toxicological studies were conducted in accordance with current regulatory requirements and in compliance with the principles of Good Laboratory Practice (GLP). Safety pharmacology studies were conducted under GLP regulations as requested by ICH S7A and B with the exception of a study investigating the effect of regorafenib on hERG K+ currents.

2.3.2. Pharmacology

Primary pharmacodynamic studies

The kinase activity of regorafenib was tested in biochemical assays by either measuring enzyme inhibition or by a competitive binding assay. Regorafenib inhibited a distinct set of kinases, including the angiogenic and stromal receptor tyrosine Kinases (RTKs) VEGFR1-3, TIE2, FGFR1 and PDGFRβ with IC50 values ranging from 4 to 311 nM, and the oncogenic RTKs KIT and RET, along with the intracellular signalling kinases C-RAF/RAF-1 and wild-type and mutant B-RAF with IC50 values in the range of ~ 2 to 30 nM. M-2 and M-5, the two pharmacologically active

metabolites of regorafenib, showed kinase selectivity profiles similar but different from regorafenib. Inhibition of kinase phosphorylation was analysed in cells expressing relevant target kinases. Regorafenib inhibited phosphorylation of VEGFR2, VEGFR3, TIE2, PDGFRβ, KIT (wild-type and mutant), mutant RET and FGFR with IC50 ranging from ~ 3-200 nM; persistent inhibition of VEGFR2 autophosphorylation was observed for 24h after removal of regorafenib from NIH-3t3/VEGFR2 cells. The antiproliferative activity of regorafenib was evaluated in a panel of tumour cell lines of different origin and on VEGF stimulated proliferation of HUVECs. Inhibition of proliferation was seen for most cell lines, although the IC50s were in the lower µM range and IC50 values could not be determined for a number of cell lines (highest concentration tested was 10 µM).

Xenografts of cancer specimens derived from patients were injected in immunodeficient mice to test the *in vivo* antitumour effect of regorafenib, orally administered at a daily dose of 10 mg/kg for 22 days. The drug, either alone or in combination with irinotecan, induced a significant growth delay in patient derived-CRC xenografts. However, in only 2 of 4 patient derived-CRC xenografts a significant growth inhibition was observed for regorafenib treated animals, and in only 1 of these 4 this response was better than oxaliplatin (a substance stated to have only limited anti-colorectal tumour effect). Potent tumour growth inhibition was seen in 8 patient-derived gastric cancer (GC) xenograft models. Dose dependent tumour growth inhibition was seen in mice for regorafenib and, with lower potency, for the two active metabolites M-2 and M-5, at oral doses of 3 or 10 mg/kg for 27 days. No correlation was observed between antitumour activity and the mutation status of either KRAS or BRAF in the injected cell lines. Regorafenib also inhibited syngeneic orthotopic or intramuscularly growing liver, breast, and brain tumours, significantly improving for example the survival of mice transplanted with a syngeneic hepatoma. The mechanistic data showed reduced vascularisation and increased apoptosis in tumour tissue.

Secondary pharmacodynamic studies

An *in vivo* assay based on the transient hypotensive effect of VEGF in anaesthetised rats was used to characterise the acute effect of regorafenib and its metabolites M-2 and M-5 after intravenous administration. Intravenous administration of 0.1 mg/kg regorafenib (10 minutes prior to VEGF injection) attenuated while injection of 1 mg/kg completely prevented the hypotensive response to VEGF. Also M-2 and M-5 inhibited the transient hypotensive effect induced by VEGF injection.

Safety pharmacology programme

In vitro data from the whole-cell voltage-clamp technique on HEK293 cells stably transfected with the HERG K+ channel indicated that regorafenib as well as M-2 and M-5 can inhibit the hERG K+ current in a concentration-dependent manner. However, exposure of rabbit cardiac Purkinje fibers to regorafenib did not induce changes of resting membrane potential, action potential amplitude, maximal depolarization velocity and action potential duration at 20 % repolarization at all concentrations tested with the exception of the highest one which was close to the limit of solubility.

For the cardiovascular and respiratory systems, four GLP-compliant studies in anesthetised dogs were submitted. A single intraduodenal administration of regorafenib as suspension at doses of 10, 30 and 100 mg/kg or a cumulative intravenous infusion of regorafenib, M-2 and M-5, at dose steps of 0.25, 0.75 and 2.25 mg/kg (30 minutes per dose step) had no effects on cardiovascular function, ECG, lung mechanics, acid/base-status, haematocrit and plasma electrolytes.

Four GLP-compliant studies in conscious male rats were conducted in order to investigate potential effects of regorafenib and its metabolites M-2 and M-5 on parameters of CNS function. Single oral doses of regorafenib (2, 10, and 50 mg/kg), M-2 (1, 5 and 20 mg/kg,) or M5 (1, 5 and 20 mg/kg) did not elicit substantial adverse CNS (behavioural, locomotor activity, body temperature) effects. No effect on nocifensive reflex responses to acute heart exposure, hexobarbital sleep and chemoconvulsion threshold dose were seen following single oral doses of regorafenib (2, 10 and 50 mg/kg).

In another GLP-compliant study, treatment with regorafenib inhibited the intestinal barium transport in rats in a statistically significant and dose-related manner.

Finally, after a single oral dose of regorafenib, a significant decrease in blood glucose concentration was seen in rats.

Pharmacodynamic drug interactions

Regorafenib was tested in an *in vivo* tumour xenograft study in combination with irinotecan and in another study with an investigational MEK inhibitor, without observing additional toxicity in either case. Regarding synergism, a beneficial effect from the addition of regorafenib to irinotecan was only observed in the most regorafenib-sensitive tumour.

2.3.3. Pharmacokinetics

The *in vivo* pharmacokinetics of regorafenib and its metabolites M-2 and M-5 was investigated in mouse, rat, rabbit, dog and monkey. Additionally, in vitro studies were performed to investigate plasma protein binding, blood cell/plasma partitioning, drug-drug interaction potential, metabolism and transport.

The permeability of regorafenib was determined in Caco-2 cells; a comparison with 22 reference compounds revealed that regorafenib is highly permeable.

Single IV and/or PO administration studies were performed in rats, dogs and monkey. The oral bioavailability of regorafenib was high in rats and independent of dose (~80%). In contrast, the absolute bioavailability in dogs decreased with increasing dose (from ~70 to 29%). Cmax was reached after 4 to 6 h in rat and after 1.6 to 2.7 h in dogs and monkeys. The volume of distribution was lower in rats than in dogs (0.9 versus 1.8 L/kg). In mice, the AUC and Cmax increased slightly more than dose proportional with increasing dose at the 1 to 20 mg/kg and a slightly less than dose proportional increase at 20 to 80 mg/kg. In rats, the AUC was dose proportional and the Cmax increased slightly less than dose proportional. In dogs, AUC and Cmax increased dose proportionally from 1 to 2.5 mg/kg and less than dose proportional from 2.5 to 10 mg/kg.

After repeated dosing, a slight to moderate increase in AUC and Cmax was observed in rat and rabbit. In contrast, AUC and Cmax decreased slightly to moderately in mice and dogs. In mice, the AUC and Cmax increased slightly more than dose proportional with increasing dose at the low to medium dose and a slightly less than dose proportional increase at the medium to high dose.

The binding of regorafenib to plasma proteins of mice, rats, rabbits, monkeys, dogs and human, investigated *in vivo*, was high (>98%) and species dependent. The main binding protein was serum albumin. The *in vitro* blood-to-plasma ratio of regorafenib (1-45 µg/L) was investigated in blood from rat, dog and human. Regorafenib was mainly distributed into plasma with a blood-to-plasma ratio of 0.63 to 0.72.

Regorafenib radioactivity was thoroughly distributed to almost all organs and tissues and there was no evidence of irreversible binding or retention of radioactivity. In terms of AUC, exposure was highest for the kidney, liver, adrenal gland, Harderian gland, submandibular gland and cardiac muscle. After 168 h, radioactivity was still present in several tissues, including thyroid, hypophysis, bone marrow, liver and kidney. After a single oral dose of [14C]-regorafenib (3 mg/kg) to pregnant albino rats a moderate penetration across the placental barrier was observed.

In vitro metabolite profiles revealed two primary phase I reactions: N oxidation at the pyridine to give M-2 and hydroxylation of the N-methyl group to give M-3. Based on comparison of metabolite profiles, humans, mice, rabbits and monkeys favour M-2 over M-3 formation. In contrast, rat and dog favour the formation of M-3 and only small amounts of metabolite M-2 were found. Incubations of regorafenib with hepatocytes showed the same species dependence. Furthermore, an important interspecies difference was the presence of two glucuronides (M-7 and M-8) in human hepatocyte incubations. Rat and dog hepatocytes were not capable of forming these conjugates.

CYP3A4 catalysed the formation of the metabolites M-2 and M-3. CYP2J2 only catalysed the formation of M-3. The formation of M-4 and M-6 were catalysed by alcohol dehydrogenase (ADH). UGT1A9 is the major enzyme involved in the glucuronidation of regorafenib and M-2 (metabolite M-7 and M-8) and UGT1A7 to a lesser extent.

The *in vivo* biotransformation of regorafenib was studied in mice, rats, dogs, and humans. Following a single oral administration of regorafenib, the parent compound was the major component in mouse, rat, dog, and human plasma. Metabolite M-2 was the main metabolite in human plasma, but was only found in small amounts in mouse plasma and not in rat and dog plasma. Furthermore, the metabolites M-5 (amide pyridine N-oxide) and M-7 (urea N-glucuronide) were only found in human plasma as minor metabolites and could not be detected in plasma of all other species. In rat and dog plasma methylhydroxylated metabolite M-3 was a major. Metabolite M-4 was found in plasma of all species, but as trace in humans and as major metabolite in rats. Metabolite M-6 was only present in considerable amounts in dog plasma, but could only be detected in traces in plasma of rats and not at all in plasma of humans and mice.

The excretion of radioactivity was mainly via the biliary/faecal route and to a minor extent via urine. However, the contribution of urine to the overall excretion played a more important role in humans than in the other species. Furthermore, regorafenib or its radioactive metabolites were secreted into the milk. No metabolite profile was identified in milk.

Regorafenib was not displaced from its plasma protein binding by any tested highly protein bound compound at clinically relevant concentrations. Regorafenib, M-2 and M-5 were inhibitors of P-glycoprotein and BCRP. Regorafenib, M-2 and M-5 are not substrates of MRP2 at clinically relevant concentrations. Regorafenib was not a substrate for P-glycoprotein, BCRP, OATP1B1, and OATP1B3. Regorafenib and metabolites M-2 and M-5 are inhibitors of P-glycoprotein and BCRP and therefore interaction may occur via these transporters. Regorafenib, M-2 and M-5 are not inhibitors of DPD, which is important in the metabolism of 5 fluorouracil. Regorafenib was not an inducer of CYP1A2, CYP2B6 and CYP3A4. However, regorafenib, M-2 and M-5 were inhibitors of CYP2C8, CYP2B6, CYP2C9, CYP2D6, UGT1A1 and UGT1A9 at clinically relevant concentrations.

2.3.4. Toxicology

Single dose toxicity

Single dose toxicity was tested in mice and rats, up to the technically maximum feasible doses (250 mg/kg orally); no signs of toxicity were observed.

Repeat dose toxicity

Repeat dose toxicity studies are summarised in the following Table 1.

Table 1: Repeat-dose toxicity studies with regorafenib

Study ID	Species/Sex/ Number/Group	Dose/Route	Duration	NOEL/ NOAEL
PH-34500 GLP	Mouse 10/sex/dose 9/sex/dose for TK	0, 5, 20, 80 mg/kg/day Oral gavage	4 weeks	ND
Major findings **≥5**: 2 mortalities, ↑ AST and ALT (F), ↓ heart weight (F), dentin alterations, hyperkeratosis of forestomach, ↓ glycogen content in liver **≥20**: 2 mortalities, emaciation (F), ↓ BW, ↑ ALT (M), glomerulopathy (F), amelioblast degeneration, interstitial oedema of tongue, deposition of iron in spleen, thickened growth plate, ↓ corpora lutea, stomal atrophy of uterus, eosinophilia of zona fasciculate of adrenal glands, atrophy of exocrine pancreas **=80**: 11 mortalities, hindleg dragging, labored breathing, ↑HB and HCT (M), ↑ MHC and MCHC, ↓ leukocytes, ↑ AST (M), ↑ chol and albumin (F), ↑ plasma protein, ↓ spleen weight, ↓ thymus and testes weight (M), atrophy of sublingual gland, dilation of gall bladder, ↓ haematopoiesis in spleen, foam cells in mesenteric lymph nodes, ↑ blood content in bone marrow, ↑ hypertrophy of lacrimal glands			
Study ID	**Species/Sex/ Number/Group**	**Dose/Route**	**Duration**	**NOEL/ NOAEL**
PH-35918 GLP	Mouse 10/sex/dose 18/sex/dose for TK	0, 1, 5, 20 mg/kg/day Oral gavage	5 weeks	1 mg/kg/day
Major findings **≥5**: ↑ food intake (F), ↑ HB, ↑ HCT (M), ↑ bilirubin (M), ↓ liver weight, hyperkeratosis of forestomach (F), hyperkeratosis of esophagus, dentin alteration, ↓ corpora lutea, oedema in uterus **=20**: ↓ BW, ↓ LYM, ↑ AST and ALT, ↑ chol (F), ↑ bilirubin (F), ↑ plasma protein, hyperkeratosis of forestomach (M), hypocellularity of bone marrow, ↑ width of epiphyseal plate (F), ameloblast and ondotoblast degeneration, keratinization in vagina			
Study ID	**Species/Sex/ Number/Group**	**Dose/Route**	**Duration**	**NOEL/ NOAEL**
PH-33468 Non-GLP	Rat 5/sex/dose 3/sex/dose for TK	0, 10, 25, 50 mg/kg/day Oral gavage	2 weeks	ND

Major findings
≥10: ↓ BW (M), ↑ HB and HCT (M), ↑ neutrophils (M), ↑ ALT and AST, other clinical chemistry changes, ↑ p450 enzymes in liver, ↓ liver weight, ↓ lung weight (F), histopathology findings in the kidney, ovary, bone marrow, growth plate, adrenals, pancreas, liver, teeth, hair follicles
≥25: ↑ Ery (M), ↑ MCHC (F), ↓ reticulocytes and thrombocytes, ↓ ovary weight, histopathology findings in stomach
=50: ↓ BW (F), ↑ neutrophils (F)

Study ID	Species/Sex/ Number/Group	Dose/Route	Duration	NOEL/ NOAEL
PH-34206 GLP	Rat 10/sex/dose 5/sex for recovery 9/sex/dose for TK	0, 1, 4, 16 mg/kg/day Oral gavage	4 weeks + 4 weeks recovery	ND

Major findings
≥1: ↑Ery and HB (M), ↑ leucocytes (M), ↑ ALT, degenerative changes in kidney (M)
≥4: ungroomed coat, ↑ HCT (M), ↑ AST, ↑ Bilirubin, ↑ B cells, ↓ CD4 and CD8 cells (F), glomerulopathy, degeneration of dentin, ↓ haematopoiesis in spleen, hypocellularity of bone marrow, chondrodystrophy
=16: pallor, ↓ BW, FC and WI, ↓ Ery, HB and HCT (F), ↑ chol, ↓ plasma protein, ↓T4, ↑ TSH, ↓ urine volume, ↑ urine protein, ↓ CD4, CD45 and CD8 cells (M), ↑ IgM and ↓ IgG, ↑ adrenal and kidney weight, ↓ thymus, heart (M) and uterus (F) weight, atrophy lymph nodes, ↓mast cells in tongue, bile duct proliferation, adrenal changes, flattened follicular epithelial of thyroid, myocardial oedema, atrophy of ovaries, ↓ corpora lutea
Recovery (no clinical lab data):
=16: 5 mortalities, apathy, emaciation, tooth changes, ↓ BW, FC and WI, kidney changes, teeth changes, bone marrow, spleen, thymus and lymph node changes, ↓ glycogen, adrenal and thyroid changes, chondrodystrophy, irregular estrous cycle

Study ID	Species/Sex/ Number/Group	Dose/Route	Duration	NOEL/ NOAEL
PH-34484 GLP	Rat 10/sex/dose 10/sex/dose for recovery 6/sex/dose for TK	0, 0.5, 2, 8 mg/kg/day Oral gavage	13 weeks + 4 weeks recovery	ND

Major findings
≥0.5: ↓ BW (M), ↓ WI, ↑ AST, ALT, ↓ urine crea (M), tubular degeneration and dilation, liver: decreased glycogen, Kupffer cell activation (M)
≥2: ↓ FC, ↑ GGT (F), ↓ liver, epididymides weight (M), kidney discoloration, glomerulopathy, liver: cytoplasmatic basophilia (M), flattened follicular epithelium of thyroid gland, ↑ haematopoiesis in spleen
=8: 2 mortalities, teeth changes (dentin, periodontal ligaments, degeneration), ↓ BW (F), ungroomed coat, ↓ ery, Hb, HCT, MCHC (F), ↑ MCV, MCH, ↑↑ reticulocytes, thrombocytes (F), ↑ neutrophils, ↓ hQuick, alb, T4, ↓ Glu (M), ↑ chol, TG, BUN, TSH, ↑ crea (M), ↑ urine pH (F), ↓ urine crea (F), ↑ kidney, spleen weight, ↓ thymus, testes, prostate weight, liver: cytoplasmatic basophilia, focal perihepatitis/peritonititis (F), pancreas; atrophy, inflammation, vasculitis, atrophy and vacuolation of tongue, hyperkeratosis and hypertrophy of stomach, hypertrophy and inflammation of duodenum, peliosis and necrosis of adrenal gland, heart edema, thymus atrophy, thickening of growth plate, chondrodystrophy (femur and sternum), atrophy of uterus, ovaries, vagina, lacrimal glands
Recovery:
≥2: ungroomed coat, teeth changes, ↓ uterus weight,), kidney discoloration
=8: 2 mortalities, , ↓ BW, ↑ MCV, MCH, ↑ neutrophils, ↑ chol, TG, BUN ↑ crea (M), ↓ alb, ↑ liver, spleen, kidney weight, pigment deposition in adrenal gland, femur and sternum changes, atrophy of ovaries, stomach and duodenum changes

Study ID	Species/Sex/ Number/Group	Dose/Route	Duration	NOEL/ NOAEL
PH-35874 GLP	Rat 10/sex/dose	0, 0.1, 0.5, 2 mg/kg/day Oral gavage	26 weeks	0.1 mg/kg/day

Major findings
≥0.1: initial ↑ in leucocytes count
≥0.5: slight ↑ Ery, Hb, HCT (F), ↑ ALT, ↓ liver weight
=2: ungroomed coat, very slight lymphocyte changes, ↑ TSH (M), ↓ kidney weight (F), Liver: ↑ pigment storage in Kupffer cells (F), periportal cytoplasmic basophilia, kidney: tubular degeneration (M), glomerulopathy, mesenteric lymph nodes: increased number of mast cells, activated germinal centres, flattened follicular epithelium of thyroid gland, valvular thickening in heart

Study ID	Species/Sex/ Number/Group	Dose/Route	Duration	NOEL/ NOAEL

PH-34182 GLP	Beagle dog 3/sex/dose 2/sex/dose for recovery	0, 5, 20, 80 mg/kg/day Oral gavage	4 weeks+ 4 weeks recovery	N.D.

Major findings
≥5: mushy\liquid faeces, dentin alterations (M)
≥20: slight ↓ BW gain, ↑ atypical leukocytes, ↑ AST, dentin alterations (F), hepatocellular hypertrophy (F), ↑ haematopoiesis in spleen, ↑ follicle necrosis of tonsils, cortical atrophy of thymus (F), chondrodystrophy (sternum)
=80: vomiting, bleeding gums, ↑ ALT, GLDH, hypertrophy of zymogenic cells in stomach, hepatocellular hypertrophy (M), acinar atrophy, cortical atrophy of thymus, hypocellularity and thickening of growth plate (femur)
Recovery:
bile duct proliferations, thickening of growth plate (femur), dentin alterations

Study ID	Species/Sex/ Number/Group	Dose/Route	Duration	NOEL/ NOAEL
PH-34580 GLP	Beagle dog 4/sex/dose 4/sex/dose for TK	0, 5, 20, 80 mg/kg/day Oral gavage	13 weeks	N.D.

Major findings
≥5: ↓ BW gain, FC, white mucus and bloody particles in faeces, alopecia, ↑ kidney weight, sparse haircoat
≥20: vomiting, gums bleeding/anaemic, swollen eyelids, ↑ ALP, ↓ thymus, ovary weight, kidney: tubular degen/regeneration, glomerulopathy, atrophy of thymus, tonsil, larynx, cecum, peyers patches, pancreas, thyroid gland, adrenal gland and sublingual gland, follicular degeneration of mesenteric lymph node, liver: bile duct proliferation, centrilobular fat accumulation, centrilobular hypertrophy, cytoplasmic change, increased fatty replacement in sternum and femur, persistent growth plate (femur), dentin alterations, lymphangiectasia in duodenum
=80: slight ↑ atypical cells, thrombocytes, ↑ ALT, GLDH, slightly ↑ AST, ↑ haematopoiesis, blood in spleen (M), degeneration of duodenum, perivascular mononuclear cell infiltration in pituitary gland

Study ID	Species/Sex/ Number/Group	Dose/Route	Duration	NOEL/ NOAEL
A45739 GLP	Beagle dog 4/sex/dose 4/sex/dose for TK	0, 1, 4, 16 mg/kg/day Oral gavage	52 weeks	N.D

Major findings
≥1: Shaking of body, scratching, thinning of fur, scab formation, wounds, papules, itching, ↑ hematomas, ↑ diarrhoea and vomiting, ↑ Relative beta-globulin (F), ↓ pancreas weight (F), inspissation in gal bladder, hyaline casts, alveolar/foamy macrophages, vacuolar degener in adrenal cortex (F), spermat. giant cells, hair growth arrest, hyperkeratosis, ↑ number of myeloid cells in sternum
≥4: ↑ monocytes (M), ↑ glu, , ↑ Relative beta-globulin (M), ↑ Relative gamma-globulin, ↑ ALP (M), ↑ kidney, pancreas weight (M), mononuclear infiltration in liver, epithelial hyperplasia in gall bladder, glomerulosclerosis (M), hyperplasia in Bowmanns Capsule and cortical mineralization (F), tub degen/regen, glomerulopathy, ↑ foll. Degener, cystic gld. dilatation, pigment clumping in skin, ↑ haematopoiesis and pigment deposit in spleen
=16: articular muscle atrophy, stomatitis, pustules, ↑ monocytes (F), ↓ Relative alb, ↓ Alb/globulin quotient, ↑ ALP (F), ↑ AST, initially ↑ ALT, ↑ GLDH, TSH and fibrinogen, ↑ urine GGT, ↑ kidney, pancreas weight (F), ↑ mandibular gland weight, ↓ thymus weight, glomerulosclerosis (F), hyperplasia in Bowmanns Capsule and cortical mineralization (M), interstit. Fibrosis, vacuolar degener in adrenal cortex (M), cystic Corpora Lutea, follicular cyst, ↓ devel. Follicles, peri-/folliculitis (skin), lymphoid hyperplasia in spleen, mineralization of tonsils

alb: albumin, ALT: alanine aminotransferase, ALP: alkaline phosphatase AST: aspartate aminotransferase, BUN: blood urea nitrogen, BW: body weight, chol: cholesterol, crea: creatinine, Ery: erythrocytes, FC: food consumption, GLDH: glutamate lactate dehydrogenase, Glu: glucose, HB: haemoglobin, HCT: haematocrit, hQuick: hepato Quick test, LYM: lymphocytes, MCH: mean corpuscular haemoglobin, MCHC: mean corpuscular haemoglobin concentration, ND: not determined, T4: Thyroxine, TG: triglycerides, TSH: thyroid stimulating hormone, WI: water intake

Genotoxicity

Regorafenib was tested *in vitro* in the Salmonella/microsome assay and a mammalian chromosome aberration assay and *in vivo* in the bone marrow micronucleus test. None of these assays indicated genotoxic potential of regorafenib.

Carcinogenicity

No studies were submitted (see discussion on non-clinical aspects).

Reproduction Toxicity

No fertility and early embryonic development studies were submitted (see discussion on Non-clinical aspects).

The influence of regorafenib on embryo-foetal development was investigated in pilot studies in rats and rabbits and in a pivotal GLP study in rabbits.

In the rabbit pivotal study, signs of maternal toxicity were observed at the dose of 1.6 mg/kg/day including a marginal to slight body weight loss, total resumptions and thus a decreased gestation rate. Post-implantation loss was severely increased at this dose level. Therefore, based on the results of this study a NOAEL of 0.8 mg/kg/day could be derived for systemic maternal toxicity. A treatment related effect on malformations was clearly observed at 1.6 mg/kg/day (mainly findings of the urinary system, the heart, and the axial skeleton) and at 0.8 mg/kg/day (mainly malposition of forelimb(s) or hind limb(s), findings of the heart and major vessels, urinary system, and skeleton [skull bones, caudal vertebral bodies]). A treatment related effect on external and visceral deviations is assumed for findings of the urinary system at 1.6 mg/kg/day and 0.8 mg/kg/day. Foetal examinations for skeletal retardations and variations revealed increased incidence of fused sternebrae and 7th cervical ribs at 0.8 mg/kg/day and 1.6 mg/kg/day. The applicant stated that, based on these results, a NOAEL of 0.4 mg/kg/day for embryo-foetal development could be derived in this study.

No pre- and post-natal development or juvenile toxicity studies were submitted (see discussion on non-clinical aspects).

Toxicokinetic data

In mice, the AUC and C_{max} increased slightly more than dose proportionally with increasing dose at the 1 to 20 mg/kg dose range and a slightly less than dose proportional increase was observed at 20 to 80 mg/kg. In rats, the AUC was dose proportional and the C_{max} increased slightly less than dose proportionally. In rabbits, the AUC and C_{max} increased dose-proportionally from 0.4 to 0.8 mg/kg and moderately more than dose proportionally from 0.8 to 1.6 mg/kg. In dogs, AUC and C_{max} increased dose proportionally from 1 to 2.5 mg/kg and less than dose proportionally from 2.5 to 10 mg/kg.

Major interspecies differences in metabolite pattern were observed. In humans, N-oxidation of the pyridine to form metabolite M-2 was much more pronounced than N-methylhydroxylation to form metabolite M-3, which was predominantly found in rats and dogs. Additionally, glucuronidation only played an important role in the biotransformation of regorafenib in humans. Four human specific metabolites were identified, namely M-2, M-5, M-7 and M-8. The human specific metabolites M-2 and M-5 are pharmacologically active. The applicant investigated the kinetics of the human specific metabolites M-2 and M-5 and not of the glucuronide metabolites M-7 and M-8.

The excretion of regorafenib and its metabolites was mainly via the faeces. However, the contribution of urine to the overall excretion was larger in humans than in the animal species. In humans, a pronounced enterohepatic circulation was observed. This can be explained by hepatic formation of primary metabolites M-2 and M-7 and their secretion into gut followed by reduction of M-2 and deconjugation of M-7 each to parent drug by microbial flora and subsequent intestinal reabsorption. This was not observed in the animal species.

Local Tolerance

No dedicated local tolerance studies have been conducted. However, various morphological changes were noted in the gastrointestinal tract of animals treated orally by gavage with the 10% coprecipitate formulation of regorafenib. Signs of degenerative and regenerative processes were seen in particular in the stomach and duodenum of mice and rats. Morphological changes in dogs were less pronounced although clinical signs of gastrointestinal intolerance were observed (bloody diarrhoea, emesis).

Other toxicity studies

No antigenicity or dependence studies were submitted.

Immunotoxicity endpoints were evaluated in the 13-week rat study. No immunotoxic potential for regorafenib was observed.

Evaluation of the systemic toxicity of the main human metabolites M-2 and M-5 in 4-week mouse repeat-dose studies with daily oral administration provided evidence that both metabolites induce less toxicity than the parent compound.

Several batches of regorafenib with a spectrum of the relevant impurities were used in the nonclinical toxicology program. All impurities were qualified in the toxicological studies at the individual levels specified. In addition, the genotoxic potential of four impurities that could be expected in the drug substance/product was experimentally evaluated in genotoxicity assays. For one of them a mutagenic potential was shown in the Ames test. Moreover, a weak mutagenic potential for the same impurity was also shown in the Comet assay (data not shown, see discussion on Non-clinical aspects).

An *in vitro* phototoxic study suggested that regorafenib is a probable phototoxic compound but this was not confirmed in the *in vivo* study conducted in mice.

2.3.5. Ecotoxicity / environmental risk assessment

Table 2: Summary of main study results

Substance (INN / Invented Name): regorafenib			
CAS-number (if available): 755037-03-7 (free base); 1019206-88-2 (monohydrate)			
PBT screening		Result	**Conclusion**
Bioaccumulation potential- log K_{ow}	OECD117	3.9	see below
PBT-assessment			
Parameter	**Result relevant**		**Conclusion**

	for conclusion				
Bioaccumulation	log K_{ow}	3.9 (HPLC determined)			
	BCF	2018 L/kg 3241 L/kg			B
Persistence	ready biodegradability	not readily biodegradable			
	$DT50_{water}$ $DT50_{system}$ $DT50_{soil}$	< 1 d >> 100 d at 22-24°C 181 d at 20±2°C			vP
Toxicity	NOEC algae NOEC Daphnia NOEC fish	PM PM PM			potentially T
	CMR	not fully investigated			
PBT-statement :	PM				
Phase I					
Calculation	**Value**	**Unit**			**Conclusion**
$PEC_{surfacewater}$	0.6	µg/L			> 0.01 threshold
$PEC_{surfacewater}$, redefined with published incidence data (EU-27)	0.112	µg/L			
Other concerns (e.g. chemical class)	antineoplastic				
Phase II Physical-chemical properties and fate					
Study type	**Test protocol**	**Results**			**Remarks**
Adsorption-Desorption	OECD 121	PM			
Ready Biodegradability Test	OECD 301	not readily biodegradable			
Aerobic and Anaerobic Transformation in Aquatic Sediment systems	OECD 308	$DT_{50,\ water}$ = < 1 d $DT_{50,\ sediment}$ = >> 100 d $DT_{50,\ whole\ system}$ = >> 100 d % shifting to sediment = 68-81% at day 2			T=22-24°C
Phase IIa Effect studies					
Study type	**Test protocol**	**Endpoint**	**value**	**Unit**	**Remarks**
Algae, Growth Inhibition Test/*Species*	OECD 201	NOEC EC10 EC50	PM	µg/L	growth rate
Daphnia sp. Reproduction Test	OECD 211	NOEC	PM	µg/L	PM
Fish, Early Life Stage Toxicity Test/*Species*	OECD 210	NOEC	PM	µg/L	PM
Activated Sludge, Respiration Inhibition Test	OECD 209	EC10 EC50	$>S_w$ [a] $>S_w$ [a]	µg/L µg/L	S_w < 56 µg/L
Phase IIb Studies					
Bioaccumulation in fish *L. macrochirus*	OECD 305	BCF	2018 3241	L/kg L/kg	normalised to 5% lipids
Aerobic and anaerobic transformation in soil	OECD 307	DT50 $\%CO_2$	181 1.1	d %	extrapolated DT50; one soil tested
Soil Microorganisms: Nitrogen Transformation Test	OECD 216	%effect	8.9	%	at 1250 mg/kg_{dw}. Not significant acc. to OECD 216 criteria
Terrestrial Plants, Growth Test / *P.sativum, R. sativus, Z. mays*	OECD 208	NOEC	≥197	mg/kg	emergence and growth, normalised to 2% o.c.

Earthworm, Acute Toxicity Tests	OECD 207	LC50	>40	mg/ kg	normalised to 2% o.c.
Collembola, Reproduction Test *F. candida*	OECD 232	NOEC	>40	mg/ kg	reproduction and mortality, normalised to 2% o.c.
Sediment dwelling organism / *C. riparius*	OECD 218	EC10= NOEC	2.7	mg/ kg	total nr or midges and mortality

[a] *Since the water solubility (S_w) was not determined (reported as a < value), the result of the study cannot be displayed correctly. Since no effect was observed at the highest tested concentration, the result is displayed as >S_w for practical reasons.*

Regorafenib is potentially PBT (persistent, bioaccumulative and toxic). The criterion can only be concluded after evaluation of the additionally requested aquatic studies. The substance is very persistent (vP). It is also bioaccumulative, but not very bioaccumulative (vB).

The revised PECsurface water was calculated at 0.112 µg/L. The Koc will have to be determined using an OECD 106 study. PECsoil and PECsediment can only be (re)calculated after the results of this study are available. A risk to the STP (Sewage Treatment Plants) is considered unlikely. Apart from the OECD 106 study, the dossier was complete. However the chronic studies with algae, Daphnia and fish are considered unreliable, the results cannot be used in the risk assessment. In conclusion, the risk assessment for the surface water, groundwater, soil and sediment compartment cannot be completed.

In view of the nature of the molecule and in the light of the recommended further studies, the CHMP is of the Opinion that a precautionary approach regarding the disposal of the medicine into the environment needs to be adopted. The SmPC and PL have been updated accordingly.

In the context of the obligation of the MAH to take due account of technical and scientific progress, the CHMP recommends the following points to be addressed:

– An adsorption/desorption study with 3 soils and 2 sludges (OECD 106)

– A toxicity study with a green algal species (OECD 201)

– A chronic toxicity study with Daphnia magna (OECD 211)

– A chronic toxicity study with fish; early life stage toxicity test (OECD 210).

2.3.6. Discussion on non-clinical aspects

Data from the *in vitro* and *in vivo* primary pharmacology studies indicate that regorafenib has broad anti-tumour activity; however, it appears that there is significant variation in the response of colon tumours to regorafenib treatment.

The pharmacological activity of regorafenib in animal species besides immunodeficient mice has not been reported. It is assumed that regorafenib has the same activity in animals when compared to humans. This assumption is supported by amino acid sequence homology and the observed effects in animals. It is however not clear if the potency of regorafenib to inhibit the different RTKs is similar across species. However, as treatment-related adverse effects were seen in animals at exposures equal to or below the clinical exposure level, further studies on this issue were not considered necessary.

Findings in the secondary pharmacology studies may indicate inhibition of VEGF-mediated signal transduction which could be expected based on the tyrosine kinase inhibition profile. Additional secondary activity studies were not submitted. However, as findings in the safety pharmacology studies are considered to be consistent with the pharmacological activity of regorafenib, no further studies were considered necessary.

Regarding the safety pharmacology, the in vitro concentrations of M2 and M5 at which significant hERG K+ inhibition was observed were lower than the maximum concentration in plasma at steady state for M2 (~6.7 µM) and M5 (~6.0 µM). However, due to the high protein binding, the concentrations of unbound substance are much lower for both (M2: ~13 nM, M5: ~3.2nM) and well below the concentration at which hERG K+ blockade can be expected. Moreover, no effects on ECG parameters were seen in isolated rabbit cardiac Purkinje fibers exposed to regorafenib and in four GLP-compliant studies in anaesthetised dogs.

In *in vivo* studies, no substantial adverse effects were seen on cardiovascular, respiratory, and CNS function.

The kinetics of regorafenib was sufficiently investigated in mouse, rat, rabbit, dog and monkey. The major animal species studied were rat and dog. Large interspecies differences were observed making the extrapolation of the pre-clinical data to humans difficult.

Repeat dose toxicity with daily administration by oral gavage of regorafenib was evaluated in mice (up to 5 weeks), rats (up to 26 weeks) and dogs (up to 52 weeks).

Studies in these species revealed a comparable toxicological profile characterised by degenerative changes, frequently accompanied by regenerative and inflammatory processes in multiple tissues in the range of or below the anticipated clinical exposure. Target organs are largely consistent with those seen with other tyrosine kinase inhibitors and most effects are considered to be of clinical relevance, as they occurred at systemic exposures in the range of or below the anticipated human exposure (based on AUC comparison). After repeated dosing to mice, rats and dogs, adverse effects were observed in a number of organs, primarily in the kidneys, liver, digestive tract, thyroid gland, lympho /haematopoietic system, endocrine system, reproductive system and skin.

Compared to dogs, rats and mice appear to be more sensitive regarding effects particularly on kidneys, gastrointestinal tract, and teeth, but less sensitive regarding effects particularly on skin and liver.

Prominent clinical signs in rats after repeated dosing consisted of changes in the teeth structure with markedly increased growth. Histologically, dentin and amenoblast degeneration were observed.

Alterations with regard to increased growth of teeth (histologically associated with dentin and amenoblast degeneration) and bones (thickening of growth plate, chondrodystrophy) are related to the pharmacological mode of action of regorafenib but are considered not to present a potential risk for adult humans, because in adults these organs are not subject to growth. However, they do indicate a potential risk for children and adolescents.

Furthermore, in the 6-month rat study, an increased incidence of thickening of the atrioventricular valves of the heart was observed at 2 mg/kg. This effect was not observed in the

4 and 13 week study in rats using higher doses and it might be an accelerated age-related physiological process. Monitoring of cardiovascular parameters including QT interval in the dog repeat-dose studies revealed no adverse effects attributed to regorafenib.

Interstitial oedema and atrophy of the tongue were seen in mice and rats, respectively, and is of unknown relevance. However, due to mucolytic activity of the compound, patients experiencing pain in the mouth are suspended from treatment and an effect like atrophy is not expected. Indeed, there were no reports of tongue atrophy or atrophic glossitis in the clinical trial program. Clinical relevance of this finding is therefore unlikely.

Dogs developed bloody diarrhoea, emesis, alopecia, stomatitis and occasionally bleeding gums/anaemia and swelling of eyelids. Hair growth arrest was observed together with other skin alterations such as epidermal and follicular hyperkeratosis, parakeratosis, comedo formation, acanthosis, hypergranulosis, pigment clumping, peri-folliculitis, crusts, fibrosis, lymphoid cell infiltration and retention of sebaceous. In the 12-month study, female dogs showed additionally signs of an effect on the hormone balance (increased incidence of vulva swelling, decreased incidence of mammary complex swelling).

The severity and extent of adverse effects in the repeat dose toxicity studies were dependent on dose and duration of exposure. The MTD declined with the prolongation of treatment in rats and dogs.

Findings in serum chemistry, analysis of liver tissue, and urinalysis in the repeat-dose toxicity studies with administration of regorafenib comprised changes indicating an influence on liver function (increased serum transaminase and glutamate dehydrogenase (GLDH) activities, increased bilirubin), kidneys (increased serum creatinin, proteinuria) and thyroid (increased thyroid stimulating hormone [TSH], reduced T4). Haematology findings indicated slight but inconsistent changes in red and white blood cell parameters (reduced erythrocyte counts, haemoglobin, haematocrit; increased neutrophil counts; atypical leucocytes) and blood coagulation (reduced or increased platelet counts; reduced clotting time).

Regorafenib was tested in a battery of genotoxicity tests, and was shown to have no genotoxic potential. No carcinogenicity studies have been performed with regorafenib. This is in line with ICH S9 guideline (Nonclinical Evaluation for Anticancer Pharmaceuticals, EMEA/CHMP/ICH/646107/2008) and considered acceptable taking into account the intended indication as well as the short life-expectancy of patients for which regorafenib is currently intended.

Specific studies with regorafenib on fertility and early embryonic development were not submitted. However, an impact of regorafenib can be expected based on the pharmacological mode of action and findings in the general repeat-dose toxicity studies, i.e. 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. Pilot embryo-foetal toxicity studies have been performed in two species, rats and rabbits, whereas the main study was only performed in rabbits. This is acceptable, since it was shown that regorafenib is embryolethal and teratogenic in rabbits, and therefore confirmation in a second species is not considered necessary. Of note, teratogenicity was also seen in the rat pilot study.

There are no data on the effect of Stivarga on human fertility. Women of childbearing potential must be informed that regorafenib may cause foetal harm. Effective contraception in men and women should be ensured during treatment and up to 8 weeks after completion of therapy. There are no data on the use of regorafenib in pregnant women. Stivarga should not be used during pregnancy unless clearly necessary and after careful consideration of the benefits for the mother and the risk to the foetus. Finally, it is unknown whether regorafenib or its metabolites are excreted in human milk. In rats, regorafenib or its metabolites are excreted in milk. A risk to the breast fed child cannot be excluded. Breast feeding must be discontinued during treatment with Stivarga.

No pre- and postnatal development or juvenile toxicity studies were performed with regorafenib in line with the ICH S9 guideline which was considered acceptable.

Special investigations on the immunotoxic potential of regorafenib performed in the frame of the 13-week rat study (splenic cell count, FACS analysis, total anti-body titre, plaque forming cell assay after immunisation) revealed no indication for a toxicologically relevant effect.

Regorafenib was found to be probably phototoxic in vitro. As there is no appropriate animal model for in vivo studies, no further studies were deemed necessary. Of note, no relevant signals emerged from the clinical studies.

One impurity tested positive in the Ames test and Comet assay, but negative in the Micronucleus test. Since these tests evaluate different endpoints, a negative Micronucleus test does not overrule the Ames test, and the impurity may be considered as possibly mutagenic. Because the indication of regorafenib does allow for higher limits of impurities, and the results of the genotoxicity tests also indicate only a weak genotoxic potential with unlikely relevance for humans, the proposed specification limit is acceptable.

In terms of local tolerance, various morphological changes (in particular signs of degenerative and regenerative processes in the stomach and duodenum in mice and rats) and clinical signs of gastrointestinal intolerance (bloody diarrhoea and emesis in dogs) were noted in the gastrointestinal tract of animals treated orally by gavage. The observed effects are most likely due to the expected mechanism-related impact of regorafenib on rapidly dividing cells.

Regorafenib is potentially PBT (persistent, bioaccumulative and toxic). The criterion can only be concluded after evaluation of the additionally requested aquatic studies. The substance is very persistent (vP). It is also bioaccumulative, but not very bioaccumulative (vB).

The revised $PEC_{surface\ water}$ was calculated at 0.112 µg/L. The K_{oc} will have to be determined using an OECD 106 study. PEC_{soil} and $PEC_{sediment}$ can only be (re)calculated after the results of this study are available. A risk to the STP (Sewage Treatment Plants) is considered unlikely. Apart from the OECD 106 study, the dossier was complete. However the chronic studies with algae, *Daphnia* and fish are considered unreliable, the results cannot be used in the risk assessment. In conclusion, the risk assessment for the surface water, groundwater, soil and sediment compartment cannot be completed. In the light of this outcome, the CHMP agreed that precautionary statements in the product information regarding the disposal of the medicine into the environment have to be adopted and the SmPC and PL were updated in accordance.

2.3.7. Conclusion on the non-clinical aspects

From the non-clinical standpoint, there are no major objections against authorisation, however additional data is needed for completion of the environmental risk assessment.

2.4. Clinical aspects

2.4.1. Introduction

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

The recommended dosing regimen is an intermittent dosing schedule: 160 mg qd for 3 weeks followed by 1 week without regorafenib medication (3/1 week(s) on/off).

GCP

The Clinical trials were performed in accordance with GCP as claimed by the applicant.

The applicant has provided a statement to the effect that clinical trials conducted outside the community were carried out in accordance with the ethical standards of Directive 2001/20/EC.

- Tabular overview of clinical studies

Table 3: Overview of clinical studies with regorafenib

Study no.	Type of study	Tumour type	Dosing	No. of patients
Phase 1: Regorafenib in healthy volunteers				
12435	Effect of ketoconazole on PK of regorafenib	N/A	Regorafenib 80 and 160 mg single dose (4 x 40 mg tablets) Ketoconazole 400 mg	24
12436	PK, metabolism, excretion, mass balance	N/A	Single dose of 120 mg regorafenib solution containing approximately 1.5 mg of 14C-radiolabeled regorafenib	4
12437	Relative bioavailability	N/A	2 single doses of 160 mg 1 x 100 mg tablets + 3 x 20 mg tablets compared to 4 x 40 mg tablets#	48
14656	Bioavailability, high-fat vs. low-fat breakfast vs. fasting state effect on PK	N/A	3 single doses of 160 mg (4 x 40 mg tablets)	24
15524	Effect of rifampin (rifampicin) on PK of regorafenib	N/A	Regorafenib 160 mg single dose (4 x 40 mg tablets) Rifampin (rifampicin) dose 600 mg	24
Phase 1: Regorafenib as single agent in cancer patients				
11650	Dose escalation, PK, PD, tumour response, safety	Advanced solid tumours	Regorafenib 10 – 220 mg od intermittent dosing schedule (3 weeks on / 1 week off)#	76 (of which 39 CRC patients)
11651	Dose escalation,	Advanced solid	Regorafenib 20 – 140 mg od	84

Study no.	Type of study	Tumour type	Dosing	No. of patients
	PK, safety	tumours	continuous dosing#	
12434	Probe substrate, PK, safety	Advanced solid tumours	Regorafenib 160 mg, od (4 x 40 mg tablets) intermittent dosing schedule (3 weeks on / 1 week off) Group A: Warfarin 10 mg, Omeprazole 40 mg, Midazolam 2 mg Group B: Rosiglitazone 4 mg	Group A: 20 (planned) 6 (actual) Group B: 20 (planned), 10 (actual)
13172	PK, safety	Advanced and refractory solid tumours	Regorafenib 160 mg od(4 x 40 mg tablets)# intermittent dosing schedule (3 weeks on / 1 week off)#	16
14814	Cardiovascular safety (QT/QTc, LVEF), PK, safety	Advanced solid tumours	Regorafenib 160 mg od (4 x 40 mg tablets) intermittent dosing schedule (3 weeks on / 1 week off)	54
14996	PK, safety	Advanced and refractory solid tumours	Regorafenib 160 mg od (4 x 40 mg tablets) intermittent dosing schedule (3 weeks on / 1 week off)	24
Phase 1: Regorafenib combined with other medicinal products in cancer patients				
11656	PK, safety	Metastatic CRC 1st or 2nd line	Regorafenib 160 mg od# on days 4–10 and 18–24 of every 4 week cycle Plus mFOLFOX6 or FOLFIRI	45
Phase 2: Regorafenib in cancer patients				
11726	Uncontrolled, single-arm study, efficacy, safety, PK	Metastatic or unresectable renal cell cancer (previously untreated patients)	Regorafenib 160 mg od: (1 x 100 mg tablets + 3 x 20 mg tablets or 4 x 40 mg tablets)# intermittent dosing schedule (3 weeks on / 1 week off)	49
14596	Uncontrolled, single-arm study, safety, efficacy, PK	Hepatocellular cancer	Regorafenib 160 mg od (4 x 40 mg tablets) intermittent dosing schedule (3 weeks on / 1 week off)	36
Phase 3: Regorafenib in metastatic CRC patients				
14387	Randomized, double-blind, placebo-controlled study; regorafenib + BSC vs. placebo, efficacy, safety, PK, biomarkers	Metastatic CRC (progressed after standard therapy)	Regorafenib 160 mg od (4 x 40 mg tablets) intermittent dosing schedule (3 weeks on / 1 week off) Matching placebo	760 Regorafenib: 505 Placebo: 255

2.4.2. Pharmacokinetics

Regorafenib pharmacokinetics was evaluated following oral administration of single doses to healthy volunteers and single or multiple doses to cancer patients. In the evaluation of the pharmacokinetics of regorafenib, consideration needs to be given to the fact that two metabolites

of regorafenib, M-2 and M-5, have demonstrated in vitro pharmacologic activity similar to that of unchanged regorafenib. Therefore, the evaluation of metabolite PK for M-2 and M-5 was included in all PK studies.

Overall, 11 Phase 1 trials have been conducted with regorafenib as a single-agent: 5 in healthy volunteers and 6 in advanced cancer patients. The healthy volunteer studies were conducted using single doses of regorafenib and included a total of 124 subjects in Europe and the USA addressing the relative bioavailability of the final tablet formulation (study 12437), food effect (study 14656), mass balance and metabolite profile (study 12436), and the interaction of regorafenib with ketoconazole and rifampin (studies 12435 and 15524, respectively).

Two of the Phase 1 studies in patients with advanced solid tumours were dose escalation studies to define the maximum tolerated dose of two different dosing schedules: intermittent dosing - 3 weeks on / 1 week off treatment (study 11650) and continuous dosing (study 11651). The recommended Phase 2 dose of 160 mg in the intermittent dosing schedule was applied in the two Asian trials (14996 and 13172, both in patients with advanced solid tumours). Finally, a cocktail drug drug interaction study (12434), and a study (14814) to evaluate cardiovascular safety were conducted.

Adequately validated methods were used to analyse regorafenib and metabolites M-2 and M-5 in plasma and urine.

Absorption

Following oral administration of a single 160 mg dose with tablets, regorafenib is absorbed with a median t_{max} ranging from approximately 3 to 4 hours with a mean maximum concentration (C_{max}) of 2.5 mg/L. The plasma concentration time curve was characterised by multiple peaks and slow elimination of regorafenib. After a single dose of 160 mg, plasma concentrations of the two active metabolites M-2 and M-5 were below those of parent compound. However, after multiple dosing at Day 21, due to the nonlinear accumulation of metabolites, plasma concentrations were similar for parent drug and metabolites.

Due to the insolubility of the drug substance in aqueous media without surfactant, no i.v. solution (for human use) was developed to conduct an absolute bioavailability (BA) study. Following single dose administration of 60 and 100 mg doses, the relative bioavailability of the final solid solution formulation of regorafenib tablets was approximately 70% -83% of the 2% w/v oral solution. Comparative bioavailability of conventional immediate release tablets was <10% of the oral solution, therefore conventional immediate release tablets were not used in the clinical studies. All studies were conducted with solid solution tablets or in some phase 1 studies as 2% w/v solution. Based on results in mass balance study 12436, showing 19% of radioactivity excreted in urine and 24% excreted in faeces in the form of metabolites following single dose administration of 120 mg oral solution, it can be estimated that at least 30-35% of regorafenib is being absorbed following administration of solid solution tablets.

In vitro investigations using a validated Caco-2 assay showed that regorafenib belongs to the class of highly permeable substances. Regorafenib therefore classifies as a Class II drug according to the criteria of the Biopharmaceutical Classification System (BCS).

Relative bioavailability and bioequivalence of different regorafenib formulations employed in the course of clinical development was demonstrated (data not shown).

Bioavailability (AUC) of regorafenib was increased by approximately 48% and 36% when administered with a high-fat and low-fat breakfast, respectively, compared with dosing under fasting conditions (study 14656). Corresponding increases in C_{max} were 73% (high fat) and 54% (low-fat). AUC and Cmax of the metabolites M-2 and M-5 were higher when regorafenib was given with a low fat breakfast compared to fasting conditions and lower when given with high fat meal compared to fasting conditions. The highest cumulative exposure of regorafenib and its metabolites was achieved when administered following a low fat breakfast.

Distribution

From Study 11650 the reported geometric mean volume of distribution for the 120 mg and 160 mg tablet doses was 99 L (range 87-137L) and 93 L (range 37-178 L), respectively. In human blood, regorafenib was mainly distributed into plasma with a concentration ratio (plasma/blood) (Cp/Cb) of 1.59 in the concentration range 1.49 to 40.7 mg/L.

Regorafenib, M-2 and M-5 are highly bound to plasma proteins > 99% over a therapeutically relevant concentration range. *In vitro* binding experiments showed that regorafenib was not displaced from the binding site by warfarin, taxol, salicylic acid, gefitinib, ibuprofen, digitoxin, cisplatin, furosemide, nifedipine, propranolol, and docetaxel at clinically relevant concentrations.

Quantitative tissue distribution studies in rats involving oral or intravenous administration of [14C] regorafenib revealed that radioactivity was thoroughly distributed to almost all organs and tissues. Blood concentrations of radioactivity were similar to the concentrations found in most organs and tissues. Blood-brain barrier penetration was low.

Elimination

Regorafenib was eliminated from plasma with a half-life of 20 to 40 hours following a single oral dose in healthy volunteers and in cancer patients. A similar range of half-life estimates (20 – 30 hours) was found for metabolite M-2. The elimination half-life of M-5 was slower, averaging approximately 60 hours, with individual values ranging from 40 to 100 hours.

In study 12436, it was shown that regorafenib was excreted in urine and faeces as unchanged drug and metabolites after oral administration of 120 mg [14C]regorafenib solution to four healthy volunteers. Renal elimination of total radioactivity accounted for approximately 19% of dose, while approximately 71% of the dose was recovered in faeces as both unchanged drug (47%) and metabolites (24%). Urinary excretion of radioactivity was almost complete by 72 hours post-dose, whereas excretion via faeces continued until 144 hours post-dose, after which the rate of excretion exhibited a near plateau. While M-2 and M-5 are the metabolites circulating in plasma, M-7 and M-8 (glucuronides of regorafenib and M-2, respectively) are excreted in urine. In faeces, regorafenib was the most predominant metabolite followed by M-6 and M-7.

In another study (11650), following administration of a 120 mg tablet at steady state (Day 21), a mean of 8.4% of the dose was recovered in urine over 24 hours as either M-8 (1.6%) or M-7

(6.8%). The corresponding excretion for the 160 mg tablet dose was lower, 0.5% as M-8 and 1.9% as M-7.

Regorafenib undergoes extensive and complex metabolism, including oxidation and glucuronidation. In man, CYP3A4 is the major CYP isoform for phase I (oxidative) metabolism of regorafenib to form M-2 and M-3. M-2 and M-3 are further metabolised to M-5. Glucuronidation of regorafenib was catalysed by human liver and kidney microsomes fortified with UGPGA. UDP-glucuronosyltransferase (UGT) 1A9 was identified to be responsible for conjugation of regorafenib with glucuronic acid, to form M-7. M-5 is not further metabolised but reduction to M-4 may take place by microflora in the gut. Also the metabolites M-7, M-8 and M-2 may be reduced and/or cleaved in the intestinal milieu to form regorafenib resulting in enterohepatic cycling *in vivo*.

Dose proportionality and time dependencies

The pharmacokinetics of regorafenib at different doses from oral solution and tablet dosage form was investigated in studies 11650 (doses 10-220 mg, intermittent schedule) and 11651 (20-140 mg, continuous administration). Following single dose administration, AUC and C_{max} of regorafenib increased with increasing dose, though not in proportion to dose. Administration of a solution (10-120 mg) resulted in dose-dependent increases in systemic exposure up to the 100 mg dose while a linear increase in exposure was not achieved when escalating to 120 mg solution. Regorafenib was administered as solid solution tablets at doses of 60, 100, 120, 160, and 220 mg to separate cohorts of cancer patients. AUC(0-tlast), and C_{max} values were consistent with dose proportionality over the dose range of 60 to 160 mg after a single dose.

Plasma concentrations of the two major metabolites M-2 and M-5 were measured along with parent drug. At low doses (below 60 mg), the plasma concentrations of both metabolites after a single dose of regorafenib were lower than those of regorafenib. A sharp increase in metabolite exposure was seen when the dose was increased from 30 to 60 mg. A more gradual increase up to 220 mg dose was observed.

Following multiple dose administration, regorafenib exposure at steady-state seemed not to increase significantly at doses ≥ 60 mg. At doses < 60 mg, the plasma concentrations of both metabolites was relatively low but increased at doses ≥ 60 mg. Pharmacokinetics of regorafenib, M-2 and M-5 is not dose proportional after multiple dosing.

Time dependent pharmacokinetics was assessed by comparing pharmacokinetics of regorafenib, M-2 and M-5 at day 21 with single dose administration of 160 mg regorafenib in study 11650. Mean steady-state $C_{max,ss}$ and $AUC(0\text{-}24)_{ss}$ values following dosing with 160 mg were 3.9 mg/L and 58.0 mg*hr/L, respectively. The accumulation of regorafenib at steady-state was approximately 2-fold as expected considering the mean elimination half-life of 20 – 40 hours. Plasma concentrations of both metabolites were below those of parent compound following single dose administration but by Day 21, plasma concentrations were similar for parent drug and metabolites due to the nonlinear accumulation of metabolites. Accumulation was greater for M-2 (5-fold) and M-5 (up to 67-fold) than for regorafenib itself.

Special populations

In study 11650, PK analyses were performed on subgroups of patients based on renal function. No consistent differences in AUC or Cmax were found between patients with mild renal impairment and those with normal renal function. When pooling phase 1/2 studies, the mean AUC(0-24)ss of 38 mgh/L for the normal renal function group was considerably lower than the value of 50 – 60 mgh/L seen in healthy volunteers with normal renal function. No trends were observed for M-2 and M-5.

The effect of hepatic impairment on pharmacokinetics of regorafenib, M-2 and M-5 was studied in hepatocellular carcinoma patients in study 11651 and in study 14596. Mild and moderate hepatic impairment did not affect regorafenib, M-2 and M-5 pharmacokinetics following single dose administration. PK of regorafenib, M-2 and M-5 at steady-state has been estimated by population-based PK modelling. The effect of hepatic impairment on the PK was estimated. It was estimated that exposure to regorafenib increased 2.2-fold in patients with moderate hepatic impairment.

Pharmacokinetics of regorafenib was similar in males and females.

Analysis of ethnic differences in PK focused on Asians and Caucasians. Separate studies were conducted in Japanese (Study 13172), Chinese (Study 14996), and Korean (Study 14596) cancer patients in which regorafenib was administered at a dose of 160 mg daily and PK data were collected. The exposure of regorafenib in various Asian populations (Chinese, Japanese, Korean) is within the same range as seen in Caucasians.

Analysis of pooled Phase 1/2 data showed a trend toward increased exposure at higher body weights.

The PK of regorafenib was not dependent on age. Mean steady-state AUC(0-24) and Cmax values of regorafenib for patients ≥ 65 years were similar to those for patents < 65 years. Although mean values suggested a higher exposure of M-2 and M-5 in patients > 65 years, there was no obvious trend.

Pharmacokinetic interaction studies

Study 12435 was a single-centre, non-randomised, open-label 2-period cross-over study evaluating the effect of 400 mg ketoconazole, a strong CYP3A4 inhibitor, on the pharmacokinetics of 80 mg and 160 mg regorafenib single doses. Each subject received two single oral doses of regorafenib with an 18-day washout period between administrations.

There was a 33% increase in mean regorafenib AUC and a 40% increase in mean Cmax following a 160 mg dose of regorafenib when given with ketoconazole. Following administration of 160 mg regorafenib, there was a 94% decrease in mean M-2 AUC and a 97% decrease in mean Cmax upon concomitant administration with ketoconazole. Similar to M-2, the mean M-5 AUC decreased 93% and the mean Cmax decreased 93% following administration of 160 mg regorafenib with ketoconazole. A similar pattern of inhibition was seen for regorafenib as well as M-2 and M-5 for the 80 mg dose of regorafenib.

Study 15524 was a single-centre, non-randomised, open-label 2-period cross-over study evaluating the effect of 600 mg rifampicin on the pharmacokinetics of 160 mg regorafenib single dose. Each subject received two single oral doses of regorafenib with a 14-day washout period between administrations.

There was a statistically significant decrease in both AUC and Cmax (approximately 50% and 20% in mean, respectively) of regorafenib, when administered concomitantly with rifampicin. There was no significant change in metabolite M-2 AUC as the 90% confidence interval included 100%, although there was a significant increase in Cmax (58%) when regorafenib was administered concomitantly with rifampicin. There was a greater than 3-fold increase in metabolite M-5 AUC and greater than 4-fold increase in Cmax when regorafenib was administered concomitantly with rifampicin.

A probe substrate study was performed (Study 12434) to evaluate the effect of regorafenib on the pharmacokinetics of probe substrates of CYP2C8 (rosiglitazone), CYP2C9 (s-warfarin), CYP2C19 (omeprazole) and CYP3A4 (midazolam). No meaningful effects on the PK of rosiglitazone, S-warfarin, omeprazole and midazolam were observed.

A drug-drug interaction study was performed (Study 11656) evaluating the combination of regorafenib with mFOLFOX6 (oxaliplatin/folinic acid/5-FU) or FOLFIRI (irinotecan/folinic acid/5-FU). On Days 4 - 10 and 18 - 24, patients received 160 mg regorafenib once daily for Cycles 1-6. For Cycle 7 onward, regorafenib was administered in a 21 days on / 7 days off schedule. A cycle was defined as 28 days. Both irinotecan and SN-38, its active metabolite, had significantly higher AUCs in Cycle 2 compared to Cycle 1, i.e. they were higher when given 5 days after regorafenib treatment compared with administration without preceding regorafenib administration. For irinotecan, the AUC in the presence of regorafenib was increased 28% with a 90% confidence interval of 107 to 154%; and for SN-38, the AUC in the presence of regorafenib was increased 44% with a 90% confidence interval of 112 to 185%. There were no significant differences with respect to Cmax.

Pharmacokinetics using human biomaterials

Regorafenib exhibited no inductive potential on major CYP isoforms (e.g. CYP1A2 and 3A4). Regorafenib potently inhibited CYP2C8 (Ki = 0.6 µM), and also considerably inhibited CYP2C9 (Ki = 4.7 µM) and CYP2B6 (Ki = 5.2 µM). The inhibitory potency towards CYP3A4 (Ki = 11.1 µM) and CYP2C19 (Ki = 16.4 µM) was less pronounced. Regorafenib is an inhibitor of Pgp and BRCP.

M-2 potently inhibited CYP2C8 (Ki = 1.0 µM) and CYP2C9 (Ki = 0.8 µM with diclofenac as substrate) and also considerably affected CYP3A4 (Ki = 4.0 µM, testosterone as substrate) as well as CYP2D6 (K = 7.8 µM). Weak to moderate inhibitory potency was observed for M-2 towards CYP2B6 (IC50 = 20 µM), and CYP3A4 (IC50 = 22 µM with midazolam as substrate).

M-5 potently inhibited CYP2C8 (Ki = 1.3 µM), whereas CYP2B6 was weakly inhibited (IC50 = 47 µM). M-5 did not alter the activities of CYP1A2, CYP2A6, CYP2C9, CYP2C19, CYP2D6, CYP2E1, and CYP3A4. Additionally, no significant time-dependent inhibition on CYP3A4 following 30 min pre-incubation of M-5 with NADPH-supplemented human liver microsomes was observed.

2.4.3. Pharmacodynamics

Mechanism of action

No clinical studies addressing the mechanism of action were submitted.

Primary and Secondary pharmacology

Biomarkers evaluation in the clinical studies included KRAS mutational status (dose finding study 11650 and pivotal phase 3 study 14387-CORRECT) and plasma protein levels VEGF and VEGFR2 in studies 11650 and 11726 in RCC patients and dynamic contrast-enhanced MRI (DCE-MRI) in study 11650. Additionally, in the pivotal study, genetic biomarker analyses were performed: the mutational status of three proto-oncogenes commonly associated with CRC (KRAS, PIK3CA and BRAF) was evaluated. Plasma protein biomarkers evaluated included those associated with angiogenesis (ANG-2, IL-6, IL-8, PlGF, VEGFR-1, TIE-1, VEGF-A, VEGF-C, VEGF-D, VEGFA- 121), as well others with known or hypothesised roles in CRC pathogenesis (BMP-7, VWF, M-CSF, SDF-1 and TIMP-2).

KRAS mutational status was evaluated in two studies: the dose finding study 11650 and the pivotal phase 3 study 14387 (CORRECT). In Study 11650 (Phase 1 mCRC), KRAS mutational status was evaluated using plasma DNA. Plasma samples from 54% (20/37) of the evaluable patients were found to be KRAS mutant and 46% (17/37) were found to be KRAS wild type. The median PFS was 84 days for KRAS mutant patients and 161 days for KRAS wild type patients. In Study 14387 (pivotal Phase 3 mCRC), historical (pre-existing) KRAS mutational data was available from 96% (729/760) of all randomised patients, of which 59% (430/729) were reported as KRAS mutant and 41% (299/729) as KRAS wild type. Subgroup analyses evaluating PFS by KRAS mutational status showed trends in favour of regorafenib-treated patients in both KRAS wild type and KRAS mutant subgroups [KRAS wild type: HR of 0.475 (95% CI: 0.362, 0.623); KRAS mutant: HR of 0.525 (95% CI: 0.425, 0.649)]. Correlative analysis also indicated a trend towards a survival benefit for regorafenib as compared to placebo in the KRAS wild type subgroup (regorafenib/placebo HR: 0.653 [95% CI: 0.476, 0.895]) as well as in the KRAS mutant subgroup (regorafenib/placebo HR: 0.867 [95% CI: 0.670, 1.123]).

PIK3CA mutational status was available from 66% of all randomised patients, of which 17% were PIK3A mutant and 83% were PIK3CA wild type. Correlative analysis for OS indicated trends in favour of regorafenib in both PIK3CA wild type (regorafenib/placebo HR: 0.75 [95% CI: 0.57, 0.99]) and PIK3CA mutant (regorafenib/placebo HR: 0.84 [95% CI: 0.47, 1.50]) subgroups. The interaction p-value among these subgroups was 0.723, indicating no significant difference in regorafenib clinical efficacy (vs. placebo) related to PIK3CA mutational status. BRAF mutational status was determined from 66% of all randomised patients, of which 3.4% were BRAF mutant and 96.6% were BRAF wild type. Due to the small number of BRAF mutant patients, a correlative analysis was not conducted based on BRAF mutational status.

Data from study 11650 and study 11726 revealed biological effects of regorafenib treatment that were in line with the activity of this compound at inhibiting VEGF signalling, i.e. increased levels of VEGF and decreased levels of VEGFR2 with regorafenib treatment. In study 11650, increased levels of VEGF and decreased levels of VEGFR2 with regorafenib treatment were observed with

regorafenib doses ≥ 60 mg. A DCE-MRI was performed at baseline, on Day 2 of Cycle 1, Day 21 of Cycles 1 - 4 and afterwards every second cycle, as well as at the final visit to assess tumour blood flow / tumour vessel permeability in a subgroup of patients. A decrease in the iAUC60 for the gadolinium curve as measured by DCE-MRI was observed at regorafenib doses ≥ 120 mg.

In study 11726, levels of VEGF increased and VEGFR2 decreased with regorafenib treatment. The consistency of the change in VEGFR2 is exemplified by the finding that each of the 28 patients evaluated exhibited a decrease in plasma VEGFR2 levels with regorafenib treatment. Other plasma proteins were found to be altered with regorafenib treatment. Some of these proteins have been linked to angiogenesis (TIE1, ANG2), where others represent kinase receptors inhibited by regorafenib (c-KIT) or proteins released following apoptotic cell death (CK18M30).

A dedicated cardiovascular study of advanced cancer patients (Study 14814) was conducted to evaluate cardiovascular safety for the 160 mg once daily dosing with regorafenib. Fifty-four (54) patients were enrolled in this cardiovascular safety study and all patients received at least one dose of 160 mg once daily regorafenib in this clinical evaluation of potential changes in QT/QTc on ECG and in LVEF. The primary variable with regard to QT/QTc was the change in QTcF from the t_{max} of regorafenib on Cycle 1 or 2, Day 21 to the average of the baseline QT intervals from the ECGs collected over 24 hours on Cycle 1, Day -1, and corrected using Fridericia's method for heart rate correction; Bazett's correction was also calculated. In addition, left ventricular ejection fraction (LVEF) was to be assessed by MUGA (multi gated acquisition) scan at baseline and at least once under on-going regorafenib treatment, typically after a minimum 2 cycles of regorafenib treatment.

The range of AUC and C_{max} values in this study fall within the full range of that seen in previous studies, and the median t_{max} (3 hours) is also similar to that seen in other studies. At the t_{max} of regorafenib, the mean changes from baseline in QTcB and QTcF were -1 and 2 msec, respectively and in both cases, the 90% confidence interval did not include the value 10 msec. Additionally, a secondary analysis of the QT/QTc variables evaluated the maximal change from baseline in QTcB and QTcF over the 24-hour measurement period on Day 21. Results for the QTcB and QTcF maximal median change from baseline were 7 and 9 msec, respectively. No patient had a QTcB or QTcF value > 500 msec during the post-treatment Holter monitoring visits (at Cycle 1 or 2, Day 21).

2.4.4. Discussion on clinical pharmacology

Regorafenib reaches mean peak plasma levels of about 2.5 mg/l at about 3 to 4 hours after a single oral dose of 160 mg given as 4 tablets each containing 40 mg. Following single doses of 60 mg or 100 mg, the average relative bioavailability of tablets compared to an oral solution was 69% and 83%, respectively.

Two metabolites of regorafenib, M-2 and M-5, have demonstrated in vitro pharmacologic activity similar to that of unchanged regorafenib. Although regorafenib, M-2 and M-5 have shown similar activity in vitro, the contribution of each moiety to clinical efficacy and toxicity is not known. Systemic exposure of regorafenib at steady state increases dose proportionally up to 60 mg and less than proportionally at doses greater than 60 mg. Accumulation of regorafenib at steady state results in about a 2 fold increase in plasma concentrations, which is consistent with the elimination half-life and dosing frequency. At steady state, regorafenib reaches mean peak

plasma levels of about 3.9 mg/L (8.1 micromolar) after oral administration of 160 mg regorafenib and the peak to trough ratio of mean plasma concentrations is less than 2. On the other hand, both metabolites, M 2 and M 5, exhibit non-linear accumulation, which might be caused by entero-hepatic recycling or saturation of the UGT1A9 pathway discussed below.

This supports the dose selection for which maximal exposure to all three active moieties was taken into consideration. The increase in total exposure to the 3 active moieties may also support the 3/1 on/off schedule over the continuous schedule because higher plasma concentrations of combination regorafenib, M-2 and M-5 can be achieved with the 160 mg dose compared to the 100 mg dose and also a higher cumulative exposure of regorafenib and its metabolites can be obtained with the 160 mg 3/1 on/off schedule. Finally, whereas plasma concentrations of M 2 and M 5 after a single dose of regorafenib are much lower than those of parent compound, steady state plasma concentrations of M 2 and M 5 are comparable to those of regorafenib.

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

The increase in exposure of regorafenib following intake of food is in line with the poor solubility characteristics of regorafenib. Alternatively, food constituents may enhance absorption of regorafenib. To maximize exposure to parent drug as well as to the active metabolites it is recommended for regorafenib to be dosed after a low-fat (light) meal. This was consistently recommended in the clinical studies.

Plasma concentration-time profiles for regorafenib as well as for the major circulating metabolites showed multiple peaks across the 24-hour dosing interval, which are attributed to enterohepatic circulation. *In vitro* protein binding of regorafenib to human plasma proteins is high (99.5%).*In vitro* protein binding of M-2 and M-5 is higher (99.8% and 99.95%, respectively) than that of regorafenib.

Metabolites M-2 and M-5 are weak substrates of P-gp. Metabolite M-5 is a weak BCRP-substrate.

Regorafenib is metabolised primarily in the liver by oxidative metabolism mediated by CYP3A4, as well as by glucuronidation mediated by UGT1A9. Two major and six minor metabolites of regorafenib have been identified in plasma. The main circulating metabolites of regorafenib in human plasma are M-2 (N oxide) and M-5 (N oxide and N desmethyl), which are pharmacologically active and have similar concentrations as regorafenib at steady state. M-2 is further metabolised by oxidative metabolism mediated by CYP3A4, as well as by glucuronidation mediated by UGT1A9. Metabolites may be reduced or hydrolysed in the gastrointestinal tract by microbial flora, allowing reabsorption of the unconjugated active substance and metabolites (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 a decreased regorafenib exposure. The clinical significance of these potential interactions is unknown, but may result in a decreased efficacy of regorafenib.

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

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

Co-administration of a strong UGT1A9 inhibitor (e.g. mefenamic acid, diflunisal, and niflumic acid) during regorafenib treatment should be avoided, as their influence on the steady-state exposure of regorafenib and its metabolites has not been studied.

Administration of rifampicin (600 mg for 9 days), a strong CYP3A4 inducer, with a single dose of regorafenib (160 mg on day 7) resulted in a reduction in AUC of regorafenib of approximately 50%, a 3 to 4 fold increase in mean exposure of the active metabolite M 5, and no change in exposure of active metabolite M 2. Other strong CYP3A4 inducers (e.g. phenytoin, carbamazepine, phenobarbital, St. John's wort) may also increase metabolism of regorafenib. Strong inducers of CYP3A4 should be avoided, or selection of an alternate concomitant medicinal product, with no or minimal potential to induce CYP3A4 should be considered.

In vitro data indicate that regorafenib as well as its active metabolite M 2 inhibit glucuronidation mediated by UGT1A1 and UGT1A9 whereas M 5 only inhibits UGT1A1 at concentrations which are achieved in vivo at steady state. Administration of regorafenib with a 5 day break prior to administration of irinotecan resulted in an increase of approximately 44% in AUC of SN 38, a substrate of UGT1A1 and an active metabolite of irinotecan. An increase in AUC of irinotecan of approximately 28% was also observed. This indicates that co administration of regorafenib may increase systemic exposure to UGT1A1 and UGT1A9 substrates.

Following oral administration, mean elimination half-life for regorafenib and its metabolite M 2 in plasma ranged 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 faeces (47% as parent compound, 24% as metabolites), and about 19% of the dose excreted in urine as glucuronides. Urinary excretion of glucuronides decreased below 10% under steady state conditions. Parent compound found in faeces could be derived from intestinal degradation of glucuronides or reduction of metabolite M 2 (N oxide), as well as unabsorbed regorafenib.

The inter- and intra-individual variability in exposure to regorafenib, M-2 and M-5 is rather high. A pop PK analysis was used to evaluate covariate effects in study 14387 and to derive exposure parameters which can be used for exposure-response analysis of this study. Intrinsic factors identified during the covariate analysis of the population PK evaluation were baseline bilirubin for regorafenib, baseline bilirubin and body weight for M-2, as well as baseline bilirubin, body weight

and sex for M-5. Bilirubin and weight increased exposure to regorafenib and M-2 by 20%. M-5 exposure was 77% higher in females than males but overall, the covariates did reduce the variability only modestly.

Overall, age did not affect the regorafenib pharmacokinetics over the studied age range (29 – 85 years). The pharmacokinetics of regorafenib is not influenced by gender. The exposure of regorafenib in various Asian populations (Chinese, Japanese, Korean) is within the same range as seen in Caucasians.

No major difference in pharmacokinetics in mild and moderate hepatic impairment following single dose administration of 100 mg regorafenib was observed. No data were available for pharmacokinetics in hepatic impairment following multiple dose administration because most patients had dose interruptions or needed a dose reduction during the first cycle. PK of regorafenib, M-2 and M-5 at steady-state has been estimated by popPK modelling. The effect of hepatic impairment on the PK was estimated. It was estimated that exposure to regorafenib increased 2.2-fold in patients with moderate hepatic impairment. Considering the aggregated of total (bound and unbound) of regorafenib, M-2 and M-5 together, the increase 1.3-fold in exposure in moderate hepatic impairment is modest. It is considered that these data are not enough for dose recommendations in moderate hepatic impairment. There are no data for patients with severe hepatic impairment. Regorafenib is mainly eliminated via the liver, and exposure might be increased in this patient population.

No dedicated study was conducted to study pharmacokinetics in patients with renal impairment. This is acceptable as excretion in urine of unchanged regorafenib was low (<1%) and excretion of the metabolites M-7 and M-8 in urine was <10% at steady-state. Available clinical data and physiology based pharmacokinetic modelling indicate similar steady state exposure of regorafenib and its metabolites M 2 and M 5 in patients with mild and moderate renal impairment compared to patients with normal renal function.

The pharmacokinetics of regorafenib has not been studied in patients with severe renal impairment or end stage renal disease. However, physiology based pharmacokinetic modelling does not predict any relevant change in exposure in these patients.

Available clinical data and physiology based pharmacokinetic modelling indicate similar steady state exposure of regorafenib and its metabolites M 2 and M 5 in patients with mild and moderate renal impairment compared to patients with normal renal function.

The pharmacokinetics of regorafenib has not been studied in patients with severe renal impairment or end stage renal disease. However, physiology based pharmacokinetic modelling does not predict any relevant change in exposure in these patients.

In vitro data indicate that regorafenib is an inhibitor of BCRP (IC50 values about 40 70 nanomolar) and P glycoprotein (IC50 value of about 2 micromolar). Co administration of regorafenib may increase the plasma concentrations of concomitant BCRP substrates, such as methotrexate, or P glycoprotein substrates, such as digoxin.

In vitro data indicate that regorafenib is a competitive inhibitor of the cytochromes CYP2C8 (Ki value of 0.6 micromolar), CYP2C9 (Ki value of 4.7 micromolar), CYP2B6 (Ki value of 5.2 micromolar) at concentrations which are achieved in vivo at steady state (peak plasma

concentration of 8.1 micromolar). The in vitro inhibitory potency towards CYP3A4 (Ki value of 11.1 micromolar) and CYP2C19 (Ki value of 16.4 micromolar) was less pronounced.

A clinical probe substrate study was performed to evaluate the effect of 14 days of dosing with 160 mg regorafenib on the pharmacokinetics of probe substrates of CYP2C8 (rosiglitazone) CYP2C9 (S warfarin), CYP 2C19 (omeprazole) and CYP3A4 (midazolam).

Pharmacokinetic data indicate that regorafenib may be given concomitantly with substrates of CYP2C8, CYP2C9, CYP3A4, and CYP2C19 without a clinically meaningful drug interaction (see also section 4.4).

Regorafenib is an oral anti-tumour agent that can inhibit multiple protein kinases, including kinases involved in tumour angiogenesis (VEGFR1, -2, -3, TIE2), oncogenesis (KIT, RET, RAF-1, BRAF, BRAFV600E), and the tumour microenvironment (PDGFR, FGFR). In the supportive study 11650, an effect on VEGF signalling was observed at regorafenib doses ≥ 60 mg but no clear exposure effect relation was apparent. In the extension cohort, VEGFR2 was decreased compared to baseline in all mCRC patients. Similar findings have been previously described for other agents that inhibit VEGFR/VEGFR2 signalling and in fact are considered to be a 'class effect' for these types of agents.

Genetic biomarker analysis has been conducted for KRAS, PIK3CA and BRAF. Plasma protein biomarkers evaluated include those associated with angiogenesis (ANG-2, IL-6, IL-8, PlGF, VEGFR-1, TIE-1, VEGF-A, VEGF-C, VEGF-D, VEGFA- 121), as well others with known or hypothesised roles in CRC pathogenesis (BMP-7, VWF, M-CSF, SDF-1 and TIMP-2). None of the biomarkers analysed appear to be conclusively predictive of regorafenib clinical activity but some concerns over the provided biomarker analysis have been raised due to the limited number of tumour tissues available, the absence of fresh biopsies performed at study entry and concerns regarding the validity of genetic measurements performed on DNA isolated from fresh plasma. Moreover, based on the historical KRAS data capturing the majority (97%) of patients enrolled in the pivotal study, both KRAS subgroups appear to do better on regorafenib treatment than on placebo, with the KRAS wild type subgroup exhibiting a stronger positive effect (see also discussion on clinical efficacy).

The results from the cardiovascular safety study are in-line with the pre-clinical safety pharmacology data indicating no relevant effect on cardiac repolarisation *in vivo*. The observed effects of regorafenib in humans at t_{max} on the QTc intervals of the ECG were minimal; the maximal median change was modest and unlikely to be of clinical significance in the setting of cancer treatment.

2.4.5. Conclusions on clinical pharmacology

The pharmacokinetics of regorafenib, M-2 and M-5 have been investigated sufficiently. Information regarding interactions has been reflected in the SmPC and remaining uncertainties regarding interactions have been addressed in the RMP.

Genetic biomarker analyses have been submitted. None of the biomarkers analysed appear to be predictive of regorafenib clinical activity.

2.5. Clinical efficacy

Support for the efficacy of regorafenib in the treatment of patients with metastatic colorectal cancer (mCRC) who have been previously treated with, or are not considered candidates for, fluoropyrimidine-based chemotherapy, an anti-VEGF therapy, and, if KRAS wild type, an anti-EGFR therapy comes from one pivotal phase III (CORRECT, 14387) trial. The results of the expansion cohort of the phase I 11650 study enrolling pre-treated patients with mCRC have been submitted as supportive, as well.

Table 4: Clinical efficacy studies of regorafenib in mCRC

			Number of patients		
Study	**Phase**	**Dosages**	**Regorafenib**	**Control**	**Endpoints**
14387 **(CORRECT)**	III	160 mg OD 3W on/1W off	500	253	**1°: OS** **2°: PFS, ORR, DCR and Safety** **3°: duration of response and SD, QoL, PK and biomarkers**
11650 **(expansion cohort)**	I	160 mg OD 3W on/1W off	23	-	**1°: BORR** **2°: PFS, PK, Safety**
Total			523	253	

2.5.1. Dose response studies

The proposed regorafenib dosing regimen of 160 mg orally once daily on a 3 weeks on/1 week off schedule in patients with metastatic CRC has been selected on the basis of nonclinical data and clinical efficacy and safety observed in the phase I dose escalation 11650 study. Data of another phase I study 11651 conducted with regorafenib administered orally once daily in a continuous regimen are also of relevance.

In the phase I 11650 dose escalation study conducted in patients with advanced solid tumours (76 patients), with one expansion cohort in patients with metastatic CRC (23 patients), doses ranging from 10 mg once daily to 220 mg once daily as oral solution (10, 30, 60, 120 mg) or tablets (120, 160, 220 mg) were administered according to a 3 weeks on/1 week off schedule in repeated cycles of 4 weeks. The Maximum Tolerated Dose (MTD) of regorafenib was 160 mg once daily (as co-precipitate tablets; with DLTs of grade 3 hand-foot skin reaction and hypertension). Pharmacokinetic analysis revealed a similar exposure at steady state for the parent compound regorafenib and the two pharmacologically active metabolites M-2 and M-5 at the MTD. Overall, 58% of all patients experienced disease control (PR+SD); 3 patients (RCC; CRC; osteosarcoma) achieved PR.

In the phase I study 11651, where regorafenib was administered orally once daily in a continuous regimen, a total of 84 patients were included, 38 patients in the dose escalation cohort, and 20 and 26 patients in two dose expansion cohorts in hepatocellular carcinoma (HCC) and non-small cell lung cancer (NSCLC), respectively. The MTD of regorafenib on the continuous dosing schedule was 100 mg once daily (with DLTs of grade 3 hand-foot skin reaction and hypertension). Overall, 37% of all patients experienced disease control (PR+SD); 4 patients (2 HCC, 1 neuro-endocrine carcinoma and 1 squamous cell carcinoma of the preorbit) achieved PR.

2.5.2. Main study

Study 14387 (CORRECT)

Methods

Study 14387 (CORRECT) was a pivotal multi-centre (114 study centres in 16 countries), randomised, double-blind, placebo-controlled phase III study comparing regorafenib plus best supportive care (BSC) versus placebo plus BSC in patients with mCRC who have progressed after standard therapy which had to include all of the following: fluoropyrimidine, oxaliplatin, irinotecan, bevacizumab and cetuximab or panitumumab (if KRAS wild type).

Participants

The CORRECT study population included patients with histologically or cytological confirmed metastatic CRC (Stage IV, adenocarcinoma), who experienced disease progression during or within 3 months following the last administration of approved standard therapies which had to include fluoropyrimidine, oxaliplatin, irinotecan, bevacizumab and cetuximab or panitumumab (if KRAS wild type), unless contraindicated or stopped before disease progression due to unacceptable toxicity or not registered in the country where the study was performed. Patients treated with oxaliplatin in an adjuvant setting were to have progressed during or within 6 months of completion of adjuvant therapy. Patients who had progressed more than 6 months after completion of oxaliplatin-containing adjuvant treatment were to be retreated with oxaliplatin-based therapy to be eligible. Patients with unknown KRAS status at screening were to have received prior anti-EGFR treatment. According to the inclusion criteria, patients were required to have an ECOG Performance Status score of 0-1, age ≥ 18 years, measurable or not measurable disease but evaluable by RECIST (version 1.1) and adequate bone marrow, renal and hepatic functions.

Patients with any CNS metastases were excluded as well as patients that received prior radiotherapy 2 or 4 weeks (depending on the extension of the field irradiated). Other main exclusion criteria were presence of uncontrolled hypertension, unstable angina pectoris or new onset of angina within 3 months, myocardial infarction within 6 months, congestive heart failure ≥ New York Heart Association class 2, cardiac arrhythmias requiring anti-arrhythmic therapy (except beta blockers or digoxin), any bleeding diathesis or haemorrhage or bleeding ≥ CTCAE grade 3 within 4 weeks, healing wound, ulcer or bone fracture, persistent proteinuria of CTCAE grade≥3 and arterial or venous thrombotic or embolic events within 6 months prior to study entry.

Treatments

Patients were randomised (2:1) to receive either regorafenib or matching placebo 160 mg (4 x 40 mg tablets) once daily orally for 3 weeks followed by 1 week off therapy (cycle of 4 weeks) plus BSC. Patients were treated until disease progression according to RECIST 1.1, clinical progression, unacceptable toxicity, and/or consent withdrawal. Regorafenib (film-coated, not divisible, gray-orange-red, oval, length 16 mm tablets) or placebo had to be taken in the morning with approximately 240 ml of water after a low-fat breakfast. Up to two regorafenib dose-reductions due to toxicity were allowed (from 160 mg to 120 mg to 80 mg). After implementation of a dose reduction, dose re-escalation was permitted provided that toxicities were resolved to baseline.

After the primary study endpoint (OS) was met at the second pre-planned interim analysis according to the DMC, study protocol was amended (amendment 3) and patients on placebo treatment who had not yet progressed were offered to cross over to regorafenib in open label treatment.

BSC included any concomitant medications or treatments: antibiotics, analgesics, radiation therapy for pain control (limited to bone metastases), corticosteroids, transfusions, psychotherapy, growth factors, palliative surgery, or any other symptomatic therapy necessary to provide BSC, except other investigational anti-tumour agents or anti-neoplastic chemo/hormonal/immuno-therapy.

During treatment, caution was required in case of concomitant treatment with agents interfering with CYP enzymes or glucuronsyl transferases UGT1A1 and 1A9, due to possible drug-drug interactions with regorafenib. Use of bisphosphonates or erythropoietin in patients under chronic treatment was allowed. Concomitant radiotherapy was allowed if target lesion(s) were not included within the radiation field and no more than 10% of the bone marrow was irradiated.

Objectives

The primary objective of the CORRECT trial was to show superiority of regorafenib plus BSC versus placebo plus BSC in terms of efficacy. Secondary objectives included comparisons in terms of safety and pharmacokinetics. A biomarker analysis was also included as exploratory.

Outcomes / endpoints

The primary study endpoint was overall survival (OS), defined as the time (days) from randomisation to death due to any cause. Patients alive at the time of analysis were censored at the last date known to be alive. Patients lost to follow-up were censored at day 1.

Secondary endpoints included progression-free survival (PFS, defined as the time [days] from randomisation to first observed disease progression [radiological or clinical, as assessed by investigators] or death due to any cause, if death occurred before disease progression was documented), Objective response rate (ORR, defined as the percentage of patients with complete response [CR] or partial response [PR] according to RECIST 1.1), and disease control rate (DCR, defined as the percentage of patients with CR, PR or stable disease [SD]).

Regarding PFS, if progression occurred after 2 consecutive missed or non-evaluable assessments (progression later than date of last evaluable scan + 16 weeks + 1 week), PFS was censored at the date of last evaluable scan. Death without progression was a PFS event only if it occurred within the 16+1 weeks of the last evaluable tumour assessment. If it occurred later, PFS was censored at the date of last evaluable tumour assessment. For patients who discontinued or withdrew treatment before progression, PFS was censored on the date of the last evaluable tumour assessment unless the patients died within 16+1 weeks after the last evaluable assessment. In this case, death was considered a PFS event. For patients who changed anticancer therapy before progression, PFS was censored at the date of last scan performed prior to the change of therapy.

Tumor assessments were performed at screening and then every 8 weeks during the treatment period until progression was documented, and also at the end of treatment visit, if applicable. Upon discontinuation of study drug patients were followed up for survival, approximately every month (telephone follow-up was acceptable), with the exception of patients who specifically withdrew consent. Patients were followed for AEs (adverse events) up to 30 days after the last dose of study drug.

Tertiary endpoints were duration of response (i.e., time from the first documented objective response of CR of PR, whichever was noted earlier, to disease progression or death [if death occurred before progression], in patients achieving CR or PR), duration of stable disease (i.e., time from randomisation to disease progression or death, calculated only in patients who failed to achieve CR or PR), and evaluation of patient reported outcomes (PROs). PROs included evaluation of Health Related Quality of life (according to EORTC QLQ-C30 and EQ-5D questionnaires).

In approximately 150 patients from selected sites, blood samples were collected for pharmacokinetic analyses of regorafenib and its metabolites at steady state.

Finally, a biomarker analysis was also included as exploratory. Biomarker analyses were performed on whole blood and plasma samples as well as archived diagnostic tumour biopsies (voluntary patients with a separate consent). Biomarker analysis included evaluation of mutation of genes of interest (e.g., BRAF, KRAS, PI3KCA), expression of several genes (eg, VEGFR, PDGFR, FGFR, c-KIT, TIE2) on archival tumour biopsies and/or blood/plasma samples.

Sample size

The study was designed to have 90% power to detect a 33.3% increase in median OS (i.e., a HR of 0.75, regorafenib over placebo). Assuming one-sided overall alpha of 0.025, power of 90%, a randomisation ratio of 2:1 between regorafenib and placebo and 2 formal interim analyses of OS during this study using an O'Brien-Fleming-type error spending function, a total of 582 death events for the final OS analysis were estimated to be required.

Randomisation

Patients were randomised to receive regorafenib or placebo with a ratio of 2:1 and they were planned to start study treatment within 7 days of randomisation. Randomisation was stratified by:

1- Prior treatment with VEGF targeting drugs (yes/no)

2- Time from diagnosis of metastatic disease (≥18 months versus <18 months)

3- Geographic region 1 (North America, Western Europe, Israel, and Australia), versus region 2 (Asia), versus region 3 (South America, Turkey and Eastern Europe)

In order to maintain a balanced representation of each region, not more than 250 patients from Asia were planned to be randomised.

Blinding (masking)

The study was double-blind.

Statistical methods

The primary population for the efficacy analysis was the ITT population, which was defined as all randomised patients, independently on whether they received or not study medication. The population for safety analysis comprised all patients who received at least 1 dose of study medication.

OS and PFS were compared using a log-rank test stratified by the same stratification factors as used for randomisation. In addition, the HR (regorafenib plus BSC group/placebo plus BSC group) for OS and its 95% confidence interval were calculated using the Cox model, stratified by the same stratification factors as above. Kaplan-Meier (KM) estimates for OS and KM survival curves were also presented for each treatment group.

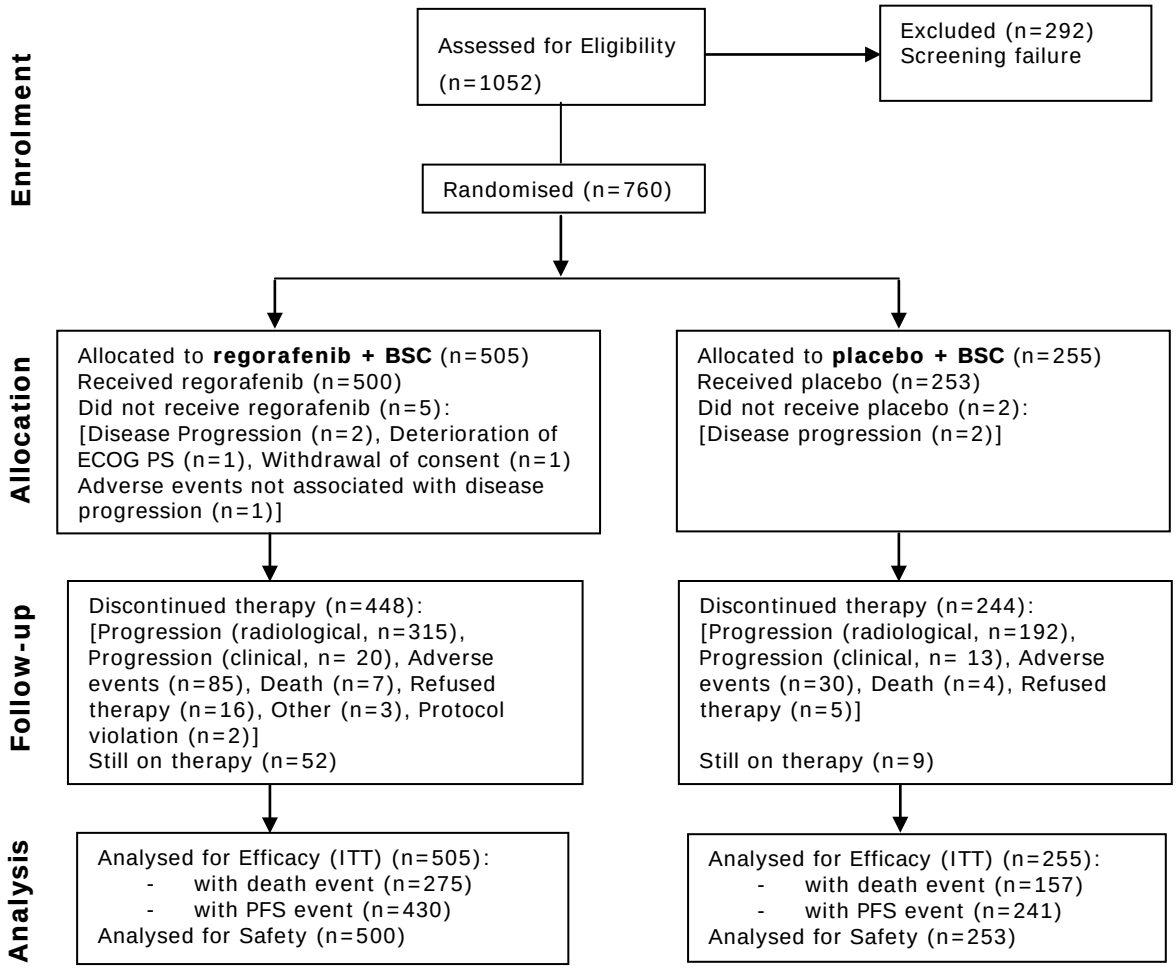
ORR and DCR were compared between treatment groups using the Cochran-Mantel-Haenszel (CMH) test adjusting for the same stratification factors as for the primary endpoint. Estimates and 95% confidence intervals were computed for each treatment group. The differences in ORR between the regorafenib and placebo group and the corresponding 95% confidence intervals were also calculated.

Two formal interim analyses were planned during the study. The first interim analysis (i.e., at approximately 30% (175 deaths) of the planned total number of events) served as a futility analysis only, and the second interim analysis (i.e., at approximately 70% (408 deaths) of the planned total number of events) was to evaluate both efficacy and futility. Stopping boundaries were calculated for the interim analyses based on the actual number of events observed up to the database cut-off date used for the interim analyses. A Lan-Demets alpha spending function determined the monitoring boundary for early stopping for efficacy so that the overall false positive rate, alpha, was less than or equal to 0.025 (one-sided). The alpha spending function was the O'Brien-Fleming-type boundary specified. Futility boundaries were calculated separately for the interim analyses, too. The futility boundaries were based on ruling out a true hazard ratio

(HR) of 0.7502 or lower (corresponding to approximately the targeted 33.3% or more increase in median overall survival over placebo). As the efficacy and futility boundaries were independent of each other, non-adherence to the futility boundaries would not inflate the overall false positive rate, alpha, to over 0.025 (one-sided).

Results

Participant flow



In total, 540 patients (71.1%) entered post-treatment survival follow-up: 353 (69.9%) from the regorafenib + BSC group and 187 (73.3 %) from the placebo + BSC group.

Recruitment

Patients were enrolled between 30 April 2010 and 22 March 2011. 52 patients in the regorafenib arm and 9 patients in the placebo arm were still on the study at the time of the clinical data cut-off (21 July 2011, second interim analysis).

Conduct of the study

A total of 432 death events (56.8%) were included at the second interim analysis (cut-off 21 July 2011), 275 (54.5%) events in the regorafenib arm and 157 events (61.6%) in the placebo arm. As the pre-specified O'Brien-Fleming-type efficacy boundary (one-sided alpha 0.009279) was crossed and the DMC proclaimed the study as positive, this interim analysis was presented as the final analysis. An updated OS analysis was performed using a later database cut-off date (13 November 2011, the day before the first placebo randomised patient crossed-over), when 97% (566) of the total planned events had occurred.

According to the Applicant, major protocol deviation/violations were reported in 7 patients who did not receive study drug and have been excluded from the 'per-protocol' population.

The most common (≥10% patients) minor deviations by term were 'Procedures, tests or measurements for this patient were not performed when scheduled' (60.6% vs 54.1% in the regorafenib and placebo groups, respectively), 'Scheduled procedures, tests or measurements for this patient were not performed within the allowed time windows' (28.5% vs 21.2%, respectively), and 'Study medication not taken or administered according to protocol' (15.6% vs 11.6%). Moreover, 13.3% of patients in each treatment group were randomized despite not meeting all inclusion/exclusion criteria, essentially consisting of presence of uncontrolled hypertension (8.3% vs 7.5%, respectively), and "INR/PTT greater than 1.5 x ULN (1.6% in both arms).

A total of 33 patients (15 in the placebo + BSC group and 18 patients in the regorafenib + BSC group) had inaccurate stratification information entered into IVRS. Two of the 33 total patients were mis-stratified for more than 1 factor. In light of the mis-stratification, sensitivity analyses on OS and PFS were also specified to be performed as unstratified analyses.

The original study protocol dated 10 February 2010 was subsequently amended 3 times, twice after the data cut-off for the second pre-planned interim analysis (considered as the final analysis).

Amendment 1 (dated 28 September 2010) essentially clarified inclusion/exclusion criteria, dose modification/delay, permitted (or not) concomitant medications, study procedures/assessments, pharmacokinetics sampling. Moreover, adverse events of special interest were updated and several minor textual changes of the study protocol were implemented.

Amendment 2 (dated 03 August 2011) essentially included recommendations for dose modification for AST, ALT and bilirubin increases related to study drug, introduction of weekly evaluation of ALT, AST and bilirubin during the first two cycles of treatment, introduction of guidance for patients developing diarrhoea, mucositis, anorexia or other events predisposing to fluid loss or inadequate fluid intake.

Amendment 3 (dated 01 November 2011) was implemented after the second interim analysis in order to allow patients on placebo treatment to receive regorafenib through open label treatment.

Baseline data

Baseline demographic and disease characteristics are summarised in the following Table 5.

Table 5: Baseline demographic and disease characteristics, 14387 (CORRECT) study

	Regorafenib n=505	Placebo n=255
Sex, n (%)		
Female	194 (38.4)	102 (40)
Male	311 (61.6)	153 (60)
Race, n (%)		
White	392 (77.6)	201 (78.8)
Black or African American	6 (1.2)	8 (3.1)
Asian	76 (15)	35 (13.7)
American Indian or Alaska native	1 (0.2)	1 (0.4)
Not reported/multiple	30 (5.9)	10 (3.9)
Age at randomization (years)		
Mean (range)	60.7 (22-82)	60.1 (25-85)
Median	61	61
< 65 years	309 (61.2)	166 (65.1)
≥ 65 years	196 (38.8)	89 (34.9)
Geographic Region, n (%)		
North America, Western Europe, Israel, Australia	420 (83.2)	212 (83.1)
Asia	69 (13.7)	35 (13.7)
South America, Turkey, Eastern Europe	16 (3.2)	8 (3.1)
ECOG Performance Status, n (%)		
0	265 (52.5)	146 (57.3)
1	240 (47.5)	109 (42.7)
Histology, n (%)		
Adenocarcinoma	495 (98)	248 (97.2)
Mucinous carcinoma (>50%, colloid type)	5 (1)	4 (1.6)
Adenosquamous carcinoma	1 (0.2)	1 (0.4)
Undifferentiated carcinoma	0	1 (0.4)
Carcinoma NOS	4 (0.8)	1 (0.4)
Primary site of disease, n (%)		
Colon	323 (64)	172 (67.4)
Rectum	151 (29.9)	69 (27.1)
Colon and rectum	30 (5.9)	14 (5.5)
Missing	1 (0.2)	0
Prior VEGF targeting drugs, n (%)		
Yes	505 (100)	255 (100)
No	0	0
Time since metastatic diagnosis, weeks		
Mean (range)	152 (18-837)	150 (10-553)
Median	133.1	128.5
< 18 months, n (%)	91 (18)	49 (19.2)
≥ 18 months, n (%)	414 (82)	97 (80.8)
Time since last progression, weeks		
Mean (range)	6.46 (0.1-50)	6.2 (0.3-52)
Median	4.99	4.56
Missing	30 (5.9)	9 (3.5)
KRAS mutation, n (%)		
No	205 (40.6)	94 (36.9)
Yes	273 (54.1)	157 (61.6)
Unknown	27 (5.3)	4 (1.6)
BRAF mutation, n (%)		
No	205 (40.6)	94 (36.9)
Yes	273 (54.1)	157 (61.5)
Unknown	27 (5.3)	4 (1.6)
Previous anticancer therapies, n (%)		
Fluoropyrimidine	505/505 (100)	255/255 (100)
Bevacizumab	505/505 (100)	255/255 (100)
Oxaliplatin	505/505 (100)	255/255 (100)
Irinotecan	505/505 (100)	255/255 (100)
Panitumumab/Cetuximab		
All patients	264/505 (52.3)	121/255 (47.5)
KRAS WT	204/205 (99.5)	94/94 (100)
KRAS mutated	33/273 (12.1)	23/157 (14.6)
KRAS unknown	27/27 (100)	4/4 (100)

Numbers analysed

All 760 randomised patients were included in the intent-to-treat (ITT) population, the primary efficacy population. Of them, the 753 patients who received at least one dose of study drug were included in the safety (SAF) population.

Outcomes and estimation

Primary objective: Overall Survival (OS)

Results are summarised in the following Table 6 and Figures 2 and 3.

Table 6: Overall Survival, 14387 (CORRECT) study, ITT population

	Placebo + BSC (N = 255)	Regorafenib + BSC (N = 505)
Number of patients (%) with event	157 (61.6)	275 (54.5)
Number of patients (%) censored	98 (38.4)	230 (45.5)
Median overall survival (days)	151	196
95% CI for median	134, 177	178, 222
Range (days, without censored values)	13-315	5-375
Range (days, including censored values)	(1** – 413**)	(5 – 401**)
Overall survival rate at		
Month 3 (95% CI)	0.727 (0.672, 0.782)	0.803 (0.768, 0.838)
Month 6 (95% CI)	0.435 (0.371, 0.498)	0.525 (0.479, 0.571)
Month 9 (95% CI)	0.308 (0.238, 0.378)	0.382 (0.329, 0.435)
Month 12 (95% CI)	0.240 (0.151, 0.330)	0.243 (0.155, 0.331)
Hazard ratio (regorafenib/placebo)[a]	0.774	
95% CI for hazard ratio	0.636, 0.942	
One-sided p-value from log rank test	0.005178	

Abbreviations: ** – censored observation; CI – confidence interval; ITT – intent to treat
a. A Hazard ratio < 1 indicates superiority of regorafenib over placebo.
Note: Stratification based on CRF data. The hazard ratio and its 95% CI was based on Cox Regression Model, stratified by prior treatment with anti-VEGF drugs (yes/no), time from diagnosis of metastatic disease (≥18 months vs <18 months) and geographical region 1 (North America, Western Europe, Israel and Australia) versus region 2 (Asia) versus region 3 (South America, Turkey and Eastern Europe).

Figure 2: Kaplan-Meier Plot of OS, 14387 (CORRECT) study, ITT population

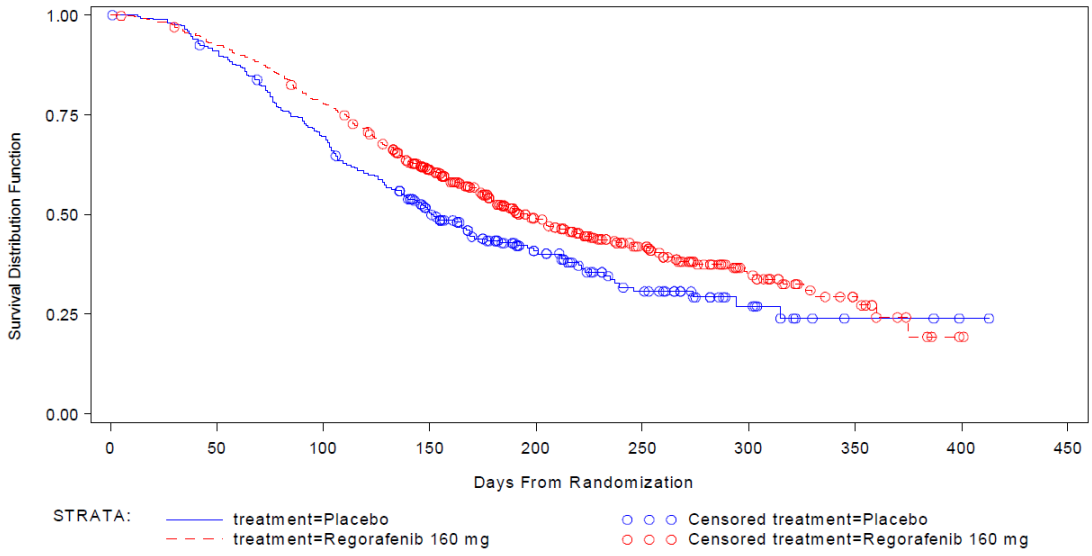
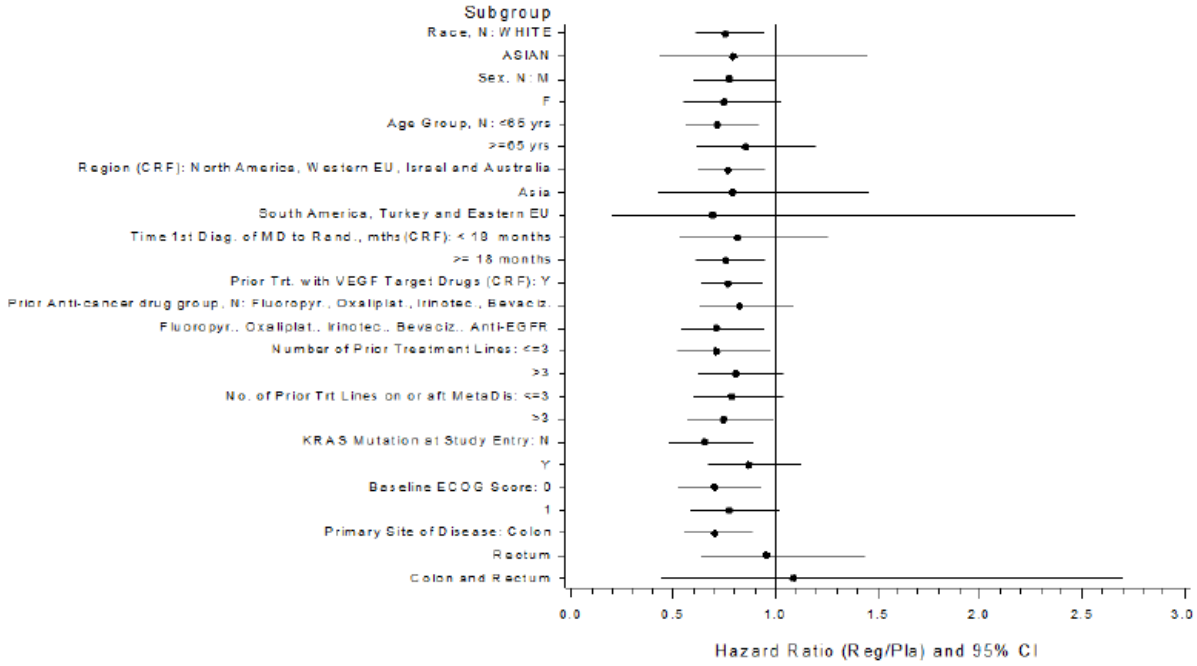


Figure 3: Forest plot for OS by subgroups, 14387 (CORRECT) study, ITT population



Results from the updated OS analysis (cut-off date 13 November 2011, the day before the first placebo randomised patient crossed-over) are summarised in the following Table 7.

Table 7: Updated Overall survival analysis (cut-off 13 November 2011), 14387 (CORRECT) study, ITT population

		Placebo (N=255)	Regorafenib (N=505)	Total (N=760)
N		255	505	760
Number (%) of subjects with event		197 (77.3%)	369 (73.1%)	566 (74.5%)
Number (%) of subjects censored		58 (22.7%)	136 (26.9%)	194 (25.5%)
Hazard ratio (Reg/Pla) [95% CI]*			0.790 (0.664,0.939)	
One-sided p-value from log rank test	Stratified (CRF data)		0.003791	
Median [95% CI]	Days	152 (134, 178)	194 (177, 214)	179 (167, 197)
Overall Survival rate at	Month 3 [95% CI]	0.727 (0.672,0.782)	0.803 (0.768,0.838)	0.778 (0.748,0.807)
	Month 6 [95% CI]	0.431 (0.369,0.492)	0.522 (0.479,0.566)	0.492 (0.456,0.527)
	Month 9 [95% CI]	0.269 (0.212,0.325)	0.349 (0.307,0.392)	0.323 (0.289,0.357)
	Month 12 [95% CI]	0.170 (0.114,0.226)	0.241 (0.198,0.283)	0.218 (0.184,0.252)

** censored observation.
Median, percentile and other 95% CIs computed using Kaplan-Meier estimates.

Secondary endpoint: Progression Free Survival (PFS)

The analysis of PFS, conducted at the time of the second interim analysis, was based on 671 (88%) PFS events: 430 (85.1%) in the regorafenib group and 241 (94.5%) in the placebo group.

Results are summarised in the following Table 8 and Figures 4 and 5.

Table 8: PFS (investigator assessment), 14387 (CORRECT) study

	Placebo + BSC (N = 255)	Regorafenib + BSC (N = 505)
Number of patients (%) with event	241 (94.5)	430 (85.1)
Number of patients (%) censored	14 (5.5)	75 (14.9)
Median PFS (days)	52	59
95% CI for median	(51, 53)	(57, 65)
Range (without censored values)	6-277	5-333
Range (days, including censored values)	(1**-277)	(1**-336**)
PFS rate at		
Month 3 (95% CI)	0.135 (0.093, 0.177)	0.420 (0.376, 0.464)
Month 6 (95% CI)	0.021 (0.000, 0.044)	0.130 (0.098, 0.163)
Month 9 (95% CI)	0.010 (0.000, 0.029)	0.051 (0.025, 0.076)
Month 12 (95% CI)	0.000 (0.000, 1.000)	A (0.000, 1.000)
Hazard ratio (regorafenib/placebo) [a]	0.494	
95% CI for hazard ratio	0.419, 0.582	
One-sided p-value from log rank test	<0.000001	

Abbreviations: ** – censored observation; CI – confidence interval; ITT – intent to treat; PFS – progression-free survival; A – value cannot be estimated due to censored data

a. A Hazard ratio < 1 indicates superiority of Regorafenib 160 mg (experimental) over Placebo (control)

Note: Median PFS and 95% CIs computed using Kaplan-Meier estimates. Hazard ratio and its 95% CI was based on Cox Regression Model, stratified by prior treatment with anti-VEGF drugs (yes/no), time from diagnosis of metastatic disease (≥18 months vs <18 months) and geographical region 1 (North America, Western Europe, Israel and Australia) versus region 2 (Asia) versus region 3 (South America, Turkey and Eastern Europe). Stratification based on CRF data.

Figure 4: Kaplan–Meier Plot of PFS, 14387 (CORRECT) study

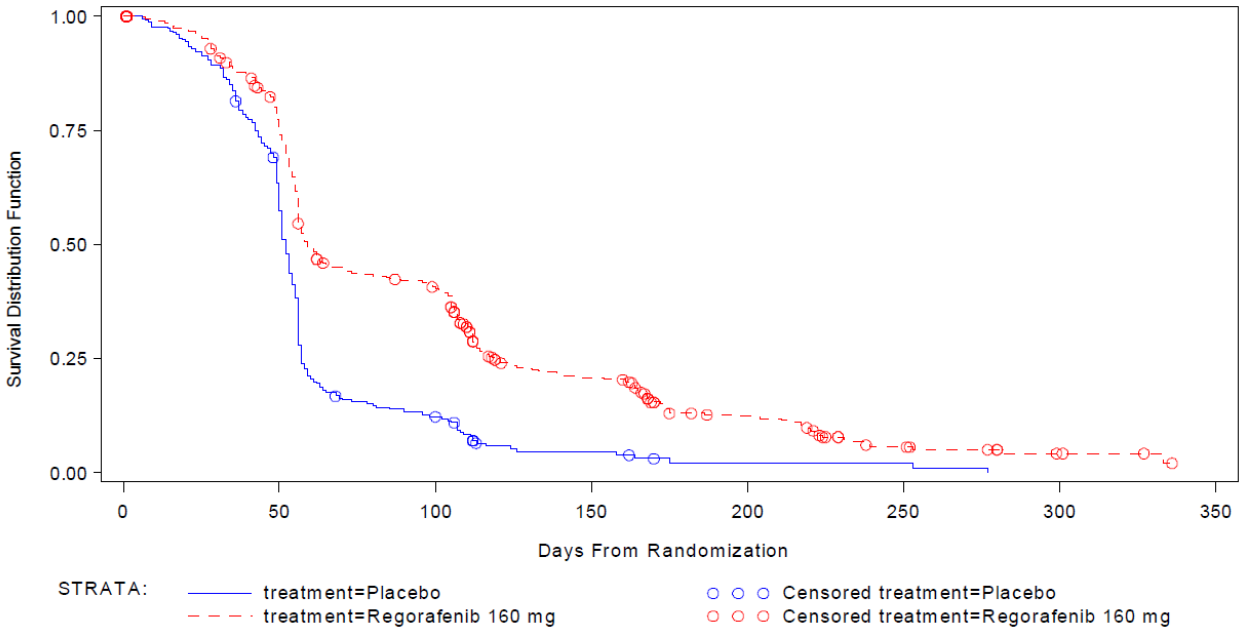
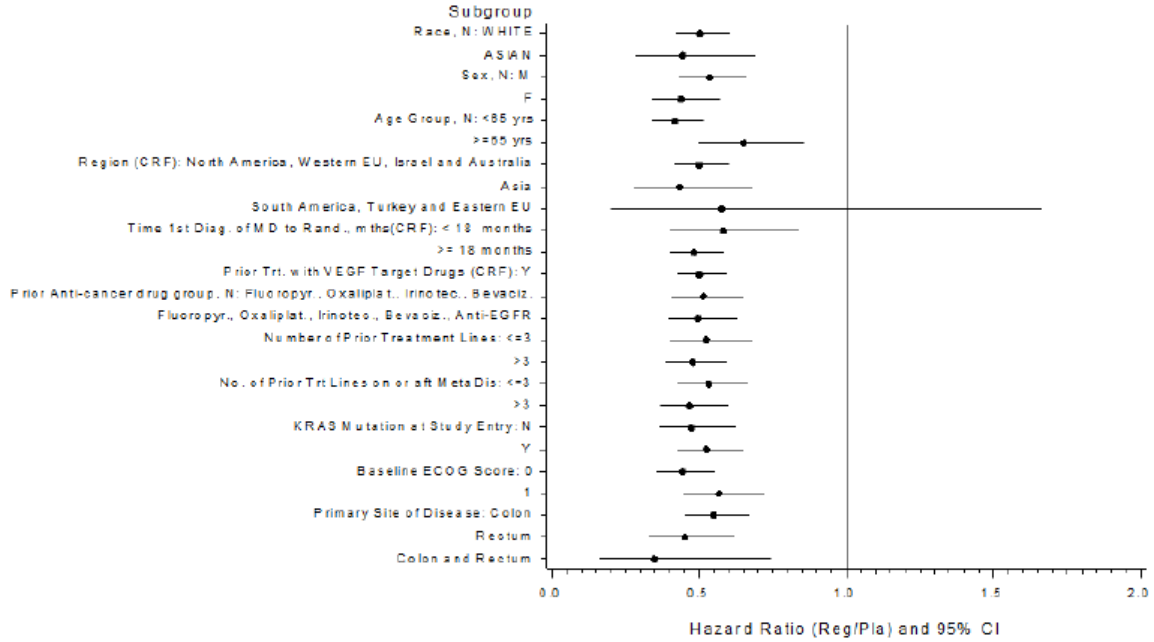


Figure 5: Forest plot for OS by subgroups, 14387 (CORRECT) study, ITT population



Secondary objective: Overall Response Rate (ORR) and Disease Control Rate (DCR)

Overall response rate (ORR=CR + PR, per RECIST 1.1, as assessed by investigator) was not statistically significant different between the two treatment arms: 1% (0+5 patients) with regorafenib +BSC versus 0.4% (0+1 pt) with placebo plus BSC.

Disease Control Rate (DCR: CR+ PR+ SD) was significantly higher with regorafenib (41%, [207 patients]) compared with placebo (14.9%, [38 patients]), essentially due to a higher rate of patients with disease stabilisation.

Tertiary objective: Duration of response and Duration of stable disease

Only 6 patients (5 treated with regorafenib and 1 with placebo) achieved tumour response. For the 5 patients treated with regorafenib median duration of response could not be evaluated due to small number of patients (range without censored values 59-64 days), whereas it was 68 days in the patient treated in the placebo group.

Duration of stable disease was not significantly different between the two treatment arms (60 days with regorafenib vs 52 days with placebo).

Tertiary endpoint: Patient-Reported Outcomes: EORTC QLQ-C30 and EQ-5D

EORTC QLQ-C30 and EQ-5D questionnaires were administered at baseline, on Day 1 of Cycles 2-4, and every other cycle thereafter and at end of treatment visit. Higher scores of the EORTC QLQ-C30 (range 0-100) and EQ-5D represent a higher level of functioning and better HRQoL. Change of ≥10 points in EORTC QLQ-C30 or, 0.07 to 0.12 points on the EQ-5D index or of 7-12 points on the visual analogue scale (VAS) are considered as clinically meaningful.

The EORTC QLQ-C30 was completed by 697 (92%) patients at baseline, 604 (79%) patients at cycle 2, and 557 (73%) patients at cycle 3. The mean EORTC QLQ-C30 score at baseline was 62.64 and 64.65 in the regorafenib and placebo groups, respectively. The mean score at the End

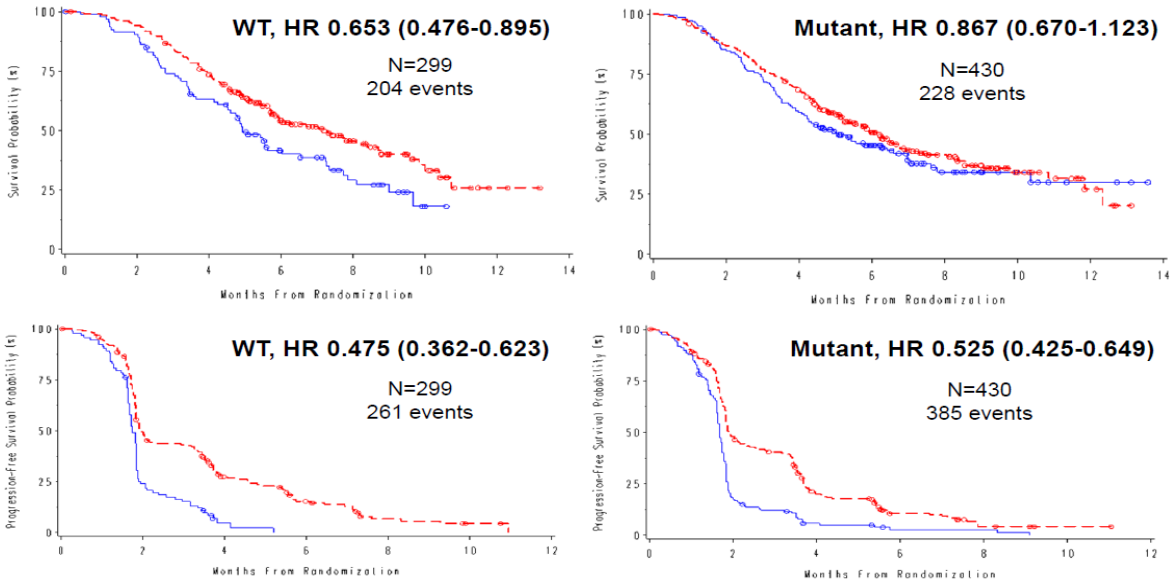
of Treatment (EOT) visit was 48.94 and 51.85, respectively. The deterioration in global score was not significantly different between the two treatment arms. The least square (LS) mean regarding time-adjusted AUC was slightly but not statistically significantly higher with placebo compared with regorafenib (58.13 vs 56.93, respectively).

The EQ-5D questionnaire was completed by 705 (93%) patients at baseline, 637 (84%) patients at cycle 2, and 601 (79%) patients at cycle 3. The mean EQ-5D index score (general health status) was 0.727 and 0.738 in the regorafenib and placebo groups, respectively at baseline, and 0.593 and 0.591, respectively, at the EOT visit. The mean EQ-5D VAS score was 65.4 and 65.8 in the regorafenib and placebo groups, respectively, at baseline and 55.5 and 57.3, respectively, at the EOT visit. Mean changes in scores from baseline for EQ-5D index and VAS were, overall, similar between the regorafenib + BSC and placebo + BSC groups, suggesting similar deterioration in both arms.

Exploratory endpoint: biomarkers

Subgroup analyses of OS and PFS by KRAS tumour status based on historical data prior to study enrolment are presented in Figure 6 .

Figure 6: OS and PFS by historical KRAS tumour status, 14387 study, ITT population



A retrospective analysis of 3 genetic biomarkers (KRAS, PIK3CA, BRAF) and 15 non-genetic biomarkers considered relevant for CRC (ANG-2, IL-6, IL-8, VEGFR-1, TIE-1, VEGF-A, VEGF-C, VEGF-D, VEGF-A-121, BMP-7, VWF, M-CSF, SDF-1 and TIMP-2), based on DNA isolated from fresh baseline plasma and archival tumour tissue specimens, was submitted.

Plasma KRAS data was generated for 66% (503) of all randomised patients, of which 69% were KRAS mutant, compared to 59% from the archival tumour tissue, and 31% were KRAS wild type. Correlative analysis for OS indicated trends in favour of regorafenib in both KRAS wild type (regorafenib/placebo HR: 0.67 [95% CI: 0.41, 1.08]) and KRAS mutant (regorafenib/placebo HR: 0.81 [95% CI: 0.61, 1.09]) subgroups. The interaction p-value comparing the HRs of the *de novo* plasma KRAS subgroups was 0.561, indicating no significant difference in regorafenib

clinical efficacy (vs. placebo) related to KRAS mutational status. Likewise, interaction p-values for subgroups in which KRAS status was determined via BEAMing of DNA isolated from archival tumour tissue were not significant. Pre-existing/historical KRAS data were available from 96% of all randomized patients, of which 59% were KRAS mutant and 41% were KRAS wild type. Correlative analysis indicated a trend towards a survival benefit for regorafenib as compared to placebo in the KRAS wild type subgroup (regorafenib/placebo HR: 0.653 [95% CI: 0.476, 0.895]) as well as in the KRAS mutant subgroup (regorafenib/placebo HR: 0.867 [95% CI: 0.670, 1.123]).

PIK3CA mutation data were available from 66% of all randomised patients, of which 17% were PIK3CA mutant and 83% were PIK3CA wild type. Correlative analysis for OS indicated trends in favour of regorafenib in both PIK3CA wild type (regorafenib/placebo HR: 0.75 [95% CI: 0.57, 0.99]) and PIK3CA mutant (regorafenib/placebo HR: 0.84 [95% CI: 0.47, 1.50]) subgroups. The interaction p-value among these subgroups was 0.723, indicating no significant difference in regorafenib clinical efficacy (vs. placebo) related to PIK3CA mutational status. Likewise, interaction p-values for subgroups in which PIK3CA status was determined via BEAMing of DNA isolated from archival tumour tissue were not significant.

Since KRAS and PIK3CA mutations may co-exist in the same tumour, subgroup analyses were also conducted based on various combinations of KRAS and PIK3CA mutations, with mutational status determined via BEAMing of DNA isolated from fresh plasma. In the KRAS mutant + PIK3CA mutant subgroup the regorafenib/placebo HR was 0.71 (95% CI: 0.37, 1.35), in the KRAS mutant + PIK3CA wild type subgroup the regorafenib/placebo HR was 0.84 (95% CI: 0.61, 1.16) and in the KRAS wild type + PIK3CAwild type subgroup the regorafenib/placebo HR was 0.57 (95% CI: 0.34, 0.96). There were too few patients in the KRAS wild type + PIK3CA mutant subgroup to permit a meaningful correlative analysis.

BRAF mutational status using DNA isolated from fresh plasma was determined from 66% of all randomized patients, of which 3.4% were BRAF mutant and 96.6% were BRAF wild type. Due to the small number of BRAF mutant patients, a correlative analysis was not conducted based on BRAF mutational status.

The non-genetic biomarker analysis in the pivotal study involved the quantification of 15 different plasma proteins at baseline, many associated with angiogenesis (ANG-2, TIE-1, VEGF-A, VEGFA-121, VEGF-C, VEGF-D, PlGF, VEGFR1, IL-6, IL-8), as well as others with known or hypothesised roles in CRC pathogenesis (SDF-1, BMP-7, M-CSF, TIMP-2 and von Willebrand Factor [VWF]). number of these proteins are either directly inhibited by regorafenib or directly interact with proteins or pathways inhibited by regorafenib (VEGFR1, VEGF-A, VEGFA-121, VEGF-C, VEGF-D, PlGF, TIE-1). Correlative analyses of OS comparing subgroups with high or low protein levels defined based on median values demonstrated that none of these proteins were predictive of regorafenib clinical activity vs placebo (i.e., no interaction p-value reached $p<0.05$). One plasma protein, TIE-1, appeared to be predictive for regorafenib clinical activity, although both ‘high’ and ‘low’ TIE-1 subgroups showed a trend towards benefitting from regorafenib. High TIE-1 levels correlated with greater regorafenib benefit than low TIE- 1 levels (regorafenib/placebo HR for OS in patients with low TIE-1: 0.87 [95% CI: 0.64, 1.20]; and in patients with high TIE-1: 0.56 [95% CI: 0.41, 0.77]; interaction p-value: 0.035). A similar analysis of plasma biomarkers vs PFS demonstrated that levels of VWF appeared to be predictive for regorafenib clinical activity.

Low VWF levels correlated with greater regorafenib benefit than high VWF levels (regorafenib/placebo HR for PFS in patients with low VWF of 0.39 [95% CI: 0.30, 0.51] and in patients with high VWF of 0.60 [95% CI: 0.46, 0.78]; interaction p-value: 0.020). Notably, in the PFS analyses TIE-1 did not correlate with regorafenib benefit; and conversely, in the OS analyses, VWF did not correlate with benefit.

Ancillary analyses

The results of the primary OS analysis were consistent with the results of an unstratified OS analysis (unstratified HR=0.773, 95% CI 0.634-0.942, p=0.005255), and with an OS analysis using stratification information from the IVRS instead of the CRF (HR=0.767, 95% CI 0.630-0.933, p=0.003905), performed due to observed mis-stratification of some patients.

Similarly, the results of the primary PFS analysis were consistent with the results of an unstratified PFS analysis (unstratified HR=0.501, 95% CI 0.425-0.590, p<0.000001), and with a PFS analysis using stratification information from the IVRS instead of the CRF (HR=0.479, 95% CI 0.405-0.565, p=0.000001), performed due to observed misstratification of some patients.

For PFS stratified per randomisation based on CRF data, new treatment initiation date in follow-up period considered as event date for patients who discontinued prior to progression, results (HR 0.497, 95% CI 0.422-0.586, p<0.000001, median PFS 59 days vs 52 days with regorafenib and placebo, respectively) were consistent with the primary PFS analysis.

For PFS stratified per randomisation based on CRF data, considering all available tumour assessment data from follow-up period, results (HR 0.497, 95% CI 0.422-0.586, p<0.000001, median PFS 59 days vs 52 days with regorafenib and placebo, respectively) were consistent with the primary PFS analysis.

For Time to Progression (TTP) stratified per randomisation based on CRF data, median was 60 days and 52 days with regorafenib and placebo, respectively, HR 0.469 (95% CI 0.396-0.556), p<0.000001. Results were similar in the analysis stratified per randomisation based on IVRS data.

Summary of main study

The following tables summarise the efficacy results from the main studies supporting the present application. These summaries should be read in conjunction with the discussion on clinical efficacy as well as the benefit risk assessment (see later sections).

Table 9: Summary of Efficacy for study 14387

Title: A randomized, double-blind, placebo-controlled phase III study of regorafenib plus BSC versus placebo plus BSC in patients with metastatic colorectal cancer (CRC) who have progressed after standard therapy		
Study identifier	14387, CORRECT	
Design	Randomised, double-blind, multicenter, phase 3 study.	
	Duration of main phase:	until disease progression or unacceptable toxicity or patient consent withdrawal or physician's decision or non-compliance with protocol

	Duration of Run-in phase:		not applicable
	Duration of Extension phase:		not applicable
Hypothesis	Superiority		
Treatments groups	regorafenib + BSC		Regorafenib 160 mg od once daily, for 21 days every 4 weeks (3 weeks on, 1 week off), 505 patients randomised
	placebo + BSC		Matching placebo od once daily, for 21 days every 4 weeks (3 weeks on, 1 week off), 255 patients randomised
Endpoints and definitions	Primary endpoint	OS	time from randomization to death due to any cause
	Secondary endpoint	PFS	Time from randomization to first observed PD (radiological or clinical) or death due to any cause
	Secondary endpoint	ORR	Percentage of patients with CR or PR as best overall response
	Secondary endpoint	DCR	Percentage of patients whose best response was not PD (i.e. CR, PR or SD)
Database lock	21 July 2011		

Results and Analysis

Analysis description	**Primary Analysis**		
Analysis population and time point description	ITT population: 760		
Descriptive statistics and estimate variability	Treatment group	regorafenib+BSC	placebo+BSC
	Number of patients	505	255
	median OS (days)	196	151
	95% CI for median	178, 222	134, 177
	median PFS (days)	59	52
	95% CI for median	57, 65	51, 53
	ORR n (%)	5 (1.0%)	1 (0.4%)
	95% CI	0.3, 2.3	0.0, 2.2
	DCR n (%)	207 (41.0%)	38 (14.9%)
	95% CI	36.7, 45.4	10.8, 19.9
Effect estimate per comparison	Primary endpoint (OS)	Comparison groups	regorafenib vs placebo
		Hazard Ratio	0.774
		(95% CI)	0.636 – 0.942
		P-value	0.005178
	Secondary endpoint	Comparison groups	regorafenib vs placebo
		Hazard Ratio	0.494

	(PFS)	(95% CI)	0.419 – 0.582
		P-value	<0.000001
	Secondary endpoint (ORR)	Comparison groups	regorafenib vs placebo
		P-value	0.188432
	Secondary endpoint (DCR)	Comparison groups	regorafenib vs placebo
		P-value	<0.000001

Analysis performed across trials (pooled analyses and meta-analysis)

Not applicable

Clinical studies in special populations

No studies in special populations have been submitted (see discussion on clinical pharmacology and discussion on clinical safety).

Supportive study

The Applicant has submitted one phase I (Study 11650) trial, the expansion cohort of which included 23 patients with mCRC.

Study 11650

Study 11650 was a single-centre, open-label, non-randomised, single-agent, dose escalation study to determine the safety, tolerability and maximum tolerated dose (MTD), recommended-phase-2-dose pharmacokinetics and to evaluate biomarkers in 76 patients with advanced solid tumours. After a dose escalation phase including doses 10 mg once daily to 220 mg once daily, an expansion cohort in patients with CRC was conducted at dose level 160 mg once daily regorafenib on an intermittent dosing schedule. Tumour response and progression were evaluated based on RECIST, v. 1.0. All patients with CRC treated at doses of ≥60 mg once daily (in the dose escalation or dose expansion part of the study) were included in a subgroup analysis. Overall, 39 patients with metastatic CRC refractory to standard treatment were enrolled in Study 11650 with intermittent dosing schedule of regorafenib, of which 23 patients were enrolled in the expansion cohort of the study. First signs of clinical activity were observed at dose levels ≥ 60 mg, which were received by 38 patients with mCRC treated. Of the 38 patients, 20 (54%) had positive KRAS mutation status, whereas 17 patients (46%) were KRAS wild type. In one case the KRAS mutation analysis was not successful.

A total of 27 patients (out of 38 patients treated at dose ≥60 mg once daily) were evaluable for response according to RECIST (v. 1.0). Best responses included a confirmed partial response (PR) in 1 patient (4%) and stable disease (SD) in 19 patients (70%), resulting in a DCR of 74% in evaluable patients. Seven patients (26%) had progressive disease. The median PFS was 107 days (95% CI 66-161; range of 1-279 days).

2.5.3. Discussion on clinical efficacy

Design and conduct of clinical studies

The applicant submitted one single pivotal study and this is acceptable by EMA. Nevertheless, the study has to be particularly compelling with respect to internal and external validity, critical relevance, statistical significance, data quality and internal consistency. Study 14387 was the pivotal, phase III, multicentre, multinational, randomised, double blind, placebo-controlled study. A total of 760 patients with mCRC previously treated with, or not considered candidates for, fluoropyrimidine-based chemotherapy, anti-VEGF therapy, and, if KRAS wild type, anti-EGFR therapy, were randomised (2:1) to receive oral regorafenib 160 mg OD (3 weeks on/1 week off) plus BSC or matching placebo plus BSC.

The two arm design of the study with placebo plus BSC as comparator is considered acceptable, as patients enrolled in the trial had received all the standard treatment options currently available in EU Countries. The use of superiority design is endorsed. The selection of OS as primary endpoint corresponds to the accepted standards of clinical cancer research and is in accordance with EMA guidelines, in view of the lack of further active therapeutic options for the target population and the poor life expectancy of these patients. PFS as secondary endpoint is considered acceptable.

Randomisation, in agreement with EMA guidelines, was stratified according to geographical region and other factors (time from diagnosis of metastatic disease, prior treatment with anti-VEGF drugs) that represent well-recognised prognostic covariates in the target population.

Major protocol modifications were introduced with the implementation of protocol amendment 3, in order to allow cross-over to regorafenib for patients treated with placebo. However, as the amendment was implemented after the cut-off date for the secondary interim OS analysis (presented as final), it is not expected to impact interpretation of the data.

The population enrolled in the pivotal study reflects the target population as mentioned by the wording of the proposed indication. The study population was similar to the general patient population with mCRC in several aspects. The great majority of patients were males (60.8%), white (78.2%), with a median age of 61 years (range, 22-85 yr), an ECOG PS 0 (54.9%) and a median time since metastatic diagnosis of 130 weeks (128 weeks with regorafenib and 133 weeks with placebo). Primary site of disease was colon in the majority of patients in both groups (67.5% and 64%). All patients had metastatic disease and were pre-treated with a VEGF inhibitor, fluoropyrimifine, oxaliplatin and irinotecan. Moreover, 99.5% of patients with KRAS wildtype or unknown status had received panitumumab and/or cetuximab.

Demographic and baseline characteristics appeared to be comparable between the two study arms. Baseline information on KRAS mutations in the tumours (historical data) was available in 478 (94.7%) patients in the regorafenib group vs 251 (98.4%) patients in the placebo group. Baseline information on BRAF mutations in the tumours (historical data) was available in 45 (8.9%) vs 27 (10.6%) patients in the regorafenib and placebo groups, respectively, and was positive in 0.8% of patients in each treatment group. Unfortunately, no distribution of tumour characteristics able to discriminate patients with slowly or rapidly progressive disease has been identified.

No significant differences in concomitant medications or in medical history between treatment arms was observed, although patients in the placebo group consistently appeared to have a slightly higher number of co-morbidities and were more pre-treated with radiotherapy (30.6% vs 26.7%).

With regard to post-study treatments, slightly more patients in the placebo received systemic anti-cancer therapy during follow-up compared with patients in the regorafenib group (29.8% vs 25.9%). Post-study treatments essentially consisted of pyrimidine analogues (20.4% vs 18.6%, respectively), other cytotoxic antibiotics (11.4% vs 7.5%), monoclonal antibodies (8.6% 7.7%), folic acid and derivatives (8.2% vs 5.5%), and platinum compounds (5.5% vs 6.9%).

The overview on systemic anticancer therapy during follow-up has been updated for the later 13 November 2011 database cut-off. Overall, the percentage of patients receiving post-study systemic anticancer therapy was comparable to the numbers reported at the second, pre-planned, formal interim analysis.

Efficacy data and additional analyses

The proposed regorafenib oral daily dose of 160 mg OD administered according to a 3 weeks on/one week off schema, which was used in the pivotal study, was supported by a phase I dose-finding study (11650). However, it should be noted that clinical data directly comparing the continuous dosing regimen with the 3 weeks on/1week off schedule are lacking. The evidence of efficacy of regorafenib in patients with mCRC is based on the results of one pivotal study (14387 or CORRECT), supported by the data of the expansion cohort of the phase I 11650 study, enrolling patients with mCRC.

The present submission for MAA is based upon the results of the second interim OS analysis presented as final performed after 432 death events (56.8%, 275 in the regorafenib arm and 157 in the placebo arm, cut-off 21 July 2011). At this analysis, the pre-specified O'Brien-Fleming-type efficacy boundary (one-sided alpha 0.009279) was crossed and the DMC assessed the results as positive. Therefore, this interim analysis was presented as the final analysis.

The results show a statistically significant improvement in OS for regorafenib compared to placebo (HR 0.77, 95% CI 0.636-0.942, p=0.005178), with a gain in median OS of 1.5 months in favour of regorafenib (median OS 196 days vs 151 days, respectively). The OS effect appeared to be consistent in the updated analysis performed with a cut-off of 13 November 2011, after 97% of death events occurred and before cross-over was allowed (median OS:194 vs 152 days, HR 0.790, 95% CI 0.664, 0.393, p=0.003791). The observed OS benefit is considered limited and its clinical relevance needs to be considered taking into account both the treatment effect on symptom control as well as drug tolerability.

The effect on OS was observed in several subgroups of the population, with the exception of patients with rectum as primary tumour localisation (220 patients, 109 events, HR 0.953, CI 0.633, 1.436). The small sample size could potentially explain the lack of effect in this subgroup. The effect on OS in patients with KRAS mutated tumours was inferior (430 patients, 228 events, HR 0.867, CI 0.670, 1.123). As mentioned previously, no imbalance in post-study therapies between the two study arms was observed from the data provided. However, the trend towards a smaller observed benefit in the KRAS mutant subgroup might be at least partly explained by a

higher rate of subsequent anti-cancer therapy in the KRAS-mutated placebo subgroup compared to the KRAS-mutated regorafenib subgroup (33.1% vs. 24.9%, respectively). Additionally, the difference could be due to imbalances in baseline characteristics of the patients included in these subgroups and for these non-randomised comparisons.

The OS results appear to be supported by the investigator-assessed PFS data. A statistically significant increase in PFS was observed with regorafenib compared with placebo (HR 0.494, 95% CI 0.419-0.582, p<0.00000). However, the difference in median PFS between the two study arms was only one week (median PFS 59 days with regorafenib vs 52 days with placebo). This could be related to the timing of protocol-specified assessment, as at the time of the first radiological evaluation (8 weeks) more than 50% of patients in both study arms had experienced disease progression already. The high rate of patients not responding to treatment in the regorafenib arm could suggest activity of the drug limited to a subgroup of the population (58% of patients were progressive after 3 months).

The treatment effect on PFS for regorafenib was consistent across different subgroups regardless of age, ECOG PS, gender, geographical region, previous treatment with a VEGF and EGFR targeting drug, primary site of disease and KRAS mutation status.

The results of a correlative analysis including 3 genetic biomarkers (KRAS, PIK3CA, BRAF) and 15 non-genetic biomarkers (ANG-2, IL-6, IL-8, P1GF, VEGFR-1, TIE1, VEGF-A, VEGF-C, VEGF-D, VEGF-A-121, BMP-7, VWF, M-CSF, SDF-1 and TIMP-2) measured in plasma and/or tumour tissue have been provided, but no specific biomarker was identified that can be used for patient selection and to predict regorafenib clinical activity. Methodological concerns over the provided biomarkers analyses have been raised due to the limited number of tumour tissues available, the absence of fresh biopsies performed at study entry and concerns regarding the validity of genetic measurements performed on DNA isolated from fresh plasma.

ORR (CR+PR) was very low and similar between the two treatment arms (1% with regorafenib and 0.4% with placebo). The claimed improvement in OS and PFS appears to be essentially driven by patients experiencing disease stabilisation under treatment. No remarkable difference between the two study arms was observed in the evaluation of Quality of life. However, a numerical trend towards lower scores (and therefore worse quality of life) for patients treated with regorafenib is consistently observed overtime by evaluation of single domains. Other patient reported outcomes able to indirectly assess clinical benefit for patients (e.g. use of analgesics, pain control, other specific disease related symptoms) have not been evaluated.

Additional expert consultation

The CHMP convened a Scientific Advisory Group in Oncology (SAG-O) to address questions related to efficacy. The SAG-O advice was the following:

1. **Does the SAG consider the clinical benefit of regorafenib adequately demonstrated in the population as a whole enrolled in the pivotal study 14387, although PFS results suggest a benefit limited only to a subgroup of the mCRC population treated (>50% of patients experiencing disease progression at the time of first radiological evaluation)?**

A statistically significant difference was observed in the primary analysis of OS in study 14387 in the overall population. The difference in median OS between regorafenib and placebo was modest (45 days). The clinical relevance of this magnitude of treatment effect is considered to be minimal.. The rapid onset of progression in the majority of patients suggests that a favourable effect is limited to a minority of patients.

Importantly, however, regorafenib was associated with significant toxicity in the majority of patients. The most-frequent drug-related adverse event was hand-foot syndrome, which was observed (any Grade) in 44.6% vs 7.1% of patients for regorafenib and placebo, respectively. The most common Grade 3 adverse events with higher frequency in the regorafenib, compared to the placebo arm in study 14387, were hand-foot syndrome (16.6% vs 0.4%), fatigue (15.0% vs 8.3%), diarrhoea (8.2% vs 2.0%), hypertension (7.6% vs 0.8%), rash/desquamation (5.8% vs 0.4%), reduced platelet counts (3.4% vs 0.4%), reduced haemoglobin (5.4% vs 3.2%), mucositis (3.2% vs 0%), hyperbilirubinaemia (6.8% vs 4.3%), AST increase (2.4% vs 1.2%), and (abdominal) pain (9.8% vs 5.7%). In the great majority of cases these events were considered drug-related. Overall, severe, life-threatening or fatal (Grade 3-5) adverse drug reactions were observed in 55.0% vs 13.8% of patients for regorafenib and placebo, respectively (page 56-58, Rapporteurs' Joint Assessment Report).

Due to the significant toxicity and the minimal efficacy the SAG was uncertain that the balance of benefits and risks is positive.

In view of the toxicity profile of regorafenib, should this product be widely available to the oncology community, appropriate educational material and risk minimisation measures should be in place to ensure appropriate monitoring and follow-up of toxicity with this oral agent.

2. **Whereas 50% or more of the patients in the experimental treatment arm have already progressed by Week 8, and few patients experienced a tumour response, the Kaplan-Meier curves for Overall Survival appear to separate already at 50 days, after only a minority of patients in both groups have died. Could the SAG offer an opinion on the internal consistency of the pattern of results observed and comment on the clinical relevance of the differences in OS for the assessment of efficacy of the product?**

The lack of a clear effect in terms of PFS may be due to a number of reasons, including the scheduled frequency of the assessment. In and of itself, the apparent discordance between PFS and OS is not considered of concern and does not necessarily suggest lack of internal consistency.

3. **Does the SAG consider the provided analyses exploring biomarkers and other clinical and tumour parameters of patients enrolled in the pivotal study 14387 adequate and compelling in order to eventually identify parameters for proper patient selection for treatment with regorafenib?**

Unfortunately, the trial was not adequately designed to ensure availability of tumour and tissue collection to maximise the likelihood of identifying important biomarkers associated with a response to treatment. Even for established biomarkers such as KRAS, the data for analysis were missing in a high proportion of patients.

Furthermore, notwithstanding the reduced data set available for biomarker analysis, the biological and statistical analyses presented were inadequate and far from compelling methodologically in ruling out identification of important biomarkers. Exhaustive explorative analyses were not conducted and even standard statistics (Kaplan-Meier estimates) have not been presented systematically to allow at least informal evaluation.

Undue importance was given by the applicant company to the risk of chance findings. However, in this context, where it is clear that a majority of patients receives no benefit from the drug whilst being exposed to significant toxicity, it is essential to conduct a systematic and in-depth exploratory analysis of all potential clinical and biological factors that may help patient selection or, at least, to generate hypotheses to be validated on independent data sets.

4. **Does the SAG foresee additional analyses to be performed with the available data and/or in future studies in order to identify patients who may benefit from treatment with regorafenib?**

It is essential to conduct a systematic and exhaustive exploratory analysis on the available data (including data from compassionate use programmes, where appropriate) of all potential factors that may help patient selection or, at least, to generate hypotheses to be validated on independent data sets.

Tabular and graphical presentations of particular statistics (Kaplan-Meier estimates, etc.), should be systematically produced. An in-depth univariate and multivariate analysis of factors associated with treatment effect should be conducted and presented.

The association between KRAS mutation and lack of response to treatment should be clarified as a matter of priority (based on the available data, if possible). Furthermore, factors associated with a treatment effect in patients with longer PFS (using different landmarks, e.g., 4, 6, 8 months) should be explored.

Additional biomarkers could be derived from exploration of the role of standard tumour biological parameters (e.g., mitotic index, Ki-67, tumour grade). In addition analysis of specific biological (intracellular) pathways known to be affected by the drug should be conducted.

Furthermore, as a non-hypothesis driven approach in a research setting, next-generation sequencing, number of circulating tumour cells, endothelial cells and endothelial progenitor cells may help to identify biomarkers for future patient selection.

Similarly, further analysis of factors associated with individual differences in drug metabolism may help to clarify the dose-response relationship and help to identify a sub-population for whom regorafenib is likely to have a better risk-benefit balance.

2.5.4. Conclusions on the clinical efficacy

This single pivotal trial demonstrated a statistically significant benefit for regorafenib in metastatic colorectal cancer patients pre-treated or unsuitable for all approved standard therapies.

Although the benefit in terms of both OS and PFS is undisputable from a statistical perspective, the magnitude of the effect is limited, no improvement has been reported on symptoms and the

median duration of stable disease is very short in the overall population. It seems that the benefit is driven by a subset of patients, considering that half of the treated population progress or die very early (58% at 3 months). Unfortunately, none of the biomarkers explored to date appears to be predictive of regorafenib clinical activity.

The CHMP considers the following measures necessary to address issues related to efficacy:

- To submit pre-specified, exploratory wild-type and mutant KRAS subgroup analyses from study 15808 (CONCUR - randomised, double-blind, placebo-controlled phase III study of regorafenib plus best supportive care (BSC) versus placebo plus BSC in Asian subjects with metastatic colorectal cancer (CRC) who have progressed after standard therapy)

To submit NRAS and BRAF biomarker analyses from the same study, subject to sample availability and confirmation of appropriate informed consent

A proposal for additional biomarkers assessment should be submitted to the CHMP within two months of the marketing authorisation.

- To submit pre-specified, exploratory genetic (including NRAS, KRAS, BRAF and PIK3CA) and non-genetic (ANG-2, IL-6, IL-8, P1GF, VEGFR-1, TIE1, VEGF-A, VEGF-C, VEGF-D, VEGF-A-121, BMP-7, VWF, M-CSF, SDF-1) appropriate biomarker analyses from study 15983 (randomised, double-blind, placebo-controlled phase-III study of adjuvant regorafenib versus placebo for patients with stage IV colorectal cancer after curative treatment of liver metastases). Genetic and non-genetic biomarker analysis should be implemented as mandatory for all enrolled patients.

Prospective serial measurement should be planned and assessed for biomarkers. The proposed protocol for biomarkers assessment should be submitted to the CHMP within two months of the marketing authorisation.

2.6. Clinical safety

Patient exposure

Overall approximately 1145 patients with cancer, including 621 patients with CRC and 124 healthy volunteers have been exposed to regorafenib in applicant-sponsored trials up to 31 December 2011.The safety database of regorafenib has been presented in 3 different populations:

- Pool 1: 188 patients enrolled in Phase 1 and Phase 2 uncontrolled studies conducted with single agent regorafenib administered on an intermittent dosing schedule (3 weeks on/ 1 week off): studies 11650, 13172, 14996, 11726, and 14596. The dose of regorafenib was 160 mg od in these studies, with the exception of the dose escalation study 11650, in which regorafenib doses from 20 to 220 mg od were administered.

- Pool 2: 84 patients enrolled in uncontrolled Phase 1 study 11651 performed with single-agent regorafenib administered continuously once daily at doses ranging from 10 to 140 mg in patients with metastatic and/or unresectable solid tumours.

- Pool 3: 753 patients in the safety population from the pivotal Phase 3 study 14387 in mCRC (500 patients having received single agent regorafenib vs 253 patients having received placebo).

Moreover, deaths and SAEs as observed in other studies performed with regorafenib administered in combination with chemotherapy or as monotherapy with other dose schedules or in other indications than mCRC were reported.

However, the safety analysis below is focused on the data available from the phase 3 pivotal study, where regorafenib was compared with placebo in the target population. In this study and as of the clinical cut-off date, the median actual daily dose was 160 mg in both study arms, which corresponded to the protocol target daily dose of 160 mg/day. The median duration of treatment was similar between regorafenib and placebo (7.27 vs 6.98 weeks, respectively, with overlapping ranges), whereas the mean was 12.08 (±9.74) and 7.78 (±5.19) weeks, respectively.

Exposure to regorafenib in the different safety populations is summarised in the following Table 10.

Table 10: Extent of exposure to regorafenib and placebo in Pools 1 to 3, safety population

	Pool 1	Pool 2	Pool 3	
	Regorafenib N = 188	Regorafenib N = 84	Regorafenib N = 500	Placebo N = 255
Overall time under treatment [a]				
Mean ±SD (weeks)	25.79 ± 33.47	19.74 ± 29.99	12.08 ± 9.74	7.78 ± 5.19
Median	14.79	11.43	7.27	6.98
Range	0.1 – 179.4	0.1 – 145.0	0.28 – 47.01	0.57 – 38.61
Actual time under treatment [b]				
Mean ±SD (weeks)	18.86 ± 24.38	18.01 ± 27.14	8.85 ± 6.78	6.29 ± 3.79
Median (range)	9.64	9.93	5.98	5.98
Range	0.1 – 132.3	0.1 – 134.1	0.28 – 35.9	0.57 – 29.92
Actual daily dose (mg) [b]				
Mean ±SD	137.38 ± 39.41	88.82 ± 29.06	147.13 ± 18.64	159.25 ± 4.85
Median	160.00	100.0	160.00	160.00
Range	10 - 220	20.0 – 140.0	85.7 – 160.0	107.00 – 160.0
Any dose modification, n (%)	112 (59.6%)	83 (98.8%)	378 (75.6%)	97 (38.3%)
Dose reduction per patient, n (%) [c]				
Any dose reduction	79 (42.0)	5 (6.0)	100 (20.0)	8 (3.2)
1	45 (23.9)	5 (6.0)	82 (16.4)	8 (3.2)
2	26 (13.8)	0	14 (2.8)	0
≥3	8 (4.2)	0	4 (0.8)	0
Dose interruptions per patient, n (%)				
Any dose interruption	148 (78.7)	83 (98.8)	352 (70.4)	95 (37.5)
1	70 (37.2)	22 (26.2)	178 (35.6)	70 (27.7)
2	27 (14.4)	32 (38.1)	94 (18.8)	19 (7.5)
≥3	51 (27.1)	29 (34.5)	80 (16.0)	6 (2.4)

Abbreviations: N – number of patients (in total); n – number of patients with the event; SAF – safety analysis set; SD = standard deviation

Adverse events

An overview of adverse events in the different safety populations is presented in Table 11.

Table 11: Overview of Adverse Events in Pools 1 to 3 (SAF)

Characteristic	Pool1 Regorafenib N = 188	Pool 2 Regorafenib N = 84	Pool 3 Regorafenib N = 500	Pool 3 Placebo N = 253
Number of patients (%) with:				
Any AE	187 (99.5)	81 (96.4)	498 (99.6)	245 (96.8)
Worst grade				
Grade 3	108 (57.4)	47 (56.0)	280 (56.0)	67 (26.5)
Grade 4	23 (12.2)	7 (8.3)	43 (8.6)	20 (7.9)
Grade 5	22 (11.7)	7 (8.3)	67 (13.4)	37 (14.6)
SAE	102 (54.3)	40 (47.6)	219 (43.8)	100 (39.5)
Leading to permanent discontinuation of study drug	60 (31.9)	25 (29.8)	88 (17.6)	32 (12.6)
Leading to dose modification	114 (60.6)	35 (41.7)	333 (66.6)	57 (22.5)
Any drug-related AE	170 (90.4)	73 (86.9)	465 (93.0)	154 (60.9)
Worst grade				
Grade 3	100 (53.2)	37 (44.0)	253 (50.6)	31 (12.3)
Grade 4	9 (4.8)	1 (1.2)	17 (3.4)	4 (1.6)
Grade 5 [a]	5 (2.7)	0	5 (1)	0
SAE	47 (25.0)	4 (4.8)	59 (11.8)	9 (3.6)
Leading to permanent discontinuation of study drug	34 (18.1)	5 (6.0)	41 (8.2)	3 (1.2)
Leading to dose modification	97 (51.6)	32 (38.1)	278 (55.6)	23 (9.1)

Abbreviations: AE – adverse event; N – number of patients; SAF – safety analysis set; SAE = serious adverse event

[a] Although there are 5 patients in the regorafenib group with drug-related grade 5 events included in this table, there were in actuality 4 patients (not 5) with grade 5 events in the regorafenib group (and none in the placebo group) assessed by the investigator as drug related. For 1 patient in the regorafenib group, a hepatic failure was incorrectly recorded as related to regorafenib; this has been corrected post clinical database lock.
Abbreviations: AE – adverse event; SAE – serious adverse event; SAF – safety population

In the pivotal 14387 (CORRECT) study, adverse events (AEs) were coded using MedDRA 14.0 and graded using the National Cancer Institute Common Toxicity Criteria (version 3.0). An overview of the most common AEs in the different safety populations is presented in Table 12.

In the pivotal study, AEs (any grade, by CTCAE term) notably more frequently observed (≥10% difference) with regorafenib compared with placebo were fatigue (63.4% vs 46.2%), hand-foot syndrome (47.0% vs 7.5%), anorexia (46.8% vs 28.5%), diarrhoea (42.8% vs 17.0%), weight loss (32.0% vs 11.1%), voice changes/dysphonia (32.0% vs 6.3%), hypertension (30.4% vs 7.9%), rash/desquamation (29.0% vs 5.1%), mucositis (functional/ symptomatic), oral cavity (28.8% vs 4.7%), fever (28.4% vs 15.4%), hyperbilirubinemia (20.0% vs 9.5%), platelet counts abnormalities (15.6% vs 2.4%), haemorrhage (20.4% vs 6.7%) and infections (25.2% vs 14.2%). The difference was mainly due to a higher incidence of grade 1-3 events. These AEs were also most frequently reported as drug-related events.

The most common Grade 3 AEs (by CTCAE term) with higher frequency in the regorafenib, compared to the placebo arm, were hand-foot syndrome (16.6% vs 0.4%), fatigue (15.0% vs 8.3%), diarrhoea (8.2% vs 2.0%]), hypertension (7.6% vs 0.8%), rash/desquamation (5.8% vs 0.4%), platelet counts abnormalities (3.4% vs 0.4%) haemoglobin abnormalities (5.4% vs 3.2%), mucositis (3.2% vs 0%), hyperbilirubinemia (6.8% vs 4.3%), AST increase (2.4% vs

1.2%), and (abdominal) pain (9.8% vs 5.7%). In the great majority of cases these events were considered drug related.

The incidence of the most common (≥ 1% patients in either treatment group) grade 4 AEs was similar between the two treatment arms. They were (regorafenib vs placebo) infections (1.6% vs 0.4%), lipase abnormalities (1.2% vs 0.4%), constitutional symptoms (1.0% vs 1.2%), hyperbilirubinemia (0.8% vs 2.0%) and fatigue (0.4% vs 2.0%).

The observed regorafenib AE profile was comparable between the Pool 1-3 populations. Overall, the most frequently reported AEs in patients treated with regorafenib were decreased appetite, palmar-plantar erythrodysesthesia syndrome, diarrhoea, fatigue, weight decreased, hypertension, dysphonia, pyrexia, asthenia, constipation, nausea, rash and pain (in the extremity, abdominal back).

Table 12: Most Common (>10 % overall in regorafenib group) AEs by MedDRA preferred term (Pool 3, study 14387, SAF)

	Pool1	Pool 2	Pool 3	
	Regorafenib	Regorafenib	Regorafenib	Placebo [a]
	N = 188	N = 84	N = 500	N = 253
Any AE n (%)	**187 (99.5)**	**81 (96.4)**	**498 (99.6)**	**245 (96.8)**
Decreased appetite	69 (36.7)	25 (29.8)	234 (46.8)	72 (28.5)
Palmar-plantar erythrodys-aesthesia syndrome	103 (54.8)	21 (25.0)	225 (45.0)	18 (7.1)
Diarrhoea	91 (48.4)	24 (28.6)	214 (42.8)	43 (17.0)
Fatigue	87 (46.3)	41 (48.8)	201 (40.2)	74 (29.2)
Weight decreased	54 (28.7)	4 (4.8)	161 (32.2)	26 (10.3)
Hypertension	65 (34.6)	24 (28.6)	152 (30.4)	20 (7.9)
Dysphonia	73 (38.8)	19 (22.6)	150 (30.0)	16 (6.3)
Pyrexia	52 (27.7)	14 (16.7)	140 (28.0)	37 (14.6)
Asthenia	9 (4.8)	4 (4.8)	132 (26.4)	45 (17.8)
Constipation	51 (27.1)	21 (25.0)	119 (23.8)	48 (19.0)
Nausea	57 (30.3)	26 (31.0)	112 (22.4)	55 (21.7)
Rash	30 (16.0)	20 (23.8)	110 (22.0)	8 (3.2)
Abdominal pain	40 (21.3)	19 (22.6)	98 (19.6)	41 (16.2)
Dyspnoea	39 (20.7)	18 (21.4)	85 (17.0)	32 (12.6)
Stomatitis	25 (13.3)	3 (3.6)	85 (17.0)	8 (3.2)
Mucosal inflammation	31 (16.5)	11 (13.1)	82 (16.4)	4 (1.6)
Vomiting	43 (22.9)	18 (21.4)	80 (16.0)	41 (16.2)
Hyperbilirubinaemia	7 (3.7)	11 (13.1)	65 (13.0)	17 (6.7)
Back pain	31 (16.5)	18 (21.4)	63 (12.6)	25 (9.9)
Anaemia	12 (6.4)	7 (8.3)	55 (11.0)	21 (8.3)
Cough	31 (16.5)	14 (16.7)	53 (10.6)	27 (10.7)
Headache	41 (21.8)	12 (14.3)	51 (10.2)	17 (6.7)

Abbreviations: AE – adverse event; N – number of patients (in total); n – number of patients with the event; SAF – safety analysis set

A patient may have had more than one AE (may appear more than once in this table)

Events are listed in decreasing frequency in the regorafenib total group

[a] Placebo group of study 14387 to be compared to Pool 3 regorafenib arm of the same study

Adverse Drug Reactions (ADRs)

From all clinical experience to date, the most frequently observed adverse drug reactions (≥30%) in patients receiving Stivarga were asthenia/fatigue, decreased appetite and food intake, hand foot skin reaction, diarrhoea, weight loss, infection, hypertension and dysphonia. The most serious adverse drug reactions in patients receiving Stivarga were severe liver injury, haemorrhage and gastrointestinal perforation. ADRs of Stivarga are summarised in the following Table 13.

Table 13: Adverse drug reactions (ADRs) reported in clinical trials in patients treated with Stivarga

System Organ Class (MedDRA)	Very common	Common	Uncommon	Rare
Infections and infestations	Infection			
Neoplasms benign, malignant and unspecified (including cysts and polyps)				Keratoacanthoma/ Squamous cell carcinoma of the skin
Blood and lymphatic system disorders	Thrombocytopenia Anaemia	Leucopenia		
Endocrine disorders		Hypothyroidism		
Metabolism and nutrition disorders	Decreased appetite and food intake	Hypokalaemia Hypophosphataemia Hypocalcaemia Hyponatraemia Hypomagnesaemia Hyperuricaemia		
Nervous system disorders	Headache	Tremor		Posterior reversible encephalopathy syndrome (PRES)
Cardiac disorders			Myocardial infarction Myocardial ischaemia	
Vascular disorders	Haemorrhage* Hypertension		Hypertensive crisis	
Respiratory, thoracic and mediastinal disorders	Dysphonia			
Gastrointestinal disorders	Diarrhoea Stomatitis	Taste disorders Dry mouth Gastro-oesophageal reflux Gastroenteritis	Gastrointestinal perforation* Gastrointestinal fistula	
Hepatobiliary disorders	Hyperbilirubinaemia	Increase in transaminases	Severe liver injury*#	
Skin and subcutaneous tissue disorders	Hand-foot skin reaction** Rash	Dry skin Alopecia Nail disorder Exfoliative rash	Erythema multiforme	Stevens-Johnson syndrome Toxic epidermal necrolysis
Musculoskeletal and connective tissue disorders		Musculoskeletal stiffness		
Renal and urinary disorders		Proteinuria		
General disorders and administration site conditions	Asthenia/fatigue Pain Fever Mucosal inflammation			
Investigations	Weight loss	Increase in amylase Increase in lipase Abnormal International normalised ratio		

* fatal cases have been reported
** palmar-plantar erythrodysesthesia syndrome in MedDRA terminology
# according to drug-induced liver injury (DILI) criteria of the international DILI expert working group

Adverse Events of special interest (AESI)

AEs of special interest (AESI) included hypertension, hand-foot skin reaction, rash, diarrhoea, myocardial ischemia, bleeding, gastrointestinal perforationhepatobiliary events, proteinuria and renal failure, impaired wound healing and thromboembolic events.

Hypertension was reported in approximately 30% of patients treated with regorafenib in all studies performed. Generally hypertension was mild or moderate in severity (grade 3 events reported in 7.6%, no grade 4 or 5) and appears to be manageable with anti-hypertensive drugs. Within the all regorafenib safety database one event of hypertensive crisis associated with development of reversible posterior leukoencephalopathy syndrome (RPLS) was observed.

Hand-foot syndrome (HFS) was observed in 47% of patients treated with regorafenib. Most events were of grade 1 or 2 severity, grade 3 events were observed in 16.6% of patients, whereas no grade 4 was reported. HFS AEs could usually be managed by dose reductions or interruptions. HFS led to permanent discontinuation, dose reduction and interruption in 7 (1.4%), 92 (18.4%) and 96 (19.2%) regorafenib treated patients, respectively.

Rash was experienced in around 47% of regorafenib-treated, with time to first onset within the first 8 weeks of therapy. Events were generally mild or moderate in severity and led to dose modifications in a low percentage of patients (2.8%). Data on skin toxicity and recommended dose modifications for management of HFS and rash are reflected in the SPC.

Gastrointestinal toxicity was also frequently observed (especially diarrhoea [42.8%] and mucositis/stomatitis [28.8%]) but events were generally of mild and moderate severity and considered manageable. In toxicology studies atrophy of the tongue has been observed in mice and rats, but no information regarding reporting of such AE in clinical studies has been provided by the Applicant.

Cardiac events have been observed in 8-26% of patients treated with regorafenib in different studies. An increased frequency of myocardial ischemia and infarction has been associated with treatment with regorafenib (1.2% vs 0.4% with regorafenib vs placebo, respectively) in the pivotal study, with a slightly increased risk in patients with cardiovascular risk factors. The incidence of other thromboembolic events did not appear to be significantly influenced by treatment with regorafenib. More patients treated with regorafenib compared with placebo (9.8% vs 7.1%) in the pivotal study experienced congestive heart failure and related symptoms, but as the difference was primarily due to peripheral oedema and no routine evaluation of LVEF was performed, the clinical relevance of such findings is unclear. By analysis of study 14814, evaluating the effect of regorafenib on LVEF and QT prolongation, regorafenib does not appear to significantly affect LVEF% and QTc interval. In the pivotal trial the incidence of atrial fibrillation was higher in the regorafenib arm. The reason of this increased incidence could be that there were more patients with supraventricular arrhythmias history in regorafenib group at baseline (5.0% of patients with a baseline history of supraventricular arrhythmias in the regorafenib group compared to 2.5% of patients in the placebo group).

Haemorrhage/bleeding events were reported in 20.4% of regorafenib-treated patients versus 6.7% of placebo-treated patients in the pivotal study, with most of events being either grade 1 (17.0% vs 4.7%) or grade 2 (1.4% vs 1.2%) and very few grade 3/4 events (1.4% vs 0.8%). The most common bleeding AE (any grade) in both treatment groups was haemorrhage

pulmonary/nose (8.8% vs 2.4%), followed by haemorrhage anus (3.2% vs 0.4%), urinary (2.2% vs 1.2%), rectum (1.2% vs 0%), and others (2% vs 0%). A total of 4 patients (0.8%) in the regorafenib arm vs no patient in the placebo arm experienced fatal bleedings, 3 of them considered as drug-related. A clear relation between haemorrhages and thrombocytopenia and/or alteration of coagulation parameters observed in regorafenib treated patients could not be made. In Pool 3, all reported respiratory tract haemorrhage (haemoptysis in 1 placebo patient, pulmonary haemorrhage in 2 regorafenib patients, 1 of which fatal) occurred in patients with baseline or lung metastases.

Similar to other inhibitors of the VEGFR pathway, a slightly increased incidence of gastrointestinal perforation or fistula was observed with regorafenib (0.8 vs 0.4%, respectively), although analysis is hampered by confounding factors related to underlying disease. By cumulative review of all regorafenib treated patients in the safety database, 7 cases, 4 of which fatal, were considered by the investigators as possibly related to regorafenib. No specific population was identified to be at higher risk.

Hyperbilirubinemia (probably related to impaired glucuronidation through UGT1A1 inhibition) and liver enzyme (AST/ALT) abnormalities were commonly observed with regorafenib (13%, 45% and 65%, respectively), and with higher incidence compared with placebo (hyperbilirubinemia: 6.7%). Most of events were grade 1 or 2 in severity. Two cases meeting Hy's Law criteria and 3 cases of severe drug-induced liver injury (DILI) events were described.

The most common hepatobiliary disorders in the pivotal study were hyperbilirubinemia, hepatic function abnormal, hepatic pain, and hepatic failure. Serious hepatobiliary disorders (including fatal events) were reported in 5.4% of patients treated with regorafenib, and more frequently than in placebo patients. There were 11 deaths due to hepatobiliary disorders, 3 (1.2%) in the placebo group and 8 (1.6%) in the regorafenib group. Hepatobiliary events resulting in death included one event of cholestasis (placebo group); 7 events of hepatic failure (placebo, 1; regorafenib, 6); and 3 events of hepatic function abnormal (placebo, 1; regorafenib, 2).

Proteinuria was more frequently reported in the regorafenib group compared with the placebo group of the pivotal study (8% vs 2.4) with 7% and 1.6%, respectively, considered related to study drug. Most events were grade 1 or 2. Grade 3 proteinuria was reported in 8 (1.6%) and 1 (0.4%) patient in the regorafenib and placebo arm, respectively. No grade 4 or 5, neither SAE of proteinuria was reported. No cases of proteinuria resulting in acute renal failure were observed. Proteinuria AEs were usually observed within the first 2 cycles of therapy and could usually be managed by dose reductions or interruptions. Proteinuria led to permanent discontinuation, dose reduction and interruption in 2 (0.4%), 3 (0.6%) and 6 (1.2%) regorafenib treated patients, respectively. Asian patients treated with regorafenib had a higher incidence of proteinuria compared with White patients (27/74, 36.5% vs 10/389, 2.6%). The rate of protenuria events, mainly Grade 1 and 2, was consistent between the pivotal trial (8.6%) and the pooled monotherapy safety set (8.2%). In 17 of the 43 patients in the pivotal trial (39.5%) and in 22 of the 63 patients in the pooled safety set (34.9%) the proteinuria event was registered as not recovered/not resolved. Considering that in one third of patients proteinuria does not recovered and renal failure cases, mainly secondary to dehydration due to diarrhoea/vomiting, have been reported from Eudravigilance, the Applicant should add information on cases with not recovery of proteinuria in Section 4.8 of the SmPC.

Renal failure was reported in <5% of patients treated with regorafenib in the studies performed and in the pivotal study the incidence of renal failure was slightly but not significantly higher in the regorafenib arm compared with the placebo arm (2.2% vs 1.6%). Most of events were grade 3 (1.8% vs 1.2% of cases), no grade 4 events and one grade 5 event were observed in the regorafenib arm. Increase in creatinine laboratory data was similar in both arms (15%).

No cases of impaired wound healing were observed in the pivotal study, whereas according to a cumulative review of all patients treated with regorafenib up to 31 December 2011 a total of 6 cases were reported (5 serious and 1 non-serious), one of which treated with placebo. Information over this AE has been added to the SPC.

No cases of interstitial lung disease have been reported in patients treated with regorafenib. In the pivotal study the most common respiratory AEs were dysphonia (30% vs 6.3%), dyspnoea (17% vs 12.6%), and cough (10.6% vs 10.7%) with overall a similar incidence of serious respiratory, thoracic and mediastinal events.

In all 3 pools, the frequency of pulmonary embolism events in regorafenib-treated patients (Pool 3: 0.8%; Pool 2: 2.4%; Pool 1: 1.1%) and other venous thromboembolic events (Pool 3: 1.2%; Pool 2: 2.4%; Pool 1: 0.5%) was relatively low, and, in Pool 3 it was similar to the placebo group (1.2% and 0.8%, respectively).

In *in vitro* assays a potential for phototoxicity was identified for regorafenib and its active metabolites M2 and M5, but it was not confirmed in pre-clinical models and only 0.5% of patients in the pivotal study reported phototoxicity related events, all of grade 1 severity.

The effect of regorafenib on QT interval was evaluated in Study 14814, conducted in patients with advanced solid tumours, where ECGs are collected by Holter monitoring over 24 hours at baseline and after at least one 21 day cycle of treatment. Overall, the effect of regorafenib at tmax on the QTc intervals of the ECG was very limited, and even with the most conservative evaluation, the maximal median change was modest and unlikely to be of clinical significance in the setting of cancer treatment. In the ECG assessment related to the pivotal 14387 study, a 12-lead ECG was performed on Day 1 of each cycle for the first 6 cycles (and at subsequent cycles at the investigator's discretion). A similar percentage of patients in either treatment group (regorafenib and placebo) had a QTcB or QTcF increase > 60 ms from baseline at end of treatment evaluation (QTcB: 3.2% vs 3.4%; QTcF: 2.2% vs 2.7%). For both QTcB and QTcF, a higher percentage of regorafenib-treated patients than placebo-treated patients had a QTcB or QTcF increase > 30 - < 60 ms from baseline (QTcB: 12.9% vs 5.5%, respectively; QTcF: 7.2% vs 2.7%, respectively). For patients in both groups, the QTcF and QTcB remained relatively constant for the duration of the study. In an analysis of AEs which could be potentially related to QT prolongation observed in patients enrolled in Study 14814 and the pivotal study 14387, no safety signals suggesting a correlation between QT prolongation and such events could be identified.

Serious adverse event / deaths / other significant events

Serious Adverse Events (SAEs)

Common SAEs in 1-3 Pools included general physical health deterioration, pyrexia, abdominal pain, pneumonia, dyspnoea, fatigue, urinary tract infection, diarrhoea, decreased appetite and infection.

In Pool 3 (pivotal 14387 study), incidence of SAEs was slightly higher with regorafenib compared with placebo (43.8% vs 39.5%). SAEs were mostly related to general physical health deterioration (7.2% vs 9.5%) and not considered related to study drug. In the regorafenib arm, there was a higher incidence of the SAEs pyrexia (2.8% vs 0.4%), abdominal pain (2.4% vs. 0.8%), diarrhoea (1.6% vs 0%), hepatic failure (1.4% vs. 0.8%), haemorrhages (1% vs 0%), and jaundice (0.4% vs 0%), whereas incidence of pneumonia (2.0% vs 1.6%) and dyspnoea (2.0% vs 1.2%) was similar between the two arms.

In Pool 2 the most frequently reported SAEs were fatigue (4.8%), chest pain (3.6%), pneumonia (3.6%), urinary tract infection (3.6%) and dyspnoea (3.6%). Two haemorrhage SAEs (3.6%) and 1 hypertensive crisis were also reported.

In Pool 1 the most frequently reported SAEs were similar to Pool 2 and 3 and consisted of infection (4.3%), fatigue (3.7%), abdominal pain (3.2%), diarrhoea (3.2%), and physical deterioration (2.7%). One case of cerebral haemorrhage SAE and 4 cases of hypertension SAE (2.1%) were also seen.

Deaths

Across patients enrolled in Pool 1-3, a total of 138 death events occurred during treatment and up to 30 days after treatment discontinuation, the majority (111 deaths) of which were associated with disease progression. Across all pools, the most common cause of death other than disease progression in regorafenib-treated patients was haemorrhage (4 patients: gastrointestinal, vaginal, pulmonary, and intracranial haemorrhages, respectively), cardiac arrest (3 patients), and pneumonia (3 patients).

In Pool 3, there were 110 total deaths reported, with a slightly higher frequency in the placebo group (13.6% with regorafenib vs 16.2% with placebo). Deaths not associated with disease progression represented a minority of the events and, in the regorafenib group, included 3 patients with haemorrhage (1 gastrointestinal, 1 vaginal, and 1 pulmonary haemorrhages), 2 patients with death due to pneumonia, 1 patient with cardiac arrest, 1 patient with general physical health deterioration, 1 intestinal obstruction, 1 cerebrovascular accident, 1 sudden death and 1 death unknown. Deaths not associated with disease progression in the placebo group included 2 sudden deaths, 2 pneumonias, 1 cardiac arrest and 1other death not further specified.

In Pool 1, there were 21 deaths, 12 associated with disease progression. Deaths not associated with disease progression included 2 cardiac arrest, 1 pulmonary embolism, 1 pneumonia, 1 haemoptysis, 1 haematoma, 1 intracranial haemorrhage; 1 intestinal obstruction; and 1 ascites.

In Pool 2, of the 7 deaths observed, 6 were associated with disease progression and one was classified as ‘other’.

Laboratory findings

The most common haematological and biochemical abnormalities in the pivotal 14387 study are summarised in the following Table 14.

Table 14: Laboratory test abnormalities, study 14387, safety population

Laboratory parameter (in % of samples investigated)	Stivarga plus BSC[§] (N=500)			Placebo plus BSC[§] (N=253)		
	All Grades*	Grade 3*	Grade 4*	All Grades*	Grade 3*	Grade 4*
Blood and lymphatic system disorders						
Haemoglobin decreased	78.5	4.7	0.6	66.3	2.8	0
Platelet count decreased	40.5	2.4	0.4	16.8	0.4	0
Neutrophil count decreased	2.8	0.6	0	0	0	0
Lymphocyte count decreased	54.1	9.3	0	34.4	3.2	0
Metabolism and nutrition disorders						
Calcium decreased	59.3	1.0	0.2	18.3	1.2	0
Potassium decreased	25.7	4.3	0	8.3	0.4	0
Phosphate decreased	57.4	30.5	0.6	11.1	3.6	0
Hepatobiliary disorders						
Bilirubin increased	44.6	9.6	2.6	17.1	5.2	3.2
AST increased	65.0	5.3	0.6	45.6	4.4	0.8
ALT increased	45.2	4.9	0.6	29.8	2.8	0.4
Renal and urinary disorders						
Proteinuria	59.7	0.4	0	34.1	0.4	0
Investigations						
INR increased**	23.7	4.2	-[#]	16.6	1.6	-[#]
Lipase increased	46.0	9.4	2.0	18.7	2.8	1.6
Amylase increased	25.5	2.2	0.4	16.7	2.0	0.4

[§] Best Supportive Care
* Common Terminology Criteria for Adverse Events (CTCAE), Version 3.0
** International normalized ratio
[#] No Grade 4 denoted in CTCAE, Version 3.0

Regarding thyroid function tests (TSH, fT3 and fT4) as observed in the pivotal study, a higher mean increase of TSH (thyroid stimulating hormone, thyrotropin) and decrease of fT3 (triiodothyronine) from baseline was reported in patients treated with regorafenib compared with placebo. In general, mean and median values of thyroid function tests were similar between baseline and end of treatment with the exception of TSH in the regorafenib arm where mean and median values at end of treatment were approximately twice the values at baseline.

Safety in special populations

A population PK analysis of the pivotal study in order to evaluate the influence of intrinsic factors (age, gender, body weight, ethnicity, renal and hepatic functions) on PK was submitted.

No safety data of regorafenib in paediatric patients are available, as there is no relevant use of Stivarga in paediatric patients in the colorectal cancer indication. Important safety information regarding the elderly population is in presented in the following Table 15.

Table 15: Overview of adverse events by age group, study 14387, safety population

	Placebo			Regorafenib 60-160 mg		
	Age <65 N=164 (100%)	Age 65-74 N=71 (100%)	Age 75-84 N=17 (100%)	Age <65 N=307 (100%)	Age 65-74 N=155 (100%)	Age 75-84 N=38 (100%)
Adverse Events						
Any event	**157 (95.7%)**	**71 (100.0%)**	**16 (94.1%)**	**305 (99.3%)**	**155 (100.0%)**	**38 (100.0%)**
Serious Adverse Events - Total	64 (39.0%)	32 (45.1%)	4 (23.5%)	137 (44.6%)	68 (43.9%)	14 (36.8%)
- Fatal	30 (18.3%)	12 (16.9%)	2 (11.8%)	42 (13.7%)	24 (15.5%)	8 (21.1%)
- Hospitalization/prolong existing hospitalization	57 (34.8%)	28 (39.4%)	3 (17.6%)	120 (39.1%)	59 (38.1%)	12 (31.6%)
- Life-threatening	6 (3.7%)	7 (9.9%)	0	18 (5.9%)	8 (5.2%)	2 (5.3%)
- Disability/incapacity	4 (2.4%)	0	1 (5.9%)	3 (1.0%)	4 (2.6%)	0
- Other (medically significant)	4 (2.4%)	2 (2.8%)	0	10 (3.3%)	7 (4.5%)	1 (2.6%)
AE leading to drop-out	18 (11.0%)	10 (14.1%)	4 (23.5%)	54 (17.6%)	26 (16.8%)	8 (21.1%)
Psychiatric disorders (SOC)	21 (12.8%)	12 (16.9%)	1 (5.9%)	40 (13.0%)	26 (16.8%)	6 (15.8%)
Nervous system disorders (SOC)	17 (10.4%)	5 (7.0%)	1 (5.9%)	69 (22.5%)	36 (23.2%)	9 (23.7%)
Accidents and injuries (SMQ)	2 (1.2%)	3 (4.2%)	0	11 (3.6%)	2 (1.3%)	0
Cardiac disorders (SOC)	12 (7.3%)	2 (2.8%)	0	26 (8.5%)	12 (7.7%)	4 (10.5%)
Vascular disorders (SOC)	15 (9.1%)	14 (19.7%)	3 (17.6%)	100 (32.6%)	56 (36.1%)	16 (42.1%)
Cerebrovascular disorders (SMQ)	0	2 (2.8%)	1 (5.9%)	2 (0.7%)	4 (2.6%)	1 (2.6%)
Infections and infestations (SOC)	30 (18.3%)	11 (15.5%)	2 (11.8%)	91 (29.6%)	53 (34.2%)	10 (26.3%)
Quality of life decreased (PT)	0	0	0	0	0	0
Drug-related Adverse Events						
Any event	**94 (57.3%)**	**49 (69.0%)**	**10 (58.8%)**	**288 (93.8%)**	**142 (91.6%)**	**35 (92.1%)**
Serious Adverse Events - Total	7 (4.3%)	2 (2.8%)	0	30 (9.8%)	24 (15.5%)	5 (13.2%)
- Fatal	0	0	0	5 (1.6%)	2 (1.3%)	1 (2.6%)
- Hospitalization/prolong existing hospitalization	5 (3.0%)	1 (1.4%)	0	25 (8.1%)	22 (14.2%)	5 (13.2%)
- Life-threatening	0	0	0	6 (2.0%)	3 (1.9%)	1 (2.6%)
- Other (medically significant)	2 (1.2%)	1 (1.4%)	0	5 (1.6%)	4 (2.6%)	1 (2.6%)
AE leading to drop-out	2 (1.2%)	1 (1.4%)	0	27 (8.8%)	11 (7.1%)	3 (7.9%)
Psychiatric disorders (SOC)	3 (1.8%)	1 (1.4%)	0	5 (1.6%)	4 (2.6%)	1 (2.6%)
Nervous system disorders (SOC)	6 (3.7%)	1 (1.4%)	0	42 (13.7%)	21 (13.5%)	6 (15.8%)
Cardiac disorders (SOC)	3 (1.8%)	0	0	10 (3.3%)	5 (3.2%)	1 (2.6%)
Vascular disorders (SOC)	8 (4.9%)	10 (14.1%)	2 (11.8%)	87 (28.3%)	49 (31.6%)	11 (28.9%)
Cerebrovascular disorders (SMQ)	0	0	0	0	2 (1.3%)	1 (2.6%)
Infections and infestations (SOC)	5 (3.0%)	0	0	27 (8.8%)	15 (9.7%)	2 (5.3%)
Quality of life decreased (PT)	0	0	0	0	0	0

The incidence of AEs was similar for female patients and male patients overall (98.3% females vs 98.9% males), in the regorafenib group (100% vs 99.3%) and in the placebo group (95.0% vs 98.0%) of the pivotal study.

In the pivotal 14387 study, the overall incidence of any AE and the incidence of most of the common AEs was similar among race groups. In the regorafenib group, compared with Caucasians, there was a higher incidence in Asians of palmar-plantar erythrodysaesthesia syndrome (78.4% vs 38%), rash (40.5% vs 19.3%), and hypertension (54.1% vs 16.5%); and a lower incidence of asthenia (1.4% vs 28.8%), abdominal pain (4.1% vs 22.4%), mucosal inflammation (4.1% vs 18.3%), dyspnoea (8.1% vs 18%), hyperbilirubinemia (8.1% vs 14.7%), diarrhoea (28.4% vs 45.8%), weight decrease (20.3% vs 33.9%), and anaemia (1.4% vs 12.9%). However, overall the same AEs were seen in all groups. Moreover, as the majority of patients treated were Whites, no firm conclusion can be made regarding other ethnic groups, in particular Blacks and Other.

No studies specifically in patients with hepatic impairment have been conducted. All patients included in the studies performed with regorafenib to date were required to have bilirubin ≤ 1.5x ULN and AST/ALT ≤ 2.5 or 5x ULN in case of liver metastases. No relevant safety data is available for patients with moderate or severe hepatic impairment.

An analysis has been provided where AEs observed in the pivotal 14387 study were reported according to three categories of AST and ALT at baseline: a) ≤ 1.5 x ULN (666 patients, 440 patients treated with regorafenib and 226 treated with placebo); b) > 1.5 xULN and ≤ 3xULN (67 patients, 44 patients treated with regorafenib and 23 treated with placebo); c) <3 xULN (7 patients, 2 patients treated with regorafenib and 5 treated with placebo). Very few patients were enrolled in the third category to draw any meaningful conclusion. In the second category, more patients treated with regorafenib experienced AEs of stomatitis (25.0%, vs. 17.0% overall), dyspnoea (34.1% vs. 17.0% overall), hyperbilirubinemia (22.7% vs. 13.0% overall), general physical health deterioration (25.0% vs. 9.2%), and peripheral oedema (22.7% vs 9.2% overall). For patients with normal hepatic function at baseline (first category), the incidence of SAEs was similar between treatment groups (42.8% with regorafenib and 38.5% with placebo); in the second category, the incidence of SAEs was higher in the regorafenib group (52.3%) and similar to the normal hepatic function group in the placebo arm (39.1%).

No studies in patients with renal impairment have been conducted. All patients included in the studies performed with regorafenib to date were required to have serum creatinin ≤ 1.5x ULN and estimated glomerular filtration rate (eGFR) ≥ 30 ml/min/1.73 m2 according to the MDRD (modified diet in renal disease) abbreviated formula. Renal function was considered normal when eGFR was ≥ 60 mL/min/1.73 m², and moderately impaired when eGFR was <60 mL/min/1.73 m². No relevant pharmacokinetics and safety data is available for patients with severe renal impairment.

In the pivotal 14387 study (Pool 3), 30 patients had moderate renal impairment at baseline (21 treated with regorafenib and 9 with placebo). The incidence of most common AEs was similar between normal and moderately renally impaired patients. In the regorafenib +BSC group, patients with impaired renal function had a higher incidence (>10%) of reported AEs of decreased appetite (57.1% vs 46.8% overall), diarrhoea (52.4% vs 42.8% overall), dysphonia (47.6% vs. 30.0% overall), rash (33.3% vs. 22.0% overall), anaemia (28.6% vs. 11.0% overall), and peripheral oedema (19.0% vs. 9.2% overall).

In the phase 1 dose escalating 11650 study, a pharmacokinetic analysis performed on patients grouped according to renal function (according to MDRD equation) showed no differences in

regorafenib AUC or Cmax between patients with mild renal impairment and those with normal renal function.

In conclusion, very few patients with impaired renal function (eGFR <60 mL/min/1.73 m2) have been treated with regorafenib in the pivotal trial. A higher rate of drug-related SAEs has been reported in patients with moderately impaired kidney function vs normal/mildly impaired kidney function (28.6% vs 11.1%).

Safety related to drug-drug interactions and other interactions

Please refer to pharmacokinetic drug interactions and the discussion on clinical pharmacology.

Discontinuation due to adverse events

Fewer regorafenib-treated patients discontinued in Pool 3 (17.6%) than in Pool 2 (29.8%) or Pool 1 (31.9%). In Pool 3 treatment discontinuation occurred more frequently with regorafenib (17.6%) compared with placebo (12.6%). The most frequent AEs causing regorafenib discontinuation were general physical health deterioration (3.6%), palmar-plantar erythrodysaesthesia syndrome (1.4%) and hepatic failure (0.8%) in Pool 3, chest pain (2.4%), fatigue (2.4%), hyperbilirubinemia (2.4%), and small intestinal obstruction (2.4%) in Pool 2, and fatigue (3.7%), palmar-plantar erythrodysaesthesia syndrome (1.6%), renal failure (1.6%), and thrombocytopenia (1.6%) in Pool 1.

Dose reductions were reported in 37.6% of regorafenib-treated patients in Pool 3, 39.4% in Pool 1 and 22.6% in Pool 2. In Pool 3 (pivotal 14387 study) dose reductions occurred more frequently with regorafenib (37.6%) compared with placebo (3.2%). The most frequent AEs causing regorafenib dose reductions in Pool 3 and 1 were palmar-plantar erythrodysaesthesia syndrome (18.2% in Pool 3 and 17.6% in Pool 1) and diarrhoea (3.8% and 4.8%, respectively), which were also the most common regorafenib-related AEs in both Pools. In Pool 2, the most common AEs causing dose reduction were palmar-plantar erythrodysaesthesia syndrome (6%), blister (4.8%), skin exfoliation (3.6%), and pain in extremity (3.6%). In Pool 3, other reasons for regorafenib dose reductions were hypertension (3.2%), fatigue (2%), rash (2%) and mucosal inflammation (1.2%). These were observed also in Pool 1 and 2 with similar frequencies.

Regarding AEs leading to dose interruptions, there was a higher incidence of dose interruptions in regorafenib treated patients in Pool 3 (60.8%) than in Pool 2 (39.3%) or Pool 1 (51.1%), and within Pool 3, in regorafenib (60.8%) compared to placebo (21.7%) arm. The most common AEs causing dose interruption in Pool 3 and Pool 1 were palmar-plantar erythrodysaesthesia syndrome (18.8% and 11.2%, respectively) and diarrhoea (6.2% and 6.4%), followed by, in Pool 3, pyrexia (4.6%), fatigue (4%), rash (3.6%), hyperbilirubinaemia (3.6%), hypertension (2.6%). Similar incidences were reported in Pool 1 and 2.

Post marketing experience

Not applicable

2.6.1. Discussion on clinical safety

Overall, the safety profile of regorafenib (Stivarga) was consistent across studies and is typical for a small molecule with targeted inhibition of the VEGFR and other tyrosine kinase-mediated pathways: hypertension, skin (hand-foot syndrome, rash) and gastrointestinal toxicities (diarrhoea, mucositis) were prominent, whereas haematologic toxicities were limited.

The analysis of the safety profile of the drug is hampered by the limited safety follow-up. Moreover, in all the phase I-III studies performed to date patients with regorafenib history of hepatic or renal impairment or with on-going or recent cardiovascular diseases were excluded.

In the pivotal 14387 study, AEs more frequently observed (≥10% difference) with regorafenib compared with placebo were fatigue (63.4% vs 46.2%), hand-foot syndrome (47.0% vs 7.5%), anorexia (46.8% vs 28.5%), diarrhoea (42.8% vs 17.0%), weight loss (32.0% vs 11.1%), dysphonia (32.0% vs 6.3%), hypertension (30.4% vs 7.9%), rash/desquamation (29.0% vs 5.1%), mucositis/stomatitis (28.8% vs 4.7%), fever (28.4% vs 15.4%), hyperbilirubinemia (20.0% vs 9.5%), platelet counts abnormalities (15.6% vs 2.4%), haemorrhage (20.4% vs 6.7%) and infections (25.2% vs 14.2%). The difference was mainly due to a higher incidence of grade 1-3 events.

In the pivotal trial, the overall incidence of hypertension was 30.4% in patients treated with Stivarga and 7.9% in patients receiving placebo. Most cases of hypertension in patients treated with Stivarga appeared during the first cycle of treatment and were mild to moderate in severity (Grades 1 and 2: 22.8%). The incidence of Grade 3 hypertension was 7.6%.

Blood pressure should be controlled prior to initiation of treatment with Stivarga. It is recommended to monitor blood pressure and to treat hypertension in accordance with standard medical practice. In cases of severe or persistent hypertension despite adequate medical management, treatment should be temporarily interrupted and/or the dose reduced at the discretion of the physician. In case of hypertensive crisis, treatment should be discontinued.

Posterior reversible encephalopathy syndrome (PRES) has been reported in association with Stivarga treatment. Signs and symptoms of PRES include seizures, headache, altered mental status, visual disturbance or cortical blindness, with or without associated hypertension. A diagnosis of PRES requires confirmation by brain imaging. In patients developing PRES, discontinuation of Stivarga, along with control of hypertension and supportive medical management of other symptoms is recommended.

In the placebo controlled phase III trial in patients with metastatic CRC the overall incidence of hand foot skin reactions was 45.2% in patients treated with Stivarga as compared to 7.1% in patients receiving placebo. Most cases of hand foot skin reactions were mild to moderate in severity (Grades 1 and 2: 28.6%) and most appeared during the first cycle of treatment with Stivarga.

Rash was experienced in around 47% of regorafenib-treated patients in the pivotal and other studies, with time to first onset within the first 8 weeks of therapy. Events were generally mild or moderate in severity and led to dose modifications in a low percentage of patients (2.8%).

Hand-foot skin reaction (HFSR) or palmar-plantar erythrodysesthesia syndrome and rash represent the most frequently observed dermatological adverse reactions with Stivarga.

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 (e.g. 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 Stivarga, or in severe or persistent cases, permanent discontinuation of Stivarga should be considered.

Gastrointestinal toxicity was also very commonly observed (especially diarrhoea [42.8%] and mucositis/stomatitis [28.8%]) but events were generally of mild and moderate severity and considered manageable. In toxicology studies, atrophy of the tongue has been observed in mice and rats, but has not been reported in patients.

Stivarga has been associated with an increased incidence of myocardial ischaemia and infarction. Patients with unstable angina or new onset angina (within 3 months of starting Stivarga therapy), recent myocardial infarction (within 6 months of starting Stivarga therapy) and those with cardiac failure New York Heart Association (NYHA) Classification 2 or higher were excluded from the clinical studies.

Patients with a history of ischaemic heart disease should be monitored for clinical signs and symptoms of myocardial ischaemia. In patients who develop cardiac ischaemia and/or infarction, interruption of Stivarga is recommended until resolution. The decision to re start Stivarga therapy should be based on careful consideration of the potential benefits and risks of the individual patient. Stivarga should be permanently discontinued if there is no resolution.

Stivarga has been associated with an increased incidence of haemorrhagic events, some of which were fatal. In the pivotal trial, the overall incidence of haemorrhage was 21.4% in patients treated with Stivarga as compared to 7.5% in patients receiving placebo. Most cases of bleeding events in patients treated with Stivarga were mild to moderate in severity (Grades 1 and 2: 19.2%), most notably epistaxis (8.8%). Fatal events in patients treated with Stivarga were uncommon (0.8%), and involved the respiratory, gastrointestinal and genitourinary tracts. Blood counts and coagulation parameters should be monitored in patients with conditions predisposing to bleeding, and in those treated with anticoagulants (e.g. warfarin and phenprocoumon) or other concomitant medicinal products that increase the risk of bleeding. In the event of severe bleeding necessitating urgent medical intervention, permanent discontinuation of Stivarga should be considered.

Gastrointestinal perforation and fistulae have been reported in patients treated with Stivarga. These events are also known to be common disease related complications in patients with intra-abdominal malignancies. Discontinuation of Stivarga is recommended in patients developing gastrointestinal perforation or fistula.

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 in 3 out of more than 1,100 Stivarga treated patients across all clinical trials (0.3%). Two of the patients had liver metastases. Liver dysfunction in these patients had an onset within the first 2 months of therapy, and was characterised by a hepatocellular pattern of injury with transaminase elevations >20xULN,

followed by bilirubin increase. Liver biopsies in 2 patients revealed hepatocellular necrosis with inflammatory cell infiltration.

It is recommended to perform liver function tests (ALT, AST and bilirubin) before initiation of treatment with Stivarga 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.

Regorafenib is a uridine diphosphate glucuronosyl transferase (UGT) 1A1 inhibitor. Mild, indirect (unconjugated) hyperbilirubinaemia may occur in patients with Gilbert's syndrome.

For patients with observed worsening of liver function tests considered related to treatment with Stivarga (i.e. where no alternative cause is evident, such as post hepatic cholestasis or disease progression), the dose modification and monitoring advice in Table 2 should be followed.

Regorafenib is eliminated mainly via the hepatic route. Close monitoring of the overall safety is recommended in patients with mild or moderate hepatic impairment (see also sections 4.2 and 5.2). Stivarga is not recommended for use in patients with severe hepatic impairment (Child Pugh C) as Stivarga has not been studied in this population and exposure might be increased in these patients.Proteinuria was more frequently reported in regorafenib-treated compared with placebo-treated patients in the pivotal study (8% vs 2.4%, grade 3: 1.6% vs 0.4%) with most events considered related to study drug.

In the pivotal trial, the overall incidence of treatment emergent proteinuria was 7.4% in patients treated with Stivarga as compared to 2.4% in patients receiving placebo . Of these events, 40.5% in the Stivarga arm and 66.7% in the placebo arm have been reported as not recovered / not resolved. No grade 4 or 5, neither proteinuria SAE nor proteinuria resulting in acute renal failure was observed. Proteinuria AEs were usually observed within the first 2 cycles of therapy and could usually be managed by dose reductions (0.6%) or interruptions (1.2%). Permanent discontinuation due to proteinuria was reported in 0.4% of patients. Renal failure was reported in <5% of patients treated with regorafenib in the studies performed and in the pivotal study the incidence of renal failure was slightly but not significantly higher in the regorafenib arm compared with the placebo arm (2.2% vs 1.6%). Most of events were grade 3 (1.8% vs 1.2% of cases). Renal failure and proteinuria was observed in patients as a result of treatment with regorafenib. Although proteinuria is a known class effect of TKI, the overall number of patients with renal failure is limited.

No cases of impaired wound healing were observed in the pivotal study, whereas according to a cumulative review of all patients treated with regorafenib up to 31 December 2011 a total of 6 cases were reported (5 serious and 1 non-serious), one of which treated with placebo. As medicinal products with anti angiogenic properties may suppress or interfere with wound healing, temporary interruption of Stivarga is recommended for precautionary reasons in patients undergoing major surgical procedures. The decision to resume treatment with Stivarga following major surgical intervention should be based on clinical judgment of adequate wound healing.

Each daily dose of 160 mg of Stivarga contains 2.427 mmol (or 55.8 mg) of sodium which should be taken into consideration by patients on a controlled sodium diet. Moreover, each daily dose of 160 mg contains 1.68 mg of lecithin (derived from soya).

In the pivotal trial, infections were more often observed in patients treated with Stivarga as compared to patients receiving placebo (all grades: 30.8% vs. 17.0%). Most infections in patients treated with Stivarga were mild to moderate in severity (Grades 1 and 2: 22.0%), and included urinary tract infections (7.2%) as well as mucocutaneous and systemic fungal infections (6.6%). No difference in fatal outcomes associated with infection between treatment groups was observed (0.6%, Stivarga arm vs. 0.8%, placebo arm).

No cases of interstitial lung disease have been reported in patients treated with regorafenib.

In *in vitro* assays as potential read-out for phototoxicity was identified for regorafenib and its active metabolites M2 and M5. Furthermore, reporting in the SmPC of ADRs observed with low frequency to date but considered of clinical relevance for the population treated (e.g. Steven Johnson syndrome) is considered important, in view also of the relatively short safety follow-up available.

Stivarga has been associated with an increased incidence of electrolyte abnormalities (including hypophosphatemia, hypocalcaemia, hyponatraemia and hypokalaemia) and metabolic abnormalities (including increases in thyroid stimulating hormone, lipase and amylase). The abnormalities are generally of mild to moderate severity, not associated with clinical manifestations, and do not usually require dose interruptions or reductions. It is recommended to monitor biochemical and metabolic parameters during Stivarga treatment and to institute appropriate replacement therapy according to standard clinical practice if required. Dose interruption or reduction, or permanent discontinuation of Stivarga should be considered in case of persistent or recurrent significant abnormalities (see section 4.2).

Overall, tests on thyroid stimulating hormone (TSH) showed post baseline >ULN in 23.1% in the regorafenib and 13.3% in the placebo arm. TSH post baseline >4 times ULN was reported in 4.0% in the regorafenib arm and in no patients in the placebo arm. Concentration of free triiodothyronine (FT3) post baseline below lower limit of normal (< LLN) was reported in 20.8% in the regorafenib arm and 15.7% in the placebo arm. Concentration of free thyroxin (FT4) post baseline <LLN was reported in 8.5% in regorafenib arm and 7.2% in the placebo arm.

Regarding the elderly, the overall incidence of any AE and the incidence of most of the common AEs across clinical studies was similar between age groups (<65 years, ≥65 years). The incidence of AEs and SAEs (42.5 vs 44.6%) was similar between the two age groups. Hypertension (28% vs 34.2%), anorexia (42.7% vs 53.4%) and headache (8.5% vs 13%) were more frequently reported in ≥65 years old patients treated with regorafenib compared with <65 years old, whereas HFS (48.5% vs 39.4%), hyperbilirubinemia (15% vs 9.8%) and back pain (15% vs 8.8%) were more frequent in the younger (<65 years) subgroup of the population. With the exception of decreased appetite and headache, similar trends were seen in the placebo group. The rate of drug-related serious adverse events was higher in patients older than 65 years (9.8% in aged <65; 15.5% in aged 65-74; 13.2% in aged 75-84), even if no difference was reported in terms of fatal cases. Moreover, based on the rate of dose modification across age group no differences can be highlighted, even if the limited number (53) of patients older than 75 years could have hampered the safety assessment in this subgroup.

The highest dose of Stivarga studied clinically was 220 mg per day. The most frequently observed adverse drug reactions at this dose were dermatological events, dysphonia, diarrhoea, 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 discontinued immediately, with best supportive care initiated by a medical professional, and the patient should be observed until clinical stabilisation.

From the safety database all the adverse reactions reported in clinical trials have been included in the Summary of Product Characteristics.

2.6.2. Conclusions on the clinical safety

The safety profile of regorafenib shows consistency across studies and is similar to the profile of other anti-angiogenic and multi-kinase inhibitors. Hypertension, skin (hand-foot syndrome, rash) and gastrointestinal toxicities (diarrhoea, mucositis) were prominent, whereas hematologic toxicities were limited. Hyperbilirubinaemia and liver enzymes aberrations were frequently observed with regorafenib, especially in patients with liver metastases. Haemorrhages, with fatal outcome in few cases, as well as myocardial ischemia and infarction have been reported with regorafenib.

Overall the toxicity related to regorafenib treatment appears to be manageable, but not negligible. In any case toxicity of regorafenib does not seem to be out of balance when compared to other anti-angiogenic and multiple tyrosine kinase inhibitors, like sorafenib.

The full evaluation of the safety profile of the drug is limited by the paucity of a long-term safety database.

2.7. Pharmacovigilance

Detailed description of the pharmacovigilance system

The CHMP considered that the Pharmacovigilance system as described by the applicant fulfils the legislative requirements.

2.8. Risk Management Plan

The CHMP received the following PRAC Advice on the submitted Risk Management Plan:

PRAC Advice

Based on the PRAC review of the Risk Management Plan version 1.4, the PRAC considers by consensus that the risk management system for regorafenib (Stivarga) in the treatment of patients with metastatic colorectal cancer (CRC) who have been previously treated with, or are not considered candidates for fluoropyrimidine-based chemotherapy, an anti-VEGF therapy, and, if KRAS wild type, an anti-EGFR therapy is acceptable.

The following minor revision is recommended for the next RMP update:

- The MAH should provide clear milestones for 14814 (An open-label, nonrandomized Phase I study of regorafenib (BAY 73-4506) to evaluate cardiovascular safety, tolerability,

pharmacokinetics and anti-tumour activity in patients with advanced solid tumours: Long-term LVEF data) as the term 'approximately 12 months after last patient last visit' is not a traceable date.

Following the PRAC advice, the applicant has submitted two subsequent RMP updates to address CHMP recommendations for inclusion of activity in KRAS mutant tumours as additional information to be provided (v 1.5) and for commitment to investigate additional biomarkers in future studies following the Oral Explanation (v 1.6).

The finally agreed content of the Risk Management Plan was the following:

Safety concerns

Table 16: Summary of the Safety Concerns

Main identified risks	• Severe drug-induced liver injury • Cardiac ischemic events • Hypertension and hypertensive crisis • Hemorrhage • Hand-foot skin reaction (HFSR) • Posterior reversible encephalopathy syndrome (RPES) • GI perforation and fistulae • Stevens-Johnson-Syndrome (SJS)/Toxic epidermal necrolysis (TEN)
Main potential risks	• Wound healing complications • Interstitial Lung Disease (ILD) • Atrial fibrillation • Reproductive and developmental toxicity • Renal failure • Phototoxicity
Additional information to be provided	• Safety in severe hepatic impairment • Safety in children • Safety in patients with a cardiac history • Safety in severe renal impairment • Interaction with antibiotics • Interaction with BCRP substrates • Activity in KRAS mutated tumours or other biomarker-defined tumour subtypes

Pharmacovigilance plans

Study	Protocol version	Protocol status	Planned date for submission of interim data	Planned date for submission of final data

Study	Protocol version	Protocol status	Planned date for submission of interim data	Planned date for submission of final data
15967 An open-label phase IIIb study of regorafenib in patients with metastatic colorectal cancer (CRC) who have progressed after standard therapy. Eudra CT No.: 2011-005836-25	Version 2.0, 3 August 2012	Final protocol available. CTA applications currently ongoing.	Not applicable	September 2014
15808 A randomized, double-blind, placebo-controlled phase III study of regorafenib plus best supportive care (BSC) versus placebo plus BSC in Asian subjects with metastatic colorectal cancer (CRC) who have progressed after standard therapy (CONCUR) Eudra CT No.: NA	Version 1.0 14 Feb 2012	Final protocol available	Not applicable	To submit final results and pre-specified, exploratory wild-type and mutant KRAS subgroup analyses: 31/08/2014 In addition an annual report will be submitted A proposal for additional biomarkers assessment should be submitted to the CHMP within two months of the marketing authorization: 31/10/2013 To submit additional genetic (NRAS, BRAF) biomarker analyses: 31/08/2015
Effect of antibiotic pretreatment on the pharmacokinetics of regorafenib in healthy volunteers	Not yet available	Not drafted	Not applicable	Q2/2015
Effect of multiple-dose regorafenib on the pharmacokinetics of a BCRP substrate in cancer patients.	Not yet available	Not drafted	Not applicable	Q4/2015
14814 An open-label, non-randomized Phase I study of Regorafenib (BAY 73-4506) to evaluate cardiovascular safety parameters, tolerability, pharmacokinetics, and anti-tumor activity in patients with advanced solid tumors Eudra CT No.: NA (US study)	Version 2.0, 4 August 2011	Final protocol available	Not applicable	Addendum to the CSR including longer term LVEF results will be generated and provided approximately 12 months after last patient last visit
15983 A Randomized, Double-blind,	Not yet available	Not drafted	An interim analysis for futility	Planned for 31/12/2020 Submission of results of

Study	Protocol version	Protocol status	Planned date for submission of interim data	Planned date for submission of final data
Placebo-controlled Phase-III Study of Adjuvant Regorafenib Versus Placebo for Patients with Stage IV Colorectal Cancer After Curative Treatment of Liver Metastases			will be conducted when approximately 95 DFS events, which is 30% of the targeted final DFS events, have been observed.	genetic (including NRAS, KRAS, BRAF and PIK3CA) and non-genetic (ANG-2, IL-6, IL-8, P1GF, VEGFR-1, TIE1, VEGF-A, VEGF-C, VEGF-D, VEGF-A-121, BMP-7, VWF, M-CSF, SDF-1) appropriate biomarker analyses: 31/12/2020 The proposed protocol for biomarkers assessment should be submitted to the CHMP within two months of the marketing authorization: 31/10/2013 In addition an annual report will be submitted

Moreover, additional biomarkers will be explored in studies 15808, 15983 and other future studies, guided by the scientific literature and with the intention of improving patient selection. Annual updates will be submitted for regulatory review.

Risk minimisation measures

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
Main Identified Risks		
Severe DILI	SmPC Section 4.2 'Dose and method of administration', sub-section 'Dose modification'; section 4.4. 'Warnings and precautions for use' and section 4.8 'Undesirable effects'	None
Cardiac ischemic events	SmPC Section 4.4. 'Warnings and precautions for use' and section 4.8 'Undesirable effects'	None
Hypertension and hypertensive crisis	SmPC Section 4.4. 'Warnings and precautions for use' and section 4.8 'Undesirable effects'	None
Hemorrhage	SmPC Section 4.4. 'Warnings and precautions for use' and section 4.8 'Undesirable effects'	None
Hand-foot skin reaction (HFSR)	SmPC Section 4.2 'Dose and method of administration', sub-section 'Dose modification'; section 4.4. 'Warnings and precautions for use' and section	None

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
	4.8 'Undesirable effects'	
Posterior reversible encephalopathy syndrome (PRES)	SmPC Section 4.4. 'Warnings and precautions for use' and section 4.8 'Undesirable effects'	None
GI perforation and fistulae	SmPC Section 4.4. ' Warnings and precautions for use' and section 4.8 'Undesirable effects'	None
Stevens-Johnson-Syndrome (SJS) /Toxic epidermal necrolysis (TEN)	SmPC Section 4.8 'Undesirable effects'	None
Main potential risks		
Wound healing complications	SmPC Section 4.4. 'Warnings and precautions for use'	None
Interstitial Lung Disease (ILD)	None	None
Atrial fibrillation	None	None
Reproductive and developmental toxicity	SmPC Section 4.6. 'Fertility, pregnancy and lactation'	None
Renal failure	None	None
Phototoxicity	None	None
Additional Information to be provided		
Safety in severe hepatic impairment	SmPC Section 4.2 'Posology and method of administration', 4.4 'Warnings and Precautions' and 5.2 'Pharmacokinetic Properties'	None
Safety in children	SmPC Section 4.2 'Posology and method of administration'	None
Safety in patients with a cardiac history	SmPC Section 4.4 'Warnings and precautions for use'	None
Safety in severe renal impairment	SmPC Section4.2 'Posology and method of administration'	None
Interaction with antibiotics	SmPC Section 4.5 'Interaction with other medicinal products and other forms of interaction'	None
Interaction with BCRP substrates	SmPC Section 4.5 'Interaction with other medicinal products and other forms of interaction'	None
Activity in KRAS mutant tumours or other biomarker-defined tumour subtypes	SmPC Section 4.4. 'Warnings and precautions for use' SmPC section 5.1 'Pharmacodynamic properties'	None

The CHMP endorsed the PRAC advice with changes.

These changes concerned the following elements of the Risk Management Plan:

- activity in KRAS mutant tumours

- identification of biomarkers to further aid definition of the target population

The CHMP justified these changes as follows:

In the pivotal study, the results of secondary endpoints reporting the majority of patients experiencing early disease progression at the time of the first radiological evaluation suggest a benefit limited to a subgroup of the population treated. In view of the substantial, although manageable, toxicity of the drug, identification of patient/tumour characteristics for proper patient selection is important, in order to avoid (unnecessary) exposure of patients in the last weeks of their life to a toxic drug. Biomarker analyses from two prospective studies (15808 [CONCUR] and 15983) could provide some further insights into the potentially differential activity of regorafenib in patients with wild-type or mutant KRAS tumours. Moreover, additional biomarkers will be explored in studies 15808, 15983 and other future studies, guided by the scientific literature and with the intention of improving patient selection. Annual updates will be submitted for regulatory review.

2.9. User consultation

The results of the user consultation with target patient groups on the package leaflet submitted by the applicant show that the package leaflet meets the criteria for readability as set out in the *Guideline on the readability of the label and package leaflet of medicinal products for human use.*

3. Benefit-Risk Balance

Benefits

Beneficial effects

The results of the pivotal study, based on the second interim analysis performed after 432 (56.8%) death events, showed a statistically significant improvement in the primary endpoint of OS for regorafenib plus BSC compared with placebo plus BSC (HR 0.77, 95% CI 0.636-0.942, p=0.005178), with a gain in median OS of 1.5 months in favour of regorafenib (median OS 196 days vs 151 days, respectively). The results were consistent at an updated OS analysis performed with later cut-off, when 97% (566) of the planned death events occurred and before cross over was allowed (median OS 194 vs 152 days, HR 0.79, 95% CI 0.664, 0.939, p=0.003791). The effect on OS was observed in several subgroups of the population. Of particular interest, the OS effect appears to be maintained also despite previous treatment with other VEGF inhibitors (i.e., bevacizumab). No imbalance in post-study therapies between the two study arms was observed from the data provided in both analyses.

The OS results appeared to be supported by the investigator-assessed PFS data (secondary study endpoint). A statistically significant increase in PFS was observed with regorafenib compared with placebo (HR 0.494, 95% CI 0.419-0.582, p<0.000001. Median PFS was formally

59 vs 52 days with regorafenib and placebo, respectively. PFS improvement was observed in all the subgroups explored according to Cox regression model.

Overall response rate (ORR: CR+PR) was very low and similar between the two treatment arms (1% with regorafenib and 0.4% with placebo). Disease control rate was significantly higher in the regorafenib arm compared with the placebo arm (41% vs 14.9%, respectively). However, duration of disease stabilisation was very similar between the two study arms (60 vs 52 days, respectively).

Considering the sought indication in a late stage of disease, the oral formulation of regorafenib could be perceived by patients as an advantage allowing the home-based care treatment.

Uncertainty in the knowledge about the beneficial effects

The clinical relevance of the observed difference in PFS is unclear, as the gain in median PFS associated with regorafenib was only 1 week (59 vs 52 days, respectively). However, the analysis was confounded by the timing of the radiological evaluation. Indeed, at the time of the first PFS assessment (8 weeks) 58% of regorafenib treated patients had experienced disease progression already.

Moreover, the reliability of the PFS results could be questioned, as an investigator-driven bias cannot be ruled out completely considering that obvious differences in treatment induced toxicities between study arms might potentially have compromised the double-blind nature of the trial.

The very high rate of patients not responding to treatment with regorafenib could suggest activity of the drug limited to a subgroup of the population. Unfortunately, from the analyses submitted, no specific biomarkers or other patient/tumour parameters were identified that could be used for patient selection. In patients enrolled in the CORRECT study, KRAS status seemed to poorly predict the PFS outcome with a statistically significant improvement being observed in patients with both mutated and wild type tumours. However, mutated KRAS status appeared to be associated with a worse PFS outcome regardless of treatment arm and in a multivariate analysis, KRAS mutation was consistently identified as potentially prognostic parameter in terms of OS and PFS. On the other hand, a differential activity of regorafenib was observed according to KRAS mutation status by Kaplan-Meier analysis, HRs and median values. Compared to the overall study population, an inferior difference was observed between the two study arms in terms of OS in patients with mutant KRAS tumours (HR 0.87, 95% CI 0.67-1.12), whereas the difference in OS was not adversely affected in the smaller subgroup of patients with wild type KRAS tumours (HR 0.66, 95% CI 0.48-0.80, p=0.007). However, there was no evidence of heterogeneity in treatment effect (non-significant interaction test) and the analyses by KRAS tumour status were non-randomised comparisons. The exploratory nature of the subgroup analyses presented does not allow any firm conclusion over this issue.

No significant difference between the two study arms was observed in the evaluation of Quality of life.

Risks

Unfavourable effects

Overall, the safety profile of regorafenib was consistent across studies and was typical for an angiogenetic and multi-tyrosine kinase inhibitor: hypertension, skin (hand-foot syndrome, rash) and gastrointestinal toxicities (diarrhoea, mucositis) were prominent, whereas hematologic toxicities were limited.

In the pivotal 14387 study, Adverse Events (AEs) more frequently observed (≥10% difference) with regorafenib compared with placebo were fatigue (63% vs 46.%, respectively), hand-foot syndrome (47.0% vs 7.5%), anorexia (47% vs 28%), diarrhoea (43% vs 17%), weight loss (32% vs 11%), dysphonia (32% vs 6%), hypertension (30% vs 8%), rash/desquamation (29% vs 5%), mucositis/stomatitis (29% vs 5%), fever (28% vs 15%), hyperbilirubinemia (20% vs 9%), platelet counts abnormalities (16% vs 2%), haemorrhages (20% vs 7%) and infections (25% vs 14%). The difference was mainly due to a higher incidence of grade 1-3 events.

Hand-foot syndrome (HFS) was observed in 47% of patients treated with regorafenib. Most events were of grade 1 or 2 severity, grade 3 events were observed in 17% of patients, whereas no grade 4 was reported. HFS AEs could usually be managed by dose reductions or interruptions. HFS led to permanent discontinuation, dose reduction and interruption in 7 (1.4%), 92 (18%) and 96 (19%) regorafenib treated patients, respectively.

Cardiac events have been observed in 8-26% of patients treated with regorafenib in different studies. An increased frequency of myocardial ischemia and infarction has been associated with treatment with regorafenib (1.2% vs 0.4% with regorafenib vs placebo, respectively) in the pivotal study, with a slightly increased risk in patients with cardiovascular risk factors. Arrhythmias (especially atrial fibrillation) were reported with higher incidence in the regorafenib arm. The incidence of other thromboembolic events did not appear to be significantly influenced by treatment with regorafenib.

The most common bleeding AE (any grade) in both treatment groups was haemorrhage pulmonary/nose (9% vs 2.4%) followed by haemorrhage anus (3% vs 0.4%), urinary (2.2% vs 1.2%), rectum (1.2% vs 0%), and others (2% vs 0%). A total of 4 pts (0.8%) in the regorafenib arm vs no patient in the placebo arm experienced fatal bleedings, 3 of them considered as drug-related. Patients experiencing bleeding events appeared to have often additional causative factors (e.g., anticoagulant use, liver cirrhosis, etc.), but a clear relation could not be made with thrombocytopenia and alteration of coagulation parameters observed in regorafenib treated patients.

Similar to other inhibitors of the VEGFR pathway, a slightly increased incidence of gastrointestinal perforation or fistula was observed with regorafenib.

Impaired wound healing was rarely reported (< 1%).

Hyperbilirubinemia (probably related to impaired glucuronidation through UGT1A1 inhibition) and liver enzyme (AST/ALT) abnormalities were commonly observed with regorafenib (13%, 45% and 65%, respectively), and with higher incidence compared with placebo. Most of events were

grade 1 or 2 in severity. Two cases meeting Hy's Law criteria and 3 cases of severe drug-induced liver injury event were described.

Renal failure was reported in <5% of patients treated with regorafenib in all the studies performed and in the pivotal study the incidence of renal failure was slightly but not significantly higher in the regorafenib arm compared with the placebo arm (2.2% vs 1.6). Most of events were grade 3 (1.8% vs 1.2% of cases).

One event of hypertensive crisis associated with development of reversible posterior leukoencephalopathy syndrome (RPLS) has been reported.

One case of serious and potentially life-threatening Steven-Johnson syndrome event has been observed.

In the pivotal trial, the rate of study treatment discontinuation due to TEAE was higher in the regorafenib arm in comparison to placebo (17.6% versus 12.6%). Moreover, a dose modification was required in regorafenib patients almost twice as much as it was needed in placebo patients (regorafenib 75.6% vs placebo 38.3%), with a rate of dose reductions of 20% vs 3.2% in the regorafenib and placebo arm, respectively.

Uncertainty in the knowledge about the unfavourable effects

Long term safety data are lacking.

In all clinical studies performed to date, patients with history of moderate or severe hepatic dysfunction (including hyperbilirubinemia > 1.5 ULN or AST/ALT increase > 5 ULN) or severe renal impairment, with ECOG PS >1 or with ongoing or recent cardiovascular diseases were excluded. Limited information is available in patients with moderate hepatic impairment (Child-Pugh B) and no data are available in patients with severe hepatic impairment (Child-Pugh C). Very few patients with impaired renal function have been treated with regorafenib in the pivotal trial.

The tolerability of the drug in patients with ECOG PS>1 is uncertain, as such patients were excluded from the pivotal phase III study. This is considered relevant as a worst performance status is not uncommon in patients treated in clinical practice.

Benefit-risk balance

Importance of favourable and unfavourable effects

Regorafenib is a new tyrosine kinase inhibitor proposed for the treatment of patients with mCRC that have exhausted, or are not candidate for, all the currently available standard anticancer treatment options. Therefore an unmet medical need for such population is readily acknowledged.

In this context the results of the pivotal 14387 study are considered of potential clinical relevance. A statistically significant improvement in OS associated with treatment with regorafenib compared with placebo, and supported by a statistically significant improvement in PFS was observed. However, the absolute gain in median OS (1.5 months) is rather modest,

whereas the median improvement in PFS consists of few weeks at best (formally the difference in median PFS between treatment arms was only 1 week). The clinical relevance of these results is modest, considering also that ORR is negligible and that there is no clear indication of a positive effect of the treatment on disease symptoms or QoL.

This modest clinical benefit has to weighed against the toxicity of regorafenib, which is, although manageable, substantial. Fatigue, hand-foot syndrome, anorexia, diarrhoea, weight loss, hypertension, rash, mucositis, fever, hyperbilirubinaemia, platelet count abnormalities, haemorrhage and infections were observed very commonly in patients treated with regorafenib, with a significantly higher incidence compared with placebo-treated patients. In particular, the incidence of AEs of special interest associated with regorafenib was very high (>30%), and appears to significantly increase overtime.

Benefit-risk balance

The efficacy results of the pivotal 14387 study show a statistically significant OS improvement associated with treatment with regorafenib (median OS gain of 1.5 months), supported by a statistically significant improvement in delay in disease progression. Moreover, a low rate of tumour shrinkage was reported (1%) and evaluation of quality of life did not show any significant difference between the two treatment arms in the pivotal study. In other words, the modest prolongation in survival appears to be essentially related to disease stabilisation for a few weeks at best.

Whether this could translate in a clinically relevant benefit for the patients treated needs to be critically weighed with the observed/expected drug-related toxicity. The safety profile of regorafenib was consistent across studies and was typical for an angiogenesis and multi-tyrosine kinase inhibitor: hypertension, skin (hand-foot syndrome, rash) and gastrointestinal toxicities (diarrhoea, mucositis) were prominent, whereas haematologic toxicities were limited. Several adverse events able to affect patient's quality of life, like (abdominal) pain, fatigue, anorexia, rash, diarrhoea, mucositis, hand-foot syndrome and hypertension were significantly more frequently reported in patients treated with regorafenib compared with placebo.

All together, the clinical relevance of the results appears to be modest. However, in the intended population of patients with metastatic colorectal cancer having exhausted all currently available therapeutic options, the benefits of regorafenib are considered to outweigh the risks associated with its use.

Discussion on the benefit-risk balance

A statistically significant improvement in OS (median OS gain of 1.5 month) has been associated with treatment with regorafenib compared with placebo in the mCRC population enrolled in the pivotal Study 14387. However, the results of secondary endpoints reporting the majority of patients experiencing early disease progression at the time of the first radiological evaluation suggest a benefit limited to a subgroup of the population treated. In view of the substantial, although manageable, toxicity of the drug, identification of patient/tumour characteristics for proper patient selection is important, in order to avoid (unnecessary) exposure of patients in the last weeks of their life to a toxic drug.

Nevertheless, the available data do not currently support a restriction of the indication in any subpopulation of patients with metastatic colorectal cancer having exhausted all available therapeutic options. A differential activity of regorafenib was observed according to KRAS mutation status by Kaplan-Meier analysis, HRs and median values. However, there was no evidence of heterogeneity in treatment effect (non-significant interaction test) and the trend towards a smaller observed benefit in the KRAS mutant subgroup might be at least partly explained by a higher rate of subsequent anti-cancer therapy in the KRAS-mutated placebo subgroup compared to the KRAS-mutated regorafenib subgroup. Additionally, the difference could be due to imbalances in baseline characteristics of the patients included in these subgroups and for these non-randomised comparisons. Overall, the exploratory nature of the subgroup analyses presented does not allow any firm conclusion over this issue.

Biomarker analyses from two prospective studies (15808 [CONCUR] and 15983) could provide some further insights into the potentially differential activity of regorafenib in patients with wild-type or mutant KRAS tumours.

4. Recommendations

Outcome

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considers by consensus that the risk-benefit balance of Stivarga in the treatment of adult patients with metastatic colorectal cancer (CRC) who have been previously treated with, or are not considered candidates for, available therapies; these include fluoropyrimidine-based chemotherapy, an anti-VEGF therapy and an anti-EGFR therapy, is favourable and therefore recommends the granting of the marketing authorisation subject to the following conditions:

Conditions or restrictions regarding supply and use

Medicinal products subject to restricted medical prescription (See Annex I: Summary of Product Characteristics, section 4.2).

Conditions and requirements of the Marketing Authorisation

- **Periodic Safety Update Reports**

The marketing authorisation holder shall submit the first periodic safety update report for this product within 6 months following authorisation. Subsequently, the marketing authorisation holder shall submit periodic safety update reports for this product in accordance with the requirements set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and published on the European medicines web-portal.

Conditions or restrictions with regard to the safe and effective use of the medicinal product

- **Risk Management Plan (RMP)**

The MAH shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the Marketing Authorisation and any agreed subsequent updates of the RMP.

In addition, an updated RMP should be submitted:

At the request of the European Medicines Agency;

Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

If the submission of a PSUR and the update of a RMP coincide, they can be submitted at the same time.

- **Obligation to conduct post-authorisation measures**

The MAH shall complete, within the stated timeframe, the below measures:

Description	Due date
To submit pre-specified, exploratory wild-type and mutant KRAS subgroup analyses from study 15808 (CONCUR - randomised, double-blind, placebo-controlled phase III study of regorafenib plus best supportive care (BSC) versus placebo plus BSC in Asian subjects with metastatic colorectal cancer (CRC) who have progressed after standard therapy)	31/08/2014
To submit NRAS and BRAF biomarker analyses from the same study, subject to sample availability and confirmation of appropriate informed consent.	31/08/2015
A proposal for additional biomarkers assessment should be submitted to the CHMP within two months of the marketing authorisation.	31/10/2013
To submit pre-specified, exploratory genetic (including NRAS, KRAS, BRAF and PIK3CA) and non-genetic (ANG-2, IL-6, IL-8, P1GF, VEGFR-1, TIE1, VEGF-A, VEGF-C, VEGF-D, VEGF-A-121, BMP-7, VWF, M-CSF, SDF-1) appropriate biomarker analyses from study 15983 (randomised, double-blind, placebo-controlled phase-III study of adjuvant regorafenib versus placebo for patients with stage IV colorectal cancer after curative treatment of liver metastases). Genetic and non-genetic biomarker analysis should be implemented as mandatory for all enrolled patients.	31/12/2020
Prospective serial measurement should be planned and assessed for biomarkers. The proposed protocol for biomarkers assessment should be submitted to the CHMP within two months of the marketing authorisation.	31/10/2013

New Active Substance Status

Based on the CHMP review of data on the quality properties of the active substance, the CHMP considers that regorafenib is qualified as a new active substance.