26 June 2014
EMA/CHMP/348464/2014 Corr[1]
Committee for Medicinal Products for Human Use (CHMP)

CHMP extension of indication variation assessment report

Stivarga

Procedure no. EMEA/H/C/002573/II/0001

Marketing authorisation holder (MAH): Bayer Pharma AG

Note

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

[1] Information on Paediatric requirements was corrected

30 Churchill Place ● Canary Wharf ● London E14 5EU ● United Kingdom
Telephone +44 (0)20 3660 6000 **Facsimile** +44 (0)20 3660 5555
Send a question via our website www.ema.europa.eu/contact

Table of contents

List of abbreviations

ADR	Adverse Drug Reaction
ALP	Alkaline phosphatease
AST	Aspartate aminotransferase
AUC	Area under the plasma concentration vs time curve
BCRP	Breast Cancer Resistance Protein
BMI	Body Mass Index
BSC	Best Supportive Care
CBR	Clinical Benefit Rate
CR	Complete Response
CSR	Clinical Study Report
DCR	Disease Control Rate
DILI	Drug-induced Liver Injury
DOR	Duration of response
ECOG PS	Eastern Cooperative Oncology Group Performance Status
EMA	European Medicines Agency
FAS	Full Analysis Set
FDA	Food and Drug Administration
GGT	Gammaglutamyl transferase
GIST	Gastrointestinal Stromal Tumour
HCC	Hepatocellular carcinoma
HCT	Hematocrit
HFSR	Hand-Foot Skin Reaction
HRQoL	Health-Related Quality of Life
KM	Kaplan-Meier
INR	International Normalised Ratio
IPE	Iteractive Parameter Estimation
ITT	Intention To Treat
IVRS	Interactive Voice Response System
LLN	Lower limit of normal
MA	Marketing Authorisation
MedDRA	Medical Dictionary for Regulatory Activities
MLG	MedDRA Labeling Grouping
MPP+	Methylphenylpyridinium+
MTD	Maximum Tolerated Dose
NCI-CTCAE	National Cancer Institute- Common Terminology Criteria for Adverse Events
NOAEL	No Observed Adverse Effect Level
NYHA	New York Heart Association
OCT	Organic cation transporter
ORR	Overall Response Rate
OS	Overall Survival
PBMQ	Product-Specific Bayer MedDRA Query
PD	Progressive Disease
PFS	Progression Free Survival
P-gp	P-glycoprotein
PND	Post natal day
PR	Partial Response
PRO	Patient Reported Outcomes
PT	Preferred Term
PTT	Partial prothrombin time
RCC	Renal Cell Cancer
RECIST	Response Evaluation Criteria In Solid Tumor
RPSFT	Rank Preserving Structural Failure Time
RR	Response Rate
SAF	Safety Analysis Set
SD	Stable Disease
SOC	System Organ Class

SMQ	Standardised MedDRA Queries
T3	Triiodothyronine
T4	Thyroxin
TEAE	Treatment-Emergent Adverse Event
TSH	Thyroid stimulating hormone, thyrotropin
TKI	Tyrosine kinase inhibitor
TTP	Time To Progression
ULN	Upper limit of normal
VEGFR	Vascular Endothelial Growth Factor Receptor

1. Background information on the procedure

1.1. Type II variation

Pursuant to Article 16 variation of Commission Regulation (EC) No 1234/2008, Bayer Pharma AG submitted to the European Medicines Agency on 4 September 2013 an application for a variation including an extension of indication.

This application concerns the following medicinal product:

Medicinal product:	**International non-proprietary name:**	**Presentations:**
Stivarga	REGORAFENIB	See Annex A

The following variation was requested:

Variation requested		**Type**
C.1.6 a	Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	II

The MAH applied for an extension of the indication to include treatment of patients with gastrointestinal stromal tumours (GIST) who have been previously treated with 2 tyrosine kinase inhibitors. Consequently, the MAH proposed the update of sections 4.1, 4.2, 4.8 and 5.1 of the SmPC.

The Package Leaflet was proposed to be updated accordingly.

The requested variation proposed amendments to the Summary of Product Characteristics and Package Leaflet.

Information on paediatric requirements

Pursuant to Article 8 of Regulation (EC) No 1901/2006, the application included an EMA Decision(s) P/0258/2012 on the agreement of a paediatric investigation plan (PIP). At the time of submission of the application, the PIP P/0258/2012 was not yet completed as some measures were deferred.

Pursuant to Article 7 of Regulation (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.

Applicant's request for consideration

Additional data protection / marketing exclusivity

The applicant requested consideration of its application in accordance with Article 14(11) of Regulation (EC) 726/2004 - one year of market protection for a new indication.

Scientific advice

The applicant received Scientific Advice from the CHMP on 22 October 2010. The Scientific Advice pertained to clinical aspects of the dossier.

1.2. Steps taken for the assessment of the product

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

Rapporteur: Pieter de Graeff Co-Rapporteur: Daniela Melchiorri

The EMA Product Team Leader: Kyriaki Tzogani

Submission date:	4 September 2013
Start of procedure:	20 September 2013
Rapporteur's assessment report circulated on:	14 November 2013
Co-Rapporteur's assessment report circulated on:	12 November 2013
PRAC Rapporteur's preliminary assessment report circulated on:	18 November 2013
PRAC Rapporteur's updated assessment report circulated on:	29 November 2013
PRAC advice on:	5 December 2013
Request for supplementary information and extension of timetable adopted by the CHMP on:	19 December 2013
MAH's responses submitted to the CHMP on:	21 March 2014
PRAC Rapporteur's assessment report circulated on:	17 April 2014
Joint Rapporteur's updated assessment report on the MAH's responses circulated on:	18 April 2014
PRAC RMP advice and assessment overview adopted by PRAC :	8 May 2014
2nd Request for supplementary information and extension of timetable adopted by the CHMP on:	22 May 2014
MAH's responses to 2nd RSI submitted to the CHMP on:	28 May 2014
PRAC Rapporteur's assessment report circulated on:	2 June 2014
Joint Rapporteur's assessment report on the MAH's responses circulated on:	5 June 2014
PRAC RMP advice and assessment overview adopted by PRAC :	12 June 2014
CHMP Opinion:	26 June 2014

CHMP AR on the request for one-year marketing protection adopted on:	26 June 2014

2. Scientific discussion

2.1. Introduction

Gastrointestinal stromal tumours (GIST) refers to a group of mesenchymal tumour of neurogenic or myogenic differentiation which lacked the immunohistochemical features of Schwann cells and did not have the ultrastructural characteristics of smooth muscle cells (Mazur MT, 1983). Gastrointestinal stromal tumours (GISTs) represent the most common sarcomas arising in the gastrointestinal tract, with a worldwide incidence reaching 10 cases per million people annually (Joensuu H, 2006).

Approximately 90% of GISTs express CD117, the antigen based on the KIT receptor tyrosine kinase (RTK) and that belongs to type III RTK subfamily, comprising, among the members, platelet-derived growth factor receptors α and β (PDGFRα and PDGFRβ). Mutations of KIT and PDGFRa genes in different exons are of clinical importance as they lead to a different response to standard tyrosine kinase inhibitor therapy (Heinrich et al., 2003; 2008; Debiec-Rychter et al., 2006; Van Glabbeke et al., 2007).

The most frequent symptoms of GIST at presentation are haemorrhage followed by abdominal pain and/or discomfort. Aggressive GISTs metastasize to the liver and other locations in the abdomen, and only rarely to the lymph nodes. Small GISTs are often detected during surgery for other conditions. Most GIST presents in the stomach (50–70%) or the small intestine (20–30%).

Surgery represents still the cornerstone of GIST treatment whenever resection is possible. Complete removal of a primary tumour is potentially curative, especially when the tumour is small and the risk classification is low. In patients with metastatic and /or unresectable GIST, molecular targeted therapy has been the focus of the therapeutic approach over the past decade. Attempts to treat GIST with systemic chemotherapy have been unsuccessful with responses typically less than 10% and associated with significant toxicities.

Imatinib mesylate, an inhibitor of KIT, PDGFR, ABL kinase, and the chimeric BCRABL, was granted a marketing authorisation for treatment of adult patients with Kit (CD 117) positive unresectable and/or metastatic gastrointestinal stromal tumours (GIST). The effectiveness of imatinib was based on objective response rates in GIST.

Sunitinib has been approved for the treatment of unresectable and/or metastatic malignant gastrointestinal stromal tumour (GIST) after failure of imatinib mesylate treatment due to resistance or intolerance on the basis of increased time to progression (TTP) and overall survival (OS) compared to placebo.

Regorafenib is an oral inhibitor acting on kinases involved in tumour angiogenesis (VEGFR1, -2, -3, TIE2), oncogenesis (KIT, RET, RAF-1, BRAF, BRAFV600E), and the tumour microenvironment (PDGFR, FGFR).

The MAH applied for the indication: ''Stivarga is indicated for the treatment of patients with gastrointestinal stromal tumours (GIST) who have been previously treated with 2 tyrosine kinase inhibitors''.

The finally applied indication was: ''Stivarga is indicated for the treatment of adult patients with unresectable or metastatic gastrointestinal stromal tumors (GIST) who progressed on or are intolerant to prior treatment with imatinib and sunitinib''.

The recommended dose is 160 mg (4 tablets of 40 mg) taken once daily for 3 weeks followed by 1 week off therapy.

2.2. Non-clinical aspects

2.2.1. Introduction

A preclinical pharmacodynamics study has been submitted with this application. The environmental risk assessment (ERA) has been updated accordingly. In addition, 8 pharmacokinetic studies and 1 juvenile toxicity study were submitted.

2.2.2. Pharmacology

Primary pharmacodynamic studies

The efficacy of regorafenib on human GIST-derived cells was assessed in xenograft models in immunodeficient mice. Tumours deriving from two cell lines, both bearing a constitutive active form of the c-KIT receptor tyrosine kinase, were generated by subcutaneous implantation. After tumour establishment, mice were treated with regorafenib at 50 mg/kg daily by oral administration. One of the cell lines, GIST-T1 bearing a deletion affecting the juxtamembrane domain, readily induced the formation of subcutaneous tumours that disappeared after 47 days of treatment but retrieved the initial volume in the following 30 days during which animals received no treatment. A subsequent cycle of regorafenib administration for 30 days led to almost complete disappearance of measurable tumours but again tumour growth restarted after drug discontinuation. The other cell line, GIST-882 in which c-KIT carries a K642E mutation, caused measurable tumour onset in about 1/3 of the host mice. Also in this case tumours became undetectable after 9 days of regorafenib administration and the effect remained until the last day of treatment (day 100). Attempts were made to generate cells resistant to regorafenib by alternating cycles of treatment and wash-out, also after serial grafting of the tumours in different mice, but a clear resistance could not be induced, however after 10 months of treatment some mice developed GIST-T1 tumours that were arrested in their growth but not reduced in volume by regorafenib. Imaging evaluation by FDG-PET showed a rapid reduction of metabolic activity already in the first days of treatment.

Secondary pharmacodynamic studies

No additional secondary pharmacodynamic studies have been submitted.

Safety pharmacology programme

No additional safety pharmacology studies have been submitted.

Pharmacodynamic drug interactions

No specific pharmacodynamic drug interactions additional studies have been submitted.

2.2.3. Pharmacokinetics

The *in vitro* permeability of the regorafenib metabolites M-2 and M-5 were investigated using a Caco-2 assay (study PH-37022). Comparison with 22 reference compounds (11 high and 11 low permeable) revealed M-2 and M-5 to be highly permeable.

In order to support the clinical development of regorafenib in the paediatric population a toxicological investigation in juvenile rats was performed (Study PH-37181). Toxicokinetic evaluation was performed after single dosing and after 20 days of treatment. At start of treatment, the animals were 15 days old. For toxicokinetic evaluation, the concentrations of regorafenib as well as the two major human plasma metabolites M-2 and M-5 were determined in plasma samples at 1.5, 4, 7 and 24 hours after administration. Toxicokinetics revealed no evidence of sex-related differences in exposure to regorafenib. A markedly more than dose proportional increase in AUC_{0-24} was observed for the high dose group, while C_{max} increased only slightly more than dose-proportional. No major changes were observed for C_{max} in the low and medium dose group between Day 1 and Day 20, while slightly higher C_{max} values were observed on Day 20 in the high dose group. A slight to moderate decrease in AUC_{0-24} between Day 1 and Day 20 was observed in the low and medium dose groups, while a slight increase was observed in the high dose group. On Day 20 C_{max} of M-2 and M-5 was low compared to exposure to regorafenib accounting for less than 1.2% compared to the respective C_{max} value of the parent compound in the respective dose group.

Studies on transporters (studies PH-37011 and PH-37006) indicated that the regorafenib metabolites M-2 and M-5 are most likely substrates of P-glycoprotein and BCRP.

M-2 at concentrations of 2 and 10 µM, is not a substrate for BCRP in BCRP-transfected MDCKII cells; however, as far as unbound concentrations are considered, an involvement of BCRP in the excretion of M-2 and M-5 cannot be excluded, and definitive answers on this interactions will be derived from clinical data.

IV administration of M2 or M5 to rats (studies PH-37018 and PH-37016) indicated that M-2 is not only eliminated by biotransformation to M-5 (via M-1) and M-8, but also excreted via bile and extra-biliary into the gut. Also M-1 and M-5 are secreted via bile and extra-biliary. In the gut, reduction by microbial gut flora results in the formation of regorafenib (out of M-2) and M-3 and M-4 (out of M-2 and M-5). M-4 was the most prominent component in faeces. These data indicated reduction of M-5 by microbial gut flora to M-4. Partly reabsorbed M-4 is further metabolized to M-6, which is finally biliary excreted into faeces.

The potential of regorafenib and its metabolites M-2 and M-5 to induce human CYP1A2, CYP3A4, and CYP2B6 mRNA expression was investigated in cultured human hepatocytes from three different human donors for 5 days (study PH-37214). The study revealed no inductive effect of regorafenib, M-2 and M-5 on human CYP1A2, CYP2B6, and CYP3A4 mRNA expression levels after repeated exposure.

The inhibitory potential of regorafenib and the two main metabolites M-2 and M-5 towards OCT1 and OCT3 was investigated in cultured hepatocytes (study PH-37023). The addition of regorafenib, M-2 and M-5 in the concentration range from 0.1 µM to 30 µM did not reduce the uptake of MPP+ (reference substrate for OCTs).

2.2.4. Toxicology

No additional single or repeated dose toxicity studies, genotoxicity and carcinogenicity, reproduction toxicity or local tolerance studies have been submitted.

Other toxicity studies

Regorafenib was administered orally (gavage) to groups of 12 male and 12 female Wistar rats per dose groups using a coprecipitate formulation with approximately 10 % regorafenib. Daily doses of 1, 2 and 4 mg/kg of regorafenib were administered over a period of approximately 3 weeks (from post natal day 15 to 35) with an application volume of 5 mL/kg. A control group of 12 males and 12 females was treated with the same volume of the vehicle only. Additional 12 males and 12 females were treated likewise at 0, 1, 2 or 4 mg/kg and were used as recovery groups undergoing necropsy 4 weeks after end of treatment (except both sexes of the highest recovery dose group, which were not treated on study day 20 and 21). Additional rats (12 per dose group and sex and 3 per control group and sex for blood sampling on day 1/2 and 6 animals per dose group and sex and 3 per control group and sex on day 20) were treated likewise and used for toxicokinetic evaluation. The major findings of the study are presented in the table below.

Table 1. Findings from Study PH-37181

Dose (mg/kg)	Findings	Cmax (µg/mL)
1	No changes in mortality, clinical signs or body weight **Hematology:** mild increase in ☐hemoglobine concentration (HB) and ☐haematocrit (HCT) in F, fully reversible at the end of the recovery period **Blood chemistry:** slight increase in total bilirubin (Bili-t) in M, fully reversible; slight decrease of protein in F **Organ weights:** reduction in absolute and relative liver weight in M, fully reversible at the end of the recovery phase; decrease in absolute and relative thymus weight in F, fully reversible **Histopathology:** diffuse hyperplasia with reduced goblet cells and inflammation in the cecum; starry sky macrophages in thymus in M	Day 1: 427 Day 20: 497
2	**Clinical Observations:** impaired general condition such as, high-stepping gait, piloerection, findings in nose in both sexes; GI effects (changed feces consistency in 1 F and distended abdomen in 1M, at necropsy); Mild to severe discoloration of teeth (12M, 2F) and severe findings in teeth, not reversible **Body weights:** slight to marked reduction in body weight in both sexes (the recovery groups were less affected than the main groups). Completely reversible in M and F **Hematology:** mild increase in erythrocyte count (ERY) in F and slight increase in neutrophil count (NEUTRO) in M, fully reversible at the end of the recovery period **Blood Chemistry:** minimal increase in Aspartate Aminotransferase (ASAT) in F, fully reversible; minimal to slight decrease of creatinine in M in the recovery phase; slight increase in Bili-t in F, fully reversible; slight decrease of protein in M **Necropsy:** thickened duodenum in 1M and 1F; change in small and large in testine at the end of the recovery period in 1M **Organ weights:** reduction in absolute and relative liver weight in F, fully reversible at the end of the recovery phase; decrease in absolute and relative thymus weight in M at the end of the treatment period, fully reversible; decrease in absolute and relative testes weight at the end of the treatment period, fully reversible at end of recovery phase. Increase in absolute and relative weights in brain, adrenal glands, lungs, kidneys, epididymides, prostate, seminal vesicles coagulation glands and ovaries **Histopathology:** slight or few changes observed at terminal sacrifice: hyperkeratosis in the forestomach; additionally gross dilation of duodenum (1 animal), minimal or slight inflammation or degeneration of crypts or glands; diffuse hyperplasia with reduced goblet cells and inflammation in the cecum, reduced germinal centers/lymphoid hyperplasia of peyer's patches in F; increased adipocyte content in sternal bone marrow. Starry sky macrophages in thymus in F; increased width of growth zones in bone marrow in few	Day 1: 929 Day 20: 1050

	animals; odontoblast degeneration and dentin alteration in teeth; flattened follicular epithelium of thyroid; degeneration of the germinal epithelium of testes	
4	**Mortality:** 2M killed in moribund state (squatting position, labored breathing, emaciation and piloerection, distended abdomen); 1F found dead and 1F killed in moribund state, on dosing day 20 (findings: high stepping gait, distended abdomen, emaciation, decreased feces excretion, decreased water intake, paleness and piloerection); 1F killed in moribund state on recovery day 25 (findings: high-stepping gait, sunken flanks, distended abdomen, emaciation and increased teeth grow on the day before death). All of these animals were assigned to the recovery group. Effects on the GI tract, adrenal glands, teeth and bones, spleen and chest cavity at necropsy **Clinical observations:** paleness, emaciation, labored breathing, squatting position and a decreased food and water intake in both sexes; effects on GI tract (changed feces consistency, distended abdomen in both sexes; diffuse hyperplasia and inflammation in the small and large intestine; decreased feces excretion in 5F) and teeth. During the recovery phase, the number of findings on teeth increased and increased urinary excretion **Body weights:** slight to marked reduction in body weight in both sexes (the recovery groups were less affected than the main groups). Completely reversible in F, still distinctly lower than in controls at the end of recovery in M **Hematology:** mild increase in erythrocyte count (ERY), HB and HCT in M fully reversible at the end of the recovery period; slight increase in neutrophil count (NEUTRO) in M and F; minimal increase still present at the M and F of the high dose at the end of recovery; slight increase of monocyte count (MONO) in M and F; trend towards reversibility **Blood Chemistry:** slight decrease of glucose and creatinine (GLUCOSE, CREA) in F **Necropsy:** Emaciation of all F and 9 out of 12 M. Discoloration of spleen in 1M and 3F. Reduction of thymus size in 2M, affected stomach areas in 4M and 7F. Change in small and large intestine consistency of both sexes and thickened duodenum in 10M and 12F; discoloration of bones in 6M, thickening of bones in 11M and discoloration of teeth in 11M and 8F **Organ weights:** decrease in absolute and relative testes weight at the end of the treatment period, fully reversible at end of recovery phase; decrease in absolute and relative heart weight in both sexes at the high dose at the end of treatment phase, fully reversible and not accompanied by any morphological change. Same alterations found in brain, lung, liver, spleen, kidney, thymus, testes, and epidymides at the end of the recovery phase **Histopathology:** Increased intercurrent mortality; Pronounced atrophy of lymphoid organs and bone marrow and emaciation (related to death or reduced general condition of the animals); emaciation and retarded development/atrophy of various organs (liver, kidneys, skin, muscle, pituitary, male and female genital organs, serous salivary glands); hypocellularity of bone marrow (related to reduced extramedullary hematopoietic activity in liver and spleen); atrophy in thymus, spleen and lymph nodes; hyperkeratosis in esophagus; increased height of the pyloric mucosa, ☐haemorrhage, inflammation, necrosis and atrophy in glandular stomach; degeneration and plump villi in the small intestine, hyperplasia of duodenum (secondary changes: inflammation and degeneration of the pancreas) and inflammation (mucosa and Brunner's glands) correlating to gross dilation; inflammation, reduced goblet cells and diffuse hyperplasia mainly in the cecum; prominent or hyperplastic bile ducts in the liver; starry sky macrophages in thymus in M and F flattened follicular epithelium of thyroid; degeneration of the seminiferous epithelium in testes; increased atretic follicles in ovaries. Delayed and impaired bones and teeth growth, with consequent gross discolorations of femur/knee, rib or teeth, and enlargement (femur/knee); increased width of cartilagineous growth zones in the bones, rarefaction and disorganization of primary spongiosa in long bone metaphyses, dentin alteration and rarefaction in the teeth, odontoblast and ameloblast degeneration. Cortical ☐haemorrhage and necrosis in the adrenal glands of several animals, secondarily to severe stress/severely reduced general condition.	Day 1: 1840 Day 20: 2610

The toxicokinetic parameters on Day 1 and Day 20 are shown in the following table.

Table 2. Study PH-37181: Toxicokinetic parameters on Day 1 and Day 20

Male&Female, Day 1

Dose	[mg/kg]	1		2		4	
Time [h]		gMean [µg/L]	gSD	gMean [µg/L]	gSD	gMean [µg/L]	gSD
1.5		216	1.50	310	2.54	854	1.55
4		427	1.34	817	1.43	1840	1.30
7		376	1.27	929	1.14	1430	1.10
24		340	1.13	657	1.12	1390	1.18

Parameter	Unit			
AUC(0-tlast)	µg·h/L	8260	17600	32800
AUC(0-tlast)norm	kg·h/L	8.26	8.81	8.21
tlast	h	24.0	24.0	24.0
Cmax	µg/L	427	929	1840
Cmax,norm	kg/L	0.427	0.465	0.460
tmax	h	4.00	7.00	4.00
C(tint)/Cmax	%	79.6	70.7	75.4
t(int)	h	24.0	24.0	24.0

Male&Female, Day 20

Dose	[mg/kg]	1		2		4	
Time [h]		gMean [µg/L]	gSD	gMean [µg/L]	gSD	gMean [µg/L]	gSD
1.5		497	1.42	982	1.44	2310	1.61
4		437	1.24	1050	1.66	2610	1.59
7		377	1.41	767	1.61	2560	1.36
24		41.4	1.49	117	2.99	823	2.20

Parameter	Unit			
AUC(0-tlast)	µg·h/L	5340	11900	41700
AUC(0-tlast)norm	kg·h/L	5.34	5.93	10.4
tlast	h	24.0	24.0	24.0
Cmax	µg/L	497	1050	2610
Cmax,norm	kg/L	0.497	0.525	0.652
tmax	h	1.50	4.00	4.00
C(tint)/Cmax	%	8.3	11.2	31.5
t(int)	h	24.0	24.0	24.0
RA-AUC(0-tlast)	%	64.7	67.3	126.9
RA-Cmax	%	116.2	113.0	141.8

raw data ID: 1

2.2.5. Ecotoxicity / environmental risk assessment

The table below summarises the main results from the ERA.

Table 3. Summary of main study results

Substance (INN / Invented Name):			
CAS-number (if available):			
PBT screening		Result	**Conclusion**
Bioaccumulation potential- log P_{ow}	OECD117	3.9 at pH 7.0	See below
PBT-assessment			
Parameter	**Result relevant for conclusion**		**Conclusion**
Bioaccumulation	log P_{ow}	3.9 at pH 7.0	see OECD 305 study
	BCF	> 2000	B
Persistence	DT50 or ready	DT50 = 181 days	P

	biodegradability				
Toxicity	NOEC	<0.14 µg/L (Fish toxicity)			T
PBT-statement :	The compound is considered as PBT				
Phase I					
Calculation	**Value**	**Unit**			**Conclusion**
PEC $_{surfacewater}$	0.0112 (proposed by the Applicant)	µg/L			> 0.01 threshold Y
Other concerns (e.g. chemical class)					N
Phase II Physical-chemical properties and fate					
Study type	**Test protocol**	**Results**			**Remarks**
Adsorption-Desorption	OECD 121	K_{oc} = 5.6			
Ready Biodegradability Test	OECD 301F	Not Readily biodegradable			
Aerobic and Anaerobic Transformation in Aquatic Sediment systems	OECD 308	$DT_{50, water}$ < 1 day $DT_{50, sediment}$ = infinite $DT_{50, whole\ system}$ = infinite % shifting to sediment = ca 100%			Because of the lack of relevant biodegradation, the test item is assumed to accumulate in the sediment.
Phase IIa Effect studies					
Study type	**Test protocol**	**Endpoint**	**value**	**Unit**	**Remarks**
Algae, Growth Inhibition Test/*Species*	OECD 201	NOEC	1.3	µg/L	*Desmodesmus subspicatus*
Daphnia sp. Reproduction Test (New study for extension)	OECD 211	NOEC	10.5	µg/L	
Fish, Early Life Stage Toxicity Test/*Species*	OECD 210	NOEC	<0.14	µg/L	*Pimephales promelas*
		EC_{10}	0.043		
Activated Sludge, Respiration Inhibition Test	OECD 209	NOEC	> 40000	µg/L	
Phase IIb Studies					
Bioaccumulation	OECD 305	BCF	2653-4102		%lipids: 6 > 2000 (B)
Aerobic and anaerobic transformation in soil	OECD 307	DT50	181 days		1 sandy loam soil
Soil Micro organisms: Nitrogen Transformation Test	OECD 216	No inhibition	1000	mg/kg	
Terrestrial Plants, Growth Test/*Species*	OECD 208	NOEC	100	mg/kg	Zea mays, Rhaphanus sativus, Pisum sativum
Earthworm, Acute Toxicity Tests	OECD 207	NOEC	100	mg/kg	*Eisenia fetida*
Collembola, Reproduction Test	OECD 232	NOEC	100	mg/kg	*Folsomia candida*
Sediment dwelling organism	OECD 218	NOEC	1.25	mg/kg	*Chironomus riparius*

2.2.6. Discussion on non-clinical aspects

Treatment with regorafenib resulted in significant reduction of tumour volume. Cessation of treatment resulted in regrowth of the tumours, but these were not regorafenib resistant, as subsequent re-challenge showed similar efficacy as the first round of treatment. The pre-clinical PD study together with the previously demonstrated anti-tumour activity indicates that regorafenib may be efficacious in the treatment of GIST.

As shown by *in vitro* results, regorafenib and its metabolites M-2 and M-5 are not inducers of human CYP1A2, CYP2B6 and CYP3A4.

In humans, it can be postulated that M-5 is eliminated from plasma by biliary and to a smaller extent by extra-biliary secretion into the gut, and that pyridine M-4 can be formed by reduction of pyridine N-oxide M-5 by microbial gut flora. Furthermore, a proportion of M-5 is converted most likely via M-4 into the carboxylic acid M-6.

M-2 and M-5 show a high permeability in *in vitro* Caco-2 assay.

Thus, drugs that are inhibitors of P-glycoprotein and BCRP could lead to drug-drug interactions with regorafenib (inhibition of the excretion of M-2 and M-5 excretion via P-glycoprotein and BCRP).

Regorafenib, M-2 and M-5 at clinically relevant concentrations are not inhibitors of OCT1 and OCT3. Based on these results, no drug-drug interactions due to the inhibition of OCT1 and OCT3 by regorafenib and its two main metabolites are expected.

The submitted juvenile toxicity study design was described in the Paediatric Investigational Plan as suggested and agreed with the PDCO of the EMA. As expected from the previously conducted repeated dose toxicity studies in adult animals, dosing with regorafenib resulted in a multitude of adverse effects, some of which were not fully reversible. Apart from the known toxicity in adults, the juvenile toxicity study indicated that paediatric patients will also be susceptible to adverse effects in bone, teeth and development of sexual organs. It should be noted that the major metabolites in rats (M-3 and M-4) are only present in trace amounts in humans. As the metabolites could be (partially) responsible for the adverse effects observed, relevance for humans is uncertain.

The MAH's proposal to refine the Fpen based on EU incidence data is not in compliance with EMA guidelines. Concerns about refinement of Fpen already expressed at the time of the Stivarga initial marketing authorization application are still valid. In particular, the MAH should provide reasonably justified market penetration data and therefore should consider to calculate differently refined PECsurfacewater. One option to be considered would be the following: PECsurfacewater calculation (refined according to GLOBOCAN2008 5-years prevalence data): Fpen = 5-years prevalence/EU2008 population = 924,835/497,659,810 = 0.0019 PECsurfacewater = DOSEai x Fpen / WASTEinhab*DILUTION factor = 160mg*0.0019 / 200*10 = 0.000152 mg/L = 0.152 µg/L.

Accordingly to EMA guidelines, PECgroundwater is PECsurfacewater * 0.25 = 0.0375 µg/L. PECsurfacewater resulting from the extension to GIST cancer (0.00774 µg/L) should then be added to this figure and PNECs calculated accordingly.

A new experiment on Daphnia sp. Reproduction Test (PH-37250) has been provided thus fixing the deviations from the guidelines identified in the initial Stivarga marketing authorisation application.

Moreover, as already highlighted at that time, deviations from the guidelines occurred in the exposure to the test substance in Earthworm, Acute Toxicity Tests, as a consequence of the poor solubility of the test molecule this was directly mixed to soil samples. However, OECD 207 defines a different protocol in case a substance is not readily soluble in water: "The test substance is dissolved in water (if soluble up to a concentration of 1000 mg/l) or in a suitable organic solvent (e.g. acetone, hexane or chloroform), as appropriate, to give a range of known concentrations".

An increasing weight effect has been recorded in fish and seedling plant toxicity tests that can be referred to the tested substance regorafenib.

At the time of the initial marketing authorisation, the CHMP recommended 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).

The results of these studies are still pending and the MAH committed to submit them by November 2014.

2.2.7. Conclusion on the non-clinical aspects

The non-clinical studies submitted by the MAH are conducted according to the current scientific guidelines and support the sought indication.

A conclusion on the environmental risk of regorafenib is not possible at present. The requested phase II studies OECD 106, OECD 201, OECD 210 and OECD 211 are still pending and the MAH committed to submit them by November 2014.

2.3. Clinical aspects

2.3.1. Introduction

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.

2.3.2. Pharmacokinetics

For the current application in GIST, PK data of regorafenib was obtained in the investigator sponsored study 14935 (PK intensive data) and in the pivotal phase 3 study 14874 (sparse PK data). Furthermore, the original popPK analysis based on study 14387 in mCRC was updated with data from the pivotal study 14874 and an exploratory exposure-response analysis for both efficacy and safety was conducted for the Phase 3 study 14874 separately, and in addition, a combined exploratory exposure-response analysis for safety was conducted for both Phase 3 studies 14874 and 14387.

Steady-state pharmacokinetics of regorafenib and metabolites were analysed in a phase 2 study 14935 in patients with histologically-confirmed metastatic and/or unresectable GIST with progression while receiving imatinib, or intolerance to imatinib, and prior failure of sunitinib due to disease progression. Blood samples for PK analysis of regorafenib and metabolites M-2, M-4, and M-5 were collected on Day 15 of cycle 1 at the following times: pre dose, 0.5, 1, 2, 3, 6 and 24 hours post-dose. 16 patients were valid for PK analysis.

Table 4 below summarizes the PK parameters of the parent compound regorafenib and its metabolites M-2 and M-5 in plasma determined after multiple doses.

Table 4. Study 14935 – Pharmacokinetic parameters of regorafenib and its metabolites M-2 and M-5 in plasma after multiple oral administration of regorafenib 160 mg once daily (Cycle 1, Day 15)

Geometric means (%CV)
n=16 men and women with GIST

Analyte	$AUC(0\text{-}24)_{ss}$ [mg·h/L]	$C_{max,ss}$ [mg/L]	$t_{max,ss}$ [1] [h]
Regorafenib	59.73 (63%)	3.96 (61%)	2.0 (0 – 24)
M-2	33.56 (110%)	2.07 (106%)	2.0 (0 – 24)
M-5 [2]	18.10 (145%)	1.17 (140%)	1.3 (0 – 24)

Source: Module 5.3.5.2, R-8715
[1] median (range)
[2] not yet at steady state

As PK data was collected on Day 15 of Cycle 1, regorafenib and M-2 are expected to be in steady state, whereas M-5 steady state concentrations are not yet achieved due to the longer half-life.

A combined exploratory exposure-response analysis for safety was conducted for both Phase 3 studies 14874 and 14387.

Study 14387 was a pivotal phase III study to evaluate the clinical efficacy and safety of regorafenib in patients with metastatic colorectal cancer who have progressed after failure of standard therapy. Study 14874 was a pivotal Phase 3 study (efficacy and safety) in patients with metastatic and/or unresectable gastrointestinal stromal tumours (GIST) whose disease had progressed despite prior treatments with at least imatinib and sunitinib.

All subjects from the phase III studies 14387 and 14874, being treated with the investigational drug (regorafenib was administered at 160 mg od p.o., 3 weeks on therapy followed by 1 week off therapy to comprise a cycle of 4 weeks, plus BSC) and being valid for PK evaluation were included in the population PK analysis. The total number of patients used for modelling was 381 from study 14387 and 80 from study 14874.

A two-stage approach was applied: first parent regorafenib was described. Subsequently the model and individual PK parameters (Empirical Bayes Estimate or EBE) of parent regorafenib were fixed and used as input to describe the PK of the metabolites. A covariate analysis was performed investigating a set of prespecified covariates by means of forward inclusion and backward deletion and applying statistical criteria. The sparse sampling in the phase III studies allowed estimation of interindividual variability on only one PK parameter per analyte. All variability was assumed to be on CL, KM-M2 and FRM5, which determine the elimination or formation of the analytes and thereby directly influence their exposure. Factors affecting the PK of regorafenib, M-2 and M-5 were investigated in Studies 14387 and 14874. In the analysis, the impact of the variability in the continuous covariates is shown by simulating both Cav,md in a typical subject with the median value for a covariate and the exposure in subjects with the 5th and 95th percentile of that covariate. For all other covariates, the median covariate values are assumed. The results are then compared to the overall variability in exposure.

The population PK model was used to evaluate intrinsic factors on the PK of regorafenib, M-2 and M-5 (study, sex, body weight, BMI, body height, age, race, as well as baseline values of the following parameters: estimated glomerular filtration rate, plasma albumin, plasma total protein, haematocrit, hemoglobin, and liver function parameters [total bilirubin, ALT, AST, alkaline phosphatase] and hepatic function categories). Of the evaluated covariates, study, BMI and bilirubin significantly influenced regorafenib CL.

These covariates also influenced the PK of the metabolites through their effect on parent regorafenib. In addition, study, race (Asian or Caucasian) and body weight were determined to have significant effects on the PK parameters KM-M2 (Michaelis constant of M-2) and FRM5 (fraction of total cleared M-2 transformed to M-5) of the population PK model. Sex had a significant effect on FRM5, whereby it only affected the PK of M-5. The median exposure of M2 and M5 was higher in Caucasians than in Asians and the median exposure of M5 was higher in females than in males

Other tested covariates (age, height, glomerular filtration rate, plasma albumin, total plasma protein, hepatic function category and hepatic function parameters [ALT, AST and alkaline phosphatase]) were not significant. Considerable variability remained in exposure of regorafenib after taking into account the effects of the significant categorical covariates (study, race and sex). All covariates with significant effect had a relatively minor impact on exposure compared to this remaining variability which could not be explained by covariates. As a result, the exposure ranges for the various covariate combinations show high overlap.

An exposure-response efficacy analysis of regorafenib in phase III study 14874 has been submitted. The primary exposure parameter was the population PK model-derived average concentration over a 24 h dosing interval after 21 daily doses of 160 mg (Cav,md). Cav,md reflects individual differences in the pharmacokinetic parameters of regorafenib and its pharmacologically active metabolites M2 and M5 without taking into account differences in individual dosing. The goal of the first part of this analysis was to describe the exposure-response relationships of regorafenib and its active metabolites in patients of Study 14874 with regard to the following parameters: PFS, OS, and ODC objective disease control rate); patients whose best response was not progressive disease (ie complete response, partial response or stable disease), using survival analysis and logistic-regression analysis. The goal of the second part of this analysis was to describe the exposure-response relationship of regorafenib with the tumour dynamics in patients of Study 14874.

No evidence was found for an exposure-response relationship for PFS and ODC or tumour dynamics with 160 mg regorafenib given in 3 weeks-on / 1 week-off dose regimen in Study 14874. Preliminary data for OS suggest that OS was longer for patients with higher total Cav,md Data for OS were preliminary in the sense that data collection for OS was ongoing at the database cut-off date. As a result, the dataset used for this analysis contained only 13 uncensored events. Therefore, any conclusions from this analysis with regard to OS should be considered as highly tentative and smaller baseline sum of tumour diameters.

2.3.3. PK/PD modelling

PH- 37281 Exploratory analysis of relationship between the exposure to regorafenib parent compound, regorafenib aggregate, and regorafenib total and relevant safety data for pooled data from GRID (Study 14874) study.

The objectives of the exploratory analyses were to explore a relationship between regorafenib (the population pharmacokinetic (Pop PK) model-derived Cav,md exposure estimate) and selected commonly occurring adverse events (AEs) in Study 14874.

For regorafenib parent compound, the only consistent exposure-dependent increase was seen for rash, total bilirubin and median indirect bilirubin. The incidence of rash increased with increasing exposure from 15.0% to 60.0%.Total bilirubin increased with increasing parent exposure from 20.0% to 60.0% (this trend was observed for grades 1, 2, and 4). Over the course of the study, mean indirect bilirubin showed tendencies towards an increase with increasing parent exposure. Regarding the correlation between the relevant safety parameters and aggregate exposure (Cav,md; micromol/L) divided into

quartiles of aggregate exposure during the study, there was a slight exposure-dependent increase in the grade 3 incidence of “any adverse event” category (from 60% in first quartile to 80% in fourth quartile).

Similar to the parent, there was no notable exposure-dependent increase in the overall incidence of all grades of analyzed AEs with increasing aggregate exposure except for total bilirubin and mean indirect bilirubin.

The incidence of diarrhea increased with increasing aggregate exposure from 40.0% to 65.0% which was mainly due to differences in grade 1 diarrhea. The incidence of rash increased from 15.0% to 65.0%. There was a slight trend for increased grade 3 hypertension with increasing aggregate exposure (from 15 to 40%) although the overall incidence did not show a clear trend towards increasing frequency with increasing exposure. Total bilirubin increased with increasing aggregate exposure from 20.0% to 60.0% which was mainly driven by an increase in grade 1. Over the course of the study, mean indirect bilirubin showed a tendency towards an increase with increasing aggregate exposure.Similar to parent, there was an exposure-dependent increase in the grade 3 incidence of “any adverse event” category.

Of note, similar to parent, no increase in AST and ALT was observed with increasing exposure; the highest incidence of grade 1 ALT and AST was reported for the lowest quartile of aggregate exposure.

The incidence of rash increased with increasing total exposure from 5.0% to 50.0%. The incidence diarrhea increased with increasing total exposure from 35.0% to 75.0% which is mainly driven by an increase in grade 1 and grade 3 diarrhea. The incidence of hypertension increased with increasing total exposure from 60.0% to 80.0% which was mainly driven by an increase of grade 3 hypertension. The incidence of hemorrhage increased with increasing total exposure from 0% to 25.0% mainly due to grade 1 hemorrhage (however, only 6 grade 1 events, and 9 events overall were reported).Total bilirubin increased with increasing total exposure from 15.0% to 40.0%. Over the course of the study, mean indirect bilirubin showed a tendency towards an increase with increasing total exposure.

Similar to parent and aggregate, there was a slight exposure-dependent increase in the grade 3 incidence of “any adverse event” category with increasing total exposure, except for a lower incidence in 3rd quartile. Of note, similar to parent and aggregate, no increase in AST and ALT was observed; the highest incidence of grade 1 ALT and AST increase was reported for the lowest quartile of total exposure.

PH-37105 Exploratory analysis of relationship between the exposure to regorafenib parent compound, regorafenib aggregate, and regorafenib total and relevant safety data for pooled data from CORRECT (study 14387) GRID (Study 14874)

The objectives of the exploratory analyses were to explore a relationship between exposure to regorafenib parent compound, aggregate regorafenib (regorafenib parent compound and its two active metabolites M-2 and M-5 adjusted for protein-binding), and total regorafenib (regorafenib parent compound and its two active metabolites M-2 and M-5 without adjustment of protein binding) and relevant safety data.

The data comparing the exposure to regorafenib parent compound, regorafenib aggregate, and regorafenib total and relevant safety data suggest no notable exposure-dependent increase in the total incidence of any AE, any SAE, diarrhoea, mucositis, HFSR, hypertension, haemorrhage, elevated ALT, elevated AST, platelets, and proteinuria. For regorafenib parent compound, regorafenib aggregate, and regorafenib total, there was no consistent exposure-dependent increase in the total incidence of Grade 4/5 or SAE outcomes. A mild trend toward an increasing frequency of AEs with increasing exposure

was noted for indirect bilirubin, total bilirubin, and rash. Causality between elevated bilirubin and regorafenib exposure cannot be determined from these data, as total bilirubin at baseline was found to influence regorafenib exposure The incidence of elevated total bilirubin and mean and median indirect bilirubin values increased with increasing Cav,md quartile for regorafenib parent, regorafenib aggregate, and regorafenib total. This observation could be attributed to inhibition of bilirubin glucuronidation by regorafenib, as in vitro studies have shown regorafenib (and its metabolites) to be a potent inhibitor of UGT1A1 and UGT1A9. However, it should also be noted that increased total bilirubin (which could indicate impaired liver function) at baseline in Study 14387 was associated with increased regorafenib levels, based on the population PK analysis.

2.3.4. Discussion on clinical pharmacology

The median exposure of regorafenib, M2 and M5 was higher in study 14387 than in study 14874. The median exposure of M2 and M5 was higher in Caucasians than in Asians and the median exposure of M5 was higher in females than in males. There was no evidence for any additional intrinsic factors impacting the PK of regorafenib, M2 or M5. All significant covariate effects had a relatively minor impact on exposure compared to the remaining unexplained variability. Therefore, the clinical relevance of the identified covariate effects is limited. The impact of all significant covariates for exposures of regorafenib and two metabolites was small compared to the remaining variability.

In the phase 3 study 14874, exposure-efficacy analysis indicated that regorafenib, aggregate, or total (regorafenib+M-2+M-5) exposure was not predictive for efficacy: no impact of exposure on PFS, OS or ODC was observed in the exposure range of study 14847. This suggests that there is little risk of underexposure at the proposed dosing. This was further supported that patients in the regorafenib group who had dose reduction did not have a shorter PFS than patients without dose reduction.

The PK of regorafenib, M-2 and M-5 are comparable in GIST patients as PK in the original application in mCRC and other cancer patients.

Consistent with the exposure-toxicity correlations observed in mCRC patients, an exposure-dependent increase was seen for rash, total bilirubin and median indirect bilirubin in GIST patients. Newly observed in study 14874 was the correlation between grade 3 AEs diarrhea and the total exposure regorafenib and metabolites

2.3.5. Conclusions on clinical pharmacology

In conclusion, no additional intrinsic factors impacting the PK of regorafenib, M2 or M5 nor a clear relationship between drug/metabolite exposure and efficacy parameters or safety data have been identified from the new pharmacological data submitted.

2.4. Clinical efficacy

2.4.1. Dose response study

No dose-response studies were submitted (see discussion on clinical efficacy).

2.4.2. Main study

Study 14874 (GRID)

Study 14874 was a pivotal multi-centre, multi-national, randomised, double-blind, placebo-controlled phase III trial comparing regorafenib plus best supportive care (BSC) versus placebo plus BSC in patients with metastatic and/or unresectable GIST who experienced disease progression or intolerance to imatinib, as well as disease progression while on sunitinib therapy.

Methods

Study participants

The GRID study population included patients with histologically confirmed metastatic and/or unresectable GIST, who experienced disease progression or intolerance to imatinib, as well as disease progression while on sunitinib therapy. Additionally disease progression after other therapies was allowed, with the exception of prior treatment with any other VEGFR inhibitor. According to the inclusion criteria, patients were required to have an ECOG Performance Status score of 0-1, age ≥ 18 years, measurable disease according by modified RECIST criteria (version 1.1) and adequate bone marrow, renal and hepatic functions.

Patients with symptomatic brain metastases or meningeal tumours were excluded as well as patients with pheochromocytoma, or with seizure disorders requiring medication. 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-arrythmic therapy (except beta blockers or digoxin), venous thrombotic events within 3 months before start, any diathesis bleeding or haemorrhage or bleeding ≥ CTCAE grade 3 within 4 weeks, healing wound, ulcer or bone fracture, persistent proteinuria of CTCAE grade≥3. Patients with interstitial lung disease with ongoing symptoms at the time of screening, with left ventricular ejection fraction (LVEF) <50%, with any malabsorption condition, with persistent proteinuria of NCI-CTCAE version 4.0 >grade 2, or either pleural effusion or ascites that caused respiratory compromise (>NCI-CTCAE version 4.0 grade 2 dyspnoea) were not allowed to participate to the study.

Treatments

A total of 199 patients were randomised (2:1) to receive either regorafenib or matching placebo 160 mg (4 x 40 mg tablets) OD orally for 3 weeks followed by 1 week off therapy (cycle of 4 weeks) plus BSC. Regorafenib or placebo has 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 grade <3 (or <2 in case of hand-foot syndrome [HFS]).

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/immune/radio-therapy.

Patients were treated until disease progression according to RECIST 1.1 (per blinded central radiology review), clinical progression, unacceptable toxicity, and/or consent withdrawal. Tumour assessments were performed every 4 weeks for the first 3 months, every 6 weeks for the subsequent 3 months, and every 8 weeks until the end of study drug administration. After central review had assessed the patients as having progressive disease (PD), patients had the option of entering an open-label phase and receiving treatment with regorafenib irrespective of the randomised treatment (regorafenib or

placebo) received. Upon discontinuation of study drug patients were followed up for survival every 3 months, with the exception of patients who specifically withdrew consent.

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 not allowed.

Objectives

The primary objective of the study was to show superiority of regorafenib plus BSC versus placebo plus BSC in terms of Progression Free Survival (PFS) as assessed by independent radiological review (IRC).

Secondary objectives included comparison between the two study arms of Overall Survival (OS), time to progression (TTP), objective tumour response rate (ORR), disease control rate (DCR, where stable disease must be at least 12 weeks in duration) and duration of response.

Exploratory objectives were evaluation of health related quality of life (according to the EORTC QLQ C30 and EQ 5D questionnaires), secondary PFS, exposure-response relationship, safety and pharmacokinetics. A biomarker analysis was also included as exploratory.

Outcomes/endpoints

The primary study endpoint was PFS, defined as the time from randomization to the date of first observed radiological progression per blinded central radiology review, or death due to any cause, if death occurred before progression. The actual date of radiological assessments was used for the calculation. Patients without tumour progression or death at the time of analysis were censored at their last date of radiological tumour assessment.

Secondary endpoints included OS (defined as the time from randomization to death due to any cause), TTP (defined as the time from randomization to radiological progression), ORR (defined as the percentage of patients with complete response [CR] or partial response [PR] according to RECIST 1.1 criteria), DCR (defined as the percentage of patients with CR, PR or stable disease [SD]) and duration of response.

Exploratory endpoints included evaluation of health related quality of life. 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) were considered as clinically meaningful.

Other exploratory endpoints included secondary PFS (defined as the time from first progression until second progression or death, during or after open-label treatment with regorafenib), exposure-response relationship, safety and pharmacokinetics.

All efficacy variables related to tumour response and disease progression were evaluated by central radiology evaluation based on RECIST, version 1.1 with the following modifications: no lymphonodes and no bone lesions were chosen as target lesions, and PET scan was not considered acceptable for radiological evaluation. Moreover, a progressively growing new tumour nodule within a pre-existing tumour mass must be expanding on at least two sequential imaging studies or must be at least 2 cm in

size and a new active lesion (e.g. enhancing with contrast or other criteria to rule out artifact) in order to be considered as evidence of progression.

Sample size

The sample size was based on the primary efficacy endpoint of PFS. Assuming a one-sided alpha of 0.01, a power of 90%, a 100% increase in median time of PFS, and an allocation ratio of 2:1 between the experimental and the control arm, approximately 122 events were required. Based on the over-recruitment of 29 patients to 199 total randomised patients, the target number of PFS events was increased to approximately 144 to maintain the grade of maturity of the study. The power to detect an improvement in PFS of 100% was increased from 90% to 94%. No interim analyses for efficacy or futility were planned for the primary efficacy endpoint PFS.

At the time of the final PFS analysis, an interim analysis of the secondary efficacy endpoint OS was designed. The O'Brien Fleming-type alpha spending approach was used for the determination of the significance thresholds, in order to control the overall 1-sided alpha for OS at 0.025 level or less. The final analysis of OS was planned when approximately 160 events have been observed which provides 84% power to detect a 67% increase in median time to death from 6 months in the control arm to 10 months in the experimental arm.

Randomisation

Patients were assigned randomly in a 2:1 ratio to receive either regorafenib plus BSC or placebo plus BSC. They were stratified by the following factors: 3rd versus 4th line therapy or beyond and geographical region (Asia versus rest of the world).

Blinding (masking)

This was a double-blind study.

Statistical methods

The primary population for the efficacy analysis is the Full Analysis Set (FAS), which is identical to the ITT analysis set and is defined as all randomised patients.

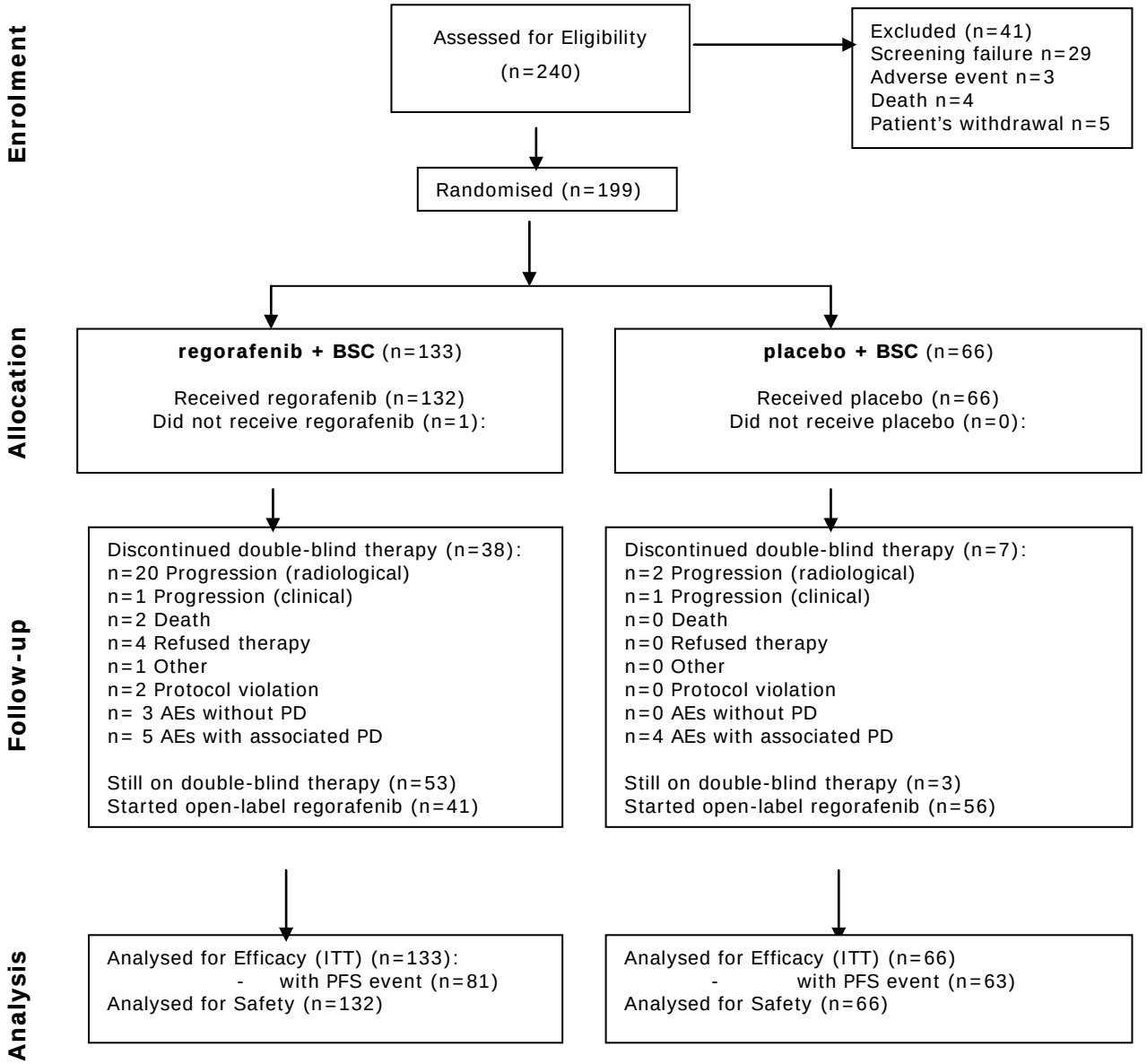
The PFS of the two treatment groups (regorafenib vs placebo) was compared using a stratified log rank test with a one-sided alpha of 0.01 stratified by the same stratification factors as used for randomization. The hazard ratio of regorafenib over placebo and its 98% CI was calculated using a stratified Cox model by the same stratification factors as used for randomisation.

Sensitivity analyses were performed as supportive to the primary PFS analysis. These included, a PFS comparison considering only the first 122 PFS events as initially planned in the protocol, PFS un-stratified analyses and PFS analyses based on local investigators assessment. Moreover, the times to first, second, etc. tumour evaluations were displayed using Kaplan-Maier curves.

Subgroup Analyses based on descriptive statistics, log-rank test p-values and hazard ratio estimates with 95% and 98% CIs for PFS were performed considering as stratification levels, age, ECOG performance status, duration of treatment with imatinib, geographical region and some subgroups with defined mutations.

Results

Participant flow



Recruitment

From January to August 2011, a total of 199 patients were randomised. A total of 57 centres across 17 countries enrolled 240 patients: Germany (32 [16%]), USA (26 [13%]), Italy (20 [10%]), France (19 [9.5%]), Japan (17 [8.5%]), South Korea (16 [8%]). All other countries had < 12 patients each.

Conduct of the study

The original study protocol dated 05 October 2010 was subsequently amended 3 times.

Amendment 1 (dated 09 February 2011) essentially implemented modified RECIST version 1.1 for evaluation of tumor progression, clarified the maximum of dose reductions allowed (two), permitted (or not) concomitant medications, study procedures during follow-up periods.

Amendment 2 (dated 26 July 2011) essentially included recommendations for monitoring of liver function and for rehydration if clinically indicated in case of diarrhea, mucositis anorexia, and clarifications regarding adverse events of special interest and hand-foot syndrome.

Amendment 3 (dated 27 September 2011) increased the number of PFS (form 122 to 144) and OS events required for analyses due to the increased current number of randomized patients (199 instead of the planned 170). Moreover, the possibility to receive open-label regorafenib after disease progression was included.

Protocol deviation/violations were reported in 80% (107) of patients treated with regorafenib and 74% (49) of patients treated with placebo. However, major protocol deviations were reported in 7.5% and 6% of patients in the regorafenib and placebo arms, respectively. Major procedural protocol deviations were primarily a failure to complete Quality of life questionnaires.

Baseline data

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

Table 5. Baseline and Demographic Characteristics in 14874 study (FAS)

Characteristic	Placebo + BSC N = 66 n (%)	Regorafenib 160mg + BSC N = 133 n (%)	Total N = 199 n (%)
Sex			
Male	42 (63.6%)	85 (63.9%)	127 (63.8%)
Female	24 (36.4%)	48 (36.1%)	72 (36.2%)
Age (years) at enrollment			
Mean (range)	58.1 (25 – 87)	58.2 (18 – 82)	58.2 (18 – 87)
Median	61.0	60.0	60.0
Age group (years)			
<65	46 (69.7%)	90 (67.7%)	136 (68.3%)
≥65	20 (30.3%)	43 (32.3%)	63 (31.7%)
Race / ethnic group			
White	45 (68.2%)	90 (67.7%)	135 (67.8%)
Black or African American	1 (1.5%)	0	1 (0.5%)
Asian	16 (24.2%)	34 (25.6%)	50 (25.1%)
Not reported	4 (6.1%)	7 (5.3%)	11 (5.5%)
Missing	0	2 (1.5%)	2 (1.0%)
Geographic region			
Asia	15 (22.7%)	32 (24.1%)	47 (23.6%)
Rest of world	51 (77.3%)	101 (75.9%)	152 (76.4%)
Geographic region			
North America	14 (21.2%)	22 (16.5%)	36 (18.1%)
USA	11 (16.7%)	15 (11.3%)	26 (13.1%)
Canada	3 (4.5%)	7 (5.3%)	10 (5.0%)
Non-North America	52 (78.8%)	111 (83.5%)	163 (81.9%)
Time since initial diagnosis to randomization			
Mean (range), weeks	310.6 (47.0–657)	296.4 (32.3–774)	300.9 (32.3–774)
Median, weeks	272.2	256.0	265.4
Time since recent progression/relapse to randomization			
Mean (range), weeks	16.71 (0.4–421)	13.29 (0.7–145)	14.42 (0.4–421)
Median, weeks	4.27	6.34	5.84
ECOG performance status			
0	37 (56.1%)	73 (54.9%)	110 (55.3%)
1	29 (43.9%)	60 (45.1%)	89 (44.7%)
Baseline BMI Group			
Missing	2 (3.0%)	7 (5.3%)	9 (4.5%)
<25 kg/m2	37 (56.1%)	75 (56.4%)	112 (56.3%)
25 to <30 kg/m2	19 (28.8%)	37 (27.8%)	56 (28.1%)
≥ 30 kg/m2	8 (12.1%)	14 (10.5%)	22 (11.1%)
Mutation biomarkers (historical data)[a]			
Not assessed/not available	30 (45.5%)	73 (54.9%)	103 (51.8%)
Any assessed information	36 (54.5%)	60 (45.1%)	96 (48.2%)
KIT Exon 11 mutation	17/36 (47.2%)	34/60 (56.7%)	51/96 (53.1%)
KIT Exon 9 mutation	6/36 (16.7%)	9/60 (15.0%)	15/96 (15.6%)
WT [No KIT and no PDGFRα mutation]	2/36 (5.6%)	6/60 (10.0%)	8/96 (8.3%)
Extent of disease at baseline			
Metastatic	38 (57.6%)	90 (67.7%)	128 (64.3%)
Unresectable	10 (15.2%)	5 (3.8%)	15 (7.5%)
Metastatic and unresectable	14 (21.2%)	35 (26.3%)	49 (24.6%)
missing	4 (6.1%)	3 (2.3%)	7 (3.5%)
Histology			
missing	4 (6.1%)	5 (3.8%)	9 (4.5%)
Spindle cells	30 (45.5%)	66 (49.6%)	96 (48.2%)
Epithelioid	4 (6.1%)	12 (9.0%)	16 (8.0%)
Mixed	10 (15.2%)	18 (13.5%)	28 (14.1%)
Unknown	18 (27.3%)	32 (24.1%)	50 (25.1%)
Number of tumor sites			
1	9 (13.6%)	16 (12.0%)	25 (12.6%)
2	20 (30.3%)	31 (23.3%)	51 (25.6%)
3	13 (19.7%)	39 (29.3%)	52 (26.1%)
4	9 (13.6%)	21 (15.8%)	30 (15.1%)
≥ 5	15 (22.7%)	26 (19.5%)	41 (20.6%)
Duration of treatment with imatinib			
< 6 months	4 (6.1%)	18 (13.5%)	22 (11.1%)
6 to <18 months	7 (10.6%)	26 (19.5%)	33 (16.6%)
≥ 18 months	55 (83.3%)	89 (66.9%)	144 (72.4%)
Prior anti-cancer drug group			
3rd line	39 (59.1%)	74 (55.6%)	113 (56.8%)
4th line and beyond	27 (40.9%)	59 (44.4%)	86 (43.2%)

a: This is information reported in the CRF (ie. not based on data from tissue submitted for the study biomarker analysis).

Numbers analysed

Table 6. Analysis sets

Analysis set	Placebo + BSC	Regorafenib+BSC	Total
SAF[a]	66 (100.0%)	132 (99.2%)	198 (99.5%)
FAS	66 (100.0%)	133 (100.0%)	199 (100.0%)
PRO[b]	62 (93.9%)	123 (92.5%)	185 (93.0%)

FAS = Full analysis set; SAF = safety analysis set; PRO = Patient reported outcomes
a: One patient in the regorafenib group was not treated with study drug.
b: Four patients from the placebo group and 10 patients from the regorafenib group did not complete the questionnaire.

Outcomes and estimation

Primary endpoint

The efficacy results in terms of the primary endpoint of PFS (cut-off date January 26, 2012) are presented in the table 7 and figures 1 and 2.

Table 7. Progression-free survival-144 PFS events, double-blind period, central assessment (FAS)

	Placebo + BSC	Regorafenib + BSC
Patients randomised	66	133
Progressive disease or died	63 (95.5%)	81 (60.9%)
Censored	3 (4.5%)	52 (39.1%)
Progression free survival (days)		
Median (95% CI)	28 (28, 32)	147 (122, 173)
Log-rank p-value (stratified)	<0.000001	
Hazard ratio (95% CI)	0.268 (0.185, 0.388)	

Figure 1. Kaplan–Meier Plot of PFS in 14874 (GRID) study

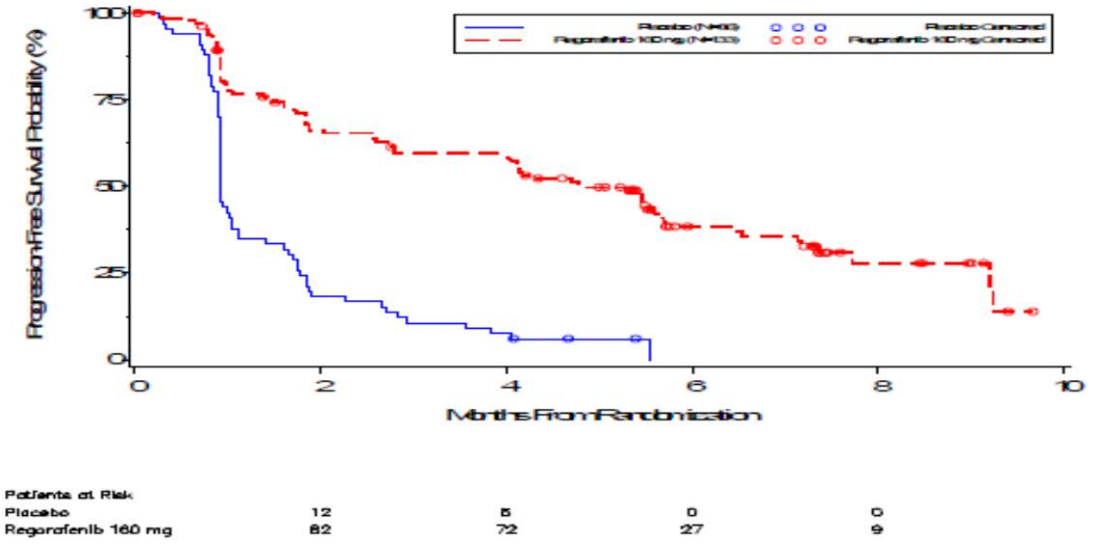
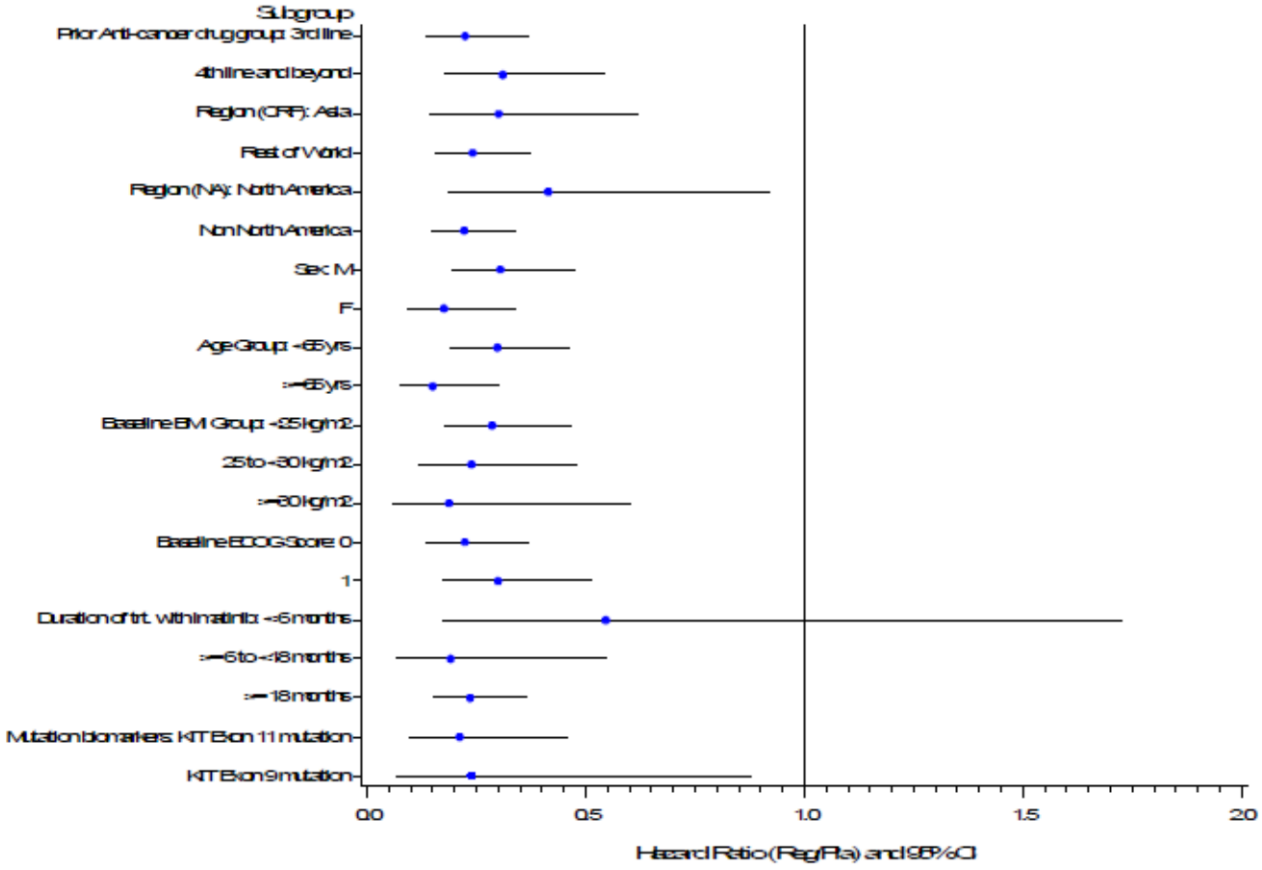


Figure 2. Forest Plot PFS study 14874



Secondary endpoints

- *Overall Survival*

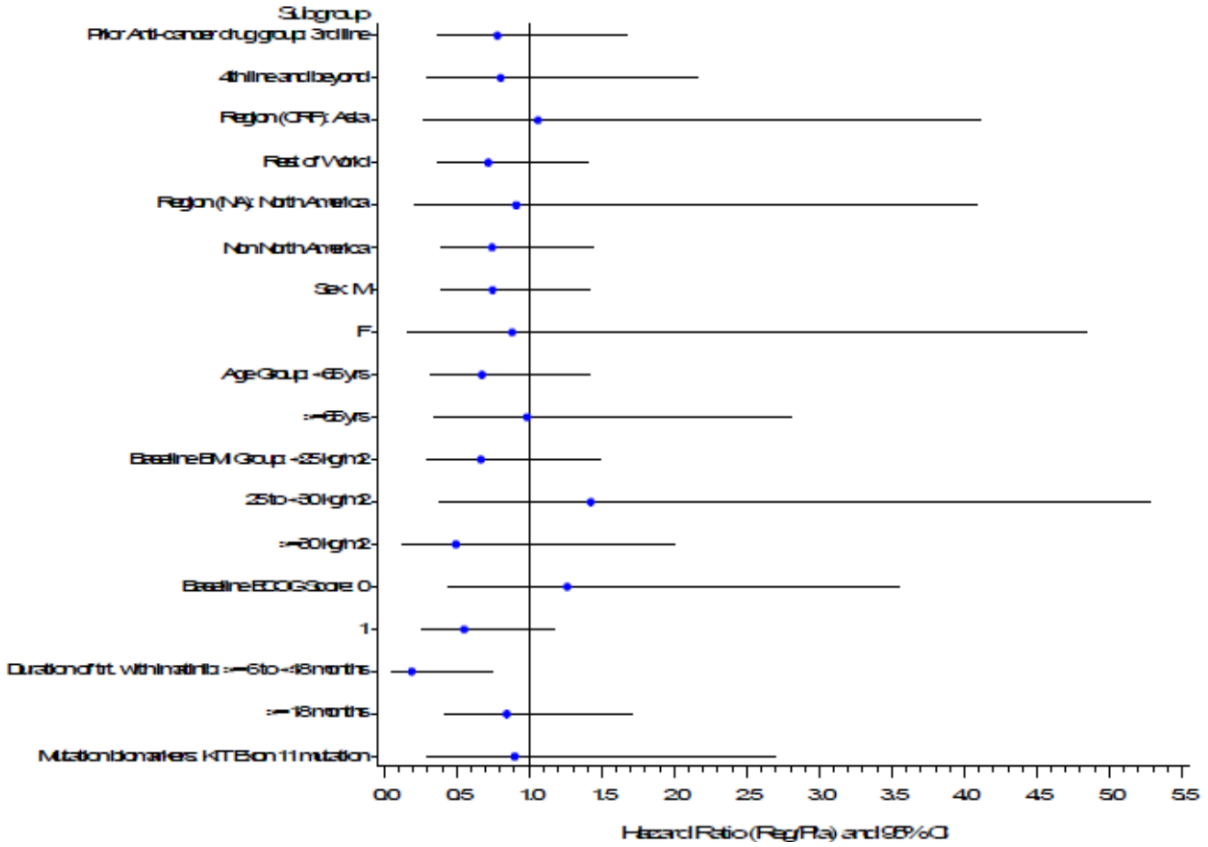
The efficacy results in terms of the secondary endpoint of OS (cut-off date January 26, 2012) are presented in the table 8 and figures 3 and 4.

Table 8. Overall Survival 14874 (GRID) Study (FAS, uncorrected and corrected for cross-over

	Placebo + BSC (N = 66)	Regorafenib + BSC (N = 133)
Number of patients (%) with event	17 (25.8%)	29 (21.8%)
Number of patients (%) censored	49 (74.2%)	104 (78.2%)
Median overall survival (days)	A	A
Range (days, without censored values): uncorrected	(10 – 207)	(9 – 255)
Range (days, without censored values): corrected RPSFT[a]	(10 - 147)	(9 - 255)
Range (days, without censored values): corrected IPE[b]	(10 - 152)	(9 – 255)
Hazard ratio (regorafenib/placebo): uncorrected	0.772	
95% CI for hazard ratio): uncorrected	(0.423,1.408)	
p-value (one-sided from log rank test)): uncorrected	0.198896	
Hazard ratio (regorafenib/placebo): corrected RPSFT[a]	0.537	
95% CI for hazard ratio): corrected RPSFT[a]	(0.286,1.007)	
p-value (one-sided from log rank test)): corrected RPSFT[a]	0.024725	
Hazard ratio (regorafenib/placebo): corrected IPE[b]	0.565	
95% CI for hazard ratio): corrected IPE[b]	(0.302,1.055)	
p-value (one-sided from log rank test)): corrected IPE[b]	0.034931	

Abbreviations: CI – confidence interval; FAS = full analysis set
a: Corrected for the effect of crossover from the placebo to the regorafenib arm on the OS endpoint by RPSFT method.
b: Corrected for the effect of crossover from the placebo to the regorafenib arm on the OS endpoint by IPE method.
A Value cannot be estimated due to censored data.
Hazard ratio and its 95% CI was based on stratified Cox Regression Model

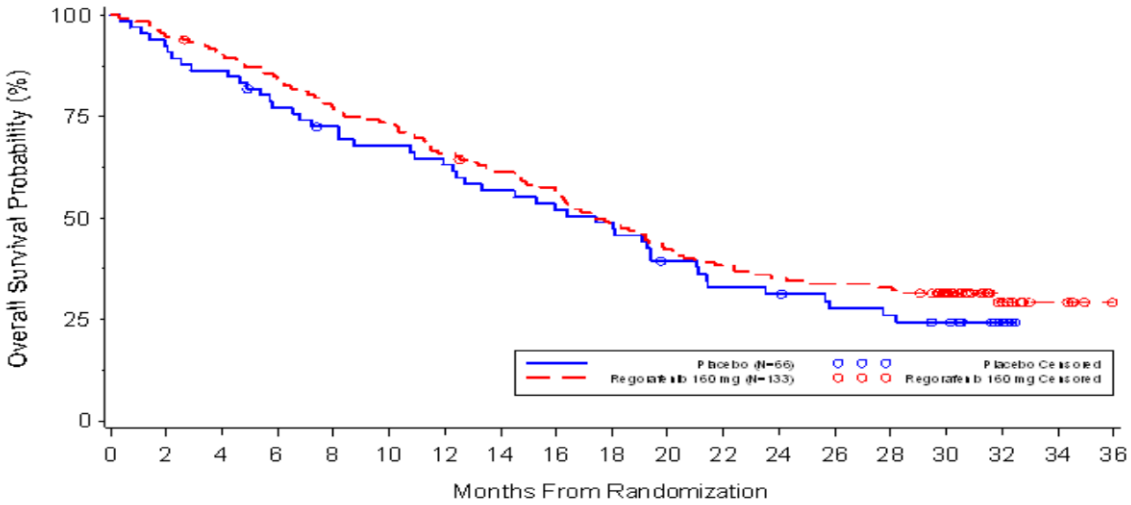
Figure 3. Forest Plot OS study 14874



Of note, at the time of the primary analysis 56 patients (84%) enrolled in the placebo arm had crossed-over to the regorafenib arm after progression was determined.

According to the updated analysis, based on 139 events (cut-off 31 January 2014, 91 [68.4%] in the regorafenib arm and 48 [72.7%] in the placebo arm) no significant difference between the two study arms was observed: median OS was 17.4 months in both arms, HR 0.85, 95% CI 0.597-1.206, p=0.180.

Figure 4. Overall survival updated analysis, Kaplan-Meier curves, data cut-off Jan 31, 2014



Patients at Risk

Placebo	61	57	50	46	43	40	36	33	31	24	20	19	16	15	12	5	0
Regorafenib 160 mg	126	119	111	102	97	87	80	74	63	55	50	46	44	43	32	11	5

- *Time to Progression (TTP)*

The percentage of patients with disease progression was 93.9% in the placebo group and 57.1% in the regorafenib group (cut-off date of 26 January 2012). Median TTP was 165 days in the regorafenib group and 28 days in the placebo group (HR 0.248, [95% CI: 0.170-0.364, p<0.000001]).
The results of an additional analysis where time to progression was evaluated according to investigator's assessment were consistent with the analysis according to central assessment (HR 0.197, p<0.000001, median TTP was 224 days vs 52 days with regorafenib and placebo, respectively.

- *Overall Response Rate (ORR) and Disease Control Rate (DCR)*

No cases of complete response (CR) were observed in both arms. Overall response rate was not statistically significant different between the two treatment arms: 4.5% with regorafenib +BSC versus 1.5% with placebo plus BSC (p=0.142097).
Disease Control Rate (DCR: CR+ PR+ SD) was 52.6% (70 patients) in regorafenib group compared with 9.1% (6 patients) in the placebo group.

- *Duration of response*

The median duration of response (central assessment) for regorafenib-treated patients was 99 days. Only one placebo treated patient reported PR and duration of response duration was 30 days.

Exploratory endpoints

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

EORTC QLQ-C30 was completed by 183 (92%) patients at baseline, 168 (84%) patients at cycle 2, and 128 (64%) patients at cycle 3. Mean changes in scores from baseline for the EORTC QLQC30 global health status and the 5 functional dimensions showed a slight deterioration in patients' QoL of similar magnitude both in the regorafenib and placebo groups. Mean changes from baseline were not clinically meaningful (ie, ≤10 points), except for the role function subscale in the regorafenib group. The analysis of time-adjusted AUC for the EORTC QLQ-C30 showed that there was no difference in the longitudinal evolution of the least-squares mean (LS Mean) total scores between placebo and regorafenib. The EORTC QLQ-C30 change from baseline at Cycles 2, 3, 4 and EOT (double-blind treatment period (PRO) are presented in the table below.

Table 9. EORTC QLQ-C30 change from baseline at Cycles 2, 3, 4 and EOT (PRO)

		Placebo + BSC (N = 62)		Regorafenib + BSC (N = 123)
	n	Mean ±SD	n	Mean ±SD
Physical function	60		123	
Cycle 2	55	-5.36 ± 15.74	113	-7.17 ± 16.96
Cycle 3	31	-5.81 ± 15.75	97	-5.96 ± 19.21
Cycle 4	17	-4.90 ± 15.37	86	-7.24 ± 18.07
EOT	2	-73.33 ± 18.86	15	-12.89 ± 19.59
Role function	59		123	
Cycle 2	54	-5.56 ± 25.49	113	-17.70 ± 33.06
Cycle 3	31	-3.76 ± 32.97	97	-17.01 ± 30.52
Cycle 4	16	4.17 ± 33.05	86	-13.95 ± 27.16
EOT	2	-33.33 ± 0	15	-32.22 ± 41.53
Emotional function	60		123	
Cycle 2	54	-0.93 ± 19.34	112	-0.32 ± 15.25
Cycle 3	31	0.81 ± 16.85	96	1.65 ± 16.82
Cycle 4	17	8.17 ± 16.62	85	2.25 ± 15.77
EOT	2	-37.50 ± 5.89	15	-11.67 ± 22.23
Social function	60		123	
Cycle 2	55	-1.21 ± 27.56	112	-6.99 ± 24.26
Cycle 3	31	-6.45 ± 32.68	96	-6.42 ± 25.86
Cycle 4	17	-1.96 ± 26.27	85	-8.04 ± 25.41
EOT	2	-58.33 ± 35.36	15	-13.33 ± 29.00
Cognitive function	60		123	
Cycle 2	55	-3.03 ± 18.45	112	-4.13 ± 17.04
Cycle 3	31	-3.76 ± 22.65	96	-1.74 ± 16.13
Cycle 4	17	-4.90 ± 26.20	85	-0.39 ± 15.85
EOT	2	-25.00 ± 11.79	15	-5.56 ± 19.59
Global health status (QoL)	60		123	
Cycle 2	54	-3.24 ± 23.87	113	-6.19 ± 23.59
Cycle 3	30	-4.17 ± 23.75	96	-7.38 ± 23.97
Cycle 4	17	2.45 ± 21.80	85	-6.57 ± 25.40
EOT	2	-37.50 ± 5.89	15	-21.11 ± 24.87

Abbreviations: EOT – end of treatment; PRO – patient reported outcome; QoL – quality of life

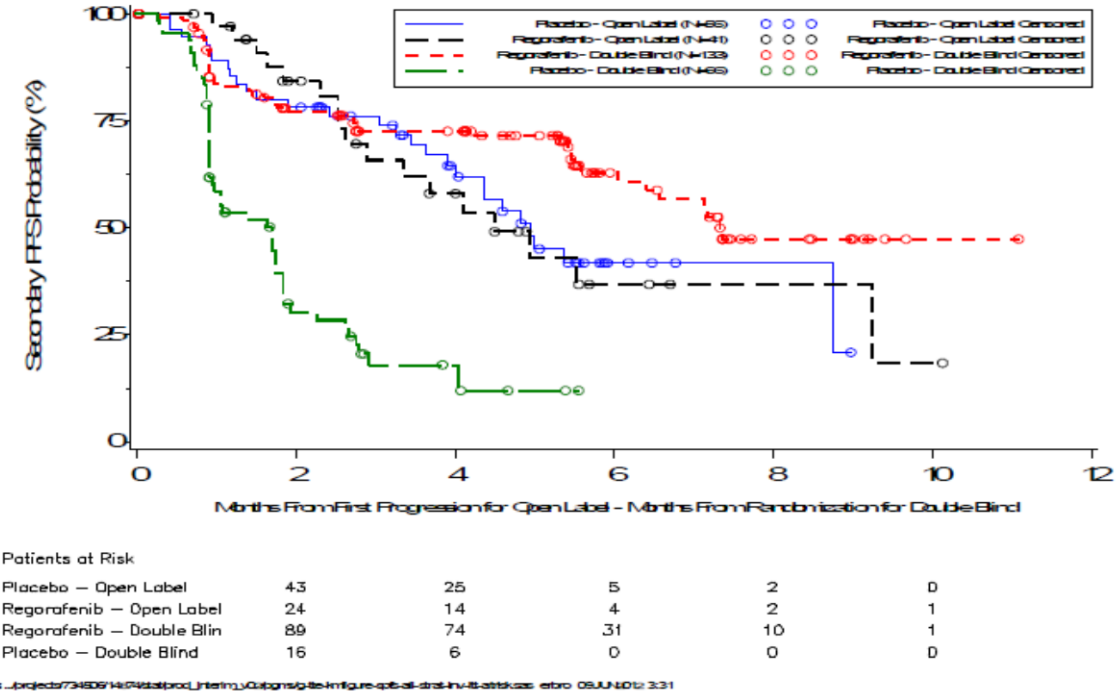
EQ-5D Questionnaire was completed by 188 (94%) patients at baseline, 163 (82%) patients at cycle 2, and 128 (64%) patients at cycle 3. Mean changes in scores from baseline for EQ-5D index and VAS were, overall, similar between the regorafenib + BSC and placebo + BSC groups. The differences in mean scores from baseline reflected a deterioration in health status for both groups. For both the EQ-5D and the VAS, only the changes from baseline at EOT were clinically important (based on the

minimum clinically important difference). The analysis of time-adjusted AUC for the EQ-5D index and VAS showed that regorafenib treatment maintained patients' health-related quality of life (data not shown).

- *Secondary PFS*

Median secondary PFS for the placebo arm (56 patients who crossed over to regorafenib) and the regorafenib arm (41 patients who continued on regorafenib) was 151 days and 137 days, respectively.

Figure 5. PFS during treatment with regorafenib, Kaplan-Meier (FAS)



- *Biomarkers*

Genetic biomarker analyses for patients with GIST were performed using data collected in the pivotal Phase 3 study 14874 ("historical" mutational status at study entry, archival tumor tissue samples and prospectively collected plasma samples) and in the Phase 2 study 14935.

Non-genetic biomarker analysis for patients with GIST was performed using data collected in the pivotal Phase 3 study 14874 (prospectively collected plasma samples, focused on quantification of the levels of 11 different proteins associated with angiogenesis, hypoxia, or GIST pathogenesis).

Biomarker analysis

- *Genetic biomarkers*

The aim of the genetic analysis of the biomarker sub-study was: 1) to determine the mutational status of KIT, PDGFRA, BRAF and KRAS and to evaluate potential correlations between biomarker subgroups and clinical outcome (PFS); 2) as additional objective, to evaluate the degree of concordance among mutational results obtained by two different techniques BEAMing using DNA obtained from fresh plasma samples and Sanger sequencing using archival tumor tissue specimens.

Biomarker specimen sampling frequencies and mutational frequencies

By BEAMing assay**:** (163 patients evaluated)

1) A KIT mutation was detected in 58% of the plasma DNA samples analysed, of which: primary KIT-Exon 9 mutations in 15% of the samples and KIT-Exon 11 mutations in 12% of the samples; secondary KIT mutations were detected in 47% of the samples.

-Half of the samples in which a primary KIT-Exon 9 alteration was identified also harboured a secondary KIT mutation, and 74% of the samples in which a primary KIT-Exon 11 alteration was identified also harboured a secondary KIT mutation.

-A primary KIT mutation was not identified in 66% of the samples in which a presumptive secondary KIT mutation was detected.

2) PDGFRA alterations were detected in 1% of the plasma DNA samples analyzed and BRAF mutations were detected in 0 of the samples.

By sequencing of archival tissue specimens (111 patients of whom 102 acceptable):

1) A KIT mutation was detected in 66% of the tissue DNA samples analyzed.

-Primary KIT-Exon 9 mutations were detected in 18% of the samples, and KIT-Exon 11 alterations in 43% of the samples; secondary KIT mutations were detected in 12% of the samples. Concordance between KIT mutations at exon 9 and 11 detected by both BEAMing in plasma DNA and sequencing in archival tumor tissue was 89% for KIT Exon 9 mutations and 79% for KIT exon 11 mutations.

2) PDGFRA mutations were detected in 3% of the tumor tissue DNA samples analyzed and BRAF mutations were detected in 0% of the samples. Activating KRAS mutations were detected in 2% of the samples.

The results showed that primary KIT mutations in exon 9 were reported at a similar percentage in the two different analysed compartments by the two techniques whereas those reported at exon 11 were detected in a different percentage of analyzed samples (12% plasma and 43% tumor tissue, respectively).The low number of exon 11 mutations detected by BEAMing technology most likely is due to the lack of the mutant specific primers to all reported exon 11 primary alterations, reflecting one of the potential limitations of plasma DNA analysis by BEAMing assay. Secondary *KIT* mutations, which have been associated with the development of resistance to TKI therapy, were more readily detected using BEAMing technology (47%) compared with tumor tissue sequencing (12%). In this case, a good coverage of secondary KIT mutations was predetermined in light of the need to detect potential secondary resistance mutations following previous TKIs treatments.

Correlation between mutational status and clinical outcome

PFS values were obtained from both primary PFS from central assessment and that determined by GRID study investigators. Secondary PFS values were not used for biomarker-related correlative analyses.

Biomarkers and potential predictive value: the subgroup of GRID patients for whom mutational status was evaluated on plasma DNA was representative of the overall GRID population. The analysed biomarker subgroups were not predictive of clinical benefit in terms of PFS.

On the contrary, the population of GRID patients for whom tumour tissue mutation data was obtained is not highly representative of the overall GRID study population. Results regarding other biomarkers subgroup did not identified a potential predictive biomarker.

Biomarkers and prognostic effects: this evaluation has been conducted in a small number of patients. The presence of a secondary KIT mutation appears to be prognostic for poor outcome (comparison of patients with a secondary KIT mutation to those without showed a HR of 1.82 when PFS values were assessed from central assessment and a HR of 2.58 using PFS values from GRID investigator assessment). Thus, a potential negative prognostic effect seems to be related to the presence of a secondary KIT mutation. However, the analysis was conducted in a limited number of samples and results should be interpreted cautiously and further validated.

Overall the results of the genetic sub-study showed that the mutational status, either primary or secondary, did not influence PFS.

Non genetic biomarkers GRID sub-study

The aim of the biomarker non genetic sub-study of GRID (61% of enrolled patients) was to evaluate the levels of 11 different proteins at baseline and Cycle 2-Day 15 on plasma samples and to evaluate potential correlations between protein levels and clinical outcome (PFS).

The proteins evaluated included those associated with angiogenesis (IGFBP-2, IL-6, IL-8, VEGF-A, VEGF-C) or hypoxia (CA9), as well others associated with GIST pathogenesis (KIT, L1-CAM, M-CSF, MK, SCF). The evaluation was performed using multiplex immunoassay or ELISA.

Ancillary analyses

PFS unstratified: median PFS was 4.8 months in the regorafenib arm and 0.9 months in the placebo arm (HR 0.255, 95% CI 0.177-0.368).

PFS per local investigator's assessment (stratified): By comparison of the central vs investigator assessment more assessments of progression were made in central assessment than in the investigator's assessment. In the placebo group, the investigators' assessment indicated 75.8% of patients with progression, compared to 93.9%, central assessment. In the regorafenib group, the investigators' assessment indicated 33.1% of patients with progression, compared to 57.1%, central assessment, up to the database cut-off date. The discordance in the placebo arm was 18.2%, caused by 12 progressions seen in central reading and not in investigator reading. The discordance in the regorafenib arm was 31.6%, caused by 37 progressions seen in central reading and not in investigator reading (27.8%) and 5 progressions seen in investigator reading and not in central reading (3.8%).

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 10. Summary of Efficacy for trial 14874

Title: A randomized, double-blind, placebo-controlled phase III study of regorafenib plus best supportive care versus placebo plus best supportive care for subjects with metastatic and/or unresectable gastrointestinal stromal tumours (GIST) whose disease has progressed despite prior treatments with at least imatinib and sunitinib	
Study identifier	2009-017957-37, GRID, 14874
Design	Multicenter, randomised, double-blind, placebo-controlled

	Duration of main phase:		Until disease progression or serious potential adverse reaction or pregnancy or second malignancy or treatment interruption longer than 28 consecutive days or more than two consecutive dose reduction or clinically significant drug-related toxicities.
Hypothesis	Superiority		
Treatments groups	Regorafenib + BSC		Regorafenib 160 mg od once daily, for 21 days every 4 weeks (3 weeks on, 1 week off), (N=133)
	Placebo + BSC		Matching placebo od once daily, for 21 days every 4 weeks (3 weeks on, 1 week off), (N=66)
Endpoints and definitions	Primary endpoint	Progression-Free Survival (PFS)	Time from randomization to radiological progression or death whichever occurs first
	Secondary endpoint	Overall Survival (OS)	Time from randomization to death due to any cause
	Secondary endpoint	Time to progression (TTP)	Time from randomization until the date of radiological progression.
	Secondary endpoint	Response rate (RR)	Proportion of patients with the best overall tumor response of partial response (PR) or complete response (CR) according to modified RECIST criteria (v. 1.1) that was achieved during treatment or within 30 days after termination of study medication.
Database lock	26 January 2012		

Results and Analysis

Analysis description	**Primary Analysis**		
Analysis population and time point description	Full Analysis Set 26 January 2012 (144 events)		
PFS (median, days) 95% CI	Treatment group	Placebo +BSC	Regorafenib +BSC
	Number of subjects	66	133
	PFS (median, days) 95% CI	28 (28, 32)	147 (122, 173)
	OS (median; days) 95% CI	NE (NE, NE)	NE (NE, NE)

	TTP (median; days) 95% CI	28 (28,34)	165 (125,174)
	RR (%) 95% CI	1.5 % (0.0 %, 8.2%)	4. 5% (1.7%, 9.6 %)

Effect estimate per comparison	Primary endpoint (PFS)	Comparison groups	Regorafenib vs placebo
		HR from stratified proportional hazards model	0.268
		95% CI	(0.185, 0.388)
		Stratified log-rank P-value	<0.000001
	Secondary endpoint: (OS)	Comparison groups	Regorafenib vs placebo
		HR from stratified proportional hazards model	0.772
		95% CI	(0.423, 1.408)
		Stratified log-rank P-value	0.199
	Secondary endpoint: (TTP)	Comparison groups	Regorafenib vs placebo
		HR from stratified Cox Regression model	0.248
		95% CI	(0.170, 0.364)
		Stratified log-rank P-value	< 0.000001
	Secondary endpoint: (RR)	Comparison groups	Regorafenib vs placebo
		Difference in proportions	- 2.99 %
		95% CI	(-7.70%, 1.72)
		P-value	0.1412097
Notes	Stratification factors for the primary analysis : 3rd versus 4th line therapy or beyond and geographical region (Asia versus rest of the world)		

Analysis description	**Final Analysis**		
Analysis population and time point description	Full Analysis Set 31 January 2014		
Descriptive statistics and estimate variability	Treatment group	Placebo +BSC	Regorafenib +BSC
	Number of subjects	66	133
	OS (median, in days)	529	529
	95% CI	454–614	373–640
Effect estimate per comparison	Overall Survival	Comparison groups	Regorafenib vs placebo
		HR	0.85
		95% CI	(0.597, 1.206)

		Stratified log-rank p-value	0.180

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

The results of the pivotal phase III study 14874 and the supportive phase II 14935 study are provided by individual study without data pooling due to the different designs and settings of the trials.

Table 11. Summary of Efficacy from clinical trials performed with regorafenib and supporting this submission for type II variation extension of indication in GIST

	14874 (GRID)		**14935**
	Regorafenib	**Placebo**	**Regorafenib**
Pts enrolled, n	133	66	34
PFS (IRC)			
Median (days)	147	28	NA
	HR 0.268 (95% CI 0.185-0.388) p<0.000001		
PFS (INV)			
Median (days)	224	52	150
	HR 0.221 (95% CI 0.141-0.345) p<0.000001		
OS (cut off 26 Jan 2012)			
Median	NA	NA	NA
	HR 0.772 (95% CI 0.423-1.408) =0.198896		
OS (cut off 31 Jan 2014)			
Median (months)	17.4	17.4	NA
	HR 0.85 (95% CI 0.597-1.206) p=0.180		
ORR			
CR	0	0	0
PR	6 (4.5%)	1 (1.5%)	4 (12%)
SD	64 (48.1%)	5 (7.6%)	22 (67%) + 4 (12%)
DCR	70 (52.6%)	6 (9.1%)	30 (88%)

Clinical studies in special populations

N/A

Supportive study

Study 14935

Study 14935 was a multi-center, open-label, non-randomized, single-arm, study designed to evaluate efficacy and safety of regorafenib in patients with metastatic and/or unresectable GIST resistant or intolerant to at least imatinib and sunitinib. Primary endpoint was clinical benefit rate (CBR) defined s objective response (CR, PR, or SD ≥16 weeks) based on investigator assessment using RECIST version 1.1. Secondary endpoints were ORR, PFS, OS and safety.

Of 34 patients enrolled, 33 received at least one dose of regorafenib. Patients were treated on an intermittent dosing schedule (3 weeks on/1 week off) with 160 mg regorafenib per day administered orally. As of 28 July 2011 after a median follow-up of 10.9 months a median of 8 cycles per patient (range 2 to 17 cycles) were administered. Twenty-one (64%) patients were still on treatment and 12 (36%) had discontinued. The most common reason for discontinuation was PD (6, 18%). Other reasons for discontinuation included investigator's decision (3 patients, 9%), unrelated intercurrent illness (1 patient, 3%), patient's decision (1 patient, 3%), and investigator's decision after an adverse event (AE) (1 patient, 3%).

Clinical benefit was documented in 26 (79%) patients (95% CI: 61%, 91%), including 4 (12%) cases of PR and 22 (67%) cases of SD ≥16 weeks. Of the remaining patients, 4 (12%) had SD ≤16 weeks, 2 (6%) had PD at the first tumour evaluation, and 1 (3%) was not evaluated because of early withdrawal. The median PFS was 10.0 months (95% CI, 8.3, 14.9 months). Six (18%) patients died. Of these, 5 (15%) patients died due to PD and 1 (3%) patient died due to an unrelated intercurrent illness. Median OS could not be evaluated due to the low number of events.

Based on historical biomarker data, 19 patients had a KIT exon 11 mutation, 3 patients had a KIT exon 9 mutation and 8 patients had no KIT or PDGFRαmutation. In one patient a BRAF exon 15 mutation was observed.

The trial showed that Kit keeps a central role in the clonal evolution of GIST, even after prolonged inhibition with approved agents, imatinib and sunitinib. The detection of activating mutation in the loop in four patients for whom matching biopsies were available shows at least two key points: 1) GIST growth and survival is still mediated by the oncogenic driver KIT even after sustained inhibition with imatinib and sunitinib, 2) the main inhibitory activity of regorafenib in GIST is possibly on Kit, despite the potential multikinase inhibitory effect. Only for descriptive purpose the only patient with BRAF exon 15 mutation progressed rapidly on regorafenib.

Literature Review

The results of the median OS observed in other studies published in the literature which were performed in GIST patients after failure of at least imatinib and sunitinib are presented in the below table.

Table 12. Overall survival in GIST patients after treatment with imatinib and sunitinib

	Treatment	N	Line	OS months (median)
Reichardt et al: 2012 (30)	Nilotinib (800 mg)	165	3+[d]	10.9
	Best supportive care[a]	83	3+	9.2[b]
	Nilotinib (800mg)	132	3[c]	13.3
	Best supportive care	65	3[c]	9.2
Kang et al: 2013 (31)	IM (400 mg)	41	3+	8.2
	Placebo	40	3+	7.5
Park et al: 2012 (32)	Sorafenib (800 mg)	31	3+	9.7
Kang et al: 2012 (36)	Dovitinib (500 mg)	30	3+	6.2
Trent et al: 2011 (37)	Dasatinib (140 mg)	50	3+	19.0
Montemurro et al: 2013 (33)	Sorafenib (800 mg)	124	3+	13.5
	Sorafenib (800 mg)	56	3[c]	17.9
	Sorafenib (800 mg)	68	4	11.0
Italiano et al: 2012 (34)	Nilotinib, Sorafenib, Imatinib	223	3+	9.2
George et al: 2013 (35)	Regorafenib (160 mg)	33	3+	27.0
Unpublished (interim OS results; ITT)	Regorafenib (160mg)	132	3+	17.4
	Best supportive care	66	3+	17.4[e]

[a] Best supportive care included imatinib and sunitinib at the investigators discretion
[b] 77% of patients crossed over to nilotinib
[c] true third line patients
[d] 3+ : two or more lines of prior therapy (including imatinib and sunitinib)
[e] 85% of patients crossed over to regorafenib, HR=0.85 in favor of regorafenib

2.4.3. Discussion on clinical efficacy

Design and conduct of clinical studies

The proposed regorafenib dose regimen is 160 mg OD administered according to a 3 weeks on/one week off schema, in line with the already approved posology in patients with metastatic colorectal cancer.

The two arms design of the pivotal 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. Although it is known that continuous kinase suppression is of utmost importance for the control of tumor growth in GIST and that re-challenging a drug to which the disease has been already exposed may be better than BSC, the benefit is expected to be marginal. The RIGHT (Rechallenge of imatinib in GIST having no effective treatment) trial, is an academically initiated phase III placebo controlled study that has been recently published (Kang et al, Lancet Oncol, 2013). The trial randomly allocated patients that exhausted available option of treatment to receive imatinib or placebo. The primary endpoint PFS favoured the resumption of imatinib compared to BSC, even though the absolute advantage benefit is limited. After a median follow-up of 5.2 months, median PFS was 1.8 months (95% CI 1.7—3.6) with imatinib compared with 0.9 months (0.9—1.7) with placebo (hazard ratio for progression or death 0.46, 95% CI 0.27—0.78; p=0.005).

Demographic and baseline characteristics appeared to be comparable between the two study arms.

Efficacy data and additional analyses

The results of the final PFS analysis showed a statistically significant improvement in PFS (centrally assessed) for regorafenib compared with placebo (HR 0.268, 95% CI 0.185-0.388, p<0.000001), with a gain in median PFS of 119 days in favour of regorafenib. The effect on PFS was observed in most subgroups of the population. The robustness of the PFS effect is supported by several sensitivity analyses, the results of which are in line with the primary analysis.

Regarding the secondary endpoints, no significant difference was observed between regorafenib and placebo in terms of OS. According to the updated analysis, no significant difference between the two study arms was observed: median OS was 17.4 months in both arms (HR 0.85, 95% CI 0.597-1.206, p=0.180). The treatment comparison is biased by the large cross-over (84.8%). The observed median OS (17.4 months) in the pivotal study was long compared to other studies published in the literature performed in GIST patients after failure of at least imatinib and sunitinib, where median OS less than 12 months is usually reported.

No difference in ORR is observed between the two treatment arms. Results of exploratory endpoints suggest no remarkable difference between the two study arms regarding Quality of life.

No substantial difference in terms of activity and/or toxicity of regorafenib appears to emerge from the comparison of the different subgroups identified by biomarkers. However, the limited sample size and the retrospective nature of the analyses do not allow to drawn any firm conclusion over this relevant issue. The CHMP requested the MAH to evaluate further biomarkers when performing future studies with regorafenib in GIST patients. The MAH has committed to provide post-approval additional biomarker analyses employing the samples available. The MAH will submit the results of the additional analyses performed as soon as available (expected 1Q 2015). The RMP has been updated to reflect this.

2.4.4. Conclusions on the clinical efficacy

The results of the pivotal 14874 trial and the supportive 14935 study are considered of clinical relevance. The statistically significant and clinically relevant improvement in PFS together with the OS results/analyses support a clinical benefit associated with regorafenib treatment in the target population.

2.5. Clinical safety

2.5.1. Introduction

Clinical safety of regorafenib was based on relevant safety data derived from the phase 1, 2 and 3 clinical studies.

As of February 2013, more than 3500 patients have been treated with regorafenib in clinical trials, primarily as a single agent but also in combination with different types of chemotherapy. Additionally, more than 500 patients have been treated in Managed Access Programs (MAPs), Expanded Access Programs (EAPs) and Compassionate Use Programs (CUPs) as of this date.

The main safety analyses are based on pooled data from completed (i.e. final or interim databases available) company-sponsored monotherapy trials in patients with cancer and by-study descriptions of

the Phase 1 studies with cancer patients not included in the pooled analyses, regorafenib combination trials in cancer patients and phase 1 studies in healthy volunteers.

Patient exposure

In analogy with the initial MAA three data pools were constructed from the clinical studies of regorafenib in cancer patients:

Pool 1 consists of the safety data of all cancer patients treated with regorafenib monotherapy in company-sponsored trials from Phase 1 to 3 (13172, 14996, 11726, 14596, 12434, 14814, 11651, 11650, 14387, and 14874, including safety data from the open-label treatment period of study 14874).

Pool 2 consists of placebo-controlled safety data from the double-blind period of the pivotal Phase 3 study 14874 in patients with GIST.

Pool 3 consists of the placebo-controlled safety data from the pivotal Phase 3 trials in patients with GIST (14874) and patients with metastatic colorectal cancer (14387).

The overall extent of exposure in all these pools is summarised in the following table.

Table 13. Extent of exposure to treatment with regorafenib

	Pool 2		Pool 1	Pool 3	
	Placebo N=66	Regorafenib N=132	Regorafenib N=1073	Placebo N=319	Regorafenib N=632
Overall time under treatment excluding time off drug/ interruptions					
Mean ±SD (weeks)	7.3 (4.5)	15.0 (8.6)	12.99 (15.36)	6.5 (4.0)	10.2 (7.7)
Median	6.0	16.0	8.71	6.0	6.4
Range	1.0–20.8	0.1–38.3	0.1–134.1	0.6–30.0	0.1–38.4
Overall time under treatment including time off drug/ interruptions					
Mean ±SD (weeks)	9.1 (5.9)	20.2 (11.6)	17.65 (20.09)	8.3 (5.3)	14.3 (10.6)
Median	7.0	22.9	11.71	7.0	10.0
Range	1–25.9	0.1–50.9	0.1–179.4	0.6–38.7	0.1–51.0
Number of cycles completed					
Mean ±SD	2.9 (1.4)	5.5 (2.8)	4.7 (5.2)	2.4 (1.3)	3.7 (2.6)
Median	2.5	6.0	3.0	2.0	3.0
Range	1-7	1-13	1-46	1-10	1-13
Actual daily dose (mg)					
Mean ±SD	159.5 (3.0)	139.8 (22.9)	138.88 (29.65)	159.3 (4.5)	145.6 (19.8)
Median	160.0	146.8	157.14	160	160
Range	139.0–160.0	88.0–160.0	10.0–220.0	107.0–160.0	85.7–160.0
Any dose modification, n (%)	17 (25.8)	95 (72.0)	845 (78.8)	114 (35.7)	473 (74.8)

SD = standard deviation; IA = integrated analysis

The safety population exposed to regorafenib in the Phase 1 to 3 clinical studies (in Pools 1 to3) included patients with a wide range of weight (median body mass index approximately 24.8 kg/m^2 ranging from 14.4–55.1 kg/m^2). 36- 40% of patients were women.

The mean age of patients exposed to regorafenib was 58.2 to 60.2 (median 60-61) years (range 18-86 years) with a sufficient number of elderly patients (32-37% were aged ≥65). With respect to race, the

patient population treated with regorafenib was predominantly White (68-76%), followed by Asian (17–26%) and Black (0–1.2%).

Baseline characteristics of patients with GIST were balanced between those regorafenib versus placebo. This regarded gender, race as well as age, age groups and BMI. Patients treated for the indication mCRC (pool 3) were older than those treated for GIST (pool 2).

Adverse events

The AE data presented in the MAA refer to treatment-emergent AEs (TEAEs). Numbers of patients in the three pools are provided in table 14.

Table 14. Overview of treatment-emergent adverse events

	Pool 2				Pool 1		Pool 3			
	Placebo N = 66 n (%)		Regorafenib N = 132 n (%)		Regorafenib N = 1073 n (%)		Placebo N = 319 n (%)		Regorafenib N =632 n (%)	
Number of patients (%) with:										
Any AE	61	(92.4)	132	(100.0)	1067	(99.4)	306	(95.9)	630	(99.7)
Worst grade:										
Grade 3	17	(25.8)	85	(64.4)	617	(57.5)	84	(26.3)	365	(57.8)
Grade 4	4	(6.1)	9	(6.8)	97	(9.0)	24	(7.5)	52	(8.2)
Grade 5 (death)	3	(4.5)	7	(5.3)	126	(11.7)	40	(12.5)	74	(11.7)
SAE	14	(21.2)	38	(28.8)	486	(45.3)	114	(35.7)	257	(40.7)
AEs leading to dose modification	11	(16.7)	92	(69.7)	697	(65.0)	68	(21.3)	425	(67.2)
AEs leading to permanent discontinuation of study drug	5	(7.6)	8	(6.1)	220	(20.5)	37	(11.6)	96	(15.2)
Any drug-related AE	45	(68.2)	130	(98.5)	1001	(93.3)	199	(62.4)	595	(94.1)
Worst grade:										
Grade 3	5	(7.6)	77	(58.3)	546	(50.9)	36	(11.3)	330	(52.2)
Grade 4	1	(1.5)	2	(1.5)	37	(3.4)	5	(1.6)	19	(3.0)
Grade 5 (death)	1	(1.5)	2	(1.5)	19	(1.8)	1	(0.3)	7	(1.1)
SAE	2	(3.0)	11	(8.3)	152	(14.2)	11	(3.4)	70	(11.1)
AEs leading to dose modification	6	(9.1)	83	(62.9)	589	(54.9)	29	(9.1)	361	(57.1)
AEs leading to permanent discontinuation of study drug	1	(1.5)	3	(2.3)	106	(9.9)	4	(1.3)	44	(7.0)

AE = adverse event; SAE = serious adverse event

In the designated pool 2 (the Phase 3 study in GIST patients) the most common TEAE in the regorafenib group was hand foot skin reaction (HFSR) (65.9% in the regorafenib group vs. 15.2% in the placebo group).

Also hypertension (59.1% vs. 27.3%), diarrhoea (46.2% vs. 9.1%), dysphonia (37.9% vs. 9.1%) and fatigue (37.1% vs. 28.8%) were observed as well as decreased appetite (31.1% vs. 21.2%), constipation (28.0% vs. 22.7%), rash (25.8% vs. 3.0%) and alopecia (24.2% vs. 1.5%).

In pool 3 (Phase 3 studies in GIST and CRC patients), the most common TEAEs in the regorafenib group were HFSR (regorafenib group 49.5% vs. 8.8% in the placebo group), diarrhoea (43.7% vs. 15.4%), decreased appetite (43.5% vs. 27.0%), fatigue (39.6% vs. 29.2%), hypertension (36.4% vs. 11.9%), and dysphonia (31.8% vs. 6.9%).

Overall, the incidence and pattern of the most common AEs are similar across all 3 pools analysed and these AE are considered in resemblance with the incidence of other drugs in this class (Table 15).

Table 15. Most common (>10% overall in any treatment group) treatment-emergent adverse events by MedDRA

	Pool 2		Pool 1	Pool 3	
	Placebo	Regorafenib	Regorafenib	Placebo	Regorafenib
Preferred Term	N = 66 n (%)	N = 132 n (%)	N = 1073 n (%)	N = 319 n (%)	N = 632 n (%)
Any event	61 (92.4)	132 (100.0)	1067 (99.4)	306 (95.9)	630 (99.7)
Palmar-plantar erythrodysaesthesia syndrome	10 (15.2)	87 (65.9)	533 (49.7)	28 (8.8)	313 (49.5)
Hypertension	18 (27.3)	78 (59.1)	387 (36.1)	38 (11.9)	230 (36.4)
Diarrhoea	6 (9.1)	61 (46.2)	459 (42.8)	49 (15.4)	276 (43.7)
Dysphonia	6 (9.1)	50 (37.9)	344 (32.1)	22 (6.9)	201 (31.8)
Fatigue	19 (28.8)	49 (37.1)	452 (42.1)	93 (29.2)	250 (39.6)
Decreased appetite	14 (21.2)	41 (31.1)	434 (40.4)	86 (27.0)	275 (43.5)
Constipation	15 (22.7)	37 (28.0)	279 (26.0)	63 (19.7)	156 (24.7)
Rash	2 (3.0)	34 (25.8)	223 (20.8)	10 (3.1)	144 (22.8)
Alopecia	1 (1.5)	32 (24.2)	157 (14.6)	5 (1.6)	70 (11.1)
Abdominal pain	12 (18.2)	31 (23.5)	233 (21.7)	53 (16.6)	129 (20.4)
Stomatitis	4 (6.1)	31 (23.5)	182 (17.0)	12 (3.8)	116 (18.4)
Pyrexia	7 (10.6)	28 (21.2)	264 (24.6)	44 (13.8)	168 (26.6)
Nausea	8 (12.1)	26 (19.7)	274 (25.5)	63 (19.7)	138 (21.8)
Mucosal inflammation	1 (1.5)	23 (17.4)	175 (16.3)	5 (1.6)	105 (16.6)
Vomiting	5 (7.6)	22 (16.7)	203 (18.9)	46 (14.4)	102 (16.1)
Headache	6 (9.1)	20 (15.2)	153 (14.3)	23 (7.2)	72 (11.4)
Asthenia	8 (12.1)	21 (15.9)	178 (16.6)	53 (16.6)	153 (24.2)
Muscle spasms	2 (3.0)	19 (14.4)	104 (9.7)	7 (2.2)	46 (7.3)
Weight decreased	5 (7.6)	18 (13.6)	255 (23.8)	31 (9.7)	179 (28.3)
Hypothyroidism	2 (3.0)	17 (12.9)	72 (6.7)	3 (0.9)	38 (6.0)
Myalgia	6 (9.1)	16 (12.1)	98 (9.1)	16 (5.0)	45 (7.1)
Pain in extremity	5 (7.6)	15 (11.4)	124 (11.6)	15 (4.7)	57 (9.0)
Anaemia	4 (6.1)	14 (10.6)	112 (10.4)	25 (7.8)	69 (10.9)
Back pain	5 (7.6)	13 (9.8)	146 (13.6)	31 (9.7)	76 (12.0)
Cough	6 (9.1)	12 (9.1)	130 (12.1)	33 (10.3)	65 (10.3)
Pruritus	8 (12.1)	11 (8.3)	78 (7.3)	19 (6.0)	35 (5.5)
Dyspnoea	2 (3.0)	8 (6.1)	179 (16.7)	34 (10.7)	93 (14.7)
Oedema peripheral	7 (10.6)	5 (3.8)	97 (9.0)	24 (7.5)	51 (8.1)
Hyperbilirubinaemia	0 (-)	2 (1.5)	97 (9.0)	17 (5.3)	67 (10.6)

MedDRA = Medical Dictionary for Regulatory Activities; PT = preferred term

Hypertension and HFSR were observed at a higher incidence in pool 2 when compared to other pools. It was noted that these incidences were also double in frequency in the placebo group of pool 2 (27.3% and 15.2% respectively) than was noted in pool 3 (8.8% and 11.9% respectively).

Although there was a notably higher incidence of infections (based on System Organ Class, SOC data) in regorafenib-treated patients than patients in placebo arm, none of the respective preferred terms (PTs) included in this SOC was observed in more than 10% of regorafenib-treated patients.

The incidences of CTC grade 3 AEs were similar in the regorafenib-treated patients across pools (64.4% in pool 2, 57.8% in pool 3, and 57.5% in pool 1).

The pattern of the most common grade 3 AEs was also similar between the pools among regorafenib treated patients. HFSR, hypertension and diarrhoea as this was noted among the most commonly reported events.

In pool 2, the higher incidence of grade 3 AEs in regorafenib treated patients (64.4%) compared to placebo treated patients (25.8%) was mainly accounted for by hypertension (27.3% in the regorafenib group vs. 4.5% in the placebo group), HFSR (22.0% vs. 1.5%), diarrhoea (7.6% vs. 0%) and rash (5.3% vs. 0%).

There were no major differences in the incidence of grade 4 AEs in regorafenib treated patients between the pools (6.8% in Pool 2; 8.2% in pool 3; 9.0% in pool 1). The incidence of grade 4 AEs in placebo treated patients was 6.1% in Pool 2, and 7.5% in pool 3.

The vast majority of grade 4 AEs by MedDRA in all pools occurred in single patients.

In pool 2, the most common grade 4 AE in regorafenib treated patients was pulmonary embolism. It was reported for 2 patients (1.5%) in the regorafenib group and none in the placebo group.

In pool 1, grade 4 pulmonary embolism occurred in 8 (0.7%) patients, and in pool 3 in 6 (0.9%) patients in the regorafenib group and in 1 (0.3%) in the placebo group. Increased lipase was the most common grade 4 AE in regorafenib-treated patients in pools 1 and 3: 9 (0.8%) and 7 (1.1%) patients, respectively.

Adverse Events of special interest

AEs of special interest include cardiac safety, renal safety, hepatobiliary events, haemorrhage, skin AE, vascular safety, GE safety, infection and wound healing.

Cardiac safety

There is overall a small increase in cardiac ischemic events in patients treated with regorafenib as compared to patients in placebo arms.

No difference between regorafenib-treated patients and patients in placebo arms was observed for congestive heart failure neither for patients with baseline risk factors or for patients without such risk factors at baseline. Events were more commonly reported in patients with baseline risk factors in both treatment groups.

The incidence of cardiac arrhythmia (SMQ) was slightly higher in patients treated with regorafenib as compared to patients in placebo groups, but in general the incidence was low, and there appeared no difference between the groups with regard to QTc prolongation.

Patients with baseline risk factors had a higher incidence in both treatment groups. However, there is no clear pattern with respect to reported cardiac arrhythmia events in regorafenib treated patients. One cardiac arrhythmia event of grade 4 and none of grade 5 have been reported. The effects of regorafenib at the time of maximum concentration on the QTc intervals of the ECG were minimal. Even the most conservative evaluation, the median maximum change, was modest and unlikely to be of clinical significance in the setting of cancer treatment.

Left ventricular ejection fraction (LVEF) was assessed by MUGA (multi gated acquisition) scan at baseline and at least once under ongoing regorafenib treatment, typically after a minimum 2 cycles of regorafenib treatment. The differences in LVEF observed between baseline and regorafenib treatment are small, statistically not significant and clinically not relevant, suggesting that regorafenib does not have a negative impact on cardiac contractility.

Renal safety

The overall incidence of proteinuria was increased in patients treated with regorafenib as compared to patients in placebo arms. Proteinuria was mostly of grade 1–2, with a low frequency of grade 3 events.

Patients with cardiovascular risk factors (diabetes, hypertension, hyperlipidaemia) did not show an increased risk of renal toxicity. In pool 3, the incidence of renal failure events (including acute renal failure) was 2.5% in the regorafenib group and 1.9% in the placebo group. There was no detrimental effect of regorafenib on estimated glomerular filtration rate (eGFR), also after analysing subgroups. No imbalance in creatinine value increase between patients treated with regorafenib and patients in placebo arms were observed in pools 2 (GIST) and 3 (GIST and mCRC).

Assessment according to Risk Injury Failure criteria showed no increased risk for patients treated with regorafenib as compared to patients in placebo arm in pools 2 and 3, neither overall nor for subgroups that were analysed.

Hepatic events

Hepatotoxicity has been identified as an important ADR in regorafenib clinical trials.

There is a treatment effect of regorafenib leading to an increase in AST / ALT, mostly grade 1–2. Bilirubin increase also occurs, and this can be partly explained by impaired glucuronidation through UGT1A1 inhibition. In pool 2, hepatic failure/injury events were observed in patients also without liver metastases in both treatment groups. General systematic medical review identified 4 cases of severe drug-induced liver injury (DILI). All 4 cases were considered drug related. Given an overall number of over 3500 patients exposed to regorafenib in interventional studies, this number corresponds to an incidence of severe DILI of approximately 0.11% (as of 28 FEB 2013).

Data seem to strongly indicate that regorafenib-induced liver dysfunction predominantly occurs during the first 2 months of treatment. Recovery was observed following drug interruption or discontinuation in most of the cases of significant transaminases elevations and in cases with mild to moderate liver dysfunction suspected to be regorafenib-related. Remedial treatments in 3 out of 4 cases of severe DILI did not prevent further deterioration.

Haemorrhage

In the two phase III trials in patients with GIST and mCRC the overall incidence of haemorrhage/bleeding events was 19.3%. Most cases of bleeding events in patients treated with regorafenib were mild to moderate in severity (Grades 1 and 2: 16.9%).

This AE did not lead to drug discontinuation in the vast majority of patients.

Skin and subcutaneous disorders

Skin and subcutaneous AEs were common in patients treated with regorafenib, especially HFSR and rash. In pool 2 the incidence of AEs of HFSR was 65.9% in the regorafenib group and 15.2% in the placebo group. The incidence of AEs of HFSR overall was 49.7% in pool 1, 49.5% in the regorafenib group in pool 2, and 8.8% in the placebo group in pool 3.

Vascular safety

Hypertension is common among patients treated with regorafenib: the majority of hypertension occurs during the first two cycles of treatment. Hypertension had a high incidence in all treatment groups across pool 2. In pool 2 the incidence in the regorafenib group was 59.1%, compared to 36.1% in Pool 1 and 36.4% in pool 3. In the placebo group the incidence was 27.3% in Pool 2 and 11.9% in pool 3.

Hypertension (overall incidence in pools 1 and 3) is more common in Asians; however, the incidence of grade 3 hypertension in Asians is similar to that in Caucasians. The incidence of hypertension is similar irrespective of baseline history of hypertension, except for grade 3 which is more common in those with pre-existing history of hypertension.

Overall, there was no indication of a venous thromboembolism signal, as the event rates were low and similar between regorafenib and placebo in pool 2 and pool 3. For arterial thromboembolism, the only signal seen was for myocardial ischaemia/infarction. For cerebrovascular or other arterial thrombosis events, no increased incidence was observed in regorafenib-treated patients.

Neurological disorders

Reversible posterior leukoencephalopathy syndrome (RPLS): One case has been reported in the Phase 3 GIST trial (14874), and it was considered to provide sufficient evidence for a causal link.

Gastrointestinal disorders

Diarrhoea and mucositis (primarily mucosal inflammation and stomatitis) are the most common gastrointestinal disorders, and the majority of cases are mild to moderate severity.

Serious gastrointestinal events are mostly reflective of the underlying disease. The data are suggestive of a possible increase in the risk of GI perforation/fistula in regorafenib-treated patients.

Infections

The data showed an increased risk of infection in regorafenib-treated patients. In the two phase III trials in patients with GIST or mCRC infections were more often observed in patients treated with regorafenib as compared to patients receiving placebo (all grades: 31.0% vs. 14.4%).

Most infections were mild to moderate in severity (Grades 1 and 2: 22.9%) and included urinary tract infections (6.8%) as well as mucocutaneous and systemic fungal infections (2.4%). There is no increased risk of clinically severe infection events with regorafenib treatment.

Wound healing

Data from the safety database including more than 3500 cancer patients treated with regorafenib in clinical trials did not provide any conclusive evidence for an increased risk of impaired wound healing following regorafenib treatment.

Serious adverse event / deaths / other significant events

Serious Adverse Events (SAEs)

The total incidence of SAEs in pool 2 was 28.8% in the regorafenib group and 21.2% in the placebo group. In the regorafenib group in pool 1 the incidence of SAEs was 45.3% and in pool 3 regorafenib group 40.7% and placebo group 35.7%.

The most commonly reported SAE in both treatment groups in pool 2 was abdominal pain (3.8% in the regorafenib group and 4.5% in the placebo group).

In pool 1 the most commonly reported SAE was general physical health deterioration (4.1%), this was also the most commonly reported SAE in both the regorafenib group (6.0%) and the placebo group (7.8%) in pool 3.

The incidence of drug-related SAEs in pool 2 was 8.3% in the regorafenib group and 3.0% in the placebo group.

In the regorafenib group, the most common drug-related SAEs were dehydration and diarrhoea, each reported in 1.5% of patients. All other drug-related SAEs were only reported in individual patients in both treatment groups.

The incidence of drug-related SAEs in pool 1 was 14.2%. The most commonly reported drug related SAEs in pool 1 were diarrhoea (1.3%), fatigue (0.9%), hypertension, dehydration and pyrexia (each reported in 0.7%).

The most commonly reported drug-related SAEs in the regorafenib group in pool 3 were diarrhoea (1.4%) and pyrexia (0.8%). In the placebo group in pool 3, drug-related SAEs were only reported in individual patients (0.3%)

Table 16. Serious adverse events in ≥1% of patients in any treatment group by MedDRA

	Pool 2				Pool 1		Pool 3			
	Placebo		Regorafenib		Regorafenib		Placebo		Regorafenib	
	N = 66		N = 132		N = 1073		N = 319		N = 632	
MedDRA PT	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
Any SAE	**14**	**(21.2)**	**38**	**(28.8)**	**486**	**(45.3)**	**114**	**(35.7)**	**257**	**(40.7)**
Abdominal pain	3	(4.5)	5	(3.8)	32	(3.0)	5	(1.6)	17	(2.7)
Ascites	0	(–)	3	(2.3)	11	(1.0)	2	(0.6)	4	(0.6)
Dehydration	1	(1.5)	3	(2.3)	13	(1.2)	3	(0.9)	6	(0.9)
Pyrexia	0	(–)	3	(2.3)	27	(2.5)	1	(0.3)	17	(2.7)
Asthenia	1	(1.5)	2	(1.5)	7	(0.7)	4	(1.3)	6	(0.9)
Diarrhoea	0	(–)	2	(1.5)	18	(1.7)	0	(–)	10	(1.6)
Gastrointestinal stromal tumour	2	(3.0)	2	(1.5)	3	(0.3)	2	(0.6)	2	(0.3)
General physical health deterioration	1	(1.5)	2	(1.5)	44	(4.1)	25	(7.8)	38	(6.0)
Pulmonary embolism	0	(–)	2	(1.5)	11	(1.0)	2	(0.6)	6	(0.9)
Tumour haemorrhage	0	(–)	2	(1.5)	5	(0.5)	0	(–)	3	(0.5)
Dyspnoea	0	(–)	1	(0.8)	18	(1.7)	3	(0.9)	11	(1.7)
Fatigue	1	(1.5)	1	(0.8)	16	(1.5)	4	(1.3)	2	(0.3)
Hepatic function abnormal	1	(1.5)	1	(0.8)	10	(0.9)	3	(0.9)	6	(0.9)
Nausea	1	(1.5)	1	(0.8)	6	(0.6)	1	(0.3)	1	(0.2)
Pneumonia	0	(–)	1	(0.8)	17	(1.6)	4	(1.3)	11	(1.7)
Cholecystectomy	1	(1.5)	0	(–)	0	(–)	1	(0.3)	0	(–)
Hyperglycaemia	1	(1.5)	0	(–)	1	(<0.1)	1	(0.3)	0	(–)
Mania	1	(1.5)	0	(–)	0	(–)	1	(0.3)	0	(–)
Mental status change	1	(1.5)	0	(–)	1	(<0.1)	1	(0.3)	0	(–)
Non-cardiac chest pain	1	(1.5)	0	(–)	0	(–)	1	(0.3)	0	(–)
Rebound effect	1	(1.5)	0	(–)	0	(–)	1	(0.3)	0	(–)
Infection	0	(–)	0	(–)	13	(1.2)	0	(–)	4	(0.6)
Hepatic failure	0	(–)	0	(–)	12	(1.1)	2	(0.6)	7	(1.1)
Intestinal obstruction	0	(–)	0	(–)	10	(0.9)	2	(0.6)	7	(1.1)
Multi-organ failure	0	(–)	0	(–)	7	(0.7)	4	(1.3)	6	(0.9)
Small intestinal obstruction	0	(–)	0	(–)	7	(0.7)	5	(1.6)	3	(0.5)
Back pain	0	(–)	0	(–)	8	(0.7)	4	(1.3)	1	(0.2)
Hyperbilirubinaemia	0	(–)	0	(–)	12	(1.1)	2	(0.6)	3	(0.5)

MedDRA = Medical Dictionary for Regulatory Activities; PT = preferred term; SAE= serious adverse event

Deaths

In pool 1 comprising all regorafenib treated patients in company-sponsored studies with an available clinical study report (1073 treated patients) including open-label phase for study 14874, there was a total of 126 deaths (11.7%) reported during treatment and up to 30 days post permanent treatment discontinuation.

The most commonly reported reason for death in this pool was progressive disease. Otherwise, AE associated with progressive disease cased death in 98 patients. One of these patients had additionally deep vein thrombosis with fatal outcome, which the investigator reported as related to regorafenib.

Twelve deaths were reported as due to AEs not associated with clinical disease progression. These included bleeding events (5 patients: upper GI haemorrhage [1]; rectal and vaginal haemorrhage [1]; pulmonary haemorrhage [1]; and intracranial haemorrhage [1]; thigh hematoma [1]), pneumonia (2 patients), cardiac arrest (1 patient), intestinal obstruction (1 patient), cerebrovascular accident (1 patient), sudden death (1 patient), and acute hepatic failure (1 patient).

Of these 12 deaths, 7 were considered by the investigators as related to regorafenib.

Four deaths were reported as 'toxicity due to study treatment': cardiac arrest (2 patients), pulmonary embolism (1 patient) and pneumonia (1 patient). Of these 4 deaths, 3 were considered by the investigators as related to regorafenib (the death due to pneumonia was considered unrelated to regorafenib).

Three deaths were reported as due to an unknown cause, however, in 2 of these, renal failure and cardiac arrest were additionally reported as events with a fatal outcome. Only one of these 3 deaths was considered by the investigator as related to regorafenib.

For 7 patients, the investigator reported a cause of death "other" in the case report form with the following specification: azotaemia and metabolic acidosis (in the same patient), haemoptysis, disease progression, worsening of general condition, large bowel perforation, cachexia, and respiratory distress syndrome. Of these 7 deaths, 3 were considered by the investigators as related to regorafenib.

In pool 2 (study 14874, patients with GIST, double-blind phase), 7 patients (5.3%) in the regorafenib group and 3 patients (4.5%) in the placebo group died either during treatment or up to 30 days post permanent treatment discontinuation.

Two patients (3.0%) in the placebo group died of progressive disease with the study observation phase, and one patient (1.5%) experienced a grade 5 event (asthenia), but the cause of death was also reported as progressive disease. In the regorafenib group, 4 patients (3.0%) died of progressive disease, 2 patients (1.5%) died of an AE not associated with clinical disease progression (1 due to cardiac arrest and 1 due to acute hepatic failure), and 1 patient (0.8%) died of other causes (azotaemia and metabolic acidosis).

Table 17. Overview of deaths during treatment and up to 30 days post permanent treatment discontinuation

	Pool 2		Pool 1	Pool 3	
	Placebo	Regorafenib	Regorafenib	Placebo	Regorafenib
	N = 66 n (%)	N = 132 n (%)	N = 1073 n (%)	N = 319 n (%)	N = 632 n (%)
All	**3 (4.5)**	**7 (5.3)**	**126 (11.7)**	**44 (13.8)**	**76 (12.0)**
AE not associated with clinical disease progression	0 (–)	2 (1.5)	12 (1.1)	3 (0.9)	10 (1.6)
AE associated with clinical disease progression	0 (–)	0 (–)	3 (0.3)	0 (–)	0 (–)
Missing	0 (–)	0 (–)	2 (0.2) [a]	0 (–)	0 (–)
Other	0 (–)	1 (0.8)	7 (0.7)	2 (0.6)	2 (0.3)
Progressive disease	3 (4.5) [b]	4 (3.0)	95 (8.9)	38 (11.9)	62 (9.8)
Toxicity due to study treatment [c]	N/A	N/A	4 (0.4)	N/A	N/A
Unknown	0 (–)	0 (–)	3 (0.3)	1 (0.3)	2 (0.3)

AE = adverse event, N/A not applicable
a. The investigator terms were "intestinal perforation" for both
b. 1 of these patients had drug-related grade 5 asthenia
c. 11651 and 11726 study-specific option in the case report form

Laboratory findings

The treatment-emergent laboratory test abnormalities reported in placebo-controlled phase III trial (double-blind phase) in patients with GIST (GRID) are presented in the table below.

Table 18. Treatment-emergent laboratory test abnormalities reported in placebo-controlled phase III trial (double-blind phase) in patients with GIST (GRID)

Laboratory parameter, (in % of samples investigated)	Stivarga plus BSC (N=132)			Placebo plus BSC (N=66)		
	All Grades*	Grade 3*	Grade 4*	All Grades*	Grade 3*	Grade 4*
Blood and lymphatic system disorders						
Haemoglobin decreased	75.0	3.0	0	72.7	1.5	0
Platelet count decreased	12.9	0.8	0	1.5	0	1.5
Neutrophil count decreased	15.9	2.3	0	12.1	3.0	0
Lymphocyte count decreased	29.5	7.6	0	24.2	3.0	0
Metabolism and nutrition disorders						
Calcium decreased	16.7	1.5	0	4.5	0	0
Potassium decreased	20.5	3.0	0	3.0	0	0
Phosphate decreased	54.5	19.7	1.5	3.1	1.5	0
Hepatobiliary disorders						
Bilirubin increased	33.3	3.0	0.8	12.1	1.5	0
AST increased	58.3	3.0	0.8	47.0	3.0	0
ALT increased	39.4	3.8	0.8	39.4	1.5	0
Renal and urinary disorders						
Proteinuria	38.5	1.5	-	39.0	1.7	-
Investigations						
INR increased**	9.3	1.6	-	12.5	4.7	-
Lipase increased	14.4	0	0.8	4.6	0	0

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

** International normalized ratio

\- No Grade 4 denoted in Common Terminology Criteria for Adverse Events (CTCAE), Version 4.0

Safety in special populations

Hepatic impairment

Regorafenib is cleared primarily by the liver. In general, no relevant differences in safety issues were observed in clinical studies between patients with mild hepatic impairment and normal hepatic function. There were few differences seen among subgroups based on hepatic function at baseline, and these differences were mostly reflective of events related to the underlying liver pathology.

Effect on variables related to hepatic function was evaluated in the combined population PK analysis of Phase 3 studies 14387 and 14874. Of the evaluated variables (total bilirubin levels at baseline, ALT, AST, alkaline phosphatase and hepatic function categories), only the total bilirubin level had shown an

influence on the PK of regorafenib and its metabolites M-2 and M-5. Higher bilirubin level at baseline was correlated with increased exposure of parent regorafenib, M-2 and not significantly with M-5.

The observed effect was not considered clinically relevant in light of the observed high overall variability in the exposure of regorafenib, M-2 and M-5.

Data from the HCC cohort (study 11651) indicated that the exposure of regorafenib and its metabolites is comparable in patients with mild hepatic impairment (Child-Pugh A) and patients with normal hepatic function. This is confirmed by multiple dose data from Korean HCC patients (Child-Pugh A) receiving 160 mg regorafenib in the intermittent dosing schedule (Study 14596) when comparing historically to data in patients with normal hepatic function. Limited data in patients with moderate hepatic impairment (Child-Pugh B) indicate similar exposure as compared to patients with normal hepatic function after a single 100 mg dose of regorafenib (Study 11651).

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

Renal impairment

Regorafenib is eliminated primarily by the liver, so renal dysfunction per se would not be expected to have a direct effect on regorafenib PK. In clinical studies, no relevant differences in safety or efficacy were observed between patients with mild or moderate renal impairment and patients with normal renal function.

The steady-state exposure of regorafenib and its metabolites is comparable in patients with mild renal impairment and patients with normal renal function (Study 11650). This finding is in line with the results of the combined population PK analysis of studies 14387 and 14874. These show no indicating of a significant influence of the factor glomerular filtration rate on the PK of regorafenib, M-2 or M-5.

Limited data from pooled Phase 1 and 2 studies further indicate that the range of exposure in patients with moderate renal impairment is comparable to that seen in patients with normal renal function.

Overall, there was no apparent relationship between regorafenib pharmacokinetics and renal function. The pharmacokinetics of regorafenib has not been studied in patients with severe renal impairment or end-stage renal disease. However, physiology-based pharmacokinetics modelling does not predict any relevant change in exposure in these patients (Study 16392).

Paediatric population

No studies in paediatric populations have been performed to date with regorafenib, therefore no data on safety of regorafenib in paediatric patients are available.

Age

In clinical studies, no relevant differences in exposure, safety or efficacy were observed between elderly (aged 65 years and above) and younger patients. Of note, HFSR was seen across all pools more often in patients below 65 years than in patients of 65 years or older. Across all clinical trials, cardiac disorder events (all grades) have been more often (20.5% vs. 10.4%) reported in regorafenib-treated patients aged 75 years or older (N=78) as compared to regorafenib-treated patients below 75 years (N=995).

Age did not affect the regorafenib pharmacokinetics over the studied age range of 29 to 85 years. In addition, in the combined population PK analysis of studies 14387 and 14874 age had no significant influence on the PK of regorafenib, M-2 and M-5. No dose adjustment is necessary in elderly patients.

The safety and efficacy of regorafenib in patients below 18 years of age have not been established. This is mentioned in the Product Information.

Race

In the regorafenib treated patients, there was a higher incidence in Asians of HFSR. Palmar-plantar erythrodysaesthesia syndrome was observed in 30 patients of Asian ethnicity (88.2%) whereas 53 patients (59.6%) were from non-Asian ethnicity.

Discontinuation due to adverse events

The incidence of AEs leading to discontinuation of study drug in pool 2 (patients with GIST, study 14874) was 6.1% (8 patients) in the regorafenib group and 7.6% (5 patients) in the placebo group.

No TEAE leading to discontinuation from treatment was reported for more than one patient in either treatment group. TEAEs leading to discontinuation of study drug for the regorafenib treated patients were acute hepatic failure, alanine aminotransferase increased, aspartate aminotransferase increased, azotaemia, hematemesis, ileus, metastatic pain, pneumonia, posterior reversible encephalopathy syndrome and for the placebo group ascites, asthenia, dehydration, gastrointestinal stromal tumour and hepatic function abnormal.

In pool 1, the incidence of AEs leading to discontinuation of study drug was 20.5%. In pool 3 the incidence was 11.6% in the placebo group and 15.2% in the regorafenib group.

General physical health deterioration was the most common AE leading to discontinuation in all treatment groups of pool 1 and 3. Its incidence was 1.8% in pool 1, 2.5% in the placebo group in pool 3, and 2.8% in the regorafenib group in pool 3. Fatigue (1.2% in pool 1 and 0.5% in pool 3) and HFSR (1.2% in Pool 1 and 1.1% in Pool 3) were the other TEAEs that led to discontinuation of study drug in ≥ 1% of regorafenib-treated patients in pool 1 and pool 3.

Post marketing experience

The so far reported SAEs in the post-marketing setting (as of February 28th 2013) are overall in line with the known safety profile of regorafenib outlined in current product information. To date, no new safety signal for regorafenib has been observed based on the received post-marketing reports.

2.5.2. Discussion on clinical safety

Median duration of the safety follow-up of patients was relatively short. An updated safety analysis when final overall survival data of the pivotal 14874 study will be available will be provided in order to address this safety issue (see RMP).

The safety profile of regorafenib is considered consistent across studies. The toxicity profile was typical for a small molecule that induces inhibition of the VEGFR and other tyrosine kinase-mediated pathways: hypertension, skin (hand-foot syndrome, rash) and gastrointestinal toxicities (diarrhoea, mucositis). Hematologic toxicity is comparably limited.

In the patients treated for GIST (pool 2) remarkably high frequencies of the most common TEAEs with regorafenib were observed also in terms of HFSR (65.9% in the regorafenib group versus 15.2% in the placebo group) and hypertension (59.1% vs 27.3%). In pool 3 (phase 3 studies in GIST and CRC patients), the most common TEAEs in the regorafenib group were also HFSR (49.5% vs 8.8%) and hypertension (36.4% vs 11.9%).

The most serious adverse drug reactions in patients receiving regorafenib were haemorrhage, severe liver injury, and gastrointestinal perforation. In the two phase III trials on patients with GIST and mCRC the overall incidence of haemorrhage events was 19.3%. Haemorrhage does not appear to be due to thrombocytopenia or a coagulation disturbance (INR or aPTT increase), hence is more likely to be a vascular effect on the endothelium. Risk factors in patients with serious bleeding events treated with regorafenib are the same as in the untreated target population (anti-coagulating drugs, presence of tumour lesions e.g. primary GI tumours for GI bleeding, lung metastases for pulmonary bleeding). Although most cases of bleeding events in patients treated with regorafenib were mild to moderate in severity (Grades 1 and 2: 16.9%), this remains a disadvantage however it is an acceptable AE in view of the nature of the disease.

Few cases encountered TEAE drug-induced liver injury (DILI) according to the international DILI working group criteria. All 4 were considered drug related. This is reflected in the SmPC.

Overall, the incidence and pattern of the most common AEs are similar across all 3 pools of patients analyzed for toxicity and the pattern was consistent with the incidence of other drugs in this class.

Of note, hypertension and HFSR were observed at a higher incidence in pool 2 for regorafenib treated patients compared to other pools. It is noted that the incidences were also higher in the placebo group of pool 2 than in pool 3. Since the longer exposure (median 22.9 weeks) in patients with GIST versus patients with mCRC (10.0 weeks), an explanation can be aggravation of the drug induced toxicity that has evolved during the early phase of treatment. HFSR events are generally mild to moderate in severity, easily manageable with dose interruptions and/or dose reductions, and are reversible in nature.

Within the regorafenib safety database on patients treated for GIST one event of hypertensive crisis associated with development of reversible posterior leukoencephalopathy syndrome (RPLS or PRES) was observed. As this ADR was also observed in the treatment for mCRC the warning on the risk in the Product Information is acceptable. Since a main cause for RPLS can be hypertension 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. Treatment with certain small molecules is often associated with proteinuria. In view of the prognosis of patients with GIST in need for 3rd line treatment with regorafenib the hazards to encounter renal failure as an eventual result of proteinuria can be considered acceptable (section 4.4 of the SmPC).

The impact of certain TKIs on the disturbance of haemostatis becomes readily known. Thrombotic microangiopathy is included in the RMP as an important potential risk.

2.5.3. Conclusions on clinical safety

The present type II application presents data on the toxicity profile that shows consistency across studies.

Prominent ADR as palmar plantar erythrodysaestesia and hypertension are known for an angiogenic and a multi-tyrosine kinase inhibitor. These ADRs were also reported from the treatment with regorafenib in patients with mCRC, albeit in particular these ADRs are reported substantially more often in patients with GIST. Other ADRs like proteinuria, rash and gastrointestinal toxicities (vomiting, diarrhea, mucositis) were also reported frequently, whereas hematologic toxicities were limited.

2.6. Risk management plan

2.6.1. PRAC advice

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 2.3, the PRAC considers by consensus that the risk management system for regorafenib (Stivarga) in the treatment of:

Unresectable or metastatic gastrointestinal stromal tumors (GIST) who have progressed on or are intolerant to prior treatment with imatinib and sunitinib is acceptable. This advice is based on the following content of the Risk Management Plan:

Safety concerns

The applicant identified the following safety concerns in the RMP:

Summary of safety concerns	
Important identified risks (confirmed by clinical data)	• Severe drug-induced liver injury (DILI) • Cardiac ischemic events • Hypertension and hypertensive crisis • Hemorrhage • Hand-foot skin reaction (HFSR) • Posterior reversible encephalopathy syndrome (PRES) • Gastroinestinal perforation and fistulae • Stevens-Johnson syndrome (SJS) /Toxic epidermal necrolysis (TEN)
Important potential risks (not refuted by clinical data or which are of unknown significance)	• Wound healing complications • Interstitial lung disease (ILD) • Atrial fibrillation • Reproductive and developmental toxicity • Renal failure • Phototoxicity • Thrombotic microangiopathies (TMA)
Missing information	• Safety in severe hepatic impairment • Safety in children

Summary of safety concerns	
	• 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 • Long-term safety in GIST patients

The PRAC agreed to the revised RMP.

Pharmacovigilance plans

Table 19. Ongoing and planned studies in the PhV development plan

Study / activity type, title and category (1-3)	Objectives	Safety concerns addressed	Status (planned, started)	Date for submission of interim or final reports (planned or actual)
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 Category (3)	• To provide Stivarga® to subjects diagnosed with metastatic CRC who have failed all approved standard therapies • To assess the safety of Stivarga® • To assess PFS	Severe DILI Cardiac ischemic events Hypertension and hypertensive crisis Hemorrhage HFSR PRES GI perforation and fistulae SJS/TEN Wound healing complications ILD Atrial fibrillation Phototoxicity Renal failure Safety in patients with a cardiac history	Final protocol Version 2.0, date: 3 August 2012	**Planned date for submission of interim data** Not applicable **Planned date for submission of final data** March 2015
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	• To provide Stivarga® to subjects diagnosed with metastatic CRC who have failed all approved standard therapies • To assess the safety of Stivarga® • To assess PFS	Atrial fibrillation Activity in KRAS mutated tumours or other biomarker-defined tumour subtypes	Final protocol Version 2.0, date: 28 Dec 2012	**Planned date for submission of interim data** Not applicable **Planned date for submission of final data**

Study / activity type, title and category (1-3)	Objectives	Safety concerns addressed	Status (planned, started)	Date for submission of interim or final reports (planned or actual)
metastatic colorectal cancer (CRC) who have progressed after standard therapy (CONCUR) Eudra CT No.: NA Category (1)				December 2014
15983 A Randomized, 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 EudraCT no.: 2012-004369-42 Category (1)	To further explore whether or not KRAS mutation status predicts regorafenib efficacy	Activity in KRAS mutated tumours or other biomarker-defined tumour subtypes	Final Protocol Version 1; date 08 August 2013	Planned date for submission of final data: 31/12/2020 Submission of results of genetic (including NRAS, KRAS, BRAF and PIK3CA) and non-genetic (ANG-2, IL-6, IL-8, PlGF, VEGFR-1, TIE1, VEGF-A, VEGF-C, VEGF-D, VEGF-A-121, BMP-7, VWF, M-CSF, SDF-1, IGFBP2) appropriate biomarker analyses: 31/12/2020 In addition an annual report will be submitted
14814 An open-label, non-randomized Phase I study of Regorafenib (BAY 73-4506) to evaluate cardiovascular safety parameters, tolerability, pharmacokinetics, and anti-tumor	To evaluate the effect of regorafenib on cardiovascular safety parameters, specifically QT/QTc intervals and LVEF	Safety in patients with a cardiac history	Final protocol Version 2; date: 4 August 2011	**Planned date for submission of interim data** Not applicable **Planned date for submission of final data** Addendum to the CSR

Study / activity type, title and category (1-3)	Objectives	Safety concerns addressed	Status (planned, started)	Date for submission of interim or final reports (planned or actual)
activity in patients with advanced solid tumors Eudra CT No.: NA Category (3)				including longer term LVEF results will be generated and provided approximately 12 months following last patient last visit or by Dec 2014, in case the last patient currently on the study continues on drug beyond December 2013
16675 Single-center, open-label, non-randomized, two-period sequential treatment study to assess the effect of neomycin on the pharmacokinetics of regorafenib in healthy male subjects. Effect of neomycin on the pharmacokinetics of regorafenib Category (3)	Objectives of the study: Comparison of the PK of regorafenib in healthy volunteers with and without concomitant antibiotic pre-treatment.	Interaction with anibiotics	Final protocol Version 2; date: 20 Aug 2013	Q2/2015
16674 A Phase I, multi-center, non-randomized, open label, drug-drug-interaction study to determine the effect of multiple doses of regorafenib (BAY 73-4506) on the pharmacokinetics of probe substrates of transport proteins P-gp (digoxin; Group A) and BCRP (rosuvastatin; Group B) in patients with advanced solid	Compare the PK of the selected BCRP substrate with and without concomitant regorafenib	Interaction with BCRP substrates	Final protocol Version 2; date:17 Dec 2013	Q4/2015

Study / activity type, title and category (1-3)	Objectives	Safety concerns addressed	Status (planned, started)	Date for submission of interim or final reports (planned or actual)
malignant tumors. Category (3)				
14874 A randomized, double-blind, placebo-controlled phase III study of regorafenib plus best supportive care versus placebo plus best supportive care for subjects with metastatic and/or unresectable gastrointestinal stromal tumors (GIST) whose disease has progressed despite prior treatments with at least imatinib and sunitinib Category (3)	To retrospectively analyze whether c-Kit Exon 11 status in plasma samples obtained from GIST patients at baseline within Study 14874 predicts regorafenib efficacy/safety To retrospectively analyze IGFBP2 using immunohistochemistry in archival tumor specimens from GIST patients enrolled in Study 14874 To analyze 280 known Oncogenes (Foundation Medicine FOUNDATION ONE panel, Next Generation Sequencing approach) in archival tumor specimens from GIST patients enrolled in Study 14874 with respect to regorafenib efficacy/safety Further safety data for GIST patients on long-term treatment with Stivarga® will be collected in ongoing 14874 GRID study.	Activity in other biomarker-defined tumour subtypes Missing information: Long-term safety data in GIST patients	Final protocol Version 4.0; date: 27 SEP 2011	Planned date for submission of "Retrospective analysis of c-Kit Exon 11 status" in plasma samples and IGFBP2 and 280 known Oncogenes (Foundation Medicine FOUNDATION ONE panel) in archival tumor specimens: Q1 2015 Planned date for submission on long-term safety data from study 14874: Q2 2015

The PRAC, having considered the data submitted, was of the opinion that the proposed post-authorisation PhV development plan is sufficient to identify and characterise the risks of the product.

The PRAC also considered that routine PhV is sufficient to monitor the effectiveness of the risk minimisation measures.

Risk minimisation measures

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
Important identified risks		

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
Severe drug-induced liver injury (DILI)	Labeling: 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'	Not applicable
Cardiac ischemic events	Labeling: SmPC Section 4.4. 'Warnings and precautions for use' and section 4.8 'Undesirable effects'	Not applicable
Hypertension and hypertensive crisis	Labeling: SmPC Section 4.4. 'Warnings and precautions for use' and section 4.8 'Undesirable effects'	Not applicable
Hemorrhage	Labeling: SmPC Section 4.4. 'Warnings and precautions for use' and section 4.8 'Undesirable effects'	Not applicable
Hand-foot skin reaction (HFSR)	Labeling: 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'	Not applicable
Posterior reversible encephalopathy syndrome (PRES)	Labeling: SmPC Section 4.4. 'Warnings and precautions for use' and section 4.8 'Undesirable effects'	Not applicable
Gastrointestinal (GI) perforation and fistulae	Labeling: SmPC Section 4.4. ' Warnings and precautions for use' and section 4.8 'Undesirable effects'	Not applicable
Stevens-Johnson syndrome (SJS)Toxic epidermal necrolysis (TEN)	Labeling: SmPC Section 4.8 'Undesirable effects'	Not applicable
Important potential risks		
Wound healing complications	Labeling: SmPC Section 4.4. 'Warnings and precautions for use'	Not applicable
Interstitial lung disease (ILD)	None	Not applicable
Atrial fibrillation	None	Not applicable
Reproductive and developmental toxicity	Labeling: Section 4.6. 'Fertility, pregnancy and lactation'	Not applicable
Renal failure	None	Not applicable
Phototoxicity	None	Not applicable

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
Thrombotic microangiopathies (TMA)	None	Not applicable
Missing information		
Safety in severe hepatic impairment	Labeling: Section 4.2 ('Posology and method of administration'), 4.4 ('Warnings and Precautions') and 5.2 ('Pharmacokinetic Properties')	Not applicable
Safety in children	Labeling: Section 4.2 'Posology and method of administration'	Not applicable
Safety in patients with a cardiac history	Labeling: Section 4.4 'Warnings and precautions for use'	Not applicable
Safety in severe renal impairment	Labeling: Section 4.2 'Posology and method of administration'	Not applicable
Interaction with antibiotics	Labeling: Section 4.5 'Interaction with other medicinal products and other forms of interaction'	Not applicable
Interaction with BCRP substrates	Labeling: Section 4.5 'Interaction with other medicinal products and other forms of interaction'	Not applicable
Activity in KRAS mutated tumours or other biomarker-defined tumour subtypes	Labeling: Section 4.4 'Warnings and precautions for use', 5.1 'Pharmacodynamic properties'	Not applicable
Long-term safety in GIST patients	None	Not applicable

The PRAC, having considered the data submitted, was of the opinion that the proposed risk minimisation measures are sufficient to minimise the risks of the product in the proposed indication.

The CHMP endorsed this advice without changes.

2.7. Update of the Product information

As a consequence of this new indication, sections 4.1, 4.2, 4.8, 5.1 and 5.3 of the SmPC have been updated. The Package Leaflet has been updated accordingly.

No full user consultation with target patient groups on the package leaflet has been performed on the basis of a bridging report making reference to Stivarga 40 mg film-coated tablets. The justification for not performing neither a full nor a focused user testing is acceptable since the main key elements have not changed (including posology instructions) and the same style of language and layout is used.

The only substantial change affects section "What Stivarga is and what it is used for" and "Possible side effects" of the PL; the latter section has changed as follows: "feeling sick (nausea)" and "vomiting"

were added as very common side effects, while “hair loss (alopecia)” was moved from common to very common side effect; “nail disorder (changes to the nail such as ridges and/or splitting)” was moved from common to uncommon side effects.

These modifications are not expected to alter the ability to understand information and to act upon of the user. Moreover, Stivarga is subject to restricted medical prescription by physicians experienced in the administration of anticancer therapy, thus the healthcare professional can adequately offer further assistance.

In conclusion, the bridging report submitted by the MAH is acceptable.

3. Benefit-Risk Balance

Benefits

Beneficial effects

The evidence of efficacy of regorafenib in patients with GIST is based on the results of one pivotal phase III study (study 14874), supported by the data of the phase II 14935 study, enrolling patients with unresectable and/or metastatic GIST who presented disease progression after at least imatinib and sunitinib.

The results of the final PFS based on 144 events (72.4%) (Cut-off 26 Jan 2012) showed a statistically significant improvement (centrally assessed) for regorafenib compared with placebo (HR 0.268, 95% CI 0.185-0.388; p<0.000001), with a gain in median PFS of 119 days in favour of regorafenib. The robustness of the PFS effect is supported by several sensitivity analyses, the results of which are in line with the primary analysis.

This effect was further substantiated by results in the secondary efficacy endpoints: Median time to progression was significantly longer in the regorafenib arm than in the placebo arm (165 days versus 28 days, HR 0.248, p<0.000001). Disease control rate (CR+PR+SD) was significantly higher in the regorafenib arm compared with the placebo arm (41% vs 14.9%, respectively).

Uncertainty in the knowledge about the beneficial effects

In the pivotal 14874 study, the collection of fresh biopsies was optional, not mandatory and plasma samples for genetic and non-genetic biomarkers were collected from patients that consented. As a result, no fresh samples are available (only 5). Therefore, although no difference in terms of activity appears to emerge from the comparison of the different subgroups identified by biomarkers, data are limited by the small sample size and the retrospective nature of the analyses. The MAH has committed to provide post-approval additional biomolecular analyses employing the samples available. The MAH will submit the results of the additional analyses performed as soon as available (expected 1Q 2015). In addition, the MAH has committed to plan adequate biomarker analyses in future studies performed with regorafenib in patients with GIST. This additional information to be provided is included in the RMP.

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 (diarrhea, mucositis) were more common, whereas hematologic toxicities

were less frequent. No new adverse reactions are reported in the pivotal phase III 14874 and the supportive phase II 14935 trial conducted in patients with GIST.

The most serious adverse drug reactions in patients receiving regorafenib were haemorrhage, severe liver injury, and gastrointestinal perforation. In the two phase III trials on patients with GIST and mCRC the overall incidence of haemorrhage events was 19.3%. Although most cases of bleeding events in patients treated with regorafenib were mild to moderate in severity (Grades 1 and 2: 16.9%), this remains a disadvantage however it is an acceptable AE in view of the nature of the disease.

Uncertainty in the knowledge about the unfavourable effects

It is noted that median duration of the safety follow-up of patients is relatively short and thus the long term safety data are not available yet. An updated safety analysis when final overall survival data of the pivotal 14874 study will be provided in order to address this safety issue. This additional information to be provided is included in the RMP.

Balance

Importance of favourable and unfavourable effects

Metastatic and/or unresectable GIST, progressive after imatinib and sunitinib, is a highly invalidating and life threatening condition with an overall infaust prognosis. Currently there are no standard of treatment options in the E.U. for this patient population. Therefore, there is an unmet medical need for a treatment in such a population. Efficacy of regorafenib for the new proposed indication is based on a significant improvement in PFS. The observed HR for PFS favouring the treatment arm appears impressive (0.268), and the gain in median PFS of around 4 months is of clinical relevance.

The adverse events reported were adequately described and were considered acceptable. Fatigue, hand-foot syndrome, anorexia, diarrhoea, weight loss, hypertension, rash, mucositis, fever, hyperbilirubinemia, platelet counts abnormalities, haemorrhage and infections were observed very commonly in patients treated with regorafenib, with a significantly higher incidence compared with placebo-treated patients. Hypertension and hand-foot syndrome were also observed at higher frequency in GIST patients when compared with patients with mCRC.

Benefit-risk balance

In view of the poor prognosis of the metastatic and/or unresectable GIST population experiencing disease progression after imatinib and sunitinib, the results of the pivotal 14874 trial and the supportive 14935 study are considered of clinical relevance. The statistically significant and clinically relevant improvement in PFS supports a clinical benefit associated with regorafenib treatment in the target population.

The ADRs of regorafenib are manageable and are considered acceptable. Therefore, the benefit-risk balance for regorafenib in the target population is positive.

4. Recommendations

Outcome

Based on the review of the submitted data, the CHMP considers the following variation acceptable and therefore recommends the variation to the terms of the Marketing Authorisation, concerning the following change:

Variation accepted		Type
C.I.6.a	Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	II

Extension of indication in the treatment of adult patients with unresectable or metastatic gastrointestinal stromal tumors (GIST) who progressed on or are intolerant to prior treatment with imatinib and sunitinib. As a consequence, sections 4.1, 4.2, 4.5, 4.8, 5.1 and 5.3 of the SmPC have been updated. The Package Leaflet has been updated accordingly. The list of local representatives was also updated in the package leaflet.

Additional data exclusivity / market protection

Furthermore, the CHMP reviewed the data submitted by the MAH, taking into account the provisions of Article 14(11) of Regulation (EC) No 726/2004, and considers that the new therapeutic indication brings significant clinical benefit in comparison with existing therapies (see appendix 1).

REFERENCES

1. Debiec-Rychter M, Sciot R, Le Cesne A, et al. for EORTC Soft Tissue and Bone Sarcoma Group; Italian Sarcoma Group; Australasian Gastrointestinal Trials Group. KIT mutations and dose selection for imatinib in patients with advanced gastrointestinal stromal tumours. Eur J Cancer 2006; 42:1093-103.

2. Heinrich MC, Corless CL, Demetri GD, Blanke CD, von Mehren M, Joensuu H, McGreevey LS, Chen CJ, Van den Abbeele AD, Druker BJ, Kiese B, Eisenberg B, Roberts PJ, Singer S, Fletcher CD, Silberman S, Dimitrijevic S, Fletcher JA. Kinase mutations and imatinib response in patients with metastatic gastrointestinal stromal tumor. J Clin Oncol. 2003 Dec 1;21(23):4342-9.

3. Joensuu H. Gastrointestinal stromal tumor (GIST). Ann Oncol 2006;17 Suppl 10:x280-x286.

4. Mazur MT, Clark HB. Am J Surg Pathol. Gastric stromal tumors. Reappraisal of histogenesis. 1983 Sep;7(6):507-19.

5. Van Glabbeke MM, Owzar K, Rankin C, Simes J, Crowley J, for GIST Meta-analysis Group (MetaGIST). Comparison of two doses of imatinib for the treatment of unresectable or metastatic gastrointestinal stromal tumors (GIST): A metaanalysis based on 1,640 patients. J Clin Oncol 2007; 25:10004.