Australian Government
Department of Health
Therapeutic Goods Administration

AusPAR Attachment 2

Extract from the Clinical Evaluation Report for Regorafenib

Proprietary Product Name: Stivarga

Sponsor: Bayer Australia Pty Ltd

First round evaluation: 22 July 2014

Second round evaluation: 22 October 2014

TGA Health Safety Regulation

About the Therapeutic Goods Administration (TGA)

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About the Extract from the Clinical Evaluation Report

- This document provides a more detailed evaluation of the clinical findings, extracted from the Clinical Evaluation Report (CER) prepared by the TGA. This extract does not include sections from the CER regarding product documentation or post market activities.
- The words [Information redacted], where they appear in this document, indicate that confidential information has been deleted.
- For the most recent Product Information (PI), please refer to the TGA website <https://www.tga.gov.au/product-information-pi>.

Contents

List of abbreviations

Abbreviation	Meaning
ACPM	Advisory committee on prescription medicines
ALT	Alanine aminotransferase
ARTG	Australian register of therapeutic goods
AST	Aspartate aminotransferase
AusPAR	Australian Public Assessment Report
BCRR	Blinded central radiology review
BMI	Body mass index
BSC	Best supportive care
Cav_{md}	Average concentration in plasma after multiple dosing
CBR	Clinical benefit rate
CCDS	Company core data sheet
CHMP, EU	Committee for Medicinal Products for Human use
CL	Clearance
CR	Complete response
CRC	Colorectal cancer
CT	Computed tomography
DCR	Disease control rate
ECG	Electrocardiogram
ECOG PS	Eastern Cooperative Oncology Group performance status
FAS	Full analysis set
FDA	US Food and Drug Administration
GIST	Gastrointestinal stromal tumours
HCC	Hepatocellular carcinoma
HFSR	Hand-foot-skin reaction

Abbreviation	Meaning
HRQoL	Health-related quality of life
IGFBP	Insulin-like growth factor binding protein
IIV	Inter-individual variability
KIT	Mast/stem cell growth factor receptor (tyrosine kinase)
KM	Kaplan-Meier
LLOQ	Lower limit of quantification
LVEF	Left ventricular ejection fraction
mCRC	Metastatic colorectal cancer
MedDRA PT	Medical Dictionary for Regulatory Activities Preferred Term
MRI	Magnetic resonance imaging
MTD	Maximum tolerated dose
MUGA	Multiple gated acquisition scan
NCE	New chemical entity
NCI-CTCAE	National Cancer Institute – Common Terminology Criteria for Adverse Events
NPC	Numerical predictive check
NSCLC	Non-small cell lung cancer
ORR	Overall response rate
OS	Overall survival
PD	Progressive disease
PDGFR	Platelet-derived growth factor receptor
PFS	Progression free survival
PI	Product information
PPES	Palmar-plantar erythrodysesthesia syndrome
PR	Partial response

Abbreviation	Meaning
PRO	Patient reported outcomes
PSUR	Periodic Safety Update Report
QoL	Quality of Life
RECIST	Response evaluation criteria in solid tumours
SAF	Safety analysis set
SAP	Statistical analysis plan
SOC	System organ class
TKI	Tyrosine Kinase inhibitor
TTP	Time to progression
ULN	Upper limit of normal
VEGF	Vascular endothelial growth factor
VPC	Visual predictive check
WT	Wild type

1. Introduction

This is a full submission to extend the indications of regorafenib.

Regorafenib is an oral anti-tumour agent that potentially blocks multiple protein kinases, including kinases involved in tumour angiogenesis (VEGFR1, -2, -3, TIE2), oncogenesis (KIT, RET, RAF-1, BRAF), and the tumour microenvironment (PDGFR, FGFR).

The currently approved indication is: treatment of patients with metastatic colorectal cancer (CRC) who have been previously treated with fluoropyrimidine-, oxaliplatin- and irinotecan-based chemotherapy, an anti-VEGF therapy, and, if KRAS wild type, an anti-EGFR therapy.

The proposed additional indication is:

> *Treatment of patients with gastrointestinal stromal tumours (GIST) who have been previously treated with two tyrosine kinase inhibitors.*

The following dosage forms and strengths are currently registered: 40 mg tablet (41.49 mg regorafenib monohydrate).

No new dosage forms or strengths are proposed.

2. Clinical rationale

As outlined in the sponsor's in covering letter of the submission, the Module 2 Clinical overview and the introduction to pivotal trial 14874:

> *GIST is the most common form of mesenchymal tumour in the gastrointestinal tract. The estimated incidence of GIST in the total population is 11 – 20 patients per million/year.*
>
> *These tumours can start anywhere in the gastrointestinal tract, but they occur most often in the stomach (50% to 70%) or the small intestine (20% to 30%)… Patients tend to be middle aged or older, with a slight male predominance… Aggressive GISTs metastasise to the liver and in the abdomen, rarely to the lymph nodes.*
>
> *The most important criteria for the assessment of the malignant potential of GISTs are tumour size and mitotic rate. Approximately 90% of GISTs express CD117, the antigen based on the KIT receptor tyrosine kinase (RTK), which can be detected by immunohistochemical KIT staining.*
>
> *Primary KIT mutations are found in approximately 70 - 80 % of GIST and occur predominantly in exon 11, occasionally in exon 9, and only rarely in exons 13 and 17. In 4 to 7% of GISTs, mutations are found in platelet-derived growth factor receptor a (PDGFRa), most frequently in exon 18.*
>
> *In patients with metastatic and/or unresectable GIST, molecular targeted therapy has been the focus of the therapeutic approach over the past decade. The role of radiation therapy is generally considered limited in the management of GIST patients. Similarly, attempts to treat GISTs with systemic chemotherapy have been unsuccessful, with responses typically less than 10% at the cost of significant toxicities.*
>
> *Imatinib (Glivec), and upon imatinib failure, sunitinib (Sutent), both tyrosine kinase inhibitors (TKIs), are currently approved for the treatment of metastatic and/or unresectable GISTs in Australia. However despite the activity of sunitinib, the majority of patients with metastatic GIST will progress within 6-9 months and there is no third line therapy with any activity against this disease approved by regulatory authorities anywhere in the world apart from the United States and Canada where STIVARGA is registered for this indication.*

Imatinib and sunitinib may fail due to the clonal emergence of secondary mutations in the tyrosine kinase receptors KIT or PDGFRα, or in signalling molecules such as BRAF which restores receptor signalling activity and leads to tumour relapse.

Treatment options are limited for patients progressing on imatinib and sunitinib. Second-generation TKIs, such as sorafenib, dasatinib, and nilotinib, have shown activity in patients with imatinib- and sunitinib-resistant GIST. Although the current NCCN guidelines allow consideration of other commercially available small molecule kinase inhibitors such as nilotinib or sorafenib, they cannot be regarded as a "standard" or "approved" treatment for patients who have progressed.

Regorafenib, an oral tumour deactivation agent that potently blocks multiple protein kinases, including kinases involved in tumour angiogenesis (vascular endothelial growth factor receptor [VEGFR]1, -2, -3, TIE2), oncogenesis (KIT, RET, RAF-1, BRAF, BRAFV600E), and the tumour microenvironment (platelet derived growth factor receptor [PDGFR], fibroblast growth factor receptor [FGFR]), may potentially overcome the mutation induced resistance through binding to structurally different mutant kinases.

Further, the sponsor's justification for the proposed label given in the Clinical Overview of the *submission states:*

The proposed label considers the currently available approved treatment options for patients with GIST. The only approved treatments for patients with GIST are the two TKIs imatinib and sunitinib. All patients in the pivotal trial (14874) had been treated with these TKIs. They had to present with disease progression on, or intolerance to, imatinib, and disease progression on sunitinib treatment. Patients with GIST have a high unmet medical need and further effective therapies are required. This application presents data demonstrating a positive benefit/risk assessment of regorafenib for this population.

Comment: The clinical rationale for the submission as stated by the sponsor would seem valid and acceptable, for the treatment of aggressive GIST not responding to currently approved therapies, and for which there is no currently approved standard treatment.

2.1. Guidance

The sponsor stated in the Clinical Overview that the development plan for GIST reflected consultation with the US FDA and CHMP, EU, where scientific advice was obtained for the Phase III program in October 2010. In general, agreement was reached with the regulatory agencies on the study design (including PFS as primary endpoint and OS as secondary endpoint, placebo plus BSC for control arm), the acceptability of one Phase III study to support the marketing authorisation, the safety database, and the SAP. It was recommended by the FDA that an interim OS analysis was required at the same time as the PFS evaluation, to confirm that any improvements in PFS are accompanied by a positive trend in OS.

No outstanding issues were identified by the TGA during pre-submission assessment (dated January 2014). By following EU guidance requirements, the application also follows the relevant TGA-adopted guidance documents.

3. Contents of the clinical dossier

3.1. Scope of the clinical dossier

The clinical dossier documented a development program of pharmacological analyses, pivotal and other clinical trials relating to the proposed extension of indications. Updated safety data was also included.

The submission contained the following clinical information which has been evaluated in this CER:

Pharmacokinetic (PK) studies

- PH-36984 (11651) Open label, Phase I study to determine the safety, tolerability, maximum tolerated dose, PK, and biomarker status of BAY 73-4506 in patients with advanced malignancies
- PH-37053 (14996) Uncontrolled, open-label, non-randomised, Phase I study to investigate the PK, safety, tolerability and efficacy of BAY 73-4506 in Chinese patients with advanced, refractory solid tumours

Comment: Interim reports of the above two studies (11651 and 14996) were previously evaluated in the application for the indication of previously treated metastatic CRC [Application PM-2012-02342-3-4, TRIM: R13/354724]. The updated CSRs submitted with this application have been evaluated only with respect to the new information provided.

One pharmacodynamic (PD)study

- PH-36866 (14814) An open-label, non-randomized Phase I study of Regorafenib (BAY 73-4506) to evaluate cardiovascular safety parameters, tolerability, pharmacokinetics, and anti-tumour activity in patients with advanced solid tumours

Comment: The interim report of the above study (14814) was previously evaluated and this submitted final report has been evaluated with respect to changes from the interim report.

Full population pharmacokinetic (Pop PK) analyses

- R-8731 (14653) Population PK analysis of regorafenib and metabolites M2 and M5 in Studies 11650 and 14387
- R-8814 (16282) Population PK analysis of regorafenib and metabolites M2 and M5 in Phase III studies 14387 and 14874

Other Pop PK analysis reports

- PH-37027 (16392) Exploratory analysis of regorafenib PK using physiologically-based PK modelling – effect of hepatic and renal impairment
- PH-37386 Regorafenib dose selection document

One pivotal efficacy/safety study in the proposed indication, and supporting analyses.

- A59137 (14874) A randomised, double-blind, placebo-controlled Phase III study of regorafenib plus best supportive care (BSC) versus placebo plus BSC for subjects with metastatic and/or unresectable GIST whose disease has progressed despite prior treatments with at least imatinib and sunitinib (GRID)
  - PH-37123 (14874) Genetic biomarker analysis of Study 14874 (GRID)
  - PH-37168 (14874) Non-genetic biomarker analysis of Study 14874 (GRID)

Supportive study in the proposed indication, and supporting document

- 14935 Efficacy and safety of regorafenib in patients with metastatic and/or unresectable GIST after failure of imatinib and sunitinib: a multicentre Phase II trial (published journal paper)

One other safety study (not related to proposed indication)

- A62282 (14596) An uncontrolled open label multicentre Phase II safety study of BAY 73-4506 in patients with hepatocellular carcinoma

One pooled safety analysis

- Global integrated analysis of safety (included in Module 2.7.4 Summary of Clinical Safety)

One protocol document related to proposed indication

- 16339 Protocol: An open-label expanded access program of regorafenib in patients with GIST after disease progression on or intolerance to imatinib and sunitinib

3.1.1. Clinical reports not evaluated

The submission also contained the following protocols and reports that have not been fully evaluated in this CER. This is because they were either not directly relevant to the proposed indication in this submission or the safety of regorafenib as monotherapy, or were an exploratory analysis (generally based on the population PK analysis):

- PH-37121 (11728) An uncontrolled, open-label Phase II study in subjects with metastatic adenocarcinoma of the colon or rectum who are receiving first line chemotherapy with mFOLFOX6 in combination with regorafenib
- 15808 Protocol: A randomised, double-blind, placebo controlled Phase III study of regorafenib plus BSC versus placebo plus BSC in Asian subjects with mCRC who have progressed after standard therapy (CONCUR)
- 15967 Protocol: An open-label Phase IIIb study of regorafenib in patients with mCRC who have progressed after standard therapy

Pop PK analysis exploratory reports

- R-8737 (14653) Exposure-response analysis of regorafenib in Phase III Study 14387.
- PH-36914 (14387) –Exploratory analysis of relationship between the exposure to regorafenib parent compound and regorafenib aggregate (regorafenib compound and its two active metabolites M2 and M5) and relevant safety data in Phase III Study 14387
- PH-37122 (14387) - Exploratory analysis of relationship between the exposure to total regorafenib (regorafenib aggregate, irrespective of plasma protein binding) and relevant safety data in Phase III Study 14387
- R-8813 (16282) Exposure-response analysis of regorafenib in Phase III GRID Study 14874 [5.3.3.5.6-1]
- PH-37281 (14874) 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 [5.3.3.5.7-1]
- PH-37105 (14387+14874) 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) and GRID (Study 14874) studies
- R-8715 (14935) A non-randomised open-label, multi-center Phase II study evaluating the efficacy and safety of regorafenib in patients with metastatic and/or unresectable GIST,

resistant or tolerant to at least imatinib and sunitinib. This was an analytical report of bio-analytical samples, and has not been evaluated in this CER.

3.2. Paediatric data

The submission did not include paediatric data. A paediatric investigation plan is in effect in the EU, while a paediatric waiver has been granted in the US due to the impracticality of performing paediatric studies for CRC, and the drug being granted orphan drug status for GIST.

Comment: Due to the low incidence of GIST in the paediatric population, paediatric data is not necessary for this submission.

3.3. Good clinical practice

It was stated that the conduct of all clinical studies submitted in this application met all local legal and regulatory requirements. All studies were stated to have been conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki and the International Conference on Harmonisation (ICH) guideline E6: Good Clinical Practice (GCP).

All population PK and exposure-response evaluations were stated to have been conducted in accordance with the recent FDA guidance on population pharmacokinetics (1999) and reported in accordance with the respective EMEA guideline (2007).

4. Pharmacokinetics

4.1. Studies providing pharmacokinetic data

Table 1 shows the studies relating to each pharmacokinetic. The main pharmacokinetic data submitted with this submission related to population pharmacokinetic analyses.

Table 1: Submitted pharmacokinetic studies.

PK topic	Subtopic		Study ID (report number)	*
PK in special populations	Target population	- Single dose		
		- Multi-dose	14996 (PH-37053, 2nd Interim report)	
	Cancer patients			
	Hepatic impairment			
	Renal impairment			
	Neonates/infants/children/adolescents			
	Elderly			
Genetic/gender-related PK	Males versus females			
	Chinese patients		14996 (PH-37053, 2nd Interim report)	*

Population PK analyses	Healthy subjects		
	Target population	14653 (R-8731) 16282 (R-8814)	* *
	Other		

* Indicates the primary aim of the study. † Bioequivalence of different formulations. § Subjects who would be eligible to receive the drug if approved for the proposed indication.

Table 2 lists pharmacokinetic results that were excluded from consideration due to study deficiencies.

Table 2: Pharmacokinetic results excluded from consideration.

Study ID	Subtopic(s)	PK results excluded
11651 (PH-36984)	Expansion cohort analysis of patients with HCC and NSCLC	Effect of hepatic impairment on regorafenib PK - not based on representative sample
14653 (R-8738)	Exposure-response analysis of regorafenib in Phase III Study 14387	Exploratory analysis – not fully evaluated
14387 (PH-36914)	Exploratory analysis of regorafenib exposure and safety data in Study 14387	Exploratory analysis – not fully evaluated
14387 (PH-37122)	Exploratory analysis of regorafenib exposure and safety data in Study 14387	Exploratory analysis – not fully evaluated
16282 (R-8813)	Exposure-response analysis of regorafenib in Study 14874	Exploratory analysis – not fully evaluated
14874 (PH-37281)	Exploratory analysis of regorafenib exposure and safety data from Study 14874	Exploratory analysis – not fully evaluated
14387+14874 (PH-37105)	Exploratory analysis of regorafenib exposure and pooled safety data from Studies 14387 and 14874	Exploratory analysis – not fully evaluated
16392 (PH-37027)	Exploratory analysis of regorafenib pharmacokinetics using physiologically-based pharmacokinetic (PBPK) modelling – effect of hepatic and renal impairment	Exploratory analysis, based on modelled parameters (no actual patients with hepatic or renal impairment) and in virtual populations, base model not submitted for evaluation.

5. Summary of pharmacokinetics

The information in the following summary is derived from conventional pharmacokinetic studies unless otherwise stated.

5.1. Physicochemical characteristics of the active substance

No new data was presented with this submission.

5.2. Pharmacokinetics in healthy subjects

No new data was presented with this submission.

5.3. Pharmacokinetics in the target population/patients with advanced malignancies

5.3.1. Absorption

No new data was presented with this submission.

As described in the PI: Regorafenib reaches mean peak plasma levels of approximately 2.5 mg/L at approximately three to four hours after a single oral dose of 160 mg regorafenib.

5.3.2. Bioavailability

No new data was presented with this submission.

As described in the PI: The mean relative bioavailability of the tablets compared to an oral solution is 69-83%.

5.3.3. Distribution

No new data was presented with this submission.

The population PK analyses used the Volume of distribution at steady state (VSS) of 88.0L as a fixed parameter, as calculated from Study 11650 (previously evaluated by the TGA).

5.3.4. Metabolism

5.3.4.1. Non-renal clearance

As described in the PI: Regorafenib has been found to be metabolised primarily in the liver by oxidative metabolism mediated by CYP3A4, as well as by glucuronidation mediated by UGT1A9.

In the population PK analyses, parent regorafenib clearance was calculated at 1.45 L/h based on data from Studies 11650, 14387 and 14784.

5.3.4.2. Pharmacokinetics of metabolites

As described in the PI: Two major and six minor metabolites of regorafenib have been identified in plasma. The main circulating metabolites of regorafenib in human plasma are M-2 (N-oxide) and M-5 (N-oxide and N-desmethyl), which are pharmacologically active and have similar concentrations as regorafenib at steady state.

In the population PK analyses a descriptive model was used to describe the data with a minimum of assumptions. Because of this, the PK parameters of the metabolite model can only be used within the context of the model, and not individually, to make statements about the formation, elimination or distribution of the active metabolites M2 and M5.

5.3.5. Excretion

No new data was presented with this submission.

5.3.6. Intra- and inter-individual variability of pharmacokinetics

The population PK analysis found considerable remaining, unexplained, variability in exposure, after taking into account the effects of the significant covariates study (which included study, sex, body weight, BMI, height, age, ethnic group, GFR, total bilirubin, ALT liver enzyme, AST liver enzyme, alkaline phosphatase, hepatic function at baseline). For parent regorafenib, there was a moderate factor of 3.5 between the 5th and 95th percentile Cav_{md} in each of the two studies. The variability in M2 exposure was higher, and the variability in exposure was highest in M5. For parent regorafenib, inclusion of covariate effects caused only a small decrease of the unexplained inter-individual variability (IIV) in CL from CV= 46 % to 44%. For the active metabolites, inclusion of the covariate effects caused a small reduction in the unexplained IIV of KM-M2 from CV= 54% to 50% and in the IIV of FRM5 from CV= 56% to 51%.

Comment: It is agreed with the sponsor that there is large unexplained inter-individual variability in the PK of regorafenib and its main metabolites M2 and M5. However, this evaluator does not agree that the degree of unexplained IIV necessarily discounts the importance of any differences determined for the assessed covariates.

5.4. Pharmacokinetics in other special populations

5.4.1. Pharmacokinetics in subjects with impaired hepatic function

The population PK Study 14653 which was developed based on the PK results from Studies 11650 and 14387 found that clearance of regorafenib and active metabolite M2 (and to a lesser extent metabolite M5) were inversely proportional to bilirubin levels at baseline. It was assessed that this covariate only contributed a small proportion to the overall regorafenib variability and was therefore not clinically significant. In this same study, baseline hepatic function, and ALT, AST, and ALP at baseline were not found to be significant covariates on PK parameters. Similar results were found in the updated population PK analysis 16282, which included data from Study 14874.

Comment: The population PK model was constructed with only a small number of subjects with moderate hepatic impairment, and most subjects had bilirubin levels within the normal range at baseline. Therefore the ability of the model to predict PK in patents with hepatic impairment is considered to be limited, and no definitive conclusions can be drawn regarding the safety of regorafenib in patients with hepatic impartment from this population PK study.

The results of Study 11651 were not considered in this evaluation, as the PK with repeat dosing was not performed for the hepatocellular cancer (HCC) cohort, which was the group used to investigate the PK in patients with hepatic impairment. The PK after a single dose of regorafenib cannot be taken to represent the PK with multiple dosing. In this study it was found that repeat dosing in NSCLC patients found a very high increase in accumulation of regorafenib and its metabolites – of the order of 14 times increase for M-5. Therefore, the PK effect of repeat dosing could be significant in patients with hepatic impairment, and further investigation with repeat dosing in this patient group is warranted.

5.4.2. Pharmacokinetics in subjects with impaired renal function

The population PK Study 14653 and its updated Study 16282 did not find any impact of baseline GFR on the PK of regorafenib or its metabolites.

Comment: Again it is noted that the population PK studies were based on data from studies which had required adequate renal function as inclusion criteria. Therefore, the ability of these population PK analyses to assess the effect of renal impairment on the PK of regorafenib is limited.

5.4.3. Pharmacokinetics according to age

The population PK Study 14653 and its updated Study 16282 did not find any impact of age on the PK of regorafenib or its metabolites.

5.4.4. Pharmacokinetics related to genetic factors

The population PK Study 14653 found there was an effect of sex on the exposure of active metabolite M5, causing relatively higher concentrations in females, and was supported by the updated population PK analysis. However, it was assessed that this covariate only contributed a small proportion to the overall metabolite M5 variability and was therefore not clinically significant.

Comment: It is agreed with the sponsor that the data do not suggest a clinically significant effect of sex on the PK of regorafenib.

5.4.5. Pharmacokinetics in different ethnic groups

The second interim report of Study 14996 (PH-37053) was submitted which assessed the PK, safety and tolerability of regorafenib administered orally as a single agent in Chinese patients with advanced solid tumours. As this was an interim report, no conclusions were drawn regarding the PK or regorafenib in this patient group, although treatment was assessed as tolerable and the safety profile for this study population with advanced underlying malignant disease manageable, suggested a sound basis for further investigation.

The population PK Study 14653 did not find any impact of ethic group (categorised as 'Caucasian', 'Asian' or 'Other') on the PK of regorafenib or its metabolites. However, the updated population PK analysis found lower exposure to the active metabolites M2 and M5 in Asians compared to Caucasian groups, although this was not considered clinically significant.

5.4.6. Pharmacokinetics according to weight and BMI

In the base population PK analysis, body weight at baseline did not have a significant effect on the PK of parent regorafenib, but the exposure of the metabolites M2 and M5 was found to decrease with increasing weight. In the updated population PK analysis, the effect of higher body weight was again correlated with decreasing exposure to M2 and a much larger effect on M5, however conversely, the clearance of regorafenib decreased with rising BMI, and thus higher BMI was correlated with increased exposure of parent regorafenib.

5.4.7. Pharmacokinetics according to pivotal study

In the updated population PK analysis, the CL of parent regorafenib was estimated to be 26.1% higher for the typical patient in Study 14874 compared to Study 14387. It could not be determined whether the study difference is caused by the different indication (CRC or GIST) or by some other difference between the two studies, as the covariate effects that are included in the final model did not explain the observed study difference.

5.5. Pharmacokinetic interactions

No new clinical data was presented with this submission. The following new in vitro data was provided in Module 2.7.2 Summary of Clinical Pharmacology Studies but not evaluated in this CER:

> *In vitro data indicate that regorafenib is not a substrate for any of the transporters studied (e.g., Pglycoprotein [P-gp], breast cancer resistance protein [BCRP], MRP-2, OAT1, OAT3, OCT2, OATP1B1 and OATP1B3). Metabolites M-2 and M-5 are weak substrates of P-gp, and M-5 is in addition a weak BCRP-substrate. Neither M-2 nor M-5 are substrates of MRP-2.*
>
> *The inhibitory effect of regorafenib, M-2 and M-5 on the efflux ratio of P-gp probe substrates was determined. Based on the IC50 value an inhibition of P-gp by regorafenib (IC50 about 2*

μM) and M-2 (IC50 about 1.5 μM) resulting in an effect on absorption of co-administered P-gp substrates cannot be ruled out. Co-administration of regorafenib may increase the plasma concentrations of concomitant P-gp substrates, such as digoxin.

The inhibitory effect of regorafenib, M-2 and M-5 on the efflux ratio of BCRP probe substrates was determined. Strong inhibitory effects on BCRP were shown for regorafenib (IC50 about 40 to 70 nM), M-2 (IC50 about 390nM) and M-5 (IC50 values of about 150 nM). Therefore, co-administration of regorafenib may increase the plasma concentrations of concomitant BCRP substrates, such as methotrexate.

Regorafenib, M-2 and M-5 showed no inhibitory effect towards MRP-2, OCT-1 and OCT-3 transporters; and regorafenib showed in addition no inhibitory effect towards OATP1B1, OATP1B3, OAT1, OAT3, -transporters (M-2 and M-5 analysis still ongoing) at concentrations which are in the range of clinically observed Cmax,ss concentrations (up to 10 μM).

5.6. Evaluator's overall conclusions on pharmacokinetics

The main pharmacokinetic data submitted with this submission related to two population pharmacokinetic analyses, both based on a base population PK model derived from Study 11650. The first analysis also used sparse sampling data from Study 14387 (R-8731), and the second analysis was an update on the first which also used data from Study 14874 (R-8814Error! Reference source not found.). These population PK analyses modelled the PK of regorafenib and its two main active metabolites M2 and M5 after multiple dosing, and looked at the impact of various pre-specified covariates.

These population PK analyses were adequately performed, however a limitation is that there were limited subjects with hepatic and renal impairment in the datasets used to construct the model (31/461 patients with mild-moderate hepatic impairment). Therefore, the ability of the models to predict the PK of patients with hepatic or renal impairment (particularly moderate or severe hepatic impairment) is limited.

The main findings of the population PK analyses were that the covariates found to have a significant impact on the PK of parent regorafenib were bilirubin level at baseline (greater exposure with higher bilirubin levels), study (greater exposure in Study 14387 compared to Study 14874), and BMI (greater exposure with higher BMI). Both metabolites M2 and M5 were also influenced by these covariates via their effect on parent regorafenib, and in addition the metabolites were also influenced by, race (lower exposure in Asian populations) and body weight (lower exposure with increasing weight). Sex also had a significant effect on the PK of M5 (higher exposure in females).

As the contribution of these covariate effects to overall variability were small (for parent regorafenib a decrease in unexplained variability in CL from CV= 46 % to 44%), none of these covariate effects were assessed by the sponsor to be clinically relevant. However, as discussed, it is the opinion of this evaluator that there is insufficient data from patients with hepatic impairment to be confident in this conclusion. Therefore it is recommended that the proposed wording in the PI be amended accordingly. The conclusions that effects of race, sex and BMI/weight on the PK of regorafenib and its metabolites are not clinically significant are considered probable however the differences with race may have significance in light of differences in the safety profile of regorafenib between races (see *Safety in special populations*). Only an interim report was provided for Study 14996 (PH-37053) in Chinese patients, and no additional conclusions have been drawn regarding the PK of regorafenib in this patient group.

The results of Study 11651 (PH-36984) were not considered in this evaluation, as the assessment of the impact of hepatic impairment on PK in a cohort of patients with hepatocellular carcinoma were based on single dosing only, and not multiple dosing as is proposed for the clinical indication. The PK after multiple dosing has been found to be

significantly different compared to single dosing, and this difference could plausibly be greater with hepatic impairment given that regorafenib is metabolised primarily by the liver and has the adverse effect of severe hepatic toxicity.

The results of several exploratory analyses of the effect of regorafenib (and metabolite) exposure levels and response and safety parameters based on the population PK analyses have not been fully evaluated, as these were exploratory in nature and not primary outcomes of the studies. These are briefly described in the Efficacy and Safety sections of this CER.

6. Pharmacodynamics

6.1. Studies providing pharmacodynamic data

One study (14814) was submitted providing pharmacodynamic data on the effect of regorafenib on cardiovascular safety parameters, specifically QT/QTc intervals and left ventricular ejection fraction (LVEF) in subjects with solid tumours. An interim report of this study was previously evaluated by the TGA, and the updated final CSR was submitted with this application.

This PD study did not have any deficiencies that excluded its results from consideration.

6.2. Summary of pharmacodynamics

Only the new results presented with Study 14814 are considered in this CER.

6.2.1. Pharmacodynamic effects

6.2.1.1. Primary pharmacodynamic effects

No new information presented in this submission.

6.2.1.2. Secondary pharmacodynamic effects

The results of Study 14814 did not reveal any evidence of QT prolongation with regorafenib use of at least 1 cycle at maximum dosing of 160 mg daily. There was minimal effect on left ventricular ejection fraction (LVEF) after at least 2 cycles of regorafenib at maximum dosing of 160 mg daily, although results with longer term follow-up in this study are pending.

Comment: The dedicated cardiovascular safety Study 14814 provides reassuring evidence that regorafenib does not have any significant effects on QT prolongation at the recommended dosage. Early results suggest minimal impact of regorafenib use on LVEF, although the results of longer-term follow up from this study would provide more definitive information. This has been posed as a question to the sponsor in *Clinical questions*.

6.2.2. Relationship between drug concentration and pharmacodynamic effects

Linear mixed effects modelling was used to assess the concentration-QT (exposure-response PK/PD) relationship in Study 14814. No apparent relevant positive correlation was found between plasma regorafenib concentration and changes in QT and QTc.

6.3. Evaluator's overall conclusions on pharmacodynamics

The final CSR for Study 14814 did not provide any evidence of an association between regorafenib use and QT prolongation after 1 cycle of maximum treatment, or clinically significant worsening of LVEF after 2 cycles of maximum treatment.

7. Dosage selection for the pivotal studies

With this submission, 'PH-37386 Regorafenib dose selection document' was included. This was a non-compartment PK evaluation dated 21 June 2013, and outlined the rationale for the selection of regorafenib dose for Phase II-III clinical development based on Phase I data from Studies 11650 and 11651. In Study 11650, regorafenib was administered at dosages from 10 mg to 220 mg orally daily with a 21 days on/7 days off schedule, and at MTD was determined to be 160 mg od with intermittent dosing. In Study 11651, regorafenib was administered orally daily in a continuous treatment regimen with a dose range from 20 mg to 140 mg, and a MTD was determined to be 100 mg od with a continuous dosing schedule.

Based on analysis of the two Phase I studies, the regorafenib dose selected for further clinical development was 160 mg once daily in the treatment schedule 21 days on/7 days off (over 100 mg once daily with continuous dosing), based on the following considerations:

- The safety/tolerability of the two MTD dosages were similar with the two dosage regimens, however for approximately the same extent of toxicity, a 20% higher total dose of regorafenib could be delivered at MTD in the intermittent schedule in a 28 day period.
- A break in dosing provided by the intermittent schedule may give patients a chance to at least partially recover from toxicities, and early clinical efficacy results did not suggest an increase in tumour flare during the treatment break period.
- The higher exposure during the dosing days in the intermittent schedule may prove advantageous with respect to anti-tumour activity in some tumours.
- An intermittent dosing schedule may offer an advantage in terms of 'combinability' with cytotoxic agents which are dosed intermittently and decrease the chances of any possible PK drug-drug interaction.

Comment: It is noted that this dose selection document was produced at a date much later than the initiation of the Phase II and III trials which it seeks to inform. The individual Phase I Studies 11650 and 11651 were previously evaluated and have not been evaluated in this CER. Nevertheless, the dosage selection for further development would seem acceptable based on the rationale outlined above, and this has been the dose and formulation used in subsequent clinical trials for a range of indications. This is also the dosage currently registered for treatment of metastatic CRC in Australia.

In Pivotal study 14874 in this submission, in line with the dose selection document, patients randomised to regorafenib received 160 mg orally once daily for 3 weeks of every 4 week (28 day) cycle (intermittent dosing: 3 weeks on/1 week off treatment). Each 160 mg dose consisted of four 40 mg immediate-release coated tablets, with rapid dissolution characteristics under in vitro test conditions. Regorafenib was to be taken in the morning with approximately 240 mL of water after a low-fat (< 30% fat) breakfast.

Comment: The dosage selection for the pivotal trial in this submission would seem acceptable and is in line with that determined in the dose selection document.

8. Clinical efficacy

Indication: Treatment of patients with gastrointestinal stromal tumours (GIST) who have been previously treated with two tyrosine kinase inhibitors

8.1. Pivotal efficacy studies

Comment: Only one single pivotal trial was submitted with this application in support of the new indication in patents with previously treated GIST. This had been discussed with the TGA and approved prior to submission, and had also been discussed with international regulatory agencies (FDA and EMA) in the drug development planning process. It is the opinion of this evaluator that Study 14874 fulfils the criteria set out in the EMA points to consider on application with one pivotal study.

8.1.1. Study 14874 (A59137, Amendment 1) GRID

8.1.1.1. Study design, objectives, locations and dates

This was a Phase III, multicentre randomised, double-blind, cross-over study to assess the safety and efficacy of regorafenib + best supportive care (BSC) compared with placebo + BSC in patients with metastatic and/or unresectable GIST and prior failure of the two tyrosine kinase inhibitors imatinib and sunitinib.

The study was conducted at 53 centres across 17 countries which randomised at least one patient. The participating countries were: United States (9 centres); Germany (6); Japan (6); China (4); South Korea (4); France (4); Canada (3); United Kingdom (3); Italy (3); Austria (2); Spain (2); Netherlands (2); Belgium (1); Finland (1); Israel (1); Poland (1); Singapore (1).

Enrolment for this study was completed in a short time from January to August 2011, and the data cut-off for the submitted CSR was 26 January 2012.

8.1.1.2. Inclusion and exclusion criteria

Main inclusion criteria included:

- Histologically-confirmed, metastatic and/or unresectable GIST
- At least one measurable lesion according to modified RECIST, version 1.1.
- Failure of at least: (1) prior imatinib (due to either disease progression or intolerance) and (2) prior sunitinib (due to progression)
- Age ≥18 years
- Eastern Cooperative Oncology Group performance status (ECOG PS) of 0 or 1
- Adequate bone marrow, liver, and renal function as assessed by laboratory measurements conducted within 7 days of starting study treatment
- Life expectancy of at least 3 months

Main exclusion criteria included:

- Patients who had received any VEGFR inhibitors other than sunitinib

A full list of inclusion and exclusion criteria was provided.

Comment: It is noted above that adequate bone marrow, liver, and renal function as assessed by laboratory requirements was required as an inclusion criterion for the study. In particular, this therefore excludes patients with impaired hepatic and renal function from inclusion, and this limits the generalisability of the results to these patient groups. Moreover, the generalisability of the population PK analyses that are based on this data is also limited.

A full list of study medication withdrawal criteria was listed.

8.1.1.3. Study treatments

Patients were randomly assigned (2:1 ratio) in a blinded fashion to one of two treatment groups:

- Regorafenib 160 mg once daily orally 3 weeks on / 1 week off + BSC (hereinafter referred to as the regorafenib group)
- Matching placebo + BSC (hereinafter referred to as the placebo group).

The study drug was to be administered orally, in the morning with approximately 240 mL of water after a low-fat breakfast.

Randomisation was stratified by

- third-line versus fourth-line or beyond; at least 50% of patients were to be third-line
- Geographical region (Asia versus rest of world)

As there were no evidence-based treatment options available for this patient population, placebo + BSC was chosen as a comparator. The sponsor reported that use of a placebo control arm was considered acceptable and supported by the US FDA and the CHMP (EU).

Patients were to continue on treatment until one of the pre-specified withdrawal criteria, which included disease progression. Doses of study drug could be delayed or reduced in case of clinically significant haematological and other toxicities (see Tables 3 and 4). Dose reductions to a dose lower than 80 mg were not allowed. If the dose needed to be reduced to a dose lower than 80 mg or there was no recovery after a 4 week treatment delay, treatment was discontinued. Following dose reduction, the dose could be re-escalated at the discretion of the investigator. 160 mg was the maximum daily dosage allowed.

Table 3: Study 14874 Regorafenib dose levels

Dose level 0 (standard dose)	160 mg po od	4 tablets of regorafenib, 40 mg/tablet, or 4 matching placebo tablets
Dose level -1	120 mg po od	3 tablets of regorafenib, 40 mg/tablet, or 3 matching placebo tablets
Dose level -2	80 mg po od	2 tablets of regorafenib, 40 mg/tablet, or 2 matching placebo tablets

po = per os, by mouth orally; od = once daily

Table 4: Study 14784 Dose modification/delay criteria for toxicities related to study drug (except hand-foot skin reaction, hypertension, and ALT and/or AST and/or bilirubin increases)

NCI-CTCAE v4.0[a]	Dose Interruption	Dose Modification[b]	Dose for Subsequent Cycles
Grade 0-2	Treat on time	No change	No change
Grade 3	Delay until ≤ Grade 2[c]	Reduce 1 dose level	If toxicity remains ≤ Grade 2, dose re-escalation can be considered at the discretion of the treating investigator. If dose is re-escalated and toxicity (≥ Grade 3) recurs, institute permanent dose reduction.
Grade 4	Delay until ≤ Grade 2[c]	Reduce by 1 dose level. Permanent discontinuation can be considered at treating investigator's discretion.	

NCI-CTCAE = National Cancer Institute - Common Terminology Criteria for Adverse Events, version 4.0 aspartate aminotransferase (AST), alanine aminotransferase (ALT)
Excludes alopecia, non-refractory nausea/vomiting, non-refractory hypersensitivity and asymptomatic laboratory abnormalities.

Table 4 continued: Dose modifications for hand-foot skin reaction

Skin Toxicity Grade (according to CTCAE v4.0 "Palmar-plantar erythrodysesthesia syndrome")	Occurrence	Suggested Dose Modification (More liberal management is allowed if judged medically appropriate by the investigator)
Grade 1: Numbness, dysesthesia, paraesthesia, tingling, painless swelling, erythema or discomfort of the hands or feet which does not disrupt the patient's normal activities.	Any	Maintain dose level and immediately institute supportive measures for symptomatic relief.
Grade 2: Painful erythema and swelling of the hands or feet and/or discomfort which affects the patient's normal activities.	1st occurrence	Consider decreasing dose by one dose level and immediately institute supportive measures. If there is no improvement, interrupt therapy for a minimum of 7 days, until toxicity resolves to Grade 0-1.[b]
	No improvement within 7 days or 2nd occurrence	Interrupt therapy until toxicity resolves to Grade 0-1. When resume treatment, treat at reduced dose level[b]
	3rd occurrence	Interrupt therapy until toxicity resolves to Grade 0-1. When resume treatment, decrease dose by one additional dose level[a,b]
	4th occurrence	Discontinue therapy.
Grade 3: Moist desquamation, ulceration, blistering or severe pain of the hands or feet, or severe discomfort that causes the patient to be unable to work or perform activities of daily living.	1st occurrence	Institute support measures immediately. Interrupt therapy for a minimum of 7 days until toxicity resolves to Grade 0-1. When resume treatment, decrease dose by one dose level[b]
	2nd occurrence	Institute support measures immediately. Interrupt therapy for a minimum of 7 days until toxicity resolves to Grade 0-1. When resume treatment, decrease dose by one additional dose level[a,b]
	3rd occurrence	Discontinue treatment permanently.

a Patients requiring > 2 dose reductions (a dose lower than 80 mg po od) should discontinue protocol therapy.
b If toxicity returns to Grade 0-1 after dose reduction, dose re-escalation was permitted at the discretion of the investigator.

Table 4 continued: Management of treatment-emergent hypertension

NCI-CTCAE v4.0 Grade	Definition	Anti-hypertensive therapy	Regorafenib dosing
Grade 1	Pre-hypertension (systolic BP 120-139 mmHg or diastolic BP 80-89 mmHg)	None	Continue regorafenib. Consider increased blood pressure monitoring.
Grade 2	Systolic BP 140-159 mmHg or diastolic BP 90-99 mmHg OR Symptomatic increase by > 20 mmHg (diastolic) if previously within normal limits	Treat with the aim to achieve diastolic BP ≤ 90 mmHg - If BP previously within normal limits, start anti-hypertensive monotherapy - If patient already on anti-hypertensive medication, titrate up the dose.	Continue regorafenib. If symptomatic, hold regorafenib until symptoms resolve AND diastolic BP ≤ 90 mmHg[a]. When regorafenib is restarted, continue at the same dose level.
Grade 3	Systolic BP ≥ 160 mmHg or diastolic BP ≥100 mmHg OR More than one drug or more intensive therapy than previously used indicated	Treat with the aim to achieve diastolic BP ≤ 90 mmHg - Start anti-hypertensive medication AND/OR - Increase current anti-hypertensive medication AND/OR - Add additional anti-hypertensive medications.	Hold regorafenib until diastolic BP ≤ 90 mmHg, and if symptomatic, until symptoms resolve[a]. When regorafenib is restarted, continue at the same dose level. If BP is not controlled with the addition of new or more intensive therapy, reduce by 1 dose level[b]. If Grade 3 hypertension recurs despite dose reduction and antihypertensive therapy, reduce another dose level[c].
Grade 4	Life-threatening consequences (eg, malignant hypertension, transient or permanent neurologic deficit, hypertensive crisis)		Discontinue therapy.

Abbreviations:
BP = blood pressure;
NCI-CTCAE = National Cancer Institute - Common Terminology Criteria for Adverse Events, version 4.0
a Patients requiring a delay of > 4 weeks should discontinue protocol therapy.
b If blood pressure remains controlled for at least one full cycle, dose re-escalation was permitted at the investigator's discretion.
c Patients requiring > 2 dose reductions (a dose lower than 80 mg po od) should discontinue protocol therapy.

Table 4 continued: Dose modifications/interruption for ALT and/or AST and/or bilirubin increases related to study drug

NCI-CTCAE v4.0	1st occurrence	Restart	Reoccurrence
baseline G0 → G1 or baseline G1 → G2	Treat on time and check AST, ALT and bilirubin 2x/week for 2 weeks followed by weekly assessments for at least 4 weeks.		Treat on time and check AST, ALT and bilirubin 2x/week for 2 weeks followed by weekly assessments for at least 4 weeks.
baseline G0 → G2	Delay until ≤ G1 and check AST, ALT, bilirubin 2x/week.	Reduce 1 dose level and check AST, ALT, bilirubin 2x/week for 2 weeks followed by weekly assessments for at least 4 weeks.[b]	Discontinue[c]
baseline any grade → G3	Delay until ≤ G1 if baseline was G0 or G1 OR until G2 if baseline was G2. Check AST, ALT, bilirubin 2x/week. If ALT or AST >8 x ULN with a concomitant rise in bilirubin (of any degree) compared to previous bilirubin values, consider permanent discontinuation at the first occurrence[c].	Reduce 1 dose level and check AST, ALT, bilirubin 2x/week for 2 weeks followed by weekly assessments for at least 4 weeks.[b]	Discontinue[c]
baseline any grade → G4	Discontinue[c]		

NCI-CTCAE = National Cancer Institute - Common Terminology Criteria for Adverse Events, version 4.0; AST =aspartate aminotransferase; ALT= alanine aminotransferase; ULN = upper limit of normal

[b] If all values remain stable for 2 full cycles, dose re-escalation may be considered at the discretion of the investigator. After re-escalation AST, ALT, bilirubin should be checked 2x/week for 2 weeks, followed by weekly assessments for at least 4 weeks

[c] In case of discontinuation, check AST, ALT, bilirubin should be checked 2x/week for 2 weeks, followed by weekly assessments until recovery to baseline

Crossover: 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. Patients were able to remain on open label regorafenib until second disease progression or at the discretion of the investigator.

Comment: The design of Study 14874 is satisfactory. The implications of un-blinding and allowing cross-over treatment on disease progression are acceptable, as this will not affect the primary efficacy outcome of progression-free survival as discussed below. However, any beneficial effect of regorafenib on overall survival will be confounded by allowing this cross-over.

8.1.1.4. Efficacy variables and outcomes

Tumour response and disease progression were evaluated using modified RECIST (v. 1.1). The radiological evaluation included a computed tomography (CT) or magnetic resonance imaging (MRI) of the chest, abdomen, and pelvis. Throughout the study, the same lesions as those identified and measured at baseline were evaluated using the same technique. Radiological measurements were performed: at baseline; every 4 weeks for the first 3 months; every 6 weeks for the subsequent 3 months (through month 6); after month 6, every 8 weeks until the end of study drug administration at the end of treatment visit. Tumour assessments (per blinded central radiology review) were performed until objective tumour progression. Patients were considered to be 'on study' until an end-of-treatment safety follow up visit at 30 +/-7 days following cessation of treatment. Following this visit, patients were considered to be 'off-study', and were followed up for survival only. In this period, assessment of survival status was performed every 3 months.

The main efficacy variables were:

Progression free survival (PFS) - defined as the time from the date of randomisation to the date of first observed radiological progression according to blinded central radiology review (BCRR) (using modified RECIST version 1.1 criteria), or death due to any cause if death occurred before progression. The actual date of radiological assessment was used as the date of

progression. Patients without tumour progression or death at the time of analysis were censored at their last date of radiological tumour assessment.

Overall survival (OS) - defined as the time from the date of randomisation until the date of death due to any cause. For the OS analysis, patients alive at the database cut-off date were censored at that date.

Time to progression (TTP) - defined as the time from the date of randomisation to the date of first radiological progression (by central assessment and investigator assessment). Patients without radiological tumour progression at the time of analysis were censored at the last date of radiological tumour assessment.

Overall response rate (ORR) - defined as the proportion of patients with a best overall tumour response of PR or CR according to modified RECIST version 1.1.

Disease control rate (DCR) - defined as the proportion of patients with a best overall tumour response of PR or CR according to modified RECIST version 1.1, plus patients with a best overall response of stable disease maintained for a minimum of 12 weeks, during treatment or within 30 days after termination of study medication.

Duration of response - defined as the number of days from the date of first documented objective response of PR or CR, whichever was noted earlier, to the date of first disease progression or death if death occurred before observation of disease progression. Patients without progression or death at the time of analysis were censored at the date of the last tumour assessment.

All efficacy variables related to tumour response and disease progression during the double blind period were evaluated based on an independent, blinded (central) assessment. In addition tumour evaluations were performed by investigator assessment during the double-blind and open-label treatment periods. All tumour assessments were performed according to modified RECIST criteria version 1.1.

- The primary efficacy outcome was PFS. Secondary outcome variables included OS, TTP, ORR, DCR and duration of response.

Subgroup analysis for PFS and OS was performed for geographic region, prior lines of treatment, age, baseline BMI, duration of imatinib treatment, Eastern Cooperative Oncology Group performance status (ECOG PS), and mutational status.

Exploratory efficacy outcomes included:

Secondary PFS - defined as the time from first progression until second progression (per investigator assessment) or death, whichever came first, during or after open-label treatment with regorafenib. Secondary PFS was analysed descriptively.

Health-related quality of life (HRQoL) - measured by the EORTC QLQ-C30 (European Organisation for Research and Treatment of Cancer Quality of Life questionnaire) version 3 and the EQ-5D (Euro quality of life, 5-dimensional quality of life measurement) questionnaires completed by patients.

Biomarker analysis – Two types of biomarker data were assessed: historical data available at study entry, and data generated from prospectively collected biomarker samples. The former was the investigator-reported pre-study baseline GIST genotype (mutations in the KIT and PDGFRα tyrosine kinase receptors), and was performed on plasma and archival tumour tissue specimens that were collected from patients who granted genetic consent. The current applications include subgroup analyses using historical KIT mutation status in Exons 9 and 11 for PFS and OS, to evaluate the potential influence of specific KIT mutations on the clinical response to regorafenib.

Comment: Choice of PFS as the primary endpoint is appropriate in this study, given that it is used routinely to assess efficacy in clinical cancer trials and considered acceptable by the relevant EMA guidelines (1). Inclusion of OS as a secondary endpoint is also appropriate, although crossover of patients from the placebo group to regorafenib treatment on disease progression is likely to affect this outcome, bringing it towards the null.

Given the importance of quality of life as an efficacy outcome in cancer treatments, the assessment of HRQoL may have been better served as a secondary rather than an exploratory outcome, in order to have more confidence in the results. This would be particularly so in order to assess benefit if an improvement in OS cannot be demonstrated.

8.1.1.5. Randomisation and blinding methods

The double-blind randomisation was performed centrally by an interactive voice response system (IVRS) and was stratified by third versus fourth line therapy or beyond and geographical region (Asia versus rest of the world). At least 50% of patients were to be receiving third line therapy. Un-blinding occurred for emergency purposes only, and was not routinely precipitated by a SAE.

Regorafenib and placebo were identical in appearance (labelled using a unique number) in order to preserve blinding, and all patients took four 40 mg tablets orally once a day.

Comment: Randomisation and blinding methods appear satisfactory.

8.1.1.6. Analysis populations

The main analysis populations were:

Full analysis set (FAS) – The primary population for efficacy analysis was the FAS population, which was defined as all randomised patients. Patients were analysed as randomised. The FAS is identical to the intent to treat (ITT) analysis set.

Safety analysis set (SAF) – Patients were included in the SAF if randomised to a treatment group and had taken at least one unit of the study medication. Patients were analysed as randomised.

Patient reported outcomes (PRO) Analysis Set (PROAS) – The population for PRO analyses was all FAS patients who had evaluable PRO assessments at baseline and at least one post-baseline assessment.

Pharmacokinetic Analysis Set (PKAS) – The population for PK analyses were comprised of all subjects with valid PK data collected after at least 14 days of uninterrupted and unmodified dosing of regorafenib.

Comment: The use of the FAS to analyse the primary efficacy outcome of PFS is appropriate and in line with standard clinical trial evaluation methodology.

8.1.1.7. Sample size

According to the protocol, 170 patients were planned to be enrolled in the study.

This calculation assumed 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, resulting in a requirement for approximately 122 events. Additional assumptions included an exponential distribution of the PFS event times, and a median time of PFS in the control group of 6 weeks. Based on this calculation, 170 subjects had to be enrolled to observe 122 events after approximately 12 months.

Due to over-recruitment of 29 subjects to 199 total randomised subjects, 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%.

Comment: The effect of the over-recruitment of patients into the study was to increase the power of the study, and thus there is no adverse impact on the strength of the efficacy results. The main impact of the over-recruitment may be to lend statistical significance to a smaller magnitude improvement in efficacy between treatment and placebo – therefore the clinical significance of any outcome needs to be scrutinised. Due to the relatively small number of patients over-recruited (29 subjects) and the fact that this treatment is already registered for the indication of metastatic CRC, there are no significant ethical safety implications.

8.1.1.8. Statistical methods

The original version of the SAP (v1.0) was dated 26 Jan 2012. The SAP was revised (v1.1) on 22 Mar 2012. Key changes to the revised version included:

- A sensitivity analysis of PFS at 122 events (see discussion on PFS below)
- Simplification of missing dates of safety events.
- Removal of a planned sensitivity analysis for PFS addressing patients censored in the primary analysis of PFS, due to data from blinded central radiology review needed for that analysis not being available.

Comment: It is noted that the first version of the SAP for Study 14874 was dated 26 January 2012, which is the same date as the data cut-off for the analysis presented in the CSR.

With respect to the primary endpoint of PFS, the proposed statistical analysis methods were the same in the pre-specified Study protocol, and the subsequent SAP, apart from the methods for the handling of missing data, which was only described in the SAP. It was specified that the actual date of radiological assessments will be used for the calculation of PFS, and missing or incomplete scans would not be considered unless they showed progression. If progression or death occurred after 2 consecutive missed or non-evaluable assessments, PFS was censored at the date of the last evaluable scan before the 2 missing assessments.

Comment: With regards to the primary efficacy variable, PFS, all relevant statistical analysis parameters were pre-specified in the statistics section of the Study protocol, apart from the handling of missing data which was only discussed in the SAP. This may present an issue in that the handling of missing data was not pre-specified prior to data collection, and this has been posed as a question to the sponsor under *Clinical questions* below.

The methods that were used for handling missing radiological assessments are likely to overestimate PFS time, by the use of the date of radiological assessment for disease progression if one assessment had been missed (thereby prolonging the disease free period), and censoring despite documented disease progression if 2 consecutive assessments were missed (thereby censoring a documented progression). However, this is not likely to be influenced by the randomised treatment, and thus is likely to impact both study arms in a similar manner.

It is also noted that a planned sensitivity analysis of censored patients was removed in the revised SAP, although this only related to patients that were censored due to un-blinding, and not censoring for other reasons. Sensitivity analysis was not performed to assess the impact of different methods of handling missing data as is recommended in the relevant EMA Guidelines (2). This has also been raised as a question to the sponsor under *Clinical questions* below.

From the data presented in the CSR, the number of patients who discontinued treatment due to non-compliance was small (2 patients in the regorafenib arm), so it could be inferred that there was minimal impact of patients who were censored following missing 2 or more consecutive tumour assessments. However, an assessment of how many patients missed one assessment prior to disease progression was not able to be ascertained from the data and this has also been posed as a question to the sponsor.

Progression-free survival – The primary analysis for PFS was to be performed when approximately 144 patients had experienced a PFS event. This was increased from the original planned analysis which was to occur after 122 PFS events, due to study over-enrolment.

The two treatment groups (regorafenib and placebo) were compared using a stratified log rank test with a one-sided alpha of 0.01 stratified by the same stratification factors as used for randomisation (third line therapy versus fourth line therapy or beyond; and geographical region).

The hazard ratio (regorafenib/placebo) for PFS and its 95% confidence interval were calculated using the Cox model, stratified by the same factors as stated above. Kaplan-Meier (KM) estimates for PFS and KM survival curves were also performed for each treatment group.

The secondary efficacy endpoints of OS, TTP, RR, and DCR were analysed descriptively and inferentially, using a one-sided significance level of $\alpha = 0.025$. Duration of response was analysed descriptively only.

Sensitivity analyses were performed to assess the times to tumour assessments for each period, different methods of PFS statistical analysis (unstratified log-rank test and Cox model), PFS based on local investigator assessment, and an analysis of concordance and discordance in radiological progression between investigators and BCRR assessments during the blinded study phase.

Subgroup analyses were performed according to stratification levels (line of treatment, geographical region), age, sex, ECOG performance status, BMI, duration of treatment with imatinib, geographical region, and mutationally-defined subgroups (KIT 11 Exon 11 or 9 mutations or Wild type GIST).

Overall survival – The final OS analysis is to be performed when approximately 160 events have been observed. This was increased from the originally planned number of 136 following the over-enrolment of patients. 160 events provide 84% power to detect a 67% increase when a 1-sided alpha of 0.025 is used.

For both the interim and the updated analyses of OS a secondary analysis of OS will be performed. This analysis applies methods to correct for the effect of crossover from the placebo to the regorafenib arm on the OS endpoint. The data were analysed for OS using two different correction methods: a correction using rank preserving structural failure time (RPSFT), and an iterative parameter estimation (IPE) method.

Time to progression – To be analysed with the same methods as PFS.

Response rate and disease control rate – These are to be compared between treatment groups using the Cochran-Mantel-Haenszel(CMH) test adjusting for the same stratification factors as for PFS, and including 95% confidence intervals.

Duration of response – Analysis will be descriptive only.

Comment: The planned statistical methods for the primary and main secondary outcomes in Study 14874 would seem appropriate, including the adjustment in required events to account for the over-enrolment of patients into the study. It is noted that at the time of this CSR, insufficient OS events had occurred to perform a final analysis, and thus the results for OS are not yet mature.

8.1.1.9. Participant flow

A total of 240 patients with metastatic and/or unresectable GIST were screened, of whom 199 (82.9%) were randomised (in a 2:1 ratio) to receive either regorafenib (N=133) or matching placebo (N=66) in the double-blind period of the study. These patients comprised the full analysis set (FAS). 198 patients in the FAS received at least 1 dose of study medication, and were included in the safety analysis set.

At the data cut-off date of 26 January 2012, treatment was ongoing in 77/133 (57.8%) patients in the regorafenib group. Of these, 53/133 (39.8%) patients were still on double-blind treatment and 24/133 (18.0%) had crossed over to open-label treatment. Overall, 41/133 (30.8%) of patients with disease progression in the regorafenib group entered the open-label phase. Of the patients initially randomised to receive placebo, 3/66 (4.5%) were still on double-blind treatment and 56/66 (84.8%) had crossed over to open-label regorafenib treatment. Of these, 33/66 (50.0%) remained on open-label regorafenib treatment at the data cut-off date.

All randomised patients were included in the full analysis set (Table 5). One patient, randomised to the regorafenib group, was excluded from the safety analysis set, as this patient did not receive any dose of study drug.

Table 5: Analysis sets in Study 14874

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.

8.1.1.10. Major protocol violations/deviations

4/66 (6.1%) of subjects randomised to the placebo group had a major protocol deviation, and 10/133 (7.5%) in the regorafenib group. All except one of these deviations were procedural deviations, relating to failure to complete the Quality of Life questionnaires. There was 1 major treatment deviation which was a patient who was randomised to the regorafenib group but did not receive any dose of study drug.

Comment: None of the major protocol deviations are likely to impact on the analysis of the primary outcome of PFS.

Protocol amendments – over the course of the study, several protocol amendments were made. Of note:

- A data monitoring committee meeting in July 2011 found a safety concern associated with hepatic toxicities ≥ Grade 3. Risk minimisation measures implemented included closer liver monitoring (from fortnightly to weekly in the first 2 months of treatment) and a revised dose modification scheme (specific to elevations in ALT, AST or bilirubin) which were implemented via protocol Amendment 2 (26 July 2011). In addition, specific monitoring of liver function was mentioned in the protocol rather than referring to general chemistry testing.
- Amendment 2 also included a clarification for reporting Hand-foot-skin reaction (HFSR) as an AE. It was noted, that CTCAE v4, used in this study, did not have a classification for HFSR. Amendment 2 instructed the sites must to select 'Palmar-plantar erythrodysesthesia syndrome' for investigator HFSR verbatim terms, as this is comparable to the old HFSR definitions in CTCAE version 3.

- As per Amendment 3 (27 September 2011), the number of PFS events required for analysis of the primary efficacy endpoint was increased from 122 to 144 PFS events, to account for the increased number of subjects enrolled. In addition, a supportive primary PFS analysis was performed that included data from all patients randomised (199), but only up to the time point when the first 122 PFS events had occurred, as was originally intended in the first version of the protocol.
- Amendment 3 also made the following change: 'After the primary endpoint of the study is reached, if the study results support a positive benefit/risk assessment for regorafenib in the trial … those subjects who are currently on placebo at that time may be offered the opportunity to receive regorafenib through open label treatment on this study.'

8.1.1.11. Baseline data

The regorafenib and placebo groups were comparable with respect to gender (total 63.8% male), age (mean 58.2 years), race/ethnic group (67.8% white, 25.1% Asian), geographic region (23.6% Asia, 76.4% Rest of world), ECOG performance (55.3% 0, 44.7% 1), BMI (65.3% <25 kg/m^2), histology (48.2% spindle cells, 8.0% epithelioid, 14.1% mixed), and Prior anti-cancer drug group (56.8% third line, 43.2% fourth line and beyond). The location of primary tumour site at initial diagnosis was similar between the two groups, with the most common location being the stomach (36.7%), followed by the jejunum (16.1%) and the ileum (11.6%).

However, there were some differences between the treatment groups with respect to:

- Time since initial diagnosis to randomisation (mean 310.6 weeks for placebo group versus 296.4 weeks for regorafenib group)
- Time since recent progression/relapse to randomisation (mean 16.71 weeks for placebo group versus 13.29 weeks for regorafenib group, however median 4.27 weeks in placebo group versus 6.34 weeks in regorafenib group)
- Mutation biomarkers – Historical tumour samples were available for 96 patients (48.2%). Of these, 53.1% (51/96) had GIST with an initial pre-study baseline mutation in KIT exon 11, 16% (15/96) had GIST harbouring an initial pre-study baseline mutation in KIT exon 9, and 8.3% (8/96) were wild type (WT) (no KIT and no PDGFRα mutation). There were some differences in the distribution of these biomarkers between the two groups, with a KIT Exon 11 mutation found in 17/36 (47.2%) of patients tested in the placebo group compared to 34/60 (56.7%) patients tested in the regorafenib group.
- Extent of disease at baseline (Metastatic disease in 57.6% of placebo group and 67.7% of regorafenib group, and Unresectable disease in 15.2% of placebo group and 3.8% of regorafenib group)
- Number of tumour sites (>2 sites in 56% in placebo group and 65% in regorafenib group)
- Duration of treatment with imatinib (≥18 months in 83.3% of the placebo group and 66.9% of the regorafenib group)

Comment: Although the baseline demographic characteristics are comparable between the placebo and regorafenib groups in Study 14874, there are some differences between the groups with respect to disease characteristics. These relate to the placebo group having experienced a longer mean duration of disease and progression than the regorafenib group (by approximately 14 weeks and 3 weeks respectively), and there being a higher proportion of metastatic disease with a greater number of tumour sites in the regorafenib group. Conversely there was a higher proportion of unresectable disease in the placebo group. The placebo group had also had a longer duration of treatment with imatinib compared to the regorafenib group. The impact of these differences in underlying disease

characteristics between the two groups may need to be considered in the interpretation of study results.

It is noted that in terms of time since recent progression/relapse to progression, the upper bound of the range in both groups is quite high (421 weeks or more than 8 years for the placebo group, and 145 weeks or 2.8 years for the regorafenib group). It is questioned whether a patient who has not experienced disease progression for more than 8 years can be considered to have advanced GIST that is representative of the target population. It is noted that the median times for time since disease progression to randomisation are considerably lower, and a request for further discussion of this issue has been posed as a question to the under *Clinical questions* below.

The higher proportion of patients with KIT Exon 11 mutations seen in the regorafenib group compared to the placebo group may have implications for the interpretation of results, while acknowledging that the overall proportion of patients who had baseline mutational status tested was relatively low at 51.8%.

The demographic and disease characteristics of the study participants would seem generally representative of the patient group for whom approval is being sought in this application (metastatic and/or unresectable GIST).

All patients took at least one concomitant medication, and agents were similar across the two groups. There was slightly higher use of natural opium alkaloids in the placebo group (47.0%) compared to the regorafenib group (30.8%).

Prior anti-cancer therapy at baseline with respect to surgery and other systemic therapies was similar between the placebo and regorafenib group although there was slightly higher prior use of nilotinib in the placebo group (30.3%) compared to the regorafenib group (21.8%), and higher prior use of cytotoxic chemotherapy in the regorafenib group (9.8%) compared to the placebo group (3.0%).

8.1.1.12. Results for the primary efficacy outcome

The primary population for the efficacy analysis was the FAS population, which was defined as all 199 randomised patients, including 66 patients randomised to placebo + BSC and 133 patients randomised to regorafenib + BSC. During the double-blind period, the mean treatment duration (±SD) for regorafenib was 20.22 (±11.63) weeks and for placebo was 9.08 (±5.89) weeks.

As of the database cut-off date (26 January 2012), PFS events (PD or death due to any cause) had been experienced by 63/66 (95.5%) patients in the placebo group and 81/133 (60.9%) patients in the regorafenib group (144/199 in total), thereby satisfying the 144 protocol pre-specified PFS events required for the primary analysis. Results for the primary analysis after the first 144 events are shown in Table 6.

Table 6: PFS results for double-blind period in Study 14874

	Placebo (N = 66)	Regorafenib (N = 133)
Patients with event; n (%)	63 (95.5)	81 (60.9)
Patients censored; n (%)	3 (4.5)	52 (39.1)
Median PFS; days (95% CI)	28 (28, 32)	147 (122, 173)
Median PFS; months [days/30.44]	0.9	4.8
PFS range excluding censored values; days	8–169	6–281
Hazard ratio [regorafenib/placebo]		0.268
95% CI for hazard ratio		0.185, 0.388
p-value (one-sided log-rank test)		<0.000001

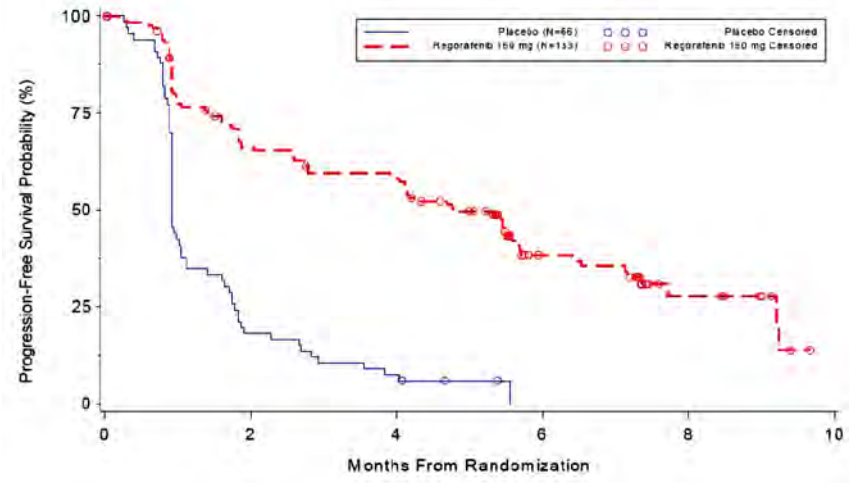
CI = confidence interval; PFS = progression-free survival

Comment: The lower CI for the median PFS in the placebo group is at 28 days (the same as the median value), presumably because the first tumour assessment occurred following 4 weeks of treatment, and thus earlier progressions were not detected. This has the potential effect of increasing the mean PFS, and therefore it is acceptable that median values are presented for the analysis.

Median PFS time was longer in the regorafenib group at 147 days (4.8 months), compared to 28 days (0.9 months) in the placebo group. The risk of progression (or death) was lower in the regorafenib group than in the placebo group (HR: 0.268, 95%CI 0.185-0.388, p<0.000001).

Kaplan-Meier curves for PFS (144 PFS events) by treatment group are shown in Figure 1, which shows the estimated Kaplan-Meier PFS rate was consistently higher in the regorafenib group than in the placebo group at all time-points.

Figure 1: Kaplan-Meier curve of PFS, central assessment, 144 events in Study 14874



These results were consistent with the supportive PFS analysis performed after the first 122 PFS events had occurred which found the percentage of patients who experienced disease progression or death to be 65 (47.4%) in the regorafenib group and 59 (89.4%) in the placebo group. A median PFS time of 129 days was seen in the regorafenib group compared to 28 days in the placebo group, giving a HR of 0.272 (95%CI: 0.185, 0.401).

A sensitivity analysis of PFS at 144 events using the investigator's assessment were also supportive of the primary analysis, with median PFS time being 224 days in the regorafenib group compared to 52 days in the placebo group, with a hazard ratio of 0.221 (95% CI: 0.141, 0.345). It was noted that median PFS times were longer in both treatment arms with investigator assessment compared to central assessment (Table 7). 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%). The difference in discordance rate between treatment groups was 13.4%, and this was assessed by the sponsor to suggest no meaningful difference in discordance rate between the treatment groups. No explanation was given for the reasons discordance in the CSR.

Table 7:Sensitivity analysis of radiological progressions: Central – Local Concordance – Discordance (FAS) in Study 14874

Randomized treatment group	Investigator reading	Central reading		
		Progression	No progression	All
Placebo	Progression	50 (75.8%)	0	50 (75.8%)
	No Progression	12 (18.2%)	4 (6.1%)	16 (24.2%)
	All	62 (93.9%)	4 (6.1%)	66 (100.0%)
Regorafenib 160 mg	Progression	39 (29.3%)	5 (3.8%)	44 (33.1%)
	No Progression	37 (27.8%)	52 (39.1%)	89 (66.9%)
	All	76 (57.1%)	57 (42.9%)	133 (100.0%)

Another sensitivity analysis of PFS on unstratified data also supported the primary analysis, with a hazard ratio of 0.255 (95%CI: 0.177, 0.368).

Comment: It is agreed with the sponsor's assessment, that the results of the primary analysis show a statistically significant and clinically meaningful advantage for regorafenib over placebo for PFS of 119 days or 3.9 months. The effect of regorafenib in this study was an extension of PFS by a factor of 425% over placebo.

Given the strength of these results, it is not expected that the differences in baseline disease characteristics will significantly impact on the PFS analysis.

The discordance between Central and Investigator assessments does not suggest any biases in favour of regorafenib for the primary PFS outcome using Central assessment, although the Investigator's assessment did favour the regorafenib over the placebo arms.

8.1.1.13. Results for other efficacy outcomes

Overall survival – At the time of data cut-off (26 January 2012), a total of 46 events had occurred, 29 events (21.8% of patients) in the regorafenib group and 17 events (25.8%) in the placebo group. Median OS time could not be estimated due to the censored data. The estimated OS HR of regorafenib to placebo was 0.772 (95% CI: 0.423, 1.408) (Table 8). The log-rank test based p-value was 0.198896. Using the pre-specified O'Brien-Fleming-type alpha spending function approach the resulting alpha for an OS interim analysis with 46 OS events, assuming a final analysis with 160 OS events, was 0.0000291. Therefore, the observed difference between treatment groups was not statistically significant at this interim analysis. Kaplan-Meier curves for OS by treatment group are shown in Figure 2.

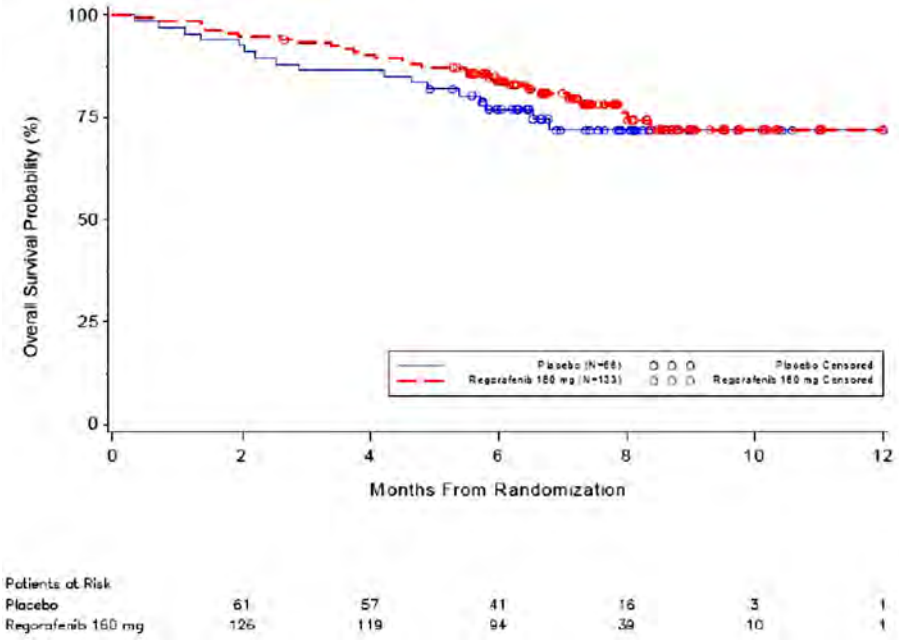
56/66 (85%) of placebo patients were crossed over to the open-label regorafenib treatment after progression. To correct for the effect of crossover from the placebo to the regorafenib group on the OS endpoint, the data were analysed using two different correction methods: a correction using the rank preserving structural failure time (RPSFT) method, and an iterative parameter estimation (IPE) method. The estimated corrected HR of regorafenib to placebo using the RPSFT and IPE correction methods were 0.537 and 0.565, respectively.

Table 3: OS, uncorrected and corrected for crossover in Study 14874

Efficacy parameter	Hazard Ratio* (95% CI)	P-value (one-sided)	Median (95% CI)	
			Placebo N = 66 n (%)	Regorafenib N = 133 n (%)
Median overall survival				
Uncorrected	0.772 (0.423, 1.408)	0.199	NA [a]	NA [a]
Corrected RPSFT	0.537 (0.286, 1.007)	0.025	NA [a]	NA [a]
Corrected IPE	0.565 (0.302, 1.055)	0.035	NA [a]	NA [a]

CI = confidence interval; HR = hazard ratio; IPE = iterative parameter estimation; NA = not assessable; PFS = progression-free survival; RPSFT = rank-preserving structural failure time
[a] not calculable due to censored data

Figure 2: Kaplan-Meier curve of OS, Study 14874



Comment: This interim data does not suggest a significant survival advantage for those subjects randomised to regorafenib compared to those randomised to placebo. It is acknowledged that this secondary endpoint of OS is difficult to interpret due to data immaturity and the median OS time not being reached. In addition, the allowance for crossover onto regorafenib treatment upon disease progression in this case makes interpretation of OS results problematic in the face of a non-statistically significant result.

Further OS follow-up data and analysis would be of benefit in assessing the impact of regorafenib on this important endpoint, and for ensuring consistency with the PFS results. This issue has been posed as a Clinical question to the sponsor (see below).

Subgroup analyses of PFS and OS - PFS and OS were evaluated in subgroups of geographic region, prior line of treatment, age, sex, baseline BMI, the duration of imatinib treatment, ECOG performance status, mutational status, and duration of sunitinib treatment (see Table 6).

Median PFS was longer in the regorafenib group compared to the placebo group across all subgroups, consistent with the primary analysis, and was statistically significant for all subgroups except for the group treated with <6 months of imatinib.

The subgroup analysis for OS was less conclusive, due to the immaturity of OS data, and the crossover of placebo patients to regorafenib treatment on disease progression. Consistent with the primary OS analysis, most subgroups had a HR <1 which was not statistically significant. However, there were some subgroups for whom the OS HR was >1 with regorafenib treatment compared to placebo, and these included being from the Asian region; baseline BMI 25 to <30 kg/m2; ECOG PS of 0 at baseline, and duration of treatment with sunitinib <6 months.

Comment: The subgroup analysis for PFS strongly supports the primary analysis, and suggests that regorafenib has a positive impact on prolonging PFS across a wide range of patient types with metastatic and/or unresectable GIST. The subgroup analysis for OS is again inconclusive due to data immaturity and the crossover of placebo subjects to regorafenib treatment on disease progression, and further data on OS as it becomes available would be beneficial.

Table 6: Summary of PFS and OS results overall and for pre-specified subgroups in Study 14874

Category	Subgroup	N	PFS			OS		
			Events	HR Regor./ Placebo	(95% CI)	Events	HR Regor./ Placebo	(95% CI)
All patients	N/A	**199**	**144**	**0.268**	**(0.185, 0.388)**	**46**	**0.772**	**(0.423, 1.408)**
Prior anticancer drug group	3rd line	113	79	0.225	(0.137, 0.368)	28	0.782	(0.366, 1.671)
	4th line and beyond	86	65	0.311	(0.178, 0.541)	18	0.806	(0.302, 2.154)
Region	Asia	47	38	0.301	(0.146, 0.621)	10	1.063	(0.275, 4.114)
	Rest of World	152	106	0.242	(0.158, 0.372)	36	0.719	(0.368, 1.406)
Region	North America	36	27	0.415	(0.187, 0.921)	7	0.912	(0.204, 4.085)
	Non North America	163	117	0.223	(0.147, 0.337)	39	0.745	(0.387, 1.436)
Sex	Male	127	93	0.305	(0.196, 0.476)	40	0.749	(0.394, 1.423)
	Female	72	51	0.176	(0.091, 0.341)	6	0.883	(0.161, 4.837)
Age	<65 years	136	99	0.299	(0.193, 0.463)	29	0.676	(0.323, 1.417)
	≥65 years	63	45	0.150	(0.075, 0.303)	17	0.987	(0.347, 2.810)
Age	<65 years	136	99	0.295	(0.188, 0.463)		ND	
	65-74 years	44	31	0.145	(0.051, 0.408)		ND	
	≥75 years	19	14	0.104	(0.020, 0.535)		ND	
Baseline BMI	<25 kg/m²	112	84	0.287	(0.177, 0.464)	25	0.668	(0.300, 1.489)
	25 to <30 kg/m²	56	40	0.239	(0.120, 0.479)	12	1.426	(0.386, 5.272)
	≥30 kg/m²	22	15	0.188	(0.058, 0.605)	8	0.497	(0.124, 1.997)
ECOG PS at baseline	0	110	77	0.224	(0.135, 0.370)	18	1.263	(0.450, 3.549)
	1	89	67	0.300	(0.175, 0.513)	28	0.553	(0.261, 1.171)
Duration of treatment with imatinib	<6 months	22	18	0.546	(0.173, 1.725)	5	NA	
	≥6 to <18 months	33	19	0.192	(0.067, 0.547)	9	0.193	(0.050, 0.740)
	≥18 months	144	107	0.236	(0.154, 0.363)	32	0.846	(0.417, 1.717)
Duration of treatment with sunitinib	<6 months	74	55	0.257	(0.140, 0.471)	21	1.346	(0.522, 3.474)
	≥6 to <18 months	79	58	0.299	(0.171, 0.523)	17	0.788	(0.288, 2.154)
	≥18 months	46	31	0.205	(0.091, 0.461)	8	0.233	(0.056, 0.978)
Mutation biomarkers	KIT Exon 11	51	40	0.212	(0.098, 0.458)	14	0.903	(0.302, 2.696)
	KIT Exon 9	15	11	0.239	(0.065, 0.876)	2	NA	

BMI = body mass index; CI = confidence interval; ECOG PS = Eastern Cooperative Oncology Group Performance Status ; FAS = full analysis set; HR = hazard ratio; NA = not assessable; ND = not done; OS = overall survival; PFS = progression-free survival

- **Secondary PFS** – was analysed descriptively only. Median secondary PFS for the regorafenib group (41 patients who continued on regorafenib) and the placebo group (56 patients who crossed over to regorafenib) was 137 days (4.5 months) and 151 days (5.0 months), respectively (based on investigator assessment).

Comment: It is agreed with the sponsor's statement that continuing treatment with regorafenib may be clinically beneficial by delaying further disease progression. However, as secondary PFS was measured using investigator assessment only, which for the primary PFS analysis produced longer results than the centrally blinded assessments, a similar lengthening effect may have been observed here and results need to be interpreted with caution.

Time to progression - The percentage of patients with disease progression was higher in the placebo group (93.9%) compared with the regorafenib group (57.1%). Centrally assessed median TTP was longer in the regorafenib group (165 days, 5.4 months) compared to the placebo group (28 days, 0.9 months). The risk of progression in the regorafenib group was lower than in the placebo group with a HR of 0.248 (95% CI 0.170, 0.364, p <0.000001).

Secondary TTP – This was defined as the time from cross-over to open-label treatment until second radiological progression during open-label treatment with regorafenib. Median

secondary TTP for the placebo group (56 patients who crossed over to regorafenib) and the regorafenib group (41 patients who continued on regorafenib) was 151 days (5.0 months) and 150 days (4.9 months), respectively.

Overall response rate - There were no CRs in either treatment group by central assessment (Table 7). A higher percentage of regorafenib-treated patients (4.5%) compared with placebo-treated patients (1.5%) had a PR. Since no patients had a CR, the ORR was the same as the rate of PR. The difference between the groups (-2.99%; 95% CI: -7.70%, 1.72%) was not statistically significant (p=0.142097) using the central assessment.

Table 7: Overall response double-blind period, - central assessment (FAS) Study 14874

Best Response	Placebo + BSC N = 66 n (%) 95% CI	Regorafenib + BSC N = 133 n (%) 95% CI	Difference (placebo – regorafenib) 95% CI p-value
CR	0 (0.0%) [0.0%, 4.4%]	0 (0.0%) [0.0%, 2.2%]	NA
PR	1 (1.5%) [0.0%, 8.2%]	6 (4.5%) [1.7%, 9.6%]	NA
SD[a]	22 (33.3%) [22.2%, 46.0%]	95 (71.4%) [63.0%, 78.9%]	NA
Progressive disease	42 (63.6%) [50.9%, 75.1%]	28 (21.1%) [14.5%, 29.0%]	NA
Not assessable	1 (1.5%) [0.0%, 8.2%]	4 (3.0%) [0.8%, 7.5%]	NA
Response (CR + PR)	1 (1.5%) [0.0%, 8.2%]	6 (4.5%) [1.7%, 9.6%]	-2.99% CI: [-7.70, 1.72] p = 0.142097
Disease control rate (CR + PR + SD[b])	6 (9.1%) [3.4%, 18.7%]	70 (52.6%) [43.8%, 61.3%]	-43.61% CI: [-54.72, -32.49] p = <0.000001

Overall response modified RECIST V1.1 from central radiological review.
Abbreviations: CI – confidence interval, CR – complete response, NA – not analyzed, PR – partial response, SD – stable disease
a: SD according to modified RECIST v1.1.
b: SD to be maintained for at least 12 weeks.

Disease control rate - According to the central assessment, the DCR was 52.6%in the regorafenib group (95% CI: 43.8, 61.3) and 9.1% in the placebo group (95% CI: 3.4, 18.7) (Table 7). This difference was statistically significant (p<0.000001).

Duration of response – the median duration of response (central assessment) for regorafenib treated patients (n=6) was 99 days (range 43-99), and for the one placebo treated patient (n=1) was 30 days.

Patient reported outcomes - The mean change from baseline in EORTC QLQ-C30 global health status/QoL and functional scales at cycles 2-4 were generally similar (<10 points, not clinically meaningful) between the two treatment groups, except for the role functioning scale (Table 8). Mean changes in scores from baseline for global health status and the 5 functional dimensions demonstrated a slight deterioration in patients' QoL of similar magnitude both in the regorafenib + BSC and placebo + BSC groups. There was a small but clinically meaningful change (≥10 points) from baseline (towards reduction in role functioning) observed in the regorafenib group but not in the placebo group based on descriptive analysis only.

Comment: Although an exploratory analysis, the analysis of patient reported outcomes did not suggest any benefit of regorafenib in terms of improvement in health-related quality of life, but rather a clinically meaningful decrease in role functioning. Overall, global health status and all 5 functional dimensions were found to deteriorate slightly for patients in both the placebo and regorafenib arm during the study period.

Table 8: EORTC QLQ-C30 change from baseline at Cycles 2,3,4 and EOT (double-blind treatment period) (RRO)

	n	Placebo + BSC (N = 62) Mean ±SD	n	Regorafenib + BSC (N = 123) 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

Genetic biomarker analyses - Historical mutation data was available from 48% of all randomised patients in the Phase III GIST Study 14874, of which 53% had a tumour with a mutation in KIT Exon 11, 16% had a tumour with a mutation in KIT Exon 9, and 8% had no KIT and no PDGFRa mutation (WT GIST). Mutational analyses indicated that both exon 11 mutant and exon 9 mutant subgroups fare better on regorafenib compared to placebo with respect to PFS, with a HR of 0.212 (95% CI: 0.098, 0.458) and 0.239 (95% CI: 0.065, 0.876) respectively.

A further exploratory genetic biomarker analysis of Study 14874 was performed using biomarker specimens collected during the study period, and was presented as a separate report (**PH-37123**). This aimed to collect data for a higher proportion of study participants than provided historical mutational data, and to assess for concordance with the historical specimens to assess for the influence of secondary mutations (that may represent 'resistance' mutations to treatment with imatinib or sunitinib). Plasma samples were obtained from 163/199 (82%) of the total randomised subjects, and were tested for KIT, PDGFRA, BRAF, and KRAS mutations.

KIT mutations were detected in 94/163 (58%) of samples analysed, with presumptive primary mutations in KIT-Exon 9 in 24/163 (15%) and KIT-Exon 11 in 19/163 (12%). Presumptive secondary KIT mutations were detected in 77/163 (47%) of the samples. It was noted that not all KIT-Exon 11 mutations were tested for, and thus the proportion of subject with KIT mutations is likely to be higher. PDGFRα alterations were detected in 2/163 (1%) of samples, and there were no BRAF mutations detected in the sample. KRAS mutations were only assessed in 2 subjects who had had these mutations identified in tumour tissue, and only one of these was found to have the same mutation in plasma. Combined, subject-matched plasma and

tumour tissue mutation data from primary KIT-Exons 9 and 11 alterations showed concordance in 84% (27/32) of the samples examined.

Analyses were conducted to evaluate potential associations between KIT mutational status and clinical response to regorafenib. This found a benefit for regorafenib *versus* placebo in all biomarker subgroups examined. The frequency of PDGFRA, BRAF, and KRAS mutations was too low for meaningful correlative analyses, however it was noted that the single patient with the KRAS mutation progressed relatively quickly on regorafenib (PFS central assessment 30 days). In conjunction with the results from a patient with BRAF mutation in Study 14935 (see *Other efficacy studies* below), it was concluded by the sponsor that GIST patients harbouring driver mutations in components of the ERK signalling pathway (ie, KRAS or BRAF) do not appear to respond favourably to kinase inhibitors such as imatinib, sunitinib or regorafenib.

Comment: It is agreed with the sponsor that although the exploratory evidence does not suggest a differential effect of regorafenib according to KIT mutations status, there may be a reduced effect in patients with KRAS or BRAF mutational status. This has implications for the cost-benefit equation for using regorafenib in these patient subgroups, and should be considered accordingly. This has been posed as a question to the sponsor under *Clinical questions* below.

Non-genetic biomarker analysis – This exploratory analysis of subjects in Study 14784 was presented as a separate report (PH-37168), which has not been fully evaluated. The levels of 11 different proteins were quantified at baseline and Day 15 of cycle 2, and were assessed for correlation with clinical outcome (PFS). Reported key findings of this analysis included the association of VEGF-A levels with more aggressive tumour but that is particularly responsive to regorafenib (a VEGFR signalling inhibitor), and a baseline to Cycle 2-Day 15 decrease in IGFBP-2 associated with regorafenib treatment.

8.2. Other efficacy studies

8.2.1. Study 14935

The sponsor stated in the clinical overview that this was an investigator-sponsored, open-label, multicentre, single-group study in patients with metastatic and/or unresectable GIST after failure of imatinib and sunitinib, based in the US. A published journal paper (3) was provided with the submission, but not the CSR.

Comment: Although the sponsor stated that this study was an investigator-sponsored study, the paper states that it was 'Supported in part by Bayer HealthCare Pharmaceuticals, which provided funding and study drug.' Clarification of the role of the sponsor in this study has been posed as a question under *Clinical questions* below.

This was a Phase II trial across 4 centres in the US. Recruitment was from February to December 2010, with a data cut-off 28 July 2011. Patients received regorafenib at 160 mg per day for 3 weeks on, 1 week off per treatment cycle.

Eligible patients had 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. Patients included were ≥ 18 years of age, had adequate organ and bone marrow function, and had an ECOG PS of 0 or 1. Exclusion criteria included (amongst others) previous treatment with sorafenib and clinically significant cardiac disease.

Of 34 patients enrolled in this study, 33 were eligible for participation, received at least one dose of regorafenib, and were evaluable for efficacy and safety. Patients remained on treatment until documentation of PD, development of unacceptable toxicity or decision to withdraw from the study. Tumour assessments were performed at the end of regorafenib dosing (day 21) after every two cycles, that is, every 8 weeks.

Comment: The timing of tumour assessments at 8 weekly intervals in this study (compared to 4 weekly in the pivotal Study 14874) will have the effect of prolonging the apparent time to progression if the progression time is taken as the time of tumour assessment imaging, although this was not specified in the published paper. In addition, the method of assessment (central or investigator) was not specified, but is assumed to be the latter. In this case, the effect of investigator assessments could be to prolong the time to progression, as was seen in the pivotal trial, where the investigators assessments of PFS were consistently longer than that of central assessment.

The primary endpoint was Clinical benefit rate (CBR), defined as the proportion of patients with a best overall tumour response of PR or CR according to RECIST version 1.1 plus patients with a best overall response of stable disease maintained for a minimum of 16 weeks. A one-stage design with 34 patients was used to distinguish a favourable true CBR of 28% from a null rate of 10% with 90% power and 8% type I error. Secondary endpoints were ORR, PFS, OS, PK, biomarkers, and safety and tolerability of regorafenib.

As the sponsor stated in the Clinical Overview, due to different study designs, no direct comparison of this study with pivotal Study 14935 was possible.

Comment: The definition CBR as used in this study differs from disease control rate (DCR) as defined in the pivotal Study 14874, in that for CBR stable disease had to be maintained for 16 weeks compared to 12 weeks for DCR. This difference in definitions means that, as stated by the sponsor, the outcomes of the two studies cannot directly be compared.

Baseline characteristics of the study group were 19/33 (58%) male, median age 56, and 23/33 (70%) had an ECOG PS of 0 and 30% of 1. The median tome receiving first-line imatinib was 21 months, and the median time receiving sunitinib was 13 months. Of the 30 patients who had mutational status available, 19 (63%) had KIT Exon 11 mutation, 3 (10%) had Exon 9 mutation, and 8 (27%) had WT for KIT and PDGFRα. One of the latter WT patients had BRAF of Exon 15.

Of 33 patients who were assigned to and received treatment with regorafenib, after a median follow-up of 10.9 months, 21 patients continued to receive regorafenib, of whom 16 also remained progression-free. Five further patients continued to receive regorafenib after assessment of disease progression because of investigator-assessed continued benefit. 12 patients discontinued study drug (6 due to disease progression, 3 due to clinical progression, and 1 each for inter-current illness, patient choice and an adverse event).

Clinical benefit (that is, CR, PR, or stable disease maintained for at least 16 weeks) was observed in 26 of 33 patients (79%; 95% CI: 61%, 91%). Overall, no patients had a CR, 4 (12%) patients had a PR, 22 (67%) patients had stable disease for ≥16 weeks, 4 (12%) patients had stable disease for ≤16 weeks, 2 (6%) patients had progressive disease, and 1 (3%) patient was not evaluable due to withdrawal from the study.

Median PFS in this study was 10.0 months (95% CI: 8.3, 14.9 months). As of the data cut-off date of 28 Jul 2011, 6 of 33 patients in this study had died. As a result, median OS has not yet been determined.

Comment: The results of this Study 14935 are consistent with those of pivotal Study 14874. As stated by the sponsor, no direct comparison of the study results can be made due to differing study designs. However, comparisons in endpoints can be made between the two studies to assess for consistency of results.

The primary endpoint of CBR (best overall tumour response of PR or CR plus patients with stable disease of at least 16 weeks) of 79% (95% CI: 61%, 91%) compares with the DCR (best overall tumour response of PR or CR plus patients with stable disease of at least 12 weeks) of 52.6% (95% CI: 43.8, 61.3) in the

regorafenib group of pivotal Study 14874. In addition, the median PFS in this study of 10.0 months (95% CI: 8.3 - 14.9) compares with the median PFS in the regorafenib arm of pivotal Study 14874 of 4.8 months (95% CI: 4.0 - 5.7).

It is noted that the magnitude of the effect of regorafenib on CBR and PFS appears greater in Study 14935 compared to DCR and PFS in pivotal Study 14874. Reasons for this apparent increase in efficacy could be as discussed above, namely the longer time periods between tumour assessments in this Study 14935 and the fact that investigator assessments rather than blinded central assessments were used, both of which have the effect of lengthening the calculated time to progression.

It is noted however, that there are similarities between this study and pivotal Study 14874. These include similar underlying population demographics and past treatment regimens (failure of 2 prior TKIs), as well as a similar regorafenib dosing regimen.

Therefore, it can be concluded that although the results of Study 14935 cannot be directly compared with the results of the pivotal Study 14874, there are similarities in the study designs. The clinical benefit calculated in the two studies is in the same direction and Study 14935 can therefore be considered supportive to the pivotal trial.

Subgroup analysis by tumour genotype found the KM estimate of PFS after pairwise comparisons showed a significantly longer PFS for patients with KIT Exon 11 mutations compared to KIT Exon 9 mutations, although both groups showed protocol-defined clinical benefit. However, as there were only 3 patients with KIT Exon 9 mutations, results need to be interpreted with caution. The PFS for patients with WT GIST was intermediate between the above two groups. It was noted that one patient with GIST containing BRAF exon 15 mutation exhibited rapid disease progression despite regorafenib administration.

Comment: The rapid progression of the patient with BRAF mutation again questions the efficacy of regorafenib in patients with these mutations. Further research is warranted to better elucidate the risk benefit equation of treatment of these patients with regorafenib.

8.3. Analyses performed across trials (pooled analyses and meta-analyses)

8.3.1. R-8737 (14653) Exposure-response analysis of regorafenib in Phase III Study 14387.

In this analysis an exposure-response analysis for Phase III Study 14387 was performed, linking individual exposure estimates to the primary and secondary efficacy endpoints and to tumour dynamics. Exposure estimates were taken from the population PK study R-8731 (14653). The planned exposure-response analysis was influenced by a bias due to increased chance of dose reduction or dose interruption for longer treatment duration, resulting in lower average concentrations over the treatment period for patients with longer treatment duration. The duration of treatment was longer in patients with complete, partial response or stable disease resulting in a lower average concentration for this group. When the analysis was corrected for this bias, no evidence was found for an exposure-response relationship with regorafenib.

Comment: The above report was not fully evaluated, as the response outcome measure was treatment efficacy in patients with metastatic CRC, which is not relevant to the proposed new indication. Moreover, this was an exploratory efficacy analysis based on the pop PK modelling, and no new safety data was presented.

8.3.2. R-8813 (16282) Exposure-response analysis of regorafenib in Phase III GRID Study 14874

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 primary efficacy parameter PFS, and the secondary efficacy parameters OS and Objective Disease Control (ODC). 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 regorafenib (Cav_{md}). It was concluded that PFS was not significantly influenced by any of the exposure measures or covariates. A highly tentative conclusion was drawn that OS was longer for patients with higher average total concentration (Cav_{md} of regorafenib, M2 and M5) and smaller baseline sum of tumour diameters. None of the exposure measures or covariates had a significant influence on the proportion of subjects with ODC.

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. It was found that the tumour shrinking effect of regorafenib diminished over time; regorafenib treatment typically caused initial tumour shrinkage; the effect of the drug was exposure-independent over the exposure range observed in these patients; and none of the tested covariate effects had a significant effect.

Comment: The above exploratory analysis was not fully evaluated, as this was not a primary objective of Study 14874 or the population PK analysis.

8.4. Evaluator's conclusions on clinical efficacy

For treatment of patients with gastrointestinal stromal tumours (GIST) who have been previously treated with two tyrosine kinase inhibitors

8.4.1. Pivotal study 14874

This was a generally well conducted study. The primary outcome of centrally assessed PFS is acceptable, with OS assessed as a secondary outcome. Queries related to the handling of missing data have been posed as questions to the sponsor.

For the primary outcome of PFS after a pre-specified 144 events, there was a statistically and clinically significant beneficial effect of regorafenib treatment of 4.8 months (95% CI: 4.0-5.7) over placebo of 0.9 months (95% CI: 0.9, 1.1), with a HR of 0.268 (95%CI 0.185, 0.388, $p<0.000001$). This result was supported by secondary and subgroup analyses, and the magnitude of this effect is sufficient that some differences in the baseline disease characteristics between the placebo and regorafenib patient groups are not likely to significantly impact on the results.

The immaturity of OS data means that no definitive conclusions can be drawn on the effect of regorafenib treatment on OS compared to placebo, although a beneficial effect of regorafenib was suggested with a HR of 0.772 (95% CI: 0.423, 1.408). Analysis of further OS data as it becomes available would be beneficial and is recommended. However, the ability of subjects randomised to the placebo group to cross over to regorafenib treatment on disease progression means that the true OS benefit attributable to regorafenib will be difficult to estimate.

Analysis of other secondary efficacy outcomes including TTP, ORR, DCR and duration of response supported the benefit shown in PFS in the primary analysis of regorafenib over placebo.

However, there was no demonstrated benefit of regorafenib in terms of Quality of Life compared to placebo, but rather a clinically meaningful decrease in role functioning was observed.

Overall, the use of one pivotal study in this submission appears acceptable. The study was satisfactorily conducted to ensure internal validity (randomisation and use of centrally blinded assessments); external validity (subjects were representative of the target group); the results were clinically relevant and statistically significant (large gains in PFS compared to placebo); data quality was good and internally consistent across subgroups and endpoints; and there were multiple centres involved across many countries representing the likely target population.

8.4.2. Supportive study 14935

Study 14935 was a Phase II study assessing the clinical benefit of regorafenib in patents with unresectable or metastatic GIST who had previously been treated with imatinib and sunitinib. The results found a CBR of 79% (95% CI: 61%, 91%) and PFS 10.0 months (95% CI: 8.3 - 14.9) with regorafenib treatment. Due to different methodologies, these results cannot be directly compared with those of the clinical trial, although it is noted that they are in a similar direction although of greater magnitude. Reasons for the different magnitude of the results may include the longer time between tumour assessments in this study, as well as the use of investigator rather than central assessments. Despite this, the results of this study are in agreement with and therefore support those of the pivotal Study 14874 in patients with metastatic or unresectable GIST.

8.4.3. Biomarker analyses

Only exploratory biomarker analyses have been performed, and thus no definitive conclusions can be drawn regarding the efficacy of regorafenib according to biomarker status. Exploratory evidence suggests a beneficial effect of regorafenib over placebo with KIT mutations. However, in two patients with KRAS and BRAF mutations, clinical outcomes were poorer. Due to the importance of risk-benefit considerations in treatment decisions, further evidence regarding the efficacy of regorafenib in patients with KRAS and BRAF mutations would be beneficial, particularly in light of documented differences in the efficacy of imatinib and sunitinib according to biomarker status. Further comment has been sought from the sponsor as a clinical question.

9. Clinical safety

9.1. Studies providing evaluable safety data

The following studies provided evaluable safety data:

9.1.1. Pivotal efficacy studies

In the pivotal Study 14874, all 198 randomised patients who had received at least one dose of study medication were included in the analysis of safety (SAF). Relevant for the analysis, this was separated into: the **double-blind treatment period** (regorafenib versus placebo) that included 132 patients randomised to receive regorafenib + BSC and 66 patients randomised to placebo + BSC (n=198 in total), and the **combined double blind and/or open-label period** (all regorafenib treated patients) which included those patients randomised to and who received regorafenib (n=132) and those randomised to placebo who crossed over to regorafenib in the open-label phase (n=56), for an overall n=188. The Safety follow-up period included a 30 (± 7) day window after last intake of study drug, after which patients entered the Survival Follow-up Period (at which time patients were followed for survival only at 3 month intervals and safety follow up was ceased).

During the Safety follow-up period in Study 14874, the following safety data were collected:

General adverse events (AEs) were assessed based on results of physical examinations, including ECOG performance status, review of all organ systems, examination of pertinent organ

systems, vital signs (heart rate, blood pressure, and temperature), weight and height; electrocardiogram (ECG) data; echocardiographic study or multiple gated acquisition (MUGA); laboratory values as well as adverse events (AEs) up to 30 days after termination of treatment. NCI CTCAE v. 4.0 was used for assessment of toxicity and serious AE reporting.

AEs of particular interest, including acute renal failure or severe proteinuria, interstitial lung disease, acute cardiac failure, clinically significant bleeding, Stevens-Johnson Syndrome and erythema multiforme, and hepatic failure, were assessed during the standard safety evaluations as defined in the protocol and were required to be immediately notified to the sponsor.

Laboratory tests, including haematology analysis, electrolyte panel, chemistry panel, thyroid function tests, coagulation panel, urinalysis and measurement of GFR were performed at baseline and according to the schedule of study assessments (generally every 2-4 weeks). Of particular note, liver function tests were performed weekly for the first 2 cycles (8 weeks) of study treatment.

9.1.2. Dose-response and non-pivotal efficacy studies

The dose-response and non-pivotal efficacy studies provided safety data, as follows:

- **Study 14935** provided data based on a published journal paper only. Only commonly occurring toxicities (occurring in ≥ 25% of patients) were presented in this paper, which limits the interpretation and analysis of this study from a safety perspective.
- **Study 14814** provided data on the effect of regorafenib on cardiovascular safety parameters, specifically QT/QTc intervals and left ventricular ejection fraction (LVEF).

9.1.3. Other studies evaluable for safety only

Study 14596 (A62282) was an uncontrolled open label multicentre Phase II safety study of regorafenib in patients with hepatocellular carcinoma (HCC), with study centres in 13 sites across Germany (5), Italy (5), South Korea (2) and Spain (1). The primary objective was to assess the safety profile of regorafenib, with secondary endpoints to assess its efficacy in HCC patients with liver function status Child-Pugh Class A who had failed prior systemic treatment with sorafenib. 36 subjects were recruited and given 160 mg regorafenib orally daily for a cycle of 3 weeks on followed by 1 week off, and were included in the ITT population and the safety analysis set (SAF). AEs were recorded at baseline and generally at 2 weekly intervals during treatment, with the option to perform monthly assessments following 6 cycles of treatment. LTFs were performed at weekly intervals for the first 2 cycles of treatment.

Comment: Study 14596 was not included in the efficacy evaluation because it was an uncontrolled study for a different indication than that proposed in this application, and had a different underlying population. Furthermore, the primary endpoint was safety rather than efficacy. The report submitted was an updated addendum of an earlier report that was previously evaluated by the TGA and included a detailed PK analysis. Only the updated safety information provided in the Addendum with this application has been evaluated in this CER.

9.1.4. Pooled safety data

Global integrated analysis – This was presented in the Module 2.7.4 Summary of Clinical Safety (2.7.4) with a data cut-off 28 February 2013. The main analysis included only completed company-sponsored studies for which a clean clinical database was available. Three data pools ware produced from 10 clinical studies of regorafenib in cancer patients:

- **Pool 1** – All regorafenib monotherapy-treated patients in completed Phase I to III studies (n=1,073) including:
  - 2 Phase III studies (14387 and 14874)

- 6 uncontrolled Phase I and II studies of regorafenib at the intended dosing regimen of 160 mg daily for 3 weeks on/1 week off treatment cycles (Studies 11726, 14596, 12434, 13172, 14814 and 14996)
- 2 Phase I dose escalation studies (11650 and 11651)

· **Pool 2** – Includes placebo-controlled safety data from the double-blind period of the pivotal Phase III study in patients with GIST (Study 14874, n=132)

· **Pool 3** - Includes placebo-controlled safety data from the double-blind phase of the Phase III studies 14387 and 14874 (n=632)

Comment: Throughout this CER, reference is primarily made to Pool 1 of the global integrated analysis, as the results of Pool 2 are presented separately as that of Pivotal Study 14874. The safety results of Study 14387 that make up the rest of Pool 3 were previously evaluated.

Bayer HealthCare safety database – Includes al SAEs from completed and ongoing studies (including combination studies) (more than 3,500 patients) and early access programs (more than 500 patients), SAEs reported within an ongoing patient support program and spontaneous reports (data cut-off 28 February 2013).

· Non-pooled studies in cancer patients included: 15808, 15967, 11728, 11656, 14458, 14935, 15579, 15344 and 15968.

· Non-pooled studies in healthy volunteers included: 12435, 12436, 12437, 14656 and 15524.

Comment: The above studies were not submitted for evaluation and have thus not been evaluated. The results from the summaries of SAEs and deaths are included below.

9.2. Patient exposure

A summary of exposure to regorafenib and comparators in clinical studies presented in this submission is provided in Table 9 and exposure to regorafenib according to dose and duration is provided in Table 10.

Pivotal Study 14874 - During the double-blind period, patients who were assigned to receive regorafenib + BSC underwent a median treatment duration of 22.94 weeks (mean 20.22 weeks) and patients who were assigned to receive placebo + BSC underwent a median of 6.98 weeks (mean 9.08 weeks). Among the placebo + BSC patients who crossed over to open-label treatment with regorafenib + BSC, the median treatment duration with regorafenib + BSC was 14.96 weeks (mean 15.26 weeks). The median treatment duration with regorafenib + BSC for all (n=188) regorafenib-treated patients across both study periods was 22.94 weeks (mean 21.12 weeks).

The median daily dose of regorafenib during the double-blind treatment period was 146.83 mg (mean 139.79 mg). Patients who crossed over from placebo received a median daily dose of 160.00 mg regorafenib (mean 146.19 mg) and the median daily dose to all regorafenib-treated patients for both study periods was 153.06 mg regorafenib (mean 140.31 mg).

Dose modifications were more common among patients who were assigned to receive regorafenib + BSC. During the double-blind period, dosing modifications were instituted for 72.0% of regorafenib-treated patients and 25.8% of placebo-treated patients. Among the placebo + BSC patients who crossed over to open-label treatment with regorafenib + BSC, dose modifications were instituted for 72.7% of patients. The overall frequency of modifications for patients who received any regorafenib during the two study periods was 73.8%.

Supportive Study 14935 – Data for this study was submitted as a published journal paper only. Therefore, the toxicity data presented was limited and only included commonly occurring

events. As of the reporting date (28 July 2011), 33 patients had been exposed to 280 cycles of regorafenib, with a median of 8 cycles (range 2-17 cycles). A breakdown of duration of treatment was not available.

Study 14596 – The median treatment duration was 19.5 weeks (mean 31.9 weeks, range 2-103 weeks) or 5.0 cycles. There were 9 subjects who were treated for 14 or more cycles in this study, taken to be equivalent to more than 12 months of treatment. The mean actual daily dose of regorafenib was 143.59 mg, with the median actual daily dose being 158.11 mg (range: 90.4 to 160.0 mg).

Table 9: Exposure to Regorafenib and comparators in clinical studies.

Study type/ Indication	Controlled studies		Uncontrolled studies	Total Regorafenib
	Regorafenib	Placebo	Regorafenib	
Clinical pharmacology				
Indication 1:metastatic or unresectable GIST				
· Pivotal	188 (132+56)	66		188
· Other			33*	33*
· **Subtotal Indication 1**				
Indication 2: HCC				
· Pivotal				
· Other			36	36
· **Subtotal Indication 2**				
TOTAL	**188**	**66**	**69**	**257**

* Full safety data not provided in published paper

Table 10: Exposure to Regorafenib in clinical studies according to dose and duration.

Study type/ Indication	Proposed dose range = Proposed maximum dose			
	≥ 3 months	≥ 6 months	≥ 12 months	Any duration
Clinical pharmacology				
Indication 1: metastatic or unresectable GIST				

Study type/ Indication	Proposed dose range = Proposed maximum dose			
	≥ 3 months	≥ 6 months	≥ 12 months	Any duration
· Placebo-controlled	133	60	0	188
· Active-controlled				
· Uncontrolled				33
· **Subtotal Indication 1**				
Indication 2: HCC				
· Placebo-controlled				
· Active-controlled				
· Uncontrolled	24	17	9	36
· **Subtotal Indication 2**				
TOTAL	**157**	**77**	**9**	**257**

Global integrated analysis – As of the data cut-off 28 February 2013, in **Pool 1**, there were 1,073 patients who were exposed to regorafenib for a mean duration of 17.65 weeks and a median duration of 11.71 weeks (range 0.1-179.4). The mean number of cycles completed was 4.7 (median 3.0, range 1-46), and the mean daily dose of regorafenib was 138.88mg (median 157.14, range 10.0-220.0).

9.3. Adverse events

9.3.1. All adverse events (irrespective of relationship to study treatment)

9.3.1.1. Pivotal studies

Study 14874 – During the double-blind period, treatment-emergent adverse events (TEAEs)[1] were experienced by 132/132 (100%) of patients randomised to receive regorafenib + BSC and by 61/66 (92.4%) of patients randomised to receive placebo + BSC. TEAEs that occurred at a >10% higher frequency in the regorafenib + BSC arm compared to the placebo + BSC arm included hypertension (59.1% versus 27.3%), HFSR (56.8% versus 13.6%), fatigue (50.0% versus 37.9%), diarrhoea (46.2% versus 9.1 %), oral mucositis (40.9% versus 7.6 %), infections and infestations (37.1% versus 7.6%), hypothyroidism (14.4% versus 3.0%), abdominal pain (26.5% versus 15.2%), maculopapular rash (18.2% versus 3.0%), alopecia (24.2% versus 1.5 %), and hoarseness (24.2% versus 6.1%). The incidence of treatment-emergent Grade 3 and 4 adverse events generally followed the same pattern as overall adverse events. During the double-blind period, Grade 3 events were more common in the regorafenib group (64.4% compared to 25.8% in the placebo group), while the incidence of Grade 4 events was similar across the two arms (6.8% in the regorafenib group versus 6.1% in the placebo group). The incidence of Grade 5 TEAEs (events leading to death) in the double-blind treatment period was

[1] Study-specific TEAEs are depicted according to NCI-CT&CAE, that is, no depiction according to MedDRA-Preferred Terms

5.3% in the regorafenib group compared to 4.5% in the placebo group, and was 8.5% in the combined treatment period overall. The latter are discussed further below.

Comment: It is noted that the incidence of AEs are higher in the regorafenib group compared to placebo across all SOCs, and there is a higher rate of Grade 3 TEAEs in the regorafenib group compared to placebo in the double-blind period.

Inspection of all TEAEs during the double blind period (CSR Table 14.3.3/3) also revealed Ear and labyrinth disorders were more commonly seen in the regorafenib arm compared to placebo (10.6% versus 3.0%), which included Hearing impaired (3.8% versus0%), Tinnitus(1.5% versus 0%), Vertigo (4.5% versus 3.0%), and Other (2.3% versus 0%). This data indicates that combined ear and labyrinth disorders are an adverse effect of regorafenib which is experienced more frequently than with placebo treatment, and, although an overall category, is of relevance for clinical decision-making and should be included as an adverse reaction in the PI.

Assessments of the incidence of TEAEs by the subgroup categories of gender, age, race, ECOG PS, region, prior therapy, and BMI were performed. In general, these analyses showed similar rates of events across subgroups, with the exception of HFSR. The frequency of HFSR was observed to be higher among Asian patients who received regorafenib + BSC (82.4%) than among non-Asians (49.4%). In addition, Grade 3 and 4 AEs were more common in regorafenib treated patients who were aged ≥ 65 years (81.4%) compared to those aged < 65 years (66.3%).

9.3.1.2. Other studies

Study 14935 – Data on all AEs was not presented, only those assessed as possibly study drug related.

Study 14596 – 36/36 (100%) of subjects experienced at least 1 TEAE , the most common being fatigue (77.8%), diarrhoea (55.6%), HFSR (52.8%), hypothyroidism (47.2%), anorexia (44.4%), nausea (41.7%), abdominal pain (41.7%), voice changes (38.9%), hypertension (36.1%), fever (36.1%), decreased haemoglobin (33.3%), constipation (33.3%), hyperbilirubinaemia (27.8%), weight loss (25.0%), ascites (25.0%) and headache (25.0%). 18 (50.0%) subjects experienced at least 1 Grade 3 TEAE, 5 (13.9%) subjects experienced at least 1 Grade 4 TEAE, and 8 (22.2%) subjects experienced at least 1 Grade 5 TEAE. A listing of TEAEs of worst Grade 3-5 which affected at least 2 subjects in Study 14596 is listed in Table 11. Prolonged QTC was observed in 2 subjects (one Grade 2 and one Grade 3), one of which was attributed to study treatment.

Table 11: TEAEs by worst CTCAE Grade 3 to 5 with total incidence ≥5% (SAF) in Study 14596

CTCAE term v 3.0	Regorafenib (160 mg) N=36 (100 %)[a]			
	Grade 3	Grade 4	Grade 5	Total
Fatigue	6 (16.7%)	2 (5.6%)		8 (22.2%)
Bilirubin (hyperbilirubinemia)	6 (16.7%)	1 (2.8%)		7 (19.5%)
Hand-foot skin reaction	5 (13.9%)			5 (13.9%)
Pain, abdomen NOS	5 (13.9%)			5 (13.9%)
Liver dysfunction	1 (2.8%)		2 (5.6%)	3 (8.3%)
Renal failure	3 (8.3%)			3 (8.3%)
Ascites	3 (8.3%)			3 (8.3%)
Hemoglobin	2 (5.6%)	1 (2.8%)		3 (8.4%)
Diarrhea	2 (5.6%)			2 (5.6%)
GGT	2 (5.6%)			2 (5.6%)
Hypophosphatemia	2 (5.6%)			2 (5.6%)
Death not associated with CTCAE Term, Disease Progression NOS			2 (5.6%)	2 (5.6%)
AST	1 (2.8%)	1 (2.8%)		2 (5.6%)
Hyponatremia	2 (5.6%)			2 (5.6%)
CNS hemorrhage			2 (5.6%)	2 (5.6%)

AST=aspartate aminotransferase; CTCAE=Common Terminology Criteria for Adverse Events; GGT=gamma-glutamyl transferase; N=number of subjects in the entire population; NOS=not otherwise specified; SAF=Safety Analysis Set, and v=version.

a Presented in order of decreasing frequency.

Comment: It can be seen from Table 11 that in the subject population of Study14596, nearly 20% of subjects experienced Grade 3 or 4 hyperbilirubinaemia, and 2 subjects (5.6%) experienced Grade 5 liver dysfunction. This compares with 2.7% of treated subjects who experienced Grade 3 or 4 hyperbilirubinaemia in pivotal Study 14874. Therefore, the risk of hepatic adverse events may be higher in subjects with HCC, or those with pre-existing hepatic impairment.

Global integrated analysis[2] – In Pool 1, overall 1067/1073 (99.4%) of subjects experienced any TEAE, of which 2.4% were of worst Grade 1, 18.7% Grade 2, 57.5% Grade 3, 9.0% Grade 4, and 11.7% were of worst Grade 5 and resulted in death. The most common AEs were HFSR (experienced by 49.7% of subjects), diarrhoea (42.8%), fatigue (42.1%), decreased appetite (40.4%), hypertension (36.1%), and dysphonia (32.1%). Other AEs of note include hyperbilirubinaemia in 97/1073 (9.0%) subjects, and infections and infestations in 389/1073 (36.3%) subjects.

Comment: Overall the incidence of AEs is high in patients treated with regorafenib, and the newly presented evidence is in keeping with that outlined in the PI. The most common AEs are consistent across the studies and pooled analyses, and include HFSR, fatigue, diarrhoea and hypertension. An increased incidence of infections and infestations was observed in the regorafenib arm compared to placebo in the pivotal study, and this was supported by the results of the Global integrated analysis.

9.3.2. Treatment-related adverse events (adverse drug reactions)

9.3.2.1. Pivotal studies

Study 14874 – Treatment-related TEAEs were reported for 130/132 (98.5%) of patients in the regorafenib + BSC arm and 45/66 (68.2%) of patients in the placebo + BSC arm. The most commonly occurring drug-related adverse events that occurred in the regorafenib-treated patients were HFSR (56.1%), hypertension (48.5%), diarrhoea (40.2%), fatigue (38.6%), and oral mucositis (37.9%), while for the placebo arm they were fatigue, hypertension and HFSR. An

[2]Pooled safety data is according to MedDRA.

overall higher incidence of infections was observed in the regorafenib + BSC arm (37.1%) as compared to placebo arm + BSC (7.6%).

Comment: The pattern of observed treatment-related AEs follows that of all TEAEs as described in Section All adverse events (irrespective of relationship to study treatment).

9.3.2.2. Other studies

Study 14935 – The most commonly observed toxicities of any grade that were at least possibly study drug related included HFSR (85%), fatigue (79%), hypertension (67%), and diarrhoea (61%). Other commonly observed toxicities included hoarseness, myalgia, headache, hypophosphataemia, nausea, anorexia, mucositis oral and alopecia. Grade 3 toxicities occurring in ≥ 5% of patients and included hypertension (36%), HFSR (24%) and hypophosphataemia (15%).[3]

Study 14596 – 35/36 (97%) subjects experienced at least 1 drug-related TEAE. The most commonly observed were HFSR (97.2%)[4], diarrhoea (53%), fatigue (53%), hypothyroidism (42%), anorexia (36%), hypertension (36%), nausea (33%), voice changes (28%) and constipation (25%). Of note, there was one report of Grade 3 prolonged QTC which was attributable to study treatment.

Global integrated analysis – In Pool 1, overall 1001/1073 (93.3%) of subjects had any drug-related AE, the most common being HFSR (49.3%), diarrhoea (33.9%), fatigue (32.1%), hypertension (31.4%), dysphonia (28.6%) and decreased appetite (26.6%).

Comment: Based on the reported incidence of adverse events and treatment-related adverse events in pivotal Study 14874 and supported by Studies 14935, 14596, and the Global integrated analysis, the most commonly occurring AEs attributed to treatment with regorafenib include HFSR, hypertension, diarrhoea, fatigue and oral mucositis. Other treatment-related AEs to consider include hypothyroidism, maculopapular rash, alopecia, hoarseness and infections. These drug-related AEs are generally in keeping with the overall TEAEs outlined in Section *All adverse events (irrespective of relationship to study treatment)*.

9.3.3. Deaths and other serious adverse events

9.3.3.1. Pivotal studies

9.3.3.1.1. Study 14874

Deaths: Up to data cut-off, 46 deaths overall were reported in Study 14874, 29/133 (21.8%) in the regorafenib + BSC group and 17/66 (25.8%) in the placebo + BSC group. During the double-blind treatment period, there were 6/133 deaths (4.6%) in the regorafenib arm compared to 2/66 (3.0%) in the placebo arm, while in the open-label period there were 3/41 (2.3%) deaths in those originally randomised to regorafenib and 5/56 (7.6%) deaths in those originally randomised to placebo, giving rise to 16/188 deaths overall while on study treatment (8.5%). Grade 5 AEs were listed as being due to 1 event each of cardiac arrest, colonic perforation, disease progression, ileus, gastric obstruction, peritoneal necrosis, multi-organ failure, hepatic failure, sepsis, acidosis, ARDS, thromboembolic event, and 2 events of acute kidney injury and 3 events of 'other' (one patient has no reasons given for death).

Comment: There were no significant differences in the number of deaths between treatment arms in pivotal Study 14874. It is noted that the crossover of patients from the placebo arm to regorafenib treatment in the open label phase of the study confounds comparison between the two groups. The data indicates that there were

[3] The most common Grade 4 AEs assessed as possibly related to the drug were hyperuricemia (2, 6.0%) and thrombotic event (1, 3.0%).
[4] Erratum: 53%

no deaths for patients while on treatment in the placebo arm during the double-blind treatment, but this may have been due to the relatively shorter time that patients remained on placebo compared to regorafenib (mean 9.1 weeks compared to 20.2 weeks during the double-blind period respectively).

7 deaths were reported as related to study drug treatment by investigators; 6 with regorafenib + BSC (n=2 in the double-blind period: cardiac arrest, acute hepatic failure; and n=4 in the open-label period: acute kidney injury, colonic perforation, adult respiratory distress syndrome, and thromboembolic event) and 1 with placebo + BSC (fatigue). Each of these deaths occurred within 30 days of last treatment with study drug. Two of the death cases reported as related to regorafenib were considered to be of specific interest: one fatal GI perforation possibly due to the anti-tumour effect of regorafenib and one acute hepatic failure compatible with regorafenib-induced fatal liver injury.

Comment: It is noted that the patient who died of acute hepatic failure [information redacted] was a 49 year old Asian male with advanced GIST who had no history of hepatic disease and underwent acute hepatic changes 9 days after beginning his second cycle of regorafenib. Both investigator and sponsor attributed the cause of death to be due to treatment with regorafenib and no alterative explanation was provided. Severe drug induced liver injury is a known adverse effect of regorafenib that is included in the PI.

The subject who died of cardiac arrest [information redacted] was a 76 year old man with a history of atrial fibrillation and hypertension on study entry, who had a sudden cardiac arrest immediately following his second cycle of blinded regorafenib treatment that resulted in death. Although the Investigator assessed that this death was possibly related to study drug, this was disputed by the sponsor. This evaluator agrees with the investigator that the event could have been related to study drug.

There were two deaths due to fatal GI perforation [information redacted] in 58 and 65 year old males, one of which was assessed as possibly due to the anti-tumour effect of regorafenib. This is of clinical relevance to consider in the treatment of patients with large GI tumours.

The death due to acute kidney injury/renal failure [information redacted] was in an 80 year old man with no history of renal impairment, and was associated with an infection. The renal failure was attributed to study drug treatment by both the investigator and sponsor.[5]

The sponsor's assessment of the other case narratives of patients who died on study treatment appeared reasonable. It is noted that there were deaths due to sepsis attributed to progressive disease which were associated with sepsis, and these may have had a contributory effect from regorafenib treatment.

SAEs: During the double-blind period, SAEs occurred in 38/132 (28.8%) of patients who received treatment with regorafenib + BSC compared to 14/66 (21.2%) of patients who received placebo + BSC. During the combined double-blind and open-label period, SAEs were reported for 63/188 (33.5%) of patients.

The most commonly affected system for SAEs was the gastrointestinal system, for which a SAE was observed in 19/132 (14.4%) of regorafenib treated patients in the double-blind period (compared to 3/66 or 4.5% of placebo treated patients), and 24/188 (12.8%) of all treated subjects in the double-blind and open-label periods. Other SAEs which were observed more commonly in the regorafenib arm compared to placebo during the double-blind period included: fever (2.3% versus 0%), infections and infestations (3.8% versus 0%), investigations

[5]There were confounding factors for the renal failure event.

(3.0% versus 0%), nervous (3.0% versus 0%), renal and urinary (2.3% versus 0%) and vascular (2.3% versus 0%). The only SAE group for which there was a higher incidence in the placebo group compared to regorafenib was General and administrative site conditions (6.1% for regorafenib versus 12.1% for placebo), which included fatigue.

Comment: Although small numbers and the longer duration of subjects on regorafenib double-blind treatment compared to placebo are acknowledged, there is a general trend towards an increased incidence of SAEs with regorafenib treatment. Of particular note, increases in the incidence of severe infections, nervous conditions, and renal impairment are potentially of clinical relevance.

Of all SAEs, during the double-blind period 11/132 (8.3%) of patients in the regorafenib arm were considered to have SAEs that were considered related to drug treatment, while for all treated patients including the open-label period, 19/188 (10.1%) of subjects had a drug-related SAE. The most commonly reported drug-related SAEs included fatigue (1.6%), diarrhoea (1.1%), dehydration (1.1%) and thromboembolic event (1.1%).

Analysis of SAEs by subgroup revealed for the regorafenib group during the double-blind period, a higher incidence of SAEs in: males compared to females (31.0% versus 25.0%); older age groups (≥ 65 years) compared to younger (44.2% versus 21.3%); Asian patients compared to non-Asian (35.3% versus 22.5%); ECOG score of 1 compared to 0 (36.7% versus 22.2%), and lower BMI of <25 compared to 25<30 and ≥30 (33.3% versus 22.2% versus 14.3%). No differences were observed according to history of prior therapy (third or fourth line).

9.3.3.2. Other studies

Study 14935 – No subjects were reported to have died while on treatment, and SAEs were not specifically reported in the published paper.

Study 14596 – 25/36 (69.4%) subjects died in the study as of the database cut-off of 01 March 2012. Of these deaths, 8 (22.2%) were assessed as treatment –emergent of worst Grade 5 by CTCAE term and included: hematoma (1 subject); CNS haemorrhage (2 subjects); death not associated with CTCAE term, disease progression NOS (2 subjects); liver dysfunction (2 subjects); and metabolic / lab, other (1 subject). Of these, only the death of 1 subject due to haematoma was considered by the investigator to be related to study treatment. 21/36 (58.3%) subjects experienced at least 1 SAE, of which 5/36 (13.9%) experienced a SAE that was determined by the investigator to be drug-related.

Comment: It is noted that 2/36 (5.6%) subjects in Study 14506 died as a result of liver dysfunction. Although it is acknowledged that this patient population with HCC may be predisposed to hepatic impairment and injury, particular caution may be warranted in the administration of regorafenib to these patients.

Global integrated analysis – in Pool 1, 126/1073 (11.7%) of subjects died during treatment and up to 30 days post permanent treatment discontinuation. The most commonly reported reason for death was progressive disease in 98/126 (77.8%). However, on inspection of the listing of Grade 5 events by MedDRA PT it can be seen that 16/1073 subjects died from hepatic-related causes, and 10/1073 subjects died from bleeding events.

In Pool 1 of the Global integrated analysis, 486/1073 (45.3%) of subjects were noted to have a SAE while on regorafenib treatment. The most common SAEs were general physical health deterioration (4.1%), abdominal pain (3.0%), pyrexia (2.5%), diarrhoea and dyspnoea (both 1.7%). The overall individual frequency of SAEs was low by MedDRA PT.

Non-pooled completed combination trials – In Study 11656, 1 patient died from acute hepatic failure which was attributed by the investigator to study treatment with regorafenib in combination with mFOLFOX6.

Ongoing studies - In the ongoing non-pooled studies including approximately 2,785 cancer patients, a total of 269 deaths were reported up to the data cut-off date of 28 February 2013. A brief listing was provided of these deaths, but no case narratives were submitted. It was noted that of the 269 deaths, 17 were associated with hepatic causes, 9 associated with cardiovascular causes, and 8 were associated with renal failure.

Comment: The most common cause of death across the submitted studies was disease progression, as would be expected in cancer patient populations. However, potential regorafenib-related deaths include those from hepatic impairment, cardiovascular and thromboembolic events, renal impairment, infections, perforations and bleeding, and these should be considered adverse events of treatment. The overall frequency of individual SAEs was low with no specific SAE predominating.

9.3.4. Discontinuation due to adverse events

9.3.4.1. Pivotal studies

Study 14874 – During the double blind period, dose modifications (interruptions, delays, reductions) or discontinuations were more common among patients who received regorafenib + BSC compared to placebo + BSC. The incidence of TEAEs leading to permanent treatment discontinuation was 8/132 (6.1%) in the regorafenib + BSC arm compared to 5/66 (7.6%) in the placebo+ BSC arm. During the combined double-blind and open-label period, AEs leading to dose modifications were reported for 132/188 (70.2%) of patients, and AEs causing discontinuations were reported for 16/188 (8.5%) of patients.

There were no predominant conditions that resulted in discontinuation of study drug. In the placebo-controlled phase, 3/132 (2.3%) of subjects in the regorafenib arm had a drug-related TEAE that resulted in discontinuation of study drug, and these included reversible leukoencephalopathy syndrome, ALT increased, AST increased, and hepatic failure. During the open-label phase, there were an additional 5/97 (5.2%) drug-related TEAEs that led to permanent discontinuation of treatment, and these included colonic perforation, thrombo-embolism, thrombocytopenia, HFSR, and hypertension.

In the double-blind period, TEAEs led to dose interruption in 58.3% in the regorafenib arm compared to 16.7% in the placebo arm. The most common AEs resulting in dose interruption in the regorafenib arm during this period were: palmar-plantar erythrodysesthesia (PPE) syndrome (23.5% in the regorafenib arm versus 0% in the placebo arm); hypertension (10.6% versus 3.0%); fatigue (4.5% versus 3.0%); diarrhoea (6.1% versus 0%); increased ALT (3.0% versus 0%) and increased bilirubin (3.0% versus 1.5%).

In the double blind period, TEAEs led to dose reduction in 50.0% in the regorafenib arm and 3.0% in the placebo arm. The most common AEs resulting in dose reduction in the regorafenib arm in the double-blind period were: PPE syndrome (31.8% in the regorafenib arm versus 0% in the placebo arm) and diarrhoea (4.5% versus 0%).

Comment: Although it is agreed with the sponsor that the proportion of patients who permanently discontinued study drug is low in both treatment arms in Study 14874, indicating that most AEs are adequately managed by dose reduction, it is also noted that a relatively high proportion of patients required dose modification due to adverse events. In particular PPE syndrome is a relatively common adverse effect that results in the need for dose modification, and hypertension, diarrhoea and liver function also require monitoring.

9.3.4.2. Other studies

Study 14935 – One patient discontinued treatment due to AEs in this study, with no further details provided for the reasons for discontinuation in the paper. 27/33 (82%) patients

required a dose reduction at some point on study based on protocol-defined toxicity. The most common reasons for dose reduction were hypertension and HFSR.

Study 14596 – 18/36 (50%) of subjects experienced at least 1 TEAE that led to permanent discontinuation of study drug, of which 7 were assessed as drug-related. 27/36 (75.0%) of subjects experienced 1or more TEAE that led to dose modifications (interruption or reduction), the most frequent causes being HFSR and diarrhoea. Overall, 35/36 (97.2%) subjects required either a dose interruption or dose delay, and 17/36 (47.2%) subjects required at least 1 dose reduction.

Comment: It is noted that there were a higher proportion of subjects in Study 14596 who discontinued treatment due to TEAEs, compared to pivotal Study 14874 (50% versus 8.5% respectively). This indicates that the AE profile may be worse in subjects with HCC compared to patients with GIST, and this could in part be due to underlying hepatic function.

Global integrated analysis – in Pool 1, overall 220/1073 (20.5%) of subjects experienced AEs leading to permanent discontinuation of study drug. The most common causes included General physical health deterioration (1.8% of all patients), fatigue (1.2%) and HFSR (1.2%).

697/1073 (65.0%) of subjects in Pool 1 had AEs leading to dose modification. The most common AEs leading to dose reduction were HFSR (209/1073 or 19.5% of all patients), diarrhoea (3.5%), hypertension (3.1%) and fatigue (2.1%), while the most common AEs leading to drug interruption were HFSR (18.0%), diarrhoea (5.0%), hypertension (4.9%), fatigue (4.7%), pyrexia (3.5%), rash (3.4%) and AST increased (2.5%).

Comment: It is agreed with the overall statement of the sponsor that although the proportion of patients who experience TEAEs is high, most of these AEs can be managed with dose modifications, with a relatively low proportion of patients discontinuing treatment due to AEs. This is particularly true for patients with the proposed indication of GIST, where the discontinuation rate in pivotal trial 14874 (8.5% for all treated patients) was lower than that for the pooled studies (20.5%) or for patients with HCC (50%).

9.4. Laboratory tests

9.4.1. Liver function

9.4.1.1. Pivotal studies

Study 14874 – In the double-blind period, AST was observed to increase in 58.3% of patients in the regorafenib arm compared to 47.0% of patients in the placebo arm. Similar incidences of ALT increases were reported between treatment groups (all grades: 39.4% regorafenib versus 39.4% placebo) with Grade 3/ 4 ALT increases in 4.6% for regorafenib and 1.5% for placebo. There was an incidence of Grade 3 events of increased ALT (3.8%), increased AST (3.0%), and increased bilirubin (3.0%) in the regorafenib arm. An increased blood bilirubin was seen in 33.3% of patients in the regorafenib arm compared to 12.1% of patients in the placebo arm.

On inspection of the source data (CSR Table 14.3.3/3), during the double blind period the regorafenib arm experienced a greater number of liver-related TEAEs compared to placebo including increased ALT (6.8% versus 1.5% respectively), increased AST (9.1% versus 4.5%) and bilirubin increased (9.8% versus 3.0%).

One regorafenib-treated patient met Hy's law criteria and died as the result of treatment-related acute hepatic failure.

Comment: Overall in the double-blind period of Study 14874, more subjects were observed to have raised LFTs in the regorafenib group compared to placebo, and there were also higher Grade 3 events and elevations classified as AEs. Apart from

hyperbilirubinaemia, the increases in ALT and AST are not listed in the proposed PI, and a recommendation is made regarding this to the Delegate.

9.4.1.2. Other studies

Study 14596 – In these subjects with HCC, treatment-emergent toxicities were seen for AST in 33/36 (91.7%) subjects, ALP in 83.3%, ALT in 72.2% and bilirubin in 63.9%. As discussed further in Section *Liver toxicity*, Grade 5 liver dysfunction was seen in 2 subjects, and Grade 3 liver dysfunction was seen in 1 subject.

Comment: Increased levels of liver abnormalities were observed in Study 14596 in subjects with HCC compared to in pivotal Study 14874. It is not possible to ascertain from the data presented wither this is due solely to the underlying disease process, or whether regorafenib treatment has exacerbated this effect.

Global integrated analysis – In Pool 1, a total of 166/1073 (15.5%) of subjects had any AE in the SOC of hepatobiliary disorders, the most common AEs being hyperbilirubinaemia (97/1073 or 9.0% of all subjects), hepatic pain (1.7%), hepatic function abnormal (1.5%) and hepatic failure (14 subjects or 1.3%). Overall 13/1073 (1.2%) subjects had a Grade 5 hepatic failure or abnormal hepatic function adverse event. Overall 16 patients met Hy's law laboratory criteria: 4 patients without malignant liver pathology in addition to 12 patients with underlying liver pathology.

Comment: The data presented in this submission confirms that treatment with regorafenib can alter hepatic function, including increases in the frequency of hyperbilirubinaemia, and an increased risk of drug-induced hepatic failure.

The integrated safety data suggests that there may be an increased risk of hepatic failure for patients treated with regorafenib who have underlying liver pathology.

9.4.2. Kidney function

9.4.2.1. Pivotal studies

Study 14874 – During the double-blind period of the study, Grade 3 proteinuria was reported in 1 (0.8%) patient who received treatment with regorafenib, which was considered related to study treatment. This was successfully managed with dose interruption.

3/132 (2.3%) regorafenib-treated patients experienced events of acute renal failure during the double-blind phase of the study (compared to 0% in the placebo arm), one each Grades 2, 3, and 5. None of these events were assessed as related to treatment with study medication. During the open-label phase, one additional Grade 5 treatment-related acute kidney injury was reported; although the investigator assessed this episode as treatment-related, the sponsor argued that the underlying advanced malignancy as well as the concurrent infection of unknown location (high CRP increase) were considered to be confounding factors or potential alternative explanations for the reported event.

In Study 14596, 3/36 (8.3%) subjects experienced Grade 3 renal failure during the study period, one of which was attributable to study treatment by the investigator.

Comment: Although the episodes of renal failure during the double-blind period of Study 14874 were not considered related to study treatment, they were all noted to be in the regorafenib arm of the study. This combined with the drug-related AE of Grade 5 renal failure in the open-label portion of the study and 3 episodes of renal failure in Study 14596 indicates a possible safety signal that acute renal failure occurs more commonly in patients treated with regorafenib, and this should be monitored. Renal toxicity is not listed as a recognised AE of regorafenib, and a recommendation has been made for the inclusion of acute kidney injury in the PI.

9.4.2.2. Other studies

Study 14596 – 7/36 subjects (19.4%) experienced proteinuria; in 6 (16.7%) subjects, these events were determined by the Investigator to be causally related to study medication.

Global integrated analysis – In Pool 1, a total of 178/1073 subjects had any AE in the SOC renal and urinary disorders, the most common being proteinuria (7.1% of all subjects), renal failure (34/1073 subjects or 3.3%), haematuria (1.9%), dysuria (1.6%).

Comment: Although rates of renal failure observed with regorafenib treatment to date remain low, given the known association between treatment with regorafenib and proteinuria and documented cases of Grade 5 renal failure attributed to regorafenib treatment, further monitoring for renal failure in patients treated with regorafenib is warranted.

9.4.3. Other clinical chemistry

9.4.3.1. Pivotal studies

Study 14874 – In the double-blind period of the study, other biochemical parameter abnormalities observed more frequently in the regorafenib arm compared to placebo included: hypophosphatemia (observed in 54.5% of patients in the regorafenib arm compared to 3.1% in the placebo arm); hypertriglyceridemia (64.4% versus 35.4%); hyperglycaemia (90.9% versus 74.2%); and hypoalbuminaemia (50% versus 31.8%).

9.4.3.2. Other studies

Study 14596 – Other commonly observed biochemical abnormalities included: hypophosphatemia (72.2%), hyponatraemia (61.1%), hypoalbuminaemia (61.1%), hypocalcaemia (58.3%) and hyperglycaemia (58.3%).

Global integrated analysis – In Pool 1, other commonly observed biochemical abnormalities included: hyperglycaemia (57.8%), hypertriglyceridaemia (54.2%), hyperphosphataemia (54.1%), hypoalbuminaemia (41.9%) and hyponatraemia (31.3%).

9.4.4. Haematology

9.4.4.1. Pivotal studies

Study 14874 – In the double-blind period of the study, the incidence of anaemia was 75.0% in the regorafenib arm and 72.2% in the placebo arm, while the incidence of thrombocytopenia was 12.9% in the regorafenib arm and 1.5% in the placebo arm. Most of these were of Grades 1 and 2. Episodes of neutropenia and lymphopenia were similar between the two treatment arms (CSR, Table 14.3.15/1).

Comment: Apart from an increase mild thrombocytopenia, there were no significant effects of regorafenib on other haematological parameters during the double-blind period of the study.

9.4.4.2. Other studies

Study 14596 – The incidence of anaemia was 86.1% (31/36 patients experiencing any AE of reduced haemoglobin), while the incidence of thromobocytopenia was 61.1% (22/36 subjects). Lymphopenia was observed in 18/36 (50%) subjects.

Global integrated analysis – In Pool 1, the incidence of anaemia was 796/1028 (77.4%), lymphocyte count decreased (49.6%), and platelet count decreased (35.5%). There were no significant changes in coagulation variables form baseline to cycle 3 in the integrated analysis.

9.4.5. Bleeding events

9.4.5.1. Pivotal studies

Study 14874 – During the double-blind period of the study, bleeding events were reported more frequently for patients who received treatment with regorafenib (15/132, 11.4%) compared to placebo (2/66, 3.0%). The most common bleeding event was Grade 1 epistaxis. 9/132 (6.8%) of regorafenib treated patients had a GI haemorrhage during the double blind period compared to 0 in the placebo group. No Grade 5 events occurred. Bleeding is known to be a class effect of VEGF inhibitors (4).

9.4.5.2. Other studies

Study 14596 – 14/36 (38.9%) subjects experienced haemorrhage/bleeding; in 7 (19.4%) subjects, these events were assessed by the Investigator as study drug-related.

Global Integrated Analysis – In Pool 1, the incidence of any haemorrhage event was observed in 222/1073 subjects (20.7%). The most common sites of bleeding were epistaxis (7.6%), haematuria (1.9%), haemoptysis (1.4%), contusion (1.1%) and gingival bleeding (1.0%).

Cumulative review across all studies – From the pool of more than 3500 cancer patients with a cut-off date 28 February 2013, there were 225 cases of haemorrhage associated with regorafenib exposure, of which fatal outcomes were reported for 19 cases (estimated fatal outcome for 0.5% of regorafenib treated patients).

Comment: Bleeding events were observed more frequently in regorafenib treated patients, with the underlying condition another predisposing factor. Most episodes are of Grade 1-2 severity although fatal outcomes have been reported. This complication is listed in the current PI.

9.4.6. Thyroid markers

9.4.6.1. Pivotal studies

Study 14874 - During the double-blind treatment period, a change towards a higher category (that is,, from below the LLN to the normal range or from the normal range to above the ULN) was observed for TSH in 24.4% of regorafenib-treated patients and 12.5% of placebo-treated patients. No events of hypothyroidism were categorised as serious.

9.4.6.2. Other studies

Study 14596 – 17/36 (47%) subjects experienced a TEAE of hypothyroidism based on TSH levels, all Grades 1 or 2.

Global integrated analysis – In Pool 1, hypothyroidism was reported as an AE in 72/1073 (6.7%) subjects.

9.4.7. Electrocardiograph

9.4.7.1. Pivotal studies

Study 14874 – There were no clinically relevant changes observed for any of the ECG parameters compared to baseline in either treatment arm during the double-blind period.

9.4.7.2. Other studies

Study 14596 – All ECG results were reported to be within the normal range thought the study for the SAF. As noted previously, 2/36 subjects were noted to have a prolonged QTC during the study period, and 1 subject experienced cardiac ischemia.

Study 14814 – There was no evidence of an association between regorafenib use and QT prolongation after 1 cycle of maximum treatment.

Global Integrated analysis – In Pool 1, there were 11/1073 (1.0%) patients who had QT prolongation on ECG, of which 4 subjects were Grade 1, 5 were Grade 2, and 2 were Grade 3. The QT prolongation was assessed as drug-related in 8/11 subjects. None of these subjects required dose modification, and the outcome was recovered in 9 subjects. None of the subjects had any adverse sequelae as a result of the QT prolongation.

Comment: Overall, there is no suggestion from the clinical trials submitted that there is a clinically significant effect of regorafenib on electrocardiograph parameters.

9.4.8. Vital signs

9.4.8.1. Pivotal studies

Study 14874 – Hypertension was observed in 78 (59.1%) patients in the regorafenib + BSC treatment arm and 18 (27.3%) patients in the placebo + BSC arm. One event of hypertension (associated with Grade 4 reversible posterior leukoencephalopathy syndrome) was categorised as a SAE. This event was resolved but led to permanent discontinuation of treatment.

No notable changes were seen in the mean heart rate from baseline to the end-of-treatment visit or in the mean body temperature or body weight in either treatment group.

9.4.8.2. Other studies

Study 14596 – Hypertension was observed in 13/36 (36.1%) subjects. Otherwise it was reported that mean values for all vital signs were generally within the normal range throughout the study.

Global integrated analysis – In Pool 1, hypertension was reported as an AE in 387/1073 (36.1%) subjects, and was reported as a SAE in 7/1073 (0.7%) subjects. There were no deaths associated with hypertension.

Comment: Hypertension is a common AE in patients treated with regorafenib, but is generally of mild-moderate severity, consistent with the known profile of this AE.

9.5. Post-marketing experience

The **Periodic Safety Update Report (PSUR) No. 2** for regorafenib covered the period 27 March 2013 until 26 September 2013, for the indications of previously treated metastatic CRC and GIST (the latter indication being approved in the US since February 2013). The reporting period included 2,987 patients in ongoing company-sponsored clinical trials, and tablet sales representing an estimated exposure of 14,331 patients. Relevant findings from this PSUR included:

- 10 case reports of atrial fibrillation, which were assessed as not having convincing evidence of a causal association – Sponsor action: no immediate action, AF to be further monitored.
- 34 cases of renal failure related events with regorafenib treatment, 16 of which were spontaneous reports and 18 were from interventional studies and early access programs. Of the latter, 5 cases were considered related to regorafenib treatment by the investigator, however sponsor assessments remained pending for some. Sponsor action: no immediate action, cases of renal failure to continue to be monitored.
- 256 cases of 'hepatic disorders', of which 137 were spontaneous reports and 128 were from studies. 75 cases were reported from interventional studies and early access programs, of which none were compatible with severe liver injury, but 5 were assigned as cases with significant transaminases increase, all possibly related to regorafenib. Of the remaining 190 post-marketing cases (53 from observational studies and 137 spontaneous reports), there were 2 cases compatible with regorafenib-induced severe liver injury (one case fatal) and 7 with significant transaminases increase, all of which assessed as possibly related to regorafenib use. It was noted that 10 of the above 14 reported cases of hepatic injury were

in Japanese patients. This was explained by the sponsor as being due to recent marketing authorisation of regorafenib in Japan, the early post-marketing phase vigilance system in that country, and the overall 75% of spontaneous reports newly received being from Japan, therefore indicating country-specific reporting differences most likely contributing to the increased number of cases. Sponsor action: cases in keeping with current description in CCDS – continue to monitor.

Comment: The large proportion of post-marketing cases of significant hepatic injury from Japan warrants further monitoring to exclude a race-specific susceptibility to hepatic impairment with regorafenib in Japanese patients. This has been posed as a question to the sponsor under *Clinical questions*.

Considering that spontaneous reports are an underestimation of the true number of cases, there is a relatively high number of reports of hepatic disorders with regorafenib in the post-marketing data, and this reaffirms the association of this adverse effect with regorafenib use.

- 8 cases of cardiac ischemia, of which 6 were assessed as related to regorafenib. One was a spontaneous report, and the remaining 7 were from studies. Sponsor action: no immediate action.
- 190 cases of hypertension, 78 of which were spontaneous reports, and 112 related to studies. No cases of hypertensive crisis were received. 83 of the total reports were considered serious, but there were no cases with a fatal outcome. Sponsor action: cases of hypertension conform with its current description as a common AE, and no action warranted.
- 123 cases of haemorrhagic events, of which 33 were spontaneous reports and 90 related to studies. 8 cases were reported with fatal outcome, of which 5 were related to cerebral haemorrhage. The most common site for bleeding was the GI tract (37%), followed by CNS (11%), urogenital (9%) and respiratory (8%). Sponsor action: cases in keeping with current knowledge, and no action warranted.
- 394 cases of HFSR, of which 237 were spontaneous reports and 157 were from studies. Notably, 231 (59%) cases were from Japan. 184 cases were reported as non-serious, 210 were reported as serious, and 18 cases required hospitalisation. There was one relevant literature publication (a meta-analysis) during the reporting period (Belum et al, 2013 (5)) which found that the incidence and risk of development of HFSR with regorafenib is high (overall incidence 60.5%, 95% CI 48.3-71.6%) and may vary significantly with tumour type (71.4% for RCC, 60.2% for GIST, 50.5% for HCC, and 46.6% for mCRC). Sponsor action: Cases in keeping with current knowledge, no action warranted.
- 2 cases of RPLS, both spontaneous reports, one of which assessed as possibly related to regorafenib treatment, and insufficient information to make an assessment for the other. Sponsor action: RPLS already contained within reference safety information, no further action warranted, continue to monitor.
- 38 case reports of GI perforation and fistula, of which 7 were spontaneous reports and 31 were from studies or compassionate use. For 18 cases of GI preformation, 5 were fatal, and 6 were considered related to regorafenib treatment. Of 14 cases of GI fistula, 1 was fatal and 3 were considered related to regorafenib, while of 6 cases of GI abscess/peritonitis, none were fatal and one was considered related to regorafenib. Sponsor action: no further action warranted.
- 26 cases of severe cutaneous events including 3 cases of potential Stevens-Johnson Syndrome (2 of which considered related to study treatment) and 1 case of Toxic epidermal necrolysis. 9 cases were from spontaneous reports, and 17 were from studies. Sponsor action: cases in keeping with known information, no action warranted.

As of 17 June 2014, there were 2 ADR reports for regorafenib in Australia on TRIM (4 reports in total, but both replicated), both related to clinical trials. These included 1 episode of Grade 2 pericarditis, and 1 episode of Grade 5 liver failure. Both events were considered by the investigators to be related to study treatment, but were considered unrelated by the sponsor.

Comment: There are no additional safety concerns arising from the post-marketing data that have not already been identified and addressed, other than the need to further monitor for a possible increased susceptibility of Japanese patients to hepatic toxicities with regorafenib treatment.

9.6. Safety issues with the potential for major regulatory impact

9.6.1. Liver toxicity

It is noted that liver dysfunction/failure events are known to be a class effect of VEGF inhibitors (4).

Study 14874: In pivotal Study 14874, one subject died as a result of treatment-related acute hepatic failure. This subject, as described in above, had advanced GIST and no history of liver disease, and was assessed as having a severe drug-induced hepatic injury and met Hy's law laboratory criteria. Severe drug induced hepatotoxicity is a known adverse effect of regorafenib and is included in the Precautions section of the PI.

It was noted that pivotal Study 14874 had as an inclusion criterion: 'Adequate liver function as assessed by the following laboratory requirements conducted within 7 days of starting study treatment: Total bilirubin ≤ 1.5 x the upper limit of normal (ULN), and Alanine aminotransferase (ALT) and aspartate aminotransferase (AST) ≤ 3.0 x ULN (≤ 5 x ULN for patients with liver involvement of their GIST)'.

Comment: It is noted that the subject in Study 14874 who experienced treatment-related hepatic failure had no history of hepatic disease or hepatic metastases. This is in contrast to previously documented acute hepatic toxicity cases associated with regorafenib, which had occurred on a background of hepatic metastases as documented in the PI. Therefore, the wording of the PI should be amended to reflect this new finding.

Based on the fact that subjects were required to have adequate hepatic function for inclusion in Study 14874, no conclusions can be drawn from this study on the safety of regorafenib in subjects with hepatic impairment. This is an important consideration given the known potential for hepatotoxicity, and has implications for the interpretation of population PK analyses based on this data (see Section Pharmacokinetics in subjects with impaired hepatic function).

As was discussed in Section *Pivotal efficacy studies*, due to safety concerns associated with hepatic toxicities ≥ Grade 3, the study protocol for Study 14874 was amended to require closer liver monitoring (from fortnightly to weekly in the first 2 months of treatment) and a revised dose modification scheme (specific to elevations in ALT, AST or bilirubin) which were implemented via protocol Amendment 2 (26 July 2011).

Comment: Given the potential for severe drug-induced hepatic toxicity as an adverse effect of regorafenib, more frequent monitoring of hepatic function and for a longer duration may be warranted than is currently recommended in the PI, which recommends LFTs be performed at least every 2 weeks for the first 2 months of treatment and then monthly thereafter. This has been posed as a question to the sponsor and included as a comment on the PI.

Study 14596: In this study in patients with HCC, it was noted that 2/36 subjects developed Grade 5 liver dysfunction, and one subject experienced Grade 3 liver dysfunction. In all subjects this was attributed to disease progression rather than to treatment with study drug.

Comment: On review of the case narratives of the subjects who died from or experienced liver dysfunction in Study 14596, the opinion of this evaluator is that it is inconclusive as to whether the cause of fatal liver dysfunction is solely due to disease progression, or whether there is a contributory component from regorafenib treatment. Regardless, the rate of death due to hepatic dysfunction is higher is this group of subjects with HCC (5.6%), and thus indicates that caution is required in the treatment of patients with hepatic impairment with regorafenib.

Global integrated analysis – In Pool 1 of the analysis, 13/1073 (1.2%) subjects had a Grade 5 hepatic failure or abnormal hepatic function adverse event. Overall 16 patients met Hy's law laboratory criteria: 4 patients without malignant liver pathology in addition to 12 patients with underlying liver pathology.

Cumulative review in all regorafenib trials – The sponsor's review of over 3,500 patients (as outlined in Module 2.7.4 Summary of Clinical Safety) identified 4 cases of severe drug-induced liver injury (DILI) all considered drug related, and 9 cases of significant transaminase increases (6 considered possibly drug-related). It was assessed that these events predominantly occur in the first 2 months of treatment (although low numbers warrant caution in interpretation). It was reported that 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. However, remedial treatments in 3 out of 4 cases of severe DILI did not prevent further deterioration. The sponsor concluded that this suggests that early recognition and timely drug withdrawal are the single most important strategy to prevent regorafenib-induced liver dysfunction from progressing to severe DILI.

Comment: This evaluator agrees with the assessment of the sponsor that early recognition and management of liver function abnormalities with drug withdrawal will help to prevent episodes of acute hepatic toxicity. However, more frequent monitoring of LFTs than 2 weekly as suggested in the PI may be warranted due to the seriousness of the condition, and initial weekly LFT monitoring as was performed in the pivotal clinical trial may be a better alternative. This has been posed as a question to the sponsor.

9.6.2. Haematological toxicity

There was no evidence of haematological toxicity due to regorafenib in pivotal Study 14874.

9.6.3. Serious skin reactions

Study 14874 - Hand-foot skin reaction (HFSR) is a known toxicity of VEGF inhibitors (4). In Study 14874, HFSR (or PPE syndrome) was observed at a higher incidence in regorafenib-treated patients (56.8%) than the placebo-treated patients (13.6%). Grade 3 HFSR were reported in 27 (20.5%) patients in the regorafenib + BSC treatment arm and 1 (1.5%) patient in the placebo + BSC arm. Hand-foot skin reactions could usually be managed by dose reductions or interruptions, and was the most common cause for these modifications. Analysis of cycle-specific and cumulative event rates revealed that the majority of patients who experienced events of HFSR were affected in their first 2 cycles of treatment. HFSRwas also more common in Asian patients compared to non-Asian patients.

Rash is also a known toxicity of VEGF inhibitors (4). During the double-blind period, maculopapular rash was reported in 18.2% of regorafenib patients compared to 3.0% of placebo patients. Most of these were Grade 1 in intensity, and were adequately managed with dose interruptions.

Global integrated analysis – In Pool 1, although any AE in the SOC skin and subcutaneous tissues was high (73.3%, the most common being HFSR), the proportion of patients having a SAE in that SOC was low at 17/1073 (1.6%) of subjects. Only 1 subject had Grade 4 Stevens-Johnson Syndrome, and 1 subject had Grade 4 rash.

Comment: Skin reactions were common in patients treated with regorafenib, however were generally mild and managed with dose interruptions or reductions, without the need to cease treatment.

9.6.4. Cardiovascular safety

Cardiac ischaemia/infarction events are a known class effect of VEGF inhibitors (4).

Study 14874 –In pivotal Study 14874, one event each of acute coronary syndrome (Grade 3, unrelated) and cardiac arrest (Grade 5, possibly related) were reported for patients who received regorafenib + BSC during the double-blind treatment period.

As described in Section *Laboratory assessments*, hypertension is also noted as a class effect of VEGF inhibitors (4) and was observed as a TEAE in 78/132 (59.1%) of subjects in the regorafenib arm in the double-blind section of the study compared to 18/66 (27.3%) of the placebo arm. Grade 3 events were reported for 36 (27.3%) patients in the regorafenib arm and 3 (4.5%) patients in the placebo arm. One event of hypertension was categorized as an SAE, associated with reversible posterior leukoencephalopathy syndrome. Analysis of cycle-specific and cumulative event rates revealed that the majority of TEAEs of hypertension occurred within the first two cycles of treatment with regorafenib.

Cardiac failure was noted in one patient in each treatment arm during the double-blind period and thus was not increased in the regorafenib arm.

Comment: From the results of Study 14874, the episode of Grade 5 sudden cardiac arrest possibly related to study drug is noted as an important cardiac related adverse event. Hypertension is also an important cardiac adverse event which can be severe, and generally occurs within the first two cycles of treatment.

Study 14814 - As discussed in Section 5, Study 14814 did not provide any evidence of an association between regorafenib use and QT prolongation after 1 cycle of maximum treatment, or clinically significant worsening of LVEF after 2 cycles of maximum treatment.

Global integrated analysis- In Pool 1, 119/1073 (11.1%) subjects had any AE in the SOC cardiac disorders, the most common being tachycardia (2.2% of all subjects), palpitations (1.9%) and atrial fibrillation (1.6%). 34/1073 (3.2%) subjects had a SAE in the SOC of cardiac disorders, the most common being cardiac ischaemic events (15 subjects or 1.5%), and AF and cardiac arrest (5 subjects or 0.5% each).

Comment: There are no new changes to the cardiac safety profile of regorafenib following evaluation of the submitted data.

9.6.5. Gastrointestinal perforation and fistulae SAEs

GI perforation and GI fistula are known class-effects of VEGF-antagonists. Based on previous assessments, GI perforation (including cases with reported fatal outcomes) and GI fistula have been determined as ADRs for regorafenib. Intra-abdominal malignancy is the main risk factor.

Cumulative review from regorafenib safety database – From more than 3,500 patients treated with regorafenib until 23 February 2013, 20 perforation events were identified in regorafenib-treated patients (estimated frequency 0.57%), of which 9 cases were fatal. This compares with an estimated frequency of 0.31% in the placebo groups of the studies. From the safety database, 13 GI fistula events were identified in regorafenib-treated patients, of which none were fatal.

Comment: This evaluator agrees with the sponsor that there is a possible increased risk of GI perforation/fistula in regorafenib treated patients. This is in keeping with the precautions already listed within the PI, although this could be reworded to reflect this possible increase in risk.

9.7. Other safety issues

9.7.1. Safety in special populations

No pregnancies were reported in Study 14874.

Subgroup analysis of Pool 1 of the **Integrated global safety analysis** found:

- No overall clinically relevant differences in the AE safety profile between **age groups** (specified as <65 years, 65-74 years, and 75-84 years), although HFSR was observed more frequently in patients <65 years of age, and decreased appetite and constipation were observed more frequently in those aged 75-84 years. In addition there were no clinically relevant differences in rates of dose modification (reduction, interruption or delay) across age groups.
- The main differences in AE by **gender** were a higher rate of dysphonia in males compared to females (37.9% versus 23.3%) and a higher rate of rash in females compared to males (27.0% versus 16.6%).
- Analysis of AEs by **race** found a higher incidence in Asian populations compared to White for several AEs including: HFSR (75.1% versus 44.0%), rash (29.4% versus 19.3%), blood bilirubin increased (16.2% versus 5.8%), AST increased (30.5% versus 4.8%), lipase increased (14.7% versus 3.4%), proteinuria (25.9% versus 2.6%) and platelet count decreased (17.3% versus 2.3%) (Table 12).

Table 12: AEs with any difference in frequency of ≥10 percentage points between any two race categories in regorafenib patients in Pool 1 (SAF) of the Integrated global analysis of safety

	Regorafenib		
	White	Asian	Other [a]
MedDRA PT	N = 800 n(%)	N = 197 n(%)	N = 63 n(%)
Diarrhoea	367 (45.9)	63 (32.0)	25 (39.7)
Fatigue	353 (44.1)	83 (42.1)	10 (15.9)
Palmar-plantar erythrodysaesthesia syndrome	352 (44.0)	148 (75.1)	27 (42.9)
Weight decreased	209 (26.1)	29 (14.7)	12 (19.0)
Pyrexia	194 (24.3)	56 (28.4)	9 (14.3)
Abdominal pain	185 (23.1)	26 (13.2)	18 (28.6)
Rash	154 (19.3)	58 (29.4)	9 (14.3)
Asthenia	143 (17.9)	8 (4.1)	25 (39.7)
Mucosal inflammation	147 (18.4)	15 (7.6)	12 (19.0)
Dyspnoea	151 (18.9)	14 (7.1)	13 (20.6)
Pain in extremity	103 (12.9)	8 (4.1)	10 (15.9)
Muscle spasms	83 (10.4)	9 (4.6)	10 (15.9)
Blood bilirubin increased	46 (5.8)	32 (16.2)	2 (3.2)
AST increased	38 (4.8)	60 (30.5)	0 (–)
Lipase increased	27 (3.4)	29 (14.7)	1 (1.6)
Blood ALP phosphatase increased	24 (3.0)	37 (18.8)	1 (1.6)
ALT increased	25 (3.1)	42 (21.3)	1 (1.6)
Proteinuria	21 (2.6)	51 (25.9)	4 (6.3)
Haemoglobin decreased	21 (2.6)	20 (10.2)	0 (–)
Hypoalbuminaemia	16 (2.0)	23 (11.7)	0 (–)
Platelet count decreased	18 (2.3)	34 (17.3)	2 (3.2)
Blood LDH increased	8 (1.0)	29 (14.7)	1 (1.6)

AE = Adverse event; SAF = Safety analysis set; MedDRA = Medical Dictionary for Regulatory Activities; PT = Preferred term, AST = Aspartate aminotransferase; ALP = Alkaline phosphatase; ALT = Alanine aminotransferase; LDH = Lactate dehydrogenase

a: Other = American Indian or Alaska native, not reported, or multiple.
For the subgroup Black or African American (N = 13), please refer to the source table

Comment: This evaluator does not agree with the assessment of the sponsor that there is a similar safety profile among the race subgroups. The data indicates there may be a different safety profile in patients of Asian race compared to other races, particularly with respect to serious AEs, hepatic impairment/toxicity and skin reactions as was discussed in other sections. Therefore, it is questioned whether alternative dosing schedules or monitoring requirements may be warranted for patients of Asian descent. A recommendation has been made to include a precaution in the draft PI and a question has been posed to the sponsor.

- Analysis of AEs by **BMI** subgroups found a similar safety profile across all groups.
- Analysis of AEs by **baseline hepatic function**, found a higher rates of Grade 5 AEs (all) in those with elevated liver enzymes at baseline compared to those with normal hepatic function (Grade 5 events 38.9% for those with ALT>3*ULN or AST>3* ULN [n=18] versus 20.4% for 1.5*ULN<AST/ALT<=3*ULN [n=98] versus 10.4% AST/ALT<=1.5*ULN [n=954]). There was a higher incidence of hyperbilirubinaemia in patients with elevated liver enzymes at baseline compared to those with normal hepatic function (44.4% versus19.4% versus 7.3% respectively).

Comment: There appears to be an increased risk of Grade 5 and hepatobiliary adverse events in patients with impaired hepatic function at baseline, despite low numbers of subjects with impaired hepatic function enrolled into the clinical trials.

- Analysis of AEs by **baseline renal function** (normal, n=963 versus at least moderately impaired renal function, n=109) found comparable incidences of AEs across both groups.

9.7.2. Safety related to drug-drug interactions and other interactions

No new data was presented on drug interactions in this submission.

9.7.3. Safety related to clinical indication (GIST versus mCRC)

In Module 2.7.4 Summary of Clinical Safety, an analysis was presented comparing AEs between the two indications of GIST (Study 14874, n=132) and mCRC (Study 14387, n=500). The overall safety profile was comparable between the two studies for cardiac disorders, renal and urinary disorders, thrombo-embolic events, gastrointestinal events (including diarrhoea and nausea/vomiting), respiratory, thoracic and mediastinal disorders (including dysphonia), metabolism and nutrition disorders (including deceased appetite), and infections and infestations.

An increased rate of adverse events was observed in mCRC patients compared to GIST for hepatobiliary disorders (19.8% versus 6.1% respectively), haematological and biochemical toxicities (hyperbilirubinaemia 13.0% versus 1.5%), and haemorrhage (21.4% versus 11.4%).

An increased rate of adverse events was observed in GIST patients compared to mCRC for HFSR (66.7% versus 45.0% respectively), alopecia (24.2% versus 7.6%), and hypertension (59.1% versus 30.4%).

Comment: The safety profile of regorafenib was generally comparable across the current indication in mCRC and the proposed indication of GIST. Generally the evidence suggests that the safety profile may be slightly more favourable in GIST, with a reduced frequency of the potentially serious AEs of hepatobiliary disorders and haemorrhage, although a higher frequency of less serious AEs including HFSR, alopecia and hypertension. Caution is required in drawing conclusions from these comparisons across studies however.

9.8. Evaluator's overall conclusions on clinical safety

The new data presented with this submission is generally consistent with the known safety profile of regorafenib. The overall rate of adverse events is high in patients treated with regorafenib, with 100% of regorafenib treated patients in pivotal Study 14874 and 99.4% of subjects in the pooled global analysis experiencing any AE. The most common AEs are consistent across the studies, and include HFSR, fatigue, diarrhoea and hypertension. A high proportion of patients (65% in pooled studies) required dose modifications in response to these AEs.

The most common cause of death across the submitted studies was disease progression, as would be expected in cancer patient populations. However, potential regorafenib-related deaths include those from hepatic impairment, cardiovascular and thromboembolic events, renal impairment, infections, perforations and bleeding, and these should be considered adverse events of treatment.

It is agreed with the overall statement of the sponsor that although the proportion of patients who experience TEAEs is high, most of these AEs can be managed with dose modifications, with a relatively low proportion of patients discontinuing treatment due to AEs.

There is some indication that the safety profile for patients treated with regorafenib for GIST may be more favourable than for patients with metastatic CRC or other indications. In treatment of GIST, there appeared to be a reduced frequency of the potentially serious AEs of hepatobiliary disorders and haemorrhage, although a higher frequency of less serious AEs including HFSR, alopecia and hypertension. In addition the discontinuation rate in pivotal trial 14874 (8.5%) for all treated patients with GIST was lower than that for the pooled studies (20.5%) or for patients with HCC (50%). Caution is required however in drawing conclusions from cross-study comparisons.

Based on the analysis of results from Study 14874 and the pooled safety results, the following safety issues were considered:

- The study designs of all studies evaluated excluded subjects with hepatic or renal impairment from inclusion. Therefore, the ability of results to assess the safety of regorafenib in subjects with hepatic and renal impairment is limited. It is the opinion of this evaluator that no definitive conclusions or recommendations can be made about the use of regorafenib in subjects with moderate hepatic or renal impairment, in contrast to the sponsor's assessment that no dosage adjustments are required in patients with moderate hepatic impairment.
- The data confirmed the risk of liver toxicity and acute hepatic failure with regorafenib use. This evaluator agrees with the assessment of the sponsor that early recognition and management of liver function abnormalities with drug withdrawal will help to prevent episodes of acute hepatic toxicity. However, due to the potential seriousness of this adverse effect, there is potential scope for increasing the hepatic monitoring recommendations from fortnightly as stated in the current PI, to weekly as occurred in the pivotal trial.
- Although rates of renal failure observed with regorafenib treatment to date remain low, given the known association between treatment with regorafenib and proteinuria and documented cases of Grade 5 renal failure attributed to regorafenib treatment, further monitoring for renal failure in patients treated with regorafenib is warranted.
- It is recommended that an additional precaution be added in the PI alerting to the increased risk of hypothyroidism.
- Other important adverse events documented that are in keeping with the known risks of regorafenib use include: sudden cardiac death; GI perforation due to anti-tumour effect; bleeding risk and hypophosphataemia.

- This evaluator does not agree with the assessment of the sponsor that there is a similar safety profile among the race subgroups. The data indicates there may be a different safety profile in patients of Asian race compared to other races, particularly with respect to serious AEs, hepatic impairment/toxicity and skin reactions as was discussed in other sections. Therefore, it is questioned whether alternative dosing schedules or monitoring requirements may be warranted for patients of Asian descent.

Study 14596 in subjects with HCC generally supported the safety findings of the pivotal study however there was a suggestion of more frequent and severe incidences of hepatic dysfunction, which included 2 Grade 5 events. This could be explained due to the underlying cause of disease, however, it is uncertain as to the extent that treatment with regorafenib may have increased the likelihood and severity of these events. It is noted that all subjects enrolled in this study had Child Pugh A classification, and therefore were assessed as having adequate baseline hepatic function, yet experienced an increased incidence of hepatic adverse events. Therefore, experience of regorafenib with moderate to severe hepatic impairment remains limited, and it is therefore prudent that regorafenib be used with caution in these subjects.

10. First round benefit-risk assessment

10.1. First round assessment of benefits

The benefits of regorafenib in the proposed usage are:

- Improvements in progression free survival: The pivotal Study 14874 in patients with advanced or metastatic GIST previously treated with two TKIs showed statistically and clinically significant improvements of median progression-free survival for patients treated with regorafenib of 4.8 months (95% CI: 4.0-5.7) over placebo of 0.9 months (95% CI: 0.9, 1.1), with a HR of 0.268 (95%CI 0.185, 0.388, p<0.000001). This result was supported by Study 14935.
- Suggested improvements in overall survival: The immaturity of OS data in Study 14874 means that no definitive conclusions can be drawn on the effect of regorafenib treatment on OS compared to placebo, although a beneficial effect of regorafenib was suggested with a HR of 0.772 (95% CI: 0.423, 1.408).
- There is possible variation in efficacy according to genetic biomarkers – this may affect the overall risk-benefit balance, and further investigation is recommended.

10.2. First round assessment of risks

The risks of regorafenib in the proposed usage are:

- The known common adverse effects including HFSR, fatigue, diarrhoea, and hypertension that are already documented.
- Known serious adverse effect of acute hepatic toxicity with fatal occurrences, GI perforation and bleeding risk, as already documented.
- Other adverse events of uncertain significance including acute renal failure, and the impact of hepatic and renal impairment and racial characteristics (Asian origin) on the overall adverse effect profile which require further investigation and monitoring. The current data do not provide sufficient evidence to make definitive recommendations in these areas.

10.3. First round assessment of benefit-risk balance

The benefit-risk balance of regorafenib is unfavourable given the proposed usage as outlined in the proposed PI, but would become favourable if the changes recommended (particularly with regards to cautions in use with hepatic impairment) are adopted, and the clinical questions are satisfactorily addressed.

10.4. First round recommendation regarding authorisation

The data submitted with this submission supports the use of regorafenib in the treatment of patients with advanced or metastatic GIST who have been previously treated with two TKIs. The median improvement in PFS in the pivotal study of 3.9 months is clinically significant in a patient population with advanced disease and no current approved treatment options. The adverse effect profile, although significant, is in keeping with that of other anticancer agents. However, there are some uncertainties with regards to the risk of acute kidney injury, and the safety in patients with hepatic impairment and between different ethnic groups that warrants caution and further investigation.

Therefore, it is recommended that regorafenib be **approved** for the proposed indication:

> *treatment of patients with gastrointestinal stromal tumours (GIST) who have been previously treated with two tyrosine kinase inhibitors,*

subject to modification of the product documentation as recommended and satisfactorily addressing the clinical questions.

As reduced efficacy was observed in the small number of patients with KRAS and BRAF mutations, consideration should be given to reassessing the benefit-risk equation of regorafenib for biomarker subgroups as more information becomes available.

11. Clinical questions

11.1. Additional expert input

A separate evaluation was performed on the population PK analyses 14653 and 16282. The results of these evaluations were presented as separate reports with questions for the sponsor.

11.2. Clinical questions

11.2.1. Pharmacokinetics

1. **Study 14996 (PH-37053)** – it is not clear from Tables 9-2 and 9-3 in the CSR how the Accumulation ratio (RAAUC) has been calculated. It is defined as the ratio of AUC τ after multiple dosing and AUC τ after single dosing; AUC τ,md/AUC τ,sd (RAAUC). However, in Table 9-2 AUC is given as 67.4 mg.h/L (n=31) and in Table 9.3 AUC τ,ss is given as 45.4 mg.h/L (n=12), with RAAUC calculated as 2.11 which does not make sense. Presumably, RAAUC has been calculated using the single dose AUC of the 12 subjects who subsequently went on to receive the Cycle 1, Day 21 160 mg dosage for the steady state calculation, but this value has not been provided. Could the sponsor please provide the Cycle 0, Day 1 PK values for the 12 subjects who subsequently went on to have the multiple dosing PK performed in Table 9-3 for comparative purposes?
2. Recommendations in in patients with hepatic impairment – It is the opinion of this evaluator that the assessment of single dose PK in 4 patients with Child-Pugh B hepatic impairment in Study 11651 is insufficient to draw conclusions on the dosage

recommendations and safety in patients with moderate hepatic impairment, considering that drug accumulation has been found to occur on repeat dosing as per the proposed dosing regimen, and regorafenib is primarily metabolised by the liver and has been associated with acute liver toxicity. Can the sponsor please address these reservations and indicate whether further studies in patients with moderate hepatic impairment are planned or in progress to support these claims?

3. Recommendations in patients with renal impairment – Can the sponsor please further justify use of the results of the physiology-based pharmacokinetics modelling to support the statements regarding the PK of regorafenib in patients with renal impairment in the PI, given that this was an exploratory analysis performed on virtual populations. In addition, the PBPK model does not take into account renal elimination of glucuronidated forms of regorafenib and its metabolites, despite the PI stating that 'approximately 19% of the dose [is] excreted in urine as glucuronides'. Particularly with regards to severe renal impairment, inclusion of this statement may be misleadingly reassuring.

11.2.2. Pharmacodynamics

4. Can the sponsor please indicate when the longer term results on LVEF outcomes will be available for Study 14814?

11.2.3. Efficacy

11.2.3.1. Pivotal study 14874:

5. The handling of missing data was not pre-specified in the Study protocol for Study 14874, but was only introduced in the Statistical Analysis Plan released at the time of data cut-off. Can the sponsor please provide a justification for this omission, and confirm that methods for handling missing data were determined prior to data analysis?

6. Can the sponsor please justify the methods used to handle missing data in Study 14874, including the effect that the selected methods have on the analysis of the results for PFS, which would seem to favour a prolonging of PFS (best-case scenario). Can the sponsor also please provide data on the number of subjects who missed a tumour assessment prior to disease progression in each treatment arm?

7. Can the sponsor please provide an explanation as to why a sensitivity analysis was not performed on the methods used to handle missing data?

8. The upper range of time since recent progression/relapse to randomisation is listed in Table 8-10 as being 421 weeks, which is equivalent to longer than 8 years. (A)Can the sponsor please discuss the rationale for treatment in a patient who has not had disease progression for this length of time? (B) Also, can the sponsor please provide data on the distribution of time since progression/relapse (preferably graphically) to randomisation for all patients enrolled in Study 14874 to allow for an assessment of the overall patient population?

9. In pivotal Study 14874, what is the status of further follow up of subjects regarding OS? Is more mature data available, and if not, when is it anticipated that it will be?

10. What further studies or monitoring is planned to assess the impact of mutational biomarker status on the efficacy of regorafenib? In particular, it may be important to understand the efficacy in patients with KRAS and BRAF mutations in order to make informed decisions regarding overall risk-benefit.

11.2.3.2. Study 14935:

11. Can the sponsor please clarify the nature of the support and funding that were provided for the conduct of Study 14935?

11.2.4. Safety

12. Can the sponsor please discuss the rationale for recommending 2 weekly monitoring of LFTs in light of the known risk of severe drug-induced hepatic toxicity, when weekly monitoring was recommended in the pivotal Study 14874?
13. Can the sponsor please discuss whether further monitoring for significant liver injury will be monitored in Japanese patients to assess whether there is increased susceptibility in this ethnic group, following on from the post-marketing findings in regorafenib PSUR No. 2?
14. Can the sponsor also please outline any risk management options for further investigating higher rates of hepatobiliary and skin adverse events in patients of Asian race, and whether further investigation is occurring, and whether differing recommendations regarding monitoring, dose adjustment or dosage may be warranted?
15. Can the sponsor please explain the inconsistencies in the data for HFSR presented in the CSR of Study 14874 (where the incidence of HFSR is listed as being 56.8% in the regorafenib group and 13.6% in the placebo group), compared to the figures listed in the draft PI and presented from the pooled Safety analysis (Pool 2 representing Study 14874) in the Module 2.7.4 Summary of Clinical Safety (where the incidence of HFSR is listed as being 65.9% in the regorafenib group and 15.2% in the placebo group)?

12. Second round evaluation of clinical data submitted in response to questions

12.1. Pharmacokinetics

12.1.1. Question 1

In response to this question, the sponsor explained the calculation of the R_AAUC in the Study.

Comment: This explanation is acceptable.

Question 2

In response to this question, the sponsor reiterated the data originally presented in the CSR. In addition: '*…to address the concerns of the clinical evaluator with respect to the limited clinical data from only 4 moderate (Child-Pugh B) hepatic impairment patients, Bayer agrees to retain the original text in the PI.*'

Comment: This response is acknowledged and accepted.

Question 3

In response to this question, the sponsor referred to previously submitted data supporting the conclusions that renal impairment may only impact the renal excretion of the (not pharmacologically active) glucuronide metabolites of regorafenib, and that renal function measured by estimated glomerular filtration rate was not found to have any relevant impact on the PK of regorafenib. A higher incidence of serious drug-related AEs in patients with renal failure in both the placebo and treatment arms in Study 14387 was used to support the assertion that the difference in patients with renal failure was independent of treatment with regorafenib and may be related to the underlying renal impairment. This data was used to support the recommendation that no dose adjustment is required in patients with renal impairment.

Comment: This explanation by the sponsor in support of not requiring dose adjustments in patients with renal impairment is accepted, although it remains that relatively small numbers of patients with renal impairment were included in the clinical studies.

The sponsor's response agreeing to retain the original PI wording regarding renal impairment is acknowledged.

12.2. Pharmacodynamics

12.2.1. Question 4

In response to this question, the sponsor provided report no. PH-36866 for Study 14814, which provided updated data as of 17 February 2012 up to the final release date of the clinical database 24 March 2014. This report provided updated safety data along with continuing LVEF evaluations. No new or updated QT/QTc data was provided with this report.

The updated results for LVEF in subjects without dose reductions are provided in the table below:

Table 13: Mean left ventricular ejection fraction (LVEF) and changes from baseline by visit (subjects valid for LEVF analysis without dose reductions; N=15)

Visit	n	Value at visit (%)		Change from baseline[a] (LVEF%)	
		Mean (±SD)	Median (min, max)	Mean (±SD)	Median (min, max)
Baseline	15	63.8 (± 7.1)	63 (50, 75)	-	-
First Post [b]	15	63.3 (± 7.1)	66 (48, 76)	-0.5 (± 8.4)	1 (-13, 17)
C2, D21	14	63.9 (± 7.0)	67 (48, 76)	-0.1 (± 8.6)	1 (-13, 17)
C5, D1 [c]	5	63.4 (± 8.7)	69 (52, 71)	-3.0 (± 5.4)	-1 (-11, 2)
C8 D1 [c]	4	68.0 (± 6.5)	68 (61, 76)	3.3 (± 4.1)	4 (-2, 8)
C11 D1 [c]	4	60.8 (± 5.7)	61 (55, 67)	-2.3 (± 8.1)	-2 (-12, 7)
C17 D1 [c]	3	69.0 (± 5.0)	69 (64, 74)	5.0 (± 2.6)	6 (2, 7)
End of study [d]	8	64.1 (± 8.7)	67 (48, 76)	3.0 (± 8.3)	3 (-6, 16)

C = cycle; D = day; LVEF = left ventricular ejection fraction; max = maximum; min = minimum; SD = standard deviation.

Note: Only visits with more than 2 valid subjects were included in this evaluation. Subject [redacted] may have missed taking 4 tablets during Cycle 1 (see Listing 16.2.5 / 2) but was included in this analysis.

a Change from baseline was calculated for each subject who had a baseline and post-baseline MUGA scan

b First post baseline assessment that occurred at any time after the first dose of regorafenib.

c Actual LVEF evaluation was conducted during the last 7 days of this cycle, per protocol

d Includes subjects valid for LVEF without dose reductions who completed the End of Treatment Visit (Listing 16.2.6 / 19).

Similar results were observed for all subjects on a minimum of 80 mg regorafenib prior to the LVEF evaluation.

Comment: The updated LVEF results provided in this final analysis of Study 14814 are in keeping with the previously evaluated interim analysis. Conclusions remain unchanged that minimal LVEF changes were observed in this study, and these were not of clinical relevance. It is agreed with the sponsor's assessment that the results suggest that regorafenib does not have a negative impact on cardiac contractility.

Safety data in this report was updated to and overall mean (± SD) time under regorafenib treatment of 127 (± 125) days and a median treatment of 92 days (range: 1 to 490 days). Safety data was consistent with that presented in the earlier interim report, and there were no new safety concerns identified.

12.3. Efficacy

12.3.1. Question 5

The sponsor's response was that the SAP was finalised prior to the database un-blinding, and the handling of missing data is more relevant to the analysis stage rather than data collection.

Comment: This explanation is accepted.

12.3.2. Question 6

The sponsor's response to this question was:

> *'The primary analysis of PFS was based on the independent, blinded, central assessment of radiological scans. As these rules were applied to both treatment arms there is no obvious source of bias in the assignment of progression dates or censoring dates.'*

Comment: Although it is agreed with the above statement, it is nonetheless noted that the handling of missing data will prolong the PFS assessment for both arms of the study. Therefore, although there is no differential bias in the assignment of progression dates, the overall magnitude of the effect will be longer, and this impacts on the interpretation of the clinical significance of the results.

The sponsor also provided data on the numbers of patients with radiological progression and the number of subjects who missed one or more tumour radiological assessments prior to radiological disease progression. The number with one missing assessment prior to disease progression was low in both arms: 2/62 (3.2%) in the placebo arm and 4/77 (5.2%) in the regorafenib arm, with no cases with more than one missing assessment.

Comment: It is agreed with the sponsor's assessment that the impact of missing data on the interpretation of PFS results is likely to be minimal.

12.3.3. Question 7

The sponsor's response to this question was that the low number of cases with a missing scan rendered a sensitivity analysis unnecessary.

Comment: This response is accepted.

12.3.4. Question 8a

The sponsor explained that this was an error (the actual time since last progression for this patient was 12 days) but that this does not impact on the interpretation of the safety and efficacy results.

Comment: This response is accepted.

12.3.5. Question 8b

The sponsor provided a graph that indicated that the majority of the patients were randomised at the time of progression, and overall most had progressed within the last 26 weeks prior to randomisation.

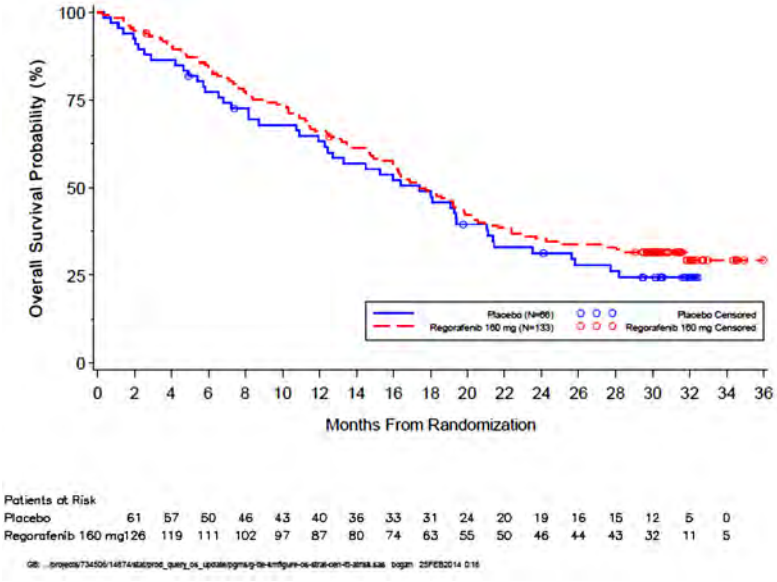
Comment: It is agreed with the sponsor that this is in keeping with the proposed indication of regorafenib for treatment of advanced GIST following treatment with 2 TKIs.

12.3.6. Question 9

In response to this question, the sponsor provided and updated analysis of OS with cut-off date 31 January 2014 (about 2 years after the first cut-off date) and showing a total of 139 death events (compared to 46 events at the previous analysis). The sponsor stated that this analysis had been prepared after a regulatory request from the European health authority, and that the final analysis of OS is planned when approximately 160 deaths have been observed (expected in the second quarter of 2015).

The uncorrected results of this analysis found a median OS of 529 days in both arms, with a HR 0.849 (95% CI: 0.597, 1.206, log rank p value = 0.179856). The Kaplan-Meier curve is shown in the figure below.

Figure 3: Kaplan-Meier curves of Overall survival (Full Analysis Set)



Study 14874 OS update cut-off 31.01.2014, uncorrected results

The OS results with cross-over correction by RPSFT method found a median OS of 263 days in the placebo arm compared to 529 days in the regorafenib arm, and HR 0.388 (95% CI: 0.259, 0.580, log rank p-value = <0.000001). Meanwhile, OS with cross-over correction by IPE method found a median OS of 306 days in the placebo arm compared to 529 days in the regorafenib arm, HR 0.508 (95% CI: 0.352, 0.734, log rank p-value = 0.000119).

Comment: This OS data is substantially updated from what was submitted in the original application, however, the results are not significantly different to the earlier analysis. Due to the fact that patients randomised to placebo were allowed to cross-over to regorafenib treatment on disease progression, the uncorrected OS results are likely to underestimate the magnitude of the beneficial effect of regorafenib over placebo. Therefore, the uncorrected HR of 0.849 supports the PFS efficacy results for the benefit of regorafenib in the proposed indication.

12.3.7. Question 10

In response to this question, the sponsor provided an assessment of the genetic and non-genetic biomarker data and scientific evidence in the public domain to suggest that neither KRAS or BRAF are frequently mutated in GIST, and no evidence is available that both oncogenes are drivers of the disease nor are RTKs other than mutations in c-KIT or PDGFR. The sponsor stated that:

> *'Based on the information presented above, there are no plans to assess whether KRAS or BRAF mutations may have an impact on the efficacy of regorafenib treatment due to the broad activity of regorafenib to c-KIT primary or secondary mutations.*
>
> *However, additional retrospective molecular analyses are being carried out upon request by the European Medicines Agency (EMA) with specimens collected in the GRID study. Archival tumour tissue was subjected to targeted Next Generation tumor DNA sequencing to determine the presence of mutations in other receptor tyrosine kinases, whereas plasma samples collected at baseline were used to identify c-KIT somatic mutations in circulating free tumour DNA (ctDNA) by Next Generation Sequencing. The analyses are on-going.'*

Comment: The explanation by the sponsor is accepted. It is accepted that the low frequency of KRAS and BRAF mutations in GIST patients will effectively preclude further investigation. However, it would be beneficial for the TGA to receive the additional

retrospective molecular analysis being carried out for the EMA when they become available for evaluation.

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12.3.8. Question 11

The sponsor declared monetary funding and provision of study drug for this study.

Comment: This is acknowledged.

12.4. Safety

12.4.1. Question 12

The sponsor provided justification for the current PI recommended liver function monitoring and dose modification schedules. This was based on discussions with key opinion leaders in the medical field, current post-marketing data and emerging evidence from an ongoing open-label Phase IIIb study in patients with metastatic CRC, all of which support the known hepatotoxicity profile and risk management recommendations.

Comment: This explanation by the sponsor is acceptable.

12.4.2. Question 13

In response to this question, the sponsor described the specific monitoring of regorafenib-associated hepatotoxicity in Japan, and ongoing Drug Use Investigations of regorafenib for CRC and GIST. The sponsor detailed that presently the data do not present any new safety signals for regorafenib, and current guidance on hepatotoxicity monitoring and associated dose modifications given within the Japanese label is considered adequate.

Comment: This explanation is acceptable.

12.4.3. Question 14

12.4.3.1. Hepatobiliary adverse events:

In response to the question of hepatobiliary adverse events, the sponsor reiterated the ongoing monitoring of Japanese subjects as discussed in the response to Question 13 above. Results are not yet available to make definitive conclusions, however it was asserted that there are no new safety signals and the current recommendations in the PI regarding LFT monitoring, dose adjustment guidance and actual dosage are considered adequate across ethnicities.

In addition, the sponsor provided the CSR for the recently completed Asian Phase III Study 15808-CONCUR, in which136 Asian patients were treated with regorafenib for metastatic CRC. No cases of hepatic failure or hepatic necrosis were reported in this study, and there were no deaths attributed to liver abnormalities. Higher incidences of all-grade liver function abnormality TEAEs were observed in the regorafenib group compared to the placebo group for blood bilirubin increased (48.5% versus 20.6% respectively); alanine aminotransferase increased (31.6% versus 17.6%); aspartate aminotransferase increased (31.6% versus 22.1%). The incidence of Grade 3-4 liver function abnormality TEAEs in the regorafenib group compared to the placebo group included: blood bilirubin increased (11.8% [4.4% Grade 4] versus 4.4% respectively); alanine aminotransferase increased (8.1% versus 1.5%); and aspartate aminotransferase (8.8% versus 0%).

Comment: The hepatic safety results presented in Study 15808 in Asian patients are higher than that observed in the pivotal Study 14874 presented in this CSR, where increased blood bilirubin was observed in 33.3% of patients in the regorafenib arm, and the incidence of Grade 3-4 events was 3.8% for increased ALT, 3.0% for increased AST and 3.0% for increased bilirubin. It is uncertain whether these

differences can be attributed to differing patient ethnicities or due to the underlying condition (there may be more patients with metastatic liver disease in Study 15808). The sponsor's assessment that current liver monitoring and dosing recommendations are adequate across ethnicities while more data on the impact of ethnicity is being collected is acceptable. It is acknowledged that dose reductions may be required more frequently in Asian patients and this risk mitigation strategy is appropriate.

12.4.3.2. Skin adverse events:

In response to this question, the sponsor reiterated the observed 30% higher rate of all grade HFSR and 10% increase in all grade rash events in Asian compared to non-Asian patients treated with regorafenib. It was stated that the majority of these events were of low grade, and rarely resulted in treatment discontinuation, but rather were well managed with dose reductions as outlined in the PI. The CSR for Study 15808 in Asian patients with metastatic CRC was again referred to, in which the incidence of HFSR was higher in the regorafenib treated group compared to placebo (74.3% versus 5.9%). The incidence of Grade 3 HFSR was 16.2% in the regorafenib group compared to 0% in the placebo group. There were no SAEs of HFSR in either group, and only 1/136 patients required treatment discontinuation due to HFSR as a result of regorafenib treatment.

Comment: The overall incidence of any grade HFSR in pivotal Study 14874 (56.8%) was lower than in Study 15808, although the incidence of Grade 3 events was higher (20.5%). In any case, it is agreed with the sponsor that the incidence of HFSR is generally high regardless of ethnicity, and the dose reduction recommendations as outlined in the PI in response to HFSR is adequate across ethnicities. Again it is noted that dose reductions may be required more commonly in Asian patients due to skin toxicities.

12.4.3.3. Question 15

The sponsor described how AEs in the CSR for Study 14874 were displayed according to NCI-CTCAE criteria, in contrast to the standard approach of the sponsor to depict MedDRA data in labelling documents. The CTCAE term 'dysesthesia' was assigned to PPES in MedDRA coding, accounting for the discrepancy.

Comment: This explanation is acceptable.

13. Second round benefit-risk assessment

13.1. Second round assessment of benefits

After consideration of the responses to clinical questions, the benefits of regorafenib in the proposed usage are unchanged from those identified in the First round evaluation.

14. Second round assessment of risks

After consideration of the responses to clinical questions, the risks of regorafenib in the proposed usage are unchanged from those identified in the First round evaluation. Questions raised have been adequately addressed by the sponsor.

14.1. Second round assessment of benefit-risk balance

The benefit-risk balance of regorafenib, given the proposed usage as described in the amended PI, is favourable.

14.2. Second round recommendation regarding authorisation

It is recommended that regorafenib be **approved** for the proposed indication:

> *Treatment of patients with gastrointestinal stromal tumours (GIST) who have been previously treated with two tyrosine kinase inhibitors.*

First round questions raised have been adequately addressed by the sponsor.

There remains one outstanding PI change that requires addressing in Table 7 of the proposed PI.

15. References

1. EMA Guideline on the evaluation of anticancer medicinal products in man. 2006.
2. EMA Guideline on Points to consider on missing data, 2001.
3. George S, Wang Q, Heinrich M, et al. Efficacy and safety of regorafenib in patients with metastatic and/or unresectable GI stromal tumour after failure of imatinib and sunitinib: A multicentre Phase II trial. Journal of Clinical Oncology, 2012; 30(19): 2401-07.
4. Chen, HX, Cleck, JN. Adverse effects of anticancer agents that target the VEGF pathway. Nat Rev Clin Oncol 2009; 6: 465-477
5. Belum VR, Wu S, Lacouture ME. Risk of hand-foot skin reaction with the novel multikinase inhibitor regorafenib: a meta-analysis. Invest New Drugs. 2013 Aug;31(4):1078-86

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