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EMA/CHMP/220738/2014
Committee for Medicinal Products for Human Use (CHMP)

# CHMP extension of indication variation assessment report

Nexavar

Procedure no.: EMEA/H/C/000690/II/0035

Marketing authorisation holder (MAH): Bayer Pharma AG

## Note

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

7 Westferry Circus ● Canary Wharf ● London E14 4HB ● United Kingdom
**Telephone** +44 (0)20 7418 8400 **Facsimile** +44 (0)20 7418 8613
**E-mail** info@ema.europa.eu **Website** www.ema.europa.eu

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# List of abbreviations

| | |
|---|---|
| AESI | adverse events of special interest |
| ADR | adverse drug reaction |
| AKT | v-akt murine thymoma viral oncogene |
| ALT | alanine aminotransferase |
| AML | acute myeloid leukemia |
| ASCO | American Society of Clinical Oncology |
| AST | aspartate aminotransferase |
| AnTC | anaplastic thyroid carcinoma |
| ATC | Anatomical Therapeutic Chemical (Classification System) |
| AUC | area under curve |
| BID | bis in die (twice daily) |
| BRAF | a serine/threonine kinase, member of the RAF kinase family; V-raf murine sarcoma viral oncogene homolog B1 |
| CCDS | company core data sheet |
| CI | confidence interval |
| c-KIT | mast/stem cell growth factor receptor (tyrosine kinase) |
| CHMP | Committee for Medicinal Products for Human Use (European Union) |
| CR | complete response |
| CSR | clinical study report |
| CT | computed tomography |
| CV | coefficient of variation |
| CTCAE | Common Terminology Criteria for adverse events |
| DCR | disease control rate |
| DOR | duration of response |
| DMC | Data Monitoring Committee |
| DTC | differentiated thyroid carcinoma |
| EAIR | exposure-adjusted incidence rate |
| EBRT | external beam radiation therapy |
| ECOG PS | Eastern Cooperative Oncology Group Performance Status |
| EGFR | epithelial growth factor receptor |
| EMA | European Medicines Agency |
| EQ-5D | EuroQol 5 dimensions questionnaire |
| ERK | extracellular signal-related kinase |
| ESMO | European Society for Medical Oncology |
| EU | European Union |
| FACT-G | Functional Assessment of Cancer Therapy-General |
| FAS | full analysis set |
| FDA | Food and Drug Administration |
| FDG | 2-[18F] fluoro-2-deoxy-D-glucose |
| FGFR1 | fibroblast growth factor receptor |
| FLT-3 | Fms-like tyrosine kinase 3 |
| FTC | follicular thyroid carcinoma |
| GBq | gigabecquerel |
| GCP | good clinical practice |
| GFR | glomerular filtration rate |
| HCC | hepatocellular carcinoma |

| | |
|---|---|
| HER-2 | human epidermal growth factor receptor 2 |
| HFSR | hand foot skin reaction |
| HR | hazard ratio |
| HRAS | v-Ha-ras Harvey rat sarcoma viral oncogene homolog |
| HRQoL | health-related quality of life |
| ICH | International Conference on Harmonization |
| INR | international normalized ratio (prothrombin time expressed in relation to normal value) |
| ISS | investigator-sponsored study |
| KIT | v-kit Hardy-Zuckerman 4 feline sarcoma viral oncogene homolog |
| KM | Kaplan-Meier |
| KRAS | Kirsten rat sarcoma viral oncogene homolog (protein), member of the RAS family of GTPases (guanosine triphosphate hydrolases) |
| MAPK | mitogen-activated protein kinase |
| MedDRA | Medical Dictionary for Regulatory Activities |
| MEK | MAPK (mitogen-activated protein kinase)/ERK kinase |
| mCi | milliCurie |
| mg | milligram |
| MID | minimally important difference |
| MRI | magnetic resonance imaging |
| MTC | medullary thyroid carcinoma |
| NA | not available |
| NCCN | National Comprehensive Cancer Network |
| NCI | National Cancer Institute |
| NR | not reached |
| NRAS | neuroblastoma RAS viral (v-ras) oncogene homolog |
| OS | overall survival |
| PBMQ | product-specific Bayer MedDRA queries |
| PD | progressive disease |
| PDGFR | platelet derived growth factor receptor |
| PEC | Predicted Environmental Concentration |
| PET | positron Emission Tomography |
| PFS | progression-free survival |
| PIK3CA | phosphatidylinositol-4,5-bisphosphonate 3-kinase, catalytic subunit alpha |
| PK | pharmacokinetics |
| PKAS | pharmacokinetic analysis set |
| po | per os (by mouth) |
| PPS | per protocol set |
| PR | partial response |
| PS | performance status |
| PTC | papillary thyroid carcinoma |
| QoL | quality of life |
| OOPD | Office of Orphan Products Development |
| RAF | serine/threonine protein kinases that are downstream effector molecules of RAS |
| RAI | radioactive iodine |
| Ras | oncogene originally isolated from rats with sarcoma |
| RCC | renal cell carcinoma |

| | |
|---|---|
| RET | a receptor tyrosine kinase “rearranged during transfection” (a proto-oncogene) |
| rhTSH | recombinant human thyroid-stimulating hormone |
| RR | Response rate |
| SAE | Serious adverse event |
| SAF | Safety analysis set |
| SAP | Statistical Analysis Plan |
| SCE | Summary of Clinical Efficacy |
| SCS | Summary of Clinical Safety |
| SD | Stable disease |
| S.D. | Standard deviation |
| SMQ | Standard MedDRA queries |
| sNDA | Supplemental New Drug Application |
| SPA | Special Protocol Assessment |
| SPFS | Secondary progression-free survival |
| SOC | System organ class |
| T3 | Triiodothyronine |
| T4 | Thyroxine |
| TEAE | Treatment-emergent adverse event |
| TNM | Tumor nodal metastatic |
| TSH | Thyroid-stimulating hormone |
| TTP | Time to progression |
| ULN | Upper limit of normal |
| U.S. | United States |
| VAS | Visual-analog scale |
| VEGF | Vascular endothelial growth factor |
| VEGFR | Vascular endothelial growth factor receptor |
| WHO | World Health Organization |

# 1. Background information on the procedure

## *1.1. Type II variation*

Pursuant to Article 16 of Commission Regulation (EC) No 1234/2008, Bayer Pharma AG submitted to the European Medicines Agency on 27 June 2013 an application for a variation including an extension of indication.

This application concerns the following medicinal product:

| **Medicinal product:** | **International non-proprietary name:** | **Presentations:** |
|---|---|---|
| Nexavar | SORAFENIB | See Annex A |

The following variation was requested:

| **Variation requested** | | **Type** |
|---|---|---|
| C.1.6.a | C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one | II |

The MAH applied for an extension of the indication for the treatment of differentiated thyroid carcinoma. Consequently, the MAH proposed the update of sections 4.1, 4.2, 4.4, 4.8, 5.1 and 5.2 of the SmPC.

The Package Leaflet was proposed to be updated in accordance.

In addition, the MAH took the opportunity to update the list of local representatives in the Package Leaflet.

Furthermore, the MAH proposed this opportunity to bring the PI in line with the latest QRD template version 9.0.

The variation proposed amendments to the SmPC and Package Leaflet.

Nexavar was designated as an orphan medicinal product EU/1/06/342 on 29 July 2004 and 11 April 2006 in the following indications respectively: treatment of renal cell carcinoma, treatment of hepatocellular carcinoma.

The new indication, which is the subject of this application, falls within separate orphan designations EU/3/13/1199 and EU/3/13/1200 granted on 13 November 2013: treatment of follicular thyroid cancer and treatment of papillary thyroid cancer. Following the CHMP positive opinion on this extension of indication, the Committee for Orphan Medicinal Products (COMP) reviewed the designation of Nexavar as an orphan medicinal product in the newly approved indication. The outcome of the COMP review can be found on the Agency's website: ema.europa.eu/Find medicine/Rare disease designations.

## *Information on paediatric requirements*

Pursuant to Article 8 of Regulation (EC) No 1901/2006, the application included an EMA Decision P/68/2010 on the granting of a product-specific waiver.

### *Information relating to orphan market exclusivity*

### Similarity

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

### *Scientific advice*

The applicant did not seek scientific advice at the CHMP.

## *1.2. Steps taken for the assessment of the product*

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

Rapporteur: Filip Josephson Co-Rapporteur: Dinah Duarte

| | |
|---|---|
| Submission date: | 27 June 2013 |
| Start of procedure: | 26 July 2013 |
| Rapporteur's preliminary assessment report circulated on: | 16 September 2013 |
| Co-Rapporteur's preliminary assessment report circulated on: | 24 September 2013 |
| PRAC Rapporteur's Risk Management Plan Assessment Report as endorsed by PRAC | 10 October 2013 |
| Joint Rapporteur's updated assessment report circulated on: | 17 October 2013 |
| Request for supplementary information and extension of timetable adopted by the CHMP on: | 24 October 2013 |
| MAH's responses submitted to the CHMP on: | 20 November 2013 |
| Rapporteur's preliminary assessment report on the MAH's responses circulated on: | 23 December 2013 |
| PRAC Rapporteur's Risk Management Plan Assessment Report as endorsed by PRAC | 9 January 2014 |
| Rapporteur's updated assessment report on the MAH's responses circulated on: | 17 January 2014 |
| 2nd Request for supplementary information and extension of timetable adopted by the CHMP on: | 23 January 2014 |
| MAH's responses submitted to the CHMP on: | 20 February 2014 |
| Rapporteur's preliminary assessment report on the MAH's responses circulated on: | 26 March 2014 |
| CHMP opinion: | 25 April 2014 |

# 2. Scientific discussion

## 2.1. Introduction

Thyroid carcinoma is a rare disease which accounts for approximately 1% of all new malignant disease, including nearly 0.5% of cancers in men and 1.5% of cancers in women. In Europe, an estimated 52,937 new cases of thyroid cancer were reported in 2012 with 6,334 deaths (EUCAN Cancer factsheets: Thyroid Cancer). Thyroid carcinoma is the most common form of endocrine neoplasm. There are three main histologic types of thyroid carcinoma: differentiated, medullary, and anaplastic. Approximately 94% of thyroid carcinomas are differentiated thyroid carcinomas (DTC), roughly 4% of thyroid carcinomas are medullary thyroid carcinomas (MTC), and the remaining 2% are anaplastic thyroid carcinomas (AnTC).

DTC originates from the follicular epithelial cells of the thyroid gland, and is either papillary thyroid carcinoma (PTC), follicular thyroid carcinoma (FTC) or poorly differentiated subtype per histological classification. Hürthle cell thyroid carcinoma is an oncocytic variant of follicular carcinoma.

Table 1: Main histological types of thyroid carcinoma and deaths due to thyroid carcinoma are shown below.

| Thyroid carcinoma type | | % of thyroid carcinomas | 10-year relative Survival (%) | Deaths by tumor type (%) |
|---|---|---|---|---|
| Differentiated | Papillary | 79% | 93% | 53% |
| | Follicular | 13% | 85% | 18% |
| | Hürthle cell | 2% | 76% | 7% |
| Medullary | | 4% | 75% | 9% |
| Anaplastic | | 2% | 14% | 14% |

Treatment of DTC encompasses surgical resection, radioactive iodine (RAI) and thyroid-stimulating hormone (TSH)-suppressive therapy. RAI can be curative also in patients who develop distant metastases. In patients no longer responding to RAI, doxorubicin is authorised in some EU Member States.

An important aspect also of metastatic disease is that some patients do not require therapy for years due to a very indolent course. Locally advanced and metastatic RAI refractory DTC, however, is often associated with symptoms such as swallowing and breathing difficulties (related to cervical and lung metastases), pain, bone fracture, and spinal cord compressions (from bone metastases). Recurrent neck lesions are responsible for one-third of the cancer-related deaths while the remaining two-thirds are a result of distant metastases which are located in the lungs (50%), bones (25%), lungs and bones (20%), or at other sites (5%).

Sorafenib, the active substance of Nexavar, is an oral multikinase inhibitor that inhibits the activity of targets present in the tumour cell (CRAF, BRAF, V600E BRAF, KIT, and FLT-3) and in the tumour vasculature (CRAF, VEGFR-2, VEGFR-3, and PDGFR-ß). The anti-angiogenic properties are of interest as VEGFs and VEGFRs often are over-expressed in cases of DTC. Inhibition of TKs upstream the Raf/MEK/ERK pathway might also be of interest.

Nexavar is currently indicated for the treatment of patients with advanced renal cell carcinoma (RCC) who have failed prior interferon-alpha or interleukin-2 based therapy or are considered unsuitable for such therapy. Nexavar is also indicated for the treatment of hepatocellular carcinoma (HCC). The recommended dosage is 400 mg bid given orally as 2 tablets of 200 mg.

The MAH applied for a new indication in differentiated thyroid cancer (DTC) and the proposed wording of the indication was:

- Treatment of patients with locally advanced or metastatic differentiated thyroid carcinoma refractory to radioactive iodine.

The proposed dose to be administered is 400 mg bid which is the same dose as in RCC and HCC.

## *2.2. Non-clinical aspects*

### 2.2.1. Introduction

The preclinical safety profile of sorafenib was assessed at the time of initial marketing authorisation in mice, rats, dogs and rabbits.

As part of this application, the applicant discussed the relevance of available non-clinical data in view of the applied indication in adults with advanced thyroid cancer patients and submitted a revised environmental risk assessment. In addition, the MAH submitted an *in vitro* report (PH-37402) investigating the influence of thyroid hormones on *in vitro* glucuronidation of sorafenib in human liver microsomes.

### 2.2.2. Pharmacology

A significant fraction of papillary thyroid carcinoma (PTC) and medullary thyroid carcinoma (MTC) are characterised by the presence of a RET receptor, which is constitutively activated either by various types of gene rearrangements (RET/PTC in PTC) or by point mutations (e.g. C634R/W or M918T occurring in MTCs including inherited multiple endocrine neoplasia (MEN) 2A and 2B, respectively). In other cases PTC and ATC contain mutated BRAF.

Sorafenib was shown to potently inhibit the enzymatic function of wild-type, mutated or RET fusion protein with IC50 values of ~ 7-50 nM. It also inhibited RET signalling, including receptor autophosphorylation and downstream signalling and cell proliferation in stably transfected cells or human thyroid cancer cells with activating RET mutations along with rearranged RET/PTC and mutated RET oncogenes with IC50 values in the lower nanomolar range. Sorafenib was also shown to potently inhibit BRAF, BRAFV600E and CRAF in biochemical assays with IC50 values between 6 and 38 nM. siRNA mediated knock-down of BRAF in the ATC cell line FRO inhibited MAPK signaling and their proliferation. This effect could be mimicked by sorafenib, suggesting that inhibition of BRAF and its mutant has therapeutic potential in thyroid cancers. Synergistic effects on the inhibition of the proliferation of MTC tumor cell lines were observed, when sorafenib was combined with a MEK inhibitor (AZD6244) but not with the mTOR inhibitor everolimus.

*In vivo*, sorafenib was efficacious in an orthotopic PTC derived TPC-1 tumor model, which expresses the RET/PTC1 fusion protein and reduced tumor volume by 94 % compared with vehicle controls when dosed orally at 80 mg/kg/d. The NPA87 model tested in the same study was later identified as melanoma cell line. In MTC derived TT cell xenografts (RET C634W) growing subcutaneously, sorafenib induced tumor regression of after oral dosing at 60 mg/kg/d.

The activity of sorafenib was also investigated in ATC derived cell lines, where it inhibited proliferation with IC50 values in the micromolar range and induced apoptosis up to 40 % at similar concentrations. Antitumor activity of sorafenib *in vivo* was published for the tumor cell lines ARO and DRO, but both cell lines were discovered later to be not of thyroid origin.

Recent mechanism of action studies in TC cell lines have shown that mutant BRAF can prevent apoptosis either by NFkB mediated upregulation of TIMP-1 in the PTC cell line BCPAP or by localizing into mitochondria which leads to elevated glucose uptake and inhibition of oxidative phosphorylation in primary tumor cells and a thyroid cell line PCCL3 with inducible BRAF expression. Sorafenib was shown

to inhibit the antiapoptotic effect in BCPAP cells, but not the effect in PCCL3 cells. Furthermore, *in vitro* studies have shown that the inhibition of the proliferation of BCPAP cells by sorafenib is reduced upon expression of the ubiquitin ligase SCFßTRCP, which downregulated VEGFR2 in these cells.

In an *in vitro* study (PH-37402), sorafenib 5 µM was incubated for 60 minutes with pooled human liver microsomes together with UDPGA, and formation of M7 was measured with HPLC-MS/MS. Positive control niflumic acid (inhibitor of UGT1A9) caused a 90% inhibition of the reaction, whereas the thyroid hormones T3 and T4 at the concentrations 2-20 µM did not influence the reaction. The concentrations of T3 and T4 chosen were well above the physiological plasma concentrations (<0.1 nM). No signs of *in vitro* inhibition of sorafenib glucuronidation were observed either for T3 or T4.

### 2.2.3. Ecotoxicity / environmental risk assessment

The ecotoxicity/environmental risk assessment was evaluated and approved in 2011 for Nexavar in the following therapeutic indications: hepatocellular carcinoma and renal cell carcinoma.

A refined $PEC_{surfacewater}$ was calculated based on maximum amount per year of sorafenib tosylate in the treatment of thyroid cancer (see Table 2).

Table 2: Summary of environmental fate/effects for sorafenib tosylate (ERA approved in 2011, updated $PEC_{surfacewater}$ calculation)

| **Substance (INN / Invented Name): Nexavar** | | | |
|---|---|---|---|
| ***PBT screening*** | | Result | **Conclusion** |
| *Bioaccumulation potential*- log $K_{ow}$ | OECD 117 | log $K_{ow}$ pH 7 (25º)≤ 4.5 | Potential PBT (**N**) |
| ***PBT-assessment*** | | | |
| **Parameter** | **Result relevant for conclusion** | | **Conclusion** |
| Bioaccumulation | log $K_{ow}$ | 3.7 | |
| | BCF | 7250<br>ratio fish/water concentration at the end of exposure | **vB** |
| Persistence | ready biodegradability | There was no degradation after 28 days<br>$DT_{50}$ (transformation in soil) - 187 days | **vP** |
| Toxicity (fish) | $EC_{10}$ mortality | 0.17 µg/L | **T** |
| **PBT-statement :** | **The compound is considered as vP and vB** | | |
| ***Phase I (refined)*** | | | |
| ***Calculation*** | **Value** | **Unit** | **Conclusion** |
| $PEC_{surfacewater}$ , default or refined (e.g. prevalence, | 0.0378 | µg/L | > 0.01 threshold (Y) |

| | | | |
|---|---|---|---|
| literature) | | | |
| ***Phase II Physical-chemical properties and fate*** | | | |
| **Study type** | **Test protocol** | **Results** | **Remarks** |
| Adsorption-Desorption | OECD 121 | *Log* $K_{oc}$ = 5.4=<br>=251 188 L/Kg<br>High affinity for soils and activated sludge | $K_{oc}$≥10 000 L/Kg |
| Ready Biodegradability Test | OECD 301F | Not readily biodegradable | |
| Aerobic and Anaerobic Transformation in Aquatic Sediment systems | OECD 308 | $DT_{50}$water=0.5 days for HOCC<br>$DT_{50}$water=0.6 days for LOCC<br>% shifting to sediment =<br>74.2 and 73.1 % at day 144 | Two aquatic sediments<br>HOCC=Higher Organic Carbonic Content<br>LOCC= Lower Organic Carbonic Content |

| ***Phase II-A Effect studies*** | | | | | |
|---|---|---|---|---|---|
| **Study type** | **Test protocol** | **Endpoint** | **value** | **Unit** | **Remarks** |
| Algae, Growth Inhibition Test/*Species* | OECD 201 | NOEC | ≥0.536 | µg/L | *Desmodesmus subspicatus*<br>(Short-term test) |
| *Daphnia* sp. Reproduction Test | OECD 211 | NOEC | ≥0.860 | µg/L | |
| Fish, Early Life Stage Toxicity Test/*Species* | OECD 210 | NOEC<br>EC10 weight<br>EC10 length<br>EC10 mortality | <1.0<br>0.47<br>0.32<br>0.17 | µg/L | *Pimephales promelas*<br>Dose concentrations between:<br>1-14.8 µg/L |
| Activated Sludge, Respiration Inhibition Test | OECD 209 | EC 50 | ≥ 32 000 | mg/L | |
| ***Phase II-B Studies*** | | | | | |
| Bioaccumulation in Fish | OECD 305 | BCF | 7250 | | ratio at the end of exposure |

| | | | | | |
|---|---|---|---|---|---|
| Aerobic transformation in soil | OECD 307 | $DT_{50}$<br><br>$DT_{90}$ | 187 days<br><br>622 days | | sandy loam soil<br><br>mineralization 0.5% |
| Soil Micro-organisms: Nitrogen Transformation Test | OECD 216 | NOEC | ≥250 | mg/kg | No effect on nitrate transformation |
| Terrestrial Plants, Growth Test/*Species* | OECD 208 | NOEC<br>LOEC | 10<br>100 | mg/kg | *Hordeum vulgare*<br>*Beta vulgaris*<br>*Lactuca sativa* |
| Earthworm, Acute Toxicity Tests | OECD 207 | NOEC | ≥1000 | mg/kg | |
| Sediment dwelling organism | OCDE 218 | NOEC | 2.5 | mg/kg | *Chironomus riparius* |
| Chronic effects on collembolan | ISO11267 | NOEC | ≥1000 | mg/kg | *Folsomia candida* |

## 2.2.4. Discussion on non-clinical aspects

Available non-clinical pharmacology data support the use of sorafenib for the treatment of patients with thyroid cancers. *In vitro* and *in vivo* studies in mice have shown that sorafenib exerted antitumor activity against thyroid cancers of various subtypes.

To explore the hypothesis of a potential inhibition of UGT1A9 by thyroxine to explain the higher exposure of sorafenib observed in thyroid cancer patients, a non-clinical study report (PH-37402) investigating the influence of thyroid hormones on *in vitro* glucuronidation of sorafenib in human liver microsomes was submitted (see also 2.3.2 pharmacokinetics aspects). Thyroid hormones T3 and T4 at the concentrations 2-20 µM were found not to influence the reaction.

The environmental risk assessment for sorafenib was performed and assessed as part of previous procedures in relation to the approved indications hepatocellular and renal cell carcinoma (EMEA/H/C/690/FUM023 and FU2/023.1). A refined $PEC_{surfacewater}$ was calculated as part of the present variation. Based on the available data, sorafenib tosylate has a high affinity for soil and activated sludge (Koc≥10 000 L/Kg), bio-accumulates and is toxic for fish (BCF=7250; EC10<0.17 µg/L), and has effects on seedling growth from 100 mg/kg, when tested on barley, sugar beet and lettuce. The ratio PEC/PNEC surface water was identified as higher than 1.

Considering the above data, sorafenib tosylate should be used according to the precautions stated in the SmPC in order to minimize any potential risks to the environment.

## 2.2.5. Conclusion on the non-clinical aspects

ERA studies have shown that sorafenib tosylate has the potential to be persistent, bioaccumulative and toxic to the environment (as reflected in section 5.3 of the SmPC). Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

## *2.3. Clinical aspects*

## 2.3.1. Introduction

**GCP**

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

Table 3: Tabular overview of clinical studies

| **Study no. (Report no.)** Regions/ countries | **Title** | **Study population** | **Dosing** | **Number of patients with DTC** | **Main outcomes** |
|---|---|---|---|---|---|
| **MAH-sponsored studies** | | | | | |
| **Pivotal, randomized, double-blind, placebo controlled study (phase 3)** | | | | | |
| **14295 (Report A57578)** Europe (Austria, Belgium, Bulgaria, Denmark, France, Germany, Italy, Netherlands, Poland, Russia, Spain, Sweden, United Kingdom), United States, and Asia (China, Japan, South Korea, Saudi Arabia). | A Double-Blind, Randomized Phase III Study Evaluating the Efficacy and Safety of Sorafenib Compared to Placebo in Locally Advanced/Metastatic RAI-Refractory Differentiated Thyroid Cancer | Patients with locally advanced /metastatic RAI-refractory DTC | 400 mg BID (800mg total daily dose), continuous treatment (28-day cycle). | Total: 417<br>Sorafenib: 207 (FAS)<br>Placebo: 210 (FAS) | Primary: PFS (central review)<br>Secondary: OS, TTP, RR, DCR, DOR, PK, safety |
| **Phase 1 / 2** | | | | | |
| **100391** United States and United Kingdom | Randomised discontinuation study of sorafenib in patients with advanced refractory cancer | Patients with advanced solid tumours | 400 mg BID | 6 | Primary: Percentage of patients progression-free |
| **100561 PH-35781 (Tolcher et al. 2011)** | Effect of BAY 43-9006 (sorafenib) on cardiovascular safety parameters in cancer patients | Patients with cancer | 400 mg BID | 3 | Primary: Effect of sorafenib on cardiovascular safety<br>Secondary: safety, PK, anti-tumour activity |

***(continued)***

| **Study no. Regions/ countries** | **Title** | **Study population** | **Dosing** | **Number of patients with thyroid carcinoma** | **Main outcomes** |
|---|---|---|---|---|---|
| **Investigator-sponsored studies (phase 2)** | | | | | |
| **12791 (Hoftijzer et al. 2009; Schneider et al 2012)** Netherlands | Does Nexavar restore radioiodine uptake in radioiodine resistant metastatic differentiated | Patients with progressive metastatic or locally advanced RAI-refractory DTC | 400 mg BID<br>26 weeks | Total: 32<br>Treated: 31 | Primary: Re-induction of RAI uptake at 26 weeks<br>Secondary:<br>radiological RR and |

| | | | | | |
|---|---|---|---|---|---|
| | thyroid carcinoma? | | | | the influence of bone metastases |
| **12636**<br>**(Ahmed et al. 2011)**<br>UK | Single centre, open-label pilot study of sorafenib in advanced metastatic thyroid cancer (MATiSSE) | Patients with metastatic advanced DTC and MTC considered unsuitable for treatment with RAI. | 400 mg BID<br>6 months | 34<br>19 with DTC<br>(15 with medullary thyroid carcinoma) | Primary: radiological RR<br>Secondary:<br>Best response at 3, 9 and 12 months;, biochemical RR,, PFS, OS, biomarker analyses, safety |
| **12192**<br>**(Gupta-Abramson et al. 2008; Brose et al 2009; Keefe et al 2011)**<br>United States | A Phase II Study of Sorafenib in Patients with Metastatic Thyroid Cancer (single centre) | Patients with metastatic, iodine-refractory thyroid carcinoma | 400 mg BID | 55<br>50 with DTC | Primary: RR (CR/PR)<br>Secondary: PFS, DOR, OS, PK, safety, RR and genetic characteristics |
| **100369**<br>**(Kloos et al. 2009)**<br>United States | Phase II Study of Sorafenib in Patients with Metastatic Thyroid Carcinoma | Patients had experienced radioactive iodine therapy failure or were not candidates to receive radioactive iodine. | 400 mg BID | 56<br>52 with DTC | Primary: Objective RR<br>Secondary: Response vs serum thyroglobulin; functional imaging; tumor genotype, signaling inhibition |
| **(Chen et al. 2011)**<br>China | Pilot study of sorafenib in Chinese patients with RAI refractory papillary thyroid cancer with pulmonary metastasis | Patients with iodine refractory metastatic papillary thyroid cancer (pulmonary metastases. | 200 mg BID | 9 | RR and PFS |
| ***(continued)*** | | | | | |
| **Number of patients**<br>**Phase 3**<br>**Phase 1 /2** | | | | **611**<br>417[a]<br>195 (170 with DTC) | |
| **Number of patients treated with sorafenib**[b]<br>**Phase 3**[b]<br>**Phase 1 /2** | | | | <br>**357 (207 + 150)**[b]<br>**194** | |
| **TOTAL** | | | | **551 (527 with DTC)** | |

Abbreviations: PFS = progression-free survival; OS = overall survival; TTP = time to progression; RR = response rate; DCR = disease control rate; DOR = duration of response; PK = pharmacokinetic FAS = full analysis set; DTC = Differentiated Thyroid Cancer ; RR = response rate; OS = overall survival; CR = complete response; PR = partial response; RAI = radioactive iodine

a: Of the 417 in the phase 3 study, 207 were in the sorafenib group and 210 were in the placebo group.

b: In Study 14295, 207 patients were randomized to sorafenib, and 150 patients randomized to placebo crossed over to sorafenib treatment following disease progression.

Study 12192 originally enrolled 30 patients. (original publication). The study design was Simon 2-stage; after 30 patients showed evidence of response, 25 more patients could be enrolled. The total number of patients enrolled was 55. (updated data)

## 2.3.2. Pharmacokinetics

Pharmacokinetics data were collected in the pivotal phase III study 14295.

## Study 14295

Study 14295 was a randomised, double-blind, placebo-controlled, multi-centre Phase 3 study to evaluate the efficacy and safety of sorafenib versus placebo in patients with locally advanced or

metastatic RAI-refractory differentiated thyroid carcinoma. Patients were randomised (stratified according to age [< 60 years, ≥ 60 years] and geographic region [North America, Europe, Asia]) in a 1:1 ratio.

***Methods***

Patients received sorafenib 400 mg per os (PO) (2 x 200 mg) twice daily (BID), continuous dosing (800 mg total daily dose) or a matching placebo.

A single blood sample was collected from each subject to characterise the exposure in the thyroid cancer population, and relate exposure to measures of efficacy and safety. The Pharmacokinetic (PK) assessment visit was to be scheduled after at least 14 days of uninterrupted/unmodified dosing of study drug. Pharmacokinetic sample collection was planned for Cycle 2 Day 1 of blinded study drug administration. If the subject did not have at least 14 days of uninterrupted/unmodified dosing of study, the PK sample could have been collected at a later cycle. If a dose interruption occurred within 14 days prior to the PK sample collection, no doses must have been missed for 3 days prior to the PK sample collection date, and no more than 3 doses could have been missed 4 to 14 days prior to the PK sample collection date. The sample was taken irrespective of time after dose, but time of dosing and sampling was collected.

Sorafenib (BAY 43-9006) concentrations were measured in plasma after protein precipitation with acetonitrile/methanol containing the internal standards followed by separation employing high-pressure liquid chromatography and tandem mass spectrometric detection (LC-MS/MS). Sparse plasma sorafenib concentration data were used to estimate steady state sorafenib exposure ($AUC_{(0-12),ss}$) using a concentration-exposure regression model developed using data from 218 patients in 7 previous studies. In this model, a concentration sample any time during the dosing interval was used to estimate $AUC_{0-12,ss}$ with a linear regression model.

When the model was validated (leave-one-out), 30% of the estimations were outside +/-30% of the AUC estimated with non-compartmental data, and 18% outside +/-40%.

The comparison with other diagnoses was performed using data from 25 other sorafenib trials, where the patients were administered sorafenib 400 mg BID, with samples collected following at least 7 days of uninterrupted dosing. $AUC_{(0-12),ss}$ values from the non-thyroid cancer pool were determined from either full concentration-time profiles using non-compartmental analysis, or sparse sampling using population PK analysis as described previously.

For the exposure-efficacy and exposure-safety analyses, sorafenib $AUC_{(0-12),ss}$ was binned into low ($1^{st}$ quartile, N = 28), medium ($2^{nd}$ and $3^{rd}$ quartiles, N = 57), and high ($4^{th}$ quartile, N = 28) exposure groups. $AUC_{(0-12),ss}$ ranges for the low, medium, and high exposure groups were 29.0-58.1, 59.2-101.8, and 101.9-186.2 mg*h/L. For efficacy, progression free survival was compared between the groups using Kaplan-Meier plots.

***Results***

113 of the 207 patients in the sorafenib arm were included in the PK analysis set. When the comparison with other diagnoses was performed, one thyroid cancer patient from another study was also included (n=114).

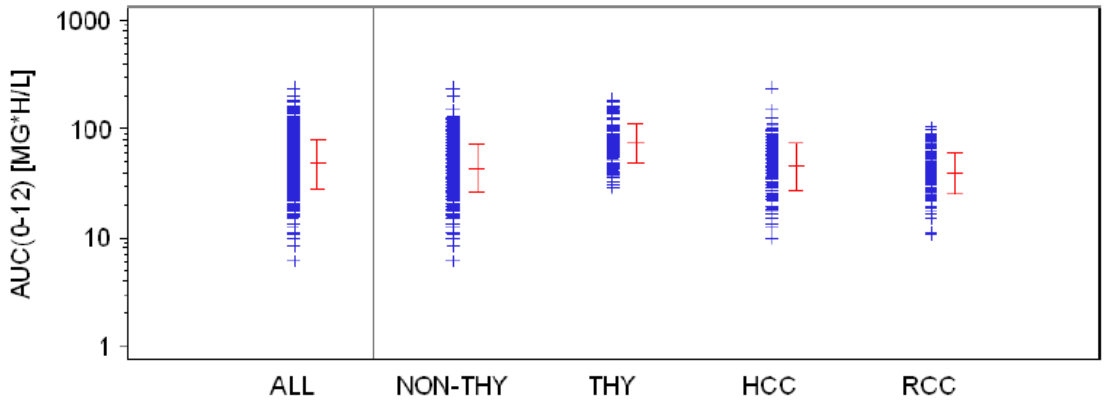
Table 4: Summary of statistics for steady-state plasma sorafenib $AUC_{(0-12),ss}$ in plasma (PK analysis set)

| Population | PK Parameter | N | Geometric Mean | Geometric CV (%) | Min | Max |
|---|---|---|---|---|---|---|
| Total PK Population | $AUC_{(0-12),ss}$ (mg*h/L) | 113 | 75.4 | 44.3 | 29.0 | 186.2 |

Previous examination of sorafenib exposure in Asian and Caucasian populations in different tumour types described the $AUC_{(0-12),ss}$ as 30% lower in the Asian population relative to the Caucasian population. In the current study, the mean $AUC_{(0-12),ss}$ was similar between Caucasian subjects and Asian subjects with thyroid cancer.

Comparison with other diagnoses (report PH-37268)

Mean $AUC_{0-12h,\ ss}$ for the PK population in the thyroid cancer study, calculated with the linear regression model, was 75 mg/lxh (CV 45%, range 29-186). This was higher than previous $AUC_{ss}$ data from other tumour types, renal cancer 39 mg/lxh (CV 45%, range 11-104) and hepatocellular cancer 45 mg/lxh (CV 52%, range 10-242).




ALL: Subjects with all tumor types.
NON-THY: Subjects with all tumor types except thyroid cancer.
THY: Subjects with thyroid cancer.
HCC = HCC subject pool.
RCC = RCC subject pool.
Each + symbol represents an individual subject's value. The red colored bars represent the mean and 95% CI. The number of subjects in each pool is listed in Table 3-2.
Source: Figure 7.4.1.1.1

Figure 1: Scatter-plot of steady-state plasma sorafenib $AUC_{(0-12),ss}$ from all tumour types, non-thyroid cancer, HCC, and RCC subject pools

Analysis of sorafenib Css Values

Additional analyses of sorafenib exposure in subjects with DTC have been completed to compare steady state concentration (Css) values in study 14295 to Css values in studies of other tumour types. In the analysis of Css values, concentration data from patients with thyroid cancer in study 14295 (N=113) and study 100561 (N=2) were compared to sorafenib concentrations from patients with either HCC (N=211) or RCC (N=151) in 20 clinical trials. The patients were similar in age, weight and height, and included primarily Caucasian (63-77%) or Asian (20-23%) patients. Geometric mean

(range) sorafenib concentration values for each tumor type and the ratio of the geometric mean values (90% CI) are presented below.

Table 5: Geometric mean sorafenib plasma concentrations (mg/L) for patients with thyroid cancer, HCC and RCC

| Statistics | THY Css (N=115) | HCC Css (N=211) | RCC Css (N=151) | Ratio of THY/HCC | Ratio of THY/RCC |
|---|---|---|---|---|---|
| Geometric mean (range) | 7.09 (1.88-20.3) | 3.94 0.673-18.4) | 3.13 (0.548-12.9) | | |
| Geometric LS-means (90% CI) | | | | 1.80 (1.62, 2.00) | 2.26 (2.02, 2.53) |

Note: THY=Thyroid cancer, HCC=Hepatocellular carcinoma, RCC=Renal carcinoma, LS means = least squares means, CI=Confidence interval

Geometric mean Css values for patients with thyroid cancer were 80% and 126% greater than Css values for subjects with HCC and RCC, respectively, confirming an elevation in sorafenib exposure in the DTC population predicted by the linear regression $AUC_{(0\ 12),ss}$ calculations.

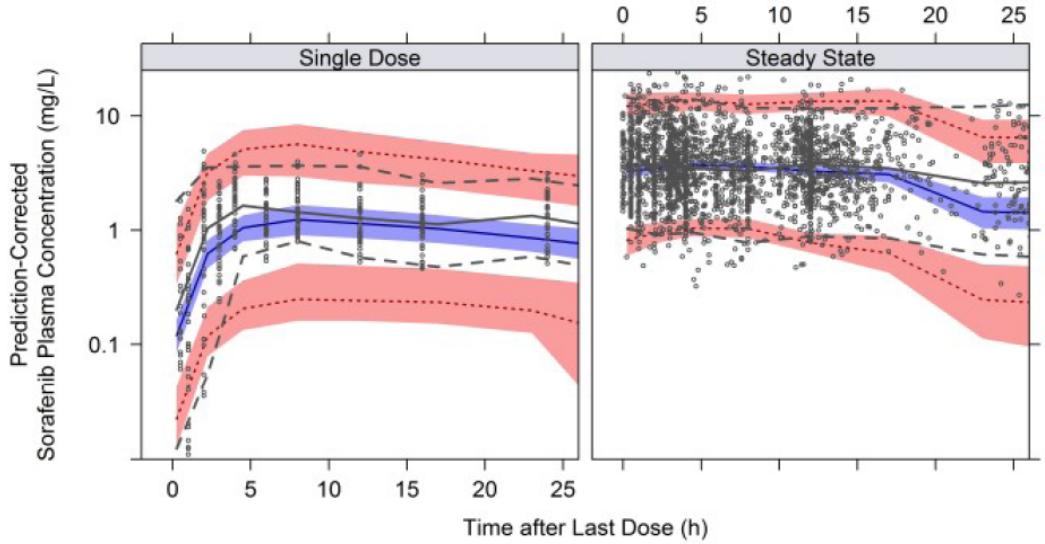
Population PK model (Report R-8977).

A population PK model was developed using sorafenib data from two Phase I studies in healthy volunteers and eight Phase II, III and IV studies in various tumour types to investigate if any subject factors or combination of factors could explain the elevated plasma sorafenib concentrations observed in study 14295.

The data set used for the modelling contained PK data from 648 men and 211 women (total of 3141 plasma concentrations), with a mean age of 61.2 years. The average body weight was 75 kg for men and 64 kg for women. The population of 859 subjects consisted of healthy volunteers (39 subjects), and patients with RCC (332 patients), HCC (332 patients) and thyroid cancer (156 patients). Race was classified as Asian (303 subjects) or non-Asian (556 subjects). The standard dosing regimen for all the studies used in the analysis was 400 mg bid, though on occasion dose adjustment was necessary following AEs. All data were used as long as the dose and the time of the dose were retrievable for each plasma concentration. The final structural PK model, which was used for the covariate search, consisted of an absorption part with 3 sequential transit compartments, and one central PK compartment with linear elimination.

The typical estimates of clearance (CL) and volume of distribution (V) were 8.08 L/h and 556 L, respectively. Covariates were identified in a stepwise covariate search that examined body weight, body mass index, race (Asian/non-Asian), gender, age, serum glutamic oxaloacetic transaminase (SGOT), serum glutamic pyruvic transaminase (SGPT), total bilirubin, alkaline phosphatase, lactate dehydrogenase (LDH), prothrombin time - international normalized ratio (PT-INR), creatinine clearance (CrCL), and comedication with CYP3A4 inducers, CYP3A4 inhibitors, UGT1A9 inhibitors, UGT1A9 inducers, or thyroxine. Subject covariates were tested on CL only, and initially co-treatment with thyroxine and female gender were identified as significant covariates leading to a reduction in clearance. Treatment with thyroxine was associated with a decrease in clearance of 43.6%, while females had 21.2% lower clearance compared to males (the typical estimate of clearance for males was 9.44 L/h and for females 7.45 L/h). This gender effect on CL implies that females are predicted to have on average a 26.7% higher exposure than males. Although thyroxine treatment was initially identified as a significant covariate, 98% of the subjects treated with thyroxine were from one study, study 14295. The study 14295 effect on CL was retained in the final model while the thyroxine effect on CL was dropped.

The figure below shows the visual predictive check of the final covariate model of all the data used for modelling.




Note: The dots are prediction-corrected data. Black lines indicate observed median (solid line), 5th and 95th percentiles (dashed lines) of the observed data. The shaded areas indicate the 95% confidence intervals around the prediction-corrected median (solid blue line), and 5th and 95th percentiles of the prediction (red dashed lines).

Figure 2: Visual predictive check of the final covariate model

The table below compares the predicted steady-state exposure by tumour type using the final population PK model.

Table 6: Summary statistics of individual predicted steady-state exposure by tumour type

| | | $AUC_{(0\text{-}12),ss}$ (mg*h/L) | | | Cavg,ss (mg/L) | | |
|---|---|---|---|---|---|---|---|
| Cancer Type | N | Geometric Mean | Geometric Mean CV (%) | Range | Geometric Mean | Geometric Mean CV (%) | Range |
| HCC | 332 | 48.9 | 50.3 | 9.8-247 | 4.08 | 50.3 | 0.816-20.6 |
| RCC | 332 | 41.1 | 34.5 | 13.1-118 | 3.43 | 34.5 | 1.09-9.8 |
| Thyroid | 156 | 95.7 | 32.1 | 46.4-205 | 7.97 | 32.1 | 3.87-17.1 |
| All | 820 | 51.8 | 53.3 | 9.8-247 | 4.32 | 53.3 | 0.816-20.6 |

The CL value for subjects in study 14295 was 49.4% lower than in other trials containing subjects with non-thyroid tumours, which implied that subjects in study 14295 were predicted to have a 103% higher exposure compared to subjects in trials with tumour types such as HCC and RCC.

PK/PD analysis (report PH-37331)

Progression free survival was numerically higher in the high-exposure group (median PFS 509 days, 95% CI 271-561) compared with the medium (294 days, 95% CI 231-393) and low (278 days; 95% CI 162-686) exposure groups. The 95% confidence intervals were however overlapping between the groups.

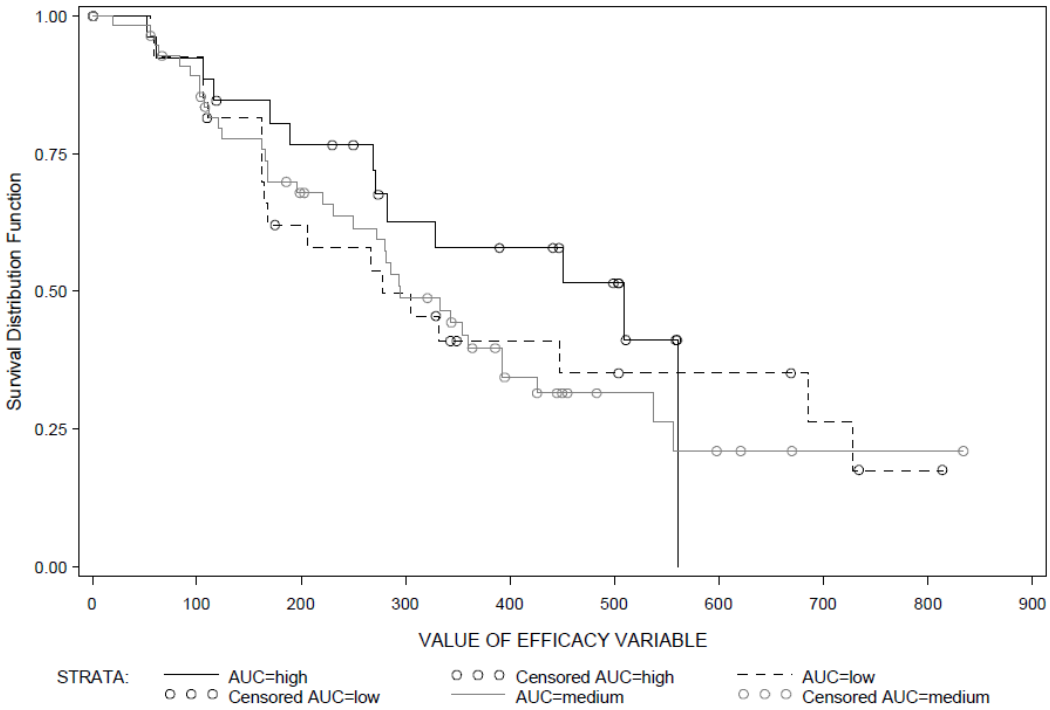



Figure 3: Progression-free survival by exposure (AUC) groups: Central assessment including clinical progression due to bone irradiation (PK analysis set)

## 2.3.3. Discussion on clinical pharmacology

In the pivotal phase III study 14295, a single blood sample was collected from each patient to characterise the exposure in the thyroid cancer population, and relate exposure to measures of efficacy and safety. Estimating AUC using the linear regression model established based on data from other diagnoses was considered problematic if sorafenib clearance is different between diagnoses. In addition, the AUC for other populations were estimated with different methods (non-compartment analyses using full concentration-time curves, or population PK modelling), which could well bias the comparisons between diagnoses. Furthermore, 45 % of the sorafenib treated population had a dose interruption or modification and was not included in the PK analysis, meaning that the PK population was a population that tolerated the drug well and may not be representative for the whole study population.

Because of these limitations, the MAH provided additional analyses of sorafenib exposure in patients with DTC: reanalysis of $C_{ss}$-values and population PK model.

The population PK analysis was in general well performed and reported. The MAH explored possible covariates associated with the increased sorafenib exposure in the population PK analysis. Thyroxine treatment and disease (study 14295, DTC subjects) were identified as significant covariates on clearance. However, the effect on clearance could not be separated due to the high correlation (nearly 100%) between the two covariates. The negative results of the covariate analysis for co-medication with CYP3A4 and UGT1A9 inhibitors/inducers were not considered an evidence of a non-significant effect on clearance since concomitant medication was evaluated as a binary variable (yes/no) with no information about doses of concomitant drugs, timing of doses or whether the patient has been on the concomitant drug for a sufficient time period at the time of blood sampling. With regards to the final model used in the population PK analysis, the goodness-of-fit plots revealed a reasonable fit for steady state data. A clear under prediction was seen for single dose data.

Overall, the additional analyses confirmed the finding that mean sorafenib exposure in patients with DTC is higher than that observed in other tumour types (95-126%). However, these analyses suggested an even higher exposure in DTC than indicated according to the linear regression model (68-92%).

In relation to the PK/PD analysis, using only data from patients who tolerated the starting dose (2x400 mg) without dose interruptions or dose adjustments also confounded the selection of patients. In addition, dose adjustments or interruptions after the PK sampling day were not taken into account in the analysis, which was considered problematic. No adjustments with respect to prognostic markers have been made. Therefore, the provided analysis of exposure versus efficacy was considered of very limited value.

Overall, the CHMP concluded that thyroid cancer patients on average have a lower sorafenib clearance and/or higher bioavailability than RCC and HCC patients. The steady-state concentrations of sorafenib administered at 400 mg bid evaluated in DTC, RCC and HCC patients showed that the highest mean concentration was observed in DTC patients (approximately twice that observed in patients with RCC and HCC), though variability was high for all tumour types (see section 5.2 of the SmPC). In clinical practice, however, dose reduction based on side effects is applied, which in the long run probably will adjust the exposure to similar levels as in the other diagnoses. The MAH has performed additional analysis of clinical data (metabolite levels, plasma levels of thyroid hormones) as well as a new *in vitro* study (see non-clinical aspects), but has not been able to explain the higher sorafenib exposure in thyroid cancer patients compared to patients with HCC or RCC. The MAH is recommended to undertake further PK studies aiming at clarifying the grounds for the increased exposure from a mechanistic perspective. A clinical study with full PK profiling before and after initiation of levothyroxin treatment could clarify whether it is the hyperthyroidism that leads to higher drug exposure, as well as if a higher exposure is due to higher bioavailability or lower clearance. Further investigations on the underlying biological mechanism are also encouraged.

### 2.3.4. Conclusions on clinical pharmacology

A higher exposure was observed in DTC patients compared to other RCC and HCC patients. The increase is estimated to be 95-126%, which is now reflected in the SmPC as a mean exposure twice as that observed in RCC and HCC. This higher exposure in these DTC patients probably contributes to a higher rate of adverse events, but in the clinic it is handled with dose reductions based on toxicity which was considered appropriate by the CHMP.

In addition, the CHMP recommends the MAH to undertake further PK studies aiming at clarifying the grounds for the increased exposure from a mechanistic perspective as such data might have a bearing for other interactions.

## *2.4. Clinical efficacy*

### 2.4.1. Main study

**Pivotal study 14295 “Decision”**

Study 14295 was a double-blind, randomised phase III study evaluating the efficacy and safety of sorafenib compared to placebo in locally advanced/metastatic Radioactive Iodine (RAI)-refractory Differentiated Thyroid Cancer (DTC).

## *Methods*

## *Study participants*

Inclusion criteria specified that only patients with DTC (papillary, follicular, Hürthle cell, and poorly differentiated carcinoma) with disease progression within 14 months of enrolment could be included in the study.

Another key inclusion criterion was that only patients refractory to RAI could be enrolled.

The definition of DTC refractory to RAI was defined as follows: Patients had to have a target lesion (per RECIST v1.0 criteria) with no iodine uptake on a diagnostic or therapeutic whole body post-RAI scan performed under conditions of a low iodine diet and adequate thyroid stimulating hormone (TSH) elevation or recombinant human TSH (rhTSH) stimulation.

Certain patients whose tumours had iodine uptake were also eligible for participation. They included the following categories of patients:

- Patients who have some iodine uptake, who had RAI treatment ≥3.7 GBq [≥100 mCi] (performed under conditions of a low iodine diet and adequate TSH elevation or rhTSH stimulation) within the last 16 months, and progression of target lesions after RAI;

or

- Patients who have some iodine uptake, who have had multiple RAI treatments, whose last RAI treatment was >16 months ago, and who had progression after each of two RAI treatments (≥3.7 GBq [≥100 mCi] each) that were done within 16 months of each other and which were each performed under the conditions of a low iodine diet and adequate TSH elevation or rhTSH stimulation;

or

- Any individual patients who had received RAI treatments with a cumulative dose ≥22.2 GBq (≥600 mCi).

Patients must have had an Eastern Cooperative Oncology Group (ECOG) performance status ≤2; adequate thyroid-stimulating hormone suppression (< 0.5 mU/L); and adequate bone marrow, liver, and renal function.

Patients were excluded if they had been treated for cancer with any licensed or investigational tyrosine kinase inhibitors; monoclonal antibodies that target vascular endothelial growth factor (VEGF) or VEGF receptors, or other targeted agents; anti-cancer treatment for thyroid carcinoma using cytotoxic chemotherapy agents (except for prior low-dose chemotherapy for radiosensitisation), or thalidomide or any of its derivatives.

## *Treatments*

Treatments consisted in matching placebo or sorafenib 400 mg twice daily. Study medication was administered on a continuous basis until disease progression, unacceptable toxicity, noncompliance, or withdrawal of consent. A cycle of therapy was defined as 28 days.

Dose interruption and reductions were allowed under certain circumstances.

Patients were allowed to be unblinded and receive open label sorafenib after experiencing a disease progression at the investigator's discretion, regardless of their initial blinded treatment assignment.

## *Objectives*

The primary objective of the study was to compare treatment groups in terms of progression free survival (PFS). The targeted improvement of 3.3 months in median PFS in the sorafenib arm (over the assumed placebo median PFS of 6 months) was selected.

The secondary objectives were to compare the treatment groups in terms of overall survival, time to progression, disease control rate, response rate, duration of response, safety, and exposure of sorafenib as measured by $AUC_{0-12}$.

The exploratory objectives were assessment of health utility values, health-related quality of life, biomarker analysis and PFS after unblinding until further disease progression.

## *Outcomes / endpoints*

Clinical efficacy

The primary efficacy endpoint was progression free survival (PFS).

PFS was defined as the time from date of randomisation to date of first observed disease progression (radiological as determined by central radiological review or clinical progression due to bone lesions that required external radiation, whichever was earlier) or death (due to any cause) if it occurred before progression was documented.

The secondary efficacy endpoints were: Overall survival (OS), Time to progression (TTP), disease control rate (DCR), response rate (RR), duration of response (DOR).

OS was defined as the time from date of randomisation to date of death due to any cause.

TTP was defined by the same rule as PFS, except that death did not count as an event.

DCR was defined as the proportion of patients whose best response was complete response (CR), partial response (PR), or stable disease (SD) that was achieved before or at the date of unblinding. Per RECIST 1.0, CR and PR were to be confirmed by another scan at least 4 weeks later. SD had to be documented at least 4 weeks after baseline.

RR was defined as the proportion of patients whose best response was CR or PR that was achieved before or at the date of unblinding. Per RECIST 1.0, CR and PR were to be confirmed by another scan at least 4 weeks later.

DOR was defined as the time from the first documented objective response of PR or CR, whichever was noted earlier, to disease progression or death (if death occurred before progression was documented).

The exploratory efficacy variables were: Health Utility Values, Health related quality of life (HRQoL), PFS after unblinding until further disease progression in subjects who had received sorafenib and continue sorafenib treatment, PFS after unblinding until further disease progression in subjects who had received placebo and crossover to sorafenib treatment.

SPFS was defined as time from re-baseline until new progression or death, whichever came first, during or after open-label treatment with sorafenib. For independent review the last tumour assessment before start of open-label treatment period was used as rebaseline. Local investigator flagged in the database the tumour images that were used as new baseline for the open-label period. Secondary PFS was analysed descriptively.

Health Utility Values were measured using the EuroQol-5 Dimensions (EQ-5D), and to analyse Health Related Quality of Life (HRQoL), the EQ-5D and the Functional Assessment of Cancer Therapy General Version 4.0 (FACT-G) were used.

For the EQ-5D, higher scores represent better health status. A change of at least 0.10 to 0.12 points on the EQ-5D index was considered clinically meaningful (using ECOG PS as the anchor). For EQ-5D VAS questionnaire a change of at least 7 points on the VAS was considered as clinically meaningful.

The total score of the FACT-G ranged from 0 to 108; the higher the score, the better the QoL. Important difference for the FACT-G total score was 3 to 7 points.

Clinical pharmacology:

Sparse plasma sorafenib concentration data were collected for pharmacokinetic analysis. Results of this analysis are reported under section 2.3.2.

### *Sample size*

Sample size was based on the primary efficacy endpoint PFS. Assuming a one-sided alpha of 0.01, a power of 90%, 55.5% increase in median time to PFS, and a randomisation ratio of 1:1 between the experimental and the control arm, 267 events were required. 420 subjects had to be enrolled to observe 267 events after approximately 29 months.

### *Randomisation*

Patients were randomised via IVRS using a 1:1 allocation of patients to either of sorafenib or placebo.

Patients were stratified at randomisation according to:

- Age (< 60 years versus ≥ 60 years)
- Geographical region (North America versus Europe versus Asia)

### *Blinding (masking)*

Blinded independent central review (BICR) was undertaken: The first examination (screening) was interpreted without knowledge of future time points and an electronic imaging CRF (eICRF) was completed. Only after the screening eICRF was locked and submitted the radiologist proceeded to the next imaging time point. The process was repeated for every time point until completion of the primary radiology review for a given case.

Patients were allowed to be unblinded and receive open label sorafenib after experiencing a disease progression.

### *Statistical methods*

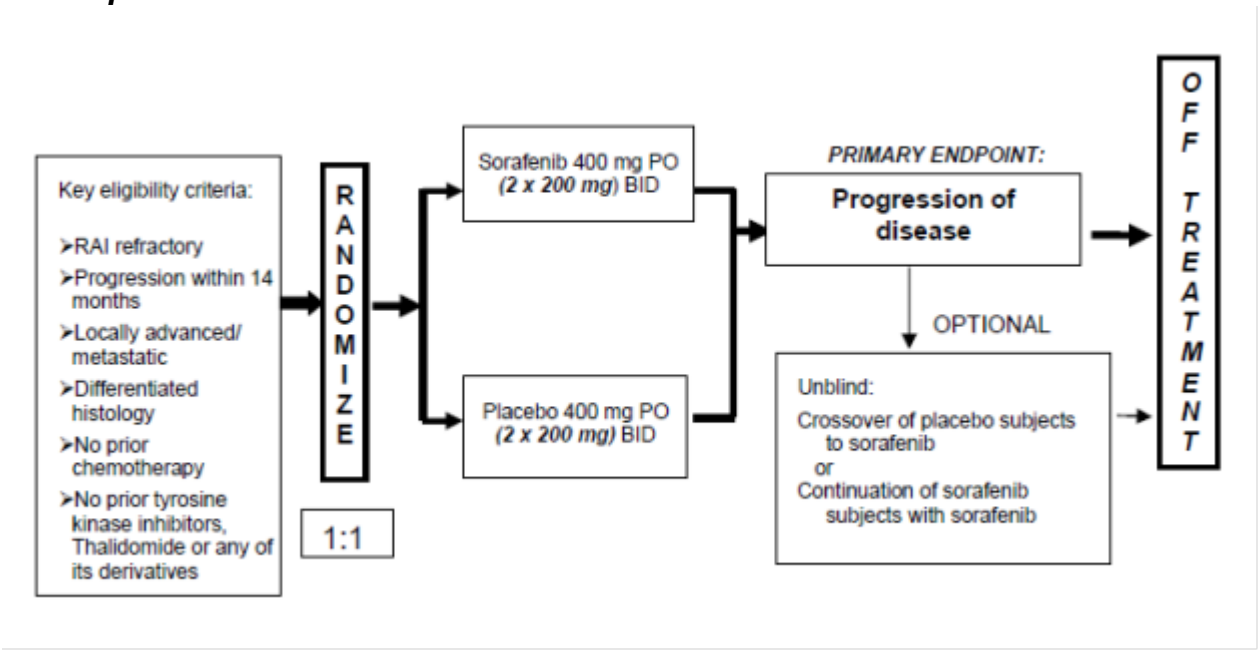
The primary population for efficacy analysis was the full analysis set (FAS) population, which was defined as all randomised patients. The FAS was identical with the intent to treat (ITT) analysis set.

The analysis for PFS was to be performed when approximately 267 subjects had a PFS event per central assessment. The two treatment groups (sorafenib and placebo) were compared using a stratified one-sided log rank test with an overall alpha of 0.01 stratified by the same stratification factors as used for randomisation.

The secondary efficacy variables OS, TTP, RR, and DCR were tested using a one-sided significance level of 0.025 ($\alpha = 0.025$).

## *Results*

### *Participant flow*




A total of 556 subjects were screened for inclusion into the study; 137 subjects failed screening for the following reasons: Protocol violation in 124 (22.3%) subjects, the majority of which were inclusion/exclusion criteria violations; Consent withdrawn by 9 (1.6%) subjects; AEs in 4 (0.7%) subjects.

A total of 419 subjects were randomised to double-blind treatment; 209 were randomised to receive sorafenib and 210 were randomised to receive placebo. Since 2 subjects were erroneously randomised the first time to sorafenib, 207 sorafenib subjects and 210 placebo subjects were considered valid for the FAS.

Table 7: Subject disposition - double-blind treatment (FAS)

| | Sorafenib N = 207 n (%) | Placebo N = 210 n (%) | Total N = 417 n (%) |
|---|---|---|---|
| **Valid for FAS** | **207 (100.0%)** | **210 (100.0%)** | **417 ( 100%)** |
| Not treated | 0 | 1 ( 0.5%) | 1 ( 0.2%) |
| **Started double-blind treatment** | **207 (100.0%)** | **209 ( 99.5%)** | **416 ( 99.8%)** |
| Ongoing with double-blind treatment | 43 ( 20.8%) | 23 ( 11.0%) | 66 ( 15.8%) |
| **Discontinued double-blind treatment without unblinding** | **75 ( 36.2%)** | **22 ( 10.5%)** | **97 ( 23.3%)** |
| Adverse event | 31 ( 15.0%) | 5 ( 2.4%) | 36 ( 8.6%) |
| Disease progression, recurrence or relapse | 20 ( 9.7%) | 3 ( 1.4%) | 23 ( 5.5%) |
| Investigator decision, not protocol driven | 1 ( 0.5%) | 1 ( 0.5%) | 2 ( 0.5%) |
| Noncompliance with study medication | 1 ( 0.5%) | 0 | 1 ( 0.2%) |
| Progression by clinical judgment | 1 ( 0.5%) | 0 | 1 ( 0.2%) |
| Consent withdrawn | 12 ( 5.8%) | 10 ( 4.8%) | 22 ( 5.3%) |
| Lost to follow-up | 3 ( 1.4%) | 1 ( 0.5%) | 4 ( 1.0%) |
| Death | 6 ( 2.9%) | 2 ( 1.0%) | 8 ( 1.9%) |
| **Entered open-label treatment period [a]** | **89 ( 43.0%)** | **164 ( 78.1%)** | **253 ( 60.7%)** |

FAS = full analysis set.

[a] Per protocol, prior to starting open-label treatment, subjects had to experience disease progression per the investigators' assessments. A total of 253 subjects entered the open-label period, and 55 sorafenib subjects and 150 placebo subjects received treatment with sorafenib in the open-label period.

Table 8: Subject disposition - open-label treatment with sorafenib (subjects who switched to open-label treatment) (FAS)

| | Original (randomized) treatment group [a] | | |
|---|---|---|---|
| | Sorafenib N = 207 n (%) | Placebo N = 210 n (%) | Total N = 417 n (%) |
| **Entered open-label treatment period [b]** | **89 ( 43.0%)** | **164 ( 78.1%)** | **253 ( 60.7%)** |
| **Unblinded, but never treated with open-label sorafenib** | **34 ( 16.4%)** | **14 ( 6.7%)** | **48 ( 11.5%)** |
| Missing | 0 | 1 ( 0.5%) | 1 ( 0.2%) |
| Adverse event | 3 ( 1.4%) | 4 ( 1.9%) | 7 ( 1.7%) |
| Consent withdrawn | 1 ( 0.5%) | 2 ( 1.0%) | 3 ( 0.7%) |
| Death | 1 ( 0.5%) | 3 ( 1.4%) | 4 ( 1.0%) |
| Disease progression, recurrence or relapse | 28 ( 13.5%) | 4 ( 1.9%) | 32 ( 7.7%) |
| Progression by clinical judgement | 1 ( 0.5%) | 0 | 1 ( 0.2%) |
| **Started open-label treatment with sorafenib** | **55 ( 26.6%)** | **150 ( 71.4%)** | **205 ( 49.2%)** |
| **Discontinued open-label treatment** | **43 ( 20.8%)** | **97 ( 46.2%)** | **140 ( 33.6%)** |
| Adverse event | 5 ( 2.4%) | 24 ( 11.4%) | 29 ( 7.0%) |
| Consent withdrawn | 4 ( 1.9%) | 13 ( 6.2%) | 17 ( 4.1%) |
| Death | 2 ( 1.0%) | 10 ( 4.8%) | 12 ( 2.9%) |
| Disease progression, recurrence or relapse | 32 ( 15.5%) | 49 ( 23.3%) | 81 ( 19.4%) |
| Lost to follow-up | 0 | 1 ( 0.5%) | 1 ( 0.2%) |
| **Ongoing with open-label treatment** | **12 ( 5.8%)** | **53 ( 25.2%)** | **65 ( 15.6%)** |

FAS = full analysis set.

[a] Following unblinding, subjects who had been randomized to receive sorafenib may have continued to receive sorafenib. Subjects who received placebo may have crossed over to sorafenib. Decisions about continuing study medication were made at the discretion of the investigators.

[b] Subjects terminated double-blind period with unblinding. Unblinding only occurred if a subject experienced progression or for a medical emergency. Three subjects were prematurely unblinded; see Section 8.2 for details.

Following discontinuation of treatment (either from the double-blind or open-label period), subjects were followed for safety until 30 days after end of treatment or until the end of study, and further followed every 3 months for survival and any post-study anti-cancer therapy until the final analysis of OS was performed.

## Recruitment

Study period: First subject, first visit: 15 October 2009

Primary completion date: 31 August 2012

Among 556 subjects enrolled, 337 were enrolled in Europe, 97 in North America and 122 in Asia.

## Conduct of the study

There were altogether 9 amendments, mainly of clarifying nature and three of the amendments were locally valid only (JPN, UK and AU). Amendment 9 (after data analysis) opened the study for cross-over prior to progression.

## Baseline data

Table 9: Demographic and baseline characteristics (FAS)

| Characteristic | Sorafenib N = 207 | Placebo N = 210 |
|---|---|---|
| **Sex** [n, (%)] | | |
| Male | 104 ( 50.2%) | 95 ( 45.2%) |
| Female | 103 ( 49.8%) | 115 ( 54.8%) |
| **Age** (years) at enrollment | | |
| Mean (± SD) | 61.5 (± 11.2) | 62.0 (± 11.7) |
| Median (range) | 63.0 (24 – 82) | 63.0 (30 – 87) |
| **Age group** (years) | | |
| <60 | 80 ( 38.6%) | 81 ( 38.6%) |
| ≥60 | 127 ( 61.4%) | 129 ( 61.4%) |
| **Race** | | |
| White | 123 ( 59.4%) | 128 ( 61.0%) |
| Black | 6 ( 2.9%) | 5 ( 2.4%) |
| Asian | 47 ( 22.7%) | 52 ( 24.8%) |
| Hispanic | 2 ( 1.0%) | 2 ( 1.0%) |
| Missing or uncodable | 29 ( 14.0%) | 23 ( 11.0%) |
| **Ethnic group** | | |
| Hispanic or Latino | 17 ( 8.2%) | 30 ( 14.3%) |
| **Geographic region** | | |
| North America | 36 ( 17.4%) | 36 ( 17.1%) |
| Europe | 124 ( 59.9%) | 125 ( 59.5%) |
| Asia | 47 ( 22.7%) | 49 ( 23.3%) |
| **Baseline thyroglobulin level** (ng/mL) | | |
| Mean | 4997 | 4729 |
| Median | 605 | 440 |
| Range | 0.9 - 30000 | 0.9 - 30000 |
| **Subjects with hypoparathyroidism**, n (%) | 14 ( 6.8%) | 21 ( 10.0%) |

| | | |
|---|---|---|
| **Locally Advanced vs. Metastases** | | |
| Locally advanced | 7 ( 3.4%) | 8 ( 3.8%) |
| Distant Metastases | 200 ( 96.6%) | 202 ( 96.2%) |
| **Clinical/radiographic status at entry** | | |
| Stable disease | 5 ( 2.4%) | 4 ( 1.9%) |
| Progressive disease | 202 ( 97.6%) | 206 ( 98.1%) |
| **Number of Target or Non-Target Lesions at Screening per investigator** | | |
| Mean | 5.8 | 5.7 |
| Median | 6.0 | 5.0 |
| **Size (sum of longest diameter, mm) of target lesions** at screening per investigator | | |
| Mean | 88.30 | 81.84 |
| Median | 75.45 | 65.00 |
| **Site of target / nontarget lesions** | | |
| Lung | 178 ( 86.0%) | 181 ( 86.2%) |
| Lymph node | 113 ( 54.6%) | 101 ( 48.1%) |
| Bone | 57 ( 27.5%) | 56 ( 26.7%) |
| Pleura | 40 ( 19.3%) | 24 ( 11.4%) |
| Head/neck | 33 ( 15.9%) | 34 ( 16.2%) |
| **Time since diagnosis** of thyroid carcinoma (weeks) | | |
| Mean | 357 | 398 |
| Median | 288 | 291 |
| **Histology per investigator assessment**[a] | | |
| Follicular carcinoma, thyroid | 44 ( 21.3%) | 55 ( 26.2%) |
| Papillary carcinoma (including follicular variant of pap) | 137 ( 66.2%) | 141 ( 67.1%) |
| Hurthle cell adenocarcinoma | 24 ( 11.6%) | 14 ( 6.7%) |
| missing | 2 ( 1.0%) | 0 ( 0.0%) |
| **Histology (central assessment)** | | |
| Papillary | 118 ( 57.0%) | 119 ( 56.7%) |
| Follicular | 50 ( 24.2%) | 56 ( 26.7%) |
| Follicular - Hürthle cell | 37 ( 17.9%) | 37 ( 17.6%) |
| Follicular - Other | 12 ( 5.8%) | 19 ( 9.0%) |
| Follicular - Missing | 1 (0.5) | 0 (0) |
| Poorly differentiated, incl. insular | 24 ( 11.6%) | 16 ( 7.6%) |
| Carcinoma, NOS | 0 ( 0.0%) | 3 ( 1.4%) |
| Medullary carcinoma | 0 ( 0.0%) | 1 ( 0.5%) |
| Oncocytic carcinoma | 2 ( 1.0%) | 0 ( 0.0%) |
| Well differentiated thyroid carcinoma | 2 ( 1.0%) | 1 ( 0.5%) |
| Non-diagnostic | 6 ( 2.9%) | 6 ( 2.9%) |
| Non-thyroid carcinoma | 0 ( 0.0%) | 1 ( 0.5%) |
| Missing | 7 ( 3.4%) | 8 ( 3.8%) |

Table 10: Prior anti-cancer therapy and surgical therapeutic procedures (FAS)

| Number (%) of subjects with any prior: | Sorafenib N = 207 | Placebo N = 210 | Total N= 417 |
|---|---|---|---|
| Thyroidectomy [a] | 207 (100.0%) | 208 ( 99.0%) | 415 ( 99.5%) |
| RAI | 207 (100.0%) | 210 (100.0%) | 417 (100.0%) |
| Surgical therapeutic procedure | 204 ( 98.6%) | 204 ( 97.1%) | 408 ( 97.8%) |
| Locoregional or EBRT [b] | 83 ( 40.1%) | 91 ( 43.3%) | 174 ( 41.7%) |
| Systemic anticancer therapy [c] | 7 ( 3.4%) | 6 ( 2.9%) | 13 ( 3.1%) |

EBRT = external beam radiation therapy; FAS = full analysis set; RAI = radioactive iodine.

[a] Thyroidectomy was defined as partial or total thyroidectomy, lobectomy, or isthmusectomy of the thyroid gland.

[b] Locoregional therapy or EBRT was defined as any kind of prior radiotherapy or radiofrequency ablation. For a summary of prior radiotherapies, see Table 14.1.2/4.

[c] For an overview of prior systemic anticancer therapies, see Table 14.1.2/5. Table 14.1.2/6 lists the subjects with prior systemic anticancer therapy and the details of the therapies

There was no systematic collection of data about the presence or absence of thyroid cancer related symptoms in the case report forms at baseline, during the study and at the time of progression.

The MAH has retrospectively reviewed MedDRA preferred terms considered likely to be thyroid cancer related: dyspnea, dyspnea exertional, pleural effusion, dysphagia, hemoptysis, chest pain, bone pain, tumour pain, spinal cord compression, cough, obstructive airways disorder, pulmonary embolism.

Overall, 84 (20.1%) subjects had a medical history finding reported using terms that are likely to be related to thyroid cancer. There were 12 subjects (2.9%), who experienced a new AE or experienced a worsening of an existing medical history finding during the screening period (up to 28 days). In addition 34% were taking analgesic or anti-inflammatory medications.

## Numbers analysed

207 sorafenib patients and 210 placebo patients were included in the FAS.

## Outcomes and estimation

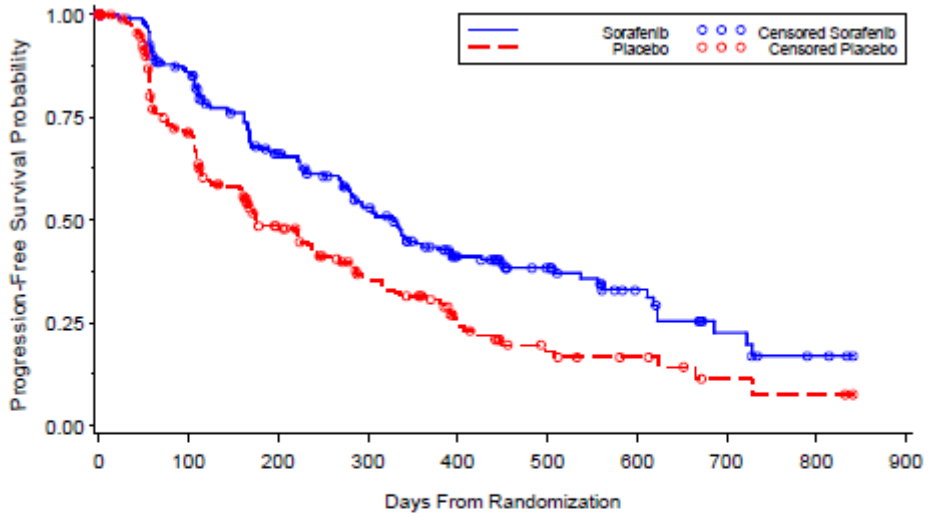
### Progression Free Survival (PFS)

Table 11: Progression-free survival, central assessment (FAS)

| | Sorafenib (N = 207) | Placebo (N = 210) |
|---|---|---|
| Number of subjects (%) with event | 113 (54.6%) | 137 (65.2%) |
| Number of subjects (%) censored | 94 (45.4%) | 73 (34.8%) |
| Median PFS (days) [95% CI] | 329 [278; 393] | 175 [160; 238] |
| Median PFS (months) [a] | 10.8 | 5.8 |
| PFS range (days; without censored values) | 20 - 728 | 14 - 728 |
| Hazard ratio (sorafenib/placebo) | 0.587 | |
| 95% CI for hazard ratio | [ 0.454; 0.758] | |
| p-value (one-sided from stratified log-rank test) | <0.0001 | |

CI = confidence interval; FAS = full analysis set; PFS = progression-free survival.
[a] Months = days/30.4.

The vast majority of patients in both treatment groups were censored due to no progression or death up to the last tumour assessment (even though tumour assessment was performed post baseline) (sorafenib, 72 (34.8%) subjects; placebo, 64 (30.5%) subjects).




Patients at Risk

| | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| Sorafenib | 207 | 157 | 110 | 81 | 49 | 33 | 18 | 8 | 3 |
| Placebo | 210 | 133 | 76 | 47 | 25 | 12 | 8 | 3 | 2 |

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Figure 4: Kaplan-Meier curve for PFS

Table 12: Sensitivity analyses of PFS (FAS)

| | Sorafenib N = 207 | Placebo N = 210 |
|---|---|---|
| **PFS – investigators' assessments** | | |
| Number of subjects (%) with event | 140 (67.6%) | 184 (87.6%) |
| Number of subjects (%) censored | 67 (32.4%) | 26 (12.4%) |
| Median PFS [95% CI], days | 330 [280; 360] | 165 [119; 175] |
| Median PFS, months [a] | 10.8 | 5.4 |
| Range (without censored values), days | 20 – 846 | 13 - 728 |
| HR (sorafenib/placebo) | 0.485 | |
| 95% CI for hazard ratio | [0.386; 0.609] | |
| p-value (one sided from stratified log-rank test) | <0.0001 | |
| **PFS – investigators' assessments; radiological progression only** | | |
| Number of subjects (%) with event | 126 (60.9%) | 164 (78.1%) |
| Number of subjects (%) censored | 81 (39.1%) | 46 (21.9%) |
| Median PFS [95% CI], days | 338 [305; 393] | 174 [162; 224] |
| Median PFS, months [a] | 11.1 | 5.7 |
| Range (without censored values), days | 20 - 846 | 13 - 728 |
| Hazard ratio (sorafenib/placebo) | 0.478 | |
| 95% CI for hazard ratio | [0.375; 0.608] | |
| p-value (one sided from stratified log-rank test) | <0.0001 | |
| **PFS – central assessment; radiological and all clinical progression** | | |
| Number of subjects (%) with event | 115 (55.6%) | 145 (69.0%) |
| Number of subjects (%) censored | 92 (44.4%) | 65 (31.0%) |
| Median PFS [95% CI], days | 326 [278; 378] | 169 [125; 224] |
| Median PFS, months [a] | 10.7 | 5.6 |
| Range (without censored values), days | 20 - 728 | 14 - 728 |
| Hazard ratio (sorafenib/placebo) | 0.567 | |
| 95% CI for hazard ratio | [0.441; 0.729] | |
| p-value (one sided from stratified log-rank test) | <0.0001 | |
| **PFS – central assessment; radiological progression only** | | |
| Number of subjects (%) with event | 108 (52.2%) | 131 (62.4%) |
| Number of subjects (%) censored | 99 (47.8%) | 79 (37.6%) |
| Median PFS [95% CI], days | 333 [283; 426] | 200 [162; 262] |
| Median PFS, months [a] | 10.9 | 6.6 |
| Range (without censored values), days | 20 - 728 | 20 - 728 |
| Hazard ratio (sorafenib/placebo) | 0.584 | |
| 95% CI for hazard ratio | [0.449; 0.759] | |
| p-value (one sided from stratified log-rank test) | <0.0001 | |

CI = confidence interval; FAS = full analysis set; HR = hazard ratio; PFS = progression-free survival.
[a] Months = days/30.4.
Median and 95% CIs computed using Kaplan-Meier estimates.

## Overall Survival (OS)

Table 13: Overall survival (FAS – data cut-off 31 May 2013)

| | Sorafenib (N = 207) | Placebo (N = 210) |
|---|---|---|
| Number of subjects (%) with event | 66 (31.9%) | 72 (34.3%) |
| Number of subjects (%) censored | 141 (68.1%) | 138 (65.7%) |
| Median overall survival (days) | Value could not be estimated [a] | 1110 |
| Range (days, including censored values) | (54 – 1283) [b] | (1 – 1268) [b] |
| Range (days, without censored values) | 57 - 967 | 26 - 1110 |
| Hazard ratio (sorafenib/placebo): uncorrected | 0.884 | |
| 95% Confidence Interval for hazard ratio: uncorrected | [0.633; 1.236] | |
| p-value (one-sided from stratified log-rank test): uncorrected | 0.2359 | |

[a] value could not be estimated due to censored data.
[b] censored observation

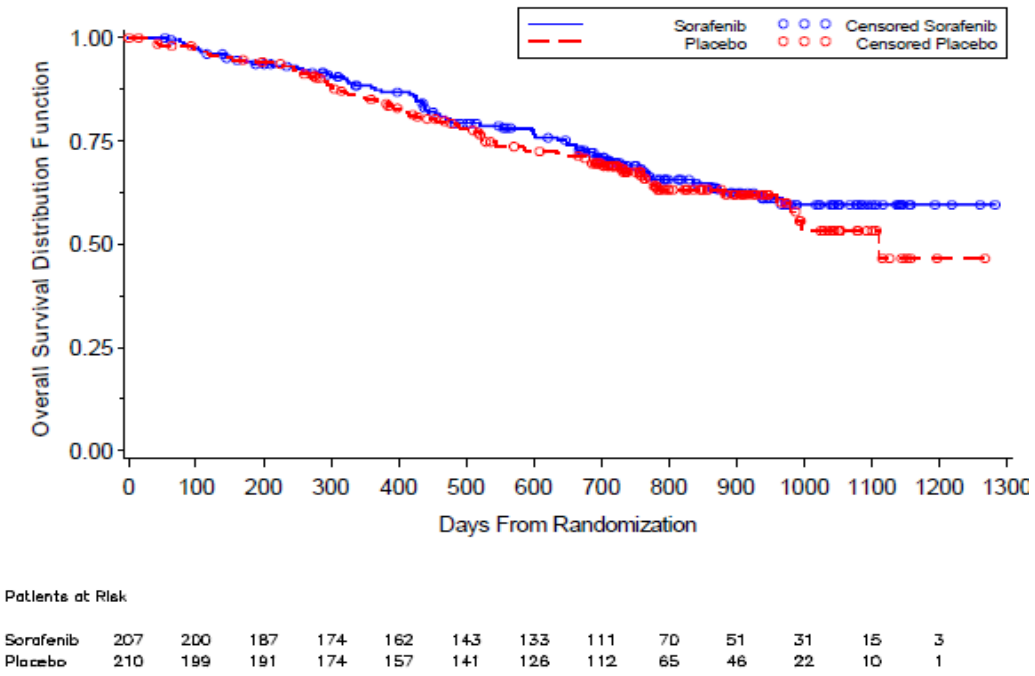


Figure 5: Kaplan-Meier curve for Overall Survival

**Time to Progression (TTP)**

Table 14: Time to progression - central assessment (FAS)

| | Central assessment | | Investigators' assessments | |
|---|---|---|---|---|
| | Sorafenib (N = 207) | Placebo (N = 210) | Sorafenib (N = 207) | Placebo (N = 210) |
| Total with event (progressed); n (%) | 105 (50.7%) | 135 (64.3%) | 135 (65.2%) | 181 (86.2%) |
| Total censored; n (%) | 102 (49.3%) | 75 (35.7%) | 72 (34.8%) | 29 (13.8%) |
| Median TTP, days | 337 | 175 [95% CI] | 334 | 165 [281; |
| [283; 451] | [160; 238] Median TTP, months [a] | | 381] | [133; 175] |
| 11.1 | 5.8 | | 11.0 | 5.4 |
| Range (without censored values) | (20 - 728) | (14 - 728) | (20 - 846) | (13 - 728) |
| HR (sorafenib/placebo) | 0.557 | | 0.473 [0.375; | |
| 95% CI for HR | [0.429; 0.724] | | 0.596] | |
| p-value (one-sided from stratified rank test) | <0.0001 log- | | <0.0001 | |

CI = confidence interval; FAS = full analyses set; HR = hazard ratio; TTP = time to progression.

[a] Months = days/30.4.

Median and other 95% CIs computed using Kaplan-Meier estimates. HR and its 95% CI were based on stratified Cox Regression Model.

**Response Rate (RR)**

The RR was 12.2% in the sorafenib group and 0.5% in the placebo group by central assessment. The difference between the groups was 11.8% (95% CI: 7.0%, 16.5%) and was statistically significant (p<0.0001) using the central assessment.

**Disease control rate (DCR)**

Table 15: Overall response (confirmed) by central assessment (PPS)

| | Sorafenib N = 196 | | Placebo N = 201 | |
|---|---|---|---|---|
| **Best Response** | **n (%)** | **[95% CI]** | **n (%)** | **[95% CI]** |
| CR | 0 | 0 | 0 | 0 |
| PR | 24 (12.24%) | [ 8.01%;17.67%] | 1 (0.50%) | [ 0.01%; 2.74%] |
| SD [a] | 145 (73.98%) | [67.25%;79.97%] | 149 (74.13%) | [67.50%;80.03%] |
| PD | 20 (10.20%) | [ 6.35%;15.32%] | 46 (22.89%) | [17.27%;29.32%] |
| Progression by clinical judgement | | | 1 (0.50%) | [0.01%;2.74%] |
| NA | 7 ( 3.57%) | [1.45%; 7.22%] | 4 (1.99%) | [0.54%;5.02%] |
| **Response (CR + PR)** | **24 (12.24%)** | **[8.01%;17.67%]** | **1 (0.50%)** | **[0.01%;2.74%]** |
| p-value (one-sided) | <0.0001 | | | |
| DCR (CR + PR + SD) [b] | 169 (86.22%) | [80.59%;90.72%] | 150 (74.63%) | [68.03%;80.49%] |
| p-value (one-sided) | 0.0015 | | | |

CI = confidence interval; CR = complete response; DCR = disease control rate; NA = not analyzed; PD = progressive disease; PPS = per protocol analysis set; PR = partial response; SD = stable disease.

[a] SD was assessed at 4 weeks for this analysis.

[b] Subjects with CR, PR, or SD for at least one month.

**Duration of response (DOR)**

A best response of at least PR was observed in 24 patients in the sorafenib group, and 1 patient in the placebo group, according to central assessment. In the placebo group, the one patient with a PR had a duration of response of 609 days or 20.2 months. In the sorafenib group, the median DOR was 309 days or 10.2 months.

**Maximum reduction in target lesion size**

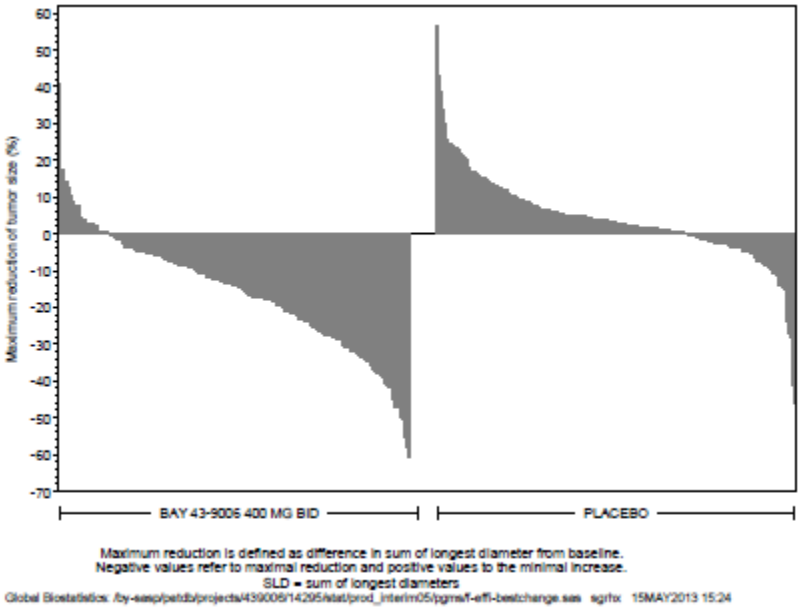


Figure 6: Maximum reduction in tumour size of target lesions – central assessment (PPS)

**Exploratory analyses**

- **Secondary PFS (SPFS)**

In the sorafenib arm, 55 patients (27%) started open label treatment with sorafenib. 23 patients entered open label treatment after disease progression. 9 patients received continued therapy after disease progression without a second event of PFS.

The table below presents centrally assessed SPFS results for the sorafenib subjects who continued sorafenib treatment and for the placebo subjects who crossed over to sorafenib treatment.

Table 16: Secondary PFS; central assessment (FAS – subjects valid for SPFS)

| Treatment period | Secondary PFS (FAS) Open-Label [a] (sorafenib treatment) | |
|---|---|---|
| Original randomized treatment group | Sorafenib (N = 46) | Placebo (N = 137) |
| Number of subjects (%) with event | 29 (63.0%) | 65 (47.4%) |
| Number of subjects (%) censored | 17 (37.0%) | 72 (52.6%) |
| Median (days) | 204 | 292 |
| Median (months) [b] | 6.7 | 9.6 |
| 95% CI for median | [118; 260] | [239; 355] |
| Range (without censored values) | 50 - 343 | 35 - 569 |

CI = confidence interval; FAS = full analysis set; SPFS = secondary progression-free survival.
The FAS – valid for SPFS analysis set included subjects who started open-label sorafenib treatment, had a re-baseline (new baseline) scan, and at least one post re-baseline radiographic assessment.
[a] Secondary PFS is defined as time from re-baseline (following first progression) until second progression or death, whichever came first, during or after open-label treatment with sorafenib.
[b] Months = days/30.4.
Median and 95% CIs computed using Kaplan-Meier estimates.

- **Patient reported outcome (Health Utility Values, Health Related Quality of Life (HRQoL))**

EQ-5D

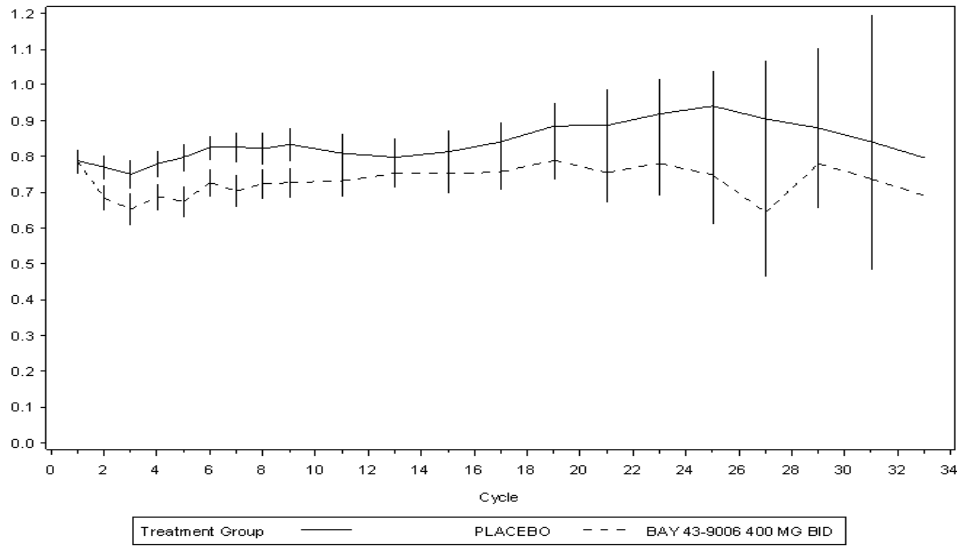


Figure 7: EQ-5D Index questionnaire – means and 95% confidence interval (PROAS)

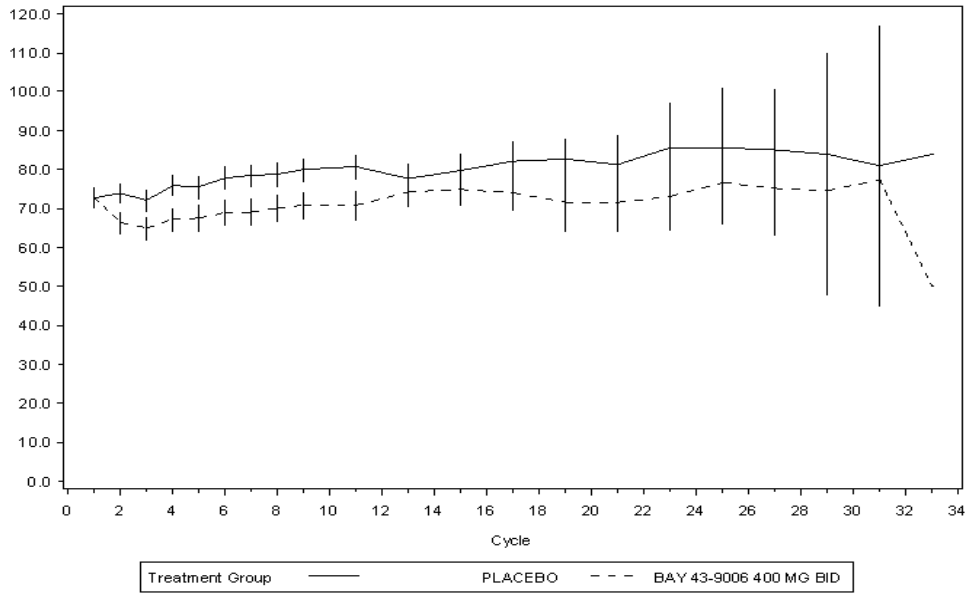


Figure 8: EQ-5D VAS questionnaire – means and 95% confidence intervals (PROAS)

Table 17: Number of subjects and their response to individual items in EQ-5D Index (double-blind period, sorafenib arm, study 14295, Cycles 1-3, PRO analysis set)

| | Cycle 1 Day 1 | Cycle 2 Day 1 | Cycle 3 Day 1 |
|---|---|---|---|
| **Number of subjects** | 193 (100%) | 182 (100%) | 175 (100%) |
| **Mobility** | | | |
| Answer | | | |
| I have no problems in walking about | 149 ( 77.2%) | 94 ( 51.6%) | 78 ( 44.6%) |
| I have some problems in walking about | 44 ( 22.8%) | 87 ( 47.8%) | 93 ( 53.1%) |
| I am confined to bed | 0 | 1 ( 0.5%) | 4 ( 2.3%) |
| **Self-care** | | | |
| Answer | | | |
| I have no problems with self-care | 173 ( 89.6%) | 150 ( 82.4%) | 147 ( 83.5%) |
| I have some problems washing or dressing myself | 20 ( 10.4%) | 31 ( 17.0%) | 27 ( 15.3%) |
| I am unable to wash or dress myself | 0 | 1 ( 0.5%) | 2 ( 1.1%) |
| **Usual activities** | | | |
| Answer | | | |
| I have no problems in performing my usual activities | 135 ( 69.9%) | 88 ( 48.4%) | 84 ( 47.7%) |
| I have some problems with performing my usual activities | 53 ( 27.5%) | 84 ( 46.2%) | 81 ( 46.0%) |
| I am unable to perform my usual activities | 5 ( 2.6%) | 10 ( 5.5%) | 11 ( 6.3%) |
| **Pain/discomfort** | | | |
| Answer | | | |
| I have no pain or discomfort | 101 ( 52.3%) | 42 ( 23.1%) | 43 ( 24.4%) |
| I have moderate pain or discomfort | 84 ( 43.5%) | 133 ( 73.1%) | 116 ( 65.9%) |
| I have extreme pain or discomfort | 8 ( 4.1%) | 7 ( 3.8%) | 17 ( 9.7%) |
| **Anxiety/depression** | | | |
| Answer | | | |
| I am not anxious or depressed | 117 ( 60.6%) | 103 ( 56.6%) | 104 ( 59.1%) |
| I am moderately anxious or depressed | 73 ( 37.8%) | 72 ( 39.6%) | 65 ( 36.9%) |
| I am extremely anxious or depressed | 3 ( 1.6%) | 7 ( 3.8%) | 7 ( 4.0%) |

FACT-G

Table 18: Analysis of treatment effect on FACT-G subscale and total scores, double-blind period, time-adjusted AUC (PROAS)

| | Sorafenib | | | Placebo | | |
|---|---|---|---|---|---|---|
| **Subscale** | **n** | **Mean** | **SD** | **n** | **Mean** | **SD** |
| Physical well-being | 194 | 20.548 | 4.502 | 195 | 23.033 | 4.479 |
| Social/family well-being | 194 | 21.477 | 4.836 | 195 | 21.751 | 4.446 |
| Emotional well-being | 195 | 17.678 | 4.445 | 195 | 17.832 | 3.707 |
| Functional well-being | 196 | 17.196 | 5.759 | 195 | 18.372 | 5.563 |
| **FACT-G total score** | **193** | **76.885** | **15.271** | **194** | **80.967** | **13.934** |

AUC = area under the curve; FACT-G = Functional Assessment of Cancer Therapy – General; PROAS = patient reported outcomes analysis set; SD = standard deviation.

Table 19: Number of subjects and their response to individual items in FACT-G physical well-being domain (double-blind period, sorafenib arm, study 14295, Cycles 1-3, PRO analysis set)

| | Cycle 1 Day 1 | Cycle 2 Day 1 | Cycle 3 Day 1 |
|---|---|---|---|
| **Number of subjects** | 196 (100%) | 186 (100%) | 178 (100%) |
| **I have lack of energy** | | | |
| Answer | | | |
| Missing | 1 ( 0.5%) | 0 | 1 ( 0.6%) |
| Not at all | 75 ( 38.3%) | 33 ( 17.7%) | 31 ( 17.4%) |
| A little bit | 60 ( 30.6%) | 62 ( 33.3%) | 55 ( 30.9%) |
| Somewhat | 42 ( 21.4%) | 57 ( 30.6%) | 63 ( 35.4%) |
| Quite a bit | 16 ( 8.2%) | 22 ( 11.8%) | 22 ( 12.4%) |
| Very much | 2 ( 1.0%) | 12 ( 6.5%) | 6 ( 3.4%) |
| **I have nausea** | | | |
| Answer | | | |
| Missing | 2 ( 1.0%) | 1 ( 0.5%) | 1 ( 0.6%) |
| Not at all | 174 ( 88.8%) | 138 ( 74.2%) | 121 ( 68.0%) |
| A little bit | 13 ( 6.6%) | 28 ( 15.1%) | 35 ( 19.7%) |
| Somewhat | 7 ( 3.6%) | 9 ( 4.8%) | 14 ( 7.9%) |
| Quite a bit | 0 | 7 ( 3.8%) | 6 ( 3.4%) |
| Very much | 0 | 3 ( 1.6%) | 1 ( 0.6%) |
| **Because of my physical condition, I have trouble meeting the needs of my family** | | | |
| Answer | | | |
| Missing | 2 ( 1.0%) | 1 ( 0.5%) | 0 |
| Not at all | 107 ( 54.6%) | 69 ( 37.1%) | 64 ( 36.0%) |
| A little bit | 42 ( 21.4%) | 49 ( 26.3%) | 46 ( 25.8%) |
| Somewhat | 29 ( 14.8%) | 33 ( 17.7%) | 39 ( 21.9%) |
| Quite a bit | 7 ( 3.6%) | 23 ( 12.4%) | 18 ( 10.1%) |
| Very much | 9 ( 4.6%) | 11 ( 5.9%) | 11 ( 6.2%) |
| **I have pain** | | | |
| Answer | | | |
| Missing | 3 ( 1.5%) | 0 | 1 ( 0.6%) |
| Not at all | 94 ( 48.0%) | 37 ( 19.9%) | 40 ( 22.5%) |
| A little bit | 51 ( 26.0%) | 63 ( 33.9%) | 64 ( 36.0%) |
| Somewhat | 26 ( 13.3%) | 52 ( 28.0%) | 41 ( 23.0%) |
| Quite a bit | 19 ( 9.7%) | 26 ( 14.0%) | 24 ( 13.5%) |
| Very much | 3 ( 1.5%) | 8 ( 4.3%) | 8 ( 4.5%) |
| **I am bothered by side effects** | | | |
| Answer | | | |
| Missing | 17 ( 8.7%) | 1 ( 0.5%) | 1 ( 0.6%) |
| Not at all | 136 ( 69.4%) | 28 ( 15.1%) | 24 ( 13.5%) |
| A little bit | 28 ( 14.3%) | 54 ( 29.0%) | 55 ( 30.9%) |
| Somewhat | 12 ( 6.1%) | 48 ( 25.8%) | 54 ( 30.3%) |
| Quite a bit | 2 ( 1.0%) | 35 ( 18.8%) | 28 ( 15.7%) |
| Very much | 1 ( 0.5%) | 20 ( 10.8%) | 16 ( 9.0%) |
| **I feel ill** | | | |
| Answer | | | |
| Missing | 5 ( 2.6%) | 2 ( 1.1%) | 2 ( 1.1%) |
| Not at all | 105 ( 53.6%) | 69 ( 37.1%) | 56 ( 31.5%) |
| A little bit | 41 ( 20.9%) | 48 ( 25.8%) | 55 ( 30.9%) |
| Somewhat | 31 ( 15.8%) | 39 ( 21.0%) | 39 ( 21.9%) |
| Quite a bit | 9 ( 4.6%) | 21 ( 11.3%) | 16 ( 9.0%) |
| Very much | 5 ( 2.6%) | 7 ( 3.8%) | 10 ( 5.6%) |
| **I am forced to spend time in bed** | | | |
| Answer | | | |
| Missing | 5 ( 2.6%) | 1 ( 0.5%) | 1 ( 0.6%) |
| Not at all | 149 ( 76.0%) | 116 ( 62.4%) | 113 ( 63.5%) |
| A little bit | 26 ( 13.3%) | 29 ( 15.6%) | 36 ( 20.2%) |
| Somewhat | 11 ( 5.6%) | 25 ( 13.4%) | 18 ( 10.1%) |
| Quite a bit | 4 ( 2.0%) | 12 ( 6.5%) | 8 ( 4.5%) |
| Very much | 1 ( 0.5%) | 3 ( 1.6%) | 2 ( 1.1%) |

Table 20: Summary of patterns of changes in the total score of FACT-G in subjects randomized to sorafenib (double-blind period, study 14295)

| Pattern | Subjects N=197 (100%) |
|---|---|
| **Improvement in score** | 30 ( 15%) |
| Improvement only | 12[h] ( 6%) |
| Improvement then decrease | 18[i] ( 9%) |
| **No change in score** | 52[g] ( 26%) |
| **Decrease in score** | 107 ( 54%) |
| Gradual decrease | 30[a] ( 15%) |
| Decrease then improvement | 33[b] ( 17%) |
| Decrease then leveling off | 12[c] ( 6%) |
| Decrease then improvement then decrease | 16[d] ( 8%) |
| Severe decrease | 11[e] ( 6%) |
| Late decrease | 5[f] ( 3%) |
| **No pattern could be identified or FACT-G total score is missing** | 8[j] ( 4%) |

Table 21: Number of subjects and their response to the question "I am bothered by side effects" in FACT-G physical well-being domain (double-blind period, sorafenib arm, study 14295, Cycles 1-13, PRO analysis set)

| | | I am bothered by side effects | | | | | |
|---|---|---|---|---|---|---|---|
| Visit | Number of subjects | Missing n (%) | Not at all n (%) | A little bit n (%) | Some-what n (%) | Quite a bit n (%) | Very much n (%) |
| **Cycle 1 Day 1** | 196 | 17 (8.7) | 136 (69.4) | 28 (14.3) | 12 (6.1) | 2 (1.0) | 1 (0.5) |
| **Cycle 2 Day 1** | 186 | 1 (0.5) | 28 (15.1) | 54 (29.0) | 48 (25.8) | 35 (18.8) | 20 (10.8) |
| **Cycle 3 Day 1** | 178 | 1 (0.6) | 24 (13.5) | 55 (30.9) | 54 (30.3) | 28 (15.7) | 16 (9.0) |
| **Cycle 4 Day 1** | 165 | 1 (0.6) | 21 (12.7) | 62 (37.6) | 39 (23.6) | 32 (19.4) | 10 (6.1) |
| **Cycle 5 Day 1** | 158 | 1 (0.6) | 22 (13.9) | 56 (35.4) | 46 (29.1) | 19 (12.0) | 14 (8.9) |
| **Cycle 6 Day 1** | 149 | 0 | 16 (10.7) | 67 (45.0) | 41 (27.5) | 18 (12.1) | 7 (4.7) |
| **Cycle 7 Day 1** | 143 | 2 (1.4) | 15 (10.5) | 54 (37.8) | 48 (33.6) | 19 (13.3) | 5 (3.5) |
| **Cycle 8 Day 1** | 133 | 3 (2.3) | 18 (13.5) | 59 (44.4) | 31 (23.3) | 18 (13.5) | 4 (3.0) |
| **Cycle 9 Day 1** | 125 | 2 (1.6) | 19 (15.2) | 53 (42.4) | 33 (26.4) | 12 (9.6) | 6 (4.8) |
| **Cycle 11 Day 1** | 113 | 2 (1.8) | 14 (12.4) | 49 (43.4) | 33 (29.2) | 10 (8.8) | 5 (4.4) |
| **Cycle 13 Day 1** | 87 | 0 | 12 (13.8) | 40 (46.0) | 28 (32.2) | 7 (8.0) | 0 |

- **Biomarker analysis**

Tumour genetic results were available from 256 of the 417 randomised subjects (61.4% of the study population). Mutations were examined in archival tumour samples using the OncoCarta 1.0 panel.

Table 22: The 19 genes tested for mutations by OncoCarta Panel 1.0.

| | | | |
|---|---|---|---|
| ABL1 | EGFR | JAK-2 | NRAS |
| AKT1 | ERBB2 | KIT | PDGFA |
| AKT2 | FGFR1 | MET | PIK3CA |
| BRAF | FGFR3 | HRAS | RET |
| CDK4 | FLT3 | KRAS | |

Baseline plasma samples were analysed for levels of 15 different proteins. Baseline plasma proteins are being analysed for predictive, as well as prognostic value. Plasma protein biomarkers will be analysed as both continuous variables as well as dichotomized variables. Data analysis is ongoing and results will be reported separately.

## Ancillary analyses

Table 23: Progression-free survival (days) by pre-planned subgroup (FAS)

| Variable<br>Subgroup | N | No. of Events | No. Censored | Hazard Ratio [95% CI] (Sorafenib/Placebo) | Median, days (months) [a] Sorafenib | Placebo |
|---|---|---|---|---|---|---|
| **Overall** | **417** | **250** | **167** | **0.587 [ 0.454; 0.758]** | **329 (10.8)** | **175 (5.8)** |
| **Geographical region** | | | | | | |
| Europe | 249 | 163 | 86 | 0.62 [0.45; 0.84] | 281 ( 9.2) | 167 ( 5.5) |
| North America | 72 | 42 | 30 | 0.71 [0.39; 1.32] | 250 ( 8.2) | 233 ( 7.7) |
| Asia | 96 | 45 | 51 | 0.50 [0.27; 0.93] | 556 (18.3) | 287 ( 9.4) |
| **Age** | | | | | | |
| < 60 years | 161 | 103 | 58 | 0.55 [0.38; 0.82] | 305 (10.0) | 165 ( 5.4) |
| ≥ 60 years | 256 | 147 | 109 | 0.62 [0.45; 0.87] | 337 (11.1) | 175 ( 5.8) |
| **Sex** | | | | | | |
| Male | 199 | 126 | 73 | 0.69 [0.49; 0.98] | 294 ( 9.7) | 220 ( 7.2) |
| Female | 218 | 124 | 94 | 0.50 [0.35; 0.73] | 340 (11.2) | 167 ( 5.5) |
| **Histology subtype** | | | | | | |
| Papillary | 235 | 121 | 114 | 0.52 [0.36; 0.75] | 556 (18.3) | 280 ( 9.2) |
| Follicular-Hurthle Cell | 74 | 54 | 20 | 0.44 [0.25; 0.78] | 283 ( 9.3) | 113 ( 3.7) |
| Follicular - Other | 31 | 23 | 8 | 0.73 [0.31; 1.74] | 247 ( 8.1) | 124 ( 4.1) |
| Poorly Differentiated | 38 | 31 | 7 | 0.74 [0.35; 1.57] | 168 ( 5.5) | 157 ( 5.2) |
| **Metastases** | | | | | | |
| Lung only yes | 70 | 38 | 32 | 0.35 [0.17; 0.71] | 623 (20.5) | 284 ( 9.3) |
| Lung only no | 347 | 212 | 135 | 0.62 [0.47; 0.81] | 293 ( 9.6) | 165 ( 5.4) |
| Bone yes | 113 | 79 | 34 | 0.52 [0.34; 0.82] | 221 ( 7.3) | 103 ( 3.4) |
| Bone no | 304 | 171 | 133 | 0.59 [0.44; 0.80] | 378 (12.4) | 243 ( 8.0) |
| **FDG-PET uptake** | | | | | | |
| Negative | 29 | 16 | 13 | 0.58 [0.20; 1.68] | --- | 161 ( 5.3) |
| Positive | 320 | 188 | 132 | 0.54 [0.40; 0.72] | 333 (10.9) | 175 ( 5.8) |
| **Prior RAI cumulative dose** | | | | | | |
| < 600 mCi | 264 | 159 | 105 | 0.56 [0.41; 0.77] | 340 (11.2) | 200 ( 6.6) |
| ≥ 600 mCi | 133 | 80 | 53 | 0.64 [0.41; 0.99] | 278 ( 9.1) | 124 ( 4.1) |
| **No. of target/non target lesions)** | | | | | | |
| < median | 163 | 91 | 72 | 0.69 [0.45; 1.06] | 343 (11.3) | 268 (8.8) |
| ≥ median | 254 | 159 | 95 | 0.51 [0.37; 0.70] | 309 (10.2) | 125 (4.1) |
| **Target lesion size** | | | | | | |
| < median | 208 | 114 | 94 | 0.69 [0.47; 1.00] | 393 (12.9) | 304 (10.0) |
| ≥ median | 209 | 136 | 73 | 0.44 [0.31; 0.63] | 278 ( 9.1) | 112 ( 3.7) |

CI = confidence interval; FAS = full analysis set; FDG = 2-[18F] fluoro-2-deoxy-D-glucose; mCi = milliCurie; PET = positron-emission tomography; PFS = progression-free survival; RAI = radioactive iodine.

[a] Months = days/30.4.
A hazard ratio < 1 means in favor of sorafenib over placebo.
Hazard ratios and CIs are based on the unstratified Cox Regression Model.

Progression-free survival was analysed post-hoc for additional subgroups including by category of lesion size (Table 24).

Table 24: Progression-free survival (days) by category of lesion size—central assessment (FAS)-

| Variable Subgroup | N | No. of Events | No. Censored | Hazard Ratio [95% CI] (Sorafenib/Placebo) | Median, days Sorafenib | Median, days Placebo |
|---|---|---|---|---|---|---|
| **Lesion category: Maximum Target Lesion Size (Investigator assessment)** | | | | | | |
| < 1.5 cm | 54 | 27 | 27 | 0.87 [0.40; 1.89] | 509 | 403 |
| ≥ 1.5 cm | 361 | 221 | 140 | 0.54 [0.41; 0.71] | 294 | 168 |
| < 2 cm | 107 | 57 | 50 | 0.82 [0.48; 1.39] | 426 | 380 |
| ≥ 2 cm | 308 | 191 | 117 | 0.50 [0.38; 0.67] | 294 | 142 |
| < 3 cm | 216 | 123 | 93 | 0.64 [0.45; 0.92] | 393 | 294 |
| ≥ 3 cm | 199 | 125 | 74 | 0.49 [0.35; 0.71] | 267 | 113 |
| < 4 cm | 294 | 164 | 130 | 0.63 [0.46; 0.86] | 354 | 268 |
| ≥ 4 cm | 121 | 84 | 37 | 0.43 [0.28; 0.67] | 189 | 109 |
| **Lesion category: Number of Target Lesions (Investigator assessment)** | | | | | | |
| Less Than 3 | 155 | 89 | 66 | 0.74 [0.49; 1.13] | 329 | 268 |
| 3 Or More | 260 | 159 | 101 | 0.51 [0.37; 0.69] | 309 | 162 |
| Less Than 4 | 213 | 123 | 90 | 0.70 [0.49; 1.00] | 326 | 243 |
| 4 Or More | 202 | 125 | 77 | 0.47 [0.33; 0.68] | 332 | 142 |
| Less Than 5 | 281 | 167 | 114 | 0.63 [0.46; 0.86] | 329 | 222 |
| 5 Or More | 134 | 81 | 53 | 0.50 [0.32; 0.78] | 309 | 162 |

Table 25: Progression free survival - central assessment incl. clinical progression due to bone irradiation by time since most recent progression to enrolment (FAS data, cut-off 31 AUG 2012)

| Treatment group | Sorafenib N=207 | Placebo N=210 |
|---|---|---|
| **Time since most recent progression ≤ 3 months** | | |
| Number of subjects | 135 (100.0 %) | 140 (100.0 %) |
| Number of subjects (%) with event | 79 (58.5 %) | 92 (65.7 %) |
| Number of subjects (%) censored | 56 (41.5 %) | 48 (34.3 %) |
| 25th percentile [95% CI], days | 143 [106; 168] | 58 [56; 84] |
| Median [95% CI], days | 309 [250; 393] | 170 [112; 224] |
| 75th percentile [95% CI], days | 623 [556; 728] | 365 [286; 665] |
| Range (including censored values), days | (1 - 834)** | (1 - 832)** |
| Range (without censored values), days | (24 - 728) | (14 - 665) |
| PFS rate at 3 months [95 % CI] | 0.86 [0.79; 0.91] | 0.68 [0.59; 0.75] |
| PFS rate at 6 months [95 % CI] | 0.65 [0.56; 0.73] | 0.46 [0.37; 0.55] |
| PFS rate at 9 months [95 % CI] | 0.55 [0.46; 0.64] | 0.36 [0.27; 0.45] |
| PFS rate at 12 months [95 % CI] | 0.42 [0.33; 0.51] | 0.25 [0.17; 0.34] |
| PFS rate at 18 months [95 % CI] | 0.36 [0.27; 0.46] | 0.16 [0.09; 0.26] |
| PFS rate at 24 months [95 % CI] | 0.12 [0.04; 0.25] | 0.11 [0.03; 0.24] |
| HR [sorafenib/placebo] | 0.56 | |
| 95% CI for hazard ratio | [0.42; 0.77] | |
| **Time since most recent progression > 3 months** | | |
| Number of subjects | 72 (100.0 %) | 70 (100.0 %) |
| Number of subjects (%) with event | 34 (47.2 %) | 45 (64.3 %) |
| Number of subjects (%) censored | 38 (52.8 %) | 25 (35.7 %) |
| 25th percentile [95% CI], days | 168 [110; 278] | 106 [63; 160] |
| Median [95% CI], days | 337 [278; 509] | 262 [165; 391] |
| 75th percentile [95% CI], days | A [448; A] | 498 [391; 728] |
| Range (including censored values), days | (1 - 841)** | (1 - 841)** |
| Range (without censored values), days | (20 - 623) | (20 - 728) |
| PFS rate at 3 months [95 % CI] | 0.89 [0.79; 0.95] | 0.80 [0.68; 0.88] |
| PFS rate at 6 months [95 % CI] | 0.72 [0.59; 0.82] | 0.54 [0.40; 0.65] |
| PFS rate at 9 months [95 % CI] | 0.65 [0.51; 0.76] | 0.48 [0.35; 0.60] |
| PFS rate at 12 months [95 % CI] | 0.47 [0.33; 0.60] | 0.42 [0.29; 0.54] |
| PFS rate at 18 months [95 % CI] | 0.34 [0.20; 0.49] | 0.19 [0.08; 0.32] |
| PFS rate at 24 months [95 % CI] | 0.29 [0.14; 0.45] | 0.07 [0.01; 0.24] |
| HR [sorafenib/placebo] | 0.65 | |
| 95% CI for hazard ratio | [0.41; 1.01] | |
| Interaction p-value | 0.594 | |

The results for patients who were retrospectively categorized as symptomatic at baseline (median PFS sorafenib, 326 days; placebo, 109 days, HR [95%CI] 0.386 [0.207; 0.720]) were numerically superior to the results in asymptomatic patients (median PFS sorafenib 329 days, placebo 220 days HR [95%CI] 0.602 [0.448; 0.807]).

## Summary of main study

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

Table 26: Summary of Efficacy for study 14295

| **Title:** A double-blind, randomised Phase III study evaluating the efficacy and safety of sorafenib compared to placebo in locally advanced/metastatic RAI-refractory differentiated thyroid cancer | | | |
|---|---|---|---|
| Study identifier | 14295, NCT00984282, 2009-012007-25 | | |
| Design | Double blind, placebo-controlled, randomised, multicentre | | |
| | Duration of main phase:<br><br><br>Duration of run-in phase:<br>Duration of extension phase: | | Until disease progression, unacceptable toxicity, non-compliance or withdrawal of consent<br>not applicable<br>not applicable |
| Hypothesis | Superiority | | |
| Treatment groups | sorafenib | | 400 mg (administered as 2 x 200 mg) orally twice daily; N=207 |
| | placebo | | 2 matching placebo tablets orally twice daily; N=210 |
| Endpoints and definitions | Primary endpoint | Progression Free Survival (PFS) | Time from randomisation to first observed disease progression (radiological as determined by central radiological review or clinical progression due to bone lesions that required external radiation, whichever was earlier) or death (due to any cause) |
| | Secondary endpoint | Overall Survival (OS) | Time from randomisation to death due to any cause |
| | Secondary endpoint | Time to progression (TTP) | Time from randomisation to first observed disease progression (radiological as determined by central radiological review or clinical progression due to bone lesions that required external radiation, whichever was earlier) |
| | Secondary endpoint | Disease control rate (DCR) | Proportion of patients whose best response was complete response (CR), partial response (PR), or stable disease (SD) that was achieved before or at the date of unblinding |

| | | | |
|---|---|---|---|
| | Secondary endpoint | Response rate (RR) | Proportion of patients whose best response was CR or PR that was achieved before or at the date of unblinding |
| | Secondary endpoint | Duration of response (DOR) | Time from the first documented objective response of PR or CR, whichever was noted earlier, to disease progression or death |
| | Exploratory endpoint | Secondary PFS (SPFS) | Time from re-baseline (last tumour assessment before start of open-label treatment period) until new progression or death, whichever came first, during or after open-label treatment with sorafenib |
| Database lock | 31 August 2012 | | |

**Results and analysis**

| **Analysis description** | **Primary analysis** | | |
|---|---|---|---|
| Analysis population and time point description | Intent to treat, 31/08/2012 (99 events of death observed)<br>Central assessment | | |
| Descriptive statistics and estimate variability | **Treatment group** | **sorafenib** | **placebo** |
| | Number of subjects | 207 | 210 |
| | PFS (median, in days) | 329 (10.8 months) | 175 (5.8 months) |
| | [95% CI] | [278;393] | [160;238] |
| | OS (median, in days) | Cannot be estimated | Cannot be estimated |
| | [95% CI] | n/a | n/a |
| | TTP (median, in days) | 337 (11.1 months) | 175 (5.8 months) |
| | [95% CI] | [283; 451] | [160; 238] |
| | DCR (n (%)) | 169 (86.22%) | 150 (74.63%) |
| | [95% CI] | [80.59%;90.72%] | [68.03%;80.49%] |
| | RR (n (%)) | 24 (12.24%) | 1 (0.50%) |
| | [95% CI] | [8.01%;17.67%] | [0.01%;2.74%] |
| | DOR (median, in days) | 309 | Cannot be estimated (duration of response was 609 days for the patient) |
| | [95% CI] | [226; 505] | n/a |
| | **Treatment Group** | **sorafenib** | **placebo** |
| | Number of subjects | 46 | 137 |
| | SPFS (median, in days) | 204 (6.7 months) | 292 (9.6 months) |
| | [95% CI] | [118; 260] | [239; 355] |

| | | | |
|---|---|---|---|
| Effect estimate per comparison | Primary endpoint (PFS) | Comparison groups | sorafenib vs placebo |
| | | HR | 0.587 |
| | | [95% CI] | [0.454; 0.758] |
| | | P-value | <0.0001 |
| | Secondary endpoint (OS) | Comparison groups | sorafenib vs placebo |
| | | HR (uncorrected) | 0.884 |
| | | [95% CI] (uncorrected) | [0.633; 1.236] |
| | | P-value (uncorrected) | 0.2359 |
| | Secondary endpoint (TTP) | Comparison groups | sorafenib vs placebo |
| | | HR | 0.557 |
| | | [95% CI] | [0.429; 0.724] |
| | | P-value | <0.0001 |

## Supportive studies

The efficacy results of 5 single centre, single arm, investigator-sponsored studies (ISS) that included DTC patients are summarised in the table below.

Table 27: Efficacy outcomes (phase 2 investigator sponsored studies)

| **Efficacy parameter** | **12791 N = 32** | **12636 N = 34** | **12192 N = 47** | **100369[a] N = 41** | **China[c] N = 9** |
|---|---|---|---|---|---|
| **Type** of thyroid carcinoma | DTC | DTC or MTC | DTC | PTC | PTC |
| Median **PFS**, months (range) | 18[d] (7-29) | NR at 19 months | 21.5 (14-23) | 15 (10-28) | 9.7 (NA) |
| Median **OS,** months (range) | 34.5[d] (19-50) | NR | 32 (18-47) | 23 (18-43) 37.5 (4-43)[b] | NR |
| **RR** n (%) | 8 (31)[d] | 21%[e] | 18 (38) | 6 (15) | 3 (33) |
| **SD** n (%) | 11 (42)[d] | 65%[e] | 22 (47) | 25 (61) | 4 (44) |
| **SD** ≥ 6 months n (%) | NA- | NA | NA | 23 (56) | NA |
| **PD,** n (%) | 15 (58) | 14%[e] | NR | 5 (12) | 2 (22) |
| Patients analyzed | 26 patients assessable | NA | All patients (FAS) | All patients (FAS) | All patients (FAS) |

NR = not reached; NA = not available; DTC = differentiated thyroid carcinoma; PTC = papillary thyroid carcinoma; PFS = progression-free survival; OS = overall survival; RR = response rate; SD = stable disease; PD = progressive disease

Studies analyzed all patients treated (FAS population) in that specific category, with the following exceptions: study 14295 analyzed the per-protocol set for response rate; and study 12791 analyzed patients "eligible for efficacy analysis" defined as those reaching first radiological evaluation at 6 months.

a: 100369: PTC patients, both chemotherapy naïve and with no prior chemotherapy.

b: 100369: Median OS was 23 months for chemotherapy naïve patients and 37.5 months with prior chemotherapy.

c: China: Patients were treated with 200 mg sorafenib BID.

d: 12791: Based on the number of patients eligible for efficacy analysis (26 assessable patients)

e: 12636: At 12 months on study.

## 2.4.2. Discussion on clinical efficacy

Overall, the design of the pivotal study is considered conventional and acceptable. Progression within 14 months as inclusion criterion might appear long, but is commonly used in metastatic DTC. Of note, symptomatic disease was not required. The definition of Radioactive Iodine (RAI)-Refractory differentiated thyroid cancer is also considered appropriate. The study included optional cross-over as

off label use of alternative TKIs (and sorafenib) was foreseen to be prevalent at least in the US. This is not considered ideal but is accepted by the CHMP.

In terms of demographic and baseline characteristics data, the vast majority of patients had metastatic disease and few patients entered the study with stable disease (i.e. non-progression within 14 months). Time of documented progressive disease until enrolment was not reported. Poorly differentiated tumours were eligible provided that the histology had neither medullary differentiation nor anaplastic features. Overall, no imbalances of likely importance were observed.

The median PFS was 10.8 months for sorafenib treated group compared with 5.8 months in the placebo group (HR: 0.587; 95%CI 0.454 – 0.758; p-value <0.0001). The results were considered clinically and statistically robust.

There were no particular findings as regards differential sorafenib activity in subgroups analysis. With respect to prognosis, low tumour burden (target lesions < median), lung only and papillary histology appeared to be associated with relatively good prognosis as expected. This might also be the case for the subgroup “Asia” however the numbers are too small to draw conclusions. PFS was also analysed post-hoc for additional subgroups. A post-hoc subgroup analysis by maximum tumour size showed a treatment effect for PFS in favour of sorafenib over placebo for patients with maximum tumour size of 1.5 cm or larger (HR 0.54 (95% CI: 0.41 - 0.71)) whereas a numerically lower effect was reported in patients with a maximum tumour size of less than 1.5 cm (HR 0.87 (95% CI: 0.40 - 1.89). Before initiating treatment, physicians are recommended to carefully evaluate the prognosis in the individual patient considering maximum lesion size, symptoms related to the disease and progression rate (see section 4.4 and 5.1 of the SmPC).

In the updated OS analysis (cut-off May 2013), the event rate was 32% and 34%, respectively, with an HR of 0.884 (95%CI 0.633 - 1.236). This is expected in a slowly progressive disease with a high cross-over rate.

The response rate was low, about 12%, compared with single arm study data, about 25%. Due to the rather slowly progressive nature of the disease, stable disease (SD) as defined here 4 weeks, is not considered informative.

This study opened for optional open label treatment of sorafenib also after disease progression on sorafenib and cross over from placebo to sorafenib. Altogether, about 27% of patients entered open label treatment from the sorafenib arm and 71% of patients cross over from the placebo group. The median PFS after cross-over (SPFS) from placebo was about 10 months which was rather similar to PFS first-line in the sorafenib arm.

With respect to patient reported outcome (PRO), a negative effect was observed in the sorafenib arm on the EQ-5D index. This was not unexpected taking adverse reactions into account (see also clinical safety). Also EQ-5D VAS seemed to capture negative effects. In terms of FACT-G score, a small but likely relevant difference in total score in favour of placebo, driven by “physical well-being”, was observed. HRQoL as estimated by EQ-5D and FACT-G decreased early and then remained stable despite dose reductions. The MAH discussed PRO items that were likely to be sensitive to the reported adverse reactions. Items in EQ-5D sensitive to adverse reactions included mobility, usual activities and pain/discomfort. Most issues in the physical well-being domain of FACT-G seemed sensitive to AEs, most notable “bothered by side effects” where “quite a bit” and “very much” increased from 2% prior to cycle 1, to about 30% prior to cycle 2 and about 25% prior to cycle 3. Despite dose reductions and interruptions, about 15% of the patients reported after cycle 6 that they were quite a bit or very much bothered by side effects. On the other hand about 55% were not at all or a little bit bothered at cycle 6 and on.

Analyses of FACT-G total score revealed that changes in the HRQoL on an individual subject level were heterogeneous. About 50% of patients showed a more than 7 points (“minimally important difference”) decrease in total score and about 15% showed an improvement.

The case report form (CRF) did not capture symptoms likely to be related to the underlying disease, but retrospectively it was found that about 20% of patients had symptoms likely to be related to thyroid cancer at baseline. Positive effects on total EQ-5D or FACT-G were not reported in this group of patients, but PFS tended to be more favourable (HR [95%CI] 0.386 [0.207; 0.720] compared to asymptomatic patients (HR [95%CI] 0.602 [0.448; 0.807]). In the placebo group median time to PFS was shorter than in the full study population partially ”validating” the more advanced stage of ”symptomatic” patients.

Progression rate is also likely to be of importance, but no such data are available. Patients enrolled within 3 months of documented progression, however, had a slightly better HR than the complementary set.

The MAH undertook additional subgroup analyses, and no baseline factors predictive of HRQoL on therapy have been identified.

It is accepted that delaying tumour progression is likely to be associated with delaying symptomatic progression. However, the clinical benefit and appropriateness of initiating therapy in asymptomatic patients was questioned, not least as sorafenib is associated with adverse reactions negatively affecting patients HRQoL. By necessity, this should be an individualised decision taking into account tumour progression rate, organ involvement, patient wish, etc. No co-variates predictive of sorafenib anti-tumour activity have been identified and delay in initiation of treatment seems unlikely to be an issue. In this context, the indication has been revised to reflect that sorafenib is for use in patients with progressive RAI refractory DTC.

In the pivotal study and as expected papillary dominated (about 60%), followed by follicular/Hürthle cell (18%), poorly differentiated (about 10%) and “follicular other” (6%). Statistically significant and similar effects were observed in “papillary” and “follicular-Hürthle cell” (HR was 0.52 and 0.44, respectively), whilst the point estimates were a bit poorer (HR of 0.74 and 0.73, respectively) and not statistically significant in “poorly differentiated” and “follicular other”. Hürthle cell is considered a variant of follicular and clinically it is not meaningful to differentiate between these entities, especially not in case of RAI refractory disease. Therefore, “poorly differentiated” is excluded from the indication (see section 4.2 of the SmPC).

With respect to the exploratory biomarker analysis performed in the pivotal study, archival samples provided no mutation data of potential interest as regards predictive or prognostic value. Plasma biomarkers, including factors considered to be of importance for angiogenesis, have not been analysed yet and should be submitted as soon as available.

Data from five single centre, single arm, investigator sponsored studies were also submitted as supportive information. As frequently is the case, higher ORR were reported in these single arm, single centre studies. These studies, however, only provide supportive evidence of activity in RAI refractory DTC.

### 2.4.3. Conclusions on the clinical efficacy

Sorafenib has shown a clinically meaningful benefit in patients with metastatic differentiated thyroid cancer refractory to radioiodine therapy, with a difference of 5 months in median PFS in comparison to placebo (HR: 0.587; 95%CI 0.454 – 0.758; p-value <0.0001).

EQ-5D and FACT-G data were compatible with a negative effect of sorafenib on HRQoL. Baseline factors predictive of increased risk have not been identified, but it should be noticed that about half of the patients were 'not at all' or 'only a bit bothered' by side effects and that dose reductions were only partly successful in alleviating symptoms. Repeat evaluation of benefit and risk is recommended taking anti-tumour activity and tolerability into account (see section 4.4 of the SmPC).

Factors such as size of tumour lesions and symptoms are considered important to be taken into account prior to initiation of therapy. Progression rate is also likely to be of importance although no such data were available. Patients enrolled within 3 months of documented progression, however, had a slightly better HR than the complementary set. Therefore, the CHMP considered the prognosis in the individual patient considering maximum lesion size, symptoms related to the disease and progression rate should be carefully considered before initiating treatment with sorafenib (see section 4.4 of the SmPC).

## *2.5. Clinical safety*

### 2.5.1. Introduction

### Patient exposure

Overall, approximately 15,715 patients with cancer, including 366 patients with DTC, have been exposed to sorafenib in MAH-sponsored trials up to March 2013. The completed studies, including phase 2 ISS studies, comprise treatment with sorafenib in 527 patients with DTC. In addition, 1739 patients with thyroid carcinoma have been treated with sorafenib in a US patient support program.

As of March 2013, the total estimated worldwide exposure to commercial sorafenib and sorafenib in clinical studies is over 293,000 patients.

***Study 14295***

A total of 417 patients (sorafenib 207; placebo 210) were randomised into Study 14295 but 1 placebo patient initiated double-blind treatment. Thus, the safety analysis set (SAF) was comprised of 416 patients.

In the open label phase of the study, 150 patients randomised to placebo received open label sorafenib, therefore the number of patients exposed to sorafenib in study 14295 is 357. Sorafenib patients received a mean of 81.4% of the planned dose and placebo patients received a mean of 99.2% of the planned dose. One hundred forty-one patients (68.1%) experienced at least one dose reduction of double blind sorafenib compared to 11.5% of patients with at least one dose reduction of double blind placebo. The most common reason for dose reduction of double-blind drug was an AE (73.9% in sorafenib patients and 57.1% placebo patients). At least one dose interruption was also more common in sorafenib patients compared to placebo patients (76.8% and 54.5%, respectively). The predominant reason for interruption in sorafenib patients was an AE (75.3%).

The median duration of therapy in the double-blind period was 46 weeks (range 0.3-135) for patients receiving sorafenib and 28 weeks (range 1.7–132) for patients receiving placebo.

Table 28: Comparative Sorafenib Exposure Data for Study 14295 (double-blind period) and Monotherapy Studies for Approved Indications

| Study No | Indication | No. Treated Subjects | Median DOT[b] (wk) | Median Daily Dose (mg/day) | Frequency of Dose Reduction (%) | Frequency of Dose Interruption (%) | Re-escalation Allowed? (Y/N) |
|---|---|---|---|---|---|---|---|
| 14295 | Advanced RAI-refractory DTC | 207 | 46.1 | 708.4 | 68.1 | 76.8 | Y |
| 11213 | Treatment-refractory, unresectable, or metastatic RCC | 451 | 40.1 | 790.5 | 50.1[a] | | Y |
| 11849 | Treatment-naïve or refractory HCC | 149 | 13.4 | 796.5 | 36.2 | 45.6 | Y |
| 100554 | Treatment-naïve advanced HCC | 297 | 23.0 | 797.2 | 32.1 | 51.5 | Y |

a. Combined rate of dose reductions and interruptions.
b. DOT = duration of treatment
Source: Module 5.3.5.1, Report A57578; Report MRR-00147; Report MRR-00315; and Report A45053 Addendum 2

## Adverse events

Table 29: Study 14295 – Overview of Adverse Events (Safety Analysis Set)

| | Double-blind Treatment | | Double-blind + Open-label Sorafenib[a] | Open-label Sorafenib After Crossover (Prior Placebo)[b] |
|---|---|---|---|---|
| | Sorafenib | Placebo | | |
| | N=207 n (%) | N=209 n (%) | N=207 n (%) | N=150 n (%) |
| Any AE | 204 (98.6) | 183 (87.6) | 204 (98.6) | 149 (99.3) |
| Worst grade: | | | | |
| Grade 3 | 109 (52.7) | 49 (23.4) | 111 (53.6) | 69 (46.0) |
| Grade 4 | 24 (11.6) | 14 (6.7) | 27 (13.0 | 10 (6.7) |
| Grade 5 (death) | 14 (6.8) | 6 (2.9) | 19 (9.2) | 22 (14.7) |
| Serious | 77 (37.2) | 55 (26.3) | 87 (42.0) | 66 (44.0) |
| Causing discontinuation of study drug | 39 (18.8) | 8 (3.8) | 46 (22.2) | 28 (18.7) |
| Requiring dose modification | 161 (77.8) | 63 (30.1) | 166 (80.2) | 110 (73.3) |
| Any drug-related AE | 200 (96.6) | 112 (53.6) | 201 (97.1) | 145 (96.7) |
| Worst grade: | | | | |
| Grade 3 | 100 (48.3) | 11 (5.3) | 103 (49.8) | 66 (44.0) |
| Grade 4 | 12 (5.8) | 3 (1.4) | 12 (5.8) | 1 (0.7) |
| Grade 5 (death) | 1 (0.5) | 1 (0.5) | 1 (0.5) | 1 (0.7) |
| Serious | 26 (12.6) | 8 (3.8) | 27 (13.0) | 17 (11.3) |
| Causing discontinuation of study drug | 29 (14.0) | 3 (1.4) | 33 (15.9) | 14 (9.3) |
| Requiring dose modification | 142 (68.6) | 22 (10.5) | 144 (69.6) | 96 (64.0) |
| Any disease-related AE | 155 (74.9) | 135 (64.6) | 159 (76.8) | 102 (68.0) |
| Worst grade: | | | | |
| Grade 3 | 55 (26.6) | 35 (16.7) | 60 (29.0) | 32 (21.3) |
| Grade 4 | 12 (5.8) | 8 (3.8) | 13 (6.3) | 4 (2.7) |
| Grade 5 (death) | 13 (6.3) | 6 (2.9) | 17 (8.2) | 21 (14.0) |
| Serious | 48 (23.2) | 45 (21.5) | 54 (26.1) | 51 (34.0) |
| Causing discontinuation of study drug | 11 (5.3) | 7 (3.3) | 16 (7.7) | 16 (10.7) |
| Requiring dose modification | 63 (30.4) | 43 (20.6) | 72 (34.8) | 47 (31.3) |

a. Subjects were randomized to sorafenib, unblinded, and continued sorafenib treatment (on open-label). AEs are those reported during both the double-blind and open label periods (cumulative), during treatment with sorafenib
b. Subjects were randomized to placebo, unblinded, and crossed over to open-label sorafenib treatment. AEs are those reported during the open-label period only, during treatment with sorafenib

Table 30: Study 14295 - Incidence of Any TEAE by MedDRA SOC

| | Double-blind Treatment | | Double-blind + Open-label Sorafenib[a] | Open-label Sorafenib After Crossover (Prior Placebo)[b] |
|---|---|---|---|---|
| | Sorafenib | Placebo | | |
| | N=207<br>n (%) | N=209<br>n (%) | N=207<br>n (%) | N=150<br>n (%) |
| **All MedDRA SOCs[c]** | 204 (98.6) | 183 (87.6) | 204 (98.6) | 149 (99.3) |
| Skin and Subcutaneous Tissue Disorders | 192 (92.8) | 72 (34.4) | 194 (93.7) | 135 (90.0) |
| Gastrointestinal Disorders | 176 (85.0) | 88 (42.1) | 179 (86.5) | 118 (78.7) |
| Investigations | 146 (70.5) | 70 (33.5) | 151 (72.9) | 90 (60.0) |
| General Disorders and Administrative Site Conditions | 137 (66.2) | 81 (38.8) | 143 (69.1) | 84 (56.0) |
| Metabolism and Nutrition Disorders | 103 (49.8) | 32 (15.3) | 107 (51.7) | 65 (43.3) |
| Musculoskeletal and Connective Tissue Disorders | 100 (48.3) | 84 (40.2) | 106 (51.2) | 61 (40.7) |
| Respiratory, Thoracic and Mediastinal Disorders | 100 (48.3) | 79 (37.8) | 105 (50.7) | 74 (49.3) |
| Nervous System Disorders | 92 (44.4) | 45 (21.5) | 97 (46.9) | 54 (36.0) |
| Vascular Disorders | 90 (43.5) | 27 (12.9) | 92 (44.4) | 48 (32.0) |
| Infections and Infestations | 82 (39.6) | 54 (25.8) | 89 (43.0) | 48 (32.0) |
| Psychiatric Disorders | 29 (14.0) | 15 (7.2) | 32 (15.5) | 20 (13.3) |
| Renal and Urinary Disorders | 27 (13.0) | 10 (4.8) | 29 (14.0) | 8 (5.3) |
| Blood and Lymphatic System Disorders | 26 (12.6) | 14 (6.7) | 27 (13.0) | 34 (22.7) |
| Neoplasms Benign, Malignant and Unspecified[d] | 24 (11.6) | 24 (11.5) | 29 (14.0) | 22 (14.7) |
| Reproductive System and Breast Disorders | 24 (11.6) | 6 (2.9) | 24 (11.6) | 17 (11.3) |
| Injury, Poisoning and Procedural Complications | 21 (10.1) | 22 (10.5) | 25 (12.1) | 10 (6.7) |
| Cardiac Disorders | 21 (10.1) | 17 (8.1) | 24 (11.6) | 16 (10.7) |
| Eye Disorders | 19 (9.2) | 18 (8.6) | 20 (9.7) | 11 (7.3) |
| Ear and Labyrinth Disorders | 12 (5.8) | 5 (2.4) | 15 (7.2) | 5 (3.3) |
| Surgical and Medical Procedures | 7 (3.4) | 1 (0.5) | 7 (3.4) | 2 (1.3) |
| Hepatobiliary Disorders | 6 (2.9) | 4 (1.9) | 6 (2.9) | 2 (1.3) |
| Endocrine Disorders | 5 (2.4) | 5 (2.4) | 5 (2.4) | 3 (2.0) |
| Immune System Disorders | 5 (2.4) | 3 (1.4) | 5 (2.4) | 2 (1.3) |
| Social Circumstances | 0 | 0 | 0 | 2 (1.3) |

a. Subjects were randomized to sorafenib, unblinded, and continued sorafenib treatment (on open-label). AEs are those reported during both the double-blind and open label periods (cumulative), during treatment with sorafenib

b. Subjects were randomized to placebo, unblinded, and crossed over to open-label sorafenib treatment. AEs are those reported during the open-label period only, during treatment with sorafenib

c. SOCs are ordered from highest to lowest frequency in the double-blind sorafenib group.

d. Including cysts and polyps

Table 31: Study 14295 - Incidence of Common Adverse Events (Reported for ≥ 10% of Sorafenib Subjects during Double-blind Period) by MedDRA SOC and PT and CTCAE Grade

| | | Double-blind Treatment | | Double-blind + Open-label Sorafenib[a] | Open-label Sorafenib After Crossover (Prior Placebo)[b] |
|---|---|---|---|---|---|
| | | Sorafenib | Placebo | | |
| | | N=207 n (%) | N=209 n (%) | N=207 n (%) | N=150 n (%) |
| **Any Adverse Event** | **Total** | 204 (98.6) | 183 (87.6) | 204 (98.6) | 149 (99.3) |
| **Skin & Subcutaneous Tissue Disorders** | | | | | |
| Palmar-plantar | Total | 143 (69.1) | 16 (7.7) | 145 (70.0) | 85 (56.7) |
| erythrodysaesthesia | Grade 1-2 | 103 (49.8) | 16 (7.7) | 104 (50.2) | 63 (42.0) |
| syndrome | Grade 3 | 40 (19.3) | 0 | 41 (19.8) | 22 (14.7) |
| | Grade 4 | 0 | 0 | 0 | 0 |
| | Grade 5 | 0 | 0 | 0 | 0 |
| Alopecia | Total | 138 (66.7) | 16 (7.7) | 139 (67.1) | 85 (56.7) |
| | Grade 1-2 | 138 (66.7) | 16 (7.7) | 139 (67.1) | 85 (56.7) |
| | Grade 3 | 0 | 0 | 0 | 0 |
| | Grade 4 | 0 | 0 | 0 | 0 |
| | Grade 5 | 0 | 0 | 0 | 0 |
| Rash | Total | 73 (35.3) | 15 (7.2) | 74 (35.7) | 44 (29.3) |
| | Grade 1-2 | 63 (30.4) | 15 (7.2) | 64 (30.9) | 39 (26.0) |
| | Grade 3 | 10 (4.8) | 0 | 10 (4.8) | 5 (3.3) |
| | Grade 4 | 0 | 0 | 0 | 0 |
| | Grade 5 | 0 | 0 | 0 | 0 |
| Pruritus | Total | 42 (20.3) | 22 (10.5) | 42 (20.3) | 18 (12.0) |
| | Grade 1-2 | 41 (19.8) | 22 (10.5) | 41 (19.8) | 18 (12.0) |
| | Grade 3 | 1 (0.5) | 0 | 1 (0.5) | 0 |
| | Grade 4 | 0 | 0 | 0 | 0 |
| | Grade 5 | 0 | 0 | 0 | 0 |
| Dry skin[c] | Total | 27 (13.0) | 10 (4.8) | 28 (13.5) | 14 (9.3) |
| | Grade 1-2 | 26 (12.5) | 10 (4.8) | 27 (13.0) | 14 (9.3) |
| | Grade 3 | 1 (0.5) | 0 | 1 (0.5) | 0 |
| | Grade 4 | 0 | 0 | 0 | 0 |
| | Grade 5 | 0 | 0 | 0 | 0 |
| Erythema | Total | 21 (10.1) | 1 (0.5) | 21 (10.1) | 13 (8.7) |
| | Grade 1-2 | 21 (10.1) | 1 (0.5) | 21 (10.1) | 13 (8.7) |
| | Grade 3 | 0 | 0 | 0 | 0 |
| | Grade 4 | 0 | 0 | 0 | 0 |
| | Grade 5 | 0 | 0 | 0 | 0 |
| **Gastrointestinal Disorders** | | | | | |
| Diarrhoea | Total | 140 (67.6) | 31 (14.8) | 143 (69.1) | 84 (56.0) |
| | Grade 1-2 | 128 (61.8) | 29 (13.9) | 131 (63.3) | 78 (52.0) |
| | Grade 3 | 11 (5.3) | 2 (1.0) | 11 (5.3) | 6 (4.0) |
| | Grade 4 | 1 (0.5) | 0 | 1 (0.5) | 0 |
| | Grade 5 | 0 | 0 | 0 | 0 |
| Nausea | Total | 43 (20.8) | 24 (11.5) | 45 (21.7) | 41 (27.3) |
| | Grade 1-2 | 43 (20.8) | 24 (11.5) | 45 (21.7) | 40 (26.7) |
| | Grade 3 | 0 | 0 | 0 | 1 (0.7) |
| | Grade 4 | 0 | 0 | 0 | 0 |
| | Grade 5 | 0 | 0 | 0 | 0 |
| Constipation | Total | 32 (15.5) | 16 (7.7) | 35 (16.9) | 25 (16.7) |
| | Grade 1-2 | 32 (15.5) | 15 (7.2) | 35 (16.9) | 24 (16.0) |
| | Grade 3 | 0 | 1 (0.5) | 0 | 1 (0.7) |
| | Grade 4 | 0 | 0 | 0 | 0 |
| | Grade 5 | 0 | 0 | 0 | 0 |

| | | Double-blind Treatment | | Double-blind + Open-label Sorafenib[a] | Open-label Sorafenib After Crossover (Prior Placebo)[b] |
|---|---|---|---|---|---|
| | | Sorafenib | Placebo | | |
| | | N=207 n (%) | N=209 n (%) | N=207 n (%) | N=150 n (%) |
| Stomatitis | Total | 23 (11.1) | 5 (2.4) | 23 (11.1) | 14 (9.3) |
| | Grade 1-2 | 22 (10.6) | 5 (2.4) | 22 (10.6) | 12 (8.0) |
| | Grade 3 | 1 (0.5) | 0 | 1 (0.5) | 2 (1.3) |
| | Grade 4 | 0 | 0 | 0 | 0 |
| | Grade 5 | 0 | 0 | 0 | 0 |
| Vomiting | Total | 23 (11.1) | 12 (5.7) | 23 (11.1) | 11 (7.3) |
| | Grade 1-2 | 22 (10.6) | 12 (5.7) | 22 (10.6) | 10 (6.7) |
| | Grade 3 | 1 (0.5) | 0 | 1 (0.5) | 1 (0.7) |
| | Grade 4 | 0 | 0 | 0 | 0 |
| | Grade 5 | 0 | 0 | 0 | 0 |
| Abdominal pain | Total | 22 (10.6) | 6 (2.9) | 24 (11.6) | 17 (11.3) |
| | Grade 1-2 | 20 (9.6) | 5 (2.4) | 22 (10.6) | 14 (9.3) |
| | Grade 3 | 2 (1.0) | 1 (0.5) | 2 (1.0) | 3 (2.0) |
| | Grade 4 | 0 | 0 | 0 | 0 |
| | Grade 5 | 0 | 0 | 0 | 0 |
| **Investigations** | | | | | |
| Weight decreased | Total | 101 (48.8) | 29 (13.9) | 104 (50.2) | 62 (41.3) |
| | Grade 1-2 | 89 (43.0) | 27 (12.9) | 88 (42.5) | 50 (33.3) |
| | Grade 3 | 12 (5.8) | 2 (1.0) | 16 (7.7) | 12 (8.0) |
| | Grade 4 | 0 | 0 | 0 | 0 |
| | Grade 5 | 0 | 0 | 0 | 0 |
| Blood TSH increased[d] | Total | 69 (33.3) | 28 (13.4) | 72 (34.8) | 35 (23.3) |
| | Grade 1-2 | 69 (33.3) | 28 (13.4) | 72 (34.8) | 35 (23.3) |
| | Grade 3 | 0 | 0 | 0 | 0 |
| | Grade 4 | 0 | 0 | 0 | 0 |
| | Grade 5 | 0 | 0 | 0 | 0 |
| Alanine aminotransferase increased | Total | 26 (12.6) | 9 (4.3) | 26 (12.6) | 12 (8.0) |
| | Grade 1-2 | 20 (9.7) | 9 (4.3) | 20 (9.7) | 10 (6.7) |
| | Grade 3 | 5 (2.4) | 0 | 5 (2.4) | 1 (0.7) |
| | Grade 4 | 1 (0.5) | 0 | 1 (0.5) | 1 (0.7) |
| | Grade 5 | 0 | 0 | 0 | 0 |
| Aspartate aminotransferase increased | Total | 23 (11.1) | 5 (2.4) | 23 (11.1) | 9 (6.0) |
| | Grade 1-2 | 21 (10.1) | 5 (2.4) | 21 (10.1) | 8 (5.3) |
| | Grade 3 | 2 (1.0) | 0 | 2 (1.0) | 0 |
| | Grade 4 | 0 | 0 | 0 | 1 (0.7) |
| | Grade 5 | 0 | 0 | 0 | 0 |
| **General Disorders and Administrative Site Conditions** | | | | | |
| Fatigue | Total | 85 (41.1) | 42 (20.1) | 87 (42.0) | 37 (24.7) |
| | Grade 1-2 | 75 (36.2) | 40 (19.1) | 77 (37.2) | 35 (23.4) |
| | Grade 3 | 10 (4.8) | 2 (1.0) | 10 (4.8) | 2 (1.3) |
| | Grade 4 | 0 | 0 | 0 | 0 |
| | Grade 5 | 0 | 0 | 0 | 0 |
| Asthenia | Total | 25 (12.1) | 14 (6.7) | 27 (13.0) | 19 (12.7) |
| | Grade 1-2 | 25 (12.1) | 14 (6.7) | 26 (12.5) | 15 (10.0) |
| | Grade 3 | 0 | 0 | 1 (0.5) | 4 (2.7) |
| | Grade 4 | 0 | 0 | 0 | 0 |
| | Grade 5 | 0 | 0 | 0 | 0 |

| | | Double-blind Treatment | | Double-blind + Open-label Sorafenib[a] | Open-label Sorafenib After Crossover (Prior Placebo)[b] |
|---|---|---|---|---|---|
| | | Sorafenib | Placebo | | |
| | | N=207 n (%) | N=209 n (%) | N=207 n (%) | N=150 n (%) |
| Pyrexia | Total | 22 (10.6) | 10 (4.8) | 24 (11.6) | 19 (12.7) |
| | Grade 1-2 | 20 (9.6) | 10 (4.8) | 22 (10.6) | 19 (12.7) |
| | Grade 3 | 2 (1.0) | 0 | 2 (1.0) | 0 |
| | Grade 4 | 0 | 0 | 0 | 0 |
| | Grade 5 | 0 | 0 | 0 | 0 |
| Mucosal inflammation | Total | 21 (10.1) | 1 (0.5) | 22 (10.6) | 13 (8.7) |
| | Grade 1-2 | 18 (8.6) | 1 (0.5) | 19 (9.1) | 13 (8.7) |
| | Grade 3 | 2 (1.0) | 0 | 2 (1.0) | 0 |
| | Grade 4 | 1 (0.5) | 0 | 1 (0.5) | 0 |
| | Grade 5 | 0 | 0 | 0 | 0 |
| **Metabolism & Nutrition Disorders** | | | | | |
| Decreased appetite | Total | 63 (30.4) | 10 (4.8) | 66 (31.9) | 38 (25.3) |
| | Grade 1-2 | 59 (28.5) | 10 (4.8) | 62 (30.0) | 36 (24.0) |
| | Grade 3 | 4 (1.9) | 0 | 4 (1.9) | 2 (1.3) |
| | Grade 4 | 0 | 0 | 0 | 0 |
| | Grade 5 | 0 | 0 | 0 | 0 |
| Hypocalcemia | Total | 34 (16.4) | 10 (4.8) | 36 (17.4) | 21 (14.0) |
| | Grade 1-2 | 16 (7.8) | 7 (3.3) | 17 (8.2) | 16 (10.7) |
| | Grade 3 | 12 (5.8) | 1 (0.5) | 13 (6.3) | 3 (2.0) |
| | Grade 4 | 6 (2.9) | 2 (1.0) | 6 (2.9) | 2 (1.3) |
| | Grade 5 | 0 | 0 | 0 | 0 |
| **Musculoskeletal and Connective Tissue Disorders** | | | | | |
| Pain in extremity | Total | 30 (14.5) | 14 (6.7) | 33 (15.9) | 22 (14.7) |
| | Grade 1-2 | 28 (13.5) | 14. (6.7) | 31 (14.9) | 20 (13.3) |
| | Grade 3 | 2 (1.0) | 0 | 2 (1.0) | 2 (1.3) |
| | Grade 4 | 0 | 0 | 0 | 0 |
| | Grade 5 | 0 | 0 | 0 | 0 |
| Arthralgia | Total | 21 (10.1) | 16 (7.7) | 22 (10.6) | 14 (9.3) |
| | Grade 1-2 | 21 (10.1) | 13 (6.3) | 22 (10.6) | 14 (9.3) |
| | Grade 3 | 0 | 3 (1.4) | 0 | 0 |
| | Grade 4 | 0 | 0 | 0 | 0 |
| | Grade 5 | 0 | 0 | 0 | 0 |
| Back pain | Total | 21 (10.1) | 22 (10.5) | 25 (12.1) | 15 (10.0) |
| | Grade 1-2 | 19 (9.1) | 17 (8.1) | 21 (10.2) | 10 (6.7) |
| | Grade 3 | 2 (1.0) | 4 (1.9) | 4 (1.9) | 5 (3.3) |
| | Grade 4 | 0 | 1 (0.5) | 0 | 0 |
| | Grade 5 | 0 | 0 | 0 | 0 |
| Muscle spasms | Total | 21 (10.1) | 6 (2.9) | 22 (10.6) | 6 (4.0) |
| | Grade 1-2 | 21 (10.1) | 6 (2.9) | 22 (10.6) | 6 (4.0) |
| | Grade 3 | 0 | 0 | 0 | 0 |
| | Grade 4 | 0 | 0 | 0 | 0 |
| | Grade 5 | 0 | 0 | 0 | 0 |
| **Respiratory, Thoracic & Mediastinal Disorders** | | | | | |
| Cough | Total | 31 (15.0) | 29 (13.9) | 32 (15.5) | 17 (11.3) |
| | Grade 1-2 | 31 15.0) | 29 (13.9) | 32 (15.5) | 17 (11.3) |
| | Grade 3 | 0 | 0 | 0 | 0 |
| | Grade 4 | 0 | 0 | 0 | 0 |
| | Grade 5 | 0 | 0 | 0 | 0 |

| | | Double-blind Treatment | | Double-blind + Open-label Sorafenib[a] | Open-label Sorafenib After Crossover (Prior Placebo)[b] |
|---|---|---|---|---|---|
| | | Sorafenib | Placebo | | |
| | | N=207 n (%) | N=209 n (%) | N=207 n (%) | N=150 n (%) |
| Dysphonia | Total | 26 (12.6) | 7 (3.3) | 27 (13.0) | 10 (6.7) |
| | Grade 1-2 | 25 (12.1) | 7 (3.3) | 26 (12.5) | 10 (6.7) |
| | Grade 3 | 1 (0.5) | 0 | 1 (0.5) | 0 |
| | Grade 4 | 0 | 0 | 0 | 0 |
| | Grade 5 | 0 | 0 | 0 | 0 |
| Dyspnea | Total | 25 (12.1) | 22 (10.5) | 28 (13.5) | 18 (12.0) |
| | Grade 1-2 | 15 (7.3) | 14 (6.7) | 16 (7.7) | 12 (8.0) |
| | Grade 3 | 9 (4.3) | 5 (2.4) | 10 (4.8) | 4 (2.7) |
| | Grade 4 | 0 | 2 (1.0) | 0 | 0 |
| | Grade 5 | 1 (0.5) | 1 (0.5) | 2 (1.0) | 2 (1.3) |
| **Nervous System Disorders** | | | | | |
| Headache | Total | 35 (16.9) | 13 (6.2) | 36 (17.4) | 16 (10.7) |
| | Grade 1-2 | 35 (16.9) | 13 (6.2) | 36 (17.4) | 16 (10.7) |
| | Grade 3 | 0 | 0 | 0 | 0 |
| | Grade 4 | 0 | 0 | 0 | 0 |
| | Grade 5 | 0 | 0 | 0 | 0 |
| **Vascular Disorders** | | | | | |
| Hypertension | Total | 79 (38.2) | 23 (11.0) | 81 (39.1) | 43 (28.7) |
| | Grade 1-2 | 60 (29.0) | 19 (9.1) | 62 (29.9) | 33 (22.0) |
| | Grade 3 | 19 (9.2) | 4 (1.9) | 19 (9.2) | 10 (6.7) |
| | Grade 4 | 0 | 0 | 0 | 0 |
| | Grade 5 | 0 | 0 | 0 | 0 |

a. Subjects were randomized to sorafenib, unblinded, and continued sorafenib treatment (on open-label). AEs are those reported during both the double-blind and open label periods (cumulative), during treatment with sorafenib

b. Subjects were randomized to placebo, unblinded, and crossed over to open-label sorafenib treatment. AEs are those reported during the open-label period only, during treatment with sorafenib

c. Subject 16002-0008 was randomized to placebo, but erroneously was dispensed sorafenib for cycle 1. The subject experienced 2 drug-related TEAEs during cycle 2 (within 30 days of sorafenib exposure). These events are captured under placebo treatment.

d. Because TSH suppression is standard of care for this disease, a protocol-defined non-CTCAE grading of Grade 1 = ≥ 0.5 mIU/L was used, and was coded to the term "blood TSH increased"

Source: Module 5.3.5.1, Report A57578, Table 14.3.3/18, Table 14.3.4/13, Table 14.3.3/22, and Table 14.3.4/17

Note: A similar table presenting TEAEs with incidence rates of at least 1% during double-blind+open-label treatment is provided in Module 5.3.5.1, Report A57578, Table 14.3.4/14.

Table 32: Pivotal RCC Study: Treatment-Emergent Adverse Events Occurring in at Least 10% of Patients

| Adverse Event<br>CTCAE Category/ Term | Sorafenib<br>N=384<br>n | (%) | Placebo<br>N=384<br>n | (%) |
|---|---|---|---|---|
| Any event | 325 | (84.6) | 283 | (73.7) |
| Cardiovascular, General | | | | |
| **Hypertension** | **41** | **(10.7)** | **3** | **(0.8)** |
| Constitutional symptoms | | | | |
| Fatigue | 101 | (26.3) | 90 | (23.4) |
| Dermatology/skin | | | | |
| **Rash/ desquamation** | **129** | **(33.6)** | **51** | **(13.3)** |
| **Hand -foot skin reaction** | **103** | **(26.8)** | **18** | **(4.7)** |
| **Alopecia** | **88** | **(22.9)** | **12** | **(3.1)** |
| **Pruritus** | **65** | **(16.9)** | **17** | **(4.4)** |
| Gastrointestinal symptoms | | | | |
| **Diarrhoea** | **126** | **(32.8)** | **38** | **(9.9)** |
| Nausea | 68 | (17.7) | 57 | (14.8) |
| Anorexia | 47 | (12.2) | 37 | (9.6) |
| Constipation | 45 | (11.7) | 29 | (7.6) |
| Vomiting | 43 | (11.2) | 33 | (8.6) |

**Adverse Events by Cycle**

New events of rash peaked during the first treatment cycle and new events grade 3 or more were uncommon after the first cycle. After cycle 2, the prevalence of rash grade 1 dominated. The reduced prevalence of grade 2 and higher events probably reflects dose reductions.

The incidence of hand foot skin reactions showed a similar patter to rash, onset mainly during cycle one with a total incidence of 50+%, equally divided between grade 1, 2 and 3.

The prevalence of hand foot skin reactions peaked later compared with rash. In late cycles, grade 2 events were seen in about 8% of patients (skin changes with pain limiting instrumental ADL).

Most instances of diarrhoea in sorafenib-treated subjects started early in treatment, particularly in the first cycle of treatment. New occurrences appeared in each cycle of treatment, but these were occurred at less than half the rate observed in Cycle 1. New onset may occur later than skin reactions, encompassing also grade 2 events (increase of 4-6 stools per day). In sorafenib-treated subjects, the prevalence of diarrhoea gradually increased until Cycle 6 and then remained stable thereafter. Despite dose reductions and interruptions, the prevalence of diarrhoea increased over time and grade 2 and 3 seemed not to decrease.

Fatigue was an early new event; cycle 1 dominated, also with respect to new onset grade 2 and 3 (3=not relieved by rest, limiting self-care ADL). Fatigue remained rather stable over time at about twice the level seen in the placebo group. Grade 1 dominated (relieved by rest).

Weight loss was cumulative. From cycle 7 and on about 20% of the patients showed grade 2 weight loss (10 - <20% from baseline).

Recording increased TSH > 0.5 mU/L as an adverse event was a study specific AE. The definition of this event was based on the need to suppress TSH as part of standard of care for differentiated thyroid cancer. Elevations of TSH above 0.5 mU/L were requested to be recorded as Grade 1 AEs based solely on laboratory findings.

New cases of TSH >0.5 mU/L were recruited over the full study period, the prevalence maximum was reached at cycle 5, about 18%.

The prevalence of hypocalcaemia was rather stable from cycle 3 and grade 3 or more was reported in about 2% of patients (grade 3 < 7 mg/mL, grade 4 <6 mg/mL). One event of hypocalcaemia resulted in discontinuation of sorafenib and one case was reported as a serious event.

The overall prevalence of hypertension was rather stable, grade 3 about 3% (>160 or >100 mm Hg, intensified therapy, e.g. more than one drug indicated, perhaps not too frightening from an oncology perspective).

Subjects received concomitant medications to mitigate hypertension. Overall, 6 (2.9%) subjects in the sorafenib group and 9 (4.3%) subjects in the placebo group received anti-hypertensives during the study and a total of 4 (1.9%) subjects in the sorafenib group and 3 (1.4%) subjects in the placebo group received new anti-hypertensives during the study, suggesting that most instances of hypertension did not require pharmacological treatment.

**Adverse events by ECOG**

Table 33: Sub-Group Analysis of Adverse Events by ECOG PS (0 or 1) – Overview of Adverse Events (Safety Analysis Set)

| | Sorafenib (N=207) | | Placebo (N=209) | |
|---|---|---|---|---|
| | ECOG 0 N=130 n (%) | ECOG 1 N=69 n (%) | ECOG 0 N=128 n (%) | ECOG 1 N=74 n (%) |
| **Any TEAE** | 128 (98.5) | 69 (100.0) | 110 (85.9) | 67 (90.5) |
| Worst grade: | | | | |
| Grade 3 | 78 (60.0) | 28 (40.6) | 28 (21.9) | 18 (24.3) |
| Grade 4 | 14 (10.8) | 9 (13.0) | 7 (5.5) | 7 (9.5) |
| Grade 5 (death) | 3 (2.3) | 9 (13.0) | 1 (0.8) | 5 (6.8) |
| Serious | 40 (30.8) | 34 (49.3) | 30 (23.4) | 23 (31.1) |
| Leading to discontinuation of study drug | 28 (21.5) | 10 (14.5) | 3 (2.3) | 4 (5.4) |
| Leading to dose modification | 100 (76.9) | 57 (82.6) | 35 (27.3) | 27 (36.5) |

**Adverse events by exposure group**

Table 34: Treatment-emergent adverse events of special interest during double-blind treatment period by worst CTCAE grade and sorafenib pop-AUC subgroup

| | | Number of Subjects (%) in subgroup | | |
|---|---|---|---|---|
| NCI CTCAE term | Worst NCI CTC Grade of AE | low (AUC 46-78 mg·h/L) N=39 | Medium (AUC 79-118 mg·h/L) N=78 | high (AUC 118-205 mg·h/L) N=39 |
| Any AE | Grade 1 | 0 | 5 ( 6.4%) | 2 ( 5.1%) |
| | Grade 2 | 10 ( 25.6%) | 18 ( 23.1%) | 11 ( 28.2%) |
| | Grade 3 | 23 ( 59.0%) | 39 ( 50.0%) | 19 ( 48.7%) |
| | Grade 4 | 5 ( 12.8%) | 9 ( 11.5%) | 4 ( 10.3%) |
| | Grade 5 | 1 ( 2.6%) | 7 ( 9.0%) | 3 ( 7.7%) |
| | Total | 39 (100.0%) | 78 (100.0%) | 39 (100.0%) |
| Any SAE | Grade 2 | 3 ( 7.7%) | 3 ( 3.8%) | 2 ( 5.1%) |
| | Grade 3 | 8 ( 20.5%) | 13 ( 16.7%) | 5 ( 12.8%) |
| | Grade 4 | 5 ( 12.8%) | 6 ( 7.7%) | 2 ( 5.1%) |
| | Grade 5 | 1 ( 2.6%) | 7 ( 9.0%) | 3 ( 7.7%) |
| | Total | 17 ( 43.6%) | 29 ( 37.2%) | 12 ( 30.8%) |
| Any drug-related AE | Grade 1 | 2 ( 5.1%) | 11 ( 14.1%) | 2 ( 5.1%) |
| | Grade 2 | 16 ( 41.0%) | 27 ( 34.6%) | 18 ( 46.2%) |
| | Grade 3 | 20 ( 51.3%) | 31 ( 39.7%) | 18 ( 46.2%) |
| | Grade 4 | 1 ( 2.6%) | 5 ( 6.4%) | 1 ( 2.6%) |
| | Grade 5 | 0 | 1 ( 1.3%) | 0 |
| | Total | 39 (100.0%) | 75 ( 96.2%) | 39 (100.0%) |
| Any AE causing permanent discontinuation | Grade 1 | 0 | 0 | 1 ( 2.6%) |
| | Grade 2 | 2 ( 5.1%) | 2 ( 2.6%) | 2 ( 5.1%) |
| | Grade 3 | 1 ( 2.6%) | 6 ( 7.7%) | 3 ( 7.7%) |
| | Grade 4 | 2 ( 5.1%) | 1 ( 1.3%) | 0 |
| | Grade 5 | 0 | 1 ( 1.3%) | 1 ( 2.6%) |
| | Total | 5 ( 12.8%) | 10 ( 12.8%) | 7 ( 17.9%) |
| Any AE causing dose modification (but no discontinuation) | Grade 1 | 0 | 4 ( 5.1%) | 2 ( 5.1%) |
| | Grade 2 | 9 ( 23.1%) | 11 ( 14.1%) | 10 ( 25.6%) |
| | Grade 3 | 17 ( 43.6%) | 32 ( 41.0%) | 15 ( 38.5%) |
| | Grade 4 | 5 ( 12.8%) | 6 ( 7.7%) | 3 ( 7.7%) |
| | Grade 5 | 0 | 0 | 1 ( 2.6%) |
| | Total | 31 ( 79.5%) | 53 ( 67.9%) | 31 ( 79.5%) |
| Any AE causing death | Grade 5 | 1 ( 2.6%) | 7 ( 9.0%) | 3 ( 7.7%) |
| | Total | 1 ( 2.6%) | 7 ( 9.0%) | 3 ( 7.7%) |

| | | | | |
|---|---|---|---|---|
| Hypertension | Grade 1 | 4 ( 10.3%) | 10 ( 12.8%) | 3 ( 7.7%) |
| | Grade 2 | 10 ( 25.6%) | 17 ( 21.8%) | 6 ( 15.4%) |
| | Grade 3 | 5 ( 12.8%) | 5 ( 6.4%) | 5 ( 12.8%) |
| | Total | 19 ( 48.7%) | 32 ( 41.0%) | 14 ( 35.9%) |
| Diarrhea | Grade 1 | 20 ( 51.3%) | 33 ( 42.3%) | 15 ( 38.5%) |
| | Grade 2 | 7 ( 17.9%) | 17 ( 21.8%) | 17 ( 43.6%) |
| | Grade 3 | 3 ( 7.7%) | 4 ( 5.1%) | 1 ( 2.6%) |
| | Grade 4 | 0 | 1 ( 1.3%) | 0 |
| | Total | 30 ( 76.9%) | 55 ( 70.5%) | 33 ( 84.6%) |
| HFSR (hand-foot skin reaction) | Grade 1 | 15 ( 38.5%) | 28 ( 35.9%) | 11 ( 28.2%) |
| | Grade 2 | 10 ( 25.6%) | 22 ( 28.2%) | 13 ( 33.3%) |
| | Grade 3 | 8 ( 20.5%) | 8 ( 10.3%) | 6 ( 15.4%) |
| | Total | 33 ( 84.6%) | 58 ( 74.4%) | 30 ( 76.9%) |

Global Biostatistics: /by-sasp/patdb/projects/439006/14295/stat/prod_interim10/pgms/t-ae-pk-sup.sas eqfcl 29OCT2013 14:56
Source: bay43_9006_14295_ema_poppk, Table 16.1.9.2 / 6d

## Serious adverse event / deaths / other significant events

Table 35: Study 14295 - Summary of Deaths Reported During Double-blind Treatment or up to 30 Days After Discontinuing Double-blind Treatment

| ge (yr) / Sex / Race | Last Dose (mg) | Day of Death[a] | MedDRA Term with Fatal Outcome | Cause of Death | Relationship, as Assessed by the Investigator, to Study Drug | Relationship, as Assessed by the Investigator, to Underlying Disease |
|---|---|---|---|---|---|---|
| Sorafenib | | | | | | |
| 24 / M / White | 800 | 77 / 03 | Dyspnea | Progressive disease | No | Yes |
| 63 / F / White | 600 | 82 / 24 | Thyroid cancer metastatic | Metastatic thyroid carcinoma | No | Yes |
| 71 / M / White | 600 | 95 / 17 | Pleural effusion | Progressive disease | No | Yes |
| 69 / M / White | 800 | 104 / 13 | Tracheal obstruction | Progressive disease | No | Yes |
| 66 / F / White | 800 | 107 / 07 | General physical health deterioration | Progressive disease | No | Yes |
| 73 / F / White | 400 | 117 / 10 | Death | Unknown | No | No |
| 73 / F / Not Reported | 400 | 144 / 0 | Death | Other | No | Yes |
| 58 / F / White | 600 | 250 / 21 | Disease progression | Progressive disease | No | Yes |
| 56 / M / Asian | 800 | 295 / 15 | Lung infection | Other | No | Yes |
| 70 / M / White | 400 | 324 / 0 | Chronic obstructive pulmonary disease | Other | No | Yes |
| 53 / M / White | 600 | 375 / 11 | Pneumonia | Progressive disease | No | Yes |
| 52 / M / White | 800 | 427 / 0 | Myocardial infarction | Toxicity due to study treatment | Yes | Yes |
| Placebo | | | | | | |
| 64 / M / White | 600 | 27 / 4 | Arrhythmia | Progressive disease | No | Yes |
| 61 / M / Asian | 800 | 33 / 17 | Pulmonary embolism | Other | No | Yes |
| 49 / M / White | 800 | 47 / 28 | Dypsnea | Progressive disease | No | Yes |
| 61 / M / White | 800 | 99 / 30 | Pneumonia | Progressive disease | No | Yes |
| 73 / F / White | 600 | 289 / 0 | Subdural hematoma | Toxicity due to study treatment | Yes | Yes |
| 63 / M / White | 400 | 413 / 21 | Thyroid cancer metastatic | Progressive disease | No | Yes |

START of double-blind treatment/ Relative to STOP of double-blind treatment

Two deaths were considered related to the study drug by the investigators:

A 52-year-old Caucasian male died of a myocardial infarction (MI) that was considered to be related to the study drug as well as the underlying condition, although obesity, ex-smoker, advanced thyroid carcinoma with hypothyroidism, heartburn, and hypertension were also cited.

The subject died during cycle 16, 427 days after initiating treatment. Double-blind treatment at 800 mg sorafenib daily was ongoing at the time of death.

A 73-year-old Caucasian female died of a subdural hematoma that was considered to be related to the study drug as well as the underlying condition. During cycle 11, the subject fell and hit her head. She was hospitalized and a large subdural hematoma was diagnosed. A CT of the cervical spine (without

contrast) revealed a vertical fracture of C4, which appeared to represent a pathologic fracture, suspicious for bony metastases, and probably a second metastatic lesion involving the occipital bone.

Abnormal laboratory values included: prolonged partial thromboplastin time (PTT): 35.8

Table 36: Study 14295 - Incidence of Serious Reports of the Most Common SAEs (Reported for ≥ 1% of Sorafenib Subjects During Double-blind Treatment) by MedDRA SOC and PT

| | Double-blind Treatment | | Double-blind + Open-label Sorafenib[a] | Open-label Sorafenib After Crossover (Prior Placebo)[b] |
|---|---|---|---|---|
| | Sorafenib | Placebo | | |
| | N=207 n (%) | N=209 n (%) | N=207 n (%) | N=150 n (%) |
| **Neoplasms Benign, Malignant & Unspecified[c]** | | | | |
| Metastases to bone | 2 (1.0) | 0 | 3 (1.4) | 1 (0.7) |
| Metastases to spine | 2 (1.0) | 1 (0.5) | 2 (1.0) | 2 (1.3) |
| Squamous cell carcinoma skin | 7 (3.4) | 0 | 8 (3.9) | 0 |
| **Respiratory, Thoracic & Mediastinal Disorders** | | | | |
| Dyspnea | 6 (2.9) | 7 (3.3) | 7 (3.4) | 5 (3.3) |
| Pleural effusion | 5 (2.4) | 4 (1.9) | 8 (3.9) | 5 (3.3) |
| **General Disorders and Administrative Site Conditions** | | | | |
| Death | 2 (1.0) | 0 | 2 (1.0) | 0 |
| Fatigue | 2 (1.0) | 1 (0.5) | 2 (1.0) | 0 |
| General physical health deterioration | 2 (1.0) | 0 | 2 (1.0) | 0 |
| Pyrexia | 2 (1.0) | 0 | 2 (1.0) | 0 |
| **Cardiac Disorders** | | | | |
| Myocardial infarction | 2 (1.0) | 0 | 2 (1.0) | 0 |
| Supraventricular tachycardia | 2 (1.0) | 0 | 2 (1.0) | 0 |
| **Nervous System Disorders** | | | | |
| Cerebrovascular accident | 2 (1.0) | 1 (0.5) | 2 (1.0) | 0 |
| **Hepatobiliary Disorders** | | | | |
| Hepatic function abnormal | 2 (1.0) | 0 | 2 (1.0) | 0 |
| **Skin & Subcutaneous Tissue Disorders** | | | | |
| Rash | 2 (1.0) | 0 | 2 (1.0) | 1 (0.7) |
| **Investigations** | | | | |
| Weight decreased | 2 (1.0) | 1 (0.5) | 2 (1.0) | 0 |

a. Subjects were randomized to sorafenib, unblinded, and continued sorafenib treatment (on open-label). AEs are those reported during both the double-blind and open label periods (cumulative), during treatment with sorafenib
b. Subjects were randomized to placebo, unblinded, and crossed over to open-label sorafenib treatment. AEs are those reported during the open-label period only, during treatment with sorafenib
c. Including cysts and polyps

*Squamous cell carcinoma skin*

A product specific search using the term keratoacanthoma /squamous cell carcinoma that occurred in the both double-blind and open-label period of study 14295 was conducted. In 8 subjects treated with sorafenib, grade 3 squamous cell carcinoma of skin was reported 8.6 to 84 weeks following start of treatment: 3 subjects, 8.6, 10.3, and 12.4 weeks; 2 subjects, 28 – 29.9 weeks; and 3 subjects, 41.9, 55.3, and 84 weeks after start of treatment. The subjects all recovered/ event was resolved. There were no reports of grade 3 squamous cell carcinoma in subjects treated with placebo.

Grade 1 keratoacanthoma was reported in 6 subjects treated with sorafenib, 3 subjects randomized to sorafenib, and 3 subjects randomized to placebo with events reported following the start of open-label sorafenib. The grade 1 keratoacanthomas occurred 2.6 to 31.7 weeks following start of sorafenib treatment (either double-blind or open-label); in 2 subjects 2.6 and 4.1 weeks, 3 subjects 12.4 – 18.4 weeks, and in one subject 31.7 weeks. Grade 1 keratoacanthoma was reported in 1 subject 49.7 weeks following start of treatment with placebo (this subject did not receive open-label sorafenib). Grade 2 keratoacanthoma was reported in two subjects randomized to sorafenib (duration of exposure was 80.4 weeks and could not be calculated due to missing date of onset following the start of sorafenib therapy). The outcome of these AEs was recovered/resolved in all cases except one where the outcome was not reported.

## Laboratory findings

*Hematology:* Overall, the mean changes from baseline were modest illustrating that most patients had no or low grade events.

*Thyroid function:* TSH levels were intentionally therapeutically brought to below normal levels (inclusion criteria TSH < 0.5 mIU/L) and patients in this study were to be maintained at TSH <0.5 mIU/L. Those patients whose TSH values rose above this threshold were reported using the protocol-specified AE which was coded to term “blood TSH increased” though this designation was not consistent with a patient having TSH levels that were above normal limits. Based upon these criteria, the incidence of blood TSH increased during the double-blind period was 33.3% in sorafenib-treated patients versus 13.4% in placebo-treated patients The greater incidence of TSH > 0.5 mIU/L in patients who received treatment with sorafenib was anticipated based on the observation that sorafenib is believed to enhance T4 and T3 metabolism by possibly increasing type-3 deiodination and by a sorafenib-related decrease in the clearance of thyrotropin

*Other clinical chemistry measurements:* During the double-blind period, the most commonly observed biochemical abnormalities (> 30% patients) in the sorafenib group were: elevation of ALT (58.9%), elevation of AST (53.6%), hyperglycaemia (52.7%), and hypocalcaemia (35.7%).

Grade 3 or 4 toxicities were uncommon. Grade 3 events which occurred in more than 1 patient who received treatment with sorafenib were observed for hypophosphatemia (12.6%), hypocalcaemia (6.8%), ALT (3.4%), hyperglycaemia (2.9%), hyponatraemia (2.9%), amylase (2.4%), lipase (2.4%), hypokalaemia (1.9%), and AST (1.0%).

Grade 4 biochemical abnormalities that occurred in more than 1 patient during the double-blind treatment period were: hypocalcemia (3.4%), amylase (1.4%), ALT (1.0%), AST (1.0%), and hyperkalaemia (1.0%). Clinically, these abnormalities had limited impact, as evidenced by the low rate of treatment discontinuation due to AEs based on laboratory abnormalities.

Table 37: Treatment-emergent laboratory test abnormalities reported in DTC patient, double blind period

| Laboratory parameter, (in % of samples investigated) | Sorafenib N=207 | | | Placebo N=209 | | |
|---|---|---|---|---|---|---|
| | All Grades* | Grade 3* | Grade 4* | All Grades* | Grade 3* | Grade 4* |
| Blood and lymphatic system disorders | | | | | | |
| Anaemia | 30.9 | 0.5 | 0 | 23.4 | 0.5 | 0 |
| Thrombocytopenia | 18.4 | 0 | 0 | 9.6 | 0 | 0 |
| Neutropenia | 19.8 | 0.5 | 0.5 | 12 | 0 | 0 |
| Lymphopenia | 42 | 9.7 | 0.5 | 25.8 | 5.3 | 0 |
| Metabolism and nutrition disorders | | | | | | |
| Hypokalaemia | 17.9 | 1.9 | 0 | 2.4 | 0 | 0 |
| Hypophosphatemia** | 19.3 | 12.6 | 0 | 2.4 | 1.4 | 0 |
| Hepatobiliary disorders | | | | | | |
| Bilirubin increased | 8.7 | 0 | 0 | 4.8 | 0 | 0 |
| ALT increased | 58.9 | 3.4 | 1.0 | 24.4 | 0 | 0 |
| AST increased | 53.6 | 1.0 | 1.0 | 14.8 | 0 | 0 |
| Investigations | | | | | | |
| Amylase increased | 12.6 | 2.4 | 1.4 | 6.2 | 0 | 1.0 |
| Lipase increased | 11.1 | 2.4 | 0 | 2.9 | 0.5 | 0 |

* Common Terminology Criteria for Adverse Events (CTCAE), version 3.0
** The aetiology of hypophosphatemia associated with sorafenib is not known.

## Safety in special populations

**Adverse Events by Region**

Of the total 207 subjects treated with double-blind sorafenib, 124 were from Europe, 47 from Asia and 36 from North America. Low numbers make comparisons non-informative.

**Adverse Events by Sex**

No clinically meaningful differences.

**Adverse Events by BMI**

As a flat dose is prescribed, the relationship between BMI and AEs was reported with cut-off <25, 25 to 30, >30. No apparent association was seen.

**Adverse Events by age**

Table 38: Study 14295 – Sub-Group Analysis of Adverse Events by Age (<75 years vs ≥75 years) – Overview of Adverse Events (Safety Analysis Set)

| | Sorafenib (N=207) | | Placebo (N=209) | |
|---|---|---|---|---|
| | <75 years N=182 n (%) | ≥75 years N=25 n (%) | <75 years N=179 n (%) | ≥75 years N=30 n (%) |
| **Any TEAE** | 179 (98.4) | 25 (100.0) | 154 (86.0) | 29 (96.7) |
| Worst grade: | | | | |
| Grade 3 | 95 (52.2) | 14 (56.0) | 45 (25.1) | 4 (13.3) |
| Grade 4 | 17 (9.3) | 7 (28.0) | 10 (5.6) | 4 (13.3) |
| Grade 5 (death) | 14 (7.7) | 0 | 6 (3.4) | 0 |
| Serious | 64 (35.2) | 13 (52.0) | 46 (25.7) | 9 (30.0) |
| Leading to discontinuation of study drug | 32 (17.6) | 7 (28.0) | 5 (2.8) | 3 (10.0) |
| Leading to dose modification | 140 (76.9) | 21 (84.0) | 55 (30.7) | 8 (26.7) |

Abbreviations: TEAE= treatment-emergent adverse event

Table 39: Study 14295 – Sub-Group Analysis of Adverse Events by Age (<60 years vs ≥60 years) – Overview of Adverse Events (Safety Analysis Set)

| | Sorafenib (N=207) | | Placebo (N=209) | |
|---|---|---|---|---|
| | <60 years N=80 n (%) | ≥60 years N=127 n (%) | <60 years N=81 n (%) | ≥60 years N=128 n (%) |
| **Any TEAE** | 80 (100.0) | 124 (97.6) | 72 (88.9) | 111 (86.7) |
| Worst grade: | | | | |
| Grade 3 | 45 (56.3) | 64 (50.4) | 20 (24.7) | 29 (22.7) |
| Grade 4 | 12 (15.0) | 12 (9.4) | 7 (8.6) | 7 (5.5) |
| Grade 5 (death) | 5 (6.3) | 9 (7.1) | 1 (1.2) | 5 (3.9) |
| Serious | 28 (35.0) | 49 (38.6) | 24 (29.6) | 31 (24.2) |
| Leading to discontinuation of study drug | 12 (15.0) | 27 (21.3) | 3 (3.7) | 5 (3.9) |
| Leading to dose modification | 62 (77.5) | 99 (78.0) | 26 (32.1) | 37 (28.9) |

## Discontinuation due to adverse events

*Discontinuations, interruptions and dose reductions*

The guidance on dose modification (reduction, interruption or discontinuation) in the study protocol 14295 aimed to maintain subjects on treatment in case of grade 1 AEs with full dose and in case of grade 2 or 3 events with reduced dose.

Table 40: Study 14295 - Incidence of AEs by MedDRA PT Leading to Permanent Discontinuation of Study Drug in ≥ 2 Subjects Treated with Sorafenib

| System Order Class<br>Preferred term | Double-blind Treatment | | Double-blind + Open-label Sorafenib[a] | Open-label Sorafenib After Crossover (Prior Placebo)[b] |
|---|---|---|---|---|
| | Sorafenib | Placebo | | |
| | N=207<br>n (%) | N=209<br>n (%) | N=207<br>n (%) | N=150<br>n (%) |
| **Any AE Leading to Discontinuation** | **39 (18.8)** | **8 (3.8)** | **46 (22.2)** | **28 (18.7)** |
| **Skin and Subcutaneous Tissue Disorders** | **15 (7.2)** | **0** | **16 (7.7)** | **7 (4.7)** |
| Dry skin | 1 (0.5) | 0 | 2 (1.0) | 0 |
| Palmar-plantar erythrodysaesthesia syndrome | 11 (5.3) | 0 | 12 (5.8) | 4 (2.7) |
| Rash | 3 (1.4) | 0 | 3 (1.4) | 2 (1.3) |
| **Respiratory, Thoracic and Mediastinal disorders** | **8 (3.9)** | **1 (0.5)** | **9 (4.3)** | **6 (4.0)** |
| Dyspnea | 2 (1.0) | 1 (0.5) | 2 (1.0) | 1 (0.7) |
| Epistaxis | 2 (1.0) | 0 | 2 (1.0) | 0 |
| Pleural effusion | 2 (1.0) | 0 | 2 (1.0) | 0 |
| **Investigations** | **7 (3.4)** | **2 (1.0)** | **9 (4.3)** | **5 (3.3)** |
| Alanine aminotransferase increased | 2 (1.0) | 0 | 2 (1.0) | 1 (0.7) |
| Weight decreased | 1 (0.5) | 2 (1.0) | 2 (1.0) | 3 (2.0) |
| **Gastrointestinal Disorders** | **5 (2.4)** | **1 (0.5)** | **6 (2.9)** | **2 (1.3)** |
| Diarrhea | 2 (1.0) | 0 | 2 (1.0) | 1 (0.7) |
| **General Disorders and Administration Site Conditions** | **4 (1.9)** | **0** | **6 (2.9)** | 3 (2.0) |
| Fatigue | 2 (1.0) | 0 | 3 (1.4) | 1 (0.7) |
| General physical health deterioration | 1 (0.5) | 0 | 2 (1.0) | 1 (0.7) |
| **Musculoskeletal and Connective Tissue Disorders** | **3 (1.4)** | **0** | **3 (1.4)** | **2 (1.3)** |
| Bone pain | 2 (1.0) | 0 | 2 (1.0) | 1 (0.7) |

a. Subjects were randomized to sorafenib, unblinded, and continued sorafenib treatment (on open-label). AEs are those reported during both the double-blind and open label periods (cumulative), during treatment with sorafenib

b. Subjects were randomized to placebo, unblinded, and crossed over to open-label sorafenib treatment. AEs are those reported during the open-label period only, during treatment with sorafenib

Table 41: Incidence of AEs by MedDRA SOC and PT Requiring a Dose Interruption in ≥ 2 Subjects

| System Order Class<br>Preferred term | Double-blind Treatment | | Double-blind + Open-label Sorafenib[a] | Open-label Sorafenib After Crossover (Prior Placebo)[b] |
|---|---|---|---|---|
| | Sorafenib | Placebo | | |
| | N=207<br>n (%) | N=209<br>n (%) | N=207<br>n (%) | N=150<br>n (%) |
| **Any AE Leading to Dose Interruption** | **137 (66.2)** | **54 (25.8)** | **142 (68.6)** | **81 (54.0)** |
| **Skin and Subcutaneous Tissue Disorders** | **68 (32.9)** | **0** | **68 (32.9)** | **33 (22.0)** |
| Palmar-plantar erythrodysaesthesia syndrome | 54 (26.1) | 0 | 54 (26.1) | 25 (16.7) |
| Rash | 12 (5.8) | 0 | 12 (5.8) | 10 (6.7) |
| Alopecia | 3 (1.4) | 0 | 3 (1.4) | 2 (1.3) |
| Rash maculo-papular | 3 (1.4) | 0 | 3 (1.4) | 1 (0.7) |
| Urticaria | 2 (1.0) | 0 | 2 (1.0) | 1 (0.7) |
| Dermatitis exfoliative | 2 (1.0) | 0 | 2 (1.0) | 0 |
| Skin reaction | 1 (0.5) | 0 | 1 (0.5) | 2 (1.3) |
| Erythema | 0 | 0 | 0 | 2 (1.3) |
| Exfoliative rash | 2 (1.0) | 0 | 2 (1.0) | 1 (0.7) |
| **Gastrointestinal Disorders** | **27 (13.0)** | **7 (3.3)** | **29 (14.0)** | **20 (13.3)** |
| Diarrhea | 7 (3.4) | 2 (1.0) | 7 (3.4) | 4 (2.7) |
| Abdominal pain | 5 (2.4) | 0 | 5 (2.4) | 3 (2.0) |
| Dysphagia | 3 (1.4) | 0 | 5 (2.4) | 2 (1.3) |
| Stomatitis | 3 (1.4) | 0 | 3 (1.4) | 2 (1.3) |
| Abdominal pain upper | 2 (1.0) | 0 | 2 (1.0) | 1 (0.7) |
| Nausea | 2 (1.0) | 1 (0.5) | 2 (1.0) | 1 (0.7) |
| Vomiting | 2 (1.0) | 1 (0.5) | 2 (1.0) | 0 |

| | | | | |
|---|---|---|---|---|
| **General Disorders and Administration Site Conditions** | **23 (11.1)** | **6 (2.9)** | **26 (12.6)** | **9 (6.0)** |
| Fatigue | 12 (5.8) | 2 (1.0) | 14 (6.8) | 3 (2.0) |
| Mucosal inflammation | 3 (1.4) | 0 | 3 (1.4) | 1 (0.7) |
| Asthenia | 2 (1.0) | 0 | 3 (1.4) | 2 (1.3) |
| General physical health deterioration | 1 (0.5) | 0 | 1 (0.5) | 3 (2.0) |
| **Vascular Disorders** | **17 (8.2)** | **3 (1.4)** | **17 (8.2)** | **6 (4.0)** |
| Hypertension | 16 (7.7) | 3 (1.4) | 16 (7.7) | 6 (4.0) |
| **Investigations** | **16 (7.7)** | **5 (2.4)** | **18 (8.7)** | **8 (5.3)** |
| Weight decreased | 5 (2.4) | 2 (1.0) | 7 (3.4) | 4 (2.7) |
| Alanine aminotransferase increased | 5 (2.4) | 0 | 5 (2.4) | 1 (0.7) |
| Aspartate aminotransferase increased | 4 (1.9) | 0 | 4 (1.9) | 0 |
| Amylase increased | 3 (1.4) | 2 (1.0) | 3 (1.4) | 0 |
| **Metabolism and Nutrition Disorders** | **12 (5.8)** | **1 (0.5)** | **13 (6.3)** | **14 (9.3)** |
| Decreased appetite | 5 (2.4) | 0 | 5 (2.4) | 4 (2.7) |
| Hypocalcaemia | 3 (1.4) | 0 | 3 (1.4) | 3 (2.0) |
| Hypophosphataemia | 3 (1.4) | 0 | 3 (1.4) | 5 (3.3) |
| Dehydration | 1 (0.5) | 1 (0.5) | 1 (0.5) | 2 (1.3) |
| **Respiratory, thoracic and mediastinal disorders** | **12 (5.8)** | **14 (6.7)** | **18 (8.7)** | **11 (7.3)** |
| Dyspnea | 4 (1.9) | 4 (1.9) | 5 (2.4) | 3 (2.0) |
| Dysphonia | 2 (1.0) | 1 (0.5) | 2 (1.0) | 1 (0.7) |
| Pleural effusion | 2 (1.0) | 4 (1.9) | 5 (2.4) | 2 (1.3) |
| Hemoptysis | 1 (0.5) | 2 (1.0) | 2 (1.0) | 2 (1.3) |
| Oropharyngeal pain | 0 | 0 | 0 | 2 (1.3) |
| **Musculoskeletal and Connective Tissue Disorders** | **11 (5.3)** | **4 (1.9)** | **13 (6.3)** | **9 (6.0)** |
| Pain in extremity | 4 (1.9) | 0 | 4 (1.9) | 1 (0.7) |
| Bone pain | 3 (1.4) | 0 | 3 (1.4) | 1 (0.7) |
| Musculoskeletal pain | 2 (1.0) | 1 (0.5) | 2 (1.0) | 0 |
| Back pain | 1 (0.5) | 1 (0.5) | 2 (1.0) | 3 (2.0) |
| Musculoskeletal chest pain | 1 (0.5) | 0 | 1 (0.5) | 2 (1.3) |
| Bone lesion | 0 | 0 | 0 | 2 (1.3) |
| **Neoplasms Benign, Malignant and Unspecified (incl cysts and polyps)** | **8 (3.9)** | **10 (4.8)** | **10 (4.8)** | **5 (3.3)** |
| Metastases to spine | 2 (1.0) | 1 (0.5) | 2 (1.0) | 1 (0.7) |
| Metastases to bone | 1 (0.5) | 0 | 2 (1.0) | 1 (0.7) |
| Metastatic pain | 2 (1.0) | 2 (1.0) | 2 (1.0) | 0 |
| **Nervous System Disorders** | **6 (2.9)** | **10 (4.8)** | **8 (3.9)** | **5 (3.3)** |
| Spinal cord compression | 0 | 3 (1.4) | 1 (0.5) | 1 (0.7) |
| **Infections and Infestations** | **6 (2.9)** | **5 (2.4)** | **6 (2.9)** | **8 (5.3)** |
| Influenza | 1 (0.5) | 2 (1.0) | 1 (0.5) | 1 (0.7) |
| Upper respiratory tract infection | 2 (1.0) | 0 | 2 (1.0) | 0 |
| **Surgical and Medical Procedures** | **5 (2.4)** | **0** | **5 (2.4)** | **2 (1.3)** |
| Tooth extraction | 3 (1.4) | 0 | 3 (1.4) | 0 |
| **Cardiac Disorders** | **4 (1.9)** | **1 (0.5)** | **4 (1.9)** | **6 (4.0)** |
| Supraventricular tachycardia | 1 (0.5) | 0 | 2 (1.0) | 0 |
| Atrial fibrillation | 0 | 1 (0.5) | 0 | 2 (1.3) |
| **Blood and Lymphatic System Disorders** | **3 (1.4)** | **2 (1.0)** | **4 (1.9)** | **5 (3.3)** |
| Anemia | 2 (1.0) | 2 (1.0) | 2 (1.0) | 2 (1.3) |

Table 42: Study 14295 - Incidence of AEs by MedDRA PT Leading to Dose Reduction of Study Drug in ≥ 2 Subjects

| System Order Class<br>Preferred term | Double-blind Treatment | | Double-blind + Open-label Sorafenib[a] | Open-label Sorafenib After Crossover (Prior Placebo)[b] |
|---|---|---|---|---|
| | Sorafenib | Placebo | | |
| | N=207<br>n (%) | N=209<br>n (%) | N=207<br>n (%) | N=150<br>n (%) |
| **Any AE Leading to Dose Reduction** | 133 (64.3) | 19 (9.1) | 136 (65.7) | 94 (62.7) |
| **Skin and Subcutaneous Tissue Disorders** | 80 (38.6) | 1 (0.5) | 80 (38.6) | 48 (32.0) |
| Palmar-plantar erythrodysaesthesia syndrome | 69 (33.3) | 1 (0.5) | 69 (33.3) | 35 (23.3) |
| Rash | 12 (5.8) | 0 | 12 (5.8) | 7 (4.7) |
| Skin reaction | 1 (0.5) | 0 | 1 (0.5) | 2 (1.3) |
| **Gastrointestinal Disorders** | 36 (17.4) | 3 (1.4) | 37 (17.9) | 28 (18.7) |
| Diarrhea | 27 (13.0) | 1 (0.5) | 27 (13.0) | 18 (12.0) |
| Abdominal pain upper | 2 (1.0) | 1 (0.5) | 2 (1.0) | 1 (0.5) |
| Mouth ulceration | 2 (1.0) | 0 | 2 (1.0) | 0 |
| Dysphagia | 1 (0.5) | 0 | 2 (1.0) | 2 (1.3) |
| Nausea | 1 (0.5) | 0 | 1 (0.5) | 3 (2.0) |
| Oral pain | 1 (0.5) | 0 | 1 (0.5) | 2 (1.3) |
| Stomatitis | 0 | 0 | 0 | 3 (2.0) |
| **Investigations** | 24 (11.6) | 3 (1.4) | 25 (12.1) | 17 (11.3) |
| Weight decreased | 13 (6.3) | 1 (0.5) | 14 (6.8) | 14 (9.3) |
| Aspartate aminotransferase increased | 4 (1.9) | 0 | 4 (1.9) | 2 (1.3) |
| Alanine aminotransferase increased | 3 (1.4) | 0 | 3 (1.4) | 3 (2.0) |
| Amylase increased | 3 (1.4) | 1 (0.5) | 3 (1.4) | 0 |
| **General Disorders and Administration Site Conditions** | 13 (6.3) | 5 (2.4) | 16 (7.7) | 10 (6.7) |
| Fatigue | 6 (2.9) | 3 (1.4) | 8 (3.9) | 3 (2.0) |
| Asthenia | 2 (1.0) | 1 (0.5) | 3 (1.4) | 3 (2.0) |
| Mucosal inflammation | 2 (1.0) | 1 (0.5) | 2 (1.0) | 2 (1.3) |
| **Metabolism and Nutrition Disorders** | 13 (6.3) | 0 | 15 (7.2) | 14 (9.3) |
| Hypocalcaemia | 5 (2.4) | 0 | 7 (3.4) | 6 (4.0) |
| Decreased appetite | 4 (1.9) | 0 | 4 (1.9) | 5 (3.3) |
| Hypophosphataemia | 3 (1.4) | 0 | 3 (1.4) | 2 (1.3) |
| Hypoalbuminaemia | 1 (0.5) | 0 | 1 (0.5) | 0 |
| **Vascular Disorders** | 13 (6.3) | 2 (1.0) | 13 (6.3) | 4 (2.7) |
| Hypertension | 12 (5.8) | 1 (0.5) | 12 (5.8) | 4 (2.7) |
| **Musculoskeletal and Connective Tissue Disorders** | 5 (2.4) | 3 (1.4) | 6 (2.9) | 5 (3.3) |
| Bone pain | 3 (1.4) | 0 | 3 (1.4) | 1 (0.7) |
| Pain in extremity | 2 (1.0) | 0 | 2 (1.0) | 1 (0.7) |
| Musculoskeletal pain | 1 (0.5) | 0 | 1 (0.5) | 1 (0.7) |
| **Blood and Lymphatic system Disorders** | 4 (1.9) | 0 | 4 (.9) | 5 (3.3) |
| Anemia | 1 (0.5) | 0 | 1 (0.5) | 2 (1.3) |
| Neutropenia | 1 (0.5) | 0 | 1 (0.5) | 2 (1.3) |

The most common reason for dose reduction for both grade 3 and grade 2 adverse events was hand foot skin reaction. Among the 56 subjects whose initial dose reduction was for a grade 3 AE, 27 had HFSR as reason for dose reduction. Among the 70 subjects whose initial dose reduction was for a grade 2 event, 25 had HFSR as reason for the dose reduction. Following dose reduction for HFSR, investigators commonly attempted dose re-escalation (59% of subjects following a grade 3 HFSR event and 68% of the subjects following a grade 2 adverse event).

Data on the grade of rash, HFSR, diarrhoea and fatigue after first dose reduction or dose interruption followed by dose reduction caused by the following AEs (grade 2 and 3): rash, hand foot skin reactions, diarrhoea and fatigue, were submitted. As the patterns of AEs post dose reduction were rather similar, only reductions caused by HFSR are presented.

Table 43: Summary of the highest grading of selected adverse events (rash, hand foot skin reaction, diarrhoea and fatigue)

After first dose reduction or dose interruption followed by dose reduction for Grade 3 hand foot skin reactions

| | Subjects n (%) |
|---|---|
| **First dose reduction for grade 3 HFSR** | **27 ( 100%)** |
| Dose escalated after initial dose reduction | 16 ( 59%) |
| Dose not escalated after initial dose reduction | 11 ( 41%) |
| **HFSR – highest grade after first dose reduction** | |
| Grade 1 | 14[a] ( 52%) |
| Grade 2 | 6[b] ( 22%) |
| Grade 3 | 6[c] ( 22%) |
| Any grade | 26 ( 96%) |
| None (resolved) | 1[d] |
| **Diarrhoea – highest grade after first dose reduction** | |
| Grade 1 | 15[e] ( 56%) |
| Grade 2 | 3[f] ( 11%) |
| Grade 3 | 1[g] ( 4%) |
| Grade 4 | 0 ( 0%) |
| Any grade | 19 ( 70%) |
| **Fatigue – highest grade after first dose reduction** | |
| Grade 1 | 9[h] ( 33%) |
| Grade 2 | 4[i] ( 15%) |
| Grade 3 | 0 ( 0%) |
| Grade 4 | 0 ( 0%) |
| Any grade | 13 ( 48%) |
| **Rash – highest grade after first dose reduction** | |
| Grade 1 | 9[j] ( 33%) |
| Grade 2 | 1[k] ( 4%) |
| Grade 3 | 1[l] ( 4%) |
| Grade 4 | 0 ( 0%) |
| Any grade | 11 ( 41%) |

After first dose reductions for Grade 2 hand foot skin reactions

| | Subjects n (%) |
|---|---|
| **First dose reduction for a grade 2 HFSR** | **25 ( 100%)** |
| Dose escalated after initial dose reduction | 17 ( 68%) |
| Dose not escalated after initial dose reduction | 8 ( 32%) |
| **HFSR – highest grade after first dose reduction** | |
| Grade 1 | 12[a] ( 48%) |
| Grade 2 | 13[b] ( 52%) |
| Grade 3 | 0 ( 0%) |
| Any grade | 25 (100%) |
| **Diarrhoea – highest grade after first dose reduction** | |
| Grade 1 | 11[c] ( 44%) |
| Grade 2 | 2[d] ( 8%) |
| Grade 3 | 1[e] ( 4%) |
| Grade 4 | 0 ( 0%) |
| Any grade | 14 ( 56%) |
| **Fatigue – highest grade after first dose reduction** | |
| Grade 1 | 7[f] ( 28%) |
| Grade 2 | 2[g] ( 8%) |
| Grade 3 | 3[h] ( 12%) |
| Grade 4 | 0 ( 0%) |
| Any grade | 12 ( 48%) |
| **Rash – highest grade after first dose reduction** | |
| Grade 1 | 7[i] ( 28%) |
| Grade 2 | 3[j] ( 12%) |
| Grade 3 | 0 ( 0%) |
| Grade 4 | 0 ( 0%) |
| Any grade | 10 ( 40%) |

Table 44: Subjects on reduced / interrupted dose or withdrawn for other reasons than PD, per cycle (full analysis set/cut-off 31 August 2012)

| Cycle number (Day 1) | | Sorafenib N=207 | Placebo N=210 |
|---|---|---|---|
| Cycle 1 | N at risk | 207 (100.0%) | 210 (100.0%) |
| | Number (%) on interrupted dose | 76 ( 36.7%) | 12 ( 5.7%) |
| | Number (%) on reduced dose | 72 ( 34.8%) | 38 ( 18.1%) |
| | Number (%) withdrawn for other than PD | 9 ( 4.3%) | 2 ( 1.0%) |
| Cycle 2 | N at risk | 196 (100.0%) | 203 (100.0%) |
| | Number (%) on interrupted dose | 51 ( 26.0%) | 12 ( 5.9%) |
| | Number (%) on reduced dose | 105 ( 53.6%) | 36 ( 17.7%) |
| | Number (%) withdrawn for other than PD | 3 ( 1.5%) | 1 ( 0.5%) |
| Cycle 3 | N at risk | 189 (100.0%) | 193 (100.0%) |
| | Number (%) on interrupted dose | 31 ( 16.4%) | 22 ( 11.4%) |
| | Number (%) on reduced dose | 109 ( 57.7%) | 28 ( 14.5%) |
| | Number (%) withdrawn for other than PD | 3 ( 1.6%) | 2 ( 1.0%) |
| Cycle 4 | N at risk | 175 (100.0%) | 165 (100.0%) |
| | Number (%) on interrupted dose | 22 ( 12.6%) | 14 ( 8.5%) |
| | Number (%) on reduced dose | 97 ( 55.4%) | 29 ( 17.6%) |
| | Number (%) withdrawn for other than PD | 3 ( 1.7%) | 0 |
| Cycle 5 | N at risk | 165 (100.0%) | 148 (100.0%) |
| | Number (%) on interrupted dose | 15 ( 9.6%) | 12 ( 8.1%) |
| | Number (%) on reduced dose | 97 ( 58.8%) | 24 ( 16.2%) |
| | Number (%) withdrawn for other than PD | 1 ( 0.6%) | 1 ( 0.7%) |
| Cycle 6 | N at risk | 157 (100.0%) | 124 (100.0%) |
| | Number (%) on interrupted dose | 15 ( 9.6%) | 7 ( 5.6%) |
| | Number (%) on reduced dose | 93 ( 59.2%) | 24 ( 19.4%) |
| | Number (%) withdrawn for other than PD | 2 ( 1.3%) | 0 |
| Cycle 7 | N at risk | 152 (100.0%) | 111 (100.0%) |
| | Number (%) on interrupted dose | 13 ( 8.6%) | 7 ( 6.3%) |
| | Number (%) on reduced dose | 88 ( 57.9%) | 20 ( 18.0%) |
| | Number (%) withdrawn for other than PD | 2 ( 1.3%) | 0 |
| Cycle 8 | N at risk | 141 (100.0%) | 104 (100.0%) |
| | Number (%) on interrupted dose | 11 ( 7.8%) | 10 ( 9.6%) |
| | Number (%) on reduced dose | 86 ( 61.0%) | 17 ( 16.3%) |
| | Number (%) withdrawn for other than PD | 3 ( 2.1%) | 0 |
| Cycle 9 | N at risk | 132 (100.0%) | 92 (100.0%) |
| | Number (%) on interrupted dose | 7 ( 5.3%) | 4 ( 4.3%) |
| | Number (%) on reduced dose | 81 ( 61.4%) | 16 ( 17.4%) |
| | Number (%) withdrawn for other than PD | 0 | 0 |

## 2.5.2. Discussion on clinical safety

Median duration of therapy in the DTC study was clearly longer than in hepatocellular cancer (HCC), but reasonably comparable to renal cell carcinoma (RCC). Despite this, dose reductions/interruptions were more frequently undertaken in the DTC study and median dose intensity was lower.

Due to adverse reactions it is expected that double blind conditions in study 14295 were protected only in a rather small proportion of sorafenib patients. About 60% of patients experience grade 3/4 adverse events (AEs)/Adverse drug reactions on treatment with sorafenib. Also, an increased incidence of grade 5 events was observed in the sorafenib arms.

An evaluation of the exposure-safety relationship including all subjects in study 14295 with available PK data using predicted AUC values from the PPK analysis was provided. No association between sorafenib exposure and frequency or severity of AEs were found. However, the analysis was limited since early exposure was related to the frequency of AEs at any time without taking into consideration dose adjustments or interruptions during treatment which may have distorted the relationship. Nevertheless, adverse events data presented per cycle showed that early AEs of grade >2 (e.g. HFS and hypertension) were handled by dose reductions as the frequency decreased over time and thereby indirectly showed a relationship between dose and AEs.

AEs leading to discontinuation of sorafenib were frequent, about 20% combining drug-related and disease-related events with a difference to placebo about 14%. Adverse events leading to dose-reduction in the placebo arm were of multiple categories, with no particular pattern, and most of them admittedly attributable to disease causes, easily comprised within the expectable errors of the imputation rules. Overall, 19% on sorafenib versus 4% on placebo discontinued therapy permanently due to AEs, the most common adverse event being hand-foot skin reactions, 5%. 37% of patients had dose interruption and 35% had dose reduction in cycle 1.

Skin reactions led to dose interruptions in about 1 in 3 patients and altogether 2 out of 3 underwent dose interruptions for any cause to be compared with RCC patients where 10% had interruption of therapy.

The incidence of ARs by MedDRA SOC and PT requiring a dose interruption in ≥ 2 patients reflects the overall AR pattern for sorafenib. Dose reductions were undertaken for typical side effects, but at a very high overall frequency, two thirds of the patients.

The adverse reactions reported were in general well-known for sorafenib but seemed to occur at a clearly higher percentage of patients than in RCC (see table 32 from the pivotal RCC study). The frequencies of several known adverse reactions for sorafenib have been adequately updated in the product information. In the analysis of cumulative safety data (including study 14295), new adverse drug reactions were also reported with sorafenib: mucosal inflammation, dysgeusia, muscle spasm hyperkeratosis and flushing. These adverse reactions have been added to section 4.8 of the SmPC.

With regard to the reports of deaths, reliable causality assessments were in most cases impossible as causes might be underlying disease, co-morbidities, study drug or an interaction between drug and medical conditions. However, more patients died as a TEAE in the sorafenib arm. This might at least partly be explained by a longer observation period.

Cases of squamous cell carcinoma were reported in the pivotal study. Squamous cell carcinoma is mechanistically related to B-RAF inhibition. The incidence of keratoacanthoma/squamous cell cancer of the skin was clearly unbalanced with a much higher incidence in the sorafenib arm. Although it is acknowledged that patients with thyroid cancer are at increased risk to develop secondary neoplasia, keratoacanthoma or squamous cell cancer of the skin are usually not part of these. Keratoacanthoma and squamous cell cancer of the skin were usually late events but well within the life span of trial patients, and in some cases occurring early in the course of treatment (as early as 3 weeks after treatment onset). The frequency of keratoacanthoma/squamous cell cancer has been revised to ‘common’ in the SmPC. No information is available on the pattern of genetic events in theses lesions was noticed.

Hypocalcaemia grade 3 and 4 occurred in 6.8% and 3.4% of sorafenib-treated patients with differentiated thyroid cancer. The underlying causes of hypocalcaemia and secondary hyperparathyroidism have not been conclusively defined, but the reason for the observed increased risk in patients with thyroid cancer is highly likely to be related to thyroidectomy. Cases of Torsades de Pointes (TdP) have not been identified in the safety data base, but the number of patients with thyroid cancer is limited. Severe hypocalcaemia should be corrected to prevent complications such as QT-prolongation or torsade de pointes (see section 4.4 of the SmPC). The RMP has been updated to list TdP as an important potential risk.

TSH increase grade 1-2 was observed in about 1 in 3 patients treated with sorafenib, versus about 1 in 8 placebo patients. Therefore, when using sorafenib in differentiated thyroid carcinoma patients, close monitoring of TSH level is recommended (see section 4.4 of the SmPC).

There was no safety data in patients with untreated tracheal, bronchial, and oesophageal infiltration. Due to the potential risk of bleeding, tracheal, bronchial, and oesophageal infiltration should be treated with localised therapy prior to administering sorafenib in patients with differentiated thyroid carcinoma (see section 4.4 of the SmPC).

The MAH provided data on the prevalence and incidence of particular adverse reactions (rash, HFSR, diarrhoea, fatigue weight loss, TSH, hypocalcemia, hypertension) with grade by treatment cycle. Most adverse reactions occurred early and already during cycle 1 about 70% of patients underwent dose reduction/interruption. Percentage of patients with dose interruption decreased over time from close to 40% to about 5%, whilst patients on reduced dose increased from about 1/3 to about 60% already at cycles 2 to 3; combining them, around 70% from cycle 1 to cycle 9.

Some events, such as rash and perhaps hand-foot skin reactions appeared sensitive to dose reductions whilst this appeared not to be the case for diarrhoea and fatigue, for example. Data on the grade of rash, HFSR, diarrhoea and fatigue after first dose reduction or dose interruption followed by dose reduction showed similar patterns of AEs post dose reduction. Dose reduction was partially effective in reducing adverse events.

The protocol of study 14295 provided recommendations for dose reductions/interruptions for haematological events, non-haematological events (except skin toxicity and hypertension), hypertension and skin toxicity. When dose reduction is necessary during the treatment of differentiated thyroid carcinoma, the dose should be reduced to 600 mg daily in divided doses (two tablets of 200 mg and one tablet of 200 mg twelve hours apart). If additional dose reduction is necessary, Nexavar may be reduced to 400 mg daily in divided doses of 200 mg twelve hours apart and if necessary further reduced to one tablet of 200 mg once daily. After improvement of non-haematological adverse reactions, the dose of Nexavar may be increased. This is adequately reflected in the SmPC. In order to assess whether a less toxic dose regimen can be implemented whilst maintaining efficacy in the DTC population, it is proposed that a time-to-event (TTE) analysis be performed using data from the phase III pivotal trial 14295. The MAH is recommended to submit the results once available.

Adverse events by ECOG were presented. SAEs and grade 5 events were reported in patients with ECOG 1 (sorafenib and placebo arm). A subgroup analysis of AE by age was also presented. Numbers were very small, but it appeared that sorafenib was rather poorly tolerated in patients >75 years of age. Using a cut-off of 60, no meaningful differences were seen.

## 2.5.3. Conclusions on clinical safety

For unknown reasons the exposure to sorafenib is increased in patients with DTC compared with RCC and HCC. This resulted in a higher frequency and severity of common adverse drug reactions.

Most adverse reactions occurred early and already during cycle 1 about 70% of patients underwent dose reduction/interruption. Therefore, as recommended in the SmPC, there should be a repeat evaluation of the benefits and risks, taking into account the anti-tumour activity and tolerability of the treatment, and management of suspected adverse drug reactions may require temporary interruption or dose reduction of sorafenib therapy early in the treatment.

## 2.5.4. PSUR cycle

The PSUR cycle remains unchanged.

The annex II related to the PSUR refers to the EURD list which remains unchanged.

## *2.6. Risk management plan*

### 2.6.1. PRAC advice

The CHMP received the following PRAC advice on the submitted Risk Management Plan.

### PRAC Advice

The PRAC considered that the risk management system version 12 could be acceptable with revisions required as described in the attached PRAC endorsed PRAC Rapporteur assessment report.

The CHMP endorsed this advice without changes.

The MAH implemented the changes requested in the RMP by PRAC and CHMP. The CHMP endorsed the changes to the Risk Management Plan with the following content (new text marked as underlined, deletions marked as strikethrough):

***Safety concerns***

| **Summary of safety concerns** | |
|---|---|
| Important identified risks | Severe skin adverse events Hand-foot skin reaction (HFSR)<br>Hypertension<br>Reversible posterior leukoencephalopathy syndrome (RPLS)<br>Hemorrhage including lung hemorrhage, gastrointestinal (GI) hemorrhage and cerebral hemorrhage<br>Arterial thrombosis (myocardial infarction)<br>Congestive heart failure (CHF)<br>Squamous cell cancer of the skin<br>Gastrointestinal perforation<br>Symptomatic pancreatitis and increases in lipase and amylase<br>Hypophosphatemia<br>Safety and efficacy in patients with non-small cell cancer of the lung (NSCLC) with squamous histology<br>Renal dysfunction<br>Interstitial lung disease-like events<br>Drug-induced hepatitis |
| Important potential risks | Arterial thrombosis (cerebral Ischemia)<br>Wound healing complications<br>Microangiopathy<br><u>Torsade De Pointes</u><br>Pregnancy |
| Missing information | Safety in children and adolescents<br>Safety and efficacy in patiens with hepatocellular cancer (HCC) and Child-Pugh B liver dysfunction |

***Pharmacovigilance plan***

Table 45: On-going and planned studies additional PhV studies / activities in the Pharmacovigilance Plan

| Study/activity type, title and category (1-3) | Objectives | Safety concerns addressed | Status | Date for submission of interim or final reports |
|---|---|---|---|---|
| E2805 (ASSURE) ECOG Study "A randomized, Double-Blind Phase III Trial of Adjuvant Sunitinib versus Sorafenib versus Placebo in Patients with Resected Renal Cell Carcinoma" (category 3) | Assessment of longitudinal cardiac function through serial MUGA scanning. | Congestive heart failure | started | Final data are expected in 2016; Interim analysis presented at ASCO 2012 annual meeting |

***Risk minimisation measures***

| Safety concern | Routine risk minimisation measures | Additional risk minimisation measures |
|---|---|---|
| Severe skin adverse events | *Text in Summary of Product Characteristics (SmPC):*<br>Section 4.4 Warnings and Precautions:<br>Hand-foot skin reaction (palmar-plantar erythrodysaesthesia) and rash represent the most common adverse drug reactions with Nexavar. Rash and hand-foot skin reaction are usually CTC (Common Toxicity Criteria) Grade 1 and 2 and generally appear during the first six weeks of treatment with Nexavar. Management of dermatological toxicities may include topical therapies for symptomatic relief, temporary treatment interruption and/or dose modification of Nexavar, or in severe or persistent cases, permanent discontinuation of Nexavar (see section 4.8).<br>Stevens-Johnson syndrome is listed as a rare adverse drug reaction (ADR) and erythema multiforme as an uncommon ADR in Section 4.8 of the SmPC. | None |
| Hand-foot skin reaction | *Text in SmPC:*<br>Section 4.4 Warnings and Precautions:<br>Hand-foot skin reaction (palmar-plantar erythrodysaesthesia) and rash represent the most common adverse drug reactions with Nexavar. Rash and hand-foot skin reaction are usually CTC (Common Toxicity Criteria) Grade 1 and 2 and generally appear during the first six weeks of treatment with Nexavar. Management of dermatological toxicities may include topical therapies for symptomatic relief, temporary treatment interruption and/or dose modification of Nexavar, or in severe or persistent cases, permanent discontinuation of Nexavar (see section 4.8). | None |

| Safety concern | Routine risk minimisation measures | Additional risk minimisation measures |
|---|---|---|
| | HFSR is listed as a very common ADR in Section 4.8 of the SmPC. | |
| Hypertension | *Text in SmPC:*<br>Section 4.4 Warnings and Precautions:<br>An increased incidence of arterial hypertension was observed in Nexavar®-treated patients. Hypertension was usually mild to moderate, occurred early in the course of treatment, and was amenable to management with standard antihypertensive therapy. Blood pressure should be monitored regularly and treated, if required, in accordance with standard medical practice. In cases of severe or persistent hypertension, or hypertensive crisis despite institution of antihypertensive therapy, permanent discontinuation of Nexavar should be considered (see section 4.8).<br>Hypertension is listed as a very commong and hypertensive crisis as an uncommong ADR in Section 4.8 of the SmPC. | None |
| Reversible posterior leukoencephalopathy syndrome | RPLS is listed as an uncommon ADR in Section 4.8 of the SmPC. | None |
| Hemorrhage including lung hemorrhage, gastroinestinal hemorrhage and cerebral hemorrhage | *Text in SmPC:*<br>Section 4.4 Warnings and Precautions:<br>An increased risk of bleeding may occur following Nexavar administration. If any bleeding event necessitates medical intervention it is recommended that permanent discontinuation of Nexavar should be considered (see section 4.8).<br>Disease specific warnings:<br>*Haemorrhage in DTC*<br>Due to the potential risk of bleeding, tracheal, bronchial, and oesophageal infiltration should be treated with localized therapy prior to administering Nexavar® in patients with differentiated thyroid carcinoma.<br>Section 4.8. Undesirable Effects<br>Hemorrhage (including from the respiratory tract and GI tract and cerebral hemorrhage, which may be fatal or life-threatening in nature) is listed as a very common ADR in Section 4.8 of the SmPC. | None |
| Arterial thrombosis (myocardial infarction) | *Text in SmPC:*<br>Section 4.4 Warnings and Precautions:<br>In a randomised, placebo-controlled, double-blind study (study 1, see section 5.1) the incidence of treatment-emergent cardiac ischaemia/infarction events was higher in the Nexavar group (4.9 %) compared with the placebo group (0.4 %). In study 3 (see section 5.1) the incidence of treatment-emergent cardiac ischaemia/infarction events was 2.7 % in Nexavar patients compared with 1.3 % in the placebo group. Patients with unstable coronary artery disease or recent | None |

| Safety concern | Routine risk minimisation measures | Additional risk minimisation measures |
|---|---|---|
| | myocardial infarction were excluded from these studies. Temporary or permanent discontinuation of Nexavar should be considered in patients who develop cardiac ischaemia and/or infarction (see section 4.8).<br>Cardiac ischemia and/or infarction are listed as common ADRs in section 4.8 of the SmPC. | |
| Congestive heart failure | CHF is a listed event in the ADR section 4.8 of the SmPC. | None |
| Squamous cell cancer of the skin | Keratoacanthoma/squamous cell carcinoma of the skin are listed as common ADRs in section 4.8 of the SmPC. | None |
| Gastrointestinal perforation | GI perforation is listed as an uncommon ADR in section 4.8 of the SmPC. | None |
| Symptomatic pancreatitis and increases in lipase and amylase | Lipase increase and amylase increase are listed as very common ADRs in section 4.8 of the SmPC. Laboratory data of lipase and amylase are reported in section 4.8 (laboratory test abnormalities).<br>Pancreatitis is listed as an uncommon ADR in section 4.8 of the SmPC. | None |
| Hypophosphatemia | Hypophosphatemia is listed as a very common ADR in section 4.8 of the SmPC. Laboratory data of hypophosphatemia are reported in section 4.8 (laboratory test abnormalities). | None |
| Safety and efficacy in patients with non-small cell lung cancer of the lung (NSCLC) with squamous histology | *Text in SmPC*<br>Section 4.4 Warnings and Precautions:<br>Higher mortality has been reported in patients with squamous cell carcinoma of the lung treated with sorafenib in combination with platinum-based chemotherapies. In two randomised trials investigating patients with Non-Small Cell Lung Cancer in the subgroup of patients with squamous cell carcinoma treated with sorafenib as add-on to paclitaxel/carboplatin, the HR for overall survival was found to be 1.81 (95% CI 1.19; 2.74) and as add-on to gemcitabine/cisplatin 1.22 (95% CI 0.82; 1.80). No single cause of death dominated, but higher incidence of respiratory failure, hemorrhages and infectious adverse events were observed in patients treated with sorafenib as add-on to platinum-based chemotherapies.<br>Findings of inferior survival in squamous cell NSCLC patients from the ESCAPE trial have been included in Secion 4.4. of the SmPC. No additional labeling is considered to be required by Bayer at this time.<br>The Nexavar® SmPC does not contain reference to unapproved indications. However the use in this indication is considered to be small, and potentially has fallen since the publication of the ESCAPE data. Bayer will continue to monitor off label use in lung cancer patients. | None |
| Renal dysfunction | *Text in SmPC* | None |

| Safety concern | Routine risk minimisation measures | Additional risk minimisation measures |
|---|---|---|
| | Section 4.2 Posology and Method of Administration:<br>Renal impairment<br>No dose adjustment is required in patients with mild, moderate or severe renal impairment. No data is available in patients requiring dialysis (see section 5.2). Monitoring of fluid balance and electrolytes in patients at risk of renal dysfunction is advised.<br>Renal failure is listed as a common ADR in section 4.8 of the SmPC. | |
| Interstitial lung-disease like events | Interstitial lung disease-like events have been added as an uncommon and potentially life-threating/fatal ADR in section 4.8 of the ADR. | None |
| Drug-induced hepatitis | The company has included drug-induced hepatitis as a rare and potentially life-threating/fatal ADR in section 4.8 of the ADR. | None |
| Arterial thrombosis (cerebral ischemia) | Cerebral ischemia is not a listed as an ADR for Nexavar as a causal association is not established. | None |
| Wound healing complications | *Text in SmPC*<br>Section 4.4 Warnings and Precautions:<br>No formal studies of the effect of sorafenib on wound healing have been conducted. Temporary interruption of Nexavar therapy is recommended for precautionary reasons in patients undergoing major surgical procedures. There is limited clinical experience regarding the timing of reinitiation of therapy following major surgical intervention. Therefore, the decision to resume Nexavar® therapy following a major surgical intervention should be based on clinical judgement of adequate wound healing. | None |
| Microangiopathy | Microangiopathy is not listed as an ADR for Nexavar. | None |
| Torsade de pointes | *Text in SmPC*<br>Section 4.4 Warnings and Precautions:<br>QT interval prolongation<br>Nexavar has been shown to prolong the QT/QTc interval (see section 5.1), which may lead to an increased risk for ventricular arrhythmias. Use sorafenib with caution in patients who have, or may develop prolongation of QTc, such as patients with a congenital long QT syndrome, patients treated with a high cumulative dose of anthracycline therapy, patients taking certain anti-arrhythmic medicines or other medicinal products that lead to QT prolongation, and those with electrolyte disturbances such as hypokalaemia, hypocalcaemia, or hypomagnesaemia. When using Nexavar in these patients, periodic monitoring with on-treatment electrocardiograms and electrolytes (magnesium, potassium, calcium) should be considered. | None |

| Safety concern | Routine risk minimisation measures | Additional risk minimisation measures |
|---|---|---|
| | Disease specific warnings:<br>*Hypocalcaemia in DTC*<br>When using sorafenib in patients with differentiated thyroid carcinoma, close monitoring of blood calcium level is recommended. In clinical trials, hypocalcaemia was more frequent and more severe in patients with differentiated thyroid carcinoma, especially with a history of hypoparathyroidism, compared to patients with renal cell or hepatocellular carcinoma. Hypocalcaemia grade 3 and 4 occurred in 6.8% and 3.4% of sorafenib-treated patients with differentiated thyroid cancer. (see section 4.8). Severe hypocalcaemia should be corrected to prevent complications such as QT-prolongation or torsade de pointes (see section QT prolongation).<br>QT prolongation is listed as a rare ADR in section 4.8 of the ADR.<br>5.1 Pharmacodynamic properties<br>In a clinical pharmacology study, QT/QTc measurements were recorded in 31 patients at baseline (pre-treatment) and post-treatment. After one 28-day treatment cycle, at the time of maximum concentration of sorafenib, QTcB was prolonged by 4 ±19 msec and QTcF by 9 ±18 msec, as compared to placebo treatment at baseline. No subject showed a QTcB or QTcF >500 msec during the post-treatment ECG monitoring (see section 4.4). | |
| Pregnancy | *Text in SmPC*<br>Section 4.6 Pregnancy and breast-feeding:<br>Pregnancy<br>There are no data on the use of sorafenib in pregnant women. Studies in animals have shown reproductive toxicity including malformations (see section 5.3). In rats, sorafenib and its metabolites were demonstrated to cross the placenta and sorafenib is anticipated to cause harmful effects on the foetus. Nexavar should not be used during pregnancy unless clearly necessary, after careful consideration of the needs of the mother and the risk to the foetus.<br>Women of childbearing potential must use effective contraception during treatment.<br>Breast-feeding<br>It is not known whether sorafenib is excreted in human milk. In animals, sorafenib and/or its metabolites were excreted in milk. Because sorafenib could harm infant growth and development (see section 5.3), women must not breastfeed during sorafenib treatment. | None |
| Use in children and adolescents | *Text in SmPC*<br>Section 4.2 Posology and method of administration<br>Paediatric population<br>The safety and efficacy of Nexavar in | None |

| Safety concern | Routine risk minimisation measures | Additional risk minimisation measures |
|---|---|---|
| | children and adolescents aged < 18 years have not yet been established. No data are available.<br>Section 5.3 Preclinical safety data<br>After repeated dosing to young and growing dogs effects on bone and teeth were observed at exposures below the clinical exposure. Changes consisted in irregular thickening of the femoral growth plate, hypocellularity of the bone marrow next to the altered growth plate and alterations of the dentin composition. Similar effects were not induced in adult dogs. | |
| Safety and efficacy in patients with hepatocellular carcinoma (HCC) and Child-Pugh B liver dysfunction | *Text in SmPC*<br>Section 4.2 Posology and method of administration<br>Hepatic impairment<br>No dose adjustment is required in patients with Child Pugh A or B (mild to moderate) hepatic impairment. No data is available on patients with Child Pugh C (severe) hepatic impairment (see sections 4.4 and 5.2).<br>Section 4.4 Warnings and Precautions:<br>Hepatic impairment<br>No data is available on patients with Child Pugh C (severe) hepatic impairment. Since sorafenib is mainly eliminated via the hepatic route exposure might be increased in patients with severe hepatic impairment (see sections 4.2 and 5.2).<br>Section 5.2 Pharmacokinetic properties<br>Hepatic impairment<br>In hepatocellular carcinoma (HCC) patients with Child-Pugh A or B (mild to moderate) hepatic impairment, exposure values were comparable and within the range observed in patients without hepatic impairment. The pharmacokinetics (PK) of sorafenib in Child-Pugh A and B non-HCC patients were similar to the PK in healthy volunteers. There are no data for patients with Child-Pugh C (severe) hepatic impairment. Sorafenib is mainly eliminated via the liver, and exposure might be increased in this patient population. | None |

## *2.7. Update of the Product information*

As a consequence of this new indication, sections 4.1, 4.2, 4.4, 4.8, 5.1, 5.2, 5.3 and 6.6 of the SmPC have been updated (see discussions on non-clinical aspects, clinical pharmacology, clinical efficacy and clinical safety).

The Package Leaflet is updated accordingly.

Changes were also made to the PI to bring it in line with the current Agency/QRD template version 9.0.

In addition the MAH took the opportunity to update the list of the local representatives in the package leaflet.

### *2.8. User consultation*

A justification for not performing a full user consultation with target patient groups on the package leaflet has been submitted by the applicant and has been found acceptable for the following reasons:

The Package Leaflet submitted as part of the present application is based on the current Package Leaflet which has proven readability. Since the main issues of the package leaflet have already been tested, no new user testing was considered necessary. The changes made to the package leaflet to align with the SmPC are limited.

However, since the last user testing for Nexavar had been conducted in 2005 the MAH plans to perform a new user testing within a year, which is also recommended by the CHMP.

# 3. Benefit-Risk Balance

## Benefits

## Beneficial effects

Evidence of efficacy is provided by a randomised phase III trial that included a representative sample of patients and showed a clinically significant difference of five months in the primary objective progression free survival relatively to placebo. Median PFS time was 10.8 months in the sorafenib arm versus 5.8 months in the placebo arm (HR=0.587, 95%CI: 0.454; 0.758). PFS data appeared statistically robust (<0.0001).

No important heterogeneities with respect to relative activity were observed from planned subgroup analysis, but as expected patients with a lower tumour burden, lung only metastases and papillary histology had a better prognosis. In an additional post-hoc analysis by maximum tumour size, patients with a maximum tumour size of less than 1.5 cm appeared to have less benefit with a HR of 0.87 (95% CI: 0.40 - 1.89). In addition, the results for patients who were retrospectively categorized as symptomatic at baseline (median PFS sorafenib, 326 days; placebo, 109 days, HR [95%CI] 0.386 [0.207; 0.720]) were numerically superior to the results in asymptomatic patients (median PFS sorafenib 329 days, placebo 220 days HR [95%CI] 0.602 [0.448; 0.807]).

The independently reviewed confirmed ORR was about 12%.

## Uncertainty in the knowledge about the beneficial effects

Patients with likely symptomatic disease were only identified retrospectively as there was no systematic collection of data about the presence or absence of thyroid cancer related symptoms in the case report forms at baseline. Information about further progression at the time of enrolment in comparison to most recent progression was also not collected in study 14295. However, based on the available data, the CHMP considered that maximum lesion size, symptoms related to the disease and progression rate are important factors to be considered when evaluating the prognosis in the individual patient before initiating treatment (see section 4.4 of the SmPC).

## Risks

### Unfavourable effects

The reported adverse events and serious adverse events in the pivotal and in the phase II studies were in general in line with adverse events described for the use of sorafenib in previously approved indications. However, a higher frequency and severity of common adverse drug reactions were identified. Particularly, hypocalcaemia was more frequent and more severe in patients with differentiated thyroid carcinoma, especially with a history of hypoparathyroidism, compared to patients with renal cell or hepatocellular carcinoma. Therefore, close monitoring of blood calcium level is recommended and severe hypocalcaemia should be corrected to prevent complications such as QT-prolongation or torsade de pointes. In addition, increases in TSH levels were observed in patients with DTC treated with sorafenib and close monitoring is also recommended.

Most adverse reactions occurred early and already during cycle 1 about 70% of patients underwent dose reduction and or interruption. Dose reductions were partially successful in alleviating symptoms. Therefore, when to initiate therapy is a critical clinical decision point as well as if to continue therapy in case of disturbing side effects (see sections 4.2 and 4.4 of the SmPC).

### Uncertainty in the knowledge about the unfavourable effects

There is no safety data in patients with untreated tracheal, bronchial, and oesophageal infiltration. Due to the potential risk of bleeding, tracheal, bronchial, and oesophageal infiltration should be treated with localised therapy prior to administering sorafenib (see section 4.4 of the SmPC).

For unknown reasons, exposure to sorafenib is doubled in patients with thyroid cancer and this is likely to be the main cause of increased adverse reactions resulting in a stable, negative impact on HRQoL as estimated by FACT-G and EQ5D. The MAH is recommended to undertake further pharmacokinetic studies aiming at clarifying the grounds for the increased exposure from a mechanistic perspective.

## Benefit-Risk Balance

### Importance of favourable and unfavourable effects

In the full study population a statistically convincing PFS benefit of about 5 months (HR: 0.587) has been shown and is considered clinically relevant.

Baseline factors predictive of increased risk have not been identified, but it should be noticed that about half of the patients were ‘not at all’ or ‘only a bit bothered’ by side effects and that dose reductions were partly successful in alleviating symptoms. Due to the character of all frequent adverse drug reactions they are highly likely to be fully reversible after stopping therapy. Therefore, adverse reactions are expected to be managed through dose interruptions and dose reductions. Repeat evaluation of benefit and risk is also recommended taking anti-tumour activity and tolerability into account.

### Benefit-risk balance

The benefit risk balance of Nexavar in the treatment of patients with progressive, locally advanced or metastatic, differentiated (papillary/follicular/Hürthle cell) thyroid carcinoma, refractory to radioactive iodine is considered positive.

### Discussion on the Benefit-Risk Balance

Based on the available safety and efficacy data, the CHMP recommended the approval of sorafenib for use in patient with progressive DTC refractory to radioactive iodine and considered that the prognosis in the individual patient should be carefully assessed considering maximum lesion size, symptoms related to the disease and progression rate. In addition, the CHMP considered that the risk of adverse reactions could be mitigated with appropriate evaluation and monitoring of the patient's symptoms by the physician. Management of suspected adverse drug reactions may require temporary interruption or dose reduction of sorafenib therapy.

The MAH is also recommended to further investigate a less toxic dose regimen/starting dose while preserving efficacy in the target population.

# 4. Recommendations

## *Final Outcome*

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

| **Variation accepted** | | **Type** |
|---|---|---|
| C.1.6 a) | C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one | II |

Extension of the indication for the treatment of progressive, locally advanced or metastatic, differentiated (papillary/follicular/Hürthle cell) thyroid carcinoma, refractory to radioactive iodine. The SmPC was revised in order to add warnings on the risk of bleeding, hypocalcaemia and TSH suppression as well as reflect relevant non-clinical and clinical safety and efficacy data in patients with differentiated thyroid carcinoma. As a consequence, sections 4.1, 4.2, 4.4, 4.8, 5.1, 5.2, 5.3 and 6.6 of the SmPC have been updated. The Package Leaflet is updated in accordance.

In addition, the MAH took the opportunity to update the list of local representatives in the Package Leaflet.

Furthermore, the PI is brought in line with the latest QRD template version 9.0.

The variation proposed amendments to the SmPC and Package Leaflet.