EU RISK MANAGEMENT PLAN (RMP)

NEXAVAR®

BAY 43-9006
(Sorafenib)

No. 13.1

Date of Report:
07 JAN 2025

EU Risk Management Plan (RMP) for Nexavar (Sorafenib)

RMP version to be assessed as part of this application:

RMP Version number: 13.1

Data lock point for this RMP: 07 NOV 2024

Date of final sign off: 07 JAN 2025

Rationale for submitting an updated RMP:

Based on the submission of a type II variation request (Procedure No. EMEA/H/C/000690/II/0059) to the European Medicines Agency (EMA) on 19 APR 2024 to update section 5.3 of the Summary of Product Characteristics (SmPC), the agency requested the following text for inclusion in section 5.3 of the SmPC and requested Bayer to adapt the SmPC and European Union (EU) RMP accordingly.

"In a 2-year mouse carcinogenicity study there were cases of colon adenocarcinoma associated with severe hyperplasia and inflammation, and in a 2-year rat carcinogenicity study there were cases of pancreatic islet cell adenoma. Systemic exposures achieved in both carcinogenicity studies were below clinical exposures in humans at the recommended dose. The observed cases were few in numbers and the clinical relevance of these findings is unknown."

Summary of significant changes in this RMP:

- Part I: No changes
- Part II: Module SI: Epidemiology of the Indications and Target Population data updated
- Part II: Module SII: Non-clinical data updated
- Part II: Module SIII: No changes
- Part II: Module SIV: Non-clinical data updated
- Part II: Module SV: Sales date has been updated as per latest PBRER
- Part II: Module SVI: No Changes
- Part II: Module SVII: Important Identified and potential risks have been removed to ensure compliance with the new definition of important potential/identified risks as per GVP Module V, Rev. 2
- Part II: Module SVIII: Important Identified and potential risks have been removed to ensure compliance with the new definition of important potential/identified risks as per GVP Module V, Rev. 2
- Part III: Follow up Questionnaires were removed. Risk related data has been removed
- Part IV: No changes
- Part V: Risk Related data has been removed
- Part VI: Risk related data has been updated

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- Part VII: Annex 4 was no longer applicable after removal of the important identified risks, therefore it is updated with not applicable. Annex 8 have been updated to reflect the significant changes to the risk management plan over time

Other RMP Version under Evaluation: None

Details of the currently approved RMP:

Version number: 12.2

Approved with procedure: EMEA/H/C/0690/ IB/0049

Date of approval (opinion date): 14 FEB 2019

QPPV signature:

EU QPPV name	Dr Jutta Pospisil
Contact person for this RMP	[redacted]
E-mail address of contact person	[redacted]

Electronic QPPV signature is attached at the end of the document.

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List of Abbreviations

%	Percent
>	Greater Than
<	Less Than
≥	Greater than or equal to
≤	Less than or equal to
=	Equal to
ACE	Angiotensin-Converting Enzyme
ADR	Adverse Drug Reaction
AFP	Alpha-Fetoprotein
AE	Adverse Event
ALT	Alanine Transaminase
AML	Acute Myeloid Leukaemia
ANC	Absolute Neutrophil Count
ASR	Age-Standardised Rate
ASSURE	Adjuvant Sorafenib or Sunitinib for Unfavourable Renal Carcinoma
AST	Aspartate Transaminase
ATC	Anatomical Therapeutic Chemical
AUC	Area Under the Curve
BCRP	Breast Cancer Resistance Protein
Bid	Twice Daily (*bis in diem*)
BMI	Body Mass Index
BSA	Body Surface Area

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CHF	Congestive Heart Failure
CI	Confidence Interval
C_{max}	Concentration Maximum
CMSAF	Controlled Monotherapy Safety Set
CNS	Central Nervous System
COPD	Chronic Obstructive Pulmonary Disease
CTC	Common Terminology Criteria
CTCAE	Common Terminology Criteria for Adverse Events
CYP	Cytochrome P450
DILI	Drug-Induced Liver Injury
DLT	Dose-Limiting Toxicity
DNA	Deoxyribonucleic Acid
DTC	Differentiated Thyroid Carcinoma
EAIR	Exposure-Adjusted Incidence Rate
EAP	Early Access Programme
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eGFR	Estimated Glomerular Filtration Rate
EMA	European Medicines Agency
EPAR	European Public Assessment Report
ERK	Extracellular Signal-Regulated Kinase
EU	European Union
ESMO	European Society for Medical Oncology

FLT3	Fms-Related Tyrosine Kinase 3
FTC	Follicular Thyroid Carcinoma
GI	Gastrointestinal
GIST	Gastrointestinal Stromal Tumour
GLOBOCAN	Global Cancer Observatory
GVP	Good Pharmacovigilance Practices
HBV	Hepatitis B Virus
HCC	Hepatocellular Carcinoma
HCV	Hepatitis C Virus
HD	Haemodialysis
hERG	Human Ether-à-go-go-Related Gene
HFSR	Hand-Foot Skin Reaction
I-131	Iodine-131
ICI	Immune Checkpoint Inhibitors
ICH	International Conference on Harmonisation
IFN	Interferon
IKZ	Integraal kankercentrum zuid (comprehensive cancer centre south)
ILD	Interstitial Lung Disease
INR	International Normalised Ratio
LVEF	Left Ventricular Ejection Fraction
MAH	Marketing Authorisation Holder
MDRD	Modification of Diet In Renal Disease
MedDRA	Medical Dictionary for Regulatory Activities

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MI	Myocardial Infarction
MG	Milligram
MKI	Multikinase Inhibitors
mRCC	Metastatic Renal Cell Carcinoma
MTC	Medullary Thyroid Carcinomas
mTOR	Mammalian Target of Rapamycin
MSAF	Monotherapy Safety Set
mSv	Millisieverts
NCI	National Cancer Institute
NGS	Next-generation sequencing
NOS	Not Otherwise Specified
NSAID	Non-Steroidal Anti-Inflammatory Drug
NAFLD	Non-Alcoholic Fatty Liver Disease
NASH	Non-Alcoholic Steatohepatitis
NSCLC	Non-Small Cell Lung Cancer
NTRK	Neurotrophic Tyrosine Receptor Kinase
NYHA	New York Heart Association
OATP	Organic Anion Transporter Polypeptide
OCA	Oncocytic carcinoma of the thyroid
PAP	Patient Assistance Program
PBMQ	Product-specific Bayer MedDRA Query
PBRER	Periodic Benefit Risk Evaluation Report
PDTC	Poorly Differentiated Thyroid Carcinoma

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PDGFR-β	Platelet-Derived Growth Factor Receptor Beta
PFS	Progression-Free Survival
PK	Pharmacokinetic(s)
PKI	Protein Kinase Inhibitor
PRAC	Pharmacovigilance Risk Assessment Committee
PRES	Posterior Reversible Encephalopathy Syndrome
PS	Performance Status
PSUR	Periodic Safety Update Report
PT	Preferred term(
PT	Prothrombin time
PTC	Papillary Thyroid Carcinomas
PTT	Partial Thromboplastin Time
PV	Pharmacovigilance
Qd	Once a day (*quaque die*)
QTc	Corrected QT interval
RAF	Rapidly Accelerated Fibrosarcoma
RAI	Radioactive Iodine
RAS	Rat Sarcoma
RCC	Renal Cell Carcinoma
RET	Rearranged During Transfection
RMP	Risk Management Plan
RNA	Ribonucleic Acid
RPLS	Reversible Posterior Leukoencephalopathy Syndrome

SAE	Serious Adverse Event
SCC	Squamous Cell Cancer
SCr	Serum Creatinine
SJS	Stevens-Johnson Syndrome
SmPC	Summary of Product Characteristics
SMQ	Standardised MedDRA Query
SOC	System Organ Class
SPP	Specialty Pharmacy Provider
STEMI	ST Segment Elevation Myocardial Infarction
TACE	Transcatheter Arterial Chemoembolization
TdP	Torsade de pointes
TEN	Toxic Epidermal Necrolysis
TKI	Tyrosine Kinase Inhibitors
TMA	Thrombotic Microangiopathy
UGT	Uridine Diphosphate-Glucuronosyltransferase
ULN	Upper Limit Of Normal
US	United States
VEGF(R)	Vascular Endothelial Growth Factor (Receptor)
VS	Versus
WHO	World Health Organisation

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Table Part I-1: Product(s) overview

Active substance(s) (INN or common name):	Sorafenib (as tosylate)
Pharmaco-therapeutic group (ATC Code):	Protein kinase inhibitors, L01XE05
Name of Marketing Authorisation Holder or Applicant:	Bayer AG
Medicinal products to which this RMP refers:	Nexavar
Invented name(s) in the European Economic Area (EEA)	Nexavar
Marketing authorisation procedure	Centralised
Brief description of the product	Chemical class Sorafenib (an oral bis-aryl urea compound) Summary of mode of action Nexavar has demonstrated both anti-proliferative and anti-angiogenic properties *in vitro* and *in vivo*. Multikinase inhibitor that inhibits the activity of targets present in the tumour cell (CRAF, BRAF, V600E BRAF, KIT, RET and FLT-3) and in the tumour vasculature (VEGFR-1, VEGFR-2, VEGFR-3, and PDGFR-ß). Important information about its composition: The oral film-coated tablet is a 200 mg coated tablet (calculated as free base sorafenib). The formulation is presented as an immediate-release dosage form, i.e., the active ingredient is completely dissolved under *in vitro* test conditions within a short period of time. The tablets are red in colour and have a weight of approximately 350 mg and a round shape of 10 mm diameter. For blinding purpose in clinical studies, undebossed tablets and corresponding placebo tablets are available. In addition to the blinded clinical supply material, some open-label studies will use debossed tablets with the Bayer cross on one side and “200” on the other side. All the tablets contain microcrystalline cellulose, croscarmellose sodium, hydroxypropyl methyl cellulose; magnesium stearate, sodium lauryl sulphate, and a film coat of hydroxypropyl methyl cellulose, PEG, titanium dioxide, and red iron oxide.
Hyperlink to the Product Information	Link to **Summary of Product Characteristics**
Indication(s) in the EEA	Current: Advanced renal cell carcinoma (RCC)

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Table Part I-1: Product(s) overview

	Hepatocellular carcinoma (HCC) Locally advanced or metastatic differentiated thyroid carcinoma (DTC) refractory to radioactive iodine (RAI)
Dosage in the EEA	Current: 400 mg (2 tablets of 200 mg) twice daily (equivalent to a total daily dose of 800 mg) Proposed: Not applicable
Pharmaceutical form(s) and strengths	Current: Film-coated tablet, 200 mg Proposed: Not applicable
Is/will the product be subject to additional monitoring in the EU	No

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Part II: Module SI - Epidemiology of the indication(s) and target population(s)

Part II: Module SI - Epidemiology of the Indications and Target Population

SI.1 Indications

Hepatocellular carcinoma

Nexavar is indicated for the treatment of hepatocellular carcinoma (HCC).

Renal cell carcinoma

Nexavar is 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.

Differentiated thyroid carcinoma

Nexavar is indicated for the treatment of patients with progressive, locally advanced or metastatic, differentiated (papillary/follicular/Hürthle cell) thyroid carcinoma (DTC), refractory to radioactive iodine.

SI.1.1 Advanced Renal Cell Carcinoma

Incidence and prevalence:

The age-standardized incidence of kidney cancer (per 100,000) is highest in North America (12.2) and Northern Europe/Australia and New Zealand (10.3); rates are lowest in Middle Africa (1.0) (1). More than one-third of incident cases occur in Europe, with nearly 139,000 incident cases expected in 2020 (2).

In the United States (US), kidney cancer incidence is anticipated to be 16.4 per 100,000, yielding roughly 76,000 new cases in 2021 (2). Approximately 85% of all primary kidney cancers are comprised by RCC, and approximately 70% have clear cell histology, (3). RCC incidence has increased over the last few decades in the US and most of Europe (4, 5). The 5--year prevalence of kidney cancer in Europe is 405,983 cases (1). Demographics of the indication population and risk factors for the disease: Kidney cancer incidence increases by age with a median age at diagnosis of 64-years in the US (6). In most countries, it is roughly twice as common among males compared to females (1).

Established risk factors for RCC include obesity, smoking, hypertension, and chronic kidney disease; other probable risk factors include low physical activity, diabetes, occupational chemical exposure, radiation exposure, and analgesic use (5, 7, 8).

Natural history of the indicated condition, including mortality and morbidity:

Worldwide, kidney cancer age-standardized mortality rates (per 100,000) are highest in Central/Eastern Europe (3.4) and Western Europe (2.8); 54,000 deaths occurred in Europe during 2020 (1). Prognosis has improved significantly in the US and Europe, due in part to the advent of tyrosine kinase inhibitors (TKI) therapy (9), (4). The majority (65%) of kidney cancers diagnosed in the US is localized and 16% of tumour’s are metastatic (6). The overall 5-year survival in Europe and the US is 60% and 76%, respectively (6), (10). Clear cell

histology, accounting for the majority of RCC, is associated with a better prognosis than non-clear cell RCC (11).

Main treatment options:

Surgical resection is the primary treatment for localized disease (3). There is little evidence of benefit with adjuvant therapy for most patients with locally advanced disease. Approved and emerging targeted therapies for advanced or relapsed RCC include checkpoint inhibitors, anti-vascular endothelial growth factor (VEGF) antibodies, TKI, and mammalian target of rapamycin (mTOR) protein inhibitors.

Vascular endothelial growth factor targeting agents entered the clinic in 2005 and remained the standard frontline treatment options until 2018. Currently, immune checkpoint inhibitor (ICI)–based doublets are now the new standard of care. In patients with a contraindication to ICIs, or where ICIs are not available, tyrosine kinase inhibitors are recommended in the treatment of first-line advanced/metastatic disease. Second-line use of tyrosine kinase inhibitors following a first-line ICI is recommended where selection of the agents depend on the treatment used in in first-line.

Important comorbidities

Cardiovascular or cerebrovascular diseases, hypertension, chronic obstructive pulmonary disease, diabetes, and other prevalent comorbidities among elderly populations are frequently observed in cancer patients (12).

Specific concomitant diseases recorded at baseline in the company-sponsored post-marketing surveillance study in advanced RCC (PREDICT study), an international, multi centre observational study (N = 2,311) (13), are presented in Table Part II-1.

Table Part II-1: Concomitant diseases at baseline of patients with advanced RCC in the PREDICT study (efficacy population) (13)

Specific concomitant diseases/conditions	Total N=2,311 (100%)	
	n	(%)
Hypertension	674	(29.2)
Diabetes mellitus	225	(9.7)
Heart failure	86	(3.7)
Angina pectoris	60	(2.6)
Myocardial infarction	51	(2.2)
Hand-foot skin reaction in the past	43	(1.9)
Ischaemic stroke	30	(1.3)
Leukocytopenia	23	(1.0)
Thrombocytopenia	17	(0.7)
Transient ischaemic attack	15	(0.6)
Pulmonary embolism in the past 12 months	14	(0.6)
Haemorrhagic stroke	8	(0.3)

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Table Part II-1: Concomitant diseases at baseline of patients with advanced RCC in the PREDICT study (efficacy population) (13)

Specific concomitant diseases/conditions	Total N=2,311 (100%)	
	n	(%)
Squamous cell carcinoma of the skin	7	(0.3)
Phlebitis in the past 12 months	4	(0.2)

RCC = Renal cell carcinoma, n/N: Number, %: percentage.

In the epidemiological literature, hypertension and obesity have been identified as important comorbidities, both of them positively associated with the risk of developing RCC. Although hypertension and obesity themselves are strongly associated with each other, both of them appear to be independently associated with the risk of developing RCC. For other comorbidities (e.g. diabetes mellitus, end stage renal disease) the evidence for an association with RCC is less conclusive (14).

Important comedications:

Renal cell carcinoma (PREDICT study): For the majority of the patients (67.8%, n = 1,568/2,311), no concomitant medications were recorded, whereas 32.2% (n = 743/2,311) received sorafenib in combination with one or more concomitant medications. Overall, 4.9% (n = 114/2,311) of patients received one concomitant medication, while 5.0% (n = 116/2,311), 4.3% (n =99/2,311), and 17.9% (n = 414/2, 311) received two, three and more than three concomitant medications, respectively. The most common concomitant medications in this study population were loperamide, omeprazole/pantoprazole, metoclopramide, acetylsalicylic acid, angiotensin-converting-enzyme (ACE) inhibitors, angiotensin receptor blockers, betablockers, calcium channel blockers, diuretics, statins, allopurinol, non-steroidal anti-inflammatory drugs, corticosteroids and bisphosphonates.

For further details, please see the respective study report (available on request):

Renal cell carcinoma: PREDICT study report (report number PH-36479) as of 03 MAR 2011.

SI.1.2 Hepatocellular Carcinoma

Hepatocellular Carcinoma is the most common primary malignancy of the liver, accounting for 70-85% of the total liver cancer burden worldwide. It is the sixth most common neoplasm in the world, the second most common cause of cancer-related death (15), and the leading cause of death in patients with cirrhosis in Europe and the US (16-18).

Incidence and prevalence:

Primary liver cancer includes HCC (comprising 75%-85% of cases) and intrahepatic cholangiocarcinoma (10%-15%), as well as other rare types (19). According to the 2021 Orphanet report, the estimated IR of HCC in Europe is 3.2 per 100,000 (20). In the US, the overall incidence of HCC was 7.7 per 100,000 during1992-2015, increasing from 4.1 per 100,000 in 1992 to 9.5 per 100,000 in 2015 (21). According to Global Cancer

Observatory (GLOBOCAN) estimates, HCC is currently the tumour with the sixth highest number of new cases in 2020 and the third leading cause of death worldwide (22).

According to the 2021 Orphanet report, the estimated prevalence rate of HCC in Europe is 15.0 per 100,000 (20).

Demographics of the population in the authorised indication and risk factors for the disease:

The major risk factors for the development of HCC are cirrhosis and chronic liver disease, regardless of aetiology (23). Specific risk factors include viral infections caused by hepatitis B (HBV) and/or hepatitis C (HCV), chronic alcohol consumption, particular comorbidities or other conditions such as non-alcoholic fatty liver disease (NAFLD), non-alcoholic steatohepatitis (NASH), genetic haemochromatosis, co-infection with HBV/HCV, and human immunodeficiency virus (HIV). HCC occurs more often in males than in females, with an overall male-to-female ratio of 3.6 (24).

A retrospective analysis of patients at liver transplantation centres in the US found that nearly 50% and about 15% of patients were infected with HBV or HCV, respectively, with approximately 5% of patients having markers of both infections (25). Data from large population-based studies have also identified high serum deoxyribonucleic acid (DNA) HBV and ribonucleic acid (RNA) HCV viral load as independent risk factors for developing HCC in patients with chronic infection (26-28).

The HCC differ according to the geographical distribution (29). In Africa and Southern Asia, the role of aflatoxin B1 and HBV infection-which is acquired at birth or early in life-is highly predominant. In these patients, HCC develops often at a young age and in the absence of cirrhosis. By contrast, in Japan, Egypt and in Southern Europe, HCV is the main cause of HCC which occurs in older patients, nearly all of them with advanced fibrosis or cirrhosis.

In Northern and Central European countries, HCV infection and alcohol are the main causes of cirrhosis.

The incidence of HCC is increasing in the US, particular in the population infected by HCV. The annual IR among patients with HCV-related cirrhosis has been estimated to be between 2% and 8% (30). A meta-analysis including 68 studies with 27,854 patients with untreated HBV showed an annual HCC incidence 0.88 per 100 person-years, with an incidence of 3.16 per 100 person-years for patients with cirrhosis (31).

Main treatment options

Most patients are diagnosed at advanced stages, when curative treatments, including resection, liver transplantation, and ablation, are no longer feasible (23).

Combination therapies with ICI (atezolizumab plus bevacizumab or durvalumab plus tremelimumab) are considered as first-line standard of care. Sorafenib and Lenvatinib remain as alternative treatment options in first-line.

Following first-line ICI combinations a switch to TKI is generally recommended.

Treatment options approved as second-line are regorafenib, cabozantinib, ramucirumab in patients with high high (≥400 ng/mL) alpha-fetoprotein (AFP) levels. In addition immune check inhibitors (pembrolizumab, nivolumab and combination of nivolumab/ ipilimumab approved in the US) as second-line treatment (32).

Natural history of the indicated condition in the untreated population, including mortality and morbidity:

The HCC usually occurs in the setting of liver cirrhosis, because of chronic infections with HBV or HCV viruses, alcohol consumption, NASH, or diabetes (33). A meta-analysis of survival rates of untreated patients in randomised clinical trials of HCC, reported that the 1-year and 2-year survival rate of untreated patients from 30 randomised controlled trials was 17.5% and 7.3%, respectively (34). Data on age-adjusted mortality in 8,561 HCC patients in Austria suggest a median OS of 4.5-months for men and 3.2-months for women with 1-year/5-year survival rates of 33/11% and 28/10%, respectively (35, 36).

Important comorbidities

Characteristics of patients diagnosed with HCC were reported from a large health care claims database in the US for the time period 2002-2008 (37). Data at baseline (at HCC diagnosis) showed that three most frequent comorbidities in a cohort of 4,406 patients with HCC were mild diabetes (33.1%), various mild chronic liver diseases (29.3%), and Chronic obstructive pulmonary disease (COPD) (20.8%). A matched cohort (44,060 controls matched for age, sex, region and health plan type) showed frequencies of 19.2%, 0.5%, and 18.2% for the same specific concomitant conditions.

Important comedications:

Hepatocellular carcinoma (GIDEON study): Concomitant medication at baseline was reported for 80.1%. The most common medications at anatomical therapeutic chemical (ATC) Level 1 were addressing alimentary tract and metabolism (54.3%), followed by cardiovascular system (51.9%), anti-infectives for systemic use (26.4%), and blood and blood-forming organs (23.4%), while at ATC Level 2, drugs for acid-related disorders (31.0%), diuretics (24.1%), and antivirals for systemic use (23.5%) were most common. The most common concomitant medications were ursodeoxycholic acid, omeprazole/pantoprazole, antidiabetics, antivirals for systemic use, interferon (IFN), acetylsalicylic acid, corticosteroids, ACE inhibitors, angiotensin receptor blockers, betablockers, calcium channel blockers, diuretics and analgesics.

For further details, please see the respective study report (available on request):

Hepatocellular carcinoma: GIDEON study report, Table 14.1.1.4

SI.1.3 Radioactive Iodine (RAI)-Refractory Differentiated Thyroid Cancer

Thyroid cancer has three histological types with distinctly varying prognosis. Of the major histologic types, about 90% are papillary thyroid carcinomas (PTC), 4% follicular thyroid carcinomas (FTC), 2% Huürthle-cell carcinomas, 2% medullary thyroid carcinomas (MTC), and 1% anaplastic thyroid carcinomas (ATC). MTCs are neuroendocrine tumours arising

from calcitonin-producing C-cells (parafollicular cells). Other rare thyroid cancers, with some exceptions (e.g. squamous cell, lymphoma, mesenchymal tumours), arise from follicular cells (38).

The 2022 world health organization (WHO) classification introduces a distinction of high-grade cancers from well-differentiated follicular cell-derived carcinomas and MTC. Former type of "Differentiated thyroid carcinoma (PTC, FTC, or Oncocytic carcinoma of the thyroid [OCA]) with high grade features" was renamed as "Differentiated high-grade thyroid carcinoma" (DHGTC). The DHGTCs exhibit more advanced histopathologic stages and lower radioactive iodine avidity than well-differentiated thyroid cancers (DTC) (PTC, FTC, and OCA). The overall prognosis of DHGTC is similar to that of poorly differentiated thyroid carcinoma (PDTC). High-grade MTCs occur in approximately 25% of cases and have worse prognosis than low-grade MTC. Therefore, patients with DHGTC and high-grade MTC require more intense treatments and should be more closely followed up for recurrence (39).

Radioactive iodine -refractory, recurrent, or metastatic disease is prognostically more worrisome, and death from thyroid cancer within 3-years under these circumstances is common (40).

Specific epidemiological data on RAI-refractory DTC are not available. The RAI-refractory thyroid cancer is rare, with an estimated incidence of four cases per million population (5% of patients with clinical cancer) (41). The sections below give some overview on the general epidemiology of thyroid cancer.

Incidence and prevalence

Thyroid cancer incidence has been rising in developed countries (US and Europe) over the past 3 decades and this trend has often been attributed to heightened medical surveillance, the use of improved diagnostics, and changes in risk factors (42-44).

Thyroid cancer is considerably more common in females than in males with a female: male sex ratio of 3:1. Elevated rates are estimated in Eastern Asia (23.0 per 100,000 in both sexes) and North America (11.9 per 100,000, both sexes). The 2022 worldwide incidence of thyroid cancer was 821,173 cases with an age-standardised rate (ASR) to the world population of 9.1 per 100,000.

It is estimated that about 47,485 people will die of thyroid cancer in 2022 (45).

Demographics of the target population

Thyroid cancer incidence rates differ by race and ethnicity. In the US, rates are twice as high among Whites as compared to Blacks and notably elevated among Asians, especially those from Southeast Asia. The incidence patterns by Hispanic ethnicity are unclear (46). In the EU the trend seems similar. Differences in incidence between males and females by region are presented below.

Thyroid cancer predominately affects women, carries a worse prognosis in older age, and may have higher mortality in men (47).

Thyroid cancer incidences and mortality rate in Europe and rest of the world in 2022 (47) are presented by region in **Annex 7.2**.

Risk factors for the disease

Radiation exposure is the major known risk factor for thyroid cancer. In contrast to the six-fold rise in medical radiation exposure that occurred from 1980 to 2006 in the US, per capita radiation exposure to the population decreased by 20% between 2006 and 2016. The U.S. annual individual (per capita) effective dose from diagnostic and interventional medical procedures was estimated to have been 2.9 millisieverts (mSv) in 2006 and 2.3 mSv in 2016, with the collective doses being 885,000 and 755,000 person-sievert, respectively. The reasons for this decline are likely multifactorial, including awareness of radiation dose, education, attempts to optimize doses, newer technology, changes in practices, and reduction in reimbursement (48). Radiation exposure (including from nuclear fallout) increases the risk of benign and malignant thyroid nodules, is associated with multicentric cancers, and shifts the incidence of thyroid cancer to an earlier age group. A small increase in thyroid cancer has been observed in adult patients irradiated with I-131. The incidence of follicular thyroid carcinoma varies widely in different parts of the world, and is higher in iodine deficient regions (49). Other factors that might contribute to an increased risk of thyroid cancer include increased prevalence of autoimmune thyroiditis (50).

Mortality and morbidity

Mortality from the disease is much lower than incidence, with an estimated 44,000 deaths for both sexes combined in 2022 (51).

The ASR (per 100,000 persons) is presented by regions in **Annex 7.2** above.

Metastases and recurrence of thyroid cancer:

Distant metastases can develop in 7% to 23% of patients with DTC, depending on site and extent of disease, patient’s age, histology of tumour, and treatment. An age of 45-years or more, site other than lung only or bone only, and symptoms at the time of diagnosis are associated with poorer outcomes (52).

Recurrence rate of the disease, or metastases, can reach 30% within a 30-year period (53).

Main treatment options

The main treatment options for DTC are partial thyroidectomy, total thyroidectomy, postoperative thyroxine for thyroid stimulating hormone suppression, or postoperative RAI therapy (54). Locoregional metastases may be resected. Metastases to bone and lung may be treated by external beam radiation. If the tumour is non-RAI-avid, cytotoxic chemotherapeutic agents are generally associated with no more than 25% partial response rates, complete remission has been rare, and toxicities from these treatments are considerable.

Current treatment guidelines for RAI-refractory DTC acknowledge the shortcomings of cytotoxic chemotherapy.

The European Society for Medical Oncology (ESMO) guidelines recommendations (55) include:

- Cabozantinib is an option to treat adults with RAI-refractory advanced/metastatic DTCs that have progressed following treatment with multikinase inhibitors (MKIs).
- In Europe, selpercatinib is an option to treat adults with advanced/metastatic Rearranged during transfection (RET) fusion-positive DTCs who have already received MKI therapy with sorafenib, lenvatinib or both.
- In the United States, selpercatinib is an option to treat adults and adolescents aged ≥12-years with RAI-refractory advanced/metastatic RET fusion-positive DTCs, regardless of whether or not they have received MKI therapy with sorafenib, lenvatinib or both.
- In the US, pralsetinib is an option to treat adults and adolescents ≥12-years of age with advanced or metastatic RET fusion-positive DTC who require systemic therapy and are RAI-refractory.
- Larotrectinib is an option for the treatment of adults and paediatric patients with metastatic neurotrophic tyrosine receptor kinase (NTRK) fusion-positive solid tumours, not amenable to surgery, that have no satisfactory treatment options.
- Entrectinib is an option for treating adults and adolescents aged ≥12-years with metastatic or unresectable NTRK fusion-positive solid tumours that have progressed in spite of standard-of-care treatment.
- If a systemic therapy of advanced/metastatic DTCs is planned, a genetic test targeting actionable cancer mutations should be considered to individualise therapy. Next-generation sequencing (NGS) analysis is the preferred approach, if available.

Important comorbidities

Comorbidity may be an important contributing factor to differences in the treatment and outcome of thyroid cancer, especially in older patients. It might also provide information on aetiology and mortality. In addition, increasing incidence and improved prognosis of thyroid cancer have led to concern about the development of second primary cancers, especially after RAI treatment (56, 57).

The Eindhoven Cancer Registry, Comprehensive Cancer Centre South (IKZ) in the Netherlands (56) analysed demographic, histological and treatment data of 417 patients with thyroid cancer diagnosed between 01 JAN 1993 and 31 DEC 2002. A total of 265 patients had papillary (64%; mean age 47-years), 88 follicular (21%; mean age 54-years), 14 medullary (3%; mean age 49-years), and 24 anaplastic (Six (6)%; mean age 68-years) histology, and 18 patients were classified as ‘other or unknown’ thyroid cancer. Information on comorbidity was available for 378 patients (91%). Comorbidity was present in 32% of the patients; 23% had one and 12% had two or more concomitant diseases.

Hypertension was the most frequent comorbidity (18%), followed by cancer (7%), cardiovascular diseases (6%), and diabetes mellitus (6%). The prevalence of hypertension was twice as high as expected in the general Dutch population in all age groups. Six

(6) patients >60-years of age had tuberculosis. Initial surgical treatment was negatively correlated to the presence of concomitant diseases in patients <70-years of age (p = 0.02), but not in patients ≥70-years of age.

The overall comorbidity prevalence of 32% was lower than the rates found in studies from the same region in other cancer types such as breast or prostate cancer, Hodgkin's lymphoma or non-Hodgkin's lymphoma. This was explained by the relatively low age at diagnosis, the predominance of females (who had less cardiovascular diseases) and the absence of an association with smoking as a risk factor for thyroid cancer (56). The same study also showed that the age-specific prevalence of comorbidity in thyroid cancer patients was similar to that in a cohort of unselected patients with various cancer types originating from the same region.

Important comedications:

Based on data from a randomised controlled trial (DECISION study) in patients with RAI-refractory thyroid cancer, the following categories of concomitant medications, taken at least once during the double-blind period, were most frequently (>30%) encountered: Thyroid therapy, analgesics, drugs for acid-related disorders, dermatological preparations, systemic antibacterials, agents acting on the renin-angiotensin system, anti-inflammatory and antirheumatic products, topical products for joint and muscular pain, ophthalmological, and nasal preparations.

For further details, please see the respective study report (available on request):

Radioactive iodine-refractory DTC: DECISION study report (study number: 14295), Section 14.1.

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SII.1. Key Safety Findings

Key safety findings from non-clinical studies and relevance to human usage are presented in Table Part II SII-1.

Table Part II SII-1: Key safety findings from non-clinical studies and relevance to human usage

Key safety findings (from non-clinical studies)	Relevance to human usage
Single and repeat-dose toxicity: Systemic toxicity studies were conducted in rats, mice and dogs. After repeated dosing, gastrointestinal toxicity was dose-limiting in dogs. Degeneration and regeneration processes were observed in multiple organs including liver, kidneys, lymphoreticular/ hematopoietic system, gastrointestinal tract, pancreas, adrenals, reproductive organs, skin, teeth, and bone at doses and corresponding plasma concentrations of sorafenib that were in the range of human therapeutic exposures at the dose of 400 mg sorafenib bid. The lesions were either fully reversible or showed a tendency towards reversibility.	Human toxicities of sorafenib were identified in clinical studies and post-marketing observations and are summarised in Section 4.8 of the SmPC. See sections below for more detailed information on particular toxicities.
Reproductive toxicity: Repeat-dose and developmental toxicity studies have demonstrated adverse effects on the male and female reproductive system and embryo-/foetal toxicity. No specific fertility and early embryonic development studies were conducted.	Data on fertility and reproductive toxicity are of relevance for human use. Warnings are reflected in Sections 4.6 and 5.3 of the SmPC.
Developmental toxicity: Developmental toxicity studies have shown embryo- and foetal toxicity of sorafenib. A peri-postnatal study was not conducted. Repeat-dose toxicity studies in young and growing rats and dogs have demonstrated adverse effects on the structure and function of bone and teeth. No studies in juvenile animals (exposed shortly after birth) were conducted.	Effects at therapeutic doses/exposure on bone and teeth in children and adolescents cannot be excluded. Warnings on the use of sorafenib during pregnancy and breast feeding are reflected in Sections 4.6 and 5.3 of the SmPC.
Nephrotoxicity: Signs for nephrotoxicity of sorafenib were seen in single studies including an antidiuretic effect in a safety pharmacology study after single administration. Histopathological findings in rats were seen at doses close to or exceeding the	Effects on kidney functions were routinely monitored in clinical trials. Human findings are summarised in Section 4.8 of the SmPC.

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Table Part II SII-1: Key safety findings from non-clinical studies and relevance to human usage

Key safety findings (from non-clinical studies)	Relevance to human usage
maximum tolerated dose. No functional impairment was seen in toxicity studies. The findings observed were not fully reversible in the respective recovery periods.	
Hepatotoxicity: Liver toxicity, i.e. increased transaminases as well as histopathological findings, was described in non-clinical toxicity studies. The findings were not fully reversible in the respective recovery periods.	Effects on liver functions were routinely monitored in clinical trials. Human findings are summarised in Section 4.8 of the SmPC.
Genotoxicity: Sorafenib induced chromosomal aberrations in Chinese hamster ovary cells *in vitro* in the presence of metabolic activation. Sorafenib was not genotoxic in the Ames test or in the *in vivo* mouse micronucleus assay. One intermediate in the manufacturing process, which is also present in the final active substance (<0.15%), was positive for mutagenesis in an *in vitro* bacterial cell assay (Ames test).	As the target population of Nexavar has a reduced life expectancy, genotoxicity is considered to be of limited relevance. Data are summarised in Section 5.3 of the SmPC.
Carcinogenicity: In a 2-year mouse carcinogenicity study there were cases of colon adenocarcinoma associated with severe hyperplasia and inflammation, and in a 2-year rat carcinogenicity study there were cases of pancreatic islet cell adenoma. Systemic exposures achieved in both carcinogenicity studies were below clinical exposures in humans at the recommended dose.	The observed cases were few in numbers and the clinical relevance of these findings is unknown. Data are reflected in Section 5.3 of SmPC.
General safety pharmacology: Inhibition of human potassium channel (hERG) by sorafenib was shown *in vitro*, indicating that sorafenib has the potential to prolong QT/QTc interval. No findings on ECGs were seen in non-clinical studies. No other relevant findings were seen in safety pharmacology studies including studies addressing effects on the CNS.	Data on QT/QTc prolongation are of relevance for human use. Warnings are reflected in Section 4.4 of the SmPC.
Mechanisms for drug interaction: In human liver microsomes, sorafenib competitively inhibited CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6 and CYP3A4. In human hepatocytes, sorafenib did not induce CYP1A2 and CYP3A4.	Data on potential drug-drug interaction are of relevance for human use. Warnings are reflected in Sections 4.4 and 4.5 of the SmPC.

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Table Part II SII-1: Key safety findings from non-clinical studies and relevance to human usage

Key safety findings (from non-clinical studies)	Relevance to human usage
In vitro, sorafenib inhibits glucoronidation by UGT1A1 and UGT1A9. Sorafenib is a weak to moderate substrate of P-glycoprotein and BCRP *in vitro* and inhibits transport of probe substrates. No interaction with OATPs was detected.	
Other toxicity-related information or data: Sorafenib was not phototoxic in an *in vitro* assay. No relevant cardiotoxic potential of sorafenib was detected in *in vitro* studies as well as in electron microscopic evaluation of heart tissue derived from a repeat-dose toxicity study in mice. Extended testing for CNS effects in chronic toxicity studies in rats did not reveal relevant effects. Exocrine pancreas was identified as a target organ of toxicity in non-clinical studies by histopathology as well as by increased levels of serum pancreas enzymes. Marked skin toxicity was seen in dogs including hair loss, inflammatory changes, and atrophy/degeneration of hair follicles.	Data are of potential relevance for human use. Increased lipase and amylase are known human toxicities of sorafenib and included in Section 4.8 of the SmPC. It is unknown whether skin toxicities observed in dogs corresponds to the described human skin toxicities.

Bid: Twice daily (*bis in diem*), BCRP: Breast cancer resistance protein, CNS: Central nervous system, CYP: Cytrochrome P450, ECG: Electrocardiogram, hERG: Inhibition of human potassium channel, OATP: Organic anion transporter polypeptide, QTc: Corrected QT interval, SmPC: Summary of Product Characteristics, UGT: Uridine diphosphate-Glucuronosyltransferase.

SII.2. Conclusions on Non-Clinical Data

Undesirable effects in humans have been confirmed during clinical development or in post-marketing experience concerning the liver, kidneys, skin, pancreas, gastrointestinal tract and bone marrow. A cardiac effect study in humans confirmed a QT-prolonging effect. Torsade de pointes is described as a potential risk in Part II: Module SVII - Identified and Potential Risks.

The findings confirmed in clinical development or post-marketing experience are adequately addressed in the Summary of Product Characteristics (SmPC).

Reproductive toxicity has not been systematically studied in humans. The SmPC advises that women should avoid becoming pregnant while on therapy and that Sorafenib should not be used during pregnancy. As of 29 APR 2018, case retrieval from global safety database using search criteria of the System Organ Class (SOC) “Pregnancy, puerperium and perinatal conditions” revealed only 24 reports of pregnancy. Outcome of pregnancy, when available, revealed five pregnancies with elective termination, one with spontaneous abortion at nine

weeks, five normal births, one premature birth at 35 weeks of gestation with no other events, and one live birth with congenital abnormalities.

Overall, the accumulating experience from literature and cases in Bayer's safety database suggests that the safety profile of sorafenib use in children and adolescents is similar to that known for adults.

In a 2-year mouse carcinogenicity study there were cases of colon adenocarcinoma associated with severe hyperplasia and inflammation, and in a 2-year rat carcinogenicity study there were cases of pancreatic islet cell adenoma. Systemic exposures achieved in both carcinogenicity studies were below clinical exposures in humans at the recommended dose. The observed cases were few in numbers and the clinical relevance of these findings is unknown.

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SIII.1. Clinical Trial Exposure

Exposure data was pooled for analysis. For the purpose of exposure and event rate analyses, 2 pools are presented throughout the document:

- Controlled monotherapy safety set (CMSAF): Controlled safety data from randomised placebo-controlled Phase III studies
- Monotherapy safety set (MSAF): Monotherapy, i.e. all Nexavar treated patients from Phase I, II, and III trials, regardless of whether or not treatment was administered in a blinded phase or open label phase. This does not include the early access programme (EAP) studies due to their specific requirement for adverse event documentation.

The clinical studies included for integrated analysis of safety are shown in in Table Part II SIII-1 and Table Part II SIII-2 for the CMSAF and MSAF, respectively. Detailed data on demographics and exposure to Nexavar are available for 4,400 patients in the CMSAF and for 4,803 patients in the MSAF. A total of 4,402 patients from CMSAF were valid for safety. However, in each arm, one patient was excluded from further analysis due to the reasons explained in the footnote of Table Part II SIII-1.

The duration of exposure is presented in Table Part II SIII-3 for all cancer types and in Table Part II SIII-4 by indication.

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Table Part II SIII-1: Clinical studies for integrated analysis of safety for CMSAF – sample sizes by study (all enrolled subjects)

Study	Number of subjects enrolled	Treatment group	Number of subjects randomised	Number of subjects valid for safety	Study title
All studies	5,789	Total	4,426	4,402	
		BAY 43-9006	2,251	2,239	
		Placebo	2,175	2,163	
11213 (TARGET)	904	Total	904	903	A Phase III randomized study of BAY 43-9006 in patients with unresectable and/or metastatic renal cell cancer
		BAY 43-9006	452	452	
		Placebo	452	451	
11721	552	Total	458	456	Phase III Study of BAY 43-9006 in Patients with Advanced Hepatocellular Carcinoma (HCC) Treated After Transcatheter Arterial Chemoembolization (TACE)
		BAY 43-9006	229	229	
		Placebo	229	227	
11849 (Asia Pacific)	271	Total	226	224	A randomized, double-blind, placebo-controlled study of sorafenib in patients with advanced hepatocellular carcinoma (HCC)
		BAY 43-9006	150	149	
		Placebo	76	75	
12414 (STORM)	1602	Total	1,114	1,107	A Phase III randomized, double-blind, placebo-controlled study of sorafenib as adjuvant treatment for hepatocellular carcinoma after surgical resection or local ablation
		BAY 43-9006	562	559	
		Placebo	552	548	
13266 (MISSION)	1002	Total	703	697	A Phase III, multi-centre, placebo-controlled trial of Sorafenib (BAY 43-9006) in patients with relapsed or refractory advanced predominantly non squamous NSCLC after two or three previous treatment regimens for advanced disease
		BAY 43-9006	350	346	
		Placebo	353	351	
14295 (DECISION)	556	Total	419	416	
		BAY 43-9006	209	207	

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Table Part II SIII-1: Clinical studies for integrated analysis of safety for CMSAF – sample sizes by study (all enrolled subjects)

Study	Number of subjects enrolled	Treatment group	Number of subjects randomised	Number of subjects valid for safety	Study title
		Placebo	210	209	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
100554 (SHARP)	902	Total	602	599	A Phase III randomized, placebo-controlled study of sorafenib in patients with advanced hepatocellular carcinoma
		BAY 43-9006	299	297	
		Placebo	303	302	

CMSAF: Controlled monotherapy safety set, HCC: Hepatocellular carcinoma, NSCLC: Non-small cell lung cancer, TACE: Transcatheter arterial chemoembolization.
Note: One subject randomized to Placebo in Study 11213 is valid for safety but has no study medication data and no adverse events. This subject is excluded from further analysis.
Note: One subject randomised to Bay 43-9006 in Study 11213 is valid for safety but started treatment after end of double-blind part. This subject is excluded from further analysis.
Source: Bay 43-9006 Tables for Risk Management Plan (CMSAF), Table 1/1

Table Part II SIII-2: Clinical studies for integrated analysis of safety for MSAF – sample sizes by study (all enrolled subjects)

	Number of subjects		
Study	Valid for safety	Monotherapy treated	Study title
All studies	7,056	4,803	
100277	41	41	Phase I study to determine the safety and PK of BAY 43-9006 for 28 days in patients with advanced, refractory solid tumours
100283	69	69	Investigation of safety, tolerability, and PK after administration of BAY 43-9006 given as a single dose once every week to patients with advanced, refractory solid tumours in a non-randomized, non-controlled, non-blinded, single-centre design

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Table Part II SIII-2: Clinical studies for integrated analysis of safety for MSAF – sample sizes by study (all enrolled subjects)

	Number of subjects		
Study	**Valid for safety**	**Monotherapy treated**	**Study title**
100313	6	6	Phase I Study to Determine the Safety, Maximum Tolerated Dose, Pharmacokinetics and Pharmacodynamics of BAY 43-9006 Tosylate (BAY 54-9085) in Repeated Cycles of 1 Week On I 3 Weeks Off in Patients with Advanced, Refractory Solid Tumours.
100342	19	19	Phase I study to determine the safety, maximum tolerated dose, PK and impact on biomarkers of BAY 43-9006 tosylate (BAY 54-9085) in repeated cycles of 1 week on/1 week off in patients with advanced, refractory solid tumours
100391	501	501	Randomized Discontinuation Study of Sorafenib in Subjects with Advanced Refractory Cancer
100554	599	344	A Phase III randomized, placebo-controlled study of sorafenib in patients with advanced HCC
100555	54	54	A phase II, multicentre uncontrolled trial of BAY 43-9006 in subjects with metastatic breast cancer
100557	52	52	A Phase II, multicentre, uncontrolled trial of BAY 43-9006 in patients with relapsed or refractory advanced non-small cell lung carcinoma
100561	53	53	Effect of BAY 43-9006 (sorafenib) on cardiovascular safety parameters in cancer patients
10658	18	18	Investigation of safety, tolerability, pharmacokinetics and pharmacodynamics after administration of BAY 43-9006 given twice daily to Japanese patients with advanced refractory solid tumours in a non-randomised, non-controlled, non-blinded manner
10874	137	137	A Phase II multicentre uncontrolled trial of BAY 43-9006 in subjects with advanced HCC
10875	27	27	Phase I study of BAY 43-9006 in Japanese patients with HCC
10926	21	21	Evaluation of drug-drug interaction potential of BAY 43-9006 (sorafenib) through effects on cytochrome P450 metabolic enzymes (CYP3A4, CYP2C19, CYP2D6) in patients with advanced metastatic melanoma
10941	10	10	Open Label Multi-Centric Phase II Study of the Raf Kinase Inhibitor BAY 43-9006 in CML Patients Resistant to Gleevec (Imatinib)

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Table Part II SIII-2: Clinical studies for integrated analysis of safety for MSAF – sample sizes by study (all enrolled subjects)

	Number of subjects		
Study	**Valid for safety**	**Monotherapy treated**	**Study title**
11213	903	668	A Phase III randomized study of BAY 43-9006 in patients with unresectable and/or metastatic renal cell carcinoma
11493	44	44	Protocol No. 10164 (Part 1 11493) Phase I Study to Determine the Safety and Pharmacokinetics of sorafenib alone or in combination with chemotherapy for 21 Days on seven days off in Patients with Advanced, Refractory Solid tumours
11497	13	13	Investigation of safety, tolerability and pharmacokinetics after administration of BAY 43-9006 given twice daily to Japanese patients with advanced refractory solid tumours in a nonrandomized, uncontrolled, non-blinded manner (Investigation of 400 mg bid and 600 mg bid)
11515	131	131	Biomarker Report relating to BAY 43-9006 Study 11515: Phase II study of sorafenib in Japanese subjects with RCC
11547	1	1	A Phase II Study of BAY 43-9006 Prior to and Following Nephrectomy in Patients with Metastatic RCC
11559	39	39	A multicentre uncontrolled study of sorafenib in patients with unresectable and/or metastatic renal cell carcinoma
11721	456	229	Phase III Study of BAY 43-9006 in Patients with Advanced HCC Treated After TACE
11848	187	158	A randomised, open-label, multi-centre phase II study of first-line treatment with BAY 43-9006 (Sorafenib) *vs* standard treatment with Interferon alpha-2a in patients with unresectable and/or metastatic RCC
11849	224	155	A randomized, double-blinded, placebo-controlled study of sorafenib in patients with advanced HCC
12007	246	123	A Double-Blind, Randomized Phase II Study Evaluating the Efficacy and Safety of Sorafenib Compared to Placebo in Ovarian Epithelial Cancer or Primary Peritoneal Cancer Patients who have achieved a Complete Clinical Response after Standard Platinum/ Taxane Containing Chemotherapy

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Table Part II SIII-2: Clinical studies for integrated analysis of safety for MSAF – sample sizes by study (all enrolled subjects)

	Number of subjects		
Study	**Valid for safety**	**Monotherapy treated**	**Study title**
12414	1,107	559	A Phase III randomized, double-blind, placebo-controlled study of sorafenib as adjuvant treatment for hepatocellular carcinoma after surgical resection or local ablation
12782	16	10	RCC Sutent failures, standard treatment sorafenib 400mg bid *vs* standard treatment sorafenib plus IFN 3 MIU 5TIW. Randomized open 110-120 patients. Primary outcome PFS.
12913	83	83	A Phase II, Multi-centre, Open-label Study to Assess the Efficacy, Safety, Tolerability and Pharmacokinetics of Intra patient Dose Escalation of Sorafenib as First Line Treatment for Metastatic Renal Cell Carcinoma
12917	717	355	A Phase III randomized, placebo-controlled, double-blind trial of Sorafenib plus Erlotinib *vs*. Sorafenib plus Placebo as First Line systemic treatment for HCC
13266	697	346	A Phase III, multi-centre, placebo–controlled trial of Sorafenib (BAY 43-9006) in patients with relapsed or refractory advanced predominantly non squamous NSCLC after two or three previous treatment regimens
14295	416	368	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
14898	151	151	A phase IV, single-arm, open-label study of sorafenib (Nexavar) in advanced HCC
17073	18	18	A multi-centre, single-arm, open-label Phase II study to evaluate the safety, efficacy and pharmacokinetics of sorafenib in Japanese patients with anaplastic thyroid carcinoma or locally advanced or metastatic medullary thyroid carcinoma

CML: Chronic myelogenous leukaemia, CYP: Cytochrome P450, HCC: Hepatocellular carcinoma, IFN: Interferon, MSAF: Monotherapy safety set, NSCLC: Non-small cell lung cancer, PFS: Progression-free survival, PK: Pharmacokinetics, RCC: Renal cell carcinoma.
Source: Bay 43-9006 Tables for Risk Management Plan (MSAF), Table 1/1

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Table Part II SIII-3: Duration of exposure (all cancer types combined)

Integrated analysis pool	CMSAF				MSAF	
Treatment	**Nexavar**		**Placebo**		**Nexavar**	
Duration of exposure (at least)	**Persons**	**Person time[a]**	**Persons**	**Person time[a]**	**Persons**	**Person time[a]**
<1 month	216	9.3	126	6.7	532	23.7
1 to <3 months	536	88.1	754	115.7	1,236	207.3
3 to <6 months	453	167.6	416	152.9	879	323.3
6 to <12 months	479	349.0	329	240.5	910	658.9
12 to <24 months	333	450.6	254	347.4	701	994.3
≥24 months	221	703.1	283	936.9	545	1,665.2
Total	2,238	1,767.8	2,162	1,800.2	4,803	3,872.7

CMSAF: Controlled monotherapy safety set, MSAF: Monotherapy safety set.

[a] Total exposure for persons is given in years. For calculation, a month equals 30 days and a year equals 360 days.

Note: Time spent on placebo is not counted towards person time, but time preceding and following placebo treatment.

Note: Duration of ongoing patients is calculated by using the study specific cut-off date as day of last treatment.

Sources: Bay 43-9006 Tables for Risk Management Plan (CMSAF), Table 3/1
Bay 43-9006 Tables for Risk Management Plan (MSAF), Table 3/1

Table Part II SIII-4: Duration of exposure (by indication)

Integrated analysis pool	CMSAF				MSAF	
Treatment	**Nexavar**		**Placebo**		**Nexavar**	
Duration of exposure (at least)	**Persons**	**Person time[a]**	**Persons**	**Person time[a]**	**Persons**	**Person time[a]**
DTC						
<1 month	12	0.5	7	0.4	24	1.1
1 to <3 months	21	3.7	41	7.2	39	6.9
3 to <6 months	26	9.4	54	19.3	51	18.3
6 to <12 months	55	41.5	46	34.0	98	72.9
12 to <24 months	79	108.8	56	73.8	91	125.1
≥24 months	14	32.3	5	11.8	93	318.6
Total	207	196.1	209	146.4	396	542.9
RCC						
<1 month	12	0.4	28	1.3	68	2.9
1 to <3 months	87	15.3	229	35.4	208	35.9
3 to <6 months	147	53.9	123	44.4	241	90.0

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Table Part II SIII-4: Duration of exposure (by indication)

Integrated analysis pool	CMSAF				MSAF	
Treatment	**Nexavar**		**Placebo**		**Nexavar**	
Duration of exposure (at least)	**Persons**	**Person time[a]**	**Persons**	**Person time[a]**	**Persons**	**Person time[a]**
6 to <12 months	152	106.3	61	43.2	348	251.2
12 to <24 months	53	61.5	9	11.2	288	414.7
≥24 months					164	433.6
Total	451	237.4	450	135.4	1,317	1,228.3
HCC						
<1 month	70	3.0	27	1.4	166	7.3
1 to <3 months	200	33.0	213	34.5	399	64.6
3 to <6 months	149	55.5	136	50.0	329	120.4
6 to <12 months	149	111.1	129	94.3	263	188.7
12 to <24 months	100	136.5	87	117.5	178	247.3
≥24 months	7	15.7	12	28.8	75	192.4
Total	675	354.8	604	326.5	1,410	820.7
Adjuvant HCC						
<1 month	76	3.3	15	0.8	76	3.3
1 to <3 months	78	12.5	52	7.8	78	12.5
3 to <6 months	53	18.8	48	19.1	53	18.8
6 to <12 months	67	51.6	75	56.3	67	51.6
12 to <24 months	90	129.9	92	132.2	90	129.9
≥24 months	195	644.5	266	896.4	195	671.3
Total	559	860.5	548	1,112.6	559	887.3
Other tumour types						
<1 month	46	2.1	49	2.9	198	9.1
1 to <3 months	150	23.6	219	30.8	512	87.4
3 to <6 months	78	30.0	55	20.1	205	75.8
6 to <12 months	56	38.5	18	12.6	134	94.6
12 to <24 months	11	14.0	10	12.9	54	77.3
≥24 months	5	10.6	0	0.0	18	49.4
Total	346	118.9	351	79.3	1,121	393.5

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Table Part II SIII-4: Duration of exposure (by indication)

Integrated analysis pool	CMSAF				MSAF	
Treatment	Nexavar		Placebo		Nexavar	
Duration of exposure (at least)	Persons	Person time[a]	Persons	Person time[a]	Persons	Person time[a]

CMSAF: Controlled monotherapy safety set, DTC: Differentiated thyroid carcinoma, HCC: Hepatocellular carcinoma, MSAF: Monotherapy safety set, RCC: Renal cell carcinoma.
[a] Total exposure for persons is given in years. For calculation, a month equals 30 days and a year equals 360 days.
Note: Time spent on placebo is not counted towards person time, but time preceding and following placebo treatment.
Note: Duration of ongoing patients is calculated by using the study specific cut-off date as day of last treatment.
Sources: Bay 43-9006 Tables for Risk Management Plan (CMSAF), Table 3/1
Bay 43-9006 Tables for Risk Management Plan (MSAF), Table 3/1

SIII.1.1 Duration of Exposure by Initial Dose

The duration of exposure by initial dose presented in Table Part II SIII-5 for all cancer types and in Table Part II SIII-6 by indication.

Table Part II SIII-5: Duration of exposure by initial dose (all cancer types combined)

Integrated analysis pool	CMSAF				MSAF	
Treatment	Nexavar		Placebo		Nexavar	
Dose of exposure	Persons	Person time[a]	Persons	Person time[a]	Persons	Person time[a]
Missing					5	2.1
200 mg	0	0.0	2	5.3	65	27.1
400 mg	24	24.2	27	27.8	540	477.3
600 mg					17	8.6
800 mg	2,214	1,743.5	2,133	1,767.1	4,066	3,317.4
1,200 mg					25	11.0
1,600 mg					9	1.6
Other					76	27.7
Total	2,238	1,767.8	2,162	1,800.2	4,803	3,872.7

CMSAF: Controlled monotherapy safety set, MSAF: Monotherapy safety set.
[a] Total exposure for persons is given in years. For calculation, a month equals 30 days and a year equals 360 days.
Note: Time spent on placebo is not counted towards person time, but time preceding and following placebo treatment.
Note: Duration of ongoing patients is calculated by using the study specific cut-off date as day of last treatment.
Sources: Bay 43-9006 Tables for Risk Management Plan (CMSAF), Table 3/3
Bay 43-9006 Tables for Risk Management Plan (MSAF), Table 3/3

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Table Part II SIII-6: Duration of exposure by initial dose (by indication)

Integrated analysis pool	CMSAF				MSAF	
Treatment	**Nexavar**		**Placebo**		**Nexavar**	
Dose of exposure	**Persons**	**Person time[a]**	**Persons**	**Person time[a]**	**Persons**	**Person time[a]**
DTC						
200 mg	0	0.0	1	1.5		
400 mg	13	13.3	15	12.0	37	33.8
600 mg					2	3.3
800 mg	194	182.8	193	132.9	357	505.9
Total	207	196.1	209	146.4	396	542.9
RCC						
Missing					3	2.0
200 mg					9	6.4
400 mg					380	377.9
600 mg					3	2.4
800 mg	451	237.4	450	135.4	914	832.8
1,200 mg					5	4.0
Other					3	2.7
Total	451	237.4	450	135.4	1,317	1,228.3
HCC						
Missing					1	0.0
200 mg					19	9.2
400 mg	1	0.4	2	2.5	63	31.7
600 mg					1	0.3
800 mg	674	354.4	602	324.0	1,316	772.4
Other					10	7.0
Total	675	354.8	604	326.5	1,410	820.7
Adjuvant HCC						
200 mg	0	0.0	1	3.8		
400 mg	8	9.2	8	11.9	8	9.2
800 mg	551	851.3	539	1,096.9	551	878.1
Total	559	860.5	548	1,112.6	559	887.3

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Table Part II SIII-6: Duration of exposure by initial dose (by indication)

Integrated analysis pool	CMSAF				MSAF	
Treatment	**Nexavar**		**Placebo**		**Nexavar**	
Dose of exposure	**Persons**	**Person time[a]**	**Persons**	**Person time[a]**	**Persons**	**Person time[a]**
Other cancer types						
Missing					1	0.1
200 mg					37	11.5
400 mg	2	1.2	2	1.4	52	24.7
600 mg					11	2.6
800 mg	344	117.6	349	77.9	928	328.2
1,200 mg					20	7.0
1,600 mg					9	1.6
Other					63	17.9
Total	346	118.9	351	79.3	1,121	393.5

CMSAF: Controlled monotherapy safety set, DTC: Differentiated thyroid carcinoma, HCC: Hepatocellular carcinoma, MSAF: Monotherapy safety set, RCC: Renal cell carcinoma.
[a] Total exposure for persons is given in years. For calculation, a month equals 30 days and a year equals 360 days.
Note: Time spent on placebo is not counted towards person time, but time preceding and following placebo treatment.
Note: Duration of ongoing patients is calculated by using the study specific cut-off date as day of last treatment.
Sources: Bay 43-9006 Tables for Risk Management Plan (CMSAF), Table 3/3
Bay 43-9006 Tables for Risk Management Plan (MSAF), Table 3/3

SIII.1.2 Duration of Exposure by Age Group and Gender

The duration of exposure by age group and gender is presented in Table Part II SIII-7 for all cancer types and in Table Part II SIII-8 by indication.

Table Part II SIII-7: Duration of exposure by age group and gender (all cancer types combined)

Integrated analysis pool		CMSAF				MSAF	
Treatment		**Nexavar**		**Placebo**		**Nexavar**	
Age groups (years)	**Gender**	**Persons**	**Person time[a]**	**Persons**	**Person time[a]**	**Persons**	**Person time[a]**
≥16 to <18	Male					1	1.1
	Female						
	Total					1	1.1

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Table Part II SIII-7: Duration of exposure by age group and gender (all cancer types combined)

Integrated analysis pool		CMSAF				MSAF	
Treatment		Nexavar		Placebo		Nexavar	
Age groups (years)	Gender	Persons	Person time[a]	Persons	Person time[a]	Persons	Person time[a]
≥18 to <65	Male	1,005	927.0	937	870.8	1,992	1,762.5
	Female	371	257.9	326	200.8	996	717.7
	Total	1,376	1,184.9	1,263	1,071.6	2,988	2,480.1
≥65 to <75	Male	452	352.6	478	414.9	943	791.6
	Female	195	113.5	175	126.5	425	320.5
	Total	647	466.2	653	541.4	1,368	1,112.1
≥75 to <85	Male	153	76.5	172	126.5	301	190.3
	Female	55	37.2	64	56.3	127	79.9
	Total	208	113.7	236	182.9	428	270.2
≥85	Male	4	1.8	1	0.6	12	7.0
	Female	3	1.3	9	3.8	6	2.1
	Total	7	3.0	10	4.4	18	9.1
Total	Male	1,614	1,357.9	1,588	1,412.9	3,249	2,752.5
	Female	624	409.8	574	387.4	1,554	1,120.2
	Total	2,238	1,767.8	2,162	1,800.2	4,803	3,872.7

CMSAF: Controlled monotherapy safety set, MSAF: Monotherapy safety set.
[a] Total exposure for persons is given in years. For calculation, a month equals 30 days and a year equals 360 days.
Note: Time spent on placebo is not counted towards person time, but time preceding and following placebo treatment.
Note: Duration of ongoing patients is calculated by using the study specific cut-off date as day of last treatment.
Sources: Bay 43-9006 Tables for Risk Management Plan (CMSAF), Tables 3/4 and 3/5
Bay 43-9006 Tables for Risk Management Plan (MSAF), Tables 3/4 and 3/5

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Table Part II SIII-8: Duration of exposure by age group and gender (by indication)

Integrated analysis pool		CMSAF				MSAF	
Treatment		Nexavar		Placebo		Nexavar	
Age groups (years)	Gender	Persons	Person time[a]	Persons	Person time[a]	Persons	Person time[a]
DTC							
≥18 to <65	Male	63	62.5	51	36.0	105	141.0
	Female	56	54.5	66	39.8	116	172.4
	Total	119	117.0	117	75.8	221	313.5
≥65 to <75	Male	26	26.4	30	22.3	59	89.2
	Female	37	33.0	32	22.3	66	79.8
	Total	63	59.4	62	44.6	125	169.0
≥75 to <85	Male	15	12.1	13	11.6	29	40.3
	Female	10	7.7	13	11.6	19	18.3
	Total	25	19.8	26	23.2	48	58.6
≥85	Male					1	1.3
	Female	0	0.0	4	2.8	1	0.5
	Total	0	0.0	4	2.8	2	1.8
Total	Male	104	101.0	94	69.9	194	271.9
	Female	103	95.2	115	76.5	202	271.0
	Total	207	196.1	209	146.4	396	542.9
RCC							
≥18 to <65	Male	209	110.4	252	77.9	625	587.0
	Female	95	51.0	74	22.3	244	213.4
	Total	304	161.5	326	100.2	869	800.5
≥65 to <75	Male	94	52.8	76	20.9	261	263.5
	Female	35	14.7	34	9.7	116	105.7
	Total	129	67.6	110	30.6	377	369.1
≥75 to <85	Male	11	4.7	11	3.9	47	43.1
	Female	6	3.6	3	0.7	21	15.0
	Total	17	8.2	14	4.6	68	58.0
≥85	Male	1	0.1	0	0.0	3	0.7
	Female	-	-	-	-	-	-
	Total	1	0.1	0	0.0	3	0.7
Total	Male	315	168.0	339	102.7	936	894.2
	Female	136	69.4	111	32.7	381	334.1
	Total	451	237.4	450	135.4	1,317	1,228.3

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Table Part II SIII-8: Duration of exposure by age group and gender (by indication)

Integrated analysis pool		CMSAF				MSAF	
Treatment		Nexavar		Placebo		Nexavar	
Age groups (years)	Gender	Persons	Person time[a]	Persons	Person time[a]	Persons	Person time[a]
HCC							
≥16 to <18	Male					1	1.1
	Female						
	Total					1	1.1
≥18 to <65	Male	285	149.4	207	98.1	592	341.2
	Female	46	21.3	35	20.6	124	64.9
	Total	331	170.7	242	118.7	716	406.1
≥65 to <75	Male	184	106.7	188	110.4	376	239.1
	Female	48	26.3	45	26.0	96	63.1
	Total	232	133.0	233	136.5	472	302.3
≥75 to <85	Male	86	38.8	98	54.6	162	81.5
	Female	22	10.6	26	15.3	50	24.3
	Total	108	49.3	124	69.9	212	105.8
≥85	Male	3	1.7	1	0.6	7	5.0
	Female	1	0.1	4	0.9	2	0.3
	Total	4	1.8	5	1.5	9	5.3
Total	Male	558	296.5	494	263.7	1,138	668.0
	Female	117	58.3	110	62.7	272	152.7
	Total	675	354.8	604	326.5	1,410	820.7
Adjuvant HCC							
≥18 to <65	Male	319	564.3	304	636.7	319	585.4
	Female	64	89.0	53	95.9	64	92.1
	Total	383	653.4	357	732.5	383	677.4
≥65 to <75	Male	105	153.1	120	245.8	105	155.7
	Female	31	24.0	27	59.9	31	24.0
	Total	136	177.0	147	305.7	136	179.7
≥75 to <85	Male	29	16.2	30	49.4	29	16.2
	Female	10	13.1	14	25.0	10	13.1
	Total	39	29.2	44	74.4	39	29.3
≥85	Male						
	Female	1	0.9	0	0.0	1	0.9
	Total	1	0.9	0	0.0	1	0.9

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Table Part II SIII-8: Duration of exposure by age group and gender (by indication)

Integrated analysis pool		CMSAF				MSAF	
Treatment		**Nexavar**		**Placebo**		**Nexavar**	
Age groups (years)	**Gender**	**Persons**	**Person time[a]**	**Persons**	**Person time[a]**	**Persons**	**Person time[a]**
Total	Male	453	733.6	454	931.8	453	757.2
	Female	106	127.0	94	180.8	106	130.1
	Total	559	860.5	548	1,112.6	559	887.3
Other cancer types							
≥18 to <65	Male	129	40.3	123	22.2	351	107.8
	Female	110	42.0	98	22.2	448	174.8
	Total	239	82.4	221	44.5	799	282.6
≥65 to <75	Male	43	13.7	64	15.4	142	44.1
	Female	44	15.5	37	8.5	116	47.9
	Total	87	29.2	101	24.0	258	92.0
≥75 to <85	Male	12	4.8	20	7.0	34	9.2
	Female	7	2.3	8	3.8	27	9.3
	Total	19	7.1	28	10.8	61	18.5
≥85	Male					1	0.0
	Female	1	0.2	1	0.1	2	0.4
	Total	1	0.2	1	0.1	3	0.4
Total	Male	184	58.9	207	44.7	528	161.2
	Female	162	60.0	144	34.6	593	232.3
	Total	346	118.9	351	79.3	1,121	393.5

CMSAF: Controlled monotherapy safety set, DTC: Differentiated thyroid carcinoma, HCC: Hepatocellular carcinoma, MSAF: Monotherapy safety set, RCC: Renal cell carcinoma.
[a] Total exposure for persons is given in years. For calculation, a month equals 30 days and a year equals 360 days.
Note: Time spent on placebo is not counted towards person time, but time preceding and following placebo treatment.
Note: Duration of ongoing patients is calculated by using the study specific cut-off date as day of last treatment.
Sources: Bay 43-9006 Tables for Risk Management Plan (CMSAF), Tables 3/4 and 3/5
Bay 43-9006 Tables for Risk Management Plan (MSAF), Tables 3/4 and 3/5

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SIII.1.3 Duration of Exposure by Ethnic or Racial Origin

The duration of exposure by ethnic or racial origin is presented in Table Part II SIII-9 for all cancer types and in Table Part II SIII-10 by indication.

Table Part II SIII-9: Duration of exposure by ethnic or racial origin (all cancer types combined)

Integrated analysis pool	CMSAF				MSAF	
Treatment	Nexavar		Placebo		Nexavar	
Ethnic/racial origin	Persons	Person time[a]	Persons	Person time[a]	Persons	Person time[a]
Missing	151	104.1	138	58.1	234	224.8
White	1,055	704.8	1,069	699.1	2,741	2,052.7
Black or African American	31	21.1	20	22.9	95	47.1
Asian	975	918.5	898	993.9	1,589	1,448.1
Hispanic	22	15.9	30	19.2	80	53.6
Other	4	3.3	7	7.1	64	46.5
Total	2,238	1,767.8	2,162	1,800.2	4,803	3,872.7

CMSAF: Controlled monotherapy safety set, MSAF: Monotherapy safety set.
[a] Total exposure for persons is given in years. For calculation, a month equals 30 days and a year equals 360 days.
Note: Time spent on placebo is not counted towards person time, but time preceding and following placebo treatment.
Note: Duration of ongoing patients is calculated by using the study specific cut-off date as day of last treatment.
Sources: Bay 43-9006 Tables for Risk Management Plan (CMSAF), Table 3/6
Bay 43-9006 Tables for Risk Management Plan (MSAF), Table 3/6

Table Part II SIII-10: Duration of exposure by ethnic or racial origin (by indication)

Integrated analysis pool	CMSAF				MSAF	
Treatment	Nexavar		Placebo		Nexavar	
Ethnic/racial origin	Persons	Person time[a]	Persons	Person time[a]	Persons	Person time[a]
DTC						
Missing	29	33.7	22	13.0	47	75.0
White	123	110.9	128	88.5	229	308.4
Black or African-American	6	2.5	5	5.4	9	6.2
Asian	47	46.4	51	38.4	105	145.0
Hispanic	2	2.6	2	1.1	5	7.4
Other	0	0.0	1	0.1	1	1.0
Total	**207**	**196.1**	**209**	**146.4**	**396**	**542.9**

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Table Part II SIII-10: Duration of exposure by ethnic or racial origin (by indication)

Integrated analysis pool	CMSAF				MSAF	
Treatment	**Nexavar**		**Placebo**		**Nexavar**	
Ethnic/racial origin	**Persons**	**Person time[a]**	**Persons**	**Person time[a]**	**Persons**	**Person time[a]**
RCC						
Missing	102	61.0	102	39.0	150	133.8
White	334	168.8	330	92.9	911	860.0
Black or African American	2	0.6	2	0.9	12	6.5
Asian	4	1.3	9	1.7	184	178.1
Hispanic	8	4.7	7	1.0	20	19.6
Other	1	0.9	0	0.0	40	30.4
Total	**451**	**237.4**	**450**	**135.4**	**1,317**	**1,228.3**
HCC						
Missing						
White	259	153.7	272	134.3	638	397.2
Black or African American	9	3.4	4	1.5	36	15.2
Asian	402	195.5	326	188.2	690	382.7
Hispanic	5	2.2	2	2.5	27	13.9
Other					19	11.7
Total	**675**	**354.8**	**604**	326.5	**1,410**	**820.7**
Adjuvant HCC						
Missing	6	5.8	3	4.5	6	5.8
White	188	217.5	182	338.4	188	220.5
Black or African American	13	14.3	8	14.9	13	14.3
Asian	349	617.2	340	735.9	349	640.9
Hispanic	2	5.7	11	12.3	2	5.8
Other	1	0.0	4	6.6	1	0.0
Total	**559**	**860.5**	**548**	**1,112.6**	**559**	**887.3**

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Table Part II SIII-10: Duration of exposure by ethnic or racial origin (by indication)

Integrated analysis pool	CMSAF				MSAF	
Treatment	**Nexavar**		**Placebo**		**Nexavar**	
Ethnic/racial origin	**Persons**	**Person time[a]**	**Persons**	**Person time[a]**	**Persons**	**Person time[a]**
Other cancer types						
Missing	14	3.5	11	1.6	31	10.2
White	151	54.0	157	45.0	775	266.6
Black or African American	1	0.2	1	0.2	25	5.0
Asian	173	58.2	172	29.8	261	101.4
Hispanic	5	0.6	8	2.3	26	7.0
Other	2	2.3	2	0.4	3	3.4
Total	**346**	**118.9**	**351**	**79.3**	**1,121**	**393.5**

CMSAF: Controlled monotherapy safety set, DTC: Differentiated thyroid carcinoma, HCC: Hepatocellular carcinoma, MSAF: Monotherapy safety set, RCC: Renal cell carcinoma.
[a] Total exposure for persons is given in years. For calculation, a month equals 30 days and a year equals 360 days.
Note: Time spent on placebo is not counted towards person time, but time preceding and following placebo treatment.
Note: Duration of ongoing patients is calculated by using the study specific cut-off date as day of last treatment.
Sources: Bay 43-9006 Tables for Risk Management Plan (CMSAF), Table 3/6
Bay 43-9006 Tables for Risk Management Plan (MSAF), Table 3/6

SIII.1.4 Duration of Exposure by Body Mass Index (BMI)

The duration of exposure by BMI is presented in Table Part II SIII-11 for all cancer types and in Table Part II SIII-12 by indication.

Table Part II SIII-11: Duration of exposure by BMI at baseline (all cancer types combined)

Integrated analysis pool	CMSAF				MSAF	
Treatment	**Nexavar**		**Placebo**		**Nexavar**	
BMI	**Persons**	**Person time[a]**	**Persons**	**Person time[a]**	**Persons**	**Person time[a]**
Missing	1,082	1,124.4	1,042	1,258.9	1,496	1,679.5
<25	654	310.6	623	272.3	1,731	969.3
≥25 to <30	372	238.2	355	179.8	1,071	814.4
≥30	130	94.6	142	89.3	505	409.6
Total	**2,238**	**1,767.8**	**2,162**	**1,800.2**	**4,803**	**3,872.7**

BMI: Body mass index, CMSAF: Controlled monotherapy safety set, MSAF: Monotherapy safety set.
[a] Total exposure for persons is given in years. For calculation, a month equals 30 days and a year equals 360 days.

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Table Part II SIII-11: Duration of exposure by BMI at baseline (all cancer types combined)

Integrated analysis pool	CMSAF				MSAF	
Treatment	**Nexavar**		**Placebo**		**Nexavar**	
BMI	**Persons**	**Person time[a]**	**Persons**	**Person time[a]**	**Persons**	**Person time[a]**

Note: Time spent on placebo is not counted towards person time, but time preceding and following placebo treatment.
Note: Duration of ongoing patients is calculated by using the study specific cut-off date as day of last treatment.
Sources: Bay 43-9006 Tables for Risk Management Plan (CMSAF), Table 3/7
Bay 43-9006 Tables for Risk Management Plan (MSAF), Table 3/7

Table Part II SIII-12: Duration of exposure by BMI at baseline (by indication)

Integrated analysis pool	CMSAF				MSAF	
Treatment	**Nexavar**		**Placebo**		**Nexavar**	
BMI	**Persons**	**Person time[a]**	**Persons**	**Person time[a]**	**Persons**	**Person time[a]**
DTC						
Missing					20	11.4
<25	86	73.8	85	50.6	157	192.4
≥25 to <30	74	76.2	66	46.5	132	201.3
≥30	47	46.1	58	49.3	87	137.8
Total	207	196.1	209	146.4	396	542.9
RCC						
Missing	451	237.4	450	135.4	715	710.3
<25					297	212.0
≥25 to <30					197	205.5
≥30					108	100.5
Total	451	237.4	450	135.4	1,317	1,228.3
HCC						
Missing	21	12.3	14	3.7	44	27.7
<25	391	178.3	344	182.5	765	396.0
≥25 to <30	202	125.8	198	112.1	433	287.1
≥30	61	38.4	48	28.2	168	109.9
Total	675	354.8	604	326.5	1,410	820.7
Adjuvant HCC						

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Table Part II SIII-12: Duration of exposure by BMI at baseline (by indication)

Integrated analysis pool	CMSAF				MSAF	
Treatment	**Nexavar**		**Placebo**		**Nexavar**	
BMI	**Persons**	**Person time[a]**	**Persons**	**Person time[a]**	**Persons**	**Person time[a]**
Missing	559	860.5	548	1,112.6	559	887.3
<25						
≥25 to <30						
≥30						
Total	559	860.5	548	1,112.6	559	887.3
Other cancer types						
Missing	51	14.1	30	7.2	158	42.7
<25	177	58.5	194	39.1	512	168.9
≥25 to <30	96	36.1	91	21.3	309	120.5
≥30	22	10.1	36	11.7	142	61.4
Total	346	118.9	351	79.3	1,121	393.5

BMI: Body mass index, CMSAF: Controlled monotherapy safety set, DTC: Differentiated thyroid carcinoma, HCC: Hepatocellular carcinoma, MSAF: Monotherapy safety set, RCC: Renal cell carcinoma.
[a] Total exposure for persons is given in years. For calculation, a month equals 30 days and a year equals 360 days.
Note: Time spent on placebo is not counted towards person time, but time preceding and following placebo treatment.
Note: Duration of ongoing patients is calculated by using the study specific cut-off date as day of last treatment.
Sources: Bay 43-9006 Tables for Risk Management Plan (CMSAF), Table 3/7
Bay 43-9006 Tables for Risk Management Plan (MSAF), Table 3/7

SIII.1.5 Duration of Exposure by Renal and Hepatic Function

The duration of exposure by renal and hepatic function is presented in Table Part II SIII-13 for all cancer types and in Table Part II SIII-14 by indication.

Table Part II SIII-13: Duration of exposure by renal and hepatic function at baseline (all cancer types combined)

Integrated analysis pool	CMSAF				MSAF	
Treatment	**Nexavar**		**Placebo**		**Nexavar**	
Renal/hepatic function	**Persons**	**Person time[a]**	**Persons**	**Person time[a]**	**Persons**	**Person time[a]**
Renal Function[b]						
Missing	6	1.6	6	2.0	13	7.7
Normal renal function	1,958	1,600.8	1,869	1,631.6	3,953	3,156.7
Impaired renal function	274	165.3	287	166.7	837	708.3

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Table Part II SIII-13: Duration of exposure by renal and hepatic function at baseline (all cancer types combined)

Integrated analysis pool	CMSAF				MSAF	
Treatment	**Nexavar**		**Placebo**		**Nexavar**	
Renal/hepatic function	**Persons**	**Person time[a]**	**Persons**	**Person time[a]**	**Persons**	**Person time[a]**
Total	2,238	1,767.8	2,162	1,800.2	4,803	3,872.7
Hepatic Function						
Missing	11	8.8	13	7.8	34	20.7
Maximum AST and ALT ≤1.5 × ULN	1,703	1,383.3	1,674	1,399.1	3,695	3,192.6
Maximum AST and ALT >1.5 × ULN ≤3 × ULN	386	299.2	356	315.1	784	520.8
Maximum AST and ALT >3 × ULN	138	76.5	119	78.3	290	138.6
Total	2,238	1,767.8	2,162	1,800.2	4,803	3,872.7

ALT: Alanine transaminase, AST: Aspartate transaminase, CMSAF: Controlled monotherapy safety set, eGFR: Estimated glomerular filtration rate, MDRD: Modification of diet in renal disease, MSAF: Monotherapy safety set, SCr: Serum creatinine, ULN: Upper limit of normal.
[a] Total exposure for persons is given in years. For calculation, a month equals 30 days and a year equals 360 days.
[b] Renal function at baseline: normal renal function (eGFR≥60 mL/min/1.73m^2), impaired renal function (eGFR<60 mL/min/1.73m^2)
Note: Time spent on placebo is not counted towards person time, but time preceding and following placebo treatment.
Note: Duration of ongoing patients is calculated by using the study specific cut-off date as day of last treatment.
Note: eGFR was calculated according to the abbreviated MDRD formula: eGFR (mL/min/1.73m^2): k x 186 x SCr-1.154 x age-0.203, where k=1 for men and k=0.742 for women, SCr measured in mg/dL. The result should be multiplied by 1.212 for Blacks or African-Americans, by 0.881 for Japanese, and by 1.227 for Chinese. For all other subjects the multiplication factor is 1.
Sources: Bay 43-9006 Tables for Risk Management Plan (CMSAF), Tables 3/9 and 3/10
Bay 43-9006 Tables for Risk Management Plan (MSAF), Tables 3/9 and 3/10

Table Part II SIII-14: Duration of exposure by renal and hepatic function at baseline (by indication)

Integrated analysis pool	CMSAF				MSAF	
Treatment	**Nexavar**		**Placebo**		**Nexavar**	
Renal/hepatic function	**Persons**	**Person time[a]**	**Persons**	**Person time[a]**	**Persons**	**Person time[a]**
RENAL Function[b]						
DTC						
Missing						
Normal renal function	192	182.1	192	135.5	366	502.8
Impaired renal function	15	14.1	17	10.9	30	40.1

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Table Part II SIII-14: Duration of exposure by renal and hepatic function at baseline (by indication)

Integrated analysis pool	CMSAF				MSAF	
Treatment	**Nexavar**		**Placebo**		**Nexavar**	
Renal/hepatic function	**Persons**	**Person time[a]**	**Persons**	**Person time[a]**	**Persons**	**Person time[a]**
Total	207	196.1	209	146.4	396	542.9
RCC						
Missing	5	0.9	6	2.0	11	7.0
Normal renal function	282	144.3	288	81.4	767	680.9
Impaired renal function	164	92.2	156	52.0	539	540.5
Total	451	237.4	450	135.4	1,317	1,228.3
HCC						
Missing						
Normal renal function	628	330.1	554	301.2	1,292	757.5
Impaired renal function	47	24.7	50	25.3	118	63.2
Total	675	354.8	604	326.5	1,410	820.7
Adjuvant HCC						
Missing	1	0.7	0	0.0	1	0.7
Normal renal function	534	834.0	514	1,041.8	534	860.5
Impaired renal function	24	25.9	34	70.8	24	26.1
Total	559	860.5	548	1,112.6	559	887.3
Other cancer types						
Missing					1	0.0
Normal renal function	322	110.4	321	71.6	994	355.0
Impaired renal function	24	8.5	30	7.7	126	38.5
Total	346	118.9	351	79.3	1,121	393.5
HEPATIC Function						
DTC						
Missing	2	1.5	2	1.4	2	1.5
Maximum AST and ALT ≤1.5 × ULN	200	188.6	203	142.4	383	531.0
Maximum AST and ALT >1.5 × ULN ≤3 × ULN	5	6.0	4	2.6	9	9.3
Maximum AST and ALT >3 × ULN					2	1.1
Total	207	196.1	209	146.4	396	542.9
RCC						
Missing	5	0.9	6	2.0	15	10.1

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Table Part II SIII-14: Duration of exposure by renal and hepatic function at baseline (by indication)

Integrated analysis pool	CMSAF				MSAF	
Treatment	**Nexavar**		**Placebo**		**Nexavar**	
Renal/hepatic function	**Persons**	**Person time[a]**	**Persons**	**Person time[a]**	**Persons**	**Person time[a]**
Maximum AST and ALT ≤1.5 × ULN	421	224.4	428	130.4	1,231	1,166.0
Maximum AST and ALT >1.5 × ULN ≤3 × ULN	21	9.8	14	2.6	57	44.2
Maximum AST and ALT >3 × ULN	4	2.2	2	0.4	14	8.0
Total	451	237.4	450	135.4	1,317	1,228.3
HCC						
Missing	0	0.0	2	1.1	1	0.3
Maximum AST and ALT ≤1.5 × ULN	327	195.0	297	180.0	651	446.5
Maximum AST and ALT >1.5 × ULN ≤3 × ULN	255	121.7	217	110.4	538	284.3
Maximum AST and ALT >3 × ULN	93	38.2	88	35.1	220	89.6
Total	675	354.8	604	326.5	1,410	820.7
Adjuvant HCC						
Missing	3	5.8	3	3.4	3	5.8
Maximum AST and ALT ≤1.5 × ULN	425	661.1	408	869.3	425	684.0
Maximum AST and ALT >1.5 × ULN ≤3 × ULN	92	157.8	110	197.5	92	160.9
Maximum AST and ALT >3 × ULN	39	35.8	27	42.5	39	36.6
Total	559	860.5	548	1,112.6	559	887.3
Other cancer types						
Missing	1	0.6	0	0.0	13	3.1
Maximum AST and ALT ≤1.5 × ULN	330	114.1	338	76.9	1,005	365.0
Maximum AST and ALT >1.5 × ULN ≤3 × ULN	13	3.9	11	2.1	88	22.1
Maximum AST and ALT >3 × ULN	2	0.3	2	0.3	15	3.3
Total	346	118.9	351	79.3	1,121	393.5

ALT: Alanine transaminase, AST: Aspartate transaminase, CMSAF: Controlled monotherapy safety set, DTC: Differentiated thyroid carcinoma, eGFR: Estimated glomerular filtration rate, HCC: Hepatocellular carcinoma,

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Table Part II SIII-14: Duration of exposure by renal and hepatic function at baseline (by indication)

Integrated analysis pool	CMSAF				MSAF	
Treatment	Nexavar		Placebo		Nexavar	
Renal/hepatic function	Persons	Person time[a]	Persons	Person time[a]	Persons	Person time[a]

MDRD: Modification of diet in renal disease, MSAF: Monotherapy safety set, RCC: Renal cell carcinoma, SCr: Serum creatinine, ULN: Upper limit of normal.
[a] Total exposure for persons is given in years. For calculation, a month equals 30 days and a year equals 360 days.
[b] Renal function at baseline: normal renal function (eGFR≥60 mL/min/1.73m^2), impaired renal function (eGFR<60 mL/min/1.73m^2)
Note: Time spent on placebo is not counted towards person time, but time preceding and following placebo treatment.
Note: Duration of ongoing patients is calculated by using the study specific cut-off date as day of last treatment.
Note: eGFR was calculated according to the abbreviated MDRD formula: eGFR (mL/min/1.73m^2): k x 186 x SCr-1.154 x age-0.203, where k=1 for men and k=0.742 for women, SCr measured in mg/dL. The result should be multiplied by 1.212 for Blacks or African-Americans, by 0.881 for Japanese, and by 1.227 for Chinese. For all other subjects the multiplication factor is 1.
Sources: Bay 43-9006 Tables for Risk Management Plan (CMSAF), Tables 3/9 and 3/10
Bay 43-9006 Tables for Risk Management Plan (MSAF), Tables 3/9 and 3/10

SIII.1.6 Duration of Exposure by Eastern Cooperative Oncology Group (ECOG) Performance Status (PS)

The duration of exposure by Eastern Cooperative Oncology Group (ECOG) Performance Status (PS) is presented in Table Part II SIII-15 for all cancer types and in Table Part II SIII-16 by indication.

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Table Part II SIII-15: Duration of exposure by ECOG PS at baseline (all cancer types combined)

Integrated analysis pool	CMSAF				MSAF	
Treatment	Nexavar		Placebo		Nexavar	
ECOG PS	Persons	Person time[a]	Persons	Person time[a]	Persons	Person time[a]
Missing	1	0.4	2	0.6	19	6.7
0	1,403	1,387.0	1,381	1,548.5	2,724	2,653.8
1	790	366.7	743	242.3	1,927	1,163.3
2	44	13.7	36	8.9	120	44.7
3					13	4.3
4						
Total	2,238	1,767.8	2,162	1,800.2	4,803	3,872.7

CMSAF: Controlled monotherapy safety set, ECOG: Eastern Cooperative Oncology Group,
MSAF: Monotherapy safety set, PS: Performance Status.
[a] Total exposure for persons is given in years. For calculation, a month equals 30 days and a year equals 360 days.
Note: Time spent on placebo is not counted towards person time, but time preceding and following placebo treatment.
Note: Duration of ongoing patients is calculated by using the study specific cut-off date as day of last treatment.
Sources: Bay 43-9006 Tables for Risk Management Plan (CMSAF), Table 3/8
Bay 43-9006 Tables for Risk Management Plan (MSAF), Table 3/8

Table Part II SIII-16: Duration of exposure by ECOG PS at baseline (by indication)

Integrated analysis pool	CMSAF				MSAF	
Treatment	Nexavar		Placebo		Nexavar	
ECOG PS	Persons	Person time[a]	Persons	Person time[a]	Persons	Person time[a]
DTC						
Missing					18	6.4
0	132	140.3	130	100.3	219	364.3
1	70	53.0	71	42.8	143	162.4
2	5	2.8	8	3.3	15	9.1
3					1	0.8
4						
Total	207	196.1	209	146.4	396	542.9
RCC						
Missing	1	0.4	2	0.6	1	0.4

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Table Part II SIII-16: Duration of exposure by ECOG PS at baseline (by indication)

Integrated analysis pool	CMSAF				MSAF	
Treatment	**Nexavar**		**Placebo**		**Nexavar**	
ECOG PS	**Persons**	**Person time[a]**	**Persons**	**Person time[a]**	**Persons**	**Person time[a]**
0	219	124.1	210	71.4	682	703.6
1	224	109.3	235	63.0	589	505.6
2	7	3.6	3	0.4	37	17.6
3					8	1.2
4						
Total	451	237.4	450	135.4	1,317	1,228.3
HCC						
Missing						
0	390	223.0	383	235.9	834	521.8
1	254	124.6	196	85.3	533	283.9
2	31	7.2	25	5.2	40	12.7
3					3	2.2
4						
Total	675	354.8	604	326.5	1,410	820.7
Adjuvant HCC						
Missing						
0	554	859.5	545	1,110.5	554	886.2
1	5	1.1	3	2.1	5	1.1
2						
3						
4						
Total	559	860.5	548	1,112.6	559	887.3
Other cancer types						
Missing						
0	108	40.1	113	30.4	435	177.9
1	237	78.7	238	49.0	657	210.3
2	1	0.1	0	0.0	28	5.3
3					1	0.1
4						
Total	346	118.9	351	79.3	1,121	393.5

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Table Part II SIII-16: Duration of exposure by ECOG PS at baseline (by indication)

Integrated analysis pool	**CMSAF**				**MSAF**	
Treatment	**Nexavar**		**Placebo**		**Nexavar**	
ECOG PS	**Persons**	**Person time[a]**	**Persons**	**Person time[a]**	**Persons**	**Person time[a]**

CMSAF: Controlled monotherapy safety set, DTC: Differentiated thyroid carcinoma, ECOG: Eastern Cooperative Oncology Group, HCC: Hepatocellular carcinoma, MSAF: Monotherapy safety set, PS: Performance Status, RCC: Renal cell carcinoma.
[a] Total exposure for persons is given in years. For calculation, a month equals 30 days and a year equals 360 days.
Note: Time spent on placebo is not counted towards person time, but time preceding and following placebo treatment.
Note: Duration of ongoing patients is calculated by using the study specific cut-off date as day of last treatment.
Sources: Bay 43-9006 Tables for Risk Management Plan (CMSAF), Table 3/8
Bay 43-9006 Tables for Risk Management Plan (MSAF), Table 3/8

Part II: Module SIV - Populations not studied in Clinical Trials

SIV.1. Exclusion criteria in pivotal clinical studies within the development programme

Table Part II SIV-1: Exclusion criteria in pivotal clinical studies

Exclusion criteria	Reason for exclusion	Missing information Yes/No	Rationale
History of cardiac disease: congestive heart failure >New York Heart Association (NYHA) class 2; active coronary artery disease (CAD) (myocardial infarction more than 6 months prior to study entry is allowed); cardiac arrhythmias requiring anti-arrhythmic therapy (beta blockers or digoxin are permitted) or uncontrolled hypertension.	Vascular endothelial growth factor antagonists have been associated with cardiovascular side effects. Patients with a recent history of cardiac disease may be at higher risk for such AEs.	No	Congestive heart failure and arterial thrombosis (MI) are known important identified risks that are adequately characterised (see Part II: Module SVII - Identified and Potential Risks). Hypertension has been removed from the list of safety concerns as it is a known risk that requires no further characterisation and is followed up via routine pharmacovigilance, and for which the risk minimisation messages in the product information are adequately communicated.
Pregnant or breast-feeding patients. Women of childbearing potential must have a negative pregnancy test performed within seven days of the start of treatment. Both men and women enrolled in this trial must use adequate barrier birth control measures during the course of the trial.	Toxicology data suggest a teratogenic potential of sorafenib.	No	Pregnancy and exposure through breastfeeding is a known important potential risk that is adequately characterised (see Part II: Module SVII - Identified and Potential Risks).
Reduced bone marrow, liver and renal function • or haemoglobin <9.0 g/dl • or absolute neutrophil count (ANC) <1,500/mm^3	This exclusion criterion relates to ensuring patients are at a stable baseline before entering clinical studies. In order to achieve interpretable study results, confounding factors such	No	The data do not suggest a significant effect of Nexavar on the bone marrow and on coagulation parameters. No significant effect on the PK of sorafenib is expected in patients with renal or hepatic impairment.

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Table Part II SIV-1: Exclusion criteria in pivotal clinical studies

Exclusion criteria	Reason for exclusion	Missing information Yes/No	Rationale
• or platelet count <100,000/mm^3 • or total bilirubin >1.5 times the upper limit of normal (ULN) • or alanine aminotransaminase (ALT) and aspartate aminotransferase (AST) 2.5 × ULN • prothrombin time (PT)/international normalized ratio (INR) and partial thromboplastin time (PTT) >1.5 × ULN • or serum creatinine >1.5 × ULN	as significant co-morbidity were minimised.		Safety and efficacy in patients with hepatocellular carcinoma (HCC) and Child-Pugh B liver dysfunction has been removed from the missing information, based on the results of the non-interventional Study 13414 (GIDEON), which included 666 patients with Child –Pugh B status.

AE: Adverse event, AST: Aspartate transaminase, ALT: Alanine transaminase, ANC: Absolute neutrophil count, CAD: Coronary artery disease, HCC: Hepatocellular carcinoma, INR: International normalised ratio, MI: Myocardial infarction, NYHA: New York Heart Association, PK: Pharmacokinetics, PT: Prothrombin time, PTT: Partial thromboplastin time, ULN: Upper limit of normal, VEGF: Vascular endothelial growth factor.

SIV.2. Limitations to detect adverse reactions in clinical trials development programme

Table Part II SIV-2: Limitations to detect adverse reactions in clinical trials

Ability to detect adverse reactions	Limitation of trial programme and discussion of implications for target population
Which are rare	Cumulatively, 12,000 patients were exposed to sorafenib over the whole company-sponsored clinical trial programme. Around 7,000 of these patients were treated in monotherapy studies which are part of the monotherapy pool (excluding EAP). ADRs with a frequency greater than 1 in 4,000 could be detected if there were no background incidence. It is unlikely that a rare adverse reaction will impact the benefit-risk balance of Nexavar in a target population with a life-threatening disease.
Due to prolonged exposure	Gore *et al.* (58) reported safety data based on an integrated database using individual patient data from six clinical trials and two expanded-access studies evaluating sorafenib monotherapy in RCC. NCI-CTCAE v3 terms were used for the selected drug-related AEs and prevalence rates were calculated in 3-month intervals for up to 12 months based on 4,684 patients (71% male, median age 62 years, 20% prior nephrectomy, 52% prior cytokine therapy, 6.3-months mean duration of sorafenib). The selected drug-related AEs (HFSR,

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Table Part II SIV-2: Limitations to detect adverse reactions in clinical trials

Ability to detect adverse reactions	Limitation of trial programme and discussion of implications for target population
	rash/desquamation, diarrhoea, fatigue, alopecia, hypertension) were generally mild or moderate at each 3-months interval, and declined or stabilised over the following 3-month intervals with the exception of diarrhoea (25% at 0-3 months and 50% of patients at 9-12 months interval). Grade 3/4 drug-related AEs leading to dose reduction/interruption/discontinuation occurred in 15%/13%/4% (0-3 months), 5%/4%/2% (3-6 months), 3%/2%/1% (6-9 months), and 4%/3%/1% (9-12 months) of patients. Drug-related AEs, with the exception of mild/moderate diarrhoea, decreased or stabilised over 12 months of Nexavar treatment. NCI-CTCAE Grade 3/4 drug-related AEs and rates of dose reductions and treatment discontinuations generally decreased over time.
Due to cumulative effects	Based on PK results, no cumulative effect is expected in patients with renal impairment or hepatic dysfunction Child-Pugh A and B. No data are available for patients with Child-Pugh C hepatic dysfunction. As cumulative effects are unlikely, the implications for the target population are limited.
Which have a long latency	There was no relevant genotoxic risk of sorafenib in standard genotoxicity tests *in vitro* and *in vivo*. In a 2-year mouse carcinogenicity study there were cases of colon adenocarcinoma associated with severe hyperplasia and inflammation, and in a 2-year rat carcinogenicity study there were cases of pancreatic islet cell adenoma. Systemic exposures achieved in both carcinogenicity studies were below clinical exposures in humans at the recommended dose. The observed cases were few in numbers and the clinical relevance of these findings is unknown. Considering the limited life expectancy of the targeted population, adverse reactions with a long latency will have minor implications on the target population.

ADR: Adverse drug reaction, AE: Adverse event, CTCAE: Common Terminology Criteria for Adverse Events, EAP: Early access programme, HFSR: Hand-foot skin reaction, NCI: National Cancer Institute, PK: Pharmacokinetic, RCC: Renal cell carcinoma.

SIV.3. Limitations in respect to populations typically under-represented in clinical trial development programmes

SIV.3.1. Children

With the exception of study ADVL-0413 (see below), the safety and effectiveness of Nexavar in paediatric patients have not been studied.

In animal toxicology studies, after repeated dosing to young and growing dogs, effects on bone and teeth with irregular thickening of the femoral growth plate at a daily sorafenib dose of 600 mg/m^2 body surface area (BSA) (equivalent to 1.2 times the recommended clinical dose of 500 mg/m^2 on a BSA basis), hypocellularity of the bone marrow next to the altered growth plate at 200 mg/m^2/day, and alterations of the dentin composition at 600 mg/m^2/day were observed. Similar effects were not seen in adult dogs dosed with sorafenib.

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Most clinical studies have excluded patients who are under 16-years old, with the majority of studies excluding those under 18-years old. A small number of patients under 16-years have received Nexavar as part of a compassionate use program. Only a limited number of serious adverse event (SAE) reports have been received documenting SAEs in adolescents less than 18-years old. These cases do not indicate a different safety profile in adolescents compared to the adult population studied in clinical trials. A review of adverse events (AEs) in the paediatric age group received from various sources (including Bayer's Patient Support Programs, non-Bayer sponsored interventional studies, spontaneous reports, and literature reports) suggests that the safety profile in paediatric patients is similar to the known safety profile of Nexavar in adult patients. However, this data is considered limited.

The paediatric study ADVL-0413 has been completed as a part of the Pharmacovigilance Plan (see Part VII Annex 2). This study was conducted by the Cancer Therapy Evaluation Programme Children's Oncology Group and published in 2012 (59). Nexavar was administered orally every 12 hours for consecutive 28 day-cycles. Pharmacokinetics (PK) (Day 1 and steady state) and pharmacodynamics were performed during Cycle 1. Of 65 patients enrolled, 60 were eligible. In the solid tumour cohort (n = 49), 4/6 patients experienced a dose-limiting toxicity (DLT) (hypertension, pain, rash/urticaria, thrombocytopenia, increased alanine transaminase [ALT]/aspartate aminotransferase [AST]) at the starting dose (150 mg/m^2/dose) which resulted in de-escalation to 105 mg/m^2/dose. After an Institutional Review Board approved eligibility criteria modification and dose re-escalation, the maximum tolerated dose was 200 mg/m^2/dose for solid tumours and 150 mg/m^2/dose for leukaemia's. Sorafenib exposure was highly variable between patients and did not increase in proportion to dose, but was within the ranges reported in adults. Diarrhoea, rash, fatigue, and increased ALT/AST were the most common sorafenib-related toxicities. Stable disease for ≥4 cycles was observed in 14 solid tumour patients, and two patients with acute myeloid leukaemia (AML) and fms-related tyrosine kinase 3 (FLT3) internal tandem duplication experienced a decrease in bone marrow blasts to <5%. The authors concluded that the recommended Phase II dose of Nexavar administered every 12 hours continuously for children with solid tumours is 200 mg/m^2/dose and 150 mg/m^2/dose for children with leukaemia's. Sorafenib toxicities and distribution in children are similar to adults. The activity of sorafenib in children with AML and FLT3 internal tandem duplication is currently being evaluated in a National Cancer Institute (NCI) study (AML1031/NCI-2011-02670 with estimated primary completion date DEC 2018).

The Marketing Authorisation Holder (MAH) has presented an extensive summary of cases reported with use in paediatrics with each Periodic Safety Update Report (PSUR)/ Periodic Benefit Risk Evaluation Report (PBRER) and no new safety issue has been identified.

Considering that there are no ongoing additional Pharmacovigilance activities, 'Safety in children and adolescents' is removed as area of missing information.

SIV.3.2. Elderly

More than a third of the Nexavar treated patients in clinical trials were ≥65-years old. Of the 4,803 patients in the monotherapy safety set (MSAF, i.e. all Nexavar treated patients from Phase I, II, and III trials, regardless of whether or not treatment was administered in a blinded

phase or open-label phase, and excluding early access programme [EAP] studies), 1,368 patients were ≥65 to <75-years, 428 patients were ≥75 to <85 years and 18 patients were ≥85 years (see SIII.1.2).

In Study 11213 (TARGET study – MRR 00170A[1]), 32% of patients were ≥65-years old. Nexavar treated patients in the youngest age group (<45-years) were more likely to have hand-foot skin reaction (HFSR), vomiting, cough, fatigue and constitutional symptoms than patients in any other age group. AEs more common in the oldest age group (≥75-years) included nausea, fatigue and dyspnoea. The incidence of alopecia was highest in Nexavar-treated patients in the ≥65 to <75-years age group. Other AEs were generally consistent across age groups. In patients ≥75-years old, the pattern of AEs was similar to that observed in younger patients. According to the current data, no adjustments of dose are considered to be required with increasing patient age.

In Study 100554 (SHARP study – A45911), the mean age at enrolment for the patients treated with Nexavar was 64.9±11.2 years, with 59% being ≥65-years and 19% being ≥75-years. Although pain, abdomen not otherwise specified (NOS) (42.9% in Nexavar patients *vs* 25% in placebo patients) was most likely observed in the youngest age group (<45-years), the number of patients are too few to draw any definitive conclusions. The ≥65 to <75-years age group was more likely to have hypertension (12.8% in Nexavar-treated patients *vs* 3.9% in placebo patients), weight loss (34.2% *vs* 11%), anorexia (35.9% *vs* 18.9%), alopecia (16.2% *vs* 0.8%), and voice changes (12.8% *vs* 1.6%) than any other age group. HFSR (27.5% in Nexavar-treated patients *vs* 5.1% in the placebo group) was more likely in the 45 to <65-years age group.

In Study 14295, of the total 207 patients treated with double-blind sorafenib, 80 were <60-years of age and 127 were ≥60-years of age; 182 were <75-years of age and 25 were ≥75-years of age. The overall incidence of AEs did not vary by age in any clinically meaningful way (31 AUG 2012 cut-off); however, more drug-related SAEs and drug-related AEs leading to discontinuation were noted in the sorafenib-treated subjects who were ≥60-years. Similar observations were noted for sorafenib-treated subjects who were ≥75-years of age; however, the subject numbers in this age group were very low (Reference: Study 14295 Clinical Safety Summary).

Bokemeyer *et al*. (60) conducted an analysis of the integrated database of 4,684 patients with RCC treated with Nexavar for more than 12 months, including elderly patients. The patients derived from eight company-sponsored studies, six clinical trials and two expanded access programmes where Nexavar was used in monotherapy in metastatic renal cell carcinoma (mRCC). Results were as follows: 4,684 patients (71% male; median age 62-years and 41% ≥65-years of age; 87% prior nephrectomy; 52% prior cytokine therapy) were included in the integrated database. The mean daily dose was 676 mg for the total population. A total of 0/1/2/3/≥4 dosage reductions or interruptions due to an AE occurred in 57%/22%/11%/5%/5% of the patients in the total population (N = 4,684), and in 53%/24%/13%/4%/6% of patients ≥65-years (n = 1,941 patients). Overall, 1,738/4,601

[1] All study reports referenced in SIV Section 3 are available on request.

patients (38%) had a dosage reduction or interruption from 800 mg/day due to an AE, and of these, 1,488 (86%) resumed or re-escalated the dosage; 907 patients (52%) were re-escalated to the full dosage. The conclusion was that dosage reductions/interruptions mainly occurred in the first 3 months and decreased with time; 52% of patients re-escalated to full dosage. The pattern of dosage adjustments in the elderly population was similar to that observed in the entire study population.

SIV.3.3. Pregnant or Breast-Feeding Women

In rats and rabbits, sorafenib has been shown to be teratogenic, with embryo-foetal toxicity including post-implantation loss, resorptions, skeletal retardations, and retarded foetal weight. The effects occurred at doses considerably below 500 mg/m2, the recommended clinical dose on a BSA basis. The lowest observed effect on intrauterine development was at a dose of 6 mg/m2/day in rats and 36 mg/m2/day in rabbits.

A case retrieval of pregnancy and lactation cases was conducted for Nexavar (sorafenib) in the company global pharmacovigilance database cumulative until 29 APR 2018, including all clinical trial and post marketing sources using search criteria of SOC “Pregnancy, puerperium and perinatal conditions” and Standardised Medical Dictionary for Regulatory Activities Query (SMQ) “Neonatal exposures via breast milk”. No case was retrieved for lactation. For pregnancy retrieval, there were 30 relevant cases, which included 24 cases where a pregnancy was reported, with six additional linked cases (either male patient [father case] or child cases), while on treatment with sorafenib, of which 10 were direct maternal exposure and 14 were exposure through partner. No case was retrieved for lactation exposure. Of the 24 pregnancy cases, 14 were study cases which included interventional clinical trials, observational studies, patient support programme, and investigator-sponsored study; nine were spontaneous; and one was a literature case. Three (3) of the 24 pregnancy cases reported an AE: one case of postpartum haemorrhage, one case of blood pressure increased, proteinuria, and induced labour, and one case of conversion disorder (pregnancy outcome: live birth with congenital anomaly). None of these events were assessed related to sorafenib.

Outcome of pregnancy in 12 cases was not reported. Of the remaining 12 cases, 5 were normal live births, however, one case reported a premature birth (gestational age at birth was 35 weeks) and no other events; five pregnancies were terminated electively; one had spontaneous abortion at gestational age of nine weeks; and lastly one live birth (child case) had congenital anomalies: baby had congenital anomalies such as no anus (Preferred Term [PT] “Anal atresia”), one kidney (PT “Renal aplasia”) and spinal cord issues (PT “Congenital spinal cord anomaly”). No other information regarding the baby’s progress or status/outcome was available.

Per SmPC Section 4.6, women of childbearing potential must use effective contraception during Nexavar treatment.

It is not known to what extent sorafenib is excreted in human milk. When 14C labelled sorafenib was administered to lactating Wistar rats, approximately 27% of the radioactivity was secreted into the milk. The milk to plasma area under the curve (AUC) ratio was 4.9:1. Many drugs are excreted in human milk, and because the effects of sorafenib on infants have

not been studied, SmPC Section 4.6 states that women must not breast feed during treatment with Nexavar.

SIV.3.4. Patients with Hepatic Impairment

In vitro and *in vivo* data suggest that sorafenib is cleared primarily by the liver (see SmPC Section 5.2).

Of the 4,803 patients in the MSAF, 784 patients had a maximum AST and ALT between >1.5 × upper limit of normal (ULN) and ≤3 × ULN, and 290 patients had maximum AST and ALT >3 × ULN at baseline (see SIII.1.5).

In Studies 11213 (TARGET study – MRR 00170A) and 100391 (study report 00310), patients could be included in the study if their total bilirubin was <1.5 × ULN and both AST and ALT were <2.5 × ULN (or <5xULN if liver involvement of the tumour).

Baseline AST and ALT values were used to assess hepatic impairment. Patients with baseline AST and ALT <1.8 × ULN were considered to have normal hepatic function. Patients with AST or ALT between 1.8 and 3 × ULN were considered to have mild hepatic impairment, and those with AST or ALT greater than 3 × ULN were considered to have moderate hepatic impairment. In Study 11213 (TARGET study), as of 28 JAN 2005, there were four patients in the placebo group (1%) and 12 patients in the Nexavar group (3%) with mild hepatic impairment at baseline; there were two patients in the placebo group (0.6%) and four in the Nexavar group (1%) with moderate hepatic impairment at baseline. In Study 100391, only one patient had mild hepatic impairment, and one patient had moderate hepatic impairment at baseline. In Study 100554, the inclusion criteria defined that only patients with Child-Pugh A status along with albumin ≥2.8 g/dL, total bilirubin ≤3 mg/dL and ALT and AST ≤5 × ULN were eligible. Fifteen (15) out of 299 patients randomised to Nexavar in this study were Child-Pugh B or C at study entry and were considered protocol deviations. Based upon these limited numbers of patients, there was no apparent difference in the AE profile based upon baseline liver function.

In Study 100554 (SHARP study), HCC patients with moderate hepatic impairment treated with Nexavar had similar incidences of hypertension and HFSR compared to patients with normal hepatic function. Nexavar-treated patients with moderate hepatic impairment demonstrated similar incidence of pain, abdomen NOS (28.4% in Nexavar-treated patients *vs* 27.8% in placebo-treated patients), voice changes (4.5% *vs* 4.2%), and anorexia (28.4% *vs* 22.2%) to placebo patients.

In Bayer sponsored clinical pharmacology studies in HCC patients, patients with Child-Pugh B cirrhosis (n = 8) had greater exposure values than patients with Child-Pugh A cirrhosis (n = 14). These PK differences were within the range of inter-patient PK variability and did not result in a differential safety profile between the two subgroups. No PK data is available for patients with severe hepatic impairment (Child-Pugh C).

The study published by Miller *et al*. (61) also recruited patients with hepatic dysfunction into an investigator sponsored study CALGB60301. Four (4) cohorts relevant to assessment of hepatic dysfunction were assessed: Cohort 2 contained patients with bilirubin >ULN but

<1.5 × ULN and/or AST>ULN (n=12 in multidose phase, “mild”), Cohort 4 contained patients with a bilirubin >1.5 × ULN but ≤3 × ULN and any AST (n = 17 in multidose phase, “moderate”), Cohort 6 contained patients with bilirubin >3 × ULN and any AST (n=11 in multidose phase, “severe”), and Cohort 8 contained patients with albumin <2.5 mg/dL and any bilirubin or AST (n=19 in multidose phase, “very severe”). Miller *et al*. (61) stated that, based upon data from their study, the starting dose for patients with “mild” hepatic dysfunction was 400 mg twice daily (bid), 200 mg bid for moderate dysfunction and 200 mg once a day (qd) for those with very severe hepatic dysfunction. They determined that even dosing at 200 mg every third day was not tolerated in patients with severe hepatic dysfunction. The DLTs reported in this study were expected toxicities for Nexavar and as outcomes of patients with limited hepatic function. Miller *et al*. (61) concluded that sorafenib clearance did not appear to be dependent upon hepatic function in this study.

SIV.3.5. Patients with Renal Impairment

Sorafenib is primarily excreted by the liver, with 19% excreted in the urine in a single-dose healthy volunteer radiolabel study (see SmPC Section 5.2), so decreased renal function would not be expected to substantially affect exposure to sorafenib.

Of the 4,803 patients in the MSAF, 837 patients had an impaired renal function (estimated glomerular filtration rate [eGFR]<60 mL/min/1.73 m²) at baseline (see SIII.1.5).

In 4 Phase I clinical trials, steady state exposure to sorafenib was similar in patients with mild renal impairment (creatinine clearance >50-80 mL/min, n = 24) or moderate renal insufficiency (creatinine clearance 30-50 mL/min, n = 4) compared to the exposures documented in patients with normal renal function (n = 71).

In Bayer sponsored clinical pharmacology Study 11804 (MRR 1671), the PK of sorafenib were evaluated following a single 400 mg dose to subjects with normal renal function and mild, moderate and severe renal dysfunction not requiring dialysis. There was no relationship observed between sorafenib exposure and renal function.

A non-company sponsored series of 32 patients with metastatic kidney cancer has been published as a case series from the Wayne State University in Detroit (62).
Fourteen (14)/32 (44%) patients had an estimated creatinine clearance >60 mL/min when starting sorafenib. The authors concluded that the incidence of side effects was comparable between the cohort with an estimated creatinine clearance ≤60 mL/min and those >60 mL/min. They concluded, however, that adverse effects may be more severe, and that a higher proportion of patients in the ≤60 mL/min cohort required dose interruptions or reduction. No PK data have been published from this study. The authors did not detail increased renal toxicity in patients with greater renal dysfunction and concluded that sorafenib initiation is not contraindicated in patients with severe renal insufficiency.

Miller *et al*. recruited cohorts of patients with renal and hepatic impairment into an investigator sponsored study CALGB60301 (61). Four (4) cohorts relevant to assessment of renal dysfunction were assessed: Cohort 3 contained patients with a creatinine clearance 40-59 mL/min (n=16 in multidose phase, “mild”), Cohort 5 contained patients with a creatinine clearance 20-39 mL/min (n=13 in multidose phase, “moderate”), Cohort 7

contained patients with a creatinine clearance <20 mL/min (n = 4 in multidose phase, "severe") and Cohort 9 contained patients on dialysis without creatinine clearance restriction (n=17 in multidose phase). Miller *et al*. (61) stated that, based upon data from their study, the starting dose for patients with "mild" renal dysfunction was 400 mg bid, 200 mg bid for moderate dysfunction and 200 mg qd for dialysis patients – findings consistent with the results published by Parsa *et al*. (62). No dose was determined for the severe population in this study. The DLTs reported in this study were expected toxicities for sorafenib; renal failure was not identified as a DLT in any of these cohorts. Miller *et al*. (61) additionally concluded that sorafenib clearance did not appear to be dependent upon renal function in this study.

Patients with concurrent haemodialysis (HD)

Kennoki *et al*. (63) published a study that evaluated the safety and PK of sorafenib administration to chronic HD patients with mRCC. Ten (10) patients with mRCC under chronic HD therapy received sorafenib, and six participated in the PK part of the study (steady state sampling, at the dose of 200 mg bid). Median treatment duration was 11.3 months. Best tumour response was a complete response in one patient, partial response in three patients, stable disease in four patients, and progressive disease in two patients. Median progression-free survival (PFS) was 6.3 months. SAEs were found in nine patients, including an NCI-Common Terminology Criteria for Adverse Events (CTCAE) Grade 5 subarachnoid haemorrhage and a Grade 4 cerebellar haemorrhage. In the PK study, the geometric mean of maximum concentration and AUC from 0 to 10 h of plasma concentration were similar on the day of HD and the day off HD. These data were lower than those from Japanese people with healthy kidneys and normal kidney function. There was no association between objective response or the occurrence of serious AEs and PK parameters. The authors concluded that administration of sorafenib 200 mg bid provided a similar clinical benefit, but more severe AEs were noted in mRCC patients undergoing chronic HD compared to those with normal kidney function.

In summary, Kennoki *et al*. (63) conclude that exposure is similar between HD patients and patients with normal renal function. These findings are supported by a study conducted by Miller *et al*. (61), and by case reports by Shinsako et al. (64). Additionally, Hilger *et al*. (65) reported a transient increase in sorafenib concentrations during HD, but sorafenib concentrations returning to the expected range between dialysis treatments. Case reports by Ferraris *et al*. (66), Khan *et al*. (67), Rey and Villavicencio (68), Ruppin *et al*. (69), and Shinsako *et al*. (64) describe sorafenib to be well tolerated. Miller *et al*. (61) recommended a starting dose of 200 mg qd; however, the authors also recommended that the treating physician may consider a dose escalation if the starting dose is well tolerated.

In conclusion, starting doses in the published literature ranged from 200 mg qd to 400 mg bid, with dialysis patients appearing to be most commonly treated with 200 mg qd to 200 mg bid/400 mg qd. However, based on limited data from clinical trials and case reports regarding sorafenib exposure and safety for dialysis patients before, during and post-dialysis, no change to the SmPC is warranted concerning the use of Nexavar in patients on HD.

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Part II: Module SIV - Populations not studied in clinical trials

SIV.3.6. Patients with Other Relevant Co-Morbidity

Liver cirrhosis Child-Pugh B and C in patients with HCC

Approximately 80-85% of patients with HCC also have cirrhosis, with liver impairment commonly scored according to Child-Pugh classification. Based upon an assessment of the efficacy, PK, and safety data in patients with HCC and Child-Pugh A or B liver dysfunction treated in Nexavar HCC trials, the use of Nexavar in patients with HCC is not restricted by Child-Pugh status. Patients with Child-Pugh B and Child-Pugh C liver dysfunction were considered as underrepresented in the HCC registration studies for Nexavar, therefore a post marketing commitment to provide additional data on patients with Child-Pugh B liver dysfunction was made with the European Medicines Agency (EMA). This post-marketing study was completed in APR 2012 (see Study 13414, GIDEON below). Safety and efficacy of Nexavar have been characterised in patients with HCC with Child-Pugh B liver dysfunction in 4 Bayer sponsored studies (including GIDEON). Important information from these four studies is summarised below:

- Study 10874 (A45438): This study included 38 patients with HCC and Child-Pugh B liver dysfunction. Sorafenib PK at a dose of 400 mg bid were assessed in HCC patients with mild (Child-Pugh A, n = 15) or moderate (Child-Pugh B, n=6) hepatic impairment. Exposure values in patients with both Child-Pugh A and Child-Pugh B hepatic impairment were within the range observed in patients without hepatic impairment.
- Study 100554 (SHARP study): In this study, 20 randomised patients had HCC and Child-Pugh B liver dysfunction at baseline. Fourteen (14) were randomised to Nexavar and six were randomised to placebo. The overall incidence of AEs was similar between patients in the Child-Pugh A and B groups. The Child-Pugh B group had a higher incidence of SAEs (66% *vs* 50% for Child-Pugh A) and AEs leading to study discontinuation (26% *vs* 16% for Child-Pugh A). However, the incidence of drug-related AEs was lower in the Child-Pugh B group (76% *vs* 88% for Child-Pugh A). This finding is consistent with an expectation that Child-Pugh B patients would have higher rates of disease-related AEs but not necessarily any differences in drug-related AEs. A higher percentage of Child-Pugh A patients compared to the Child-Pugh B patients had diarrhoea (56% *vs* 42.9%, respectively), anorexia (29.1% *vs* 21.4%, respectively) and HFSR (22.0% *vs* 7.1%, respectively). A higher percentage of Child-Pugh B patients compared to the Child-Pugh A patients had voice changes (21.4% *vs* 8.5%, respectively) and hypertension (14.3% *vs* 9%, respectively).
- Study 12349: This was a multi-centre, open-label, non-randomised, Phase I study to evaluate the safety and PK of sorafenib in non-cancer subjects with hepatic impairment (70). Although mean AUC and concentration maximum (C_{max}) were higher in Child-Pugh A subjects compared to healthy subjects, no further increases were observed in the Child-Pugh B subjects. Mean half-life was virtually identical for all 3 cohorts. No dose adjustment for Nexavar in Child-Pugh A or B subjects is indicated based on these data.

- Study 13414 (GIDEON study): This study was a post-marketing commitment to the EMA to provide additional data on patients with Child-Pugh B liver dysfunction (see Part VII Annex 2). This was a non-interventional study to evaluate the safety and efficacy of Nexavar in patients with unresectable HCC who were candidates for systemic therapy and in whom a decision to treat with Nexavar has been made under real-life practice conditions. Among 3,202 patients valid for safety, at study entry, 1,968 (61.5%) had Child-Pugh A status, 666 (20.8%) had Child-Pugh B status, and 74 (2.3%) had Child-Pugh C status. There were 493 (15.4%) patients whose Child-Pugh score was not evaluable, and 1 patient with missing data. A summary of AEs by Child-Pugh status is presented inTable Part II SIV-3.

Based on the final results, the overall safety profile of Nexavar in Child-Pugh B patients appears to be similar to that of the overall population. Compared with Child-Pugh A patients, Child-Pugh B patients did not have a higher incidence of drug-related AEs (68.5% in Child-Pugh A *vs* 64.4% in Child-Pugh B). Most commonly reported AEs (≥15%) were diarrhoea, HFSR, fatigue and anorexia; most common Nexavar-related AEs (≥5%) were diarrhoea, HFSR, fatigue, anorexia, rash/desquamation, hypertension, alopecia and nausea. The majority of AEs were NCI-CTCAE Grade 1 or 2. The incidence of drug-related Grade 3 AEs was lower in Child-Pugh B as compared to Child-Pugh A patients (19.4% *vs* 23.7%, respectively). Drug-related Grade 4 AEs were generally low and consistent with previous studies with Nexavar, despite the inclusion of patients with poorer health and more advanced conditions (such as Child-Pugh B and Child-Pugh C patients) in this study. The AE incidences reported in this study were not remarkably higher than the incidences in other Nexavar studies.

The overall incidence of drug-related SAEs was slightly higher in Child-Pugh B as compared to Child-Pugh A patients (14.1% *vs* 8.8%, respectively). However, this increase in incidence reflected a composite of only minor increases in individual, drug-related Common Terminology Criteria (CTC) SAE terms in Child-Pugh B as compared to Child-Pugh A (representing a difference of <1% between Child-Pugh B and Child-Pugh A patients), except for liver dysfunction which showed a difference of 1.5% (incidence 2.1% in Child-Pugh B *vs* 0.6% in Child-Pugh A). Further, no specific pattern of drug-related SAEs was identified to suggest a new safety risk in Child-Pugh B patients. The majority of deaths were due to HCC or underlying liver disorder.

In summary, results from the GIDEON study indicate that the overall safety profile of Nexavar in Child-Pugh B was similar to that in Child-Pugh A patients. No new safety finding for Nexavar was identified in Child-Pugh B patients. The PK, safety, and efficacy data, when taken together, support the use of Nexavar for patients with HCC and normal liver function or Child-Pugh A or B liver impairment.

Table Part II SIV-3: Summary of AEs in Study 13414 (GIDEON study) by Child-Pugh status

n (%)	Child-Pugh A n=1,968	Child-Pugh B n=666	Child-Pugh C n=74	Not evaluable n=493	Total[a] N=3,202
AEs (all grades)	1,653 (84.0)	590 (88.6)	68 (91.9)	420 (85.2)	2,732 (85.3)
Drug-related AEs (all grades)	1,349 (68.5)	429 (64.4)	29 (39.2)	304 (61.7)	2,112 (66.0)
SAEs (all grades)	708 (36.0)	402 (60.4)	52 (70.3)	225 (45.6)	1,387 (43.3)
Drug-related SAEs (all grades)	174 (8.8)	94 (14.1)	2 (2.7)	27 (5.5)	297 (9.3)
All Grade 3	554 (28.2)	167 (25.1)	11 (14.9)	121 (24.5)	854 (26.7)
Drug-related Grade 3	467 (23.7)	129 (19.4)	8 (10.8)	86 (17.4)	691 (21.6)
All Grade 4	84 (4.3)	43 (6.5)	2 (2.7)	33 (6.7)	162 (5.1)
Drug-related Grade 4	36 (1.8)	17 (2.6)	0	10 (2.0)	63 (2.0)
All Grade 5	372 (18.9)	249 (37.4)	40 (54.1)	137 (27.8)	798 (24.9)
Drug-related Grade 5	25 (1.3)	19 (2.9)	0	2 (0.4)	46 (1.4)
AEs resulting in permanent discontinuation of sorafenib	568 (28.9)	267 (40.1)	32 (43.2)	136 (27.6)	1,004 (31.4)
Deaths[a]	349 (17.7)	239 (35.9)	38 (51.4)	132 (26.8)	758 (23.7)

AE: Adverse event, SAE: Serious adverse event.
[a]Treatment-emergent deaths (during therapy with Nexavar up to 30 days after the last dose of Nexavar) occurred in 758 patients (23.7%).

Based on these results, the safety concern “Safety and efficacy in patients with HCC and Child-Pugh B liver dysfunction” is removed as missing information.

SIV.3.7. Patients with a Disease Severity Different from the Inclusion Criteria in the Clinical Trial Population

Patients enrolled in the registrational studies had advanced disease: unresectable and/or mRCC, advanced or intermediate stage HCC (82% and 18% in Study 100554 [SHARP study], respectively) or radioactive-iodine refractory differentiated thyroid cancer.

SIV.3.8. Sub-Populations Carrying Known and Relevant Polymorphisms

There is no sub-population known that carries any relevant polymorphism relevant for treatment with Nexavar.

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SIV.3.9. Patients of Different Racial and/or Ethnic Origin

Of the 4,803 patients in the MSAF, 2,741 patients were White, 1,589 patients were Asian, 95 patients were Black or African American, and 80 patients were Hispanic (see SIII.1.3).

A Phase II study has been completed in Japanese patients (Study 11515 – Phase II study of BAY 43-9006 in Japanese subjects with RCC - A46504). Study 11515 enrolled 173 patients, of which 131 were valid for safety analysis. The safety profile of Nexavar was similar in the Japanese Study 11515 and Western Study 11213 (TARGET study). The incidence of asymptomatic abnormalities in blood pancreatic enzymes was higher in the Japanese study, although this finding is considered to be potentially due to detection bias because of the different recording frequencies in the respective study protocols. In both Japanese and Western studies, the pancreatic enzyme abnormalities were asymptomatic with no difference in rates of symptomatic pancreatitis.

A PK study (Study 12162 - PH-35765) in healthy volunteers compared sorafenib exposure in Caucasians and Asians (Japanese and Chinese) in healthy, age-matched volunteers administered sorafenib in fasted state. Administration of a single dose of 400 mg sorafenib in the fasted state resulted in a 30% smaller AUC in Asian subjects compared to Caucasians. The AUC was 25% lower in Japanese subjects and 35% lower in Chinese subjects than in Caucasian subjects. There were no appreciable differences in mean C_{max} values between Japanese and Caucasians; Chinese had a 16% lower mean C_{max} value than Caucasians.

Given the significant overlap in sorafenib C_{max} and AUC values between the Caucasian and Asian subjects in Study 12162 and response rates/PFS observed in Asian (Japanese) RCC patients at 400 mg bid (Study 11515), the small PK differences between Caucasian and Asian subjects are not considered clinically significant.

Part II: Module SV - Post-authorisation experience

SV.1. Post-authorisation exposure

SV.1.1. Method used to calculate exposure

The following describes the post authorization exposure of most recent PSUR/ PBRER No. 24.0, 01 JAN 2023 to 31 DEC 2023.

The US distribution of marketed sorafenib is performed *via* a series of Specialty Pharmacy Providers (SPPs).

For commercial supply outside the US, calculations are based upon sales value. A daily dose of 800 mg per day is assumed, with 100% compliance.

A: For US: Commercial distribution = 256 patients

B: Outside US: Commercial distribution = 16,748 patients

The US Patient Assistance Program (PAP): In the US, patients awaiting reimbursement decisions from their insurers may be eligible for supply of drug under this program. Patients who receive initial drug through the PAP and who are then transferred to commercial supply are counted under the PAP and not under US commercial distribution for this analysis.

C: US PAP: 176 patients.

Marketed Product (all markets) and Patient Assistance Program (US)

For patients receiving marketed Nexavar and for those in the US PAP, a mean duration of treatment of 159 days has been assumed (based upon US Specialty Pharmacy Provider [SPP] data).

Estimated Total Post-Authorization (Non-Clinical Trial) Exposure

(A) + **(B)** + **(C)** = 17,180 patients.

SV.1.2. Exposure

The estimated cumulative exposure to Nexavar until the cut-off date of the most recent PSUR/PBRER (No. 24.0, 01 JAN 2023 to 31 DEC 2023) was 887,527 patients.

Table Part II SV-1: Post-authorization (non-clinical trial) exposure during the period and cumulative exposure

Patient Exposure (number of patients)	Cumulative exposure to sorafenib since its International Birth Date
Commercial (incl. US PAP and US Hosp.) + ex US commercial	887,527 patients

ex.: Excluding, Hosp.: Hospital, incl.: Including, PAP: Patient Assistance Program; PBRER: Periodic Benefit-Risk Evaluation Report; PSUR: Periodic Safety Update Report, US: United States.

Part II: Module SVI - Additional EU requirements for the safety specification

SVI.1 Potential for misuse for illegal purposes

Nexavar is an oral MKI that inhibits the activity of targets present in the tumour cell (CRAF, BRAF, V600E BRAF, KIT, RET, and FLT-3) and in the tumour vasculature (VEGFR-1, VEGFR-2, VEGFR-3, and PDGFR-ß). It is indicated for the treatment of advanced renal cell carcinoma, hepatocellular carcinoma, and locally advanced or metastatic differentiated thyroid carcinoma refractory to radioactive iodine. There is no evidence of development of addiction to Nexavar and the potential for misuse for illegal purpose is unlikely.

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Part II: Module SVII - Identified and Potential Risks

SVII.1. Identification of Safety Concerns in the Initial Risk Management Plan (RMP) Submission

Not applicable. According to the EMA guidance on the format of the Risk Management Plan (RMP) in the European Union (EU) Good Pharmacovigilance Practices (GVP), Module V, Rev.2, effective since 31 MAR 2017, Section 1 of Module SVII is expected to be submitted only for initial marketing authorisation applications.

Regulatory communication on safety concerns received by the company

Table Part II SVII-1: Regulatory communication on safety concerns

Safety concern	Reason for risk classification
Important identified risks	
Severe skin adverse events	Rare skin reactions in patients receiving Nexavar are SJS and TEN. The pathophysiology of SJS/TEN is not fully understood, but might involve an immunological reaction cascade triggered by the formation of immune complexes through drug-protein interaction. Only one case of SJS and no cases of TEN were reported with Nexavar in clinical studies. The observed case of SJS was serious, of Grade 4 severity, not resolved, and not considered treatment related. Additional cases received from any other source, retrieved from the Bayer safety database, revealed 72 medically confirmed SJS cases related to Nexavar, eight medically confirmed related TEN cases, and two cases coded as TEN and SJS. Patients who experience SJS/TEN require hospital care in a specialised environment. Mortality is high with both conditions.
Reversible posterior leukoencephalopathy syndrome (RPLS)	Reversible posterior leukoencephalopathy syndrome is an uncommon event in patients treated with Nexavar. The patho mechanism remains unclear. Most reported cases with Nexavar in clinical studies were serious, and severities mostly ranged from Grades 2 to 4, but in most patients the event resolved and no fatalities were reported. Most case series and case reports in literature suggest that RPLS is usually benign. In many cases, RPLS seems to be fully reversible within a period of days to weeks, after removal of the inciting factor and control of the blood pressure. A small number have residual neurologic deficits resulting from secondary cerebral infarction or haemorrhage; some patients die as a result of increased intracranial pressure or as a complication of the underlying condition.
Haemorrhage including lung haemorrhage, GI haemorrhage and cerebral haemorrhage	Haemorrhage, including GI, respiratory tract, and cerebral haemorrhage, is a very common event in patients treated with Nexavar. As an anti-angiogenic agent, sorafenib may affect small vessels, particularly those in tumours, and thus increase the risk of bleeding.

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Table Part II SVII-1: Regulatory communication on safety concerns

Safety concern	Reason for risk classification
	Significant haemorrhage may be life threatening or potentially fatal. The majority of cases of haemorrhage reported with Nexavar in controlled clinical studies were nonserious and of Grade 1 or 2 severity, and most patients recovered. However, serious cases were reported in 92/2,238 patients (4.11%), with fatal outcome in 20 cases (0.89%), For the remaining cases, the outcome was mostly recovered/resolved. The incidence of serious and fatal cases was similar in patients treated with Nexavar and placebo.
Arterial thrombosis (myocardial infarction)	Myocardial infarction is a common event in patients treated with Nexavar VEGF blockade may increase the risk of myocardial damage. In clinical studies with Nexavar, MI was observed in 23/2,238 patients treated with Nexavar (1.03%) *vs* 7/2,162 patients treated with placebo (0.32%). Myocardial infarction and ischaemia is a severe conditions requiring immediate medical attention and hospitalisation. Myocardial infarction can be life threatening and potentially fatal. In the controlled clinical trials with Nexavar, 21 of the 23 cases reported in the Nexavar group were serious and seven of these had fatal outcomes
Congestive heart failure (CHF)	Congestive heart failure is a common event in patients treated with Nexavar. Potential mechanisms for cardiac effects of VEGF-targeted therapies include inhibition of cardiovascular repair and vascular growth due to antiangiogenic activity of these agents. Sorafenib has been shown to cause mitochondrial damage with subsequent myocyte apoptosis and fibrosis, and its cardiovascular adverse effects might be associated with Raf 1 kinase and PKI inhibition. Congestive heart failure can be life-threatening and potentially fatal. In controlled clinical trials with Nexavar, CHF was observed in 22/2,238 patients treated with Nexavar (0.98%) *vs* 11/2,162 patients treated with placebo (0.51%). The event was serious in the majority of the cases, and a fatal outcome was reported in eight of the 22 cases in Nexavar treated patients.
Squamous cell cancer of the skin	Squamous cell cancer of the skin and keratoacanthoma are common events in patients treated with Nexavar. Sorafenib is a potent inhibitor of CRAF and mutant (V600E) BRAF inhibitor that are involved in tumour progression. Treatment of tumour bearing mice with sorafenib results in the inhibition of tumour growth in models that express mutated RAS and/or BRAF and other signal pathways through other growth factors such as RAS/RAF/ERK. However, BRAF inhibitors induce the opposite effect that is, harboring upstream pathway activation of RAS or up-regulated receptor tyrosine kinases (71, 72). Su *et al*. reported in an established mouse model investigating skin carcinogenesis, that vemurafenib (BRAF inhibitor) analogue

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Table Part II SVII-1: Regulatory communication on safety concerns

Safety concern	Reason for risk classification
	was not an initiator of carcinogenesis but accelerated growth of the lesions. This result approved the assumption that sorafenib can cause SCCs through activities on the RAS pathway. In controlled clinical trials, events of SCC of the skin and keratoacanthoma occurred in 15/2,238 patients (0.67%) in the Nexavar arms and in 4/2,162 patients (0.19%) in the placebo arms. The events were assessed as drug-related in 11 of the 15 Nexavar cases, but only in one case in the placebo group. The majority of cases in the Nexavar group were of Grade 3 severity and nearly half of the SCC of the skin cases were regarded as serious. However, most of the cases resolved and no fatalities were observed. In general, keratoacanthomas and SCCs of the skin are medically significant events, and need to be diagnosed by biopsy and removed by surgical procedure.
Gastrointestinal perforation	Gastrointestinal perforation is characterised by rupture of the GI wall that may be associated in leakage of intestinal, bowel or stomach fluids causing chemical or bacterial peritonitis. The pathomechanisms are not well understood and might involve ischaemic changes in the intestinal walls and impaired regeneration. Gastrointestinal perforation is an uncommon event in patients treated with Nexavar. In controlled clinical trials, pertaining events occurred in occurred in 16/2,238 patients in the Nexavar arms (0.71%) and in 11/2,162 patients (0.51%) in the placebo arms. The majority of cases were of Grade 2 or 3 severity. The events were serious in 10 of the 16 cases in the Nexavar group and in nine of 11 cases in the placebo group, with one fatal case in each group. Gastrointestinal perforation from any cause is a medically significant event, typically requiring a surgical consultation and/or treatment, together with appropriate supportive measures in a hospital setting.
Renal dysfunction	Renal dysfunction is a common event in patients treated with Nexavar. There is little evidence supporting a primary nephrotoxic potential of Nexavar, but it might contribute indirectly to the development of renal dysfunction through the induction of diarrhoea, vomiting, dehydration with subsequent possible volume depletion, and hypotension. In the controlled clinical trials, renal dysfunction was observed in 132 patients (5.90%) in the Nexavar arms and in 53 patients (2.45%) in the placebo arms. Most cases were nonserious and of Grade 1 or 2 severity. Of the 132 cases in the Nexavar arms, 16 were serious and five of these had fatal outcomes. Renal failure may require specific monitoring of the fluid balance, diuretic treatment or haemodialysis.
Interstitial lung disease (ILD)-like events	Interstitial lung disease -like events are uncommon in patients treated with Nexavar. No Nexavar specific patho mechanisms

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Table Part II SVII-1: Regulatory communication on safety concerns

Safety concern	Reason for risk classification
	for ILD have been identified. In clinical studies with Nexavar, ILD like events were reported in 19 patients in the Nexavar arms (incidence of 0.85%) and in seven patients (0.32%) in the placebo arms. Most cases of ILD like events were nonserious, of Grade 1 or 2 severity, and most events resolved. In in the Nexavar arms, seven of the 19 cases were serious. No fatal cases occurred in the Nexavar arms, but one fatal case (0.05%) was reported for the placebo arms. Most Nexavar treated patients recovered (13 of 19 patients), while in the placebo groups, only seven of 7 patients recovered. Interstitial lung disease is a medically significant event and may lead to a fatal outcome.
Drug-induced hepatitis	Drug-induced hepatitis is a rare event in patients treated with Nexavar. It appears to be an idiosyncratic reaction to Nexavar, and the precise aetiology for this event is currently unknown. The most recent PSUR/PBRER No. 17.0 identified 29 cases with available laboratory data that met the criteria for DILI. Where adequate information was available, these cases were confounded by medical history, comorbidities or concomitant use of other potentially hepatotoxic drugs. The current reporting frequency of index cases is 55/648,907 (0.008%). Of the 55 index cases, all cases were serious. In 17 cases death occurred, and in 12 of these cases death was reported due to hepatic event. The majority of cases (40 out of 55 patients) recovered or were recovering. The event is reversible after discontinuation of Nexavar in most cases, but fatal outcomes have been observed.
Important potential risks	
Arterial thrombosis (cerebral ischaemia)	Since inhibition of VEGF is thought to result in localised endothelial instability, there is a potential for formation of microemboli and localised thrombus formation. Bevacizumab (Avastin), which also targets VEGF, has been associated with a twofold increase in serious arterial thromboembolic events in some colon cancer patients, and a 5% overall risk of serious thromboembolic events. In clinical studies with Nexavar, the incidence of cerebral ischaemia was generally low, but slightly higher in patients receiving Nexavar than in patients receiving placebo, with a risk ratio based on EAIR of 1.71 (95% CI 0.92; 3.20). Events were considered to be treatment related in a similar number of patients treated with Nexavar and placebo. Therefore, there is not enough evidence at present to assume that Nexavar causes cerebral ischaemia. Most cases in patients treated with Nexavar were serious, with severities mostly ranging from Grade 2 to 4, and seven of 20 cases observed in Nexavar treated patients were fatal. Cerebral ischaemia can be incapacitating, life threatening, and fatal.

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Table Part II SVII-1: Regulatory communication on safety concerns

Safety concern	Reason for risk classification
Wound healing complications	Antiangiogenic agents may lead to disruption of normal wound healing. In clinical studies with Nexavar, the incidence of wound healing complications was low, and similar between patients receiving Nexavar and patients receiving placebo. The risk ratio based on EAIR was 1.24 (95% CI 0.68; 2.28) and events were considered to be treatment related in a 9 of 25 patients treated with Nexavar and in none of the patients treated with placebo. There is currently not enough evidence to assume that Nexavar has a negative impact on wound healing. Most cases in patients treated with Nexavar were nonserious and of Grade 1 or 2 severity. The outcome was mostly recovered/resolved. No fatal cases were reported. In general, wound healing complications are medically significant events and may lead to increased morbidity.
Microangiopathy	Loss or inhibition of local VEGF signalling in the glomerulus results in the endothelial swelling and thrombosis observed in TMA and protein leak into the urine. In clinical studies with Nexavar, the incidence of microangiopathy was very low, and similar between patients receiving Nexavar and patients receiving placebo. The risk ratio based on EAIR was 1.06 (95% CI 0.22; 5.20) and the event was considered to be treatment related in only one patient treated with Nexavar and in none of the patients treated with placebo. Based on the information currently available, there is not enough evidence to assume that Nexavar causes microangiopathy. Only one case of microangiopathy with Nexavar was serious and none was fatal. Microangiopathy is one of the histologic findings in some patients with proteinuria. Discontinuation of anti VEGF agents may improve proteinuria in some patients.
Torsade de pointes (TdP)	The mechanism of TdP/QT prolongation involves ionic current flow during repolarisation, which affects the QT interval. A variety of changes in ionic current can result in the common effect of decreased repolarising current, reflected in a long QT, and these changes can secondarily lead to subsequent depolarising currents and sometimes action potentials. This leads to a further delay in repolarisation, which may result in TdP. The acquired conditions that predispose one to TdP either decrease the outward potassium current or interfere with the inward sodium and calcium currents, or fluxes. TdP can be incapacitating, life-threatening and fatal. In clinical studies with Nexavar, the incidence of events pertaining to the SMQ “Torsade de pointes/QT prolongation” (excluding cases from the PT “Multiple organ dysfunction syndrome”) was similar between patients receiving Nexavar and patients receiving placebo. The risk ratio based on EAIR was 0.98 (95% CI 0.69; 1.58) and the event was considered to be treatment related in fewer patients treated with Nexavar than

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Table Part II SVII-1: Regulatory communication on safety concerns

Safety concern	Reason for risk classification
	in patients treated with placebo. The majority of cases were nonserious, with a similar incidence of serious events in the Nexavar arms and the placebo arms, and most cases resolved. Three (3) cases in patients treated with Nexavar and six cases with placebo were fatal. Severities ranged from Grade 1 to 5. The PT “Torsade de pointes” was not reported in Bayer sponsored clinical studies with Nexavar. Six (6) additional cases of TdP from any other source were retrieved from the Bayer safety database, of which five occurred in patients treated with sorafenib. Therefore, there is not enough evidence to confirm that Nexavar causes TdP/QT prolongation.
Pregnancy and exposure through breastfeeding	Based on the proposed mechanism of multikinase inhibition and multiple adverse effects seen in animals at exposure levels significantly below the clinical dose, sorafenib has the potential to cause foetal harm when administered to a pregnant woman. It is not known whether sorafenib is excreted in human milk. In animals, sorafenib and/or its metabolites were excreted in milk. Preclinical studies in animals indicate that sorafenib could harm infant growth and development. A case retrieval of pregnancy and lactation cases was conducted for Nexavar (sorafenib) in the company global pharmacovigilance database cumulative until 29 APR 2018.Twenty-four (24) pregnancy cases, with six additional linked cases (male patient [father case] or child case), coincident with sorafenib were reported. Three (3) of the 24 maternal cases reported an AE during the pregnancy or delivery, assessed related to the pregnancy/delivery process and not to sorafenib. Outcome of pregnancy, when available, revealed five pregnancies with elective termination, one with spontaneous abortion at nine weeks, five normal births, one premature birth at 35 weeks of gestation with no other events, and 1 live birth with congenital abnormalities. No case was retrieved for lactation exposure. There is a potential risk of foetal harm from exposure to sorafenib in a pregnant woman.
Missing Information	None

AE: Adverse event; CHF: Congestive heart failure, CI: Confidence interval, DILI: Drug-induced liver injury, EAIR: Exposure adjusted incidence rate, ERK: Extracellular signal regulated kinase, GI: Gastrointestinal, ILD: Interstitial lung disease, MI: Myocardial infarction, PBRER: Periodic Benefit Risk Evaluation Report, PKI: Protein kinase inhibitor, PSUR: Periodic Safety Update Report, PT: Preferred Term, RAF: Rapidly accelerated fibrosarcoma, RAS: Rat sarcoma, RPLS: Reversible posterior leukoencephalopathy syndrome, SCC: Squamous cell cancer, SJS: Stevens Johnson syndrome, SMQ: Standardised Medical Dictionary for Regulatory Activities Query, TdP: Torsade de pointes, TEN: Toxic epidermal necrolysis, TMA: Thrombotic microangiopathy, VEGF: Vascular endothelial growth factor.

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SVII.2. New safety concerns and reclassification with a submission of an updated RMP

All safety concerns were reanalysed to evaluate whether or not they meet the new definition of important potential/identified risks as per GVP Module V, Rev. 2 by specifying if the risk negatively affects the benefit-risk balance of Nexavar, whether additional pharmacovigilance (PV) activities or additional risk minimisation activities are required, and whether the EU SmPC includes labelling language recommending specific clinical actions as routine risk minimisation activity for each of the safety concerns.

The risks that do no longer meet the criteria for important risks (safety concerns) were removed for the following reasons:

- No additional activities beyond routine risk minimisation measures are in place.
- The risk minimisation messages in the product information (SmPC) provide detailed, adequate, and sufficient information and guidance on these risks.
- The routine risk minimisation activities recommending clinical measures to address a risk are fully integrated into standard clinical practice.
- The risks are therefore adequately managed by current labelling information.
- There is no reasonable expectation that any additional PV activities can further characterise the risk.
- The risks are followed-up via routine PV, namely through signal detection and adverse event reporting.
- Most risks are class effects of MKIs and as such are sufficiently characterised and well known by prescribers.

Reasons for removal of important identified risks and important potential risks from the list of safety concerns are presented in Table Part II SVII-2.

Table Part II SVII-2: Reasons for removal of important identified risks and important potential risks from the list of safety concerns

Safety concerns	Reason for removal
Previously classified as important identified risks	
Severe skin adverse events	Considering the time on the market and the extensive exposure to Nexavar, this risk is now considered adequately characterised in the SmPC. Clinical management is considered common medical knowledge, which includes early recognition and removal of the offending drug to prevent progression to severe complications. No additional PV activities and risk minimisation measures are in place.
Reversible posterior leukoencephalopathy syndrome (RPLS)	Considering the time on the market and the extensive exposure to Nexavar, this risk is now considered adequately characterised in the SmPC. No additional PV activities and risk minimisation measures are in place.

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Table Part II SVII-2: Reasons for removal of important identified risks and important potential risks from the list of safety concerns

Safety concerns	Reason for removal
Previously classified as important identified risks	
Haemorrhage including lung haemorrhage, gastrointestinal (GI) haemorrhage and cerebral haemorrhage	Considering the time on the market and the extensive exposure to Nexavar, this risk is now considered adequately characterised in the SmPC. Targeted guidance for clinical action is included in the SmPC. No additional PV activities and risk minimisation measures are in place.
Arterial thrombosis (myocardial infarction)	Considering the time on the market and the extensive exposure to Nexavar, this risk is now considered adequately characterised in the SmPC. Targeted guidance for clinical action is included in the SmPC. No additional PV activities and risk minimisation measures are in place.
Congestive heart failure (CHF)	Considering the time on the market and the extensive exposure to Nexavar, this risk is now considered adequately addressed in the SmPC. No additional PV activities and risk minimisation measures are in place.
Squamous cell cancer of the skin	Considering the time on the market and the extensive exposure to Nexavar, this risk is now considered adequately addressed in the SmPC. No additional PV activities and risk minimisation measures are in place.
Gastrointestinal perforation	Considering the time on the market and the extensive exposure to Nexavar, this risk is now considered adequately characterised in the SmPC. Targeted guidance for clinical action is included in the SmPC. No additional PV activities and risk minimisation measures are in place.
Renal dysfunction	Considering the time on the market and the extensive exposure to Nexavar, this risk is now considered adequately characterised in the SmPC. Targeted guidance for clinical action is included in the SmPC. No additional PV activities and risk minimisation measures are in place.
Interstitial lung disease (ILD)-like events	Considering the time on the market and the extensive exposure to Nexavar, this risk is now considered adequately characterised in the SmPC. No additional PV activities and risk minimisation measures are in place.
Drug-induced hepatitis	Considering the time on the market and the extensive exposure to Nexavar, this risk is now considered adequately characterised in the SmPC. No additional PV activities and risk minimisation measures are in place.
Previously classified as important potential risks	
Arterial thrombosis (cerebral ischaemia)	Considering the time on the market and the extensive exposure to Nexavar, this risk is now considered adequately characterised and to have no impact on B-R balance. No additional PV activities and risk minimisation measures are in place.

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Table Part II SVII-2: Reasons for removal of important identified risks and important potential risks from the list of safety concerns

Safety concerns	Reason for removal
Previously classified as important identified risks	
Wound healing complications	Considering the time on the market and the extensive exposure to Nexavar, this risk is now considered adequately addressed in the SmPC. No additional PV activities and risk minimisation measures are in place.
Microangiopathy	Considering the time on the market and the extensive exposure to Nexavar, this risk is now considered adequately characterised and to have no impact on B-R balance. No additional PV activities and risk minimisation measures are in place.
Torsade de pointes (TdP)	Considering the time on the market and the extensive exposure to Nexavar, this risk is now considered adequately addressed in the SmPC. No additional PV activities and risk minimisation measures are in place.
Pregnancy and exposure through breastfeeding	Considering the time on the market and the extensive exposure to Nexavar, this risk is now considered adequately addressed in the SmPC. Specific clinical measures to address the risk is included in the SmPC. No additional PV activities and risk minimisation measures are in place.

CHF: Congestive heart failure, GI: Gastrointestinal HCC: Hepatocellular carcinoma, HFSR: Hand-foot skin reaction, ILD: Interstitial lung disease, NSCLC: Non-small cell cancer of the lung, MAH: Marketing authorisation holder, PBRER: Periodic Benefit Risk Evaluation Report, RPLS: Reversible posterior leukoencephalopathy syndrome, RMP: Risk Management Plan, PV: Pharmacovigilance, PSUR: Periodic Safety Update Report, SmPC: Summary of product characteristics, TdP: Torsade de pointes.

SVII.3. Details of important identified risks, important potential risks, and missing information

SVII.3.1 Presentation of Important Identified Risks and Important Potential Risks

SVII.3.1.1 Important Identified Risks

Not Applicable

SVII.3.1.2 Important Potential Risks

Not Applicable

SVII.3.2 Presentation of the missing information

There is no missing information which would constitute a safety concern.

Part II: Module SVIII - Summary of the safety concerns

Table Part II SVIII-1: Summary of safety concerns

Important identified risks	None
Important potential risks	None
Missing information	None

Part III: Pharmacovigilance plan (including post-authorisation safety studies)

III.1. Routine Pharmacovigilance Activities

Routine pharmacovigilance activities beyond adverse reaction reporting and signal detection.

Routine pharmacovigilance was and will be conducted for Nexavar as detailed in corresponding pharmacovigilance procedures that are in place at Bayer. These routine activities include the collection, follow-up, evaluation and expedited reporting of individual case reports from all respective sources, ongoing monitoring and signal detection activities, preparation of PBRER/ PSUR, and initiation of label changes as required, and are described in applicable Standard Operating Procedures.

III.1.1. Specific adverse reaction follow-up questionnaires for safety concerns

Not Applicable

III.1.2. Other forms of routine pharmacovigilance activities for safety concerns

Not Applicable

III.2. Additional pharmacovigilance activities

No additional pharmacovigilance activities are in place.

III.3. Summary table of additional pharmacovigilance activities

Not applicable.

Part IV: Plans for post-authorisation efficacy studies

No post-authorization efficacy studies are ongoing or planned, as it is not warranted.

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Part V: Risk minimization measures (including evaluation of the effectiveness of risk minimization activities)

Part V: Risk minimisation measures (including evaluation of the effectiveness of risk minimisation activities

Risk Minimisation Plan

There are no important identified/potential risks or missing information included in the list of safety concerns.

V.1. Routine risk minimisation measures

Not applicable

V.2. Additional risk minimisation measures

Not applicable

V.3. Summary of risk minimisation measures

Not Applicable

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Part VI: Summary of the risk management plan

Part VI: Summary of Risk Management Plan

This is a summary of the RMP for Nexavar. There are currently no important risks of Nexavar according to the definitions given in the GVP, Module V, Revision 2.

Nexavar's SmPC and its package leaflet give essential information to healthcare professionals and patients on how Nexavar should be used.

This summary of the RMP for Nexavar should be read in the context of all this information including the assessment report of the evaluation and its plain-language summary, all which is part of the European Public Assessment Report (EPAR).

Important new concerns or changes to the current ones will be included in updates of Nexavar's RMP.

I. The medicine and what it is used for

Nexavar is authorised for advanced RCC, HCC, and locally advanced or metastatic DTC refractory to RAI (see SmPC for the full indication). It contains sorafenib (as tosylate) as the active substance and it is given orally.

Further information about the evaluation of Nexavar's benefits can be found in Nexavar's EPAR, including in its plain-language summary, available on the European Medicines Agency (EMA) website, under the medicine's webpage:
https://www.ema.europa.eu/medicines/human/EPAR/nexavar

II. Risks associated with the medicine and activities to minimise or further characterise the risks

As none of the identified and potential risks of Nexavar are judged as important, there are no additional pharmacovigilance activities and risk minimization measures related to the product beyond those described above in this Section of the document.

II.A List of important risks and missing information

None of the identified and potential risks of Nexavar are considered important according to the definitions given in the GVP, Module V, Revision 2.

Table Part VI-1: Summary of safety concerns

Important identified risks	None
Important potential risks	None
Missing information	None

II.B Summary of important risks

There are no important identified/potential risks or missing information included in the list of safety concerns.

II.C Post-authorisation development plan

II.C.1 Studies which are conditions of the marketing authorisation

There are no studies which are conditions of the marketing authorisation or specific obligation of Nexavar.

II.C.2 Other studies in post-authorisation development plan

Not Applicable.

Part VII: Annexes

Table of Content

Annex 4 - Specific adverse drug reaction follow-up forms

Not applicable

Annex 6 - Details of proposed additional risk minimisation activities (if applicable)

Not applicable