London, 20 September 2007
Product name: **NEXAVAR**
Procedure number: EMEA/H/C/690/II/05

SCIENTIFIC DISCUSSION

Introduction

Nexavar contains sorafenib, an antineoplastic agent that acts as protein kinase inhibitor (ATC code: L01XE05). Sorafenib inhibits tumour cell proliferation and the tumour vascularisation through activating the receptor tyrosine kinases (RTKs) signalling RAS/RAF/MEK/ERK cascade pathway.

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

The Marketing Authorisation Holder (MAH) has now applied for an extension of indication to include treatment of hepatocellular carcinoma. Sections 4.1, 4.4, 4.8 and 5.1 of the SPC have been updated and the Package Leaflet has been amended accordingly. The proposed dosage for the new indication is the same as that previously approved for renal cell carcinoma, i.e. 400 mg (two tablets) twice daily.

Hepatocellular Carcinoma (HCC)

It has been estimated that world wide about 560 000 new cases of hepatocellular cancer are diagnosed per year, but in Europe HCC is an orphan disease most commonly seen in patients with cirrhosis. In the western world, an increase is foreseen due to the increased incidence of chronic hepatitis C. Other aetiologies include chronic hepatitis B and alcohol.

Table 1. Epidemiology of HCC

Region	HCC Incidence (occurrences/100,000 population) Males[17]	HCC Incidence (occurrences/100,000 population) Females[17]	No. of HCC Cases	Principal Associations
Asia, Sub-Saharan Africa	30-120	9-30	> 500,000 cases per year[1,5]	HBV, aflatoxin exposure
Japan	10-30	3-9		HCV
Southern Europe, Argentina, Switzerland	5-10	2-5		HCV
Western Europe	< 5	< 3		HCV
United States	< 5	< 3	18,000 predicted for 2005[9]	HCV, alcohol

Abbreviations: HCC, hepatocellular carcinoma; HBV, hepatitis B virus; HCV, hepatitis C virus.

(Thomas et al, JCO 2005)

Potentially curative therapies include resection, transplantation and percutaneous ablation.
In patients for whom surgery or ablation is not an option, TACE (transarterial chemoembolization) has been used in some centers. In general, it is assumed that the best candidates for TACE are those who still have well-preserved liver function (normal or Child-Pugh class A) and multinodular, asymptomatic tumors without vascular invasion. These patients constitute less than 15% of the HCC population. However, TACE is not used uniformly as a therapeutic option worldwide.

There are currently no medicinal products licensed in the EU for the treatment of HCC, but, e.g., doxorubicin alone or in combinations has some use in clinical practice. Recently (Robert Gish et al, JCO July 2007) a randomised study comparing the experimental compound nolatrexed with doxorubicin showed a survival benefit for doxorubicin. The results of this study will be discussed in relation to the outcome of the sorafenib study as appropriate (see below).

Non-clinical aspects

Study MRC-01324

Preclinical data submitted in support of this variation consists of a primary pharmacodynamic study "Sorafenib blocks the RAF/MEK/ERK pathway, inhibits tumour angiogenesis and induces tumor cell apoptosis in hepatocellular carcinoma model PLC/PRF/5" (Study MRC-0134) and a series of literature references.

Sorafenib blocks the enzyme RAF kinase and inhibits the VEGF-2/PDGFR-beta signalling cascade. Sorafenib is a multi-kinase inhibitor with activity against pathways of cell growth and angiogenesis, including serine/threonine kinases c-Raf and B-raf and the receptor tyrosine kinase RET, Flt-3 and c-Kit.

The new pharmacology data for sorafenib includes a description of the activity of sorafenib on the proliferation of human hepatocellular tumour cells and the tumour growth inhibitory effects of the compound when administered to immunodeficient mice bearing human models of hepatocellular carcinomas grown as xenografts.

HCC is characterized by the activation of intracellular signalling pathways, namely the Raf/MEK/ERK pathway (MAPK pathway), and is a highly angiogenic tumour. The Raf/MEK/ERK pathway can be activated by a number of mechanisms including the epidermal growth factor receptor (EGFR) and the receptor for hepatocytes growth factor. In addition, the hepatitis C virus (HCV) nonstructural protein NS5A has been shown to interact and activate Raf kinase, in a process crucial for viral replication, which leads to the activation of the Raf/MEK/ERK pathway and increased viral replication. This activation of Raf by NS5A can be inhibited by sorafenib. Vascular endothelial growth factor (VEGF), one of the most potent growth factor for endothelial cells, is found overexpressed in HCC. In addition, the receptor for VEGF, VEGFR2, has been found inappropriately expressed on HCC tumour cells, opening up the possibility for an autocrine VEGF/VEGFR2 loop supporting tumour cell growth.

In two models of human hepatocellular carcinoma, sorafenib inhibited tumour cell growth *in vitro* and this inhibition was associated with the down regulation of the Raf/MEK/ERK pathway. Sorafenib inhibited the proliferation of human HCC cell lines PLC/PRF/5 (p53-mutant) and HepG2 (p53-wild-type) *in vitro* with IC_{50} values of 6.3 and 4.5 μM, respectively (it is noted that likely an erroneous value for IC_{50} has been included in the pharmacology written summary; 1.6 instead of 4.5 μM). This inhibition correlated with the inhibition of the Raf/MEK/ERK pathway as measured by the phosphorylation of MEK and ERK (pMEK and pERK). Phosphorylation levels of AKT were not affected. The reduction in MEK and ERK phosphorylation led to a reduction in the proliferation marker cyclin D1 in both cell lines, consistent with the anti-proliferative activity of the compound. Further the anti-apoptotic protein Mc1-1 was reduced by sorafenib in both cell lines.

When tested *in vivo* against PLC/PRF/5 tumour grown as tumour xenograft in severe combined immunodeficiency (SCID) mice, sorafenib inhibited its growth, with partial tumour regressions seen at the highest dose used. A dose of 10 mg/kg once a day inhibited tumour growth by 49% and complete tumour stasis was seen at a dose of 30 mg/kg. In further studies using PLC/PRF/5 xenograft tumours, analysis revealed a decrease in Raf/MEK/ERK signalling (pERK) and a reduction in tumour vasculature (TUNEL staining) supporting the dual mechanism of action of sorafenib; that of targeting both tumour cell signalling and tumour angiogenesis. The reduction if Raf/MEK/ERK signalling and tumor vasculature was accompanied by an increase in tumour cell apoptosis and inhibition of tumour growth.

Discussion on Non-clinical aspects

Sorafenib was shown to exhibit antitumour activity with effects on both tumour cell signalling (Raf/MEK/ERK pathway) and angiogenesis and induced tumour cell apoptosis. Sorafenib seemed to inhibit MEK/ERK dependent and independent signalling. The non-clinical data are consistent with the

fact that sorafenib activity in HCC is coupled to inhibition of RAF/MEK/ERK signalling, induction of MEK/ERK independent pro-apoptopic effects and inhibition of angiogenesis. While comparisons on a mg/kg dose basis are uncertain, the non-clinical data *in vitro* and *in vivo* support a role of sorafenib at clinically relevant doses in the treatment of HCC.

Clinical aspects

Clinical pharmacology

Two new pharmacokinetic studies have been submitted in the present application; one phase I study in Japanese patients with HCC (Study 10875) and one population pharmacokinetic analysis on pharmacokinetic data from different studies, including the phase III study in HCC (see below). For reference, the MAH also discusses the previously submitted phase II study in patients with HCC and mild-moderate hepatic impairment (Study 10874).

Study 10874 *(submitted with original Marketing Authorisation Application)*

Study 10874 was conducted to evaluate the anti-cancer activity, safety, pharmacokinetics and tolerability of sorafenib at the 400 mg BID dose in patients with advanced inoperable HCC. Patients in this study had a baseline hepatic function status of either Child-Pugh A (n=15) or Child-Pugh B (n=6). Plasma samples were collected at steady state over the 12-hour dosing interval, at 28 days after the start of dosing.
Unfortunately, concentration data up to 12 hours were available only in 6 subjects, and therefore $AUC_{(0-8),ss}$ at 400 mg BID rather than $AUC_{(0-12),ss}$ was presented.

Sorafenib plasma pharmacokinetic parameters (presented as geometric mean, %CV except for t_{max} which is presented as median, range) in hepatically impaired cancer patients dosed 400 mg BID

Child Pugh Status		$AUC_{(0-8,ss)}$ (mg*h/L)	$C_{max,ss}$ (mg/L)	$t_{max,ss}$ (h)
Child Pugh A	N=15			
	Geometric mean (Approx. CV%)	25.4 (38.4%)	4.92 (38.7%)	1.0 (0-12)
Child Pugh B	N=6			
	Geometric mean (Approx. CV%)	30.3 (82.1%)	5.97 (73.8%)	0.5 (0-8)

It was suggested that the AUC values observed in this study were within the range of AUC observed in previous phase I studies in patients without hepatic impairment, and that the increased AUC in Child Pugh B patients was not clinically relevant. There was no correlation between AUC and toxicity and no obvious difference in tolerability between the two groups in this study.

The pharmacokinetics of the metabolites is shown in table below.

M5 $AUC_{(0-8,ss)}$ and $C_{max,ss}$ values appear to be slightly lower in Child-Pugh B patients compared to Child-Pugh A patients. However, these parameters have overlapping ranges in the two populations. The $AUC_{(0-8,ss)}$ and $C_{max,ss}$ values of M2 and M4 metabolites are similar in Child-Pugh A and B patients.

During the assessment of the original application for renal carcinoma, dose adjustments or special caution were not considered necessary in patients with mild to moderate hepatic impairment. The SPC, however, includes a warning that exposure might be increased in severe hepatic impairment, and that no data for the latter group is available.

Plasma $C_{max,ss}$ and $AUC_{(0-8,ss)}$ values of M2, M4, and M5 (geometric mean, %CV) following twice daily administration of 400 mg BID sorafenib to hepatically impaired cancer patients

Analyte	PK Parameter	Child-Pugh A (n=15)	Child-Pugh B (n=6)
BAY 67-3472 (M2: N-oxide metabolite)	$AUC_{(0-8,ss)}$ (mg*h/L)	5.38 (63.3%)	5.24 (112%)
	$C_{max,ss}$ (mg/L)	1.03 (62.4%)	0.93 (113%)
BAY 43-9007 (M4: N-demethyl metabolite)	$AUC_{(0-8),ss}$ (mg*h/L)	1.43 (97.1%)	1.68 (173%)
	$C_{max,ss}$ (mg/L)	0.31 (101%)	0.35 (158%)
BAY 68-7769 (M5: N-oxide of BAY 43-9007)	$AUC_{(0-8,ss)}$	1.98 (84.8%)[a]	1.13 (130%)
	$C_{max,ss}$ (mg/L)	0.33 (116%)	0.26 (113%)

a) n=14

Study 10875 *(new)*

This was a Phase I study to describe the safety, tolerability, and pharmacokinetics of 200 mg BID and 400 mg BID sorafenib in Japanese HCC patients. Twelve patients were evaluable in the 200 mg group (6 Child-Pugh A and 6 Child-Pugh B) and 11-14 patients were evaluable in the 400 mg group (6 Child-Pugh A and 5-8 Child-Pugh B). Eight of the Child Pugh A subjects and all of the Child Pugh B subjects were positive for hepatitis C antigen. Three Child Pugh A subjects and one Child Pugh B subject tested positive for hepatitis B.

Patients received a single dose of either 200 or 400 mg sorafenib followed by a 7 day washout period, so that the single dose pharmacokinetics could be properly evaluated. After the washout period, the twice-daily dosing regimen was begun, and additional pharmacokinetic evaluations were performed on Days 14 and 28 of multiple dosing. The pharmacokinetic results for sorafenib are shown in Table 3. At both doses there was no discernible difference in sorafenib pharmacokinetics between the Child-Pugh A and Child-Pugh B patients. The mean AUC and C_{max} tended to be lower in the Child-Pugh B patients, but this was suggested to be a consequence of the pharmacokinetic variability in both groups. Mean half-life ranged from 22 to 30 hours, which is similar to that reported for healthy volunteers. The steady-state $AUC_{(0-12)}$ values were generally consistent with the single dose AUC values, though the Day 14 and Day 28 $AUC_{(0-12)}$ values in Child-Pugh A patients on 400 mg BID were slightly greater than Day 1 AUCs. The exposures seen with the 400 mg BID dose regimen did not show a dose-proportional increase relative to the 200 mg BID regimen, also suggested possibly due to the pharmacokinetic variability of sorafenib and relatively small number of patients.

The pharmacokinetics of metabolites after 28 days of 400 mg BID dosing are shown in the table below. The results were similar for the 200 mg BID dose and on day 14, and are not presented here.

Also for the metabolites, there were no discernible differences between the Child Pugh A and the Child Pugh B group, suggesting no difference in metabolism based on Child-Pugh status.

Pharmacokinetic parameters (geometric mean, %CV) of sorafenib in Japanese HCC patients following a single 200 mg or 400 mg dose and multiple doses of 200 mg or 400 mg BID

Study Day	PK Parameter	Child-Pugh A (n=6)	Child-Pugh B (n=6)	Child-Pugh A (n=6)	Child-Pugh B (n=8/6/5)[a]
		200 mg BID		**400 mg BID**	
Single Dose	AUC (mg*h/L)	28.3 (190%)	18.6 (74%)	20.3 (90)%	26.9 (97%)
	$AUC_{(0-12)}$ (mg*h/L)	5.02 (190%)	2.75 (61%)	3.82 (86%)	3.11 (88%)
	C_{max} (mg/L)	0.81 (196%)	0.49 (68%)	0.55 (84%)	0.53 (87%)
	$t_{½}$ (h)	25.1 (30%)	30.4 (36%)	22.3 (12%)	27.2 (45%)
Cycle 1 Day 14	$AUC_{(0-12),ss}$ (mg*h/L)	25.5 (75%)	15.3 (55%)	33.5 (60%)	29.5 (59%)[b]
	$C_{max,ss}$ (mg/L)	3.36 (87%)	1.89 (62%)	4.66 (66%)	3.04 (94%)
Cycle 1 Day 28	$AUC_{(0-12),ss}$ (mg*h/L)	31.6 (102%)	20.0 (73%)	28.9 (87%)	20.7 (72%)
	$C_{max,ss}$ (mg/L)	4.22 (92%)	3.32 (79%)	3.32 (113%)	4.01 (79%)

a) n=8 single dose; n=6 Day 14; n=5 Day 28
b) n=5

Plasma PK variables of sorafenib metabolites in Japanese Child Pugh A and B patients following administration of 200 mg or 400 mg BID for 28 days (geometric mean, %CV)

		M2	M4	M5
Child-Pugh A	$AUC_{(0-12),ss}$ (mg*h/L)	4.41 (175%)	1.08 (119%)	0.97 (177%)
	Ratio[a]	12.25 (41%)	3.00 (35%)	2.70 (71%)
	$C_{max,ss}$ (mg/L)	0.5 (206%)	0.12 (154%)	0.11 (224%)
	Ratio	12.2 (36%)	2.96 (39%)	2.69 (69%)
Child-Pugh B	$AUC_{(0-12),ss}$ (mg*h/L)	2.75 (127%)	0.82 (194%)	0.48 (451%)
	Ratio	10.8 (47%)	3.23 (59%)	1.89 (161%)
	$C_{max,ss}$ (mg/L)	0.49 (115%)	0.15 (206%)	0.10 (237%)
	Ratio	10.1 (53%)	3.13 (65%)	2.13 (88%)

ratio of each metabolite to the sum of all analytes (sorafenib, M2, M4 and M5)

Population pharmacokinetic analysis (Study 12785)

Plasma sorafenib concentration data from the Phase III HCC Study 100554 (n=164) and Phase II Study 10874 (n=20) along with multiple dose pharmacokinetic data from 7 single agent Phase I studies and single dose pharmacokinetic data from 3 healthy volunteer studies, were analysed by population pharmacokinetic methods. The population pharmacokinetic model was developed based on data from twelve studies (100283, 10164, 100277, 100342, 100483, 100545, 10658, 11497, 10874, 10875, and 100554 including 479 subjects (410 cancer patients and 69 healthy subjects) with in total 6446 plasma concentration observations. Population analysis was performed with NONMEM software version V, using first order conditional estimation method with interaction.

The chosen structural model was a two compartment model with first order absorption and a lag time. Bioavailability was modelled as dose dependent and a stepwise model was considered most adequate based on objective function value. Exponential error models were used to describe interindividual variance and a proportional residual error model. Covariates were tested in a forward inclusion process using inclusion criteria of $p<0.001$ corresponding to a difference in OFV of 10.83 for 1 additional parameter (1 degree of freedom).

The influence of age, body weight, gender, ethnicity (Japanese versus non-Japanese), baseline SGOT (AST), SGPT (ALT), bilirubin, alkaline phosphatase, total protein, creatinine clearance (estimated from serum creatinine) and disease (cancer patients versus healthy subjects) on sorafenib clearance was evaluated. The effect of age, body weight, gender and ethnicity (Japanese versus non-Japanese) on the central and peripheral volumes of distribution was evaluated. The effect of total protein and disease (cancer patients versus healthy subjects) on central volume of distribution was also evaluated. The effect of ethnicity (Japanese versus non-Japanese) on absorption rate constant and bioavailability was evaluated. In the first step of the stepwise forward inclusion procedure, inclusion of ethnicity (Japanese versus non-Japanese) as a covariate for absorption rate constant resulted in a maximum decrease (24.359 points) in the value of objective function. In the second step, inclusion of SGOT (AST) as a covariate for clearance resulted in a maximum decrease (11.305 points) in the value of objective function and in the third step, inclusion of bilirubin as a covariate for clearance resulted in a maximum decrease (11.701 points) in the value of objective function. No additional covariates were identified in the fourth and final step of the covariate model building procedure. The final model together with confidence intervals obtained with nonparametric bootstrap is presented in Table 5.

Table 5 : Sorafenib population pharmacokinetic parameters

	Nonparametric bootstrap		Reproduced from Table 13-8	
	Median	[2.5th, 97.5th percentile]	Estimate	95 % confidence interval
THETA(1) - θ_{CL}, L/h	3.40	[2.86 , 4.44]	3.41	[2.71 , 4.11]
THETA(2) - θ_{V2}, L	87.5	[71.3 , 116]	87	[68 , 106]
THETA(3) - θ_{V3}, L	25.4	[16.5 , 36.3]	25.2	[15.3 , 35.1]
THETA(4) - θ_{Q}, L/h	1.37	[0.58 , 2.38]	1.39	[0.47 , 2.31]
THETA(5) - θ_{KA}, 1/h	0.224	[0.185 , 0.270]	0.221	[0.179 , 0.263]
F1 (Sorafenib dose < 200 mg) THETA(6) - θ_{F1} (Sorafenib dose between 200 mg and 400 mg [inclusive])	0.474	[0.383 , 0.669]	1 0.477	[0.353 , 0.601]
THETA(7) - θ_{F1} (Sorafenib dose > 400 mg)	0.373	[0.312 , 0.482]	0.374	[0.294 , 0.454]
THETA(8) - θ_{ALAG}, h	0.214	[0.210 , 0.227]	0.214	[0.207 , 0.221]
THETA(9) - $\theta_{KA-JAPANESE}$	–0.539	[–0.665 , –0.385]	–0.543	[–0.682 , –0.404]
THETA(10) - $\theta_{CL-SGOT}$	0.238	[0.120 , 0.362]	0.236	[0.109 , 0.363]
THETA(11) - $\theta_{CL-BILIRUBIN}$	–0.160	[–0.238 , –0.082]	–0.164	[–0.241 , –0.087]
OMEGA(1,1) - ω^2_{CL}	0.056	[0.034 , 0.082]	0.0583	[0.032 , 0.085]
OMEGA(2,2) - ω^2_{V2}	0.016	[0 , 0.083]	0.0199	[–0.0313 , 0.0711]
OMEGA(3,3) - ω^2_{V3}	0.249	[0 , 0.544]	0.248	[0.023 , 0.473]
OMEGA(4,4) - ω^2_{KA}	1.05	[0.8 , 1.323]	1.06	[0.8 , 1.32]
OMEGA(5,5) - ω^2_{F1}	0.217	[0.179 , 0.264]	0.218	[0.178 , 0.258]
SIGMA(1,1) - σ^2_{PROP}	0.225	[0.208 , 0.240]	0.225	[0.21 , 0.24]

The model included a relation to SGOT which suggested that a SGOT value > normal would result in higher clearance although not physiologically plausible. The MAH concludes that the covariate relations are not clinically relevant.

Discussion on Clinical Pharmacology

Sorafenib is eliminated via metabolism (mainly CYP3A4 and glucuronidation) and likely also to some extent by biliary excretion. Unchanged sorafenib recovered in faeces has been suggested to represent not only unabsorbed drug but also biliary excreted drug, either as parent compound or as glucuronide, which has then been cleaved to sorafenib in the gut. Metabolic hepatic impairment and possibly cholestasis might therefore be expected to affect the elimination of sorafenib.

None of the two studies in hepatically impaired patients included a control group without hepatic impairment so a direct comparison could not be made, although the AUC values observed in the studies appear to be within the range observed for healthy subjects in phase I studies. The degree of metabolic impairment vs. e.g. degree of cholestatis was not discussed for these patients and the results from HCC patients cannot readily be extrapolated to cirrhosis patients.

A new study in hepatically impaired Japanese subjects confirmed the results from a previous study in non-Japanese subjects. Based on these data, the increase in sorafenib exposure in patients with moderate hepatic impairment is marginal compared with patients with mild hepatic impairment and does not warrant dose adjustments. Unfortunately, there is no pharmacokinetic data in severe hepatic impairment, which is considered a deficiency, as also safety data from this group is lacking. The possibility to make a specific recommendation for patients with HCC and severe hepatic impairment, perhaps specifically in patients with metabolic impairment or cholestasis, would be valuable.

The MAH has made a post-authorisation commitment to discuss the possibility to obtain data on the pharmacokinetics of sorafenib in patients with severe hepatic impairment and make adequate recommendations for this group.

The submitted population pharmacokinetic analysis is not considered informative. Several problems with the model has been identified, that must be resolved if the model is going to be used in further PK/PD modelling or for simulation purposes. However, for approval of the new indication, a re-analysis is not required. Even if re-analysed, the population pharmacokinetic data is not expected to add useful information from a pharmacokinetic perspective to that already obtained in the two pharmacokinetic studies, since no data from subjects with severe renal impairment are available.

Clinical efficacy

Main studies

The efficacy of sorafenib in HCC patients is primarily based on the Phase III, randomized, double-blind, placebo-controlled trial (Study 100554), and also supported by Study 10874 (a single arm, large Phase II study in HCC).

Study 100554 (pivotal)

This was a Phase III randomized, placebo-controlled study of sorafenib in patients with advanced hepatocellular carcinoma. Period of study: 10 Mar 2005 to 17 Oct 2006.

Objectives:

Primary: Overall survival (OS) and time to symptomatic progression (TTSP).

Secondary: Time to tumour progression (TTP)
Overall disease control rate
Functional Assessment of Cancer Therapy-Hepatobiliary (FACT-Hep) response rate

Tertiary: Overall response rate, overall response duration, and time to objective response. FACT-Hep Physical Well-being (PWB) and Functional Well-being (FWB) subscale response rates.

Other (will be reported separately):
Biomarker programme

Treatment:

Sorafenib (or matching placebo) was administered orally at a dose of 400 mg (2 x 200 mg tablets) twice daily; 2 dose reductions to predefined levels of 400 mg once daily (OD) and 400 mg every other day were permitted for adverse events related to study treatment. Study treatment was administered orally on a continuous schedule, but for the purpose of data recording, the treatment period was divided into 6-week cycles. Study drug could be taken either with a low/moderate fat meal or without food. After a dose, patients did not have to wait before eating.

Treatment was continued until death or until a criterion for stopping therapy was met. Treatment beyond radiological and symptomatic progression was allowed upon request of the treating investigator.

Subjects assigned to the placebo arm were not crossed over to the sorafenib arm at any time during the study before the OS endpoint was met.

Key inclusion criteria:

- Life expectancy of at least 12 weeks
- Advanced HCC (subjects not eligible for surgical or loco-regional treatments)
- Histologically or cytologically documented HCC
- At least one tumour lesion that met both of the following criteria:
    - Measurable according to RECIST (response evaluation criteria in solid tumours)
    - Not previously treated with local therapy (such as surgery, radiation therapy, hepatic arterial therapy, chemo-embolization, radiofrequency ablation, etc.)
- Local therapy completed at least 4 weeks prior to the baseline scan.
- ECOG PS (eastern cooperative oncology group performance status) of 0, 1, or 2
- Child-Pugh class A liver function status only.

Key exclusion criteria:

- Cardiac
    - Congestive heart failure > NYHA (New York Heart Association) class 2;
    - Active coronary artery disease (CAD);
    - Cardiac arrhythmias requiring anti-arrhythmic therapy other than beta blockers or digoxin;
    - uncontrolled hypertension.
    - Myocardial infarction more than 6 months prior to study entry was permitted.
- CNS tumours including metastatic brain disease
- Subjects with clinically significant gastrointestinal bleeding within 30 days prior to study entry

Statistical Planning (SAP dated December 2006)

All randomized patients (Intent to Treat Population) will be included in the primary analyses. One-sided alpha of 0.02 and 0.005 will be used for OS and TTSP analyses, respectively.

Randomization will be stratified by geographical region [North America versus South America (including Mexico) versus Europe (including Australia/New Zealand)], ECOG performance status (0 vs 1 vs 2) and tumour burden (presence of either macroscopic vascular invasion and/or extrahepatic spread vs none).

It was expected that there will be a small number of patients with ECOG PS 2. Patients with ECOG PS 1 and 2 will be combined together for statistical analyses. The following efficacy analyses were to be performed according to the above stratification with ECOG PS 1 and 2 combined (i.e. Geographic region, ECOG 0 vs 1 and 2, and tumour burden).

The first **interim analysis** of OS was planned when approximately170 deaths were observed. The second interim analysis of OS was planned when approximately 300 deaths were observed. For OS interim analyses, an O'Brien-Fleming-type error spending function will determine the criteria for early stopping for efficacy so that the overall false positive rate (alpha) is less than or equal to 0.02 (one-sided).

The scenario in the table below serves as an example. The actual boundaries used for analyses will be calculated according to the actual number of events (deaths) for a given analysis.

Stopping Criteria and Alpha Spending at the Interim and Final Analyses of Overall Survival

		Stopping Boundaries Hazard Ratio Scale (sorafenib:placebo) (% Improvement)				
Analysis Time	# Events	Crossing Lower Bound (efficacy)	Crossing Upper Bound (lack of efficacy)	Nominal Alpha	Alpha Spent	Cumulative Alpha Spent
1st Interim	170	0.6003(66.6%)	1.29(-22.5%)	0.00045	0.00045	0.00045
2nd interim	300	0.7493(33.5%)	1.033(-3.2%)	0.00624	0.00642	0.00687
Final	424	0.8153(22.7%)	0.8153(22.7%)	0.01783	0.01313	0.02

Sensitivity analyses will be carried out for Overall Survival and TTSP as follows:
1. Stratified log-rank using stratification from IVRS
2. Non-stratified log-rank
3. Non-stratified log-rank adjusting for covariates of region, ECOG, and tumour burden from CRF (Cox regression)

Results

At the time of the data cut-off (2nd interim analysis, 17 Oct 2006) study enrolment had been completed. Altogether 602 subjects had been randomized. Among randomized subjects, 146 (24%) were randomized from Germany, 111 (18%) from Italy, 98 (16%) from France, 36 (6%) from Spain and 34 (6%) from the United States. All other countries each contributed 5% or less of subjects each.

Demographics and Baseline Characteristics in Study 100554 (Subjects Valid For Intent to Treat Population)

	Placebo (N=303)	Sorafenib (N=299)
Region[a] n (%)		
Europe	263 (87%)	263 (88%)
North America	29 (10%)	27 (9%)
South America	11 (4%)	9 (3%)
Race n (%)		
White	273 (90%)	261 (87%)
Black	4 (1%)	9 (3%)
Asian	24 (8%)	24 (8%)
Hispanic	2 (1%)	5 (2%)
Age at enrollment (years) mean±standard deviation	66.3 ±10.2	64.9 ±11.2
Age group n (%)		
<65 yrs	108 (36%)	124 (41%)
≥65 yrs	195 (64%)	175 (59%)
Sex n (%)		
Male	264 (87%)	260 (87%)
Female	39 (13%)	39 (13%)

a Europe includes Australia and New Zealand, South America includes Mexico
Abbreviations: yrs - years

Baseline Cancer Characteristics

	Placebo (N=303)	Sorafenib (N=299)
Baseline ECOG PS n(%)		
0	164 (54%)	161 (54%)
1	117 (39%)	114 (38%)
2	22 (7%)	24 (8%)
Macroscopic vascular invasion and/or Extrahepatic spread n (%)		
Absent	91 (30%)	90 (30%)
Present	212 (70%)	209 (70%)
BCLC stage n (%)		
Stage B	51 (17%)	54 (18%)
Stage C	252 (83%)	244 (82%)
Stage D	0 (0%)	1 (0.3%)
Etiology n (%)		
Hepatitis C only	82 (27%)	87 (29%)
Alcohol only	80 (26%)	79 (26%)
Hepatitis B only	55 (18%)	56 (19%)
Unknown	56 (19%)	49 (16%)
Other	29 (5%)	28 (5%)
Missing	1 (0.3%)	0 (0%)
Hepatitis from laboratory n (%)		
Hepatitis C only	81 (27%)	86 (29%)
Hepatitis B only	28 (9%)	32 (11%)
Hepatitis B & C	3 (1%)	7 (2%)
Negative serology for HCV Ab or HBs Ag	165 (55%)	149 (50%)
Missing	26 (9%)	25 (8%)
Child-Pugh status n (%)		
A	297 (98%)	284 (95%)
B	6 (2%)	14 (5%)
C	0 (0%)	1 (0.3%)
Liver cirrhosis n (%)		
Histological	95 (31%)	91 (30%)
Clinical	86 (28%)	86 (29%)
Both	38 (13%)	33 (11%)
Not confirmed	84 (28%)	89 (30%)

Abbreviations: BCLC = Barcelona Clinic Liver Cancer, ECOG = Eastern Cooperative Oncology Group, HCV Ab = HB Ag, ITT = intent to treat; and PS = performance status.

The median time from initial diagnosis to randomization was 0.4 years (range 0 to 9.2 years). The tumour histology was liver cell carcinoma in 563 subjects (93.5%), and other HCC subtypes in the remaining cases. According to the investigator, the majority (64%) of subjects was reported to have

progressive disease at the time they entered the study, and nearly half of the subjects had TNM stage IV disease at that time.

Prior Therapy for Hepatocellular Carcinoma

Characteristic	Placebo N = 303 n	(%)	Sorafenib N = 299 n	(%)
Type of therapy[a]				
Surgical	288	(95.0%)	284	(95.0%)
Surgical only[b]	114	(37.6%)	105	(35.1%)
Loco-regional only	16	(5.3%)	20	(6.7%)
Diagnostic only	34	(11.2%)	39	(13.0%)
Multiple procedures	124	(40.9%)	120	(40.1%)
Loco-regional therapy	123	(40.6%)	116	(38.8%)
TACE	90	(29.7%)	86	(28.8%)
PEI	20	(6.6%)	28	(9.4%)
RFA	12	(4.0%)	17	(5.7%)
Radiotherapy	15	(5.0%)	13	(4.3%)
Systemic anti-cancer therapy	15	(5.0%)	9	(3.0%)
Hormonal therapy	12	(4.0%)	8	(2.7%)
Cytotoxic chemotherapy	3	(1.0%)	1	(0.3%)

a Subjects may have had more than 1 type of therapy.
b Surgical only includes excision biopsy procedures.
Abbreviations: PEI = percutaneous ethanol injection, RFA = radiofrequency ablation; TACE = transarterial chemoembolization

Prior systemic therapy for HCC (except for hormonal therapy), was an exclusion criterion in this study, but was administered to 3 (1%) subjects randomized to placebo and 1 (0.3%) subject randomized to sorafenib.

Efficacy

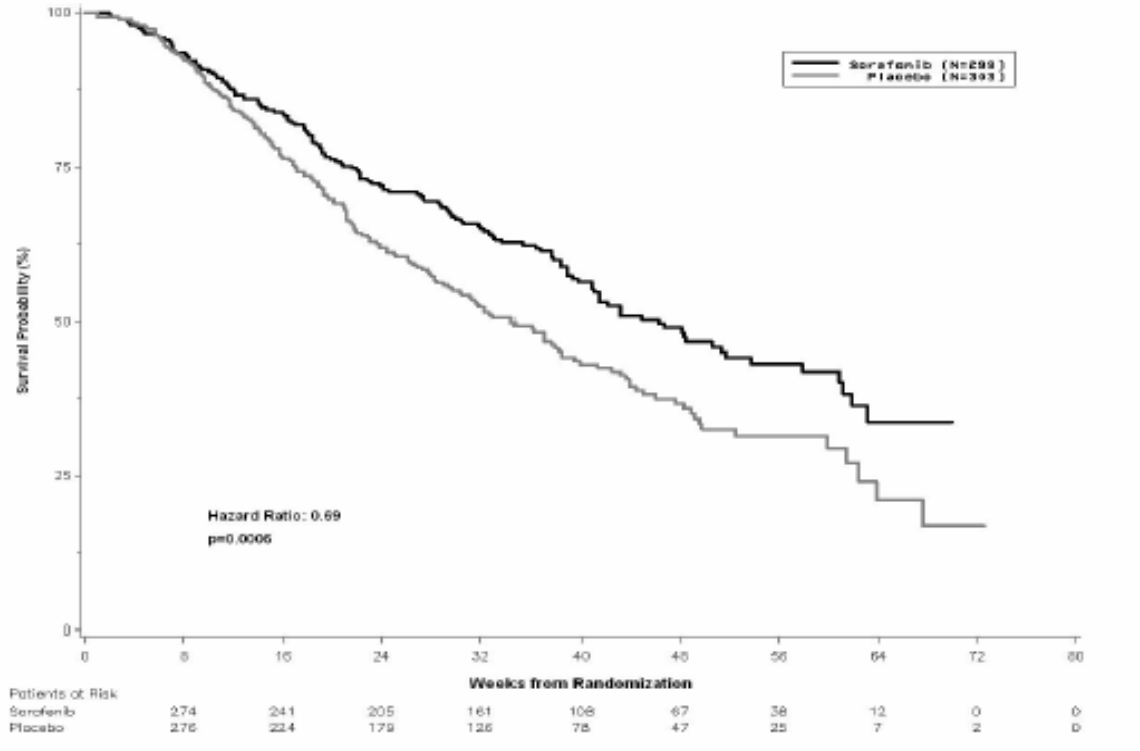
- First primary endpoint

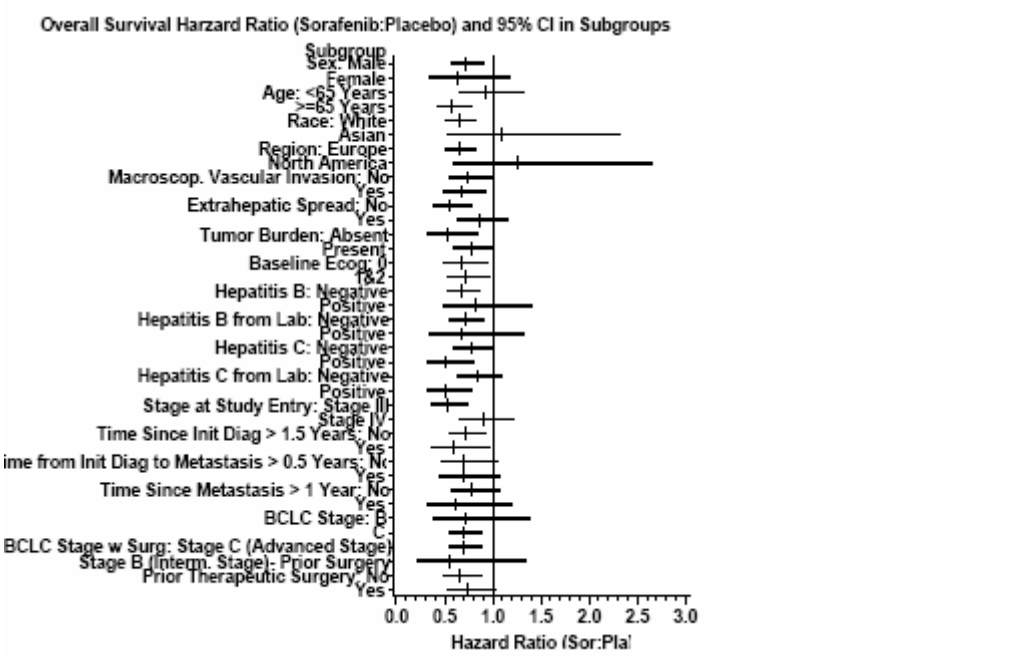
Overall Survival (2nd interim analysis, cut-off 17 October 2006)

		Placebo (N=303)	Sorafenib (N=299)
Overall survival (weeks) (*P*-value=0.000583)	N	303	299
	Number failed	178 (58.7%)	143 (47.8%)
	Number censored	125 (41.3%)	156 (52.2%)
	Median(95% CI)	34.4 (29.4, 39.4)	46.3 (40.9, 57.9)
	Hazard ratio (sorafenib/placebo)	0.6931	
	95% CI for Hazard ratio	(0.5549,0.8658)	

Abbreviations: CI = confidence interval

The stratified log-rank test had a 1-sided nominal *P*-value of 0.000583. The pre-specified nominal alpha for this analysis was 0.0077.





Age group	< 65 Yrs	232	125	107	0.92	(0.65, 1.32)	269	287
	≥ 65 Yrs	370	196	174	0.58	(0.43, 0.77)	222	362
Stage at study entry	Stage II	56	13	43	0.40	(0.13, 1.25)	348	
	Stage III	245	131	114	0.52	(0.36, 0.75)	206	426
	Stage IV	294	172	122	0.90	(0.66, 1.21)	253	268

Baseline variables that were significant in a model including treatment and the single covariate were included in a multivariate stepwise regression procedure. In this stepwise Cox regression the following conditions were associated with decreased survival regardless of treatment:

- Baseline ECOG greater than 0
- Macroscopic vascular invasion
- Presence of macroscopic vascular invasion and/or extrahepatic spread

- Child-Pugh status of B or C
- Higher than median baseline AFP
- Lower than median baseline albumin
- Higher than median baseline alkaline phosphatase
- Higher than median baseline total bilirubin.

- Second primary endpoint

Symptomatic progression was defined as a decrease of at least 4 points from baseline score based on subject responses to the FHSI-8 questionnaire with a confirmatory decline at the next actual visit, deterioration to an ECOG PS of 4, or death.

Time to symptomatic progression

		Placebo (N=303)	Sorafenib (N=299)
FHSI8-TSP (weeks)	N	303	299
(*P*-value=0.767670)	Number failed	201 (66.3%)	202 (67.6%)
	Number censored	102 (33.7%)	97 (32.4%)
	Median(95% CI)	21.1 (18.4, 27.4)	18 (15.0, 21.0)
	Hazard ratio (sorafenib/placebo)	1.0764	
	95% CI for hazard ratio	(0.8837, 1.3110)	

Abbreviations: CI = confidence interval, and FHSI8-TSP = time to symptomatic progression

- Secondary endpoints

Time to progression

TTP Based on Independent Radiological Review Up to Data Cut-off Date 12 May 2006

		Placebo (N=303)	Sorafenib (N=299)
Time to progression (weeks)	N	303	299
(*P*-value=0.000007)	Number failed	156 (51.5%)	107 (35.8%)
	Number censored	147 (48.5%)	192 (64.2%)
	Median(95% CI)	12.3 (11.7,17.1)	24 (18.0, 30.0)
	Hazard ratio (sorafenib/placebo)	0.5764	
	95% CI for hazard ratio	(0.4484,0.7410)	

a The time to progression (TTP) includes only radiologically-determined disease progression per RECIST

The independent radiology review did not continue after 12th of May, but investigator radiological assessments continued throughout the entire duration of the study and the results of TTP per investigator assessment up to the cut-off date of this report (17 Oct 2006) are presented below.

TTP Based on Investigator Assessment of Radiographic Scans

		Placebo (N=303)	Sorafenib (N=299)
Time to progression (weeks)	N	303	299
(*P*-value=0.000130)	Number failed	222 (73.3%)	181 (60.5%)
	Number censored	81 (26.7%)	118 (39.5%)
	Median (95% CI)	11.9 (11.1,12.4)	17 (13.0,18.0)
	Hazard ratio (sorafenib/placebo)	0.6889	
	95% CI for hazard ratio	(0.5634,0.8423)	

a The time to progression (TTP) includes only radiologically-determined disease progression.

Overall Best Tumour Response and Disease Control Rate by Independent Radiological Review Up to the Cut-off Date of 12 May 2006 (RECIST) in

Best response	Placebo (N=303) n (%)	Sorafenib (N=299) n (%)
Complete response (CR)	0	0
Partial response (PR)	2 (0.66)	7 (2.34)
Stable disease	204 (67.33)	211 (70.57)
Progressive disease (PD)	73 (24.09)	54 (18.06)
Not assessable	24 (7.92)	27 (9.03)
Disease control rate (DCR)	96 (31.68)	130 (43.48)

Abbreviations: CR = complete response, DCR = disease control rate, ITT = intent to treat, PD = progressive disease, PR = partial response, and RECIST = Response Evaluation Criteria in Solid Tumors

The disease control rate (DCR), (defined as at least SD for at least 28 days), was 31.7% (96 subjects) in the placebo group, compared with 43.5% (130 subjects) in the sorafenib group.

DCR rates are markedly affected by the availability of "follow-up" scans since the rate calculation requires non-progressing patients to have at least 2 follow-up scans after the baseline scan to contribute to disease control rates. If patients that did not have the opportunity to have two scans are excluded, the DCR rate is 54% (129/240) for the sorafenib group and 39% (95/242) for the placebo group.

Study 10874 (supportive)

Study 10874, a single-arm, uncontrolled international Phase II trial, enrolled patients with "advanced", measurable HCC who had not received prior systemic (excluding hormonal) therapy for HCC. Patients with rare subtypes of HCC (fibrolamellar variant, mixed cholangio-hepatocellular carcinoma) were excluded. Prior surgical and loco-regional therapy was permitted. Inclusion criteria permitted enrollment of patients with either Child-Pugh class A or Child-Pugh class B liver function status. The term "advanced" was not defined in the protocol, but was understood to mean those not suitable for potentially curative therapy (i.e., "inoperable"), and was not defined according to criteria for any specific staging system.

Study 10874 enrolled 98 patients with Child-Pugh status A and 38 patients with Child-Pugh status B (One patient had data missing for Child-Pugh scoring). No patients with Child-Pugh C were enrolled in Study 10874.

The primary endpoint was objective tumour response rate. Of 137 treated subjects from investigator assessment, 8 subjects achieved partial response (PR) and 6 achieved minor response (MR); 72 subjects had stable disease and 32 subjects had PD as their best response.

As per investigator assessment, median TTP was 18.4 weeks, and median OS was 39.4 weeks. These results were considered encouraging in comparison to historical data: the median survival of untreated patients with non-resectable HCC is cited in the literature to be less than 6 months.

Outcomes of subjects with Child-Pugh A status at baseline were seemingly better (in terms of tumour response, TTP, and OS) compared to subjects with Child-Pugh B status at baseline.

A secondary objective was to evaluate phosphorylated extracellular-signal-related kinase (pERK) in pre-treatment tumour biopsies and to explore its relationship to measures of clinical benefit.

Thirty-three (24%) treated subjects had both pERK data and clinical anti-tumour activity data. There appeared to be a statistically significant correlation between pERK levels (measured as maximum staining intensity) within the tumour and TTP.

As a result, tumours that contain higher levels of pERK may be more sensitive to the raf kinase inhibitory activity of sorafenib than those tumours that have lower levels of pERK and which may be driven by other signalling pathways.

pERK expression was comparable in subjects with Child-Pugh class A and B across different degrees of staining intensity and a retrospective analysis of the magnitude of change in the size of target lesions by Child-Pugh cirrhotic status, demonstrated similar patterns of tumour response.

Discussion on Clinical efficacy

Study 100554
The use of placebo as comparator was accepted in a CHMP scientific advice procedure in 2004 due to the absence of reference products with at that time documented favourable benefit/risk in the target population for this study. Similarly, the exclusion of patients with liver impairment > Child-Pugh A was accepted due to seemingly less favourable results in Child-Pugh B patients in an exploratory, single arm study.
Note that there are two alternative primary endpoints (i.e. efficacy established if either positive), overall survival and time to symptomatic progression (TTSP). The latter was introduced based on recommendations from FDA. Both measures are in principle acceptable from an EU perspective, but at the time of the CHMP advice, only survival was discussed (and endorsed).
From a statistical perspective, the analysis plan is acceptable, but at least the first interim analysis is conducted on too immature data.

Base line characteristics
White, European males dominated the trial and the proportion of women is smaller than expected. The percentage of patients with hepatitis B/C as the only likely etiological factor was about 45% and data are therefore considered to be reasonably informative for EU, given the variability in chronic hepatitis comparing north and south. Only few individuals with PS status 2 were included, but the percentage of patients above 65 years of age was around 60%.
The BCLC (Barcelona-clinic liver cancer) staging classification (1999) comprises four stages. Early stage (A) includes patients with asymptomatic early tumours suitable for radical therapies with curative intent. Intermediate stage (B) comprises patients with asymptomatic multinodular HCC. Advanced stage (C) includes patients with symptomatic tumours and/or an invasive tumoural pattern (vascular invasion/extrahepatic spread). End-stage disease (D) contains patients with extremely grim prognosis that should merely receive symptomatic treatment. This study enrolled mainly stage C patients (about 80%).
In comparison with the nolatrexed vs. doxorubicin study, it is noticed that in the latter study about 25% of the patients had a Child Pugh score of B and about 14% had a Karnofsky PS of ≤70. A qualified comparison is not considered possible, but it appears as if the overall prognosis is poorer in this study compared with the sorafenib study.

Efficacy results – primary endpoints
A significant difference in the median duration of overall survival has been demonstrated, in favor of the Sorafenib arm (10.6 months for the Sorafenib arm versus 7.9 months for the placebo arm).
This difference is derived from a planned interim analysis, with a reasonable number of events and the analysis is performed on the ITT population. The median duration of survival for patients in the placebo comparator arm is acceptable when compared to the historical series of advanced HCC (5 months).
Therefore, a favourable effect on overall survival has convincingly been demonstrated, even though the number of events after the median appears too low to obtain a precise estimate of the treatment effect in patients with a less unfavourable prognosis. Due to the magnitude of the treatment effect, this constitutes no concern from a regulatory perspective. Nevertheless it is proposed that the applicant should submit the most mature data set possible not being too confounded by cross-over. The MAH has made a commitment in this regard.
The nolatrexed trial was analysed when survival data were mature (about 80% event rate). Median survival in the doxorubicin arm was 32 weeks and the hazard ratio was 0.75, p=0.0068 in favour of doxorubicin.

With respect to exploratory subgroup analyses encompassing a reasonable number of patients, the treatment effect appears stable, possible exceptions being patients with metastatic disease at baseline (HR: 0.90, n=294) and patients below 65 years of age (HR: 0.92, n=232).
With respect to age, no imbalances as regards prognostic factors (see above) were identified comparing patients below and above the age of 65.

Efficacy results - secondary endpoints
No favourable effects were documented in terms of time to symptomatic progression. The MAH's interpretation is that the questionnaire might capture drug related adverse reactions as well as disease related events and that this confounds the assessment. This might be the case and it is not considered meaningful to try to further investigate to what extent other sources of possible bias such as informative censoring (e.g. "objective" tumour progression prior to symptomatic progression) contributed to this lack of demonstrated effects.

With respect to events of progression, the investigator assessment with a cut-off of 17 October is considered mature and the results are reasonably consistent with the independent review results of May 2006 and overall survival results. Results in relation to subgroups in analogy with survival data were not reported.
In the nolatrexed vs. doxorubicin trial, no difference in PFS was observed (HR 0.96) and median PFS was about 11 weeks.

Also in patients with HCC, sorafenib is mainly a cytostatic compound.
It is notable that response rates in the nolatrexed vs. doxorubicin trial (conventionally viewed as "cytotoxic" compounds) also were very low, 1 and 3%, respectively.

Results Supportive trial
Due to the very low objective response rate, it is hard to draw any conclusions as regards covariates of importance for sorafenib activity. TTP (and OS) data may be used in historical comparisons, but without a randomised control, covariates of importance for prognosis cannot be disentangled from those predictive for sorafenib activity.

Clinical safety

Patient exposure

As of May, 2007, over 10,000 patients have been treated with sorafenib (as a single agent and in combination with commonly used chemotherapy agents) in clinical trials.

In Study 100554, 599 patients received at least one dose of study medication, at 400 mg bid. The mean duration of treatment for the placebo group was 22.6 weeks (158 days) and 25.3 weeks (177 days) for the sorafenib patients.

In Study 10874, the median duration of treatment was 21.3 weeks and 30% of HCC patients received more than 24 weeks of study treatment.

This report will focus mainly on the pivotal HCC study 100554.

Number of HCC Patients Exposed Categorized by Dose and Duration in Studies 100554 and 10874

400 bid	Number of Patients 100554 Sorafenib N=297	100554 Placebo N=302	10874 Sorafenib N=137
Mean(weeks) treatment duration	25.3	22.6	19
Range	(0.9-69.9)	(0.3-72.3)	(0.14-138)
Mean average daily dose[a] (mg ± standard deviation)	711±142	775±65	707.9±153
Duration of treatment			
<12 weeks	89 (30%)	104 (34%)	58 (42%)
>12 - ≤24 weeks	66 (22%)	74 (24%)	34 (25%)
>24->48 weeks	105 (35%)	97 (32%)	27 (20%)
>48 weeks	37 (12%)	26 (9%)	14 (10%)
Missing	0 (0.0%)	1 (0.3%)	4 (2.0%)

a Mean average daily dose calculated by averaging the actual daily dose for each patient, then averaging across all patients in each treatment group.

Adverse events

Overview of Adverse Events in Studies 100554 and 10874

	100554[e] Sorafenib (N=297)		100554[e] Placebo N=302		10874[d] Total N=137	
	N	(%)	N	(%)	N	(%)
Any adverse event	290	(97.6)	291	(96.4)	133[c]	(97)
Drug-related adverse event	236	(79.5)	158	(52.3)	116[c]	(85)
Serious adverse event	153	(51.5)	164	(54.3)	77	(56)
Drug-related serious adverse event	40	(13.5)	28	(9.3)	18	(13)
Adverse event leading to permanent discontinuation of study medication	94[a]	(31.6)	107[a]	(35.4)	28	(20)
Deaths within 30 days of receiving study medication[b]	68	(22.9)	97	(32.1)	93	(68)

a Of these patients, 21 in the placebo group and 16 in the sorafenib group were reported to have stopped study treatment because of progressive disease, and 10 sorafenib patients because of death in Study 100554

b 4 patient deaths in the placebo group and 9 patient deaths in the sorafenib group that occurred after the 17 Oct 06 cut-off were not included in this table for Study 100554

c One patient had missing baseline Child-Pugh status.

d As of 31 Dec 2005

e As of 17 Oct 2006

Abbreviations: AE = adverse event or experience; N = number (entire population under study); n = number (sample of population under study) SAE = serious adverse event

Adverse events regarded as treatment related - within brackets events occurring with a higher frequency (+1%) in the sorafenib arm

Adverse Event	Sorafenib %	Placebo %
Any event	80	52
Anaemia	3.4	1.7
GI disorders (diarrhoea, nausea, pain, vomiting)	56	28
General disorders (fatigue, asthenia, pyrexia)	26	18
Weight decreased	9	1
Metabolism and nutrition (anorexia, decreased appetite, dehydration)	16	5
Musculoskeletal (spasm, pain in extremity)	11	5
Nervous system (headache, dysgeusia, dizziness)	14	9
Respiratory (dysphonia, epstaxis, dyspnea, laryngeal pain)	13	4
Skin (PPE, rash, pruritus, alopecia, dry skin, etc.)	46	24
Vascular (hypertension, flushing)	9	3

Serious adverse events and deaths

Deaths
In Study 100554, there were 165 patient deaths within 30 days of receiving study medication, 97 (32%) in the placebo arm and 68 (23%) in the sorafenib-treated arm. The cause of death was reported as HCC progression in 68 placebo patients and 55 sorafenib treated patients.

In the sorafenib patients 13 deaths were **not** attributed to disease progression including: bleeding oesophageal varices (4 patients), haemorrhage into the abdominal cavity (1 patient) and one patient each with liver dysfunction, anorexia, right ventricular failure, visceral arterial ischemia, depression (leading to suicide), renal failure, myocardial infarction and unknown.

Drug-related deaths were reported in 6 (2%) of the placebo patients and 4 (1.3%) of the sorafenib-treated patients and the causes of deaths in the sorafenib-treated group were: bleeding oesophageal varices (1), haemorrhage into abdominal cavity (1), visceral arterial ischemia (1) and renal failure of pre-renal origin (1) following dehydration.

Serious adverse events
In addition to SAE:s mentioned above, more (≥0.5%) cases in the sorafenib arm were reported for myocardial infarction (1.3%, listed), anaemia (2.4%, listed), hepatic failure (3%, not listed, to be discussed later) and anorexia (1%, listed). More cases in the placebo arm were reported for fatigue (2.6%), physical deterioration (1.7%). No additional signals were identified among SAEs reported as related.

Discontinuation/Interruption from Study due to Adverse Events
The rate of discontinuation of study drug due to adverse events was similar in the two treatment arms (35.4% for placebo and 31.6% for sorafenib patients). There were no age or gender-related differences in the rate of premature termination due to adverse events.

Study drug was temporarily interrupted in 101 (33.3%) placebo patients and in 154 (51.5%) sorafenib patients.

The most frequent adverse events resulting in permanent discontinuation of study drug in the sorafenib group were fatigue and liver dysfunction/failure in 14 (4.7%) patients each.

In the placebo group the most frequent causes for permanent discontinuation were hepatobiliary events in 13 (4.3%) and constitutional symptoms in 9 (3.0%) patients.

Hypertension/Cardiovascular Events
First appearance of diastolic blood pressure increases over 100 mm generally occurred within the first 3 cycles for both treatment groups. The majority of the first onset of systolic blood pressure increases over 160 mmHg occurred within the first 3 cycles in both treatment groups.

Summary of incidence of increased blood pressure from baseline

	Placebo (N=302) n (%)	Sorafenib (N=297) n (%)
DBP >= 100mmHg	22 (7.7%)	47 (16.7%)
DBP >= 110 mmHg	4 (1.4%)	15 (5.2%)
SBP >= 160 mmHg	46 (17.2%)	63 (24.4%)
SBP >= 180 mmHg	8 (2.8%)	22 (7.7%)

Abbreviations: DBP – diastolic blood pressure, SBP – systolic blood pressure, mmHg-millimeters of mercury.

Hypertension led to permanent discontinuation of study drug in one sorafenib patient vs. two on placebo.

Six placebo patients reported **CNS ischemic events** (3 Grade 3, 2 Grade 4, and 1 Grade 5). None of the sorafenib patients suffered any CNS ischemic event.

Cardiac ischemia/infarction was reported as an adverse event in 4 patients in the placebo group and 8 patients in the sorafenib group. All of these events were reported as serious adverse events; most were Grade 3 or 4 events: 3 placebo patients and 6 in the sorafenib group. Of the events occurring in the sorafenib group, one Grade 3 event and one Grade 4 event were assessed as drug-related. In 3 sorafenib patients, myocardial ischemic events were the reason for permanent discontinuation of study treatment. (Myocardial ischemia and infarction are listed.)

Hepatobiliary Events
Overall 34 liver dysfunction/failure adverse events were reported in sorafenib patients, thereof 21 as serious adverse events and 1 was assessed as related to study drug.

None of the 23 liver dysfunction/failure adverse events, of which 14 were reported as serious adverse events, in the placebo group were deemed drug-related. The incidence of Grade 3 or 4 liver dysfunction adverse events was similar between groups, reported in 9 placebo patients and 10 sorafenib patients.

Liver dysfunction led to permanent discontinuation of treatment in 14 sorafenib patients and 5 placebo patients, and to dose reductions in 3 (1.0%) sorafenib patients and 1 (0.3%) placebo patient.

Laboratory Abnormalities Reported as Adverse Events

NCI CTCAE term	Sorafenib (N=287) n(%)	Placebo (N=302) n(%)
Bilirubin	25 (8.8%)	26 (8.6%)
AST	9 (3.0%)	20 (6.6%)
ALT	3 (1.0%)	13 (4.3%)
Alkaline Phosphatase	4 (1.3%)	11 (3.6%)
Hypoalbuminemia	5 (1.7%)	9 (3.0%)
Lipase	6 (2.0%)	7 (2.3%)
Elevated amylase	1 (0.3%)	2 (0.7%)

Abbreviations: ALT – alanine aminotransferase, AST – aspartate aminotransferase

Hypophosphatemia (listed) was observed with increased frequency in patients treated with sorafenib: overall 96 (34.9%) sorafenib-treated patients as compared with 30 (11.2%) placebo patients. Grade 2 occurred in 67 sorafenib patients compared to 23 placebo patients and Grade 3 occurred in 29 sorafenib patients compared to 6 placebo patients. There were no occurrences of Grade 4 events.

Study 10874

In Study 10874, almost all treated patients (97%) had one or more adverse events during the study and 85% had drug-related adverse events. At least one serious adverse event was recorded in 77 (56%) patients and 18 (13%) had drug-related serious adverse events. Twenty-eight patients (20%) discontinued study treatment due to adverse events. These results were consistent with those seen in Study 100554.

In Study 10874, there were 93 (68%) deaths within 30 days of receiving study medication. Most patients died as a result of progressive disease; no death was reported by the investigator as related to study drug.

Adverse Effects by Population Subgroups

Women had a reported higher incidence of pain (28.2% versus 8.5%), alopecia (38.5% vs. 10.5%) and hand-foot skin reaction (33.3% vs. 19.4%).
The baseline AST and ALT were used to assess for hepatic impairment. Patients with a baseline AST and ALT of <1.8X the upper limit of normal (ULN) were considered to have normal hepatic function. Those with an AST or ALT greater than 3X ULN were considered to have moderate hepatic impairment. For the selected adverse events, no major differences between hepatic impairment groups were noted for diarrhea, anorexia, hand-foot skin reaction, alopecia or abdominal pain (NOS)
In Study 100554, a higher percentage of Child-Pugh A patients compared to the Child-Pugh B patients had diarrhea (56% vs. 42.9%, respectively), anorexia (29.1% vs. 21.4%, respectively) and hand-foot skin reaction (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. 9.2%, respectively).

Pharmacovigilance

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

Risk Management Plan

The MAH submitted a risk management plan, which included a risk minimisation plan.

Summary of Activities for each safety concern for Nexavar (sorafenib) (version number 6.0)

NEXAVAR: SUMMARY OF THE EU RISK MANAGEMENT PLAN

Safety concern	Proposed pharmacovigilance activities	Proposed risk minimisation activities
----------	**Important Identified Risks**	----------
Dermatological toxicities	Routine pharmacovigilance activities Additional pharmacovigilance activities: • In cases of Steven-Johnson or Lyell syndrome, a questionnaire to direct data collection on SAE's reported will be used to ensure adequate documentation.	• Warning in section 4.4 of the SPC that dermatological side effects occur generally during the first 6 months of treatment with Nexavar. • Listed as ADRs in Section 4.8 of the SPC. • Provision of information on symptom management to prescribers.
Hypertension and RPLS	Routine Pharmacovigilance activities • including additional clinical AE and laboratory data	• Warning in section 4.4 of the SPC advising regular monitoring of blood pressure. Therapy should be terminated in cases of persistent

Safety concern	Proposed pharmacovigilance activities	Proposed risk minimisation activities
	Additional pharmacovigilance activities: • A questionnaire to direct data collection on SAE's reported as hypertensive crisis or RPLS.	hypertension, or hypertensive crisis. • Listed as ADRs in section 4.8 of the SPC.
Hemorrhage	Routine Pharmacovigilance activities • including additional clinical AE data collection. Additional pharmacovigilance activities • Use of SAE follow up questionnaires to optimize data collection. • In the Phase 3 NSCLC trials, case record forms collect histological subtype of the tumor (squamous- vs. adeno-carcinomas).	• Warning in section 4.4 of the SPC on an increased risk of bleeding. Permanent termination should be considered if remedial medical intervention is required. • Listed as ADR in section 4.8 of the SPC. • Development Core Safety Information: Observation of a higher bleeding rate from cerebral metastases in malignant melanoma.
Arterial thrombosis (Myocardial Infarction)	Routine Pharmacovigilance activities • including additional clinical AE data collection through patients in Bayer sponsored clinical studies. Additional pharmacovigilance activities • Specific SAE follow up questionnaires for myocardial infarction events.	• Warning in section 4.4 of the SPC that the incidence of cardiac ischemic events was higher for the Sorafenib groups versus placebo in 2 double blind studies. • Temporary or permanent discontinuation when cardiac ischemia and/or infarction. • Cardiac ischemia and/or infarction are listed as ADR in section 4.8 of the SPC.
Increases in lipase, amylase and symptomatic pancreatitis (Symptomatic pancreatitis is an Important Potential Risk, but is covered in this section for ease of review).	Routine Pharmacovigilance activities • including additional clinical AE and laboratory data collection. Additional pharmacovigilance activities • Key Bayer sponsored clinical studies will continue to collect lipase and amylase data. • SAE questionnaires to collect data for SAE reports of significant lipase and amylase increases and clinical pancreatitis.	• Listed as ADRs in section 4.8 of the SPC and data described in section 4.8 on laboratory test abnormalities.
Hypophosphatemia	Routine Pharmacovigilance activities Additional pharmacovigilance activities • Study 12345 – a Phase 1 study: Mechanistic evaluations on sorafenib induced hypophosphatemia in patients.	• Listed as ADR in section 4.8 of the SPC.
----------	**Important Potential Risks**	----------
Symptomatic pancreatitis	(see Increases in lipase, amylase and symptomatic pancreatitis above)	
Arterial thrombosis (Cerebral ischemia)	Routine Pharmacovigilance activities • including additional clinical AE data collection Additional pharmacovigilance activities • Specific SAE follow up questionnaires on cerebrovascular ischemic events.	No activities.
Squamous cell cancer of the skin (SCC) and keratoananthoma	Routine Pharmacovigilance activities Additional pharmacovigilance activities • SAE questionnaires will be used to	• Keratoacanthoma/ squamous cell carcinoma of the skin added as an ADRs in section 4.8 of the SPC.

Safety concern	Proposed pharmacovigilance activities	Proposed risk minimisation activities
(KA)	collect data for SAE reports of KA and SCC, including central histological analysis.	
Congestive heart failure	Routine Pharmacovigilance activities Additional pharmacovigilance activity • Clinical studies containing serial MUGA scans (Studies 100565, 12345 and E2805).	• Congestive heart failure listed as ADR in section 4.8 of the SPC.
Wound healing complications **GI perforation**	Routine Pharmacovigilance activities Additional pharmacovigilance activity • Additional clinical AE data collection in cases of unplanned surgery. • SAE reports of surgical interventions for impaired wound healing. • When company sponsored adjuvant or neo adjuvant clinical trials are planned, appropriate data collection for any effects on wound healing	• Warning and Precautions Section 4.4 of the SPC states that limited clinical experience is available in cases of major surgical intervention. • Temporary interruption of Nexavar therapy if major surgical procedures. • Gastrointestinal perforation is listed as an ADR in section 4.8 of the SPC.
Pregnancy and lactation	Additional pharmacovigilance activity • All reports of pregnancy or congenital anomalies occurring on Sorafenib will be recorded and followed-up carefully.	• Warnings and Precautions Section 4.6 of the SPC: Contraindicated in case of breast feeding. Women must use effective contraception during treatment. • Bayer sponsored study protocols clearly state the requirement for pregnancy testing and adequate contraception during study.
----------	**Important missing information**	----------
Safety in children	• The safety and effectiveness of Sorafenib in pediatric patients have not yet been studied. A paediatric phase I study run by the CTEP Children's Oncology Group (Protocol ADVL-0413 – A) is ongoing	• Section 4.2 of the SPC states that sorafenib is not recommended for use in children and adolescents.

The CHMP, having considered the data submitted in the application, is of the opinion that no additional risk minimisation activities are required beyond those included in the product information.

Discussion on Clinical safety

In general, the findings in the pivotal HCC study reflect the findings in the renal cell cancer (RCC) study submitted as part of the initial Marketing Authorisation Application, but clearly more events of weight decrease were reported in the current submission. To what extent weight decrease reflects loss in lean body mass or effects on oedema, ascites, etc is unclear. The lower incidence of rash, etc might reflect the fact the fewer women were included in the HCC study.
In the safety summary, events were also reported in relation to duration of therapy, essentially confirming what would be expected, and eg that weight loss and alopecia tend to be more common in patient treated for long.

As regards hand-foot skin reactions it is noticed that 0/33 treated for 6 weeks or less reported this reaction and 8/56 of those treated 6 – 12 weeks while those treated for a longer period of time reported this reaction about twice as frequently per treatment cycle (6 w). This probably partly reflects delayed

onset but also that skin reactions is a weak marker of better prognosis. This interpretation is supported by data compatible with a modest increase (+4%) from cycle 1 to 2 in all patients treated and an event rate of 14% in cycle 1 (40/297, compared with 0/33 for those treated only for 6 weeks).
In this context it is noticed that skin reactions were reported in 28% (24/123) of patients below 65 years of age as opposed to 17% (29/174) of the elderly patients. The survival HR, however, was clearly more favourable in elderly patients, illustrating the complexity of the "skin – tumour relationship".

The opposite was the case for hypertension with more events (also taking placebo into account) reported among elderly patients, i.e. "confirming" the findings in the RCC study compatible with hypertension being a weak prognostic factor.

Diarrhoea was reported as a serious AE in 5% of sorafenib treated patients vs. 2% in the placebo group and dehydration in 3% vs. 0.3%, while the opposite was the case for "renal failure" 0 vs. 2% (with ref. to dehydration and renal failure, see above).
GI haemorrhages were more commonly reported in the placebo group (7 vs. 4%).

There is a signal as regards hepatobiliary events, however, not born out in terms of laboratory events. "Increase in bilirubin and jaundice" is listed.

Pharmacovigilance

A risk management plan was submitted. The CHMP, having considered the data submitted, was of the opinion that:

- routine pharmacovigilance was adequate to monitor the safety of the product.
- no additional risk minimisation activities were required beyond those included in the product information.

Benefit-risk assessment

In Europe hepatocellular cancer (HCC) is an uncommon disorder, but the incidence is expected to increase, mainly due to an increased number of individuals with chronic hepatitis C. Nexavar (sorafenib) was granted orphan drug designation in the EU for the treatment of HCC on 12 April 2006.

Potentially curative therapies include resection, percutaneous ablation and transplantation, but most patients are diagnosed at a stage when these interventions are no longer an option. In patients with advanced disease, doxorubicin has been used for long in clinical practice, but until recently no survival benefit has been associated with doxorubicin-based therapies.

In a doxorubicin comparative study designed to demonstrate the superiority of the experimental agent nolatrexed, however, doxorubicin therapy was shown to provide a survival benefit. Theoretically, this could be due to nolatrexed being worse than placebo, especially as no difference in PFS was demonstrated. Nolatrexed, however, belongs to a well known class of cytotoxic compounds (thymidylate synthase inhibitor) and the adverse event profile appears as expected and seemingly not worse than doxorubicin 60 mg/m^2 every three weeks. Thus the most likely explanation to the observed difference is that doxorubicin therapy also provides a survival benefit to patients with advanced HCC. Between studies comparisons should be undertaken with care, but the apparently shorter survival in the doxorubicin vs. nolatrexed study compared with the sorafenib study probably reflects differences in baseline characteristics.

Sorafenib shows high inter- and intra-patient pharmacokinetic variability in exposure with coefficients of variation around 65% and 45%, respectively. No dose adjustment is warranted in patients with moderate liver impairment (Child Pugh B) but there are no data in patients with more severe

impairment. An attempt to further characterise the pharmacokinetics of sorafenib was made in a population PK analysis, however, the results are considered non-informative.

Prior studies in patients with renal cell carcinoma have indicated that increased plasma VEGF levels are predictive of better response to treatment with sorafenib. In a single arm study in patients with HCC, increased tumour pERK expression was shown to predict a favourable course of the disease, but no biomarker data are yet available from the confirmatory study supporting this application. The MAH has made a commitment in this regard and will provide the data in accordance with agreed timelines.

Similarly a rather weak relationship has been demonstrated between anti-tumour activity and on-therapy skin reactions and hypertension in patients with RCC.

Unfortunately variability in absorption may be the most important factor explaining observed inter- and intra-individual variability in exposure. The MAH has made a commitment to further explore in population PK analyses whether variability in exposure can be explained by definable patient factors as well as the possible relationship between exposure and adverse events (skin reactions, hypertension), reduction in tumour size as a continuous variable and TTP. The prognostic and predictive value of biomarkers at baseline and, when appropriate, on therapy will also be analysed and submitted.

Benefit: A clinically meaningful survival benefit (median +3 months, HR 0.70) has been convincingly demonstrated (1-sided p-value 0.0006, interim analysis 2, pre-specified 1-sided alpha 0.0077). Survival data are consistent with time to tumour progression data, HR about 0.6. The objective tumour response rate is low, about 2%. Favourable effects on HCC-related symptoms have not been demonstrated.

Uncertainties: There is an unexplained, apparently reduced activity in patients below 65 years of age (HR 0.92, 95% CI 0.65; 1.32). Similarly the activity appears low in patients with metastatic disease (HR 0.90, 95% CI 0.66; 1.21). This has been reflected in section 5.1 of the SPC.

Only few patients with liver impairment Child Pugh class B were enrolled (n=20), but there appears to be a meaningful treatment effect, again reflected in section 5.1 of the SPC.

The number of events after the median is rather small in the submitted survival analysis. Therefore the efficacy is hard to estimate in patients with less unfavourable prognosis, but survival curves as such constitute no concern.

The MAH has made a commitment to provide updated survival data analysed at a point in time not too confounded by cross-over. The apparently reduced activity in patients with metastatic disease and in patients below 65 years of age will be further investigated taking into account biomarker data and TTP data.

Risk: Sorafenib has a reasonably well-characterized tolerability and toxicity profile dominated by diarrhoea, skin reactions and hypertension. Potentially life-threatening adverse reactions have been identified including myocardial infarction and posterior leukoencephalopathy, but the incidence is considered within acceptable limits from an oncology perspective.

Uncertainties: The number of patients with Child Pugh B status treated with sorafenib is only 14. Safety data as such constitute no concern, but the experience is limited. Only one individual with C status was treated.

There is a signal compatible with an increased incidence of liver failure in patients treated with sorafenib. “Increase in bilirubin and jaundice” is listed, but the MAH has nevertheless made a commitment to review study data from all randomised studies in order to address this issue.

Balance: The benefit/risk balance is undoubtedly favourable and there are no outstanding issues which must be resolved prior to licensure of this new indication. The CHMP therefore considered that

outstanding issues should be handled as follow-up measures, not least as biomarker data might be informative and are currently non-available.

The CHMP agreed on the following wording of the indication in section 4.1 of the SPC:

"Hepatocellular carcinoma
Nexavar is indicated for the treatment of hepatocellular carcinoma (see section 5.1)."

IV. CONCLUSION

- On 20 September 2007 the CHMP considered this Type II variation to be acceptable and agreed on the amendments to be introduced in the Summary of Product Characteristics and Package Leaflet.