CENTER FOR DRUG EVALUATION AND RESEARCH

APPROVAL PACKAGE FOR:

APPLICATION NUMBER

NDA 21-923

Clinical Pharmacology and Biopharmaceutics Review

Clinical Pharmacology and Biopharmaceutics NDA Review

Brand name: NEXAVAR®

Generic name: Sorafenib tosylate

Type of dosage form and strength(s): 200 mg film-coated tablets

Indication(s): The Applicant's proposed indication is "for the treatment of patients with advanced renal cell carcinoma."

NDA number, type: 21-923, 1P

Applicant name: Bayer Pharmaceuticals Corporation

Submission date (letter date):	8-NOV-2005	N	000	BB
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	13-OCT-2005	N	000	BB
	8-AUG-2005	N	000	BZ
	6-JUL-2005	N	000	

OCPB Division name: Division of Pharmaceutical Evaluation I

OND: **Division name**: Division of Oncologic Drug Products

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1. Executive Summary

Five Phase 4 commitments for clinical pharmacology and biopharmaceutics are recommended.

1.1. Recommendations

This NDA is acceptable from the clinical pharmacology and biopharmaceutics perspective, if the dissolution specification is changed. The acceptable dissolution specification is

USP Apparatus 2	Paddle Method
Rotation speed:	75 rpm
Volume:	900 mL
Medium:	0.1M HCl + 1% sodium lauryl sulfate (SLS)
Tolerance:	Q = [ ] n 15 minutes
Analytical Procedure(s):	[ ] at [ ] or [ ]

1.2. Identify recommended Phase 4 study commitments if the NDA is judged approvable

We recommend that the Applicant agree to:

1. Explore alternative dosing regimens in Asian patients, with the goal of arriving at a regimen that will produce the concentration time profile seen in non-Asians. First, modeling and simulation should be to identify an alternative dosage regimen that is predicted to result in Asian patients having a similar exposure as non-Asians. This regimen should then be administered to Asian patients in a multiple-dose pharmacokinetic study to determine if it performs as predicted.

2. Complete the ongoing study of the effect of sorafenib on paclitaxel (a CYP 2C8 substrate) pharmacokinetics: Study 100375.

3. Complete the ongoing investigation of the ability of biomarkers to identify patients who respond to sorafenib.

4. Complete the ongoing study examining the ability of rifampin to alter the pharmacokinetics of sorafenib.

5. Complete the ongoing study examining the pharmacokinetics of sorafenib in patients with renal impairment.

1.3 Summary of Clinical Pharmacology and Biopharmaceutics Findings (1-3 pages)

Sorafenib is a multikinase inhibitor that decreases tumor cell proliferation *in vitro*, inhibits tumor growth of the murine renal cell carcinoma, and inhibits tumor xenografts in athymic mice accompanied by a reduction of tumor angiogenesis. Sorafenib inhibits the activity of targets present in the tumor cell (CRAF, BRAF, V600E BRAF, KIT, and FLT-3) and in the tumor vasculature (CRAF, VEGFR-2, VEGFR-3, and PDGFR-ß).

After administration of NEXAVAR tablets, the mean elimination half-life of sorafenib is approximately 25 - 48 hours. The clinical regimen (400 mg bid) results in a 2.5- to 7-fold accumulation compared to single dose administration and a peak to trough ratio of mean concentrations of less than 2. Following oral administration, sorafenib reaches peak plasma levels in approximately 3 hours. When given with a moderate-fat meal, bioavailability was similar to that in the fasted state. With a high-fat meal, sorafenib bioavailability was reduced by 29% compared to administration in the fasted state. Mean C_{max} and AUC increased less than proportionally beyond doses of 400 mg administered orally twice daily. *In vitro* binding of sorafenib to human plasma proteins is 99.5%.

Sorafenib is metabolized primarily in the liver undergoing oxidative metabolism, mediated by CYP3A4, as well as glucuronidation mediated by UGT1A9. Sorafenib accounts for approximately 70-85% of the circulating analytes in plasma at steady state. Eight metabolites of sorafenib have been identified, of which five have been detected in plasma. The main circulating metabolite of sorafenib in plasma, the pyridine N-oxide, shows *in vitro* potency similar to that of sorafenib. This metabolite comprises approximately 9-16% of circulating analytes at steady state. Following oral administration of a 100 mg dose of a solution formulation of sorafenib, 96% of the dose was recovered within 14 days, with 77% of the dose excreted in feces, and 19% of the dose excreted in urine as glucuronidated metabolites. Unchanged sorafenib, accounting for 51% of the dose, was found in feces but not in urine.

Analyses of demographic data suggest that no dose adjustments are necessary for age or gender. There are no pharmacokinetic data in pediatric patients. In patients with mild (Child-Pugh A, n = 14) or moderate (Child-Pugh B, n = 8) hepatic impairment, exposure values were within the range observed in patients without hepatic impairment. The pharmacokinetics of sorafenib have not been studied in patients with severe (Child-Pugh C) hepatic impairment. In a study of drug disposition after a single oral dose of radiolabeled sorafenib to healthy subjects, 19% of the administered dose of sorafenib was excreted in urine. In four Phase 1 clinical trials, sorafenib was evaluated in patients with normal renal function and in patients with mild renal impairment (CrCl > 50 – 80 mL/min, n = 24) or moderate renal impairment (CrCl 30 – 50 mL/min, n = 4). No relationship was observed between steady state sorafenib AUC and renal function at doses of 400 mg twice daily. The pharmacokinetics of sorafenib have not been studied in patients with severe renal impairment (CrCl < 30 ml/min) or patients undergoing dialysis

Ketoconazole (400 mg), a potent inhibitor of CYP3A4, administered once daily for 7 days did not alter the mean AUC of a single oral 50 mg dose of sorafenib in healthy volunteers. Studies with human liver microsomes demonstrated that sorafenib is a competitive inhibitor of CYP2C19, CYP2D6, and CYP3A4. Administration of NEXAVAR 400 mg twice daily for 28 days did not alter the exposure of concomitantly administered midazolam (CYP3A4 substrate), dextromethorphan (CYP2D6 substrate), or omeprazole (CYP2C19 substrate). Studies with human liver microsomes demonstrated that sorafenib is a competitive inhibitor of CYP2C9. The possible effect of sorafenib on a CYP2C9 substrate was assessed indirectly in patients receiving warfarin. The mean changes from baseline in PT-INR were not higher in NEXAVAR patients compared to placebo patients. There is no clinical information on the effect of CYP3A4 inducers on the pharmacokinetics of sorafenib. Substances that are inducers of CYP3A4 activity are expected to increase metabolism of sorafenib and thus decrease sorafenib concentrations. A clinical study of the effect of rifampin on the pharmacokinetics of sorafenib is planned. In Phase 1 clinical studies, NEXAVAR has been administered with the anti-neoplastic agents gemcitabine, oxaliplatin, doxorubicin, and irinotecan. Concomitant treatment with NEXAVAR resulted in a 21% increase in the AUC of doxorubicin. When administered with irinotecan, whose active metabolite SN-38 is further metabolized by the UGT1A1 pathway, there was a 67 - 120% increase in the AUC of SN-38 and a 26 - 42% increase in the AUC of irinotecan. The clinical significance of these findings is unknown. Sorafenib inhibits CYP2B6 and CYP2C8 *in vitro*. Although not studied clinically, systemic exposure to substrates of CYP2B6 and CYP2C8 is expected to increase when co-administered with NEXAVAR. Similarly, sorafenib inhibits glucuronidation by the UGT1A1 and UGT1A9 pathways and, although not studied clinically, systemic exposure to substrates of UGT1A1 and UGT1A9 may increase when co-administered with NEXAVAR. CYP1A2 and CYP3A4 activities were not altered after treatment of cultured human hepatocytes with sorafenib, indicating that sorafenib is unlikely to be an inducer of CYP1A2 and CYP3A4 *in vivo*.

A dissolution study was performed comparing dissolution profiles of tablets manufactured with the commercial formulation to the tablet formulation used in the clinical studies. The results indicated that the tablets have comparable dissolution.

The sponsor's proposed dissolution method is not acceptable. This product with poor aqueous solubility dissolves rapidly and completely within 15 minutes using the proposed dissolution method. We recommend the following interim dissolution method and specification:

USP Apparatus 2	Paddle Method
Rotation speed:	75 rpm
Volume:	900 mL
Medium:	0.1M HCl + 1% sodium lauryl sulfate (SLS)
Tolerance:	Q = [ ] in 15 minutes
Analytical Procedure(s):	[ ]

2. *Question-Based Review*

2.1. General attributes of the drug

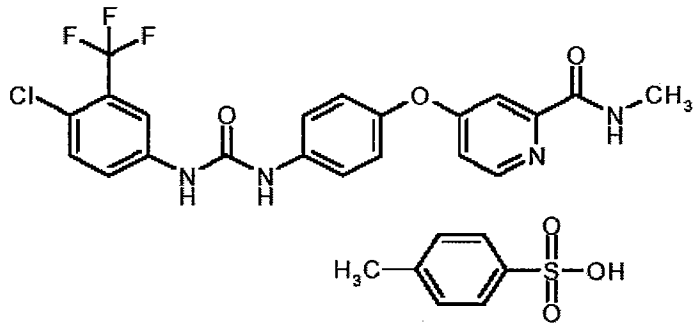
What pertinent regulatory background or history contributes to the current assessment of the clinical pharmacology and biopharmaceutics of this drug?

NEXAVAR® for the treatment of patients with advanced renal cell carcinoma (the current indication) has been granted Orphan Drug status.

2.1.1. What are the highlights of the chemistry and physical-chemical properties of the drug substance and the formulation of the drug product as they relate to clinical pharmacology and biopharmaceutics review?

The active ingredient in the drug product is sorafenib tosylate (274 mg), equivalent to 200 mg of sorafenib. Sorafenib tosylate has the chemical name 4-(4-{3-[4-Chloro-3-(trifluoromethyl) phenyl] ureido} phenoxy)-*N*2-methylpyridine-2-carboxamide 4-methylbenzenesulfonate. A structural representation is shown below as **FDA Figure 1.**

FDA Figure 1. Sorafenib – proposed package insert for NEXAVAR



Sorafenib tosylate has a molecular formula of $C_{21}H_{16}ClF_3N_4O_3$ x $C_7H_8O_3S$ and a molecular weight of 637.0 g/mole.

The inactive ingredients in the tablet core are croscarmellose sodium, microcrystalline cellulose, hypromellose, sodium lauryl sulfate and magnesium stearate. The tablet coating contains hypromellose, polyethylene glycol, titanium dioxide and ferric oxide red.

2.1.2. What are the proposed mechanism(s) of action and therapeutic indication(s)?

The following (indent, font change) are reproduced from the proposed package insert.

Mechanism of Action

Sorafenib is a multikinase inhibitor that decreases tumor cell proliferation *in vitro*.

[

]

INDICATIONS AND USAGE
NEXAVAR is indicated for the treatment of patients with advanced renal cell carcinoma.

2.1.3. What are the proposed dosage(s) and route(s) of administration?

The following (indent, font change) is reproduced from the proposed package insert.

The recommended daily dose of NEXAVAR is 400 mg (2 x 200 mg tablets) taken twice a day, [ ]. Treatment should continue until the patient is no longer clinically benefiting from therapy or until unacceptable toxicity occurs.

Management of suspected adverse drug reactions may require temporary interruption and/or dose reduction of NEXAVAR therapy. [

]

No dosage adjustment is required on the basis of patient age, gender, or body weight, or in patients with Child-Pugh A and B hepatic impairment. NEXAVAR has not been studied in patients with Child-Pugh C hepatic impairment or severe renal impairment [

]

2.2. General clinical pharmacology

2.2.1 What are the design features of the clinical pharmacology and clinical studies used to support dosing or claims?

The clinical efficacy of sorafenib in renal cell carcinoma (RCC) patients has been demonstrated in a single placebo-controlled trial (Study 11213). The results of Study 11213 are supported by a randomized discontinuation trial (Study 100391).

Study 11213 is a multi-center, randomized, double blind, placebo-controlled trial in patients with advanced renal cell carcinoma who have received prior systemic therapy. A single starting sorafenib dose was investigated: 400 mg (2x200 mg tablets) twice daily (bid). Doses were delayed or reduced for clinically significant hematologic or other toxicities that were possibly, probably, or definitely related to protocol therapy, as defined by the principal investigator. If a subject experienced several toxicities and there were conflicting recommendations, a dose modification recommendation that resulted in the lowest level was used. Dose modifications were to follow predefined dose levels:

Dose Level 1 (starting dose): 400 mg (2 · 200 mg tablets) bid
Dose Level 2: 400 mg (2 · 200 mg tablets) once daily
Dose Level 3: 400 mg (2 · 200 mg tablets) every other day (per Amendment 2)
If further dose reduction was required, the subject was discontinued from the study medication. At the discretion of the investigator, a reduced dose could be re-escalated to the previous dose level once all toxicity had resolved to National Cancer Institute's [NCI] Common Terminology Criteria for Adverse Events [CTCAE], Version 3.0, Grade ≤ 1.

The endpoints include overall survival, progression free survival (PFS) and tumor response rate. The primary analysis was intended to be overall survival, but the trial included an interim analysis of progression free survival. The results of the planned interim analysis were positive, resulting in the submission of this NDA prior to completion of the study. The results are summarized below as **FDA Table 1.**

FDA Table 1. Applicant's Table 2-5 from Page 24 of Section 2.7.3 Summary of Clinical Efficacy

Table 2-5: Progression-free Survival Based on Independent Radiological Review in Study 11213
(Population: Patients Valid for Intent to Treat)

	Sorafenib (N = 384)	Placebo (N = 385)
Total failed	147 (38.3%)	195 (50.6%)
Total censored	237 (61.7%)	190 (49.4%)
Median PFS (days)	167	84
95% confidence interval for median	(139, 174)	(78, 91)
Hazard ratio (Sorafenib/Placebo)	0.44 [p<0.000001]	
95% confidence interval for hazard ratio	(0.35, 0.55)	

PFS = progression-free survival; N = total number of patients in the group.
Source: Table 14.2/1 in Study 11213 MRR located in Module 5.3.5.1.1.

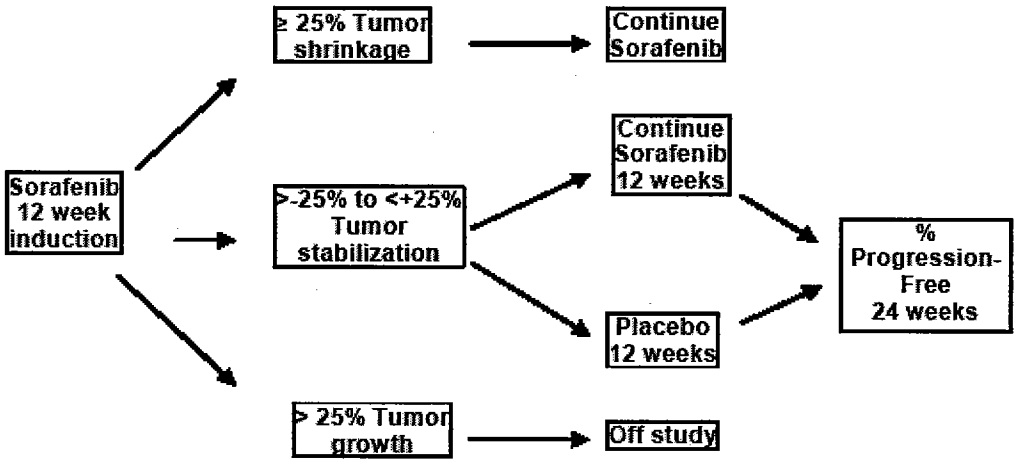
Study 100391 was a placebo-controlled, randomized discontinuation Phase II study in patients with advanced, refractory solid tumors. A single starting sorafenib dose was investigated: 400 mg (2x200 mg tablets) twice daily (bid). Doses were to be delayed or reduced for clinically significant hematological and other toxicities that were related to protocol therapy. Toxicities were graded using National Cancer Institute-Common Toxicity Criteria (NCI-CTC) Version 2.0. If a subject experienced several toxicities and there were conflicting recommendations, the recommended dose adjustment that reduced the dose to the lowest level was used. All dose modifications followed predefined dose levels:
Dose level 1: 400 mg PO bid
Dose level 2: 200 mg PO bid
Dose level 3: 200 mg PO once per day (QD)
If further dose reduction was required, the subject was withdrawn from the study. The dose of sorafenib could be increased following the same dosing regimen to obtain

optimal therapeutic levels if the toxicity that resulted in dose reduction had since resolved either spontaneously or with treatment.

FDA Figure 2. is an outline of the trial schema.

FDA Figure 2. Applicant's Figure 2-7 from Page 44 of Section 2.7.3 Summary of Clinical Efficacy

Figure 2-7: Schematic Drawing of the Sorafenib Randomized Discontinuation Design in Study 100391



A final efficacy analysis of Study 100391 was conducted when all patients had had the opportunity to reach the 12-week post-randomization timepoint. The primary endpoint was the progression-free rate at that time. The results are summarized below as **FDA Table 2.**

FDA Table 2. Applicant's Figure 2-7 from Page 53 of Section 2.7.3 Summary of Clinical Efficacy

Table 2-16: Summary of Progression Free Rate at 12 Weeks After Randomization for RCC Patients in Study 100391 (Population: Randomized RCC Patients)

	Sorafenib N=32	Placebo N=33
n	16	6
Rate (%)	50.0	18.2
95% CI	(31.9, 68.1)	(7.0, 35.5)
p-value	0.0077	

CI = confidence interval; n = number of patients who were progression-free; N = total number of patients.
Source: Table 14.2/28 in Study 100391 MRR Part B located in Module 5.3.5.2.1.

The sorafenib dose for Phase II – III clinical development was selected empirically from Phase I data.

Phase I data identified 400 mg bid as a well-tolerated dose. Doses of 600 mg bid caused a significant increase in Grade 3 and 4 toxicities, including significant GI and skin toxicities. Consistent with this, there was a significant increase in the number of patients requiring discontinuation of treatment due to toxicities at the 600 mg bid and 800 mg bid dose compared to the 400 mg bid dose. The incidence of serious adverse events and dose modifications/dose delays were also lower at the 400 mg bid dose as compared to 600 mg bid or 800 mg bid dose. Evaluation of safety data across various schedules did not show significant differences in toxicities between continuous and intermittent schedules.

Limited Phase I anti-tumor activity data indicated that the 400 mg bid (1 partial response and 1 minor response) and the 600 mg bid (1 partial response and 1 minor response) showed anti-tumor activity. Anti-tumor activity was not observed at the 100 mg bid and the 200 mg bid dose level.

Pharmacokinetic data indicated that for the same total daily dose, twice daily dosing gave a much higher exposure than a single daily dose. There was more or less a dose proportional increase in exposure with an increasing dose of sorafenib up to the 400 mg bid dose. However there was only a 13% increase in exposure going from 400 mg bid to the 600 mg bid dose and there was no further increase in sorafenib AUC when the dose was increased from 600 mg bid to 800 mg bid.

In summary, in limited Phase I investigation, the dose of 400 mg bid was found to be the maximum well-tolerated dose (for daily chronic dosing) which showed anti-tumor activity. Increasing the dose from 400 mg bid to 600 mg bid did not appear to substantially increase sorafenib's systemic exposure while significantly increasing clinical toxicities.

2.2.2 What is the basis for selecting the response endpoints (i.e., clinical or surrogate endpoints) or biomarkers (collectively called pharmacodynamics (PD)) and how are they measured in clinical pharmacology and clinical studies?

Biomarker data on RCC patients are currently not available. While Study 11213 included collection of data on tumor phosphorylated extracellular signal related kinase (p-ERK), serum human epidermal growth factor receptor type 2 (HER-2), urine vascular-endothelial growth factor receptor (VEGF), plasma proteomics, urine metabolites (by nuclear magnetic resonance), and gene expression profiling of blood cells and tumor biopsies, these data are not reported in the NDA. We are recommending that completion and reporting of these analyses be a Phase 4 commitment, should sorafenib be approved.

Biomarker data from hepatocellular carcinoma is available. The relevance of biomarker data from hepatocellular carcinoma (HCC) patients to renal cell carcinoma is not known.

Selected biomarkers exploring the mechanistic activity of sorafenib and their relationship with measures of anti-tumor activity have been obtained in a Phase II study in hepatoma patients. Baseline pERK levels were measured in the original tumor diagnostic biopsy using semi-quantitative immunohistochemistry. Baseline blood cell RNA expression patterns were measured using [ ] Correlation of data from tumor pERK measurements and the blood cell RNA expression measurement with anti-tumor activity data, have shown (Applicant's analysis) the potential to distinguish hepatocellular carcinoma patients who have progressive disease following sorafenib treatment, from those patients having stable disease, minor response or partial response with sorafenib treatment. However, this study was conducted without a placebo-controlled arm. The Applicant concludes that additional controlled clinical evaluations may help to better define the prognostic/predictive utility of these biomarkers.

2.2.3 Are the active moieties in the plasma (or other biological fluid) appropriately identified and measured to assess pharmacokinetic parameters and exposure response relationships?

The performance of the bioanalytical methods will be reviewed in Section 2.6.

With the exception of the mass balance study reported below, and a study conducted in Japanese patients, only sorafenib (parent) was measured in pharmacokinetics studies.

In a mass balance study using a 100 mg ^{14}C dose, approximately 89% of the dose was recovered as identified entities in excreta; 57% of this (51% of the dose) was recovered as parent in feces (**FDA Table 3.**).

FDA Table 3. Recovery of Dose in Excreta	
	% Dose Recovered
Feces	
Sorafenib	50.7
M3	0.4
M4	1.2
M6	19.1
Total	71.4
Urine	
M7 (Sorafenib glucuronide)	14.8
M8 (M2 glucuronide)	2.7
Total	17.5
TOTAL (Feces + Urine)	
	88.9

Metabolite M6 is a carboxylic acid derivative. Metabolite M7 is the glucuronide of the parent compound and metabolite M8 is the glucuronide of metabolite M2 (BAY 67-3472).

Of the five metabolites identified in human excreta, only M4 has been synthesized and characterized pharmacologically. In nine non-clinical assays, the *in vitro* and cellular

activities of M-4 ranged from 0.4 – 2.7 X those of sorafenib. Using the extreme value of 2.7, together with 1.2% of dose recovered as M-4 and 50.7% of dose recovered as sorafenib, M-4 would account for a maximum of 6.1% of the pharmacological activity of a NEXAVAR dose.

Although it could not be detected in excreta, M-2 accounted for 9.8% of the total drug-derived plasma AUC in solid tumor patients dosed to steady state (**FDA Table 4.**).

FDA Table 4. Relative AUCs (% total AUC) in plasma		
	Solid Tumor Patients, Steady State	**Healthy Subjects, Single Dose**
Sorafenib	81.9	73.5
M1	Not measured	0.3
M2	9.8	20.2
M3	Not measured	1.7
M4	4.1	1.7
M5	4.2	2.6

The *in vitro* and cellular activities of M-2 ranged from 0.3 – 13.0 X those of sorafenib. Using the extreme value of 13.0, together with 9.8% of the AUC as M-2, M-2 would account for a maximum of 51.6% of the pharmacological activity of a NEXAVAR dose. It should be noted that this calculation is an extreme: it assumes that 100% of the activity following dosing is related to only one of the nine processes studied non-clinically and that the relevant process is the one which most favors M-2 over sorafenib. It also assumes that the moieties which may be present but which have not been sampled for in solid tumor patients or studied for pharmacological activity (M1 and M3) are inactive. There is no basis for these assumptions. In contrast, if a similar calculation is performed for the process for which sorafenib shows the greatest positive activity difference relative to M-2, M-2 accounts for only 3.2% of the pharmacological activity of a NEXAVAR dose.

2.2.4 Exposure-response

2.2.4.1 What are the characteristics of the exposure-response relationships (dose-response, concentration-response) for *efficacy*? If relevant, indicate the time to the onset and offset of the desirable pharmacological response or clinical endpoint.

At the 400 mg bid dose, which has been evaluated in Phase II and Phase III clinical trials, the observed steady state total sorafenib Cmin,ss is greater than the IC50 for cellular proliferation observed in several of the preclinical models.

Limited Phase I anti-tumor activity data indicated that the 400 mg bid (1 partial response and 1 minor response) and the 600 mg bid (1 partial response and 1 minor response) showed anti-tumor activity. Anti-tumor activity was not observed at the 100 mg bid and the 200 mg bid dose level. Sorafenib concentrations in the 4 patients who responded were not distinguishable from those in non-responders

2.2.4.2 What are the characteristics of the exposure-response relationships (dose-response, concentration-response) for *safety*? If relevant, indicate the time to the onset and offset of the undesirable pharmacological response or clinical endpoint.

Safety data from all Phase I trials were pooled to evaluate dose limiting toxicities, adverse events, serious adverse events, discontinuations due to adverse events and dose interruption/dose-delays as a function of dose. A total of 7 studies (Studies 10164, 10658, 10922, 100277, 100283, 100313 and 100342) are in the Phase I data pool. Adverse events were collected using the National Cancer Institute-Common Toxicity Criteria (NCI-CTC) for individual studies.

Of the 197 patients in the Phase I data pool, 153 patients were administered doses of $\geq$ 100 mg bid. This subsection summarizes the safety data in patients administered $\geq$ 100 mg bid and indicates the rationale for the selection of 400 mg bid dose for Phase II-III trials based on safety.

Dose-limiting toxicities
There was some variation across the studies in the definition of dose-limiting toxicities (DLTs). In general, DLTs were defined as those toxicities that led to dose modification, dose-delay or discontinuation in Cycle 1 (DLT period of evaluation was 2 Cycles in Study 100342 which had a 7 days on/7 days off schedule). DLTs were evaluated in all Phase I trials. Data from Phase I trials where doses of $\geq$ 100 mg bid were administered are described here. In Study 100277 (28 days on/7 days off), there was a significant increase in DLTs from 400 mg bid (1/8) to 600 mg bid (3/7) indicating that 400 mg bid was better tolerated. In Study 100283 (continuous twice daily administration), there was a significant increase in DLTs from 400 mg bid (0/6) to 600 mg bid (4/12) to 800 mg bid (3/6). In Study 100342 (7 days on/7 days off), all patients (3/3) dosed 800 mg bid had a DLT. The 400 mg bid and 600 mg bid doses seemed to have similar safety and tolerability. In Study 10164 (21 days on/ 7 days off), there was a significantly higher incidence of DLTs at 600 mg bid and 800 mg bid compared to 400 mg bid. Based on these data, 400 mg bid appeared to be the highest well-tolerated dose.

Dose vs. adverse events: Overall
Treatment-emergent, drug-related adverse events per worst CTC grade, for any adverse events, were compared against the different dose groups and the results obtained are shown in FDA Table 5.

FDA Table 5. Applicant's Table 3-1 from Page 9 of MCR-01306 Sorafenib Dose Selection Document

Table 3-1: Incidence rates (percentage) of treatment-emergent drug-related adverse events per worst grade by dose[a] (Population: patients valid for safety, Phase I)

Adverse Event/ CTC Grade	100 mg bid (N=21)	200 mg bid (N=34)	300 mg bid (N=4)	400 mg bid (N=41)	600 mg bid (N=40)	800 mg bid (N=13)
Any AE						
"Severe" (3 + 4)	5 (23.8%)	10 (29.4%)	0 (0.0%)	12 (29.2%)	18 (45.0%)	8 (61.5%)

a. Dose refers to the highest dose a patient received
Source: Phase I datapool

With the exception of the 300 mg bid dose group, where there were only 4 evaluable patients, the relationship between dose and drug-related severe adverse events by worst CTC grade showed a clear dose trend (Table 3-1). There was a clear increase in severe (Grades 3 and 4) drug-related adverse events at the higher dose levels (600 mg bid: 45%; 800 mg bid 61.5%) as compared to the lower dose levels (100 mg bid: 23.8%; 400 mg bid: 29.2%).

Dose vs. selected adverse events
The relationship between dose and selected adverse events was evaluated. The system organ class selected (Gastrointestinal disorders; General disorders and Skin and subcutaneous tissue disorders) were those that had clearly shown some of the highest incidence rates of total and drug-related adverse events in the general analysis.

1. Dose vs. adverse events: Gastrointestinal disorders
Drug-related 'Gastrointestinal disorders' adverse events showed a dose relationship. Drug-related 'Gastrointestinal disorders' (all) showed an incidence rate of 42.9% for 100 mg bid, 53.7% for 400 mg bid, 57.5% for 600 mg bid and 76.9% for 800 mg bid. Severe (Grades 3 and 4) 'Gastrointestinal disorders' adverse events were 14.3% at 100 mg bid, 9.8% at 400 mg bid, 2.5% at 600 mg bid and 23.1% at 800 mg bid. 'Diarrhea' showed a dose relationship with an incidence rate of 9.5% at 100 mg bid, 43.9% at 400 mg bid, 45.0% at 600 mg bid and 46.2% at 800 mg bid. Severe (Grades 3 and 4) diarrhea occurred at 9.5% at 100 mg bid, 4.9% at 400 mg bid, 0.0% at 600 mg bid and 23.1% at 800 mg bid.

2. Dose vs. adverse events: General disorders
Drug-related 'General disorders' showed a dose relationship. Drug-related 'General disorders' (all) adverse events showed an incidence rate of 23.8% at 100 mg bid, 41.5% at 400 mg bid, 57.5% at 600 mg bid and 92.3% at 800 mg bid. Severe (Grades 3 and 4) adverse events under 'General disorders' occurred at 9.5% at 100 mg bid, 9.8% at 400 mg bid, 20.0% at 600 mg bid and 23.1% at 800 mg bid. With the exception of 100 mg bid, severe drug-related 'fatigue' showed a dose relationship with an incidence rate of 2.9% at 200 mg bid, 4.9% at 400 mg bid, 5.0% at 600 mg bid and 15.4% at 800 mg bid.

C. Dose vs. adverse events: Skin and subcutaneous disorders
Drug-related 'Skin and subcutaneous disorders' showed a dose relationship. The incidence rates of drug-related 'Skin and subcutaneous disorders' adverse events was 28.6% at 100 mg bid, 75.6% at 400 mg bid, 80.0% at 600 mg bid and 84.6% at 800 mg

bid. Severe (Grades 3 and 4) adverse events occurred in 0.0% at 100 mg bid, 7.3% at 400 mg bid, 32.5% at 600 mg bid and 23.1% at 800 mg bid. Palmar-plantar erythrodysaesthesia (hand-foot syndrome) showed the clearest dose relationship with an incidence rate of 0.0% at 100 mg bid, 12.2% at 400 mg bid, 27.5% at 600 mg bid and 30.8% at 800 mg bid. Severe (Grades 3 and 4) adverse events under Palmar-plantar erythrodysaesthesia occurred in 0.0% at 100 mg bid, 2.4% at 400 mg bid, 10.0% at 600 mg bid and 7.7% at 800 mg bid.

Serious adverse events
Drug-related serious adverse events occurred in 12.7% of the patients. With the exception of the 100 mg bid dose which showed 4 patients (19.0%) with drug-related serious adverse events, there was an increase in drug-related serious adverse events with increasing dose with the incidence rates of 14.6% at 400 mg bid, 22.5% at 600 mg bid and 30.8% at 800 mg bid.

Deaths
There were 6 deaths in the Phase I data pool. None of them were assessed to be drug related.

Discontinuations due to adverse events
Drug-related treatment-emergent adverse events causing discontinuation occurred in 7.6% of patients. With the exception of the 100 mg bid dose, there was a trend for increased discontinuation with increasing dose with most discontinuations due to adverse events occurring at 600 mg bid (7.5%) and 800 mg bid (38.5%) dose levels. At the 400 mg dose, only 1 of 41 patients (2.4%) discontinued treatment due to a drug related adverse event.

Dose reductions or interruptions
Treatment-emergent adverse events leading to dose reduction or dose delay occurred in 57 of 197 (28.9%) of patients (Table 8-12 in the Appendix). There was a clear dose relationship between dose and the incidence rates of dose reductions/dose delays. The incidence rates of dose reductions/dose delays was 14.3% at 100 mg bid, 43.9% at 400 mg bid, 50% at 600 mg bid and 46.2% at 800 mg bid.

In summary, increasing the dose from 400 mg bid to 600 mg bid caused an increase in Grade 3 and 4 toxicities, including significant GI and skin toxicities. Consistent with this, there was an increase in the number of patients requiring discontinuation of treatment due to toxicities at the 600 mg bid and 800 mg bid dose compared to the 400 mg bid dose. The incidence rates of serious adverse events and dose modifications/dose delays were also lower at the 400 mg bid dose as compared to 600 mg bid or 800 mg bid dose.

2.2.4.3 Does this drug prolong the QT or QTc interval?

A thorough QTc study designed to assess any effects of sorafenib on QT-interval was not performed. A search for the letters "qt" and q-t in the Summary of Clinical Safety identifies no occurrences. Similarly, there are no occurrences of the character string

"rhythm." Similarly, NDA section "2.7.2 Summary of Clinical Pharmacology Studies" does not contain the character strings "qt", "q-t" or "rhythm."

Six of the 19 clinical pharmacology and biopharmaceutics studies include statements regarding QT results in the body of the study report.

In Study 10927, Effect of ketoconazole on sorafenib, p. 26 includes a single statement interpreting QT results (indent, font change):

> There was no individual QT interval greater than 450 msec.

A Table summarizing the QT data from this study is reproduced below (**FDA Table 6.**).

FDA Table 6. Applicant's Table 14.3.5/2 from Page 86 of the Applicant's Report 10927-MRR 1661 - 1

7
KETOCONAZOLE

TABLE 14.3.5/2
SUMMARY STATISTICS BY VISIT FOR ECG VALUES
POPULATION: ALL SUBJECTS VALID FOR SAFETY
SUPINE POSITION

		VALUE AT VISIT				
		N	MEAN	STD	MIN	MEDIAN	MAX
HEART RATE (BPM)							
	VISIT 1 (SCREENING)	16	59.19	7.96		59.00	
	VISIT 16 (END OF STUDY)	15	60.53	8.75		62.00	
P-R INTERVAL (MSEC)							
	VISIT 1 (SCREENING)	16	154.13	22.63		148.00	
	VISIT 16 (END OF STUDY)	15	160.13	21.61		156.00	
QRS INTERVAL (MSEC)							
	VISIT 1 (SCREENING)	16	89.38	8.29		90.00	
	VISIT 16 (END OF STUDY)	15	96.00	7.09		94.00	
Q-T INTERVAL (MSEC)							
	VISIT 1 (SCREENING)	16	396.56	20.77		402.00	
	VISIT 16 (END OF STUDY)	15	405.07	28.54		404.00	
Q-T INTERVAL CORRECTED FOR HEART RATE (MSEC)							
	VISIT 1 (SCREENING)	16	391.96	15.09		393.63	
	VISIT 16 (END OF STUDY)	15	404.27	16.71		398.28	

In Study 11195, Evaluation of mass balance and metabolite profile of sorafenib, p. 88 includes the following statements (indent, font change) interpreting QT results:

> There were no consistent changes in QT / QTc following Bay 43-9006 treatment: QTc didn't increase ≥ 500 sec, there was no increase > 60 msec reported, baseline normal QTc didn't increase > 30 msec, and baseline normal QTc didn't increase 15% above baseline (see 16.2.12 / 1).

Summary data for this small study (n=4) was not tabulated.

In Study 11213, Evaluation of PK in patients with renal cell carcinoma, the following statement (indent, font change) appears on page 125:

> There were no subjects in either treatment group with QT interval corrected for heart rate (QTc) > 500 ms.

Tables summarizing the QT data from this study are reproduced below (**FDA Table 7**).

FDA Table 7. Excerpt from Applicant's Table 14.3.5/6 from Page 1386 of the Applicant's Report 11213-MRR 00170 – 1

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BAY 43-9006/11213
RCC

TABLE 14.3.5/6
ECG DESCRIPTIVE STATISTICS
POPULATION: PATIENTS VALID FOR SAFETY

30APR2005

VARIABLE = QTCF (MS)

TREATMENT GROUP	VISIT	N	MEAN	SD	MIN	MED	MAX
PLA	BASELINE	358	387.4	52.8		395.5	
	Cycle 2 Day 21	38	393.6	29.6		400.0	
	Cycle 3 Day 21	10	405.9	19.2		406.2	
	Cycle 4 Day 21	12	404.1	32.9		403.9	
	Cycle 5 Day 28	3	427.5	65.8		441.9	
	Cycle 6 Day 28	4	382.5	30.5		389.1	
	Cycle 7 Day 28	1	389.5			389.5	
	CHANGE FROM BASELINE: Cycle 2 Day 21	37	-7.0	39.4		1.2	
	CHANGE FROM BASELINE: Cycle 3 Day 21	10	-10.3	23.1		-0.2	
	CHANGE FROM BASELINE: Cycle 4 Day 21	12	23.3	70.6		-5.1	
	CHANGE FROM BASELINE: Cycle 5 Day 28	3	-1.5	97.2		15.1	
	CHANGE FROM BASELINE: Cycle 6 Day 28	4	-3.0	14.2		-3.2	
	CHANGE FROM BASELINE: Cycle 7 Day 28	1	10.5			10.5	
BAY	BASELINE	360	391.2	52.5		396.1	
	Cycle 2 Day 1	1	428.7			428.7	
	Cycle 2 Day 21	10	364.9	87.6		395.3	
	Cycle 3 Day 21	2	392.0	39.7		392.0	
	Cycle 4 Day 21	2	428.5	12.6		428.5	
	Cycle 5 Day 28	4	397.7	43.0		402.7	
	Cycle 6 Day 28	4	395.6	28.4		404.4	
	Cycle 7 Day 28	3	394.9	10.6		397.7	
	Cycle 8 Day 28	1	391.8			391.8	
	CHANGE FROM BASELINE: Cycle 2 Day 1	1	-3.3			-3.3	
	CHANGE FROM BASELINE: Cycle 2 Day 21	8	-40.3	63.4		-20.4	
	CHANGE FROM BASELINE: Cycle 3 Day 21	2	11.7	10.7		11.7	
	CHANGE FROM BASELINE: Cycle 4 Day 21	2	9.3	2.6		9.3	
	CHANGE FROM BASELINE: Cycle 5 Day 28	4	7.5	30.9		3.1	
	CHANGE FROM BASELINE: Cycle 6 Day 28	4	1.6	6.6		0.7	
	CHANGE FROM BASELINE: Cycle 7 Day 28	3	-8.0	10.9		-13.5	
	CHANGE FROM BASELINE: Cycle 8 Day 28	1	-3.1			-3.1	

NOTE: QTCB PRESENTS THE CYCLE QT INTERVAL VARIABLE CORRECTED FOR HEART RATE AND CALCULATED ACCORDING THE BAZETT'S FORMULA.
NOTE: QTCF PRESENTS THE CYCLE QT INTERVAL VARIABLE CORRECTED FOR HEART RATE AND CALCULATED ACCORDING THE FRIDERICIA'S FORMULA.

In Study 100483, Relative bioavailability study of 50 mg vs. 200 mg tablets, the following statement (indent, font change) appears on page 25:

> There was no evidence to suggest prolongation of uncorrected QT or Fridericia corrected QT (QTcF) 4 hours post-administration of BAY 43-9006 as compared to baseline. There were no individual QTcF values ≥ 450 msec. Only one subject (100483-001-1036) had an uncorrected QT > 450 msec, which occurred at Screening and predose, as well as postdose. All values from this subject were <500 msec.

Table 12-1 from this study is reproduced below as **FDA Table 8.**

FDA Table 8. Applicant's Table 12-1 from Page 25 of the Applicant's Report 100483-MRR 1653 - 2

Table 12-1: Effect of BAY 43-9006 on the heart rate, uncorrected QT and Fridericia corrected QT

	Mean ± SD		
	Heart-Rate (Beats per min.)	Uncorrected QT (msec)	QTcF (msec)
Predose (Baseline) (n=22)	59.7± 8.2	387.1 ± 26.1	384.5 ± 14.7
4 hours postdose (n=23)	55.4 ± 8.2	391.4 ± 25.7	379.3 ± 14.2
Change from baseline at 4 h postdose (n=22)	-5.2 ± 4.0	6.3 ± 9.0	-5.0 ± 7.1

Source: Table 14.3.5/2

In Study 100484, Effect of high-fat and moderate-fat breakfast on 200 mg tablets, QT interval data was collected in Treatment Arm B (high fat meal). The following statement (indent, font change) appears on page 30 of the Study Report:

> There was no evidence to suggest prolongation of uncorrected QT or Fridericia corrected QT (QTcF) 4 hours post-administration of BAY 43-9006 as compared to baseline. There were no individual QT or QTcF values ≥ 450 msec.

Table 12-1 from this study is reproduced below as **FDA Table 9.**

FDA Table 9. Applicant's Table 12-1 from Page 30 of the Applicant's Report 100484-MRR 1650 – 1

Table 12-1: Effect of BAY 43-9006 on the Heart Rate, Uncorrected QT and Fridericia Corrected QT

	Mean ± SD (N = 15)		
	Heart-Rate (Beats per min.)	Uncorrected QT (msec)	QTcF (msec)
Predose (Baseline)	57.3 ± 7.7	388.7 ± 22.3	381.3 ± 15.1
4 hours post-dose	54.4 ± 8.2	389.4 ± 23.7	375.4 ± 18.3
Change from baseline at 4 h post-dose	-2.9 ± 3.5	0.7 ± 12.2	-5.9 ± 9.7

Source: Table 14.3.5/2 in Section 14

In Study 100545, Study to evaluate relationship between dissolution rate and relative bioavailability, the following statement (indent, font change) appears on page 21:

> No clinically relevant findings were observed concerning vital signs or ECG measurements. No corrected QT interval exceeded 500 milliseconds.

QT data from this study were not summarized by the Applicant; 36 subjects were randomized; 26 subjects completed all 5 treatments.

While a thorough QT study was not performed, and, thus, the risk of QT-prolongation following NEXAVAR dosing cannot be completely ruled out, the current data support that QT-prolongation does not occur following NEXAVAR dosing. The reviewing Medical Officer was made aware of the QT data summarized above, as well as the lack of a thorough QT study, during the review cycle.

2.2.4.4 Is the dose and dosing regimen selected by the sponsor consistent with the known relationship between dose-concentration-response, and are there any unresolved dosing or administration issues?

The relationship between dose-concentration and response is largely unknown. Section 2.2.1 of this review summarizes how the clinical dose of 400 mg BID was arrived at. Briefly, limited Phase I anti-tumor activity data indicated that the 400 mg bid (1 partial response and 1 minor response) and the 600 mg bid (1 partial response and 1 minor response) showed anti-tumor activity. Anti-tumor activity was not observed at the 100 mg bid and the 200 mg bid dose level. The incidence of serious adverse events and dose modifications/dose delays were lower at the 400 mg bid dose as compared to 600 mg bid. Thus, 400 mg bid was selected for further development.

In Studies 11213 and 100391, fewer than 10% of RCC patients discontinued study drug prematurely due to adverse events. In Study 11213, the rate of discontinuation of study

drug due to adverse events was similar between the treatment group and the placebo group.

In Studies 100391 and 11213 protocol-defined interruption and dose reductions of sorafenib for specific drug-related adverse events were reported. In Study 100391, dose interruption due to adverse events was reported in 82 patients (41%), dose reduction due to an adverse event occurred in 13 patients (6%). In Study 11213, dose interruption for adverse events was reported in 55 sorafenib patients (14.3%) and 16 placebo patients (4.2%). The most common events resulting in dose interruption in the sorafenib group were hand-foot skin reaction (17 patients, 4.4%), diarrhea (8 patients, 2.1%), hypertension (5 patients, 1.3%), and rash/desquamation (5 patients, 1.3%). No other adverse events led to dose interruption in more than 4 patients in either treatment arm. Diarrhea was the most common reason for dose interruption in the placebo arm (4 patients, 1.0%) Dose reductions due to adverse events occurred in 40 (10.4%) sorafenib patients and 9 (2.3%) placebo patients. For sorafenib patients, the most common events that led to dose reductions were hand-foot skin reaction (18 patients, 4.7%), diarrhea (5 patients, 1.3%), and rash/desquamation (5 patients, 1.3%). In some patients, dose reductions were attributed to more than 1 event (eg, hand-foot skin reaction and rash). No other adverse events led to dose reduction in more than 4 patients in either treatment arm.

The data regarding dose interruptions and delays suggests that higher doses are not prudent. The efficacy of lower doses is largely unknown. Determination of an optimal dose is an unresolved dosing issue.

2.2.5 What are the PK characteristics of the drug and its major metabolite?

2.2.5.1 What are the single dose and multiple dose PK parameters? *(Provide tables to refer to in subsequent questions in this section.)*

FDA Table 10. summarizes the pharmacokinetics of sorafenib following single 400 mg doses administered to healthy volunteers in the presence or absence of food.

FDA Table 10. Applicant's Table 11-2 from Page 27 of the study report for Study 100484

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Table 11-2: Pharmacokinetic parameters geometric mean (%CV) following a single oral dose of BAY 43-9006 given in fasting condition or with food (N=14-15)

Parameter	Unit	With High Fat Meal (N=15)	With Moderate Fat Meal (N=15)	Fasting (N=14)
AUC	mg*h/L	50.18 (53)	78.94 (44)	72.52 (36)
AUC_{norm}	kg*h/L	9.01 (50)	14.18 (43)	12.96 (46)
C_{max}	mg/L	1.52 (50)	2.02 (39)	2.46 (41)
$C_{max,norm}$	kg/L	0.27 (46)	0.36 (43)	0.44 (52)
t_{max} [a]	h	4.00 (4-24)	4.60 (4-24)	4.00 (2-4)
$t_{½}$	h	21.66 (36)	23.25 (18)	25.59 (20)

Median (Range)
Source: Table 14.2/2 in Section 14

A plot of the concentration-time course for these subjects is reproduced below as **FDA Figure 3.**

FDA Figure 3. Applicant's Figure 14.2/1 from Page 50 of the Study Report for Study 100484

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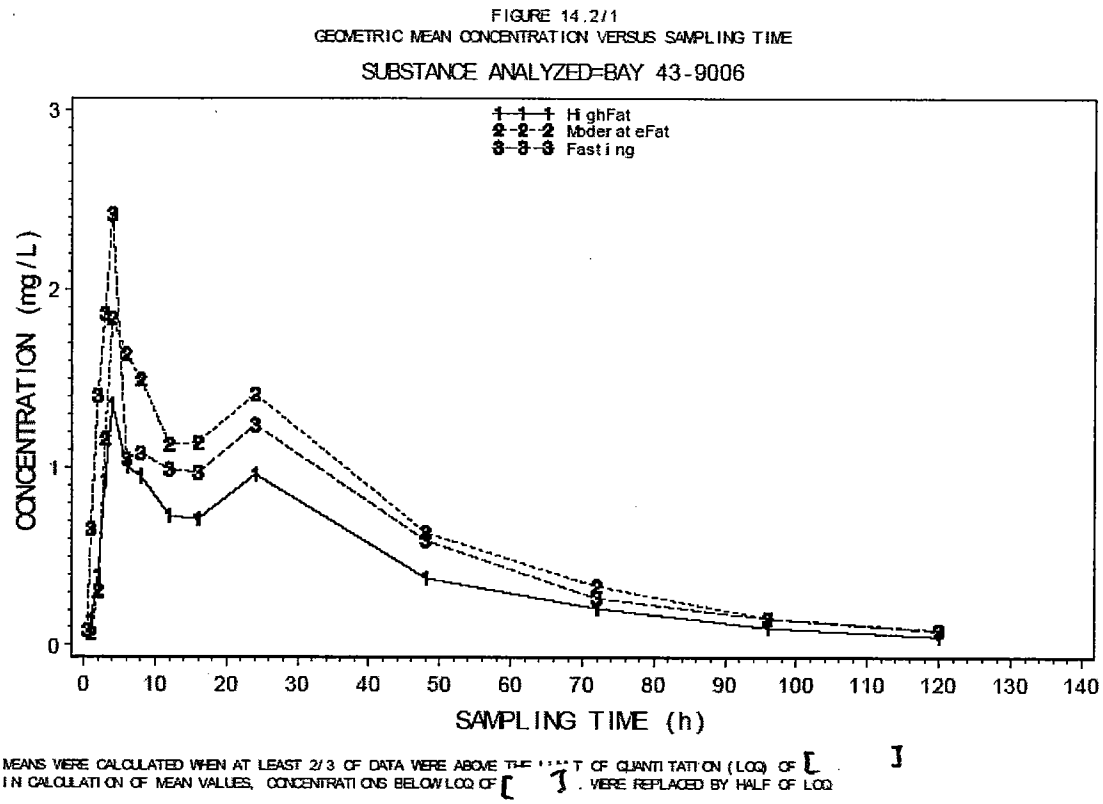

FDA Table 11. summarizes the pharmacokinetics of sorafenib following multiple dosing at the clinical regimen (400 mg bid) to cancer patients. It should be noted that only a minority of these patients (11 or fewer) had renal cell carcinoma. The remainder had solid tumors of other types.

FDA Table 11. Applicant's Table 3-6 from Page 87 of the Summary of Clinical Pharmacology Studies

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Table 3-6: Steady state plasma C_{max} and $AUC_{(0-12)}$ parameters of sorafenib and its metabolites (geometric mean, %CV) following twice daily oral administration of 400 mg sorafenib to cancer patients in Studies 10164, 100277, 100283 and 100342 (Modules 5.3.3.2.2, 5.3.3.2.3, 5.3.3.2.1, 5.3.3.2.4, respectively)

		$AUC_{(0-12),ss}$ (mg*hr/L)	$C_{max,ss}$ (mg/L)	$t_{max,ss}$[C] (hr)	$t_{1/2}$ (hr)
Sorafenib[A]	N=	27	27	27	11
	Geometric Mean/Median	64.3	7.7	3.0	24.9
	Approximate CV%/ Range	60.8	65.3	(0.0, 24.3)	32.8
M2[A]	N=	8	8	8	7
	Geometric Mean/ Median	7.7	0.88	0.0	28.7
	Approximate CV%/ Range	143.2	157.9	(0.0, 24.3)	23.2
M4[A]	N=	8	8	8	6
	Geometric Mean / Median	3.25	0.41	0.0	26.5
	Approximate CV%/ Range	153.5	197.3	(0.0, 24.3)	29.1
M5[B]	N=	3	3	3	3
	Geometric Mean / Median	3.27	0.48	0.0	52.1
	Approximate CV%/ Range	147.5	124.5	(0.0, 24.3)	12.9

[A] = steady state data after at least 7 days of dosing, [B] = steady state data after at least 21 days of dosing, [C] = median and range are presented for t_{max}

2.2.5.2 How does the PK of the drug and its major active metabolites in healthy volunteers compare to that in patients?

Within the limitations of cross-study comparisons and the different demographic characteristics between studies in healthy subjects and solid tumor patients enrolled in Phase I – type studies, a comparison between **FDA Tables 10.** and **11.** shows that there is little or no difference in the pharmacokinetics of sorafenib between healthy volunteers and patients. Metabolite pharmacokinetics were not performed in studies with healthy subjects, with the exceptions of the mass balance study (Study 11195) and Study 10927, a study of the effect of ketoconazole on the pharmacokinetics of sorafenib. A comparison of AUC data from solid tumor patients (data from **FDA Table 11.**) and the healthy subjects in the mass balance study is shown below (**FDA Table 12.**). In interpreting the % differences in M4 and M5 between the groups, it is important to remember that the absolute values for the AUCs of these metabolites are small relative to the AUC of parent drug.

FDA Table 12. Plasma AUC (ng/mL * h) as a function of subject type				
	Sorafenib	**M2**	**M4**	**M5**
Healthy Subjects, single dose (n = 4)	57.35	15.78	1.315	2.029
Solid Tumor Patients, steady-state (n = 3 - 27)	64.3	7.7	3.25	3.27
% Change	12	-51	147	61

2.2.5.3 What are the characteristics of drug absorption?

Following oral administration of a single 400 mg dose in the fasted state to healthy volunteers, sorafenib is absorbed relatively rapidly with a median Tmax of 4 hours. The single dose sorafenib plasma concentration vs. time profile is shown in **FDA Figure 3.** (Section 2.2.5.1 of this review).

Plasma concentration time data typically show 1-2 secondary post-Tmax absorption peaks at 8 or 12 and/or 24 hours post-dose suggesting enterohepatic recycling. Following

multiple dose administration of 400 mg bid sorafenib administered as tablets to cancer patients, sorafenib is absorbed with a median Tmax,ss of 3 hours (range 0.0 to 24 hours) with secondary post-Tmax absorption peaks at 8-12 and/or 24 hours post-dose. The observed steady state Tmax,ss was approximately 24 hours in some patients where plasma samples were collected after their last dose in Cycle 1, prior to the start of dosing in the next cycle. These secondary peaks indicate continued absorption possibly due to enterohepatic recycling.

2.2.5.4 What are the characteristics of drug distribution? *(Include protein binding.)*

Sorafenib is 99.5% bound to plasma proteins. Sorafenib was primarily bound to serum albumin and is also bound to a lesser extent to α-globulins, β-globulins and LDL but not to γ-globulins and α1-acid glycoprotein. Protein binding was linear across concentrations.

The distribution of sorafenib between red blood cells and plasma was evaluated *in vitro* at concentrations ranging from 0.531 to 42.5 mg/L. These data showed that sorafenib is generally distributed approximately equally between red blood cells and plasma with an average plasma to blood concentration ratio of 1.33.

Compartmental modeling of concentration-time data was not performed and no estimate of volume of distribution appears in the Applicant's **Summary of Clinical Pharmacology Studies**. Using the $t_{1/2}$ value for sorafenib in **FDA Table 11.**, the elimination rate constant (λ_Z) can be derived:

$\lambda_Z = \ln(2) \div t_{1/2} = 0.0278$

The elimination rate constant can then be used, together with the AUC value in **FDA Table 11.** (64.3), to derive a volume of distribution (V) of 223 L:

$V = (F)(D) \div [(AUC)(\lambda_Z)]$

$V/F = D \div [(AUC)(\lambda_Z)]$

$V/F = 400 \div [64.3 * 0.0278] = 223$ L.

2.2.5.5 Does the mass balance study suggest renal or hepatic as the major route of elimination?

FDA Table 3. is reproduced below. Recovery in feces suggests that the hepatic route is the primary route of elimination.

FDA Table 3. Recovery of Dose in Excreta	
	% Dose Recovered
Feces	
Sorafenib	50.7
M3	0.4

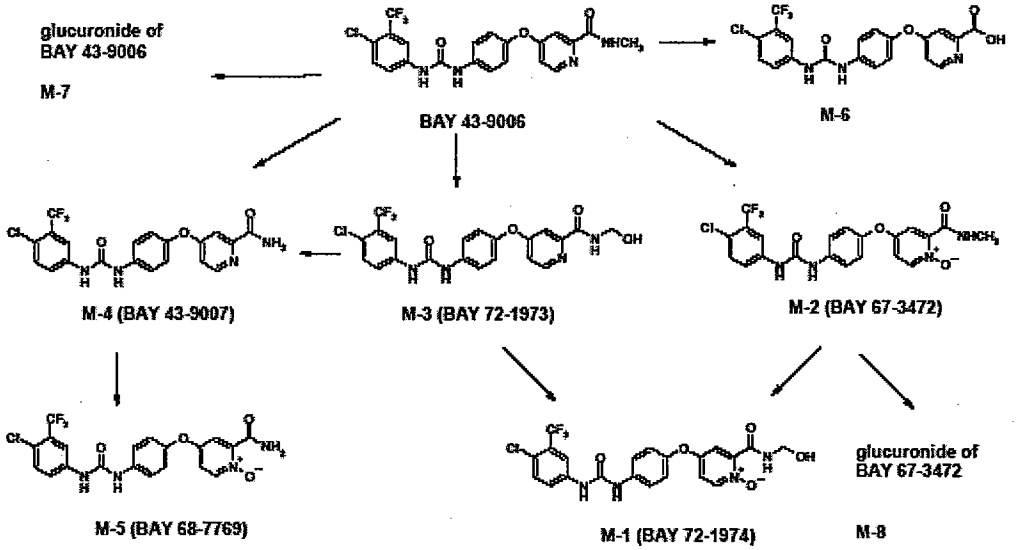
M4	1.2
M6	19.1
Total	71.4
Urine	
M7 (Sorafenib glucuronide)	14.8
M8 (M2 glucuronide)	2.7
Total	17.5
TOTAL (Feces + Urine)	
	88.9

2.2.5.6 What are the characteristics of drug metabolism?

The Applicant's Figure 2-4 shows a metabolic scheme for sorafenib (BAY 43-9006) in humans. It is reproduced below as **FDA Figure 4.**

FDA Figure 4. Applicant's Figure 2-4 from Page 41 of the Summary of Clinical Pharmacology Studies

Figure 2-4: Sorafenib – proposed metabolites in man from *in vitro* and *in vivo* studies



To identify the CYP isoforms involved in the *in vitro* phase I metabolism of sorafenib, incubations with human liver microsomes in the absence and presence of CYP isoform selective inhibitors were performed. The results are shown below (**FDA Table 13.**)

FDA Table 13. In vitro inhibition of sorafenib metabolism by reference CYP inhibitors		
Inhibtor	**CYP(s)**	**% inhibition**
1-aminobenzotriazole (1000 uM)	non-specific	96.3
Furafylline (20 uM)	1A2	8.2
Sulfaphenazole (50 uM)	2C9	13.6

Quercetin (50 uM)	2C8 & 3A4/5	40.5
Tranylcypromine (10 uM)	2C19 & 2A6	5.9
Quinidine (5 uM)	2D6	4.3
4-methylpyrazole (200 uM)	2E1	10.9
Ketoconazole (1 uM)	3A4	84.2
Ketoconazole (10 uM)	3A4	96.2
Troleandomycin (20 uM)	3A4	39.6
Troleandomycin (100 uM)	3A4	70.3

These data support that CYP3A4 is the primary CYP enzyme responsible for metabolism of sorafenib. The data with quercetin do not rule out the possibility that CYP 2C8 could contribute significantly to metabolism.

Values for the ability of each CYP-specific inhibitors to inhibit the formation of M2 and M3 (the only metabolites whose formation was studied), approximated (on a percentage basis) the ability of each inhibitor to inhibit total sorafenib breakdown.

FDA Table 3. shows that approximately 18% of the dose was excreted as glucuronides, predominantly as sorafenib glucuronide (M-7). From a panel of recombinant UGT enzymes UDP-glucuronosyltransferase 1A9 (UGT1A9) was identified as the main UGT isoform catalyzing conjugation of sorafenib with glucuronic acid to M-7 (**FDA Table 14.**).

FDA Table 14. Applicant's Table 2 from Page 12 of the Applicant's Report PH-33504-7

Table 2: [^{14}C]BAY 43-9006
Formation of M-7 catalyzed by human recombinant UGTs (0.5 mg/mL microsomal protein, 60 min).

Enzyme	BAY 54-9085 [2 µM]	BAY 54-9085 [50 µM]
	[pmol M-7/(mg·min)]	
UGT1A1	n.d.	n.d.
UGT1A3	n.d.	n.d.
UGT1A4	n.d.	n.d.
UGT1A6	n.d.	n.d.
UGT1A7	0.13	n.d.
UGT1A8	n.d.	n.d.
UGT1A9	11.14	29.9
UGT1A10	n.d.	n.d.
UGT2B4	n.d.	n.d.
UGT2B7	n.d.	n.d.
UGT2B15	n.d.	n.d.
UGT2B17	n.d.	n.d.

n.d. = not detected

Kinetic parameters were determined for UGT1A9 catalyzed glucuronidation using recombinant enzyme, human kidney microsomes, and cultured human hepatocytes. High affinity to UGT1A9 was demonstrated by Km values of 5.8 μM, 8.1 μM, and 3 - 7 μM, in the respective *in vitro* model. Formation rate of M-7 applying human liver microsomes was too low to determine kinetic parameters.

In order to estimate the contribution of N-oxidation (M2) and glucuronidation (M7) to overall sorafenib elimination in the liver, [14C]BAY 54-9085 (tosylate of sorafenib) was incubated with cultured human hepatocytes over a broad concentration range.

Formation of M7 (glucuronidation) predominated at lower substrate concentrations, whereas preferentially M2 (N-oxidation) was formed at higher concentrations of sorafenib. Intrinsic clearance (CLint = Vmax/Km) for N-oxidation was approximately 2 fold higher than for glucuronidation. These data provide evidence that N-oxidation and glucuronidation are both relevant metabolic pathways in human liver. As noted previously, kidney tissue is also capable of forming glucuronide M7.

2.2.5.7 What are the characteristics of drug excretion?

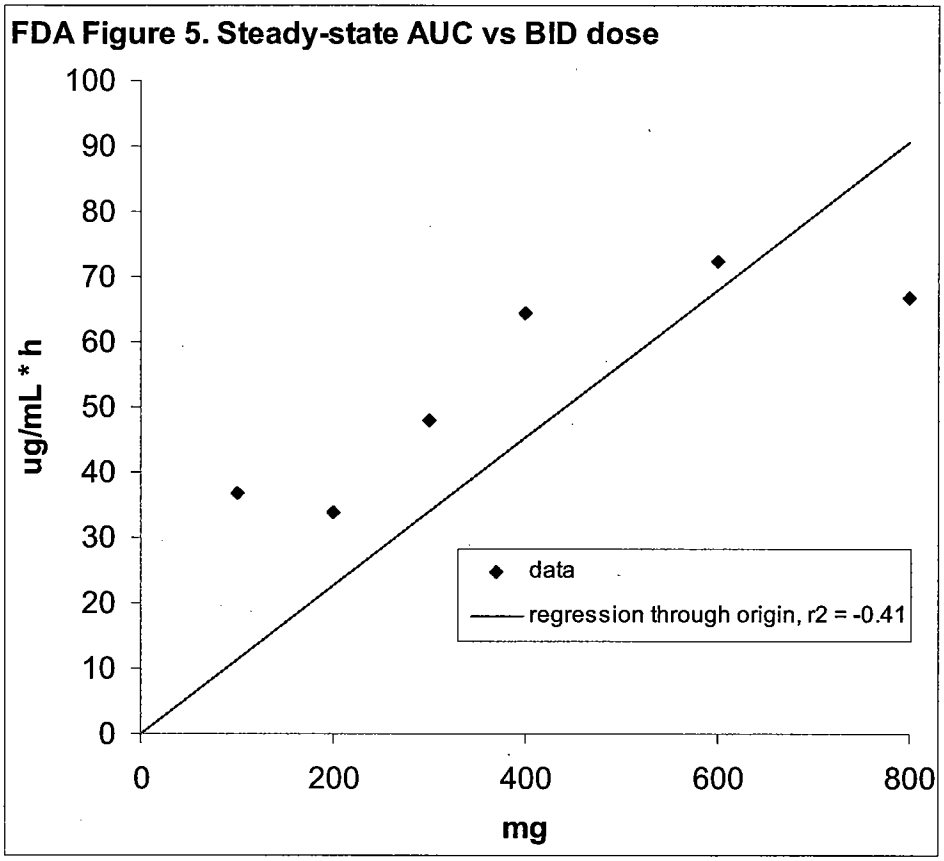
FDA Table 3. is reproduced below. Excretion occurs primarily via feces.

FDA Table 3. Recovery of Dose in Excreta	
	% Dose Recovered
Feces	
Sorafenib	50.7
M3	0.4
M4	1.2
M6	19.1
Total	71.4
Urine	
M7 (Sorafenib glucuronide)	14.8
M8 (M2 glucuronide)	2.7
Total	17.5
TOTAL (Feces + Urine)	
	88.9

2.2.5.8 Based on PK parameters, what is the degree of linearity or nonlinearity in the dose-concentration relationship?

At doses from 200 - 400 mg bid, increases in AUC were approximately dose proportional However, $AUC_{(0\text{-}12),ss}$ values at the 600 mg bid dose level were not proportionally greater than those at 400 mg bid and mean $AUC_{(0\text{-}12),ss}$ at the 800 mg dose level was not greater than that at 600 mg bid (**FDA Figure 5.**).

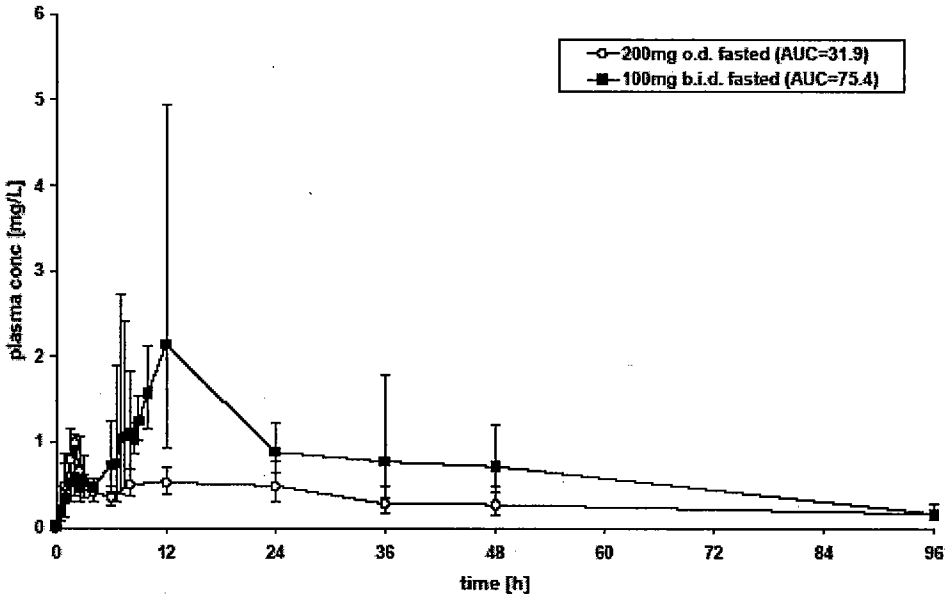
FDA Figure 5. Data from Applicant's Table 3-3 from Page 79 of the Summary of Clinical Pharmacology Studies



This lack of increase in exposure following bid dosing may be due to the limited aqueous solubility of sorafenib resulting in reduced absorption in the GI tract with higher doses. Consistent with such an effect, steady-state AUCs were more than 2-fold higher following divided dosing (100 mg bid x 1) than following undivided dosing (200 mg qd x 1) (**FDA Figure 6**).

FDA Figure 6. Applicant's Figure 3-2 from Page 78 of the of the Summary of Clinical Pharmacology Studies

Figure 3-2: Plasma sorafenib concentration time profile (geometric mean/standard deviation) following administration of 200 mg sorafenib either as one dose administered weekly, or as two 100 mg doses given on the same day, administered weekly (Study 100283, Module 5.3.3.2.1)



2.2.5.8 How do the PK parameters change with time following chronic dosing? *(This may include time to steady-state; single dose prediction of multiple dose PK; accumulation ratio.)*

The time dependency in the pharmacokinetics of sorafenib was investigated in Study 10164 where 12 h plasma concentration-time profiles were evaluated on Days 1, 7 and 21 of the study. Based upon the single dose half-life of approximately 25 h, near steady-state should occur within approximately 4 days. A comparison of the Day 7 and Day 21 AUCs is shown below (**FDA Table 15.**).

FDA Table 15. Data from Applicant's Table 14.4 / 2 from Pages 621 - 623 of the Study Report 10164-MRR 00078 - 2

FDA Table 15. Sorafenib AUC following BID dosing -- Day 21 vs Day 7			
Dose (mg BID)	**Day 7 AUC**	**Day 21 AUC**	**% change (Day 21 vs. Day 7)**
100	30.128	31.54	4.7
200	87.277	50.807	-41.8
300	52.704	41.43	-21.4
400	92.154	78.472	-14.8
600	104.858	83.96	-19.9
800	74.505	99.135	33.1

These data suggests that chronic dosing at the clinical regimen (400 mg bid) results in a slight reduction in sorafenib exposure.

2.2.5.10 What is the inter- and intra-subject variability of PK parameters in volunteers and patients, and what are the major causes of variability?

Sorafenib demonstrates moderate to high inter-subject variability in pharmacokinetics as demonstrated by % coefficients of variation (%CV) ranging from 36% to 91%. Intra-individual variability in pharmacokinetics was not assessed.

2.3. Intrinsic Factors

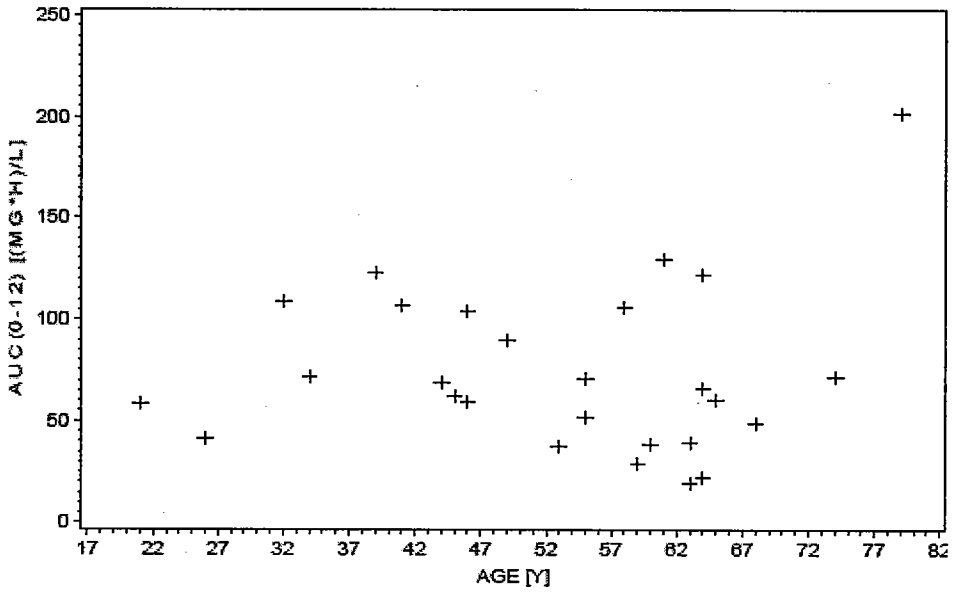
2.3.1 What intrinsic factors (age, gender, race, weight, height, disease, genetic polymorphism, pregnancy, and organ dysfunction) influence exposure (PK usually) and/or response, and what is the impact of any differences in exposure on efficacy or safety responses?

Age

There was no significant correlation between exposure and age. Data from patients treated at the 400 mg bid dose level are presented in **FDA Figure 7.**

FDA Figure 7. Applicant's Figure 3-7 from Page 92 of the Summary of Clinical Pharmacology Studies

Figure 3-7: Relationship between age and steady state plasma sorafenib $AUC_{(0-12),ss}$ values following administration of 400 mg bid sorafenib in Studies 10164, 100277, 100283 and 100342 (Modules 5.3.3.2.2, 5.3.3.2.3, 5.3.3.2.1, and 5.3.3.2.4, respectively)

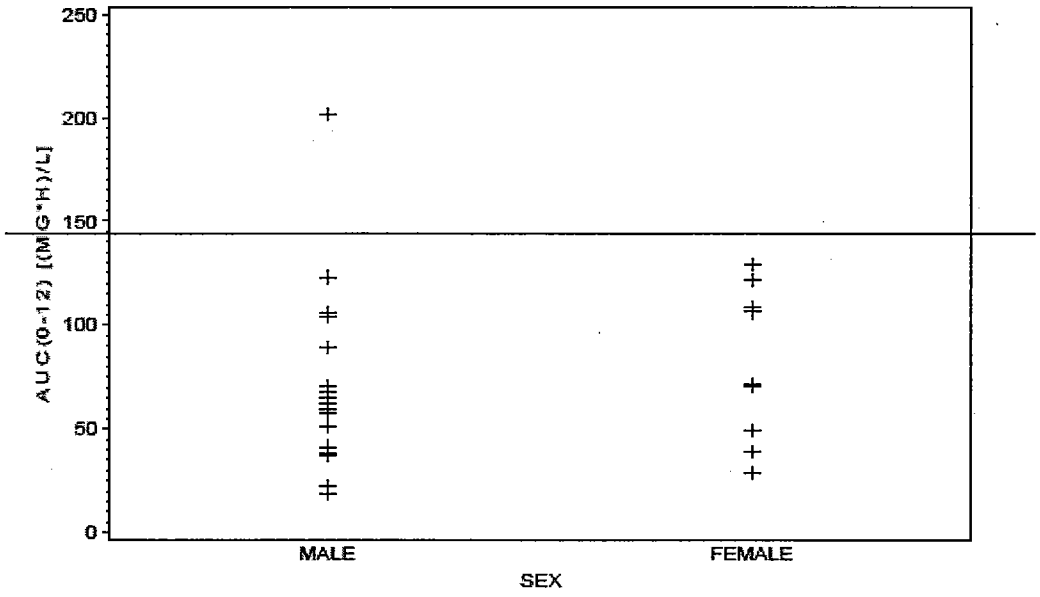


Gender

Data from patients treated at the 400 mg bid dose level are presented in **FDA Figure 6.** There appears to be a trend toward females having higher exposures than males (**FDA Figure 8.**). The effect, if any, is small.

FDA Figure 8. Applicant's Figure 3-8 from Page 93 of the Summary of Clinical Pharmacology Studies

Figure 3-8: Relationship between gender and steady state plasma sorafenib $AUC_{(0-12),ss}$ values following administration of 400 mg bid sorafenib in Studies 10164, 100277, 100283 and 100342 (Modules 5.3.3.2.2, 5.3.3.2.3, 5.3.3.2.1, and 5.3.3.2.4, respectively)



Tables showing adverse events and hazard ratio as a function of gender are reproduced below (**FDA Tables 16. and 17.**). In general, there were no considerable differences in the rates of adverse events between men and women, although women had a slightly higher incidence of the dermatologic events rash, alopecia, hand-foot skin reaction and hypertension. Similarly, no consistent treatment effect by gender was observed.

FDA Table 16. Applicant's Table 2-6 from Page 70 of the Summary of Clinical Safety

Table 2-6: Selected Treatment-Emergent Adverse Events Evaluated by Gender in Studies 100391 and 11213
(Population: RCC Patients Valid for Safety)

		Study 100391		Study 11213			
		Sorafenib		Sorafenib		Placebo	
Adverse Event	Gender	n/N	(%)	n/N	(%)	n/N	(%)
Any Event	Male	149/149	(100)	225/287	(84.3)	218/287	(76.0)
	Female	53/53	(100)	100/116	(86.2)	65/97	(67.0)
Hypertension	Male	61/149	(40.9)	26/267	(9.7)	0/287	(0.0)
	Female	25/53	(47.2)	15/116	(12.9)	3/97	(3.1)
Rash/Desquamation	Male	93/149	(62.4)	87/267	(32.6)	41/287	(14.3)
	Female	41/53	(77.4)	42/116	(36.2)	10/97	(10.3)
Hand-foot Skin Reaction	Male	91/149	(61.1)	66/267	(24.7)	15/287	(5.2)
	Female	34/53	(64.2)	37/116	(31.9)	3/97	(3.1)
Alopecia	Male	77/149	(51.7)	52/267	(19.5)	9/287	(3.1)
	Female	30/53	(56.6)	36/116	(31.0)	3/97	(3.1)
Dermatology-Other	Male	65/149	(43.6)	26/267	(9.7)	9/287	(3.1)
	Female	22/53	(41.5)	10/116	(8.6)	5/97	(5.2)
Pruritus	Male	11 /149	(7.4)	51/267	(19.1)	14/287	(4.9)
	Female	6/53	(11.3)	14/116	(12.1)	3/97	(3.1)
Flushing	Male	23/149	(15.4)	16/267	(6.0)	5/287	(1.7)
	Female	9/53	(17.0)	8/116	(6.9)	2/97	(2.1)
Diarrhea	Male	86/149	(57.7)	90/267	(33.7)	36/287	(12.5)
	Female	31/53	(58.5)	36/116	(31.0)	2/97	(2.1)
Mucositis/Stomatitis	Male	51/149	(34.2)	17/267	(6.4)	1/287	(0.3)
	Female	19/53	(35.8)	11/116	(9.5)	1/97	(1.0)
Neuropathy-sensory	Male	31/149	(20.8)	28/267	(10.5)	13/287	(4.5)
	Female	9/53	(17.0)	11/116	(9.5)	1/97	(1.0)

n=number of patients with event, N=total number of patients in the group; RCC=renal cell carcinoma.
Source: Table 16.1.15/5 in Study 100391 Part B MRR located in Module 5.3.5.2.1 and Table 16.1.13/5 in Study 11213 MRR located in Module 5.3.5.1.1.

FDA Table 17. Applicant's Table 3-17 from Page 86 of the Summary of Clinical Efficacy

Table 3-17: Hazard Ratios for Subgroup Analysis by Gender in Study 11213
(Population: Patients Valid for Intent to Treat)

Variable/Method	Subgroup	N	Hazard Ratio (Sorafenib/Placebo)	95% Confidence Interval
Progression-free survival Independent review	Male	554	0.45	(0.35, 0.58)
	Female	214	0.45	(0.29, 0.69)
Progression-free survival- Investigator assessment	Male	554	0.46	(0.36, 0.59)
	Female	214	0.39	(0.26, 0.61)
Time to disease progression- Independent review	Male	554	0.43	(0.33, 0.56)
	Female	214	0.42	(0.26, 0.66)
Time to disease progression- Investigator assessment	Male	554	0.43	(0.33, 0.56)
	Female	214	0.39	(0.25, 0.61)

N = total number of patients in the group.
Source: Tables 14.2/11, 14.2/12, 14.2/13, and 14.2/14 in Study 11213 MRR located in Module 5.3.5.1.1.

Race

An examination of the effect of ethnicities other than Caucasian and Japanese on pharmacokinetics is not included in the NDA.

FDA Table 18. compares the pharmacokinetics of Japanese and Caucasians. At the 400 mg bid dose, AUC was reduced 45% in Japanese relative to Caucasians.

FDA Table 18. Applicant's Table 3-7 from Page 95 of the Summary of Clinical Pharmacology Studies

Table 3-7: Comparison of steady state sorafenib $C_{max,ss}$ and $AUC_{(0-12),ss}$ values in Japanese patients on Day 14 (Study 10658, Study 11497) and Caucasian patients (Studies 100277, 100283, 100342, 10164)

Dose (mg) bid	Pharmacokinetic parameter	Japanese patients			Caucasian patients		
		N	Geometric Mean	%CV	N	Geometric Mean	%CV
100	$C_{max,ss}$	3	1.04	29	19	5.0	89.0
	$AUC_{(0-12),ss}$	3	9.35	21	18	39.3	76.8
200	$C_{max,ss}$	10	2.64	49	19	4.3	75.0
	$AUC_{(0-12),ss}$	10	20.2	37	18	33.7	77.9
400	$C_{max,ss}$	6	4.91	76	27	8.3	57.4
	$AUC_{(0-12),ss}$	6	36.7	73	27	67.3	56.8
600	$C_{max,ss}$	6	4.42	55	35	8.6	61.8
	$AUC_{(0-12),ss}$	6	33.8	43	35	72.5	65.7

Note: There were 3 non-Caucasian patients in the PK data pool whose data were excluded for calculating exposures in non-Japanese Caucasian patients.

The effect of ethnicity on adverse events is shown in **FDA Table 19.**

FDA Table 19. Applicant's Table 2-8 from Pages 73-74 of the Summary of Clinical Safety

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Table 2-8: Selected Treatment-Emergent Adverse Events Evaluated by Race in Studies 100391 and 11213
(Population: RCC Patients Valid for Safety)

		Study 100391		Study 11213			
		Sorafenib		Sorafenib		Placebo	
Adverse Event	Race	n/N	(%)	n/N	(%)	n/N	(%)
Any Event	Caucasian	182/182	(100)	231/276	(83.7)	195/277	(70.4)
	Black	10/10	(100)	2/2	(100)	1/1	(100)
	Asian	1/1	(100)	1/1	(100)	5/6	(83.3)
	Hispanic	9/9	(100)	6/7	(85.7)	3/3	(100)
	American Indian	NA	NA	1/1	(100)	NA	NA
	Missing	NA	NA	84/97	(86.6)	79/97	(81.4)
Hypertension	Caucasian	80/182	(44.0)	34/276	(12.3)	3/277	(1.1)
	Black	5/10	(50.0)	0/2	(0.0)	0/1	(0.0)
	Asian	0/1	(0.0)	0/1	(0.0)	0/6	(0.0)
	Hispanic	1/9	(11.1)	0/7	(0.0)	0/3	(0.0)
	American Indian	NA	NA	0/1	(0.0)	NA	NA
	Missing	NA	NA	7/97	(7.2)	0/97	(0.0)
Rash/ Desquamation	Caucasian	122/182	(67.0)	81/276	(29.3)	30/277	(10.8)
	Black	5/10	(50.0)	1/2	(50.0)	0/1	(0.0)
	Asian	1/1	(100)	0/1	(0.0)	0/6	(0.0)
	Hispanic	6/9	(66.7)	1/7	(14.3)	1/3	(33.3)
	American Indian	NA	NA	1/1	(100)	NA	NA
	Missing	NA	NA	45/97	(46.4)	20/97	(20.6)
Hand-foot Skin Reaction	Caucasian	112/182	(61.5)	76/276	(27.5)	17/277	(6.1)
	Black	7/10	(70.0)	1/2	(50.0)	0/1	(0.0)
	Asian	0/1	(0.0)	0/1	(0.0)	0/6	(0.0)
	Hispanic	6/9	(66.7)	0/7	(0.0)	0/3	(0.0)
	American Indian	NA	NA	0/1	(0.0)	NA	NA
	Missing	NA	NA	26/97	(26.8)	1/97	(1.0)
Alopecia	Caucasian	94/182	(51.6)	61/276	(22.1)	9/277	(3.2)
	Black	8/10	(80.0)	0/2	(0.0)	0/1	(0.0)
	Asian	0/1	(0.0)	0/1	(0.0)	1/6	(16.7)
	Hispanic	5/9	(55.6)	0/7	(0.0)	0/3	(0.0)
	American Indian	NA	NA	0/1	(0.0)	NA	NA
	Missing	NA	NA	27/97	(27.8)	3/97	(3.1)
Dermatology-Other	Caucasian	79/182	(43.4)	26/276	(9.4)	13/277	(4.7)
	Black	5/10	(50.0)	0/2	(0.0)	0/1	(0.0)
	Asian	0/1	(0.0)	0/1	(0.0)	0/6	(0.0)
	Hispanic	3/9	(33.3)	1/7	(14.3)	0/3	(0.0)
	American Indian	NA	NA	1/1	(100)	NA	NA
	Missing	NA	NA	8/97	(8.2)	1/97	(1.0)

Table 2-8: Selected Treatment-Emergent Adverse Events Evaluated by Race in Studies 100391 and 11213 (continued)
(Population: RCC Patients Valid for Safety)

		Study 100391		Study 11213			
		Sorafenib		Sorafenib		Placebo	
Adverse Event	Race	n/N	(%)	n/N	(%)	n/N	(%)
Pruritus	Caucasian	13/182	(7.1)	45/276	(16.3)	7/277	(2.5)
	Black	1/10	(10.0)	0/2	(0.0)	0/1	(0.0)
	Asian	1/1	(100)	0/1	(0.0)	1/6	(16.7)
	Hispanic American	2/9	(22.2)	1/7	(14.3)	1/3	(33.3)
	Indian	NA	NA	0/1	(0.0)	NA	NA
	Missing	NA	NA	19/97	(19.6)	8/97	(8.2)
Flushing	Caucasian	29/182	(15.9)	23/276	(8.3)	5/277	(1.8)
	Black	1/10	(10.0)	0/2	(0.0)	0/1	(0.0)
	Asian	0/1	(0.0)	0/1	(0.0)	0/6	(0.0)
	Hispanic American	2/9	(22.2)	0/7	(0.0)	0/3	(0.0)
	Indian	NA	NA	0/1	(0.0)	NA	NA
	Missing	NA	NA	1/97	(1.0)	2/97	(2.1)
Diarrhea	Caucasian	104/182	(57.1)	77/276	(27.9)	29/277	(10.5)
	Black	7/10	(70.0)	0/2	(0.0)	0/1	(0.0)
	Asian	1/1	(100)	0/1	(0.0)	1/6	(16.7)
	Hispanic American	5/9	(55.6)	2/7	(28.6)	1/3	(33.3)
	Indian	NA	NAv	1/1	(100)	NA	NA
	Missing	NA	NA	46/97	(47.4)	7/97	(7.2)
Mucositis/ Stomatitis	Caucasian	64/182	(35.2)	22/276	(8.0)	2/277	(0.7)
	Black	2/10	(20.0)	0/2	(0.0)	0/1	(0.0)
	Asian	0/1	(0.0)	0/1	(0.0)	0/6	(0.0)
	Hispanic American	4/9	(44.4)	0/7	(0.0)	0/3	(0.0)
	Indian	NA	NA	0/1	(0.0)	NA	NA
	Missing	NA	NA	6/97	(6.2)	0/97	(0.0)
Neuropathy-sensory	Caucasian	37/182	(20.3)	21/276	(7.6)	10/277	(3.6)
	Black	2/10	(20.0)	0/2	(0.0)	0/1	(0.0)
	Asian	0/1	(0.0)	0/1	(0.0)	0/6	(0.0)
	Hispanic American	1/9	(11.1)	0/7	(0.0)	0/3	(0.0)
	Indian	NA	NA	0/1	(0.0)	NA	NA
	Missing	NA	NA	18/97	(18.6)	4/97	(4.1)

n = number of patients with event, N = total number of patients in the group; RCC = renal cell carcinoma; NA = not applicable.

Source: Table 16.1.15/7 in Study 100391 Part B MRR located in Module 5.3.5.2.1 and Table 16.1.13/7 in Study 11213 MRR located in Module 5.3.5.1.1.

There were no obvious race-specific safety concerns, although the number of non Caucasians is too small to draw a definitive conclusion.

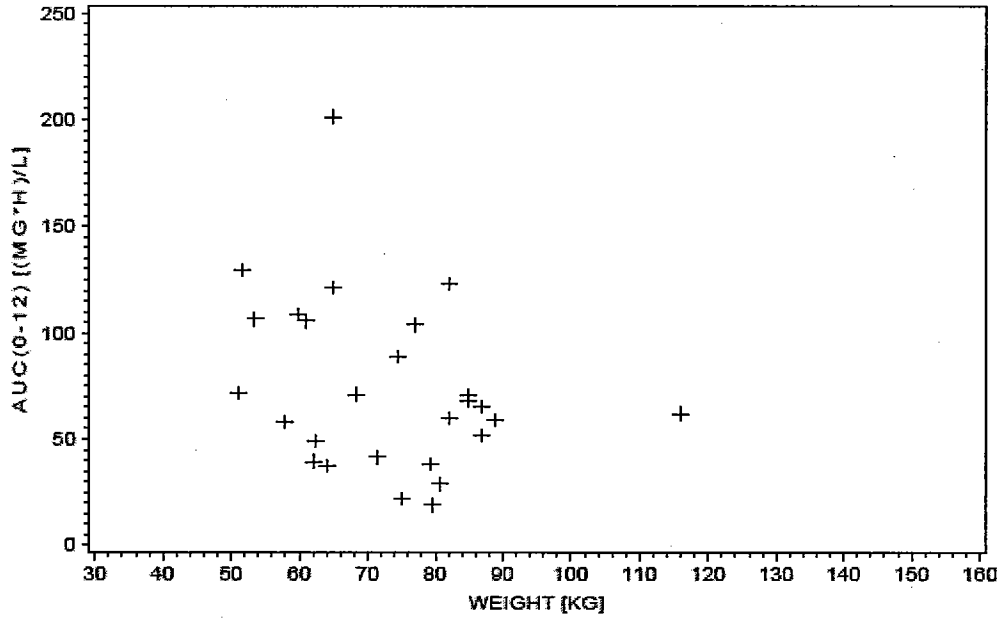
In study 11213 only 1 patient in the sorafenib group and 6 patients in the placebo group were Asians. Due to this limited number of patients in non-Caucasian race categories, formal sub-analyses of race were not conducted.

Size

There was no significant correlation between $C_{max,ss}$ or $AUC_{(0-12),ss}$, and body weight. Data from patients treated at 400 mg bid dose-level are presented below in **FDA Figure 9**.

FDA Figure 9. Applicant's Figure 3-11 from Page 96 of the Summary of Clinical Pharmacology Studies

Figure 3-11: Relationship between body weight and steady state sorafenib $AUC_{(0-12),ss}$ values following administration of 400 mg bid sorafenib in Studies 10164, 100277, 100283 and 100342 (Modules 5.3.3.2.2, 5.3.3.2.3, 5.3.3.2.1 and 5.3.3.2.4, respectively)



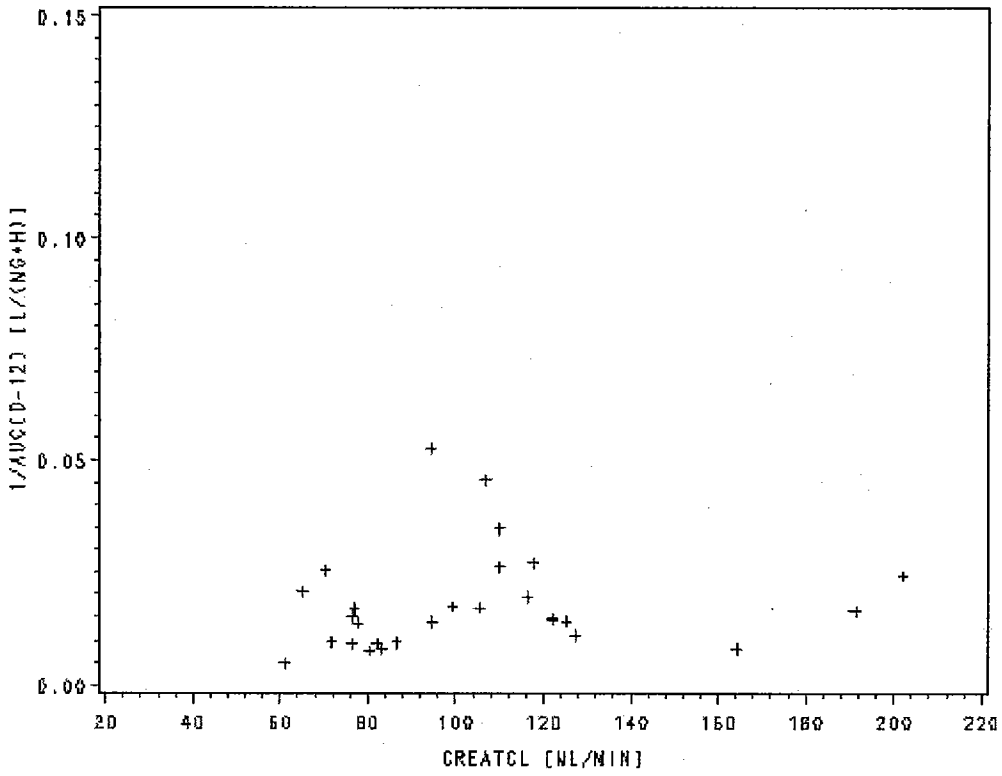
Organ dysfunction

Renal Impairment

The relationships between $1/AUC_{(0-12),ss}$, and Cockroft-Gault creatinine clearance in patients treated with 400 mg bid are presented in **FDA Figure 10.** There is no clear change in sorafenib exposure in patients with mild to moderate renal impairment.

FDA Figure 10. Applicant's Figure 3-12 from Page 97 of the Summary of Clinical Pharmacology Studies

Figure 3-12: Relationship between calculated creatinine clearance (CREATCL) and steady state plasma sorafenib $AUC_{(0-12),ss}$ values following administration of 400 mg bid sorafenib in Studies 10164, 100277, 100283, 100342, (Modules 5.3.3.2.2, 5.3.3.2.3, 5.3.3.2.1, 5.3.3.2.4, respectively)



Hepatic Impairment

Study 10874 was performed in patients with advanced hepatocellular carcinoma; all 28 patients sampled for pharmacokinetics were hepatically impaired; there was no control group. Twenty-one of the 28 patients received 400 mg bid continuously; 15 were Child-Pugh A and 6 were Child-Pugh B. Samples were collected on Day 29 of dosing (steady-state); 1 day prior or after Day 29 was allowed. As many patients did not provide 10-hour or 12-hour plasma samples, AUC_{0-8h} (instead of AUC_{0-12h}) was given primary consideration in the pharmacokinetics analysis.

As shown in **FDA Table 20.**, AUC_{0-8h} was 19% higher in Child-Pugh B patients than in Child-Pugh A patients.

FDA Table 20. Applicant's Table 2-8 from Page 35 of the Summary of Clinical Pharmacology Studies

Table 2-8: Sorafenib plasma pharmacokinetic parameters (geometric mean, %CV) in hepatically impaired cancer patients dosed 400 mg bid (Study 10874, Module 5.3.5.2.3)

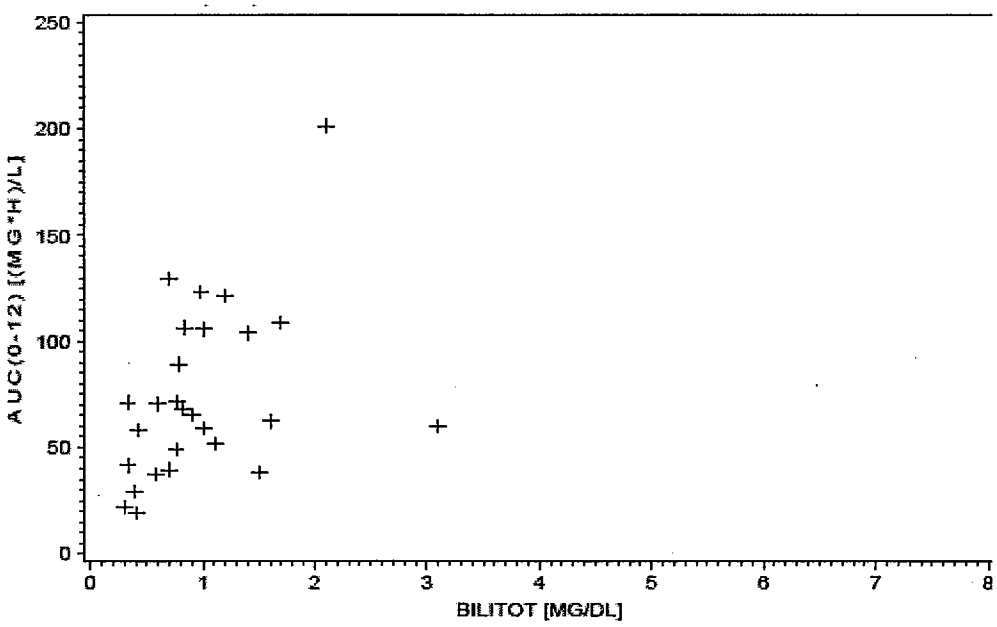
Child Pugh Status		$AUC_{[0-8],ss}$ (mg*hr/L)	$C_{max,ss}$ (mg/L)	$t_{max,ss}$ (hr)
Child Pugh A	N=14			
	Geometric mean	25.4	4.92	1.0
	Approx. CV%	38.4%	38.7%	(0-12)
Child Pugh B	N=8			
	Geometric mean	30.3	5.97	0.5
	Approx. CV%	82.1%	73.8%	(0-8)

$AUC_{(0-8)}$ was reported because plasma samples were consistently collected only up to 8 hours in all patients. Median (instead of geometric mean) and range (instead of approximate CV%) is reported for t_{max}.

Baseline serum total bilirubin was reported in cancer patients who entered Phase I trials. There was no apparent relationship between $AUC_{(0-12),ss}$, and serum total bilirubin (**FDA Figure 11**).

FDA Figure 11. Applicant's Figure 3-13 from Page 99 of the Summary of Clinical Pharmacology Studies

Figure 3-13: Relationship between serum total bilirubin (BILITOT) and steady state plasma sorafenib $AUC_{(0-12),ss}$ values following administration of 400 mg bid sorafenib in Studies 10164, 100277, 100283 and 100342, (Modules 5.3.3.2.2, 5.3.3.2.3, 5.3.3.2.1, 5.3.3.2.4, respectively)



Baseline AST and ALT values were used to assess for hepatic impairment in the primary efficacy and safety studies. Patients with baseline AST and ALT less than 1.8x ULN

were considered to have normal hepatic function. Patients with AST or ALT between 1.8 and 3x ULN normal were considered to have mild hepatic impairment, and those with AST or ALT greater than 3x ULN were considered to have moderate hepatic impairment. In Study 100391, one patient had mild hepatic impairment and one patient had moderate hepatic impairment at baseline. In Study 11213, there were 4 patients in the placebo group and 12 patients in the sorafenib group with mild hepatic impairment at baseline; there were 2 patients in the placebo group and 4 in the sorafenib group with moderate hepatic impairment at baseline. No formal analyses were done for these small groups. After examining the clinical outcomes of these patients, the Applicant concluded that the adverse event profile for sorafenib in patients with hepatic impairment and those with normal liver function are similar. These data were brought to the attention of the reviewing Medical Officer.

An analysis of effectiveness in patients with hepatic impairment was not conducted.

2.3.2 Based upon what is known about exposure-response relationships and their variability and the groups studied, healthy volunteers vs. patients vs. specific populations (examples shown below), what dosage regimen adjustments, if any, are recommended for each of these groups? If dosage regimen adjustments are not based upon exposure-response relationships, describe the alternative basis for the recommendation.

No dosage adjustment recommendations are recommended.

The clinical study upon which approval will be based used a single starting dose of 400 mg bid. Dose escalation for patients that tolerated 400 mg was not part of the study design. The study also not did include standardized dose reductions for patients that did not tolerate 400 mg bid. Thus, in the absence of pharmacokinetic data indicating that a demographic group or sub-population has significantly different plasma concentrations than those that occurred in patients administered 400 mg bid, there is no basis for adjusting regimens.

2.3.2.1 Elderly

No dosage regimen adjustments are recommended.

2.3.2.2 Pediatric patients. Also, what is the status of pediatric studies and/or any pediatric plan for study?

We are unsure of the Applicant's plans for studying pediatric patients. A waiver for pediatric studies is automatically granted under Orphan Drug regulations.

2.3.2.2 Gender

No dosage regimen adjustments are recommended.

2.3.2.4 Race

No dosage regimen adjustments are recommended.

2.3.2.5 Renal impairment

No dosage regimen adjustments are recommended.

2.3.2.6 Hepatic impairment

No dosage regimen adjustments are recommended.

2.3.2.7 What pharmacogenetics information is there in the application and is it important or not?

While Study 11213 included gene expression profiling of blood cells and tumor biopsies, these data are currently being analyzed and are not reported in the NDA. We are recommending that completion and reporting of these analyses be a Phase 4 commitment, should sorafenib be approved.

2.3.2.8 What pregnancy and lactation use information is there in the application?

There is no pregnancy and lactation use information in the application.

Sorafenib has been shown to be teratogenic and demonstrated embryo-fetal toxicity with post-implantation loss, resorptions, skeletal retardations, and retarded fetal weight in rats and rabbits. The effects occurred at doses considerably below 500 mg/m2, the recommended clinical dose on a body surface area basis.

It is not known whether sorafenib is excreted in human milk. Following administration of ^{14}C-sorafenib to lactating Wistar rats, approximately 27% of the radioactivity was recovered into the milk. The milk to plasma AUC ratio was 4.9:1.

2.3.2.9 Are there other human factors that are important to understanding the drug's efficacy and safety?

The application does not describe any "other human factors" that are important to understanding the drug's efficacy and safety.

2.4. Extrinsic Factors

2.4.1 What extrinsic factors (drugs, herbal products, diet, smoking, and alcohol use) influence dose-exposure and/or -response and what is the impact of any differences in exposure on response?

Other than drugs, extrinsic factors were not studied.

The effect of prior interferon therapy on progression-free survival and time-to-progression was analyzed and is reproduced below (**FDA Table 21.**).

FDA Table 21. Applicant's Table 3-43 from Page 104 of the Summary of Clinical Efficacy

Table 3-43: Hazard Ratios with the Subgroup Analyses by History of Prior Interferon and/or IL-2 Therapy in Study 11213
(Population: Patients Valid for Intent to Treat)

Variable	Prior Interferon and/or IL-2 Therapy	N	Hazard Ratio (Sorafenib/Placebo)	95% Confidence Interval
Progression-Free Survival - Independent Review	No	137	0.35	(0.19, 0.63)
	Yes	632	0.47	(0.37, 0.60)
Progression-Free Survival - Investigator Assessed	No	137	0.43	(0.25, 0.74)
	Yes	632	0.45	(0.35, 0.56)
Time to Disease Progression - Independent Review	No	137	0.32	(0.16, 0.62)
	Yes	632	0.45	(0.35, 0.58)
Time to Disease Progression - Investigator Assessed	No	137	0.38	(0.21, 0.68)
	Yes	632	0.43	(0.33, 0.55)

N = total number of patients in the group; IL-2 = interleukin-2.
Source: Table 14.2/11, 14.2/12, 14.2/13 and 14.2/14 in Study 11213 MRR located in Module 5.3.5.1.1.

2.4.1.1 Based upon what is known about exposure-response relationships and their variability, what dosage regimen adjustments, if any, do you recommend for each of these factors? If dosage regimen adjustments across factors are not based on the exposure-response relationships, describe the basis for the recommendation.

No dosage regimen changes are recommended.

2.4.2 Drug-drug interactions

2.4.2.1 Is there an *in vitro* basis to suspect in vivo drug-drug interactions?

Section 2.2.5.6 discusses the ability of CYP P450 enzymes to metabolize sorafenib and Section 2.4.2.3 discusses the ability of sorafenib to inhibit CYP P450 enzymes.

2.4.2.2 Is the drug a substrate of CYP enzymes? Is metabolism influenced by genetics?

Section 2.2.5.6 discusses the ability of CYP P450 enzymes to metabolize sorafenib. There is no data indicating that metabolism is influenced by genetics.

2.4.2.3 Is the drug an inhibitor and/or an inducer of CYP enzymes?

Inhibition

FDA Table 22. summarizes in vitro studies of sorafenib as a CYP inhibitor. It is derived from the Applicant's Table 5-2 on Page 25 of the Applicant's Non-clinical Pharmacokinetics Written Summary.

FDA Table 22. Inhibition of in vitro metabolism of probe CYP substrates by sorafenib			
CYP isoform	**Substrate**	**Enzyme source**	**I / Ki**
1A2	Phenacetin	Human liver microsomes	no inhibition
2D6	Dextromethorphan	Human liver microsomes	0.75
3A4	Testosterone	Human liver microsomes	0.63
	Midazolam	Human liver microsomes	0.57
1A2	Phenacetin	Recombinant enzyme	0.07
2A6	Coumarin	Recombinant enzyme	no inhibition
2B6	7-Ethoxy-trifluoromethyl-coumarin	Recombinant enzyme	2.68
2C8	Paclitaxel	Recombinant enzyme	6.92
	Amodiaquine	Recombinant enzyme	23.71
2C9	Diclofenac	Recombinant enzyme	2.27
	Tolbutamide	Recombinant enzyme	2.16
2C19	S-Mephenytoin	Recombinant enzyme	0.98
2D6	Bufuralol	Recombinant enzyme	4.15
2E1	Chloroxazone	Recombinant enzyme	no inhibition
3A4	Testosterone	Recombinant enzyme	3.39
	Testosterone	Recombinant enzyme	0.34

Because of the discrepancy between the two sets of experiments performed using testosterone in recombinant enzymes, a definitive rank order for the effects observed cannot be made; the two alternative rank orderings are:
2C8 > 2D6 > 3A4 > 2B6 > 2C9 > 2C19 > 1A2 > 2A6 = 2E1
2C8 > 2D6 > 2B6 > 2C9 > 2C19 > 3A4 > 1A2 > 2A6 = 2E1

A clinical drug-drug interaction study of the effect of steady-state sorafenib dosing on the pharmacokinetics of midazolam (CYP3A4), omeprazole (CYP2C19), and the urinary excretion of dextromethorphan (CYP2D6) was performed. Sorafenib did not alter the pharmacokinetics of midazolam (**FDA Table 23.**).

FDA Table 23. Applicant's Table 2-32 from Page 70 of the Summary of Clinical Efficacy

Table 2-32: Summary of midazolam PK parameters (geometric LS mean) following administration of 2 mg midazolam alone (Day –1) or on a background of sorafenib 400 mg bid (Day 28)

	Day -1	Day 28	LS Mean Ratio (Day 28:Day -1)	90% CI
AUC (µg*h/L)	36.69	31.05	0.85	(0.75, 0.95)
C_{max} (µg/L)	12.05	11.81	0.98	(0.88, 1.09)

Plasma sampling for omeprazole was limited to samples 3 and 6 h post-dose. The Applicant's analysis of the ratio of omeprazole to its 5-OH metabolite is reproduced below as **FDA Table 24.**

FDA Table 24. Applicant's Table 2-35 from Page 73 of the Summary of Clinical Efficacy

Table 2-35: Ratios of 5-OH omeprazole/omeprazole in plasma 3 and 6 hours after dosing of 20 mg omeprazole alone (Day -1) or on a background of 400 mg bid sorafenib (Day 28)

	Day -1	Day 28	LS Mean Ratio (Day 28:Day –1)	90% CI
3 hour sample	0.62	0.77	1.26	(1.11, 1.42)
6 hour sample	1.27	1.23	0.97	(0.68, 1.38)

The ratio of omeprazole plasma concentrations (Day 28 ÷ Day -1) was 1.40 for the 3 h timepoint and 1.27 for the 6 h timepoint (FDA analysis derived from the Applicant's Table 14.4/11.3 on Page 323-4 of the Applicant's Study Report 10926 MRC 01293 – 1.).

The Applicant's analysis of the urinary excretion of dextromethorphan and its metabolite dextrorphan is reproduced below as **FDA Table 25.**

FDA Table 25. Applicant's Table 2-34 from Page 72 of the Summary of Clinical Efficacy

Table 2-34: **Summary of urinary excretion ratio of dextromethorphan to dextrorphan following administration of 30 mg dextromethorphan alone (Day -1) or on a background of 400 mg bid sorafenib (Day 28)**

	Day -1	Day 28	LS Mean Ratio (Day 28:Day -1)	90% CI
DM ratio	0.0053	0.0050	0.95	0.70, 1.30

The Applicant has an ongoing study to examine the effect of sorafenib on paclitaxel (a CYP 2C8 substrate) pharmacokinetics: Study 100375, Effect of sorafenib on paclitaxel and carboplatin safety and PK.

In Study 11213, percent change in PT-INR was assessed for patients treated with the CYP 2C9 substrate warfarin. Compared to placebo, sorafenib does not appear to increase PT-INR in patients on warfarin (**FDA Table 26.**).

FDA Table 26. Applicant's Table 3-23 from Page 120 of the Summary of Clinical Efficacy

Table 3-23: **Percent change in PT-INR from baseline following concomitant use of warfarin and sorafenib in Study 11213 (Module 5.3.5.1.1)**

PT-INR variable	Statistic	Sorafenib N (% incidence rate)	Placebo N (% incidence rate)
> 50% increase from baseline	N (% incidence rate)	4 (36.4%)	6 (60%)
> 100% increase from baseline	N (% incidence rate)	2 (18.2%)	2 (20.0%)
Maximum % increase from baseline	N, Mean % maximum change	11, 68.9%	10, 109%

Induction

The potential of sorafenib to induce human CYP1A2 and 3A4 was investigated in cultured human hepatocytes of two different donors. Cells were exposed with 0.01 to 50 µg/mL sorafenib for five days in comparison to the prototypic inducers omeprazole (OME, CYP1A2), rifampicin (RIF, CYP3A4), and phenobarbital (PB, CYP3A4).

The study revealed no inductive effect of sorafenib on human CYP1A2 and CYP3A4 after repeated exposure, whereas OME (100 µM), RIF (50 µM), and PB (2 mM) showed their inducer-specific changes of the CYP isoform activities.

Assessment of the induction potential of sorafenib was hampered at higher concentrations of sorafenib by the loss of cell viability, measured as reduction of the tetrazolium dye MTT. At 10 and 50 µg/mL sorafenib a decrease of the MTT reduction activity to less than 5 % of control was observed. This effect was accompanied by a loss of CYP enzyme activities.

In conclusion, these results provide evidence, that sorafenib is not an inducer of human CYP1A2 and 3A4 up to a concentration of at least 3 µg/mL (corresponding to an unbound *in vitro* concentration of approximately 800 ng/mL). Following repeated administration of 400 mg b.i.d. sorafenib (as its tosylate BAY 54-9085) to patients, plasma levels reached 7.7 mg/L, corresponding to an unbound fraction (fu: 0.5 %) in plasma of 38.5 ng/mL. This unbound concentration of sorafenib in plasma is 20-fold lower than the unbound concentration in the cellular assay. Therefore, the risk of sorafenib causing clinically significant drug interactions through induction of CYP enzymes is low.

2.4.2.4 Is the drug a substrate and/or an inhibitor of P-glycoprotein transport processes?

Permeability evaluations in Caco-2 cells indicate that sorafenib is a highly permeable compound. The efflux ratio of sorafenib for transport from basolateral → apical side to transport from the apical → basolateral side of Caco-2 cells, ranged from 2.9 to 4.7. Given that sorafenib is highly permeable, the degree of efflux is not expected to result in an effect on overall absorption in man.

The inhibitory potency of sorafenib towards the human P-gp (P-glycoprotein) efflux pump was determined in two *in vitro* cell assays. In the Calcein-AM assay, no effect on the efflux of Calcein-AM was observed up to a concentration of 50 µM. Sorafenib does not show any affinity for the human P-gp multi-drug resistance protein in this *in vitro* assay. The second assay examined the active efflux of loperamide and dipyridamole in L-MDR1 cells. These P-gp substrates showed high efflux ratios in these cells. The P-gp mediated efflux of loperamide and dipyridamole was inhibited by increasing concentrations of sorafenib. The IC_{50} for the inhibition of loperamide and dipyridamole efflux was 0.84 µM and 1.24 µM, respectively. These IC_{50} values are significantly lower than the plasma concentrations observed during clinical studies. The different results obtained within the two assays reported here may appear to be inconsistent, however it is known that some P-gp substrates like digoxin show false negative results in the Calcein-AM assay.

These *in vitro* assays indicate that sorafenib has an inhibitory potency towards the human P-gp efflux pump. Since available data indicate that plasma sorafenib concentrations in clinical trials at 400 mg bid are several-fold greater than the measured IC_{50} values, there is a potential that sorafenib may inhibit the transport of drugs by the P- gp pathway. However, literature suggests that in vitro P-gp results may not always be predictive of in

vivo drug absorption-related interactions (Lin J. Clinical Relevance of P-Glycoprotein in Drug Therapy. Drug Metabolism Reviews 2003;Vol. 35, No. 4:417-454). As an example, dipyridamole has a similar P-gp inhibitory potency of sorafenib, yet does not cause a significant increase in digoxin exposure (Verstuyft C et al. Dipyridamole enhances digoxin bioavailability via Pglycoprotein. Clin Pharmacol Ther;2003 Jan;73(1):51-60.). Thus, the likelihood that sorafenib will cause clinically significant interactions when co-administered with substrates of P-gp is unknown.

2.4.2.5 Are there other metabolic/transporter pathways that may be important?

Sorafenib inhibits UGT1A1 and UGT1A9 with K_I values of 1 - 2 μM (I/K_I values of 8.3 – 16.6).

2.4.2.6 Does the label specify co-administration of another drug (e.g., combination therapy in oncology) and, if so, has the interaction potential between these drugs been evaluated?

No, the indication is for monotherapy.

2.4.2.7 What other co-medications are likely to be administered to the target patient population?

Vitamin K antagonists such as warfarin were reported as concomitant medications in 25 placebo patients (6.5%) and 17 sorafenib patients (2.6%) in Study 11213, and in 13 patients (6.4%) in Study 100391. Analysis of adverse events according to use of vitamin K antagonists showed that there was no increased rate of adverse events in patients who were taking vitamin K antagonists, although the numbers taking these medications were low. Of the 13 patients in Study 100391, who were receiving concomitant vitamin K antagonists, 5 patients (38.5%) had an adverse event in the CTCAE category Hemorrhage: 1 patient had Grade 3 hematuria, and the remaining patients had Grade 1 events (hemoptysis, epistaxis and hemorrhage-other).

Hemorrhagic events were reported in 40/189 patients (38.5%) who were not receiving vitamin K antagonists; these included 1 Grade 5 event, 7 Grade 3 events and 31 Grade 1 events. Of the 17 sorafenib patients in Study 11213 who were receiving concomitant vitamin K antagonists, 2 (11.8%) had an adverse event in the CTCAE category Hemorrhage/Bleeding: 1 was Grade 2 genitourinary bleeding, and 1 was Grade 3 gastrointestinal bleeding.

One of the 25 placebo patients (5.3%) who were receiving concomitant vitamin K inhibitors had a hemorrhagic event (Grade 1 epistaxis). Narratives for these events are found in Section 14.3 of the report for Study 11213 located in Module 5.3.5.1.1. Bleeding events are discussed in detail in Section 2.1.5.6. In Study 11213, percent change in PT-INR was assessed for patients treated with warfarin. Compared to placebo, sorafenib does not appear to increase PT-INR in patients on warfarin. In general, these

data do not suggest an interaction between vitamin K antagonists and sorafenib, however, coagulation parameters should be monitored and doses of vitamin K antagonists adjusted accordingly while taking sorafenib.

2.4.2.8 Are there any in vivo drug-drug interaction studies that indicate the exposure alone and/or exposure-response relationships are different when drugs are co-administered?

Ketoconazole

Sorafenib pharmacokinetics were evaluated following a single 50 mg sorafenib dose prior to and during multiple dosing of 400 mg ketoconazole administered once daily for 7 days. Ketoconazole does not increase the exposure of sorafenib **FDA Table 27**. This is consistent with the observation that sorafenib is metabolized by two parallel pathways: oxidative metabolism and glucuronidation.

FDA Table 27. Applicant's Table 3-8 from Page 103 of the Summary of Clinical Pharmacology

Table 3-8: Sorafenib plasma AUC and C_{max} parameters and ratios of (geometric least square means) in the presence and absence of ketoconazole administration (Study 10927, Module 5.3.3.4.1)

Sorafenib PK parameter	Sorafenib (reference) Geo. LS Mean	Sorafenib + ketoconazole (treatment) Geo. LS Mean	Ratio of LS Mean	Lower limit of 90% CI	Upper limit of 90% CI
AUC (mg*hr/L)	11.0	9.82	0.89	0.69	1.14
C_{max} (mg/L)	0.46	0.34	0.74	0.56	0.97
$t_{1/2}$ (hr)	29.0	29.4	1.01	0.80	1.29

LS mean = least squares mean; CI = confidence interval.

Ketoconazole is also a strong inhibitor of the P-gp transporter. Since this clinical study did not show an effect of ketoconazole on sorafenib PK, it is concluded that co-administration of ketoconazole-like inhibitors of P-gp transport are unlikely to significantly alter the pharmacokinetics of sorafenib in plasma *in vivo*.

Gemcitabine

Gemcitabine is converted by cytidine deaminase to deoxydifluorouridine (dFdU). Since a clinical trial was being conducted to evaluate the combination of sorafenib with gemcitabine, pharmacokinetic evaluations were performed to determine if there was an interaction between these two agents.

Even though a pharmacokinetic interaction between sorafenib and gemcitabine was not anticipated based on known metabolic/elimination pathways, the possibility of an interaction between these two agents was evaluated as part of a Phase I combination study.

In this dose-escalation study, gemcitabine was administered as a one-half hour intravenous infusion at a dose of 1,000 mg/m2 weekly for seven weeks followed by a one-week holiday. After this eight week period, gemcitabine was administered at a dose of 1,000 mg/m2 weekly for three weeks followed by a one-week washout. Sorafenib was administered continuously starting on Day 2 of Cycle 1 at doses of 100, 200 and 400 mg bid in Cohorts 1, 2, and 3, respectively.

Gemcitabine pharmacokinetics were evaluated on Day 1 (Day 1, Cycle 1) in the absence of sorafenib and on Day 15 (Day 15, Cycle 1) in the presence of sorafenib. Sorafenib pharmacokinetics were evaluated on Day 14 (Day 14, Cycle 1) in the absence of gemcitabine and on Day 15 (Day 15, Cycle 1) in the presence of gemcitabine. Results for the 400 mg bid cohort are shown in **FDA Table 28.**

FDA Table 28. Pharmacokinetics following co-administration of gemcitabine and sorafenib*

AUC 0-t	Cmax
Gemcitabine	
1.41 (C.I. not calculated)	1.41 (0.57 – 3.52)
dFdU	
0.91 (0.74 – 1.18)	1.10 (0.98 – 1.23)
Sorafenib	
0.92 (0.39 – 2.19)	0.83 (0.40 – 1.70)

*values are mean (90% confidence interval) of the ratio of each drug given concomitantly and alone. n = 4 for all groups

While the small numbers (n = 4) and the poor timing of sampling for gemcitabine (half-life of gemcitabine is approximately 45 minutes and sampling was predose, 0.5, 1, 2, 4, 8, 12 and 24 h), make conclusions tenative, it appears that there is no pronounced pharmacokinetic drug interaction from this combination.

Oxaliplatin

Oxaliplatin undergoes rapid and extensive non-enzymatic biotransformation. Sorafenib is metabolized by CYP3A4 and glucuronidation and inhibits a variety of cytochrome P450 drug metabolizing enzymes. Even though a pharmacokinetic interaction between sorafenib and oxaliplatin was not anticipated based on known metabolic/elimination pathways, the possibility of an interaction between these two agents was evaluated as part of a Phase I combination study.

In this dose-escalating study, 130 mg/m2 oxaliplatin was administered as a 2-hour IV infusion on Day 1 of each three-week cycle. Sorafenib was administered continuously

starting from Day 4 of Cycle 1. The dose of sorafenib was 200 mg bid in Cohort 1 (50 mg tablets), 400 mg bid in Cohort 2 (50 mg tablets) and 400 mg bid in Cohorts 3 and 4 (200 mg tablets). Cancer patients in Cohort 4 had previously progressed on oxaliplatin containing therapy.

Plasma samples to characterize the pharmacokinetics of total and unbound platinum were collected up to 48 hours post-dose on Day 1 of Cycle 1 and Day 1 of Cycle 2. Plasma samples to characterize the pharmacokinetics of sorafenib were collected up to 12 hours post-dose on Day 21 of Cycle 1 and Day 1 of Cycle 2. AUC was calculated up to 8 hours. Results for Cohorts 3 and 4 are shown in **FDA Table 29.**

FDA Table 29. Pharmacokinetics following co-administration of oxaliplatin and sorafenib*

	AUC 0-t	Cmax
	Total free platinum	
No prior Pt, n=9	0.91 (0.79 - 1.06)	0.74 (0.46 - 1.19)
Prior Pt n=8	0.93 (0.79 - 1.10)	0.78 (0.45 - 1.34)
	Sorafenib	
No prior Pt, n=9	0.91 (0.69 - 1.21)	0.95 (0.75 - 1.20)
Prior Pt n=8	1.12 (0.87 - 1.42)	1.09 (0.83 - 1.44)

*values are mean (90% confidence interval) of the ratio of each drug given concomitantly and alone.

It appears that there is no pronounced pharmacokinetic drug interaction from this combination.

Doxorubicin

Doxorubicin is metabolized by CYP3A4. Sorafenib is an inhibitor of CYP3A4 ($I/K_i \geq 0.57$ – Section 2.4.2.3) and is also metabolized by CYP3A4. Therefore, there is the potential for interaction when these two agents are co-administered.

Cancer patients were administered a single 60 mg/m^2 IV infusion of doxorubicin every 21 days, starting on Day 1 (Cycle 1). Following safety and pharmacokinetic evaluations for three days after the first dose of doxorubicin, sorafenib was administered at doses of 100, 200 or 400 mg twice daily, continuously, starting on Day 4. Pharmacokinetic profiles of doxorubicin and doxorubicinol were evaluated on Days 1-3 (without sorafenib) of Cycle 1 and Days 1-3 of Cycle 2 (following multiple doses of sorafenib). Sorafenib pharmacokinetics were evaluated on Day 21 of Cycle 1 prior to the second dose of doxorubicin, and on Day 1 of Cycle 2 after the second dose of doxorubicin. Sorafenib AUC was calculated up to 8 hours in many patients.

The safety and PK of sorafenib in combination with doxorubicin was evaluated using 50 mg sorafenib tablets at sorafenib doses of 100 mg bid (Cohort 1), 200 mg bid (Cohort 2), and 400 mg bid (Cohort 3). In Cohorts 4 and 5, the 400 mg bid administration of sorafenib was repeated using 200 mg tablets. Sorafenib safety and PK were evaluated in metastatic cancer patients (any cancer type) in Cohorts 1-4 and in advanced or metastatic

HCC or cholangiocellular carcinoma (CCC) patients in Cohort 5. Results for Cohorts 4 and 5 are shown in **FDA Table 30.**

FDA Table 30. Pharmacokinetics following co-administration of doxorubicin and sorafenib*

	AUC 0-t	Cmax
	Doxorubicin	
any cancer type, n=7	1.01 (0.85 - 1.19)	0.74 (0.54 - 1.02)
HCC or CCC, n=12	1.21 (0.95 - 1.54)	1.34 (0.89 - 2.00)
	Doxorubicinol	
any cancer type, n=7	1.18 (1.03 - 1.34)	1.18 (0.96 - 1.46)
HCC or CCC, n=12	1.06 (0.97 - 1.16)	1.17 (1.06 - 1.29)
	Sorafenib	
any cancer type, n=7	1.07 (0.73 - 1.57)	1.26 (0.91 - 1.75)
HCC or CCC, n=12	1.02 (0.75 - 1.40)	0.85 (0.63 - 1.15)

*values are mean (90% confidence interval) of the ratio of each drug given concomitantly and alone.

It appears that there is no pronounced pharmacokinetic drug interaction from this combination.

Irinotecan

Irinotecan is metabolically activated by carboxylesterases to SN-38. Additionally, irinotecan is metabolically inactivated by CYP3A4 to other metabolites. SN-38, the active metabolite of irinotecan, is glucuronidated by the UGT1A1 pathway. Sorafenib is a inhibitor of CYP3A4 ($I/K_i \geq 0.57$ – Section 2.4.2.3). Additionally, it is metabolized by CYP3A4 and UGT1A9 pathway. *In vitro* studies with estradiol and SN-38 as substrates revealed sorafenib to be a potent inhibitor of UGT1A1. Therefore, there is a potential for an interaction between sorafenib and irinotecan/SN-38.

In this dose escalating study sorafenib was administered orally using a continuous schedule with the exception of Cycle 1 when sorafenib administration started on Day 4. In this study, each cycle was six weeks in duration. Sorafenib was administered at 100 mg bid in Cohort 1 (50 mg tablet), 200 mg bid in Cohort 2 (50 mg tablets), 400 mg bid in Cohort 3 (50 mg tablets) and 400 mg bid in Cohort 4 (200 mg tablets). Irinotecan was administered in Cohorts 1, 2 and 3 as a 1.5 hour intravenous infusion at a dose of 125 mg/m2 weekly for four weeks followed by two weeks without administration of irinotecan. In Cohort 4 irinotecan was administered at a substantially reduced and fixed dose of 140 mg weekly for four weeks followed by two weeks without administration of irinotecan.

The pharmacokinetic profiles of irinotecan and SN-38 were determined up to 48 hours post dose on Days 1 - 3 of Cycle 1 and on Days 1 - 3 of Cycle 2. The pharmacokinetic profiles of sorafenib were determined up to 12 hours post-dose on Day 42 of Cycle 1 and on Day 1 of Cycle 2. AUC was calculated up to 10 hours. Results for Cohort 4 are shown in **FDA Table 31.**

FDA Table 31. Pharmacokinetics following co-administration of irinotecan and sorafenib*	
AUC 0-t	**Cmax**
Irinotecan	
1.42 (1.14 - 1.78)	1.73 (1.57 - 1.90)
SN-38	
1.67 (1.27 - 2.19)	1.67 (1.30 - 2.14)
Sorafenib	
1.05 (0.83 - 1.33)	0.93 (0.69 - 1.27)
*values are mean (90% confidence interval) of the ratio of each drug given concomitantly and alone. n = 6 for all groups	

It appears that sorafenib co-administration increases both irinotecan exposure (42% increase in AUC, 73% increase in Cmax) and SN-38 exposure (67% increase in both AUC and Cmax). There is no pronounced change in sorafenib exposure as a consequence of co-administration with irinotecan.

2.4.2.9 Is there a known mechanistic basis for pharmacodynamic drug-drug interactions, if any?

No pharmacodynamic drug-drug interactions have been described and there is no mechanistic basis to hypothesize that pharmacodynamic drug-drug interactions may occur.

2.4.2.10 Are there any unresolved questions related to metabolism, active metabolites, metabolic drug interactions, or protein binding?

The ability of rifampin to alter the pharmacokinetics of sorafenib is an unresolved issue, as is the ability of sorafenib to alter the pharmacokinetics of co-administered CYP 2C8 substrates such as paclitaxel. We are recommending that these issues be resolved by making completion of the Applicant's ongoing studies Phase 4 commitments.

2.4.2 What issues related to dose, dosing regimens, or administration are unresolved and represent significant omissions?

Lack of data on the ability of less toxic regimens to produce efficacy is an unresolved significant omission.

2.5. General Biopharmaceutics

2.5.1 Based on the biopharmaceutics classification system (BCS) principles, in what class is this drug and formulation? What solubility, permeability, and dissolution data support this classification?

Based upon in vitro data, the Applicant characterizes sorafenib is a BCS Class 2 compound (low solubility/high permeability). An absolute bioavailability study was not performed, and the mass balance study showed that greater than 50% of an oral dose is excreted as parent in feces. Thus, in vivo determination of permeability is not possible.

Permeability of sorafenib tosylate through the Caco-2 monolayer was determined using 0.1 μM and 1 μM [^{14}C]sorafenib tosylate. The permeability coefficient P_{app} was calculated by the equation P_{app} = dc/dt * V / (A * Co) (cm/s) with dc/dt as slope of the concentration / time curve, V as volume of acceptor chamber, A as surface area of Caco-2 monolayer and Co as initial concentration of test drug following 1 h pre-incubation in the donor chamber. Comparison of sorafenib at 1 μM with reference compounds revealed a permeability similar to ketoprofen, metoprolol, and fluvastatin and resulted in sorafenib being classified as a highly permeable compound.

Dissolution data appears in Appendix 4.2

2.5.2 What is the relative bioavailability of the proposed to-be-marketed formulation to the pivotal clinical trial formulation?

Dissolution study results indicate that the proposed to-be-marketed formulation and the pivotal clinical trial formulation have comparable dissolution.

See **Appendix 4.2.** for the complete review of the comparison of the proposed to-be-marketed formulation to the pivotal clinical trial formulation.

2.5.3 What is the effect of food on the bioavailability (BA) of the drug from the dosage form? What dosing recommendation should be made, if any, regarding administration of the product in relation to meals or meal types?

In Study 100484 single 400 mg doses were given under fasted conditions, with a moderate fat meal, and with a high fat meal. Compared to dosing under fasted conditions, mean AUC was reduced by about 29% following administration with the high-fat meal, and mean C_{max} was reduced by 38%, with both changes being statistically significant. However, when given with a moderate fat meal, mean AUC increased by approximately 14%, and mean C_{max} decreased by 17%, which were not statistically significant. These results are presented in **FDA Table 32.**, below.

FDA Table 32. Applicant's Table 2-2 from Page 4 of the Applicant's Study Report 100484-MRR 1650 - 1

Table 2-2: Point estimators (LS means) and two-sided 90% confidence intervals for the ratios of the primary parameters AUC and C_{max} of BAY 43-9006 (results of ANOVA, all subjects valid for PK, N=14-15)

Ratio	Parameter	Estimated ratio (%)	90% confidence interval (%)
High Fat/Fasting	AUC	0.71	56–91
	C_{max}	0.62	48-79
Moderate Fat vs Fasting	AUC	1.14	89-144
	C_{max}	0.83	65-107
High Fat vs Moderate Fat	AUC	0.63	50-79
	C_{max}	0.74	58-95

In Study 11213, drug was to be taken either without food or with a moderate fat meal. Study 100391 did not specify how drug should be taken relative to food. We recommended that sorafenib be administered in the fasted state.

2.5.4 When would a fed BE study be appropriate and was one conducted?

Such a study would not be appropriate and was not conducted.

2.5.5 How do the dissolution conditions and specifications ensure in vivo performance and quality of the product?

The sponsor's proposed dissolution method is not acceptable. This product has poor aqueous solubility, but dissolves rapidly and completely within 15 minutes using the proposed dissolution method. For NDA approval, we recommend the following dissolution method and specification:

USP Apparatus 2	Paddle Method
Rotation speed:	75 rpm
Volume:	900 mL
Medium:	0.1M HCl + 1% sodium lauryl sulfate (SLS)
Tolerance:	Q = [ ] in 15 minutes
Analytical Procedure(s):	[ ]

]

See **Appendix 4.2** for the complete review of dissolution.

2.5.6 If different strength formulations are not bioequivalent based on standard criteria, what clinical safety and efficacy data support the approval of the various strengths of the to-be-marketed product?

Only one presentation, a 200 mg film-coated tablet, is being marketed.

2.5.7 If the NDA is for a modified release formulation of an approved immediate product without supportive safety and efficacy studies, what

dosing regimen changes are necessary, if any, in the presence or absence of PK-PD relationship?

The NDA is not for a modified release formulation of an approved immediate release product.

2.5.8 If unapproved products or altered approved products were used as active controls, how is BE to the approved product demonstrated? What is the basis for using either *in vitro* or in vivo data to evaluate BE?

Unapproved products or altered approved products were not used as active controls

2.5.9 What other significant, unresolved issues related to *in vitro* dissolution or in vivo BA and BE need to be addressed?

There are no significant, unresolved issues related to *in vitro* dissolution or in vivo BA and BE.

2.5 Analytical section

2.6.1 How are the active moieties identified and measured in the plasma in the clinical pharmacology and biopharmaceutics studies?

The ^{14}C study was used to identify circulating moieties (see Section 2.2.3). The methods used for measurement will be described in Section 2.6.4.

2.6.2 Which metabolites have been selected for analysis and why?

Seven metabolites were measured in humans; in most studies only parent sorafenib was reported. The decision not to routinely report metabolites was likely made based upon the Applicants conclusion that < 20% of the activity following dosing resides in any single moiety other than parent. See Section 2.2.3 for a discussion of the activity of metabolites.

2.6.3 For all moieties measured, is free, bound, or total measured? What is the basis for that decision, if any, and is it appropriate?

Total sorafenib was measured. Protein binding in humans was 99.5%. However, protein binding was linear across concentrations. While measurement of free drug would have potentially improved the ability to draw conclusions from the concentration data, the linearity across concentrations is evidence that, on average, free drug is a constant fraction of total drug. Thus, total drug should, on average, reflect free drug.

2.6.4 What bioanalytical methods are used to assess concentrations?

2.6.4.1 What is the range of the standard curve? How does it relate to the requirements for clinical studies? What curve fitting techniques are used?

2.6.4.2 What are the lower and upper limits of quantification (LLOQ/ULOQ)?
2.6.4.3 What are the accuracy, precision, and selectivity at these limits?
2.6.4.4 What is the sample stability under the conditions used in the study (long-term, freeze-thaw, sample-handling, sample transport, autosampler)?
2.6.4.5 What is the QC sample plan?

During the course of the clinical development, different [ ] assays were developed and validated for the simultaneous determination sorafenib and its metabolites M1, M2, M3, M4, and M5 in plasma. In human urine, sorafenib and metabolite M2 were determined, and metabolites M7 and M8 representing glucuronides of sorafenib and M2, respectively, were determined after enzymatic hydrolysis.

Sample processing for plasma involved either [ ] followed by [ ] Sample processing of urine involved dilution of urine samples followed by [ ]

The lower limit of quantitation (LLOQ) in plasma was [ ] µg/L for sorafenib (varied by study),[ ] µg /L for M1 and [ ] µg/L for metabolites M2, M3, M4 and M5. Upper calibration ranges were changed in different methods and ranged from [ ] µg /L for different analytes.

The lower limit of quantitation (LLOQ) in urine was approximately — µg /L for sorafenib and metabolite M2. Metabolites M7 and M8, glucuronides of parent drug and metabolite M2, respectively, were measured indirectly as sorafenib and M2 after hydrolyzing the corresponding glucuronide. The LLOQ for both analytes was approximately — µg /L based on the conversion factor. Upper calibration range was approximately [ ] µg/L for sorafenib and metabolite M2 and approximately [ ] for metabolites M7 and M8.

Precision for all analytes for all methods was within —, and accuracy was within [ ]

Stability of all analytes was determined under sample handling conditions and for the duration the samples from clinical studies were stored prior to analysis. All analytes were stable under those conditions.

Review of the analytical methods for each indivdual study are included in **Appendix 4.3** of this review.

3 Detailed Labeling Recommendations

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Applicant's Original	OCPB Reviewer's Recommended Changes
Absorption and Distribution Following oral administration, sorafenib reaches peak plasma levels in approximately 3 hours. When given with a moderate-fat meal, bioavailability was similar to that in the fasted state. With a high-fat meal, sorafenib bioavailability was reduced by 29% compared to [ ] administration in the fasted state. It is recommended that NEXAVAR be administered [ ] (see **DOSAGE AND ADMINISTRATION** section). Mean C_{max} and AUC increased less than proportionally beyond doses of 400 mg administered orally twice daily. *In vitro* binding of sorafenib to human plasma proteins is 99.5%.	It is recommended that NEXAVAR be administered [ ] (see **DOSAGE AND ADMINISTRATION** section).

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4 *Appendices*

4.1 Package insert (proposed)

4.2 Review of dissolution

4.3 Review of analytical methods

4.4 Cover sheet and OCPB filing/review form

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Appendix 4.1 Package insert (proposed)

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1.14.1.3 Draft Labeling Text

The Nonclinical Reviewable Unit (RU) submitted on April 28, 2005 included draft labeling text, for the associated portions. BAYER has modified the Pregnancy Category (from – to D) and has included the revised text of the draft label in this submission.

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Appendix 4.2 Review of dissolution

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OFFICE OF CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS
DISSOLUTION REVIEW

NDA: 21-923	Submission Date (s): 7/06/2005 11/8/2005
Brand Name	Nexavar®
Generic Name	Sorafenib tosylate (BAY 43-9006)
Reviewer	Carol Noory
Primary Reviewer	Gene Williams
Team Leader	Brian Booth
OCPB Division	HFD-860
OND Division	Oncology HFD-150
Sponsor	Bayer Pharmaceutical Corporation West Haven, CT 06516
Formulation; Strength(s)	200 mg oral tablet
Indication	Cancer (Raf kinase Inhibitor

Summary

The sponsor is proposing to market the product in 200 mg oral tablets. The dissolution method development package was submitted with the NDA. This review is an evaluation of the dissolution method development study and the comparability of the proposed commercial tablet formulation to the tablets used in the Phase III clinical/primary stability studies.

1. A study was performed comparing the dissolution profiles of tablets manufactured with the commercial formulation ([ ] magnesium stearate) to the pilot scale tablet formulation ([ ], magnesium stearate). The results indicated that the tablets have comparable dissolution the paddle method, ~ rpm and 0.1M HCl [ ] SLS. The change in coating within the range of [ ] does not appear to have an effect on the in vitro performance using the method selected.

2. The firm developed and validated a dissolution procedure for sorafenib tablets.
3. Two analytical procedures for the quantification of the drug substance were evaluated and validated, [ ] Both analytical procedures were found to be interchangeable.

Comments:

1. The sponsor's proposed dissolution method is not acceptable. This product with poor aqueous solubility dissolves rapidly and completely within 15 minutes using the proposed dissolution method. In consideration of the dissolution studies conducted using the conditions recommended [ ] completed on the commercial formulation using a drug substance manufactured using an [ ] process different from the current proposed commercial US formulation, the paddle at — rpm does not need to be studied further. It appears that the most appropriate method may be the paddle method at 75 rpm using 0.1M HCl + 1% SLS. The dissolution specification should be set at Q= [ ] at 15 minutes.

II. Recommendation

1. After evaluation of all of the dissolution data submitted, including the dissolution studies conducted using the conditions recommended [ ] the following dissolution method and specification is recommended:

USP Apparatus 2	Paddle Method
Rotation speed:	75 rpm
Volume:	900 mL
Medium:	0.1M HCl + 1% sodium lauryl sulfate (SLS)
Tolerance:	Q [ ] 15 minutes
Analytical Procedure(s):	[ ]
	[ ]

This recommendation should be forwarded to the sponsor.

A. Carol Noory
Division of Pharmaceutical Evaluation I

Responses to Questions in QBR

C.6. What is the in vivo relationship of the proposed to-be-marketed formulation to the pivotal clinical trial formulation?

An f2 comparison of the dissolution profiles between the commercial formulation and the pilot formulation using 0.1M HCl + [ ] SLS as the medium and the paddle method with a rotation speed of [ ] rpm indicate that the commercial scale batch with [ ] has a comparable dissolution profile to the pilot scale clinical batch containing [ ] in the formulation. It appears that the debossing of the product has no effect on the in vitro performance using the dissolution method selected. The change in coating within the range of [ ] does not appear to have an effect on the in vitro performance using the dissolution method selected.

Dissolution Information Submitted:
The initial formulation was a 50 mg [ ] Sorafenib tosylate tablet used in Phase I trials started in 2000. In Phase II, the 200 mg dose strength was introduced, using [ ], as used for the 50 mg tablet. The major difference between the two dose strength was [ ] of the 200 mg tablets. At the end of 2002 the manufacturing process of the 200 mg dose strength was transferred from West Haven CT (USA) to Bayer AG, Leverkusen (Germany). During this transfer minor process adjustments [ ] were made, but the composition of the drug product remained unchanged.

During the scale-up from pilot to commercial batches, the target level of [ ] was increased from [ ] and a range [ ] was proposed. In addition tablet debossing was implemented to provide for identification of the tablets and tablet coating ranges were proposed. The coating components will have a fixed ratio [ ] A comparison of the formulations of the tablet core and the coating are presented in Table 1:

Table 1: Composition of sorafenib tosylate tablet formulations used in clinical trials and the proposed commercial product.

Composition [mg/tablet]	Tablet 50 mg *(Bayer Corp)* clinical studies	Tablet 200 mg *(Bayer Corp)* clinical studies	Tablet 0.2 g *(Bayer HealthCare AG)* clinical studies	Tablet 0.2 g *(Bayer HealthCare AG)* commercial product
Tablet core:				
BAY 54-9085	[			
Microcrystalline cellulose				
Croscarmellose sodium				
Hypromellose				
Magnesium stearate				
Sodium laurilsulfate				
Weight				
Film-coating:				
Hypromellose				
Titanium dioxide				
Ferric oxide (red)				
Weight of film coat				]
Total tablet weight	85.0	350.0		
Tablet shape and dimensions	6 mm round	10 mm round		

a Deviations from the target value, within the given range, may be applied only if the target value results in

b Deviations from the target value, within the given range, may be applied only if the target value results [ ]
In any case, the ratio of coating components is fixed: [ ]

c [

274 mg of sorafenib tosylate is equivalent to 200 mg of sorafenib.

The firm has proposed a range for the ingredients as seen in table 1. Changes to the core consist of [ ] magnesium stearate. The firm has indicated that this change is [ ] tablets. The other changes are to the coating. These are considered Level 1 changes according to the SUPAC IR guidance. Level 1 changes are those that are unlikely to have any

detectable impact on formulation quality and performance. In order to evaluate the impact [ ] amount proposed, the firm manufactured lots with those proportions and has submitted comparative dissolution profiles to support the changes made to the formulation of Sorafenib tosylate tablets. The effect of scale-up to commercial scale was evaluated with 5 batches. The formulation differences are shown in the following table.

Table 2: Batches tested to assess influence of scaling up to commercial scale

Batch Number	Scale	Magnesium Stearate[1]	Debossing	Coating %[2]	Studies
BX0167H	Clinical Pilot Scale	—	No	100%	Used in Phase III
BX0167J	Clinical Pilot Scale	—	No	100%	Used in Phase III
BX0167J6	Clinical Pilot Scale	—	No	100%	Used in Phase III
BXA0L43	Commercial	—	Yes	100%	
BXA0L43	Commercial	—	Yes	100%	
1. [ ]					
2. [ ]					

The firm used the following dissolution to procedures to assess the potential influence of scaling up from pilot to commercial scale and to evaluate the ranges proposed and the minor process modifications.

Apparatus: USP Paddle Method
RPMs: — rpm and — rpm
Volume of Medium: 900 mL
Medium: pH 1: 0.1M hydrochloric acid
+ 1% sodium lauryl sulfate (SLS)
pH 2:] hydrochloric acid
+ 1% sodium lauryl sulfate (SLS)
Assay: [ ]
Specification: Q= — in 15 minutes

Results are shown in the following table.

Table 3: Dissolution results for lots tested to compare debossing vs. not debossing and [illegible] vs. [illegible]

Batch	pH	N=	15 minutes	30 minutes	45 minutes	60 minutes
BX0167H	1	6				
St. dev.						
BX0167H	2	6				
St. dev.						
BXAOL43-	1	12				
St. dev.						
BXAOL43-	2	6				
St. dev.						
BXAOL43-	1	12				
St. dev.						
BXAOL43-	2	12				
St. dev.						

Evaluation of Formulation Comparability:

Dissolution profiles using the method mentioned above were generated using two media, 0.1M HCL + 1% SLS (pH 1) and — HCL + 1% SLS (pH 2). The f2 value for the commercial batch BXAOL43[illegible] was compared to Clinical batch BX0167H in both 0.1M HCL + 1% SLS (pH 1) and — HCL + 1% SLS (pH 2). The results were — at pH 1 and — at pH 2. The results are illustrated in the following figures:

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Figure 1: Comparative Dissolution Profiles of Sorafenib Tosylate 200 mg tablets
Paddle — rpm; 0.1M HCl + 1% SLS

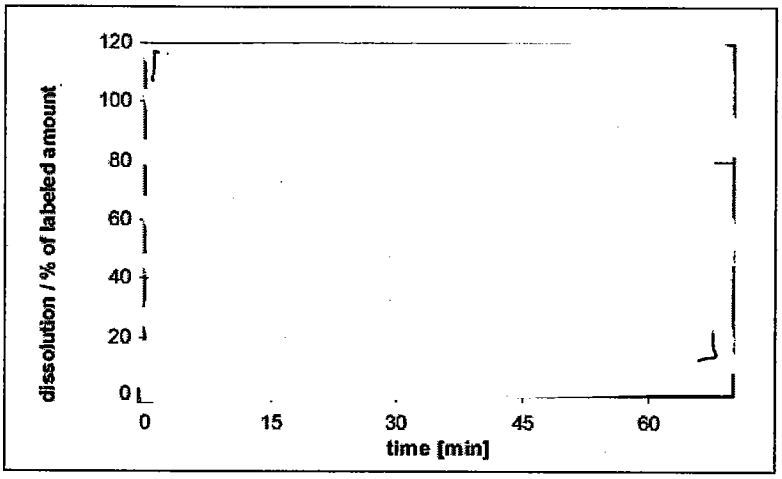
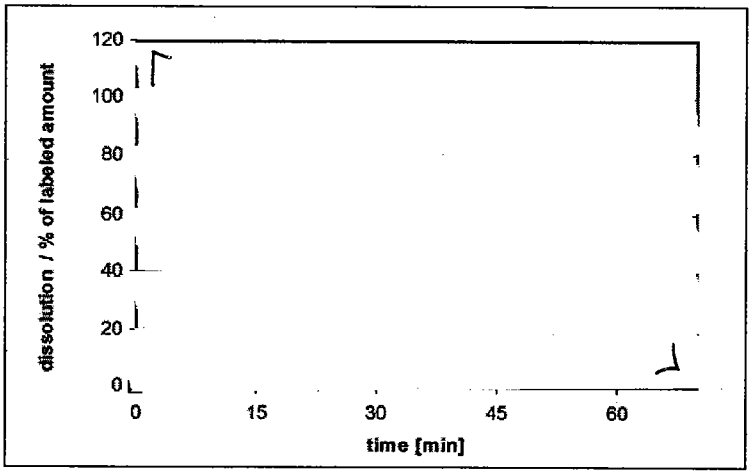


Figure 2: Comparative dissolution profiles of sorafenib tosylate 200 mg tablets
Paddle Method — rpm, — HCl + 1% SLS, pH 2



Comment: Using the method selected the formulation appear to be comparable. However, f2 comparisons are not recommended for dissolution curves which have only one or two points which can be evaluated. At the request of FDA, the sponsor provided comparative dissolution studies using the pilot and commercial scales lots of 200 mg sorafenib tosylate tablets using the paddle

method with a rotation speed of — rpm and a medium of 0.1M HCl + [ ] SLS.
The following batches were used:

BATCHES USED IN COMPARABILITY STUDY			
Batches	Mag Stearate (%)	Coating (%)	Batch size
BXA0T4N	\	100%	Commercial
BX01W11	\	100%	Pilot

The following dissolution method was used to generate the profiles:

Apparatus: Paddle Method
Rotation speed: — rpm
Medium: 0.1M HCl + [ ] sodium lauryl sulfate
Volume: 900 mL
Analytical Method: [ ]

The results are shown in the following table. F2 results are also provided.

F2 COMPARABILITY OF COMMERCIAL VS PILOT BATCH						
Batch	N=	parameter	15 min	30 min	45 min	60 min
BX01W11	12	Mean	55	64	69	72
Reference		%CV	[ ]			
		Min	[ ]			
		Max	[ ]			
BXA0T4N	12	Mean	62	68	71	75
Test		%CV	[ ]			
		Min	[ ]			
		Max	[ ]			
F2-value =67						

Comment: The batches tested give a comparable dissolution profile using the paddle method, — rpm and 0.1M HCl + [ ] SLS as the medium.

Evaluation of Proposed Ranges:

Effect of increased level of lubricant:
The change in the magnesium stearate concentration in the formulation was evaluated by testing Lot BXAOL43 a commercial scale lot which was split at the

[ ] and then processed with either [ ] magnesium stearate as the target value. These tablets were debossed. Dissolution profiles using the method mentioned above were generated using two media, 0.1M HCL + 1% SLS (pH 1) and ¯ HCL + 1% SLS (pH 2). The f2 value for the commercial batch BXAOL43 [ ] was compared to commercial batch BXAOL43 [ ] The results were — at pH 1 and ¯ at pH 2. The dissolution results are shown in the following figures. All dissolution profiles resulted in complete dissolution within 15 minutes.

Figure 3: Comparative Dissolution Profiles of Sorafenib Tosylate 200 mg tablets
Paddle rpm; 0.1M HCl + 1% SLS

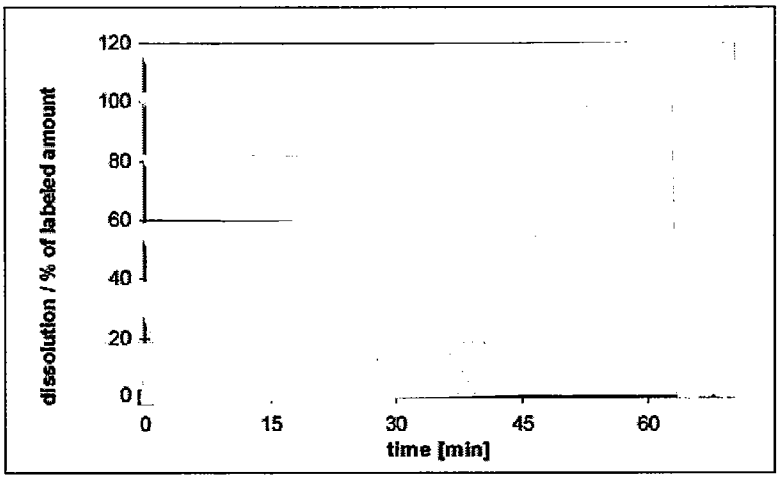
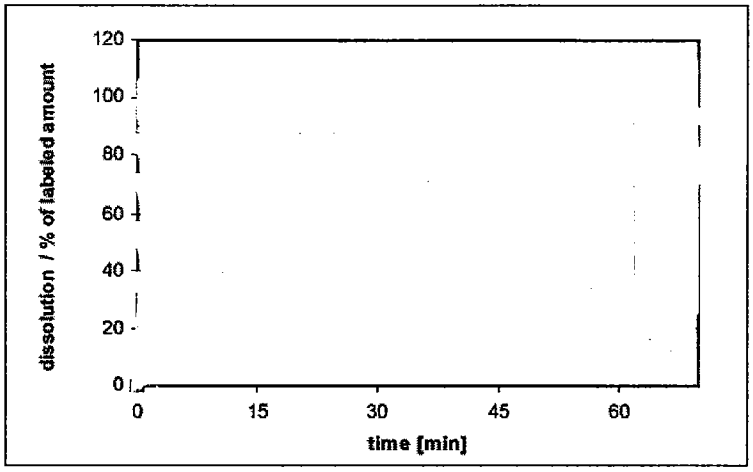


Figure 4: Comparative dissolution profiles of sorafenib tosylate 200 mg tablets
Paddle Method — rpm, — HCl + 1% SLS, pH 2



Commercial lot BXAOL43 with either [redacted] was further evaluated using the paddle method with —rpm and — rpm and the following media:

0.1M HCl + 1% SLS, pH 1.0
— HCl + 1% SLS, pH 2.0
— buffer + 1% SLS, pH 4.5
— buffer + 1% SLS, pH 6.8
— 1% SLS

The results are shown in the following figures. The f2 results are shown in the following tables.

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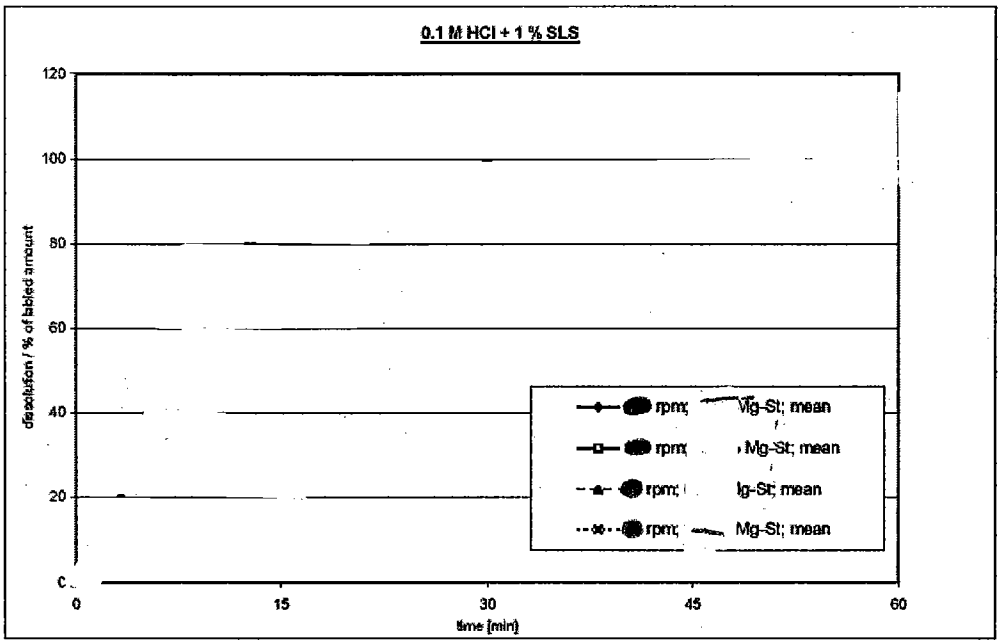
Figure 5: Comparative Dissolution Profiles of Sorafenib Tosylate 200 mg tablets manufactured with [ ] Magnesium Stearate, at — rpm and — rpm, 0.1M HCl + 1% SLS, pH 1



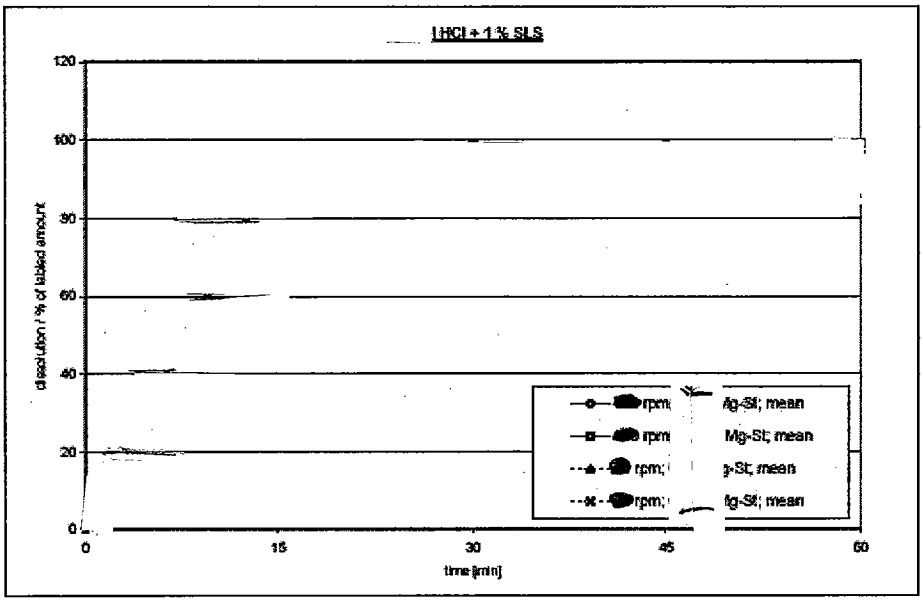
f2-value at pH 1, — rpm

Reference: BXA0L43 [ ] Magnesium stearate	
Test batch	f_2-value
BXA0L43 [ ] Magnesium stearate	98

f2-value at pH 1, — rpm

Reference: BXA0L43 [ ] Magnesium stearate	
Test batch	f_2-value
BXA0L43 [ ] Magnesium stearate	87

Figure 6: Comparative Dissolution Profiles of Sorafenib Tosylate 200 mg tablets manufactured with [redacted] rpm, [redacted] HCl, pH 2



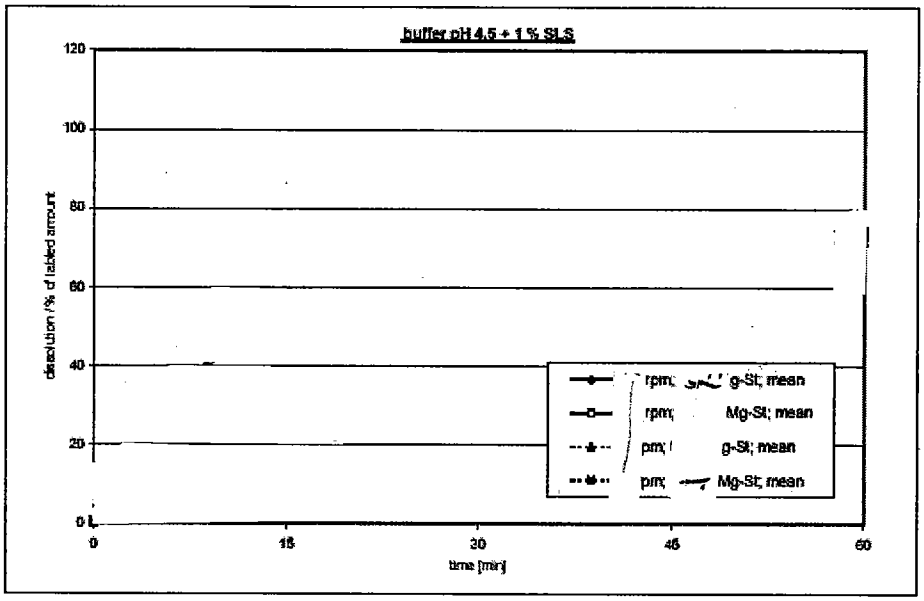
f2-value at pH 2, [redacted] rpm

Reference: BXA0L43 [redacted] % Magnesium stearate	
Test batch	f_2-value
BXA0L43 [redacted] Magnesium stearate	98

f2-value at pH 2, [redacted] rpm

Reference: BXA0L43 [redacted] % Magnesium stearate	
Test batch	f_2-value
BXA0L43 [redacted] Magnesium stearate	93

Figure 7: Comparative Dissolution Profiles of Sorafenib tosylate 200 mg tablets manufactured with [ ] magnesium stearate, at — rpm and — rpm, pH 4.5 — buffer +1% SLS



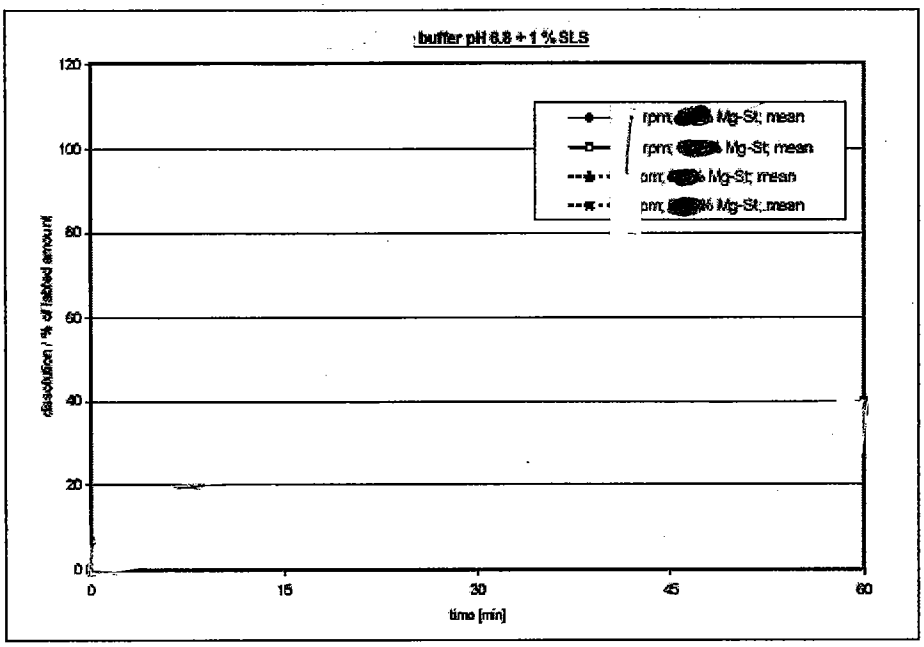
f2-value at pH 4.5, — rpm

Reference: BXA0L43 [ ] Magnesium stearate	
Test batch	f_2-value
BXA0L43	98
[ ] Magnesium stearate	

f2-value at pH 4.5, — rpm

Reference: BXA0L43 [ ] Magnesium stearate	
Test batch	f_2-value
BXA0L43	83
[ ] Magnesium stearate	

Figure 8: Comparative Dissolution Profiles of Sorafenib tosylate 200 mg tablets manufactured with [ ] magnesium stearate, at — rpm and — rpm, — buffer +1% SLS, pH 6.8



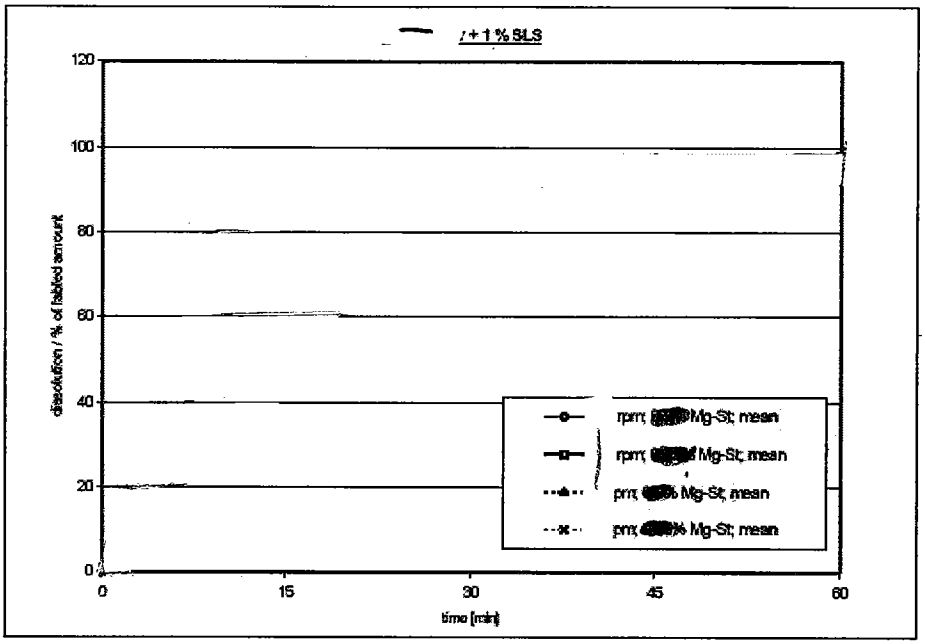
f2-value at pH 6.8, — rpm

Reference: BXA0L43	
[ ] Magnesium stearate	
Test batch	f_2-value
BXA0L43	96
[ ] Magnesium stearate	

f2-value at pH 6.8, — rpm

Reference: BXA0L43	
[ ] Magnesium stearate	
Test batch	f_2-value
BXA0L43	97
[ ] Magnesium stearate	

Figure 9: Comparative Dissolution Profiles of Sorafenib tosylate 200 mg tablets manufactured with [ ]Magnesium Stearate, at — rpm and — rpm, — + 1% SLS



f2-value in dem. , — rpm

Reference: BXA0L43 [ ]Magnesium stearate	
Test batch	f_2-value
BXA0L43	99
[ ]agnesium stearate	

f2-value in dem. — rpm

Reference: BXA0L43 [ ] Magnesium stearate	
Test batch	f_2-value
BXA0L43	94
Magnesium stearate	

Effect of Debossing:

To test the impact of debossing on the in vitro performance, another lot, BX0167H with [ ]nagnesium stearate which was not debossed was tested and compared to the [ ] debossed lot BXAOL43. Dissolution profiles using the method mentioned above were generated using two media, 0.1M HCL + 1% SLS (pH 1) and — HCL + 1% SLS (pH 2).

Effect of Range for coating amount:

The firm is requesting a range of [ ] of the tablet target coating weight. The different coating amount within a range of [ ] will only be utilized in [ ]

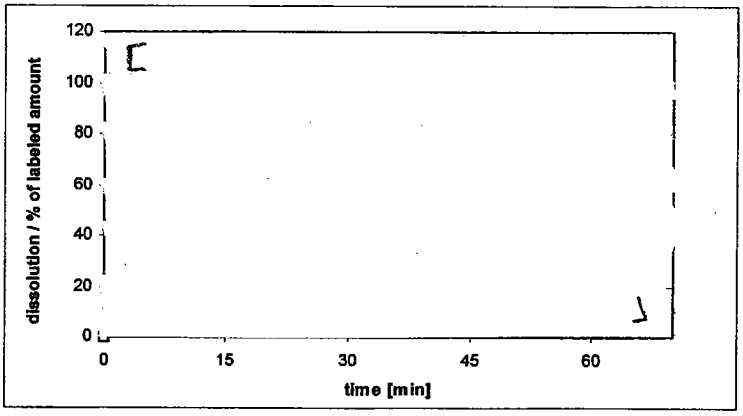
[ ] Lab scale batches were prepared to determine the impact of the scale-up range of [ ] for the coating level. The following lab scale batches were tested.

BATCH NUMBER	SCALE	MAGNESIUM STEARATE CONTENT	DEBOSSING	COATING AMOUNT MG/TABLET	COATING %
041109-A	Lab scale	[ ]	Yes	[ ]	[ ]
041109-A	Lab scale	[ ]	Yes	[ ]	[ ]
041109-A	Lab scale	[ ]	Yes	[ ]	[ ]

The results are shown in the following table and illustrated in the following graphs.

BATCH	PH	N=	15 MIN	30 MIN	45 MIN	60 MIN
041109-A- [ ] coating	1	6	[ ]			
COV						
041109-A- [ ] coating	1	6				
COV						
041109-A- [ ] coating	1	6				
COV						[ ]

Figure 2 - Comparative Dissolution Profiles of Sorafenib Tosylate Tablets with Different Coating Amounts



A comparison of the results of the dissolution profiles using the method selected indicates that the dissolution profiles are comparable.

C.7. Are the Sponsor's proposed dissolution medium and specifications acceptable?

The sponsor's proposed dissolution method uses the paddle apparatus at — rpm with 900 mL 0.1M HCl + 1% sodium lauryl sulfate (SLS) and a tolerance specification of Q= — % in 15 minutes. The dissolution method proposed is not acceptable. This low solubility product dissolves [ ] in 15 minutes. The dissolution study shows that the product reaches an asymptote in 15 minutes when using the paddle method rotating at either — rpm or — rpm and the following media: 0.1 M HCl + 1% SLS; — HCl + 1% SLS; — buffer + 1% SLS; pH 4.5; and — buffer + 1% SLS, pH 6.8. The only media that did not reach an asymptote in 15 minutes was — 1% SLS. The firm submitted additional studies conducted using conditions recommended by [ ] The formulation of the drug product is the same as that proposed in this NDA; however, the sorafenib tosylate drug substance used in the formulation was produced using the [ ] process. This change in the manufacture of the active ingredient was planned as a post approval change in the U.S. The studies compare the commercial scale batch (Batch BXA0T4N) to the pilot scale batch (Batch BX01W11) of 200 mg sorafenib tosylate tablets using the Paddle Method, — rpm and — rpm and the following media:

0.1 M HCl, pH 1.2 + 1% SLS

pH [ ]

pH 6.8 [ ] buffer [ ] + 1% SLS

[ ] + 1% SLS

Pilot scale batches BX020NE and BXA0L43 were also tested. The results are given in the following table:

DISSOLUTION USING 1% SLS; PADDLE – RPM (N=6)							
Batch	Media	parameter	15 min	30 min	45 min	60 min	90 min
BX020NE	pH 1.2 + 1% SLS	Mean	62	70	75	79	85
– rpm		%CV					
		Min	[				
		Max					]
	pH 4.0 + 1% SLS	Mean	50	69	78	81	83
		%CV					
		Min	[				
		Max					]
	pH 6.8 + 1% SLS	Mean	29	32	34	36	38
		%CV					
		Min	[				
		Max					]
	– + 1% SLS	Mean	60	72	77	81	86
		%CV					
		Min	[				
		Max					]
BX01W11	pH 1.2 + 1% SLS	Mean	59	70	74	79	86
– rpm		%CV					
		Min	[				
		Max					]
	pH 4.0 + 1% SLS	Mean	31	39	43	47	52
		%CV					
		Min	[				
		Max					]
	pH 6.8 + 1% SLS	Mean	15	21	25	29	33
		%CV					
		Min	[				
		Max					]
	– + 1% SLS	Mean	47	62	71	78	85
		%CV					
		Min	[				
		Max					]
BXA0L43	pH 1.2 + 1% SLS	Mean	59	66	71	76	82
– rpm		%CV					

		Min	[				
		Max					]
	pH 4.0 + 1% SLS	Mean	53	71	80	84	86
		%CV					
		Min	[				
		Max					]
	pH 6.8 + 1% SLS	Mean	27	30	32	33	36
		%CV					
		Min	[				
		Max					]
	— + 1% SLS	Mean	56	68	74	77	83
		%CV					
		Min	[				
		Max					]
BXA0T4P	pH 1.2 + 1% SLS	Mean	61	68	72	75	81
— rpm		%CV					
		Min	[				
		Max					]
	pH 4.0 + 1% SLS	Mean	51	70	78	83	86
		%CV					
		Min	[				
		Max					]
	pH 6.8 + 1% SLS	Mean	33	36	38	39	41
		%CV					
		Min	[				
		Max					]
	— + 1% SLS	Mean	57	68	73	77	82
		%CV					
		Min	[				
		Max					]

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Appendix 2: Analytical Method Validation for Dissolution Testing

The firm submitted an analytical method validation report for the quantitation of drug dissolved from Sorafenib tosylate 200 mg tablets measured [ ] The validation data demonstrate that the analytical procedure is suitable to measure the dissolution rate in 900 mL of 0.1 M hydrochloric acid + 1 % SLS.

1. Method Validation:

[

]

table 2: retention times of the impurities

Peak	Compound	Retention times [min.]
[		]

table 3: retention times of the impurities

Peak	Compound	Retention times [min.]
[		]

A summary of the results is given in the following table.

SUMMARY OF VALIDATION CHARACTERISTICS OF THE METHOD		
Parameter	Test	Results
Specificity:	demonstrated in the presence of impurities	
Linearity of standard solution	Range [ ]	[ ] [ ]
Linearity of test solution	Range [ ]	[ ] [ ]
Quantitation limit:	Range of test solutions [ ]	[ ] Results = [ ]
Accuracy:	Range of [ ] test solutions compared to standard solutions	[ ]
Precision: Injection repeatability	[ ]	RSD [ ]
Precision: Repeatability of the method	test solution separately [ ]	RSD [ ]
Intermediate Precision:	• [ ]	No difference under comparable conditions

	• two different [ ], at least two different days;	([ ] level)
Range:	[ ]	CI evaluated at initial determination [ ]
Stability of test solution:	Test solutions (accuracy testing) kept for [ ] at 40 °C, h. compared to freshly prepared standard solutions of the same concentration level.	stable for at least [ ] at 40 °C
* The reported concentration levels (%) of the reference standard in the standard solutions and the test solutions are based on a tablet containing 200 mg of Sorafenib (free base).		

A graphic representation of the linearity of the standard solutions is shown in the following figure.

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- Procedure: The area of each solution was measured six times. A summary of the data obtained is given in table 14.

table 14: summary of results obtained for robustness

Analytical parameter	Standard condition	Variation range
[		]

The results of the tests for robustness are given in the following table.

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Appendix 4.3 Review of analytical methods

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Appendix 4.4 Cover sheet and OCPB filing/review form

Office of Clinical Pharmacology and Biopharmaceutics
New Drug Application Filing and Review Form

General Information About the Submission

	Information		Information
NDA Number	21-923	Brand Name	NEXAVAR®
OCPB Division	Division V	Generic Name	sorafenib
Medical Division	Oncology	Drug Class	Multi-kinase inhibitor
OCPB Reviewer	Gene M. Williams, Ph.D.	Indication(s)	Applicant's Proposed: "NEXAVAR is indicated for the treatment of patients with advanced renal cell carcinoma."
OCPB Team Leader	Brian Booth, Ph.D.	Dosage Form	200 mg tablets
		Dosing Regimen	400 mg BID
Date of Submission	July 6, 2005	Route of Administration	oral
Estimated Due Date of OCPB Review		Sponsor	Bayer Corp.
PDUFA Due Date	January 6, 2005	Priority Classification	1P
Division Due Date	December 2, 2005		

Clin. Pharm. and Biopharm. Information

	"X" if included at filing	Number of studies submitted	Number of studies reviewed	Critical Comments If any
STUDY TYPE				
Table of Contents present and sufficient to locate reports, tables, data, etc.	x			
Tabular Listing of All Human Studies	x			
HPK Summary	x			
Labeling	x			
Reference Bioanalytical and Analytical Methods	x			
I. Clinical Pharmacology				
Mass balance:	x	1	1	
Isozyme characterization:	x	5	5	
Blood/plasma ratio:				
Plasma protein binding:	X	1	1	
Pharmacokinetics (e.g., Phase I) -				
Healthy Volunteers-				
single dose:				
multiple dose:				
Patients-				
single dose:				
multiple dose:	x	7	7	
Dose proportionality -				
fasting / non-fasting single dose:				
fasting / non-fasting multiple dose:				
Drug-drug interaction studies -				
In-vivo effects on primary drug:	x	1	1	
In-vivo effects of primary drug:	x	5	5	
In-vitro:				
Subpopulation studies -				
ethnicity:				
gender:				
pediatrics:				
geriatrics:				

renal impairment:				
hepatic impairment:				
PD:				
Phase 2:				
Phase 3:				
PK/PD:				
Phase 1 and/or 2, proof of concept:				
Phase 3 clinical trial:				
Population Analyses -				
Data rich:				
Data sparse:				
II. Biopharmaceutics				
Absolute bioavailability:				
Relative bioavailability -				
solution as reference:	x	1	0	
alternate formulation as reference:	x	1	0	
Bioequivalence studies -				
traditional design; single / multi dose:				
replicate design; single / multi dose:				
Food-drug interaction studies:	x	1	1	
In-Vitro Release BE	x			
(IVIVC):				
Bio-wavier request based on BCS				
BCS class	x			
III. Other CPB Studies				
Genotype/phenotype studies:				
Chronopharmacokinetics				
Pediatric development plan				
Literature References				
Total Number of Studies		23	21	

Filability and QBR comments		
	"X" if yes	Comments
Application filable?	x	
Comments sent to firm?		
QBR questions (key issues to be considered)	Comparability of clinical trial formulation to to-be-marketed formulation, pharmacokinetics in Asians, drug interactions	
Other comments or information not included above		
Primary reviewer Signature and Date		
Secondary reviewer Signature and Date		

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Gene Williams
11/23/2005 06:00:40 PM
BIOPHARMACEUTICS

Brian Booth
11/28/2005 07:04:19 AM
BIOPHARMACEUTICS

Shiew-Mei Huang
11/28/2005 08:18:12 AM
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