Clinical Study Synopsis

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The study listed may include approved and non-approved formulations or treatment regimens. Data may differ from published or presented data and are a reflection of the limited information provided here. The results from a single trial need to be considered in the context of the totality of the available clinical research results for a drug. The results from a single study may not reflect the overall results for a drug.

Bayer HealthCare

Clinical Trial Results Synopsis

Study Design Description		
Study Sponsor:	Bayer HealthCare AG	
Study Number:	12913	NCT00618982
Study Phase:	IIb	
Official Study Title:	A phase II, multi-center, open-label study to assess the efficacy, safety, tolerability and pharmacokinetics of intrapatient dose escalation of sorafenib as first line treatment for metastatic renal cell carcinoma	
Therapeutic Area:	Oncology	
Test Product		
Name of Test Product:	Sorafenib (Nexavar, BAY43-9006)	
Name of Active Ingredient:	Sorafenib	
Dose and Mode of Administration:	The initial dose of sorafenib was 400 mg twice daily (bid) administered orally on a continuous basis. Intrasubject dose escalation was performed, provided no grade 3 or 4 toxicities (except for alopecia, nausea and vomiting) were observed. The dose levels were: Dose level 1 (Day 1 - 28, 400 mg bid), Dose level 2 (Day 29 - 56, 600 mg bid), and Dose level 3 (Day 57 onwards, 800 mg bid).	
Reference Therapy/Placebo		
Reference Therapy:	Not applicable	
Dose and Mode of Administration:	Not applicable	
Duration of Treatment:	Each dose of the study drug was administered for 28 days on continuous basis. Subjects continued treatment until progressive disease, unacceptable toxicity, withdrawal of consent, investigator's decision to stop the treatment or study stop occurred.	
Studied period:	**Date of first subjects' first visit:**	04 FEB 2008
	Date of last subjects' last visit:	13 JAN 2011
Premature Study Suspension / Termination:	No	
Substantial Study Protocol Amendments:	Amendment no. 1 (dated 31 MAR 2008) specified the following modifications: • Correction of errors in the inclusion criteria. In particular, removal of "unresectable" from the second inclusion criterion and confirmation that a total nephrectomy was required. • Alteration of the confirmatory scan requirements. During the first 6 cycles, a PR, CR, or SD was to be confirmed at the next protocol scheduled scan, rather than performing an additional confirmatory scan after 4 weeks. Once 6 cycles of treatment had been completed, the scan frequency was reduced to every 12 weeks. During this time, a PR, CR, or SD could be confirmed by an additional scan at least 4 weeks later. • Removal of the need for an internal Data and Safety Monitoring Board (DSMB). Only an external Data Monitoring Committee (DMC) was required.	

	• Clarification of the PK sampling schedule. PK sampling was to be conducted only at the completion of the first cycle at each dose level. • ECG and thyroid function tests were to be carried out prior to ingestion of the first dose of sorafenib only on Day 1 of the first treatment cycle. • Clarification of the MSKCC grading system version to be used. Amendment no. 2 (dated 16 MAR 2009) was enacted to provide clarification regarding statistical analyses to be performed at the time of the interim analysis. It specified that the primary efficacy endpoint (Response Rate) was to be calculated using the sub group of subjects from the intent-to-treat population who had been treated for 6 months with 4 months at their highest tolerated dose. Amendment no. 3 (dated 29 MAY 2009), applicable to the UK only, was enacted to allow subjects who met the study disease progression criteria but were still deriving significant clinical benefit from the study medication to continue on treatment, in agreement with the sponsor. As the study medication was not approved in this indication for subjects in the UK and they had no alternative treatment options, it was considered unethical to withdraw treatment in these circumstances. It was necessary to amend the protocol due to the UK regulatory authority (MHRA) requirements which prevented the implementation of a compassionate use or named patient program for UK licensed products.
Study Centre(s):	The study was conducted at 19 investigational sites in 5 countries: 3 centers in Germany, 6 centers in France, 4 centers in the United Kingdom, 3 centers in Italy, and 3 centers in Poland.
Methodology:	This uncontrolled study consisted of a screening visit (28 days prior to the start of the study drug) and a treatment period which began from the first dose of the study drug and continued until unacceptable toxicity or progressive disease occurred, or it was decided to stop the study following review of the response rate analysis. During the treatment phase, radiological assessments were performed every 8 weeks (=every 2 cycles) by the investigators. A complete response (CR), partial response (PR), or stable disease (SD) was confirmed at the next scheduled computed tomography (CT) scan (8 weeks later). After completion of 6 treatment cycles at the highest tolerated dose level, assessments were performed every 12 weeks. The PR, CR, or SD identified after 6 cycles of treatment was confirmed by an additional scan at least 4 weeks later. The CT scans of the chest, abdomen and pelvis were also performed. Samples for pharmacokinetic (PK) assessment were drawn from all subjects on Day 28 of completion of the first cycle at each dose level (400 mg, 600 mg, and 800 mg). Blood PK samples were drawn at the following time points in relation to the morning oral dose of sorafenib: pre-dose (a few minutes before dosing), 2, 4, 6, 8, 10, and 12 h post-dose. A sample was drawn during screening to serve as a blank. A Data Monitoring Committee (DMC) was instituted for this study in order to ensure its ongoing safety and to oversee the response rate analyses. Recommendation for trial continuation was guided by the results of these reviews.

Indication/ Main Inclusion Criteria:	Main indication: Metastatic renal cell carcinoma (mRCC). Main Inclusion Criteria: Subjects aged ≥18 years with histologically or cytologically confirmed metastatic clear cell RCC (renal cell carcinoma), who had not received any prior systemic anticancer therapy. In addition the following criteria were to be fulfilled: • Subjects with at least one uni-dimensional measurable lesion (by CT scan or magnetic resonance imaging), assessed according to Response Evaluation Criteria in Solid Tumors (RECIST version 1.0) • Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1 • Memorial Sloan Kettering Cancer Center (MSKCC) good or intermediate category • Life expectancy of at least 12 weeks • Adequate bone marrow, liver, and renal function assessed within 7 days prior to treatment • Prior total nephrectomy Prior palliative radiotherapy to metastatic lesion(s) was permitted
Study Objectives:	**Overall:** To evaluate the efficacy, safety, tolerability and pharmacokinetics of intrasubject dose escalation in previously untreated subjects with mRCC. **Primary:** To assess the response rates (by independent assessment) observed in subjects treated with a continuous, daily dose of 400 mg bid sorafenib dose escalated up to 800 mg bid. **Secondary:** The secondary objectives were as follows: • Safety and tolerability • Pharmacokinetics • Progression-free survival (PFS) • Time to progression (TTP)
Evaluation Criteria:	**Efficacy (Primary):** The primary efficacy variable was the response rate (RR = CR + PR): • after 6 cycles of treatment with at least 4 cycles at the highest tolerable dose (for the interim analysis), and • during the whole study (final analysis). **Efficacy (Secondary):** The secondary efficacy variables included: • PFS • TTP

	Tumor response and progression were evaluated based on RECIST (version 1.0). Assessments of tumor scans showing CR, PR, and SD were also performed by an independent radiologist. **Safety:** Adverse events (AEs) were assessed using the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE), Version 3.0. Other safety assessments included: vital signs, physical examination, electrocardiogram (ECG), and laboratory tests.
	Pharmacokinetics: Pharmacokinetic parameters will be estimated using available concentration-time data. The following pharmacokinetic parameters were calculated for sorafenib, and metabolites M2, M4, and M5: $AUC_{(0-10),ss}$, $AUC_{(0-12),ss}$, C_{max}, t_{max}, and $C_{trough,\ steady\ state}$.
Statistical Methods:	**Population:** All efficacy analyses were performed in the intent-to-treat (ITT) population, which was defined as all subjects who took at least one dose of sorafenib with at least one valid efficacy evaluation post-baseline. A "modified ITT" population was used in the analysis of the primary variable, RR, which included subjects treated for at least 6 cycles with at least 4 cycles at their highest tolerated dose. Safety analyses were performed in the safety analysis set (SAF) consisting of all subjects who received at least one dose of sorafenib and had any data after baseline. **Efficacy (Primary):** The RR (CR + PR) by independent assessment was presented with its 95% confidence interval (CI) in the ITT and modified ITT populations, overall and by dose (defined as the dose taken the longest time over the study period considered). An interim analysis was performed for the best response observed during the first 6 cycles (conducted in the ITT population) and the final analysis was performed for the best response over the whole study. The RR rate based on investigator's assessments was calculated for information. In addition, the Disease Control Rate (DCR) was presented with 95% CI. **Efficacy (Secondary):** The product-limit estimates of the survival distribution function (Kaplan-Meier) were presented for PFS and TTP. **Safety:**

	• Summary statistics were used in the analysis of safety parameters. The incidence of adverse events (percentage of subjects, not of events) was presented by NCI (National Cancer Institute) CTC (Common Toxicity Criteria) worst grade and dose.
	Pharmacokinetics: Summary statistics of plasma concentrations at each sampling time was presented by dose, day, and cycle (i.e., Day 28 of Cycle 1 at 400 mg, Day 28 of Cycle 1 at 600 mg, and Day 28 of Cycle 1 at 800 mg). In addition, relationships between PK parameters/trough plasma concentrations and parameters for anti-tumor activity and/or toxicity were also explored. AUC and C_{max} were analyzed after normalizing for dose to evaluate dose proportionality. Plots of dose-normalized AUC and C_{max} by dose was provided.
Number of Subjects:	A total of 89 subjects were enrolled and of these, 83 were treated with sorafenib and constituted the SAF (6 subjects were screening failures). A total of 67 subjects were valid for the ITT population; 18 subjects were treated for at least 6 months with 4 months at their highest tolerated dose and were thus valid for the mITT population.

Study Results

Results Summary — Subject Disposition and Baseline

Of the 83 subjects treated, 44 (53.0%) were discontinued from treatment due to disease progression, recurrence or relapse, 28 (33.7%) due to AE, 2 (2.4%) due to investigator decision, and 1 each due to "clinical endpoint reached", withdrawal of consent, or protocol violation. A total of 6 subjects (7.2%) completed all the planned treatments.

In the SAF population, a total of 54 (65.1%) subjects were males. The mean age was 60.3 ± 10.5 years (range: 33.0 - 80.0 years). The mean BMI (body mass index) was 27.02 kg/m^2 (range: 19.53 - 40.72 kg/m^2). With the exception of 2 Asian subjects, all subjects were White. All but 1 subject entered the study with stage IV disease; one subject had stage III disease at study entry. A total of 15 (18.1%) subjects presented with stable disease and 68 (81.9%) with progressive disease. The pre-treatment ECOG performance status was "0" in 49 (59.0%) subjects and "1" in 34 (41.0%) subjects.

Results Summary — Efficacy

Primary efficacy results considering the entire study period are summarized in Table 1. The results in the ITT population considering the first 6 treatment cycles were identical to those observed for the entire study period.

Table 1: Best tumor response according to RECIST (version 1.0) - Independent Central Assessment (entire study period)

Response category	modified ITT population N=18 (100%) n (%) [95% CI]	ITT population N=67 (100%) n (%) [95% CI]
Complete response (CR)	0	0
Partial response (PR)	8 (44.4%)	12 (17.9%)
Stable disease (SD)	10 (55.6%)	46 (68.7%)
Progressive disease (PD)	0	9 (13.4%)
Response rate (CR+PR)	8 (44.4%) [21.5; 69.2]%	12 (17.9%) [9.6; 29.2]%
Disease control rate (CR+PR+SD)	18 (100%) [81.5; 100]%	58 (86.6%) [76.0; 93.7]%

Abbreviations: CI - Confidence interval; RECIST - Response Evaluation Criteria in Solid Tumors

Best tumor response differentiated by the highest tolerated dose, defined as the dose taken for the longest time during the study, is presented in Table 2.

Table 2: Best tumor response according to RECIST (version 1.0) - Independent Central Assessment (entire study period) by dose taken for the longest time (ITT population)

	Daily dose of sorafenib		
Response category	800 mg N=25 n (%) [95% CI]	1200 mg N=12 n (%) [95% CI]	1600 mg N=20 n (%) [95% CI]
Complete response (CR)	0	0	0
Partial response (PR)	1 (4.0%)	2 (16.7%)	7 (35.0%)
Stable disease (SD)	15 (60.0%)	10 (83.3%)	13 (65.0%)
Progressive disease (PD)	9 (36.0%)	0	0
RR (CR+PR)	1 (4.0%) [0.1; 20.4]%	2 (16.7%) [2.1; 48.4]%	7 (35.0%) [15.4; 59.2]%
DCR (CR+PR+SD)	16 (64.0%) [42.5; 82.0]%	12 (100%) [73.5; 100]%	20 (100%) [83.2; 100]%

Note: The dose taken for the longest time was 200 mg/day in 3 patients and 400 mg/day in 7 patients.
Abbreviations: CI - Confidence interval; DCR – Disease control rate; RECIST - Response Evaluation Criteria in Solid Tumors; RR – Response rate

The median PFS was 7.6 months (95% CI: 6.3; 11.7); the progression-free rate was 63.6% at Month 6 and 34.1% at Month 12 (46 subjects with progression; 21 subjects censored; ITT population, independent central assessment). Results of the analysis of TTP were identical to those of PFS, since no subject died before disease progression was diagnosed.

Results Summary — Safety

A mean of 10.7 ± 9.6 (median: 8.0; range: 1.0 - 38.0) cycles (1 cycle = 28 days) were administered (SAF). A total of 53.0% of the subjects received at least 8 cycles of sorafenib. The median duration of treatment was 225 days, i.e. approximately 7.5 months (range: 7 days – 1072 days). The average daily dose was 676 mg for Cycle 1, 822 mg for Cycle 2, 1016 mg for Cycle 3, 1041 mg for Cycle 4, 1048 mg for Cycle 5, and 967 mg for the subsequent cycles. A total of 66.3% of subjects had at least one dose reduction, 71.6% of which were due to AEs. In total, 63.9% of subjects had at least one dose interruption, 90.8% of which were due to AEs.

Treatment-emergent AEs were reported for all of the 83 subjects. The most frequent (≥20%) were hand-foot skin reaction (66.3%), diarrhea (63.9%), rash/desquamation (56.6%), fatigue (54.2%), hypertension (48.2%), alopecia (43.4%), mucositis (functional/symptomatic), oral cavity (32.5%), dry skin (27.7%), nausea (26.5%), anorexia (25.3%), dermatology – other (22.9%), and hypophosphatemia (20.5%).

Grade 3 AEs occurred in 61 (73.5%) subjects, Grade 4 AEs in 13 (15.7%) subjects and only one Grade 5 AE occurred in 1 (1.2%) subject. The most frequent Grade 3 AEs (≥5%) were hand-foot skin reaction (25.3%), fatigue (15.7%), hypophosphatemia (15.7%), rash/desquamation (13.3%), diarrhea (12.0%), increased lipase (12.0%), hypertension (6.0%), and increased ALT (6.0%). Grade 4 AEs occurring in more than 1 subject were hyponatremia (2.4%) and increased lipase (2.4%). One (1.2%) Grade 5 AE (cardiac general – other, specified as cardiopulmonary failure) was reported.

Treatment-emergent AEs by dose at first occurrence of event (≥10% of subjects in any category) are summarized in Table 3.

Table 3: Number (percentage) of subjects with treatment-emergent AEs (any grade) by dose at first occurrence (≥10 % of subjects in any category) (SAF)

	Daily sorafenib dose at first occurrence of event				
	1600 mg N=40	1200 mg N=52	800 mg N=83	400 mg N=38	200 mg N=10
Any event	1 (2.5%)	-	76 (91.6%)	5 (13.2%)	1 (10.0%)
Leukocytes	-	-	1 (1.2%)	-	1 (10.0%)
Neutrophils	-	-	2 (2.4%)	-	1 (10.0%)
Platelets	1 (2.5%)	1 (1.9%)	4 (4.8%)	-	1 (10.0%)
Hypertension	2 (5.0%)	2 (3.8%)	29 (34.9%)	4 (10.5%)	2 (20.0%)
Hypotension	1 (2.5%)	2 (3.8%)	-	-	1 (10.0%)
Fatigue	5 (12.5%)	4 (7.7%)	29 (34.9%)	2 (5.3%)	2 (20.0%)
Weight loss	7 (17.5%)	2 (3.8%)	5 (6.0%)	-	-
Alopecia	5 (12.5%)	9 (17.3%)	16 (19.3%)	5 (13.2%)	1 (10.0%)
Dermatology – other	2 (5.0%)	3 (5.8%)	9 (10.8%)	5 (13.2%)	-
Dry skin	5 (12.5%)	3 (5.8%)	13 (15.7%)	1 (2.6%)	1 (10.0%)
Hand-foot skin reaction	4 (10.0%)	5 (9.6%)	43 (51.8%)	3 (7.9%)	-
Pruritus	-	2 (3.8%)	10 (12.0%)	2 (5.3%)	-
Rash/desquamation	2 (5.0%)	5 (9.6%)	38 (45.8%)	1 (2.6%)	1 (10.0%)
Anorexia	6 (15.0%)	8 (15.4%)	6 (7.2%)	-	1 (10.0%)
Diarrhea	9 (22.5%)	19 (36.5%)	21 (25.3%)	3 (7.9%)	1 (10.0%)
	Daily sorafenib dose at first occurrence of event				
	1600 mg N=40	1200 mg N=52	800 mg N=83	400 mg N=38	200 mg N=10
Mucositis (functional /symptomatic), oral cavity	1 (2.5%)	4 (7.7%)	19 (22.9%)	2 (5.3%)	1 (10.0%)
Nausea	5 (12.5%)	3 (5.8%)	10 (12.0%)	2 (5.3%)	2 (20.0%)
Obstruction, GI, colon	-	-	-	-	1 (10.0%)
Taste alteration	2 (5.0%)	3 (5.8%)	4 (4.8%)	1 (2.6%)	1 (10.0%)
Vomiting	5 (12.5%)	2 (3.8%)	8 (9.6%)	1 (2.6%)	-
Cholecystitis	-	-	-	-	1 (10.0%)
Infection (documented clinically), lung (pneumonia)	-	-	1 (1.2%)	-	1 (10.0%)
Infection (documented clinically), urinary tract NOS	-	-	2 (2.4%)	-	1 (10.0%)
Alkaline phosphatase	-	-	1 (1.2%)	-	1 (10.0%)
Hypoalbuminemia	-	-	3 (3.6%)	1 (2.6%)	1 (10.0%)
Hypocalcemia	5 (12.5%)	-	1 (1.2%)	-	-
Hyponatremia	-	-	4 (4.8%)	-	1 (10.0%)
Hypophosphatemia	-	3 (5.8%)	13 (15.7%)	1 (2.6%)	-
Musculoskeletal – other	1 (2.5%)	3 (5.8%)	4 (4.8%)	2 (5.3%)	1 (10.0%)
Confusion	1 (2.5%)	-	1 (1.2%)	-	1 (10.0%)
Dizziness	-	2 (3.8%)	1 (1.2%)	1 (2.6%)	1 (10.0%)
Pain, abdomen NOS	1 (2.5%)	2 (3.8%)	6 (7.2%)	1 (2.6%)	1 (10.0%)
Pain, back	4 (10.0%)	2 (3.8%)	2 (2.4%)	-	1 (10.0%)
Pain, chest wall	-	1 (1.9%)	1 (1.2%)	-	1 (10.0%)
Pain, extremity – limb	2 (5.0%)	2 (3.8%)	2 (2.4%)	1 (2.6%)	1 (10.0%)
Pulmonary – other	1 (2.5%)	-	1 (1.2%)	-	1 (10.0%)

N - Number of patients who were exposed at this dose for at least one day.
Abbreviations: GI – gastrointestinal; NOS – not otherwise specified

Drug-related AEs were reported in 98.8% of subjects. Most frequent (≥20%) were hand-foot skin reaction (66.3%), diarrhea (63.9%), rash/desquamation (53.0%), fatigue (50.6%), alopecia (43.4%), hypertension (43.4%), mucositis (functional/symptomatic), oral cavity (30.1%), dry skin (26.5%), and anorexia (20.5%). In total, 72.3% of subjects experienced drug-related AEs with maximum severity of Grade 3 and 9.6% of Grade 4; there was no drug-related Grade 5 AE. Most frequent (≥10%) drug-related Grade 3 AEs were hand-foot skin reaction (25.3%), hypophosphatemia (14.5%), rash/desquamation (13.3%), fatigue (13.3%), and diarrhea (12.0%). The only drug-related Grade 4 AE occurring in more than 1 subject was hyponatremia (2 subjects, 2.4%).

Treatment-emergent serious adverse events (SAEs) occurred in 44 (53.0%) subjects. The most common SAEs were fatigue, rash/desquamation, GI (gastrointestinal)–other, hyponatremia and intraoperative injury–other (each reported in 3 subjects [3.6%]) and left ventricular systolic dysfunction, dermatology-other, hand-foot skin reaction, diarrhea, hepatobiliary-other, infection (documented clinically)-lung (pneumonia), musculoskeletal-other, pain-back, pleural effusion, renal failure, secondary malignancy (possibly related to cancer treatment), and thrombosis/thrombus/embolism (each reported in 2 subjects [2.4%]). SAEs which were reported in 1 subject each (1.2%) comprised allergic reaction, hemoglobin, cardiac arrhythmia-other, cardiac general-other, hypotension, constitutional symptoms-other, fever, erythema multiforme, colitis, cholecystitis, infection (documented clinically)-kidney, infection with normal absolute neutrophil count (ANC)-abdomen NOS, infection with normal ANC-anal/perianal, infection with normal ANC-sinus, hypercalcemia, hyperglycemia, hyperkalemia, hypocalcemia, hypomagnesemia, hypophosphatemia, fracture, confusion, dizziness, neurology-other, neuropathy: motor, pain-abdomen NOS, pain-bone, pain-breast, pain-chest/thorax NOS, pain-joint, pain-other, pain-stomach, and airway obstruction-bronchus.

Drug-related SAEs were reported in 28 (33.7%) subjects (most commonly fatigue, rash/desquamation, and hyponatremia, each reported in 3 subjects). In total 21 (25.3%) subjects experienced drug-related SAEs with maximum severity of Grade 3 and 5 (6.0%) of Grade 4. There were no drug-related Grade 5 SAEs.

Two deaths were reported, one of which occurred within 30 days after the last dose of study drug (cardio-pulmonary failure; not related to study drug) and one outside the study period (cardio-pulmonary failure caused by progressive RCC).

AEs leading to withdrawal from the study treatment occurred in 43.4% of subjects. The most common were rash/desquamation (7.2%) and hand-foot skin reaction (4.8%). AEs leading to dose reduction were most commonly diarrhea (16.9%), hand-foot skin reaction (15.7%) and, rash/desquamation (10.8%), and AEs leading to dose interruption hand - foot skin reaction (24.1%), diarrhea (14.5%), hypertension (13.3%), and rash/desquamation (13.3%).

The most common Grade 3 laboratory abnormalities were hypophosphatemia (40.0%), elevation of lipase (15.9%), elevation of ALT (alanine aminotransferase) (9.6%), elevation of AST (aspartate aminotransferase) (9.6%), hyponatremia (9.6%), and INR (International Normalized Ratio) abnormality (9.1%); the most common Grade 4 abnormalities were elevation of lipase (6.1%) and hypophosphatemia (2.5%).

No significant changes in vital signs were observed.

Results Summary — Pharmacokinetics

Overall, the PK of sorafenib and its metabolites were similar across the different doses.

Table 4 summarizes parameters of sorafenib and its metabolites, M2 (BAY 67-3472), M4 (BAY 43-9007) and M5 (BAY 68-7769), as geometric means and coefficients of variation, except t_{max}, which is summarized as the median and range. Sorafenib PK parameters (AUC and C_{max}) were similar at the 400 mg and 600 mg bid dose levels. Sorafenib AUC and C_{max} for the 800 mg bid dose level were slightly lower than at 400 mg and 600 mg bid, with $AUC_{(0-8),ss}$ 11% lower, $AUC_{(0-10),ss}$ 12% lower, $AUC_{(0-12),ss}$ 18% lower, and $C_{max,ss}$ 12% lower at the 800 mg bid relative to the 400 mg dose level.
The planned analysis of $C_{trough,\ steady\ state}$ for sorafenib, and its metabolites M2, M4, and M5 was not conducted.

Table 4: Pharmacokinetic parameters of sorafenib and its metabolites, M2, M4, and M5, following 28 days of twice daily dosing of sorafenib at 400 mg BID, 600 mg BID, and 800 mg BID (geometric mean (%CV), all subjects valid for PK)

		Dose					
Parameter	Units	N	400 mg BID	N	600 mg BID	N	800 mg BID
Sorafenib							
$AUC_{(0-10)ss}$	mg*h/L	40	50.0 (39.2%)	30	51.2 (43.7%)	26	43.8 (47.8%)
$AUC_{(0-12)ss}$	mg*h/L	32	57.2 (39.1%)	23	57.6 (46.1%)	19	47.0 (51.9%)
C_{max}	mg/L	40	7.53 (38.0%)	31	7.62 (39.3%)	28	6.64 (42.1%)
t_{max}[a]	h	40	2.00 (0.00-12.0)	31	2.00 (0.00-12.0)	28	2.00 (0.00-12.0)
M2 (BAY 67-3472)							
$AUC_{(0-10)ss}$	mg*h/L	40	8.80 (74.3%)	30	10.4 (82.1%)	27	8.23 (87.2%)
$AUC_{(0-12)ss}$	mg*h/L	32	9.58 (78.2%)	23	11.2 (75.9%)	20	8.41 (94.6%)
C_{max}	mg/L	40	1.31 (80.8%)	31	1.51 (81.4%)	28	1.30 (88.5%)
t_{max}[a]	h	40	2.00 (0.00-10.3)	31	2.00 (0.00-12.0)	28	1.00 (0.00-12.0)
M4 (BAY 43-9007)							
$AUC_{(0-10)ss}$	mg*h/L	40	3.10 (80.8%)	30	3.04 (86.5%)	26	2.22 (77.2%)
$AUC_{(0-12)ss}$	mg*h/L	32	3.33 (77.2%)	23	3.25 (77.8%)	19	2.39 (83.5%)
C_{max}	mg/L	40	0.480 (90.1%)	31	0.467 (88.0%)	28	0.358 (82.8%)
t_{max}[a]	h	40	0.00 (0.00-10.1)	31	2.00 (0.00-12.0)	28	2.00 (0.00-12.0)
M5 (BAY 68-7769)							
$AUC_{(0-10)ss}$	mg*h/L	40	2.65 (140%)	30	3.44 (142%)	27	3.03 (137%)
$AUC_{(0-12)ss}$	mg*h/L	31	3.03 (118%)	23	3.55 (136%)	20	3.19 (162%)
C_{max}	mg/L	40	0.402 (145%)	31	0.524 (137%)	28	0.490 (145%)
t_{max}[a]	h	40	0.00 (0.00-12.0)	31	2.00 (0.00-12.0)	28	0.00 (0.00-12.0)

[a] Median and range
Abbreviations: AUC – area under the curve, BID – bis in die (twice daily), C_{max} - maximum concentration in plasma, CV - coefficient of variation, t_{max} - time to maximum concentration

Conclusion(s)

In this study, dose escalation beyond 400 mg bid up to 800 mg bid sorafenib and continuation on this dose level was not feasible in the majority of subjects with treatment-naive mRCC. Dose reductions and treatment interruptions due to toxicity were frequent. The response rate was 17.9%, and the disease control rate was 86.6% in the 67 subjects who took at least one dose of sorafenib with at least one valid efficacy evaluation. The median PFS for the same subject population was 7.6 months (95% CI: 6.3; 11.7). The response rate and disease control rate in the 18 subjects who were treated for at least 6 months with 4 months at their highest tolerated dose were 44.4% and 100%, respectively. Response rates and disease control rates appeared to be better in subjects treated for the longest time with doses beyond 800 mg/day. There were no unexpected safety findings. The frequency and severity of adverse events appeared to be higher than what was previously reported in subjects treated with 400 mg bid sorafenib. The pharmacokinetic data indicate a lack of dose proportionality when the dose was escalated from 800 mg/day to 1600 mg /day, which was likely the result of limited absorption due to low aqueous solubility of sorafenib.

Publication(s):	None		
Date Created or Date Last Updated:	23 JUL 2013	**Date of Clinical Study Report:**	28 JAN 2013

Investigational Site List

Marketing Authorization Holder in Germany	
Name	Bayer Pharma AG
Postal Address	D-13342 Berlin, Deutschland
Sponsor in Germany	
Legal Entity Name	Bayer Healthcare AG
Postal Address	D-51368, Leverkusen, Germany

List of Investigational Sites

No	Facility Name	Street	ZIP Code	City	Country
1	Centre Hospitalier Départemental-La Roche sur Yon	Centre Hospitalier Départemental Les Oudairies Service de Médecine Interne et d'Hémato-Oncologie	85925	LA ROCHE SUR YON	FRANCE
2	Centre René Gauducheau - Nantes	Centre René Gauducheau Service d'Oncologie Médicale Boulevard Jacques Monot	44805	NANTES	FRANCE
3	Hôpital Bretonneau - Tours	Hôpital Bretonneau Service d'Oncologie Médicale 2 Boulevard Tonnelle	37044	TOURS	FRANCE

4	Hôpital de la Timone - Marseille	Assistance Publique Hôpital de la Timone Service de Radiothérapie-Oncologie 264 rue Saint-Pierre	13385	MARSEILLE	FRANCE
5	Hôpital Saint André - Bordeaux	C.H.U Bordeaux - Groupe Hospitalier Saint André-Jean Abadie Hôpital Saint André Service d'Oncologie Médicale et de Radiothérapie 1, rue Jean Burguet	33000	BORDEAUX	FRANCE
6	Hôpital Saint Louis - Paris	Hôpital Saint Louis Service d'oncologie médicale Avenue Claude Vellefaux	75475	PARIS CEDEX 10	FRANCE
7	Johannes-Gutenberg-Universität Mainz	III. Medizinische Klinik und Poliklinik Bereich Hämatologie und Onkologie Langenbeckstr. 1	55131	Mainz	GERMANY
8	Kliniken der Medizinischen Hochschule Hannover	Klinik für Urologie Carl-Neuberg-Str. 1	30625	Hannover	GERMANY

9	Klinikum der Friedrich-Schiller-Universität Jena	Klinik und Poliklinik für Urologie Lessingstr. 1	07740	Jena	GERMANY
10	IRCCS Centro di Riferimento Oncologico	Oncologia Medica A Via F.Gallini, 2	33081	Aviano	ITALY
11	IRCCS Istituto Nazionale Tumori	Oncologia Medica 2 Via G.Venezian, 1	20133	Milano	ITALY
12	IRCCS Policlinico San Matteo	Medicina Interna ed Oncologia Medica Piazzale Golgi, 19	27100	Pavia	ITALY
13	Centrum Onkologii - Instytut im. M.Sklodowskiej-Curie	Klinika Nowotworow Ukladu Moczowego ul. W.K. Roentgena 5	02-781	Warszawa	POLAND
14	NZOZ ONKO-MED	Al. Wojska Polskiego 30	10-226	Olsztyn	POLAND
15	Wojskowy Instytut Medyczny	Klinika Onkologii CSK MON ul. Szaserow 128	04-141	Warszawa	POLAND
16	Beatson West of Scotland Cancer Centre	1053 Great Western Road	G12 0YN	Glasgow	UNITED KINGDOM
17	Christie Hospital	CRC Department of Medical Oncology, Christie CRC Research Centre Christie Hospital NHS Trust 550 Wilmslow Road Withington	M20 4BX	Manchester	UNITED KINGDOM
18	Royal Marsden Hospital (London)	Department of Medicine Fulham Road	SW3 6JJ	London	UNITED KINGDOM
19	Velindre Hospital	Whitchurch Cardiff CF14 7TB	CF14 7TB	Cardiff	UNITED KINGDOM

Product Identification Information

Product Type	Drug
US Brand/Trade Name(s)	Nexavar
Brand/Trade Name(s) ex-US	Nexavar
Generic Name	Sorafenib
Main Product Company Code	BAY43-9006
Other Company Code(s)	BAY54-9085
Chemical Description	**(1)** 2-Pyridinecarboxamide, 4-[4-[[[[4-chloro-3trifluoromethyl)phenyl]amino]carbonyl]amino]phenoxy]-N-methyl-**(2)** 4-(4-{3.[4-chloro-3-(trifluoromethyl)phenyl]ureido}phenoxy)-N2-methylpyridine-2-carboxamide
Other Product Aliases	Sorafenib tosylate

Date of last Update/Change: 28 Apr 2012