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 Pharmaceuticals Inc.	
Study Number:	100554	NCT00105443
Study Phase:	III	
Official Study Title:	A Phase III randomized, placebo-controlled study of sorafenib in patients with advanced hepatocellular carcinoma	
Therapeutic Area:	Oncology	
Test Product		
Name of Test Product:	Sorafenib (Nexavar, BAY43-9006)	
Name of Active Ingredient:	Sorafenib	
Dose and Mode of Administration:	A dose of 400 mg (2 x 200 mg tablets) bid was administered orally; 2 dose reductions to predefined levels of 400 mg once daily (OD) and 400 mg every other day were permitted for adverse events (AEs) related to the study treatment.	
Reference Therapy/Placebo		
Reference Therapy:	Placebo	
Dose and Mode of Administration:	Placebo tablets matching in appearance were orally administered twice daily (bid).	
Duration of Treatment:	The treatment was continued until death or until a criterion for stopping therapy was met. Treatment beyond radiological and symptomatic progression was allowed upon request of the treating investigator. Subjects assigned to the placebo arm were not crossed over to the sorafenib arm at any time during the study before the overall (OS) endpoint was met.	
Studied period:	Date of first subjects' first visit:	10 MAR 2005
	Date of last subjects' last visit:	21 NOV 2008
Premature Study Suspension / Termination:	No	
Substantial Study Protocol Amendments:	Amendment no. 1 (dated 13 DEC 2004) specified the following changes: • The study design was modified to clarify that details of any new anti-tumor chemotherapy received should be collected during the follow-up period, in addition to the survival status; it was also clarified that, if study drug was discontinued, information related to the first new regimen of new anti-tumor chemotherapy after discontinuation was to be collected. • A new inclusion criterion (albumin value ≥2.8 g/dL) was added to reflect the exclusion list for Child-Pugh classification. • A new criterion for stopping study treatment was added in order to clearly define disease progression: a 4-point change from baseline in Functional Assessment of Cancer Therapy	

	Hepatobiliary Symptom Index questionnaire (FHSI-8) score, confirmed by the following visit, in conjunction with radiographic progression of disease. • A new Global Symptoms Question was added and was completed in conjunction with the FHSI-8 questionnaire, during the treatment period, to support the magnitude of FHSI-8 change to be defined as symptomatic progression. • The Eastern Cooperative Oncology Group (ECOG) performance status (PS) (0 versus 1 versus 2) was amended to ECOG PS (0 versus 1 and 2) for all analyses of overall survival, time to symptomatic progression and all secondary endpoints, as it was expected that there would be a small number of subjects with ECOG PS of 2, and so subjects with an ECOG PS of 1 and 2 would be combined together for statistical analyses. Amendment no. 2 (dated 21 JAN 2005) was introduced to ensure that study centers in Germany complied with German Radiation Protection Authority regulations and that consistency was adhered to throughout the study; the use of MRI was mandated for all tumor measurements. Amendment no. 3 (dated 28 NOV 2006) specified the following changes: • The assays of additional biomarkers of sorafenib anti-tumor activity and/or its mechanism of action were included, given the advances in the field of cancer biomarkers and the understanding of anti-vascular endothelial growth factor (VEGF)-R2 compounds; these assays included the analysis of soluble VEGF-R2 and circulating Ras in already-collected plasma samples (no additional sampling was necessary). • A new extension with crossover phase of the study was intoduced to ensure that, in the event that the interim or final data definitively showed that subjects administered sorafenib had a statistically significant prolongation in overall survival over placebo, all subjects ongoing in the double-blind portion of the study, as well as all subjects in follow-up at that point, had the opportunity to continue treatment (provided that the investigator believed a subject would derive benefit from treatment with sorafenib, there were no safety concerns in restarting, and consent was obtained). • The type and frequency of data collection after the extension with crossover point was defined. Although it was not outlined in the protocol, some subjects were permitted to continue with study treatment even after radiological and symptomatic progression, based on the investigator's opinion and with the sponsor's agreement; these subjects continued to receive treatment and follow the study visit schedule.
Study Centre(s):	This multinational study was conducted at 121 centers from 21 countries: Argentina (3 centers), Australia (6 centers), Belgium (5 centers), Brazil (1 center), Bulgaria (3 centers), Canada (6 centers), Chile (2 centers), France (10 centers), Germany (17 centers), Greece (3 centers), Israel (3 centers), Italy (13 centers), Mexico (2 centers), New Zealand (2 centers), Poland (4 centers), Romania (3 centers),

	Russia (5 centers), Spain (10 centers), Switzerland (2 centers), the United Kingdom (UK) (5 centers), and the US (16 centers).
Methodology:	This was a phase 3, multicenter, international, randomized, double-blind study evaluating the clinical benefits of sorafenib versus placebo in subjects with advanced hepatocellular carcinoma (HCC). Following a screening period of 28 days, subjects were randomized to receive either sorafenib at a dose of 400 mg (2 x 200 mg tablets) twice daily (bid), or matching placebo bid. Study treatment was administered orally on a continuous schedule, but for the purpose of data recording, the treatment period was divided into 6-week cycles. Study visits occurred every 3 weeks during the treatment period for evaluation of safety and drug accountability. Subjects were to continue to take sorafenib or placebo until radiological or symptomatic progression, death, or discontinuation for adverse events (AEs) or other reasons. Continuation of treatment beyond radiological or symptomatic progression was allowed upon request of the treating investigator, if judged that clinical benefit could be derived from the continuation of treatment. An "end of treatment" visit was performed 21 to 35 days after the last dose of study medication. Subjects were then entered into a follow-up period, during which information on survival status and any new anti-cancer treatment was collected every 3 months. Tumor measurements were obtained during screening, every 6 weeks during the treatment period (within 10 days prior to the end of each 6-week cycle), and at the end of treatment visit. In this study, two formal interim analyses of OS were performed during the study: the first one at approximately 170 survival events (up to the data cut off date 12 MAY 2006) and the second one when approximately 300 deaths were observed (up to the data cut off date 17 OCT 2006). The primary analysis of Time to symptomatic progression (TTSP) was performed at the end of study when the final analysis of OS was conducted or if the study was stopped at interim analyses. If the results showed definitively that sorafenib prolonged OS, all subjects ongoing in the double-blind phase, as well as all subjects in follow-up at that point, were given an opportunity to enter into an "extension with crossover" study phase, in order to make sorafenib available to all randomized subjects and to the collect safety data. All randomized subjects were given the option of entering the extension with crossover phase of the study provided they met the eligibility requirements. Subjects who withdrew from the study were permitted to re-enter the study during the extension with crossover phase. For ongoing subjects, the extension/crossover visits were performed in lieu of the subject's next regularly scheduled visit. All blinded study medication was returned. Study visits were performed every 8 weeks (±1 week), although additional visits were permitted at the investigator's discretion. The primary objective of this phase of the

	study was to make sorafenib available to all randomized subjects. Only additional safety data were collected during this phase. However, the active collection of information relating to deaths for purposes of the clinical database was stopped at the time of the crossover; however, any death information provided by the sites after this time was documented.
Indication/ Main Inclusion Criteria:	Indication: Hepatocellular carcinoma Main inclusion criteria: Subjects with advanced, documented, measurable HCC, with an ECOG PS of 0, 1, or 2, Child-Pugh Class A, and who had not received prior systemic anti-cancer treatment for HCC were to be enrolled in the study. Eligible subjects had a life expectancy of at least 12 weeks.
Study Objectives:	Overall: Not applicable Primary: To evaluate overall survival (OS) and time to symptomatic progression (TTSP) in subjects treated with sorafenib versus those treated with placebo (reported separately). Secondary: • To evaluate time to progression (TTP) between subjects treated with sorafenib and those treated with placebo. • To evaluate overall disease control rate. • To evaluate the Functional Assessment of Cancer Therapy-Hepatobiliary (FACT-Hep) response rate. Tertiary: • To evaluate the overall response rate, overall response duration, and time to objective response. • To evaluate the FACT-Hep Physical Well-being (PWB) and Functional Well-being (FWB) subscale response rates. Other: • To characterize the population pharmacokinetics (PK) of sorafenib. • To evaluate possible and potentially predictive assays of clinical benefit through an exploratory assessment of the correlation between various biomarkers and key clinical endpoints (i.e., response, TTP, TTSP, and OS).
Evaluation Criteria:	Efficacy (Primary): The primary outcome measure was OS, measured from the date of randomization until the date of death due to any cause. For subjects alive or lost to follow-up at the time of analysis, time to death was censored at their last date of follow-up. Another primary outcome measure was the Time to symptomatic progression (TTSP), defined as the time from randomization to the first documented symptomatic progression.

	Efficacy (Secondary): • Time to progression (defined as the time from randomization to radiologically documented disease progression). • Disease control rate, defined as the proportion of subjects with a best response rating of complete response (CR), partial response (PR), or stable disease (SD) that was maintained at least 28 days from the first manifestation of that rating. • Functional assessment of cancer therapy-hepatobiliary (FACT-Hep) questionnaire response rate (patient reported outcomes [PRO]) from randomization to end of treatment. Efficacy (Tertiary): • Overall response rate, according to the Response Evaluation Criteria in Solid Tumors (RECIST). • Time to response (measured from the date of randomization to the date that an objective tumor response was achieved; evaluated only for subjects who achieved PR or CR). • Overall response duration (measured from the date of first documented objective response to disease progression; only evaluated for subjects who achieved PR or CR). • Patient reported outcome as measured by the response rates to the PWB and FWB subscales of the FACT-Hep questionnaire. Safety: Safety variables included AEs (graded according to National Cancer Institute [NCI]-Common Terminology Criteria for Adverse Events [CTCAE] Version 3.0), laboratory changes (hematology, clinical chemistry, and urinalysis), changes in vital signs (blood pressure, heart rate, respiratory rate, and temperature), and electrocardiogram (ECG). Study visits for evaluation of safety occurred every 3 weeks during the treatment period; safety was also evaluated during screening and at the end of treatment visit. The Data Monitoring Committee (DMC) held safety review meetings approximately every 6 months after initiation of enrollment. The study data were reviewed for clinically important differences between the treatment groups in serious adverse events (SAEs), toxicities, and deaths. The DMC also reviewed the SAE data monthly.
	Pharmacokinetics: Population PK parameters. Other: Correlation between various biomarkers and key clinical endpoints.
Statistical Methods:	Population: The intent-to-treat (ITT) population consisting of all 602 randomized subjects was used for the for the efficacy analyses. The population for safety analyses included all subjects who had received at least one dose of study medication.

	Efficacy (Primary): The ITT population was included in the analyses of the primary endpoints, OS and TTSP. The 2 treatment groups (sorafenib and placebo) were compared using a 1-sided log-rank test with an overall alpha of 0.02 (for OS) and 0.005 (for TTSP), stratified by region, ECOG PS and "tumor burden". The overall alpha for both primary endpoints was 0.025 (1-sided). An alpha spending function was used to ensure that the false positive rate (alpha) for OS was less than or equal to 0.02 (1-sided). In addition to the final analyses of OS and TTSP, 2 formal interim analyses of OS were conducted during the study. The updated survival data and other efficacy data were presented using descriptive statistics; no p-values were provided. Efficacy (Secondary and Tertiary): The primary analysis of TTP based on independent radiological assessment (using data up to the cut-off date for the first interim analysis of OS, 12 MAY 2006) was delayed until the end of the study. A secondary analysis of TTP was performed based on investigator radiological assessment, which included data up to 17 OCT 2006. An additional hybrid secondary analysis of TTP combining both independent and investigator radiological assessment was also planned. Disease control rates and objective tumor response rate were compared between treatment groups using the Cochran-Mantel-Haenszel (CMH) test with a 1-sided alpha of 0.025, adjusted by region, ECOG PS, and "tumor burden". For the analyses of time to response and duration of response, the 2 treatment groups were summarized descriptively. For the analyses of secondary and tertiary efficacy endpoints, no adjustments of significance levels were made to account for multiple efficacy endpoints. A 1-sided alpha level of 0.025 was used for each analysis. Safety: Statistical summaries were provided by treatment group, treatment duration, average daily dose taken, and percentage of planned dose received. Subjects with dose reduction or interruption, subjects with dose delay, and the number of dose reductions/interruptions/delays per subject were also summarized. All AEs and hematological/biochemical toxicities based on laboratory measurements were summarized by treatment group and NCI-CTCAE Version 3.0 worst grade. The incidence of deaths, drug-related AEs, treatment-emergent SAEs, and AEs leading to discontinuation of the investigational product and/or withdrawal from the study were summarized.

	Pharmacokinetics: Descriptive statistics were provided on the trough plasma sorafenib concentrations. Population PK parameters were estimated using available plasma concentration-time data. Other: A biomarker analysis was used to generate hypotheses and was considered exploratory in nature.
Number of Subjects:	A total of 902 subjects with HCC were enrolled in this study; 602 were randomized (representing full accrual) and were valid for the efficacy analyses (ITT population), and 599 received at least 1 dose of study medication and were valid for the safety analyses. Of the 602 subjects, 299 were randomized to sorafenib and 303 to placebo.

Study Results

Results Summary — Subject Disposition and Baseline

Of the 602 randomized subjects, three subjects did not receive the study drug and were therefore not valid for safety analyses.

Of the 299 subjects randomized to sorafenib, most (87.0%) subjects were men. The proportion of men (87.0%) and women (13.0%) in the sorafenib group was similar to that observed for the placebo (all) group (87.1% and 12.9%, respectively). The mean age for the ITT population was 64.9 years (range: 21 - 89 years), average height was 170.6 cm (range: 150 - 200 cm) and average weight was 76.1 kg (range: 42 - 127.6 kg). Most of the subjects in the placebo (all) group (90.1%) and sorafenib group (87.3%) were White (Caucasian).

A total of 104 (17.3%) subjects entered the crossover period, including 47 (15.5%) subjects randomized to the placebo group who crossed over to sorafenib and 57 (19.1%) subjects randomized to the sorafenib group who continued sorafenib. The 2 most common reasons overall for discontinuing crossover study treatment were switch to commercial drug (34 [32.7%] subjects) and AE (30 [28.8%] subjects).

Results Summary — Efficacy

At the time of the analysis (up to the cut off date of 17 OCT 2006), 602 subjects with HCC had been randomized to sorafenib or placebo, and accrual in the study was completed (the last subject was randomized in this study on 11 APR 2006). Randomization was stratified according to "tumor burden", ECOG PS, and geographical region. Results revealed that the stratification and prognostic criteria were balanced between the study arms. Analysis of efficacy data based on 321 survival events (178 events in the placebo arm, and 143 events in the sorafenib arm), that occurred as of 17 OCT 2006 revealed that sorafenib significantly prolonged OS compared with placebo.

Median OS was 241 days in subjects randomized to placebo and 324 days in subjects randomized to sorafenib. The estimated hazard ratio for survival (sorafenib over placebo) was 0.6931, representing a 30.7% reduction in hazard (risk of death) over placebo (or 44.3% increase in survival time over placebo) (P=0.000583). This represents a clinically meaningful and statistically significant improvement in OS attributable to sorafenib treatment. The benefit of sorafenib over placebo was observed across established prognostic subgroups.

The efficacy of sorafenib was also demonstrated by the survival rates at 3 and 6 months which were 83% in the placebo arm compared with 86% in the sorafenib arm at 3 months, and 61% for placebo subjects compared with 71% for sorafenib subjects at 6 months.

Additionally, analyses of TTP based on both independent and investigator radiological assessments also revealed a statistically significantly and clinically meaningful improvement in favor of sorafenib. Median TTP based on independent review was 86 days for placebo subjects compared to 168 days for sorafenib subjects with an estimated hazard ratio (sorafenib over placebo) of 0.5764, representing a 42.4% reduction in risk of progression (or a 73.5% improvement in TTP) in subjects treated with sorafenib compared with placebo (P = 0.000007).

Additional analyses, including sensitivity analyses, for OS and TTP confirmed the primary analyses therefore demonstrating their conclusiveness.

The analysis of the co-primary endpoint TTSP demonstrated similar results in the two treatment arms. These results were not statistically significant. The effect of treatment-related side effects and underlying disease may have influenced subject responses to the PRO used to measure symptomatic progression. Sorafenib was demonstrated to maintain physical function based on subject responses to an HCC-specific quality of life assessment.

At the time of the survival analysis (from the previous cutoff date of 17 OCT 2006 through the new cutoff date of 09 FEB 2007), 602 subjects with HCC were randomized to treatment with either sorafenib (299 subjects) or placebo (303 subjects). The median OS was 243 days for subjects randomized to placebo and 327 days for subjects randomized to sorafenib. Therefore, sorafenib prolonged the OS. The estimated hazard ratio (risk of death with sorafenib versus placebo) was 0.7031 (95% CI 0.5732, 0.8626), representing a 29.7% reduction in hazard over placebo (or 42.2% increase in survival time over placebo). Consistent with the findings reported in the first analysis, this represents a clinically meaningful improvement in OS attributable to sorafenib treatment.

The efficacy of sorafenib was also demonstrated by the survival rate at 6 months, which was 71% for sorafenib-treated subjects versus 61% for placebo-treated subjects.

Additionally, analyses of TTP based on investigator radiological assessments also revealed a clinically meaningful improvement in favor of sorafenib. The median TTP based on investigator assessment was 82 days for placebo subjects and 119 days for sorafenib subjects, with an estimated hazard ratio (sorafenib over placebo) of 0.7023, representing a 29.8% reduction in risk of progression (or 42.3% improvement in TTP) in subjects treated with sorafenib compared with placebo.

Additional analyses, including sensitivity analyses for OS and TTP, confirmed the primary analyses results and demonstrated their conclusiveness.

Consistent with the original analysis (up to the cut off date of 17 OCT 2006), the analysis of the co-primary endpoint TTSP demonstrated similar results in the 2 treatment arms. The effect of treatment-related side effects and underlying disease may have influenced subject responses to the PRO used to measure symptomatic progression. Subjects treated with sorafenib maintained physical function based on minimally important difference (MID) assessment and subject responses to an HCC-specific quality of life assessment.

In conclusion, the OS results of the 09 FEB 2007 cutoff data analysis were consistent with the final formal definitive analysis reported previously with a cutoff date of 17 OCT 2006, demonstrating a significant improvement in OS for sorafenib over placebo.

The additional data acquired during the time period from 17 OCT 2006 to 09 FEB 2007 did not change the overall efficacy conclusions presented in the original analysis.

At the review of the second formal interim analysis of safety and efficacy data, the DMC concluded that the results of the primary endpoint, OS, were definitively positive, and the study was stopped early.

Results Summary — Safety

This placebo-controlled study provided an opportunity to discriminate between AEs associated with sorafenib and events associated with the underlying liver disease that, in the setting of advanced HCC, may be due to either or both the underlying liver cirrhosis and the liver cancer itself. The initial safety results from the beginning of the study to data cut-off date of 17 OCT 2006 and the additional cumulative safety results (from the cut-off date of 17 OCT 2006 to the cut-off date of 09 FEB 2007) demonstrated that sorfenib was safe and well-tolerated in the subject population.

The extension with crossover phase also allowed collection of safety data in randomized placebo subjects who crossed over to treatment with open-label sorafenib and ongoing safety monitoring in randomized sorafenib subjects who continued treatment during the crossover period. It was noted that subjects who withdrew from the double-blind randomized phase of the study were permitted to re-enter the study, if eligible, after the double-blind phase and during the extension with crossover phase.

The median duration of treatment during the double-blind phase was 22.4 weeks in the sorafenib group and 18.4 weeks in the placebo group. The median duration of treatment in the 57 randomized subjects who continued sorafenib during the crossover period and the 47 placebo subjects who crossed over to treatment with sorafenib was 37.7 weeks and 27.9 weeks, respectively. For all dosing periods, 278 (91.7%) of the 303 ITT subjects in the placebo group and 221 (73.9%) of the 299 ITT subjects in the sorafenib group received an average daily dose of 80% or more of the planned dose of study drug.

The most frequent TEAEs reported in sorafenib-treated subjects (during the double-blind and crossover periods or following crossover) were in the categories gastrointestinal, constitutional symptoms, pain, and dermatology/skin. This is consistent with the observations in the main study. The AEs of ascites, nausea, and abdominal pain rarely resulted in permanent discontinuation of treatment.

Events of hypertension, weight loss, anorexia, diarrhea, abdominal pain, hand-foot skin reaction, alopecia, and dermatology – other were reported. The majority of these events were Grade 1 or 2 and not unexpected based on the current knowledge of the safety profile for sorafenib.

Drug-related TEAEs were reported for 162 (53.6%) placebo (double-blind) subjects, 35 (74.5%) placebo crossover (post-double-blind) subjects, and 241 (81.1%) sorafenib (all) subjects.

The frequency of TEAEs in the hepatobiliary category was 21.2% in the placebo (double-blind) group, 14.9% in the placebo crossover (post-double-blind) group, and 22.6% in the sorafenib (all) group. Within this category, liver dysfunction was reported in 28 (9.3%) placebo (double-blind) subjects, 1 (2.1%) placebo crossover subject, and 38 (12.8%) sorafenib subjects. The incidence of Grades 3 and 4 liver dysfunction was 4.0% in the placebo (double-blind) group, 2.1% in the placebo crossover group, and 3.3% in the sorafenib group.

Hemorrhagic events had frequent occurrences in subjects with HCC and liver cirrhosis and were mainly due to the increases in portal pressure and impaired coagulation. In the present study, hemorrhagic events occurred in 67 (22.2%) placebo (double-blind) subjects, 5 (10.6%) placebo crossover subjects, and 71 (23.9%) sorafenib (all) subjects. Grade 3 or 4 events in this category were reported with placebo (double-blind) (30 subjects, 9.9%), sorafenib (all) (23 subjects, 7.8%), and after placebo crossover (1 subject, 2.1%). In addition, the overall incidence of bleeding events resulting in death was 4.6% (14 subjects) in the placebo (double-blind) group, 2.1% (1 subject) in the placebo crossover group, and 3.7% (11 subjects) in the sorafenib group.

Renal failure in the setting of the hepato-renal syndrome is a well-described event in subjects with cirrhosis. The overall incidence of renal failure was 2.6% (8 subjects) in the placebo (double-blind) group, 0.7% (2 subjects) in the sorafenib (all) group, and 4.3% (2 subjects) in the placebo crossover group.

Treatment-emergent SAEs were reported in 185 (61.3%) subjects in the placebo (double-blind) group, 26 (55.3%) subjects in the placebo crossover group, and 191 (64.3%) subjects in the sorafenib (all) group.

Death within 30 days of receiving study medication occurred in 111 (36.8%) subjects in the placebo (double-blind) group prior to crossover, 15 (31.9%) subjects in the placebo group following crossover to sorafenib, and 94 (31.6%) subjects in the sorafenib (all) group. Most of these deaths were due to the progression of underlying disease. It should be kept in mind that at the time of the crossover, the active collection of information relating to deaths was stopped; however, any death information provided by the sites after this time was documented.

The types of treatment-emergent AEs observed, such as those in the categories constitutional symptoms, gastrointestinal, pain, and dermatology/skin, were expected for sorafenib. TEAEs, such as hemoglobin, fatigue, fever, ascites, nausea, hepatobiliary – other, liver dysfunction, hyperbilirubinemia, abdominal pain, and pruritus, reported during double-blind placebo treatment, as well as during treatment with sorafenib, may be attributed to the underlying disease. The AEs associated with sorafenib were easily recognizable, manageable, and acceptable. The longer term safety data obtained during the extension/crossover period from randomized subjects who continued treatment with sorafenib along with those who crossed over from placebo to sorafenib are consistent with the safety data presented in the original analysis during the double-blind phase and survival analysis of this study . No unexpected events or trends were observed.

Results Summary — Pharmacokinetics

The results for the PK parameters are presented in a separate report.

Results Summary — Other

The results of the biomaker analyses are presented in a separate report.

Conclusion(s)
Hepatocellular carcinoma which is not amenable to or has progressed after loco-regional therapies is associated with a grim prognosis, and there are no effective therapeutic options available. This study is the first large, randomized, controlled study of 602 subjects that demonstrated a survival advantage with oral treatment in HCC. The results of this large, randomized, double-blind placebo-controlled study demonstrate clearly a statistically significant and clinically meaningful improvement in overall survival in subjects with HCC treated with sorafenib over placebo. The clinical benefit of sorafenib was accompanied by a favorable safety profile, with no increase in SAEs over placebo, and one that is predictable, manageable, and acceptable. The cumulative safety findings of the extension crossover phase of the study along with the efficacy and safety findings of the main and additional safety cumulative data between the two cut-off dates, further confirm the treatment benefit of sorafenib in a population of subjects with HCC.

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33	Hôpital du Bocage - Dijon	C.H.R.U. Dijon Hôpital du Bocage Service d'Hépato-gastro-entérologie 2, boulevard de Lattre de Tassigny	21000	DIJON	FRANCE
34	Hopital Jean Verdier - Bondy	Hopital Jean Verdier Avenue du 14 juillet	93143	BONDY	FRANCE
35	Hôpital Saint André - Bordeaux	C.H.U Bordeaux - Groupe Hospitalier Saint André-Jean Abadie Hôpital Saint André Service d'hépato-Gastro-Entérologie 1, rue Jean Burguet	33000	BORDEAUX	FRANCE
36	Hôpital Tenon - Paris	Hôpital Tenon Service d'hépato-gastroentérologie 4, rue de Chine	75020	PARIS	FRANCE
37	Charité Campus Benjamin Franklin	Medizinische Klinik I Gastroenterologie Hindenburgdamm 30	12200	Berlin	GERMANY
38	Johannes-Gutenberg-Universität Mainz	I. Med. Klinik und Poliklinik Langenbeckstr. 1	55131	Mainz	GERMANY

39	Kliniken der Medizinischen Hochschule Hannover	Abteilung Gastroenterologie, Hepatologie und Endokrinologie Carl-Neuberg-Str. 1	30625	Hannover	GERMANY
40	Klinikum der Eberhard-Karls-Universität Tübingen	Medizinische Klinik und Poliklinik Innere Medizin I Gastroenterologie. Hepatologie, Infektiologie Otfried-Müller-Str. 10	72076	Tübingen	GERMANY
41	Klinikum der Johann Wolfgang Goethe Universität Frankfurt	Medizinische Klinik II Abteilung f. Gastroenterologie, Hepatologie Theodor-Stern-Kai 7	60590	Frankfurt	GERMANY
42	Klinikum rechts der Isar	II. Medizinische Klinik und Poliklinik Station 2/10 Tagesklinik Ismaninger Straße 22	81675	München	GERMANY
43	LMU Klinikum der Universität München - Großhadern	Innere Medizin II Marchioninistraße 15	81377	München	GERMANY
44	Med. Fakultät der Martin-Luther-Universität Halle-Wittenberg	Medizinische Fakultät Abteilung für Innere Medizin I Ernst-Grube-Str. 40	06120	Halle	GERMANY
45	Medizinische Einrichtungen der Heinrich-Heine-Universität	Abteilung für Gastroenterologie, Hepatologie und Infektiologie Moorenstr. 5	40225	Düsseldorf	GERMANY

46	Medizinische Einrichtungen der Universität Bonn	Medizinische Klinik und Poliklinik I Gastroenterologisch-Hepatologische Ambulanz Siegmund-Freud-Straße 25	53105	Bonn	GERMANY
47	Universitätskliniken des Saarlandes	Klinik für Innere Medizin II Gastroenterologie, Hepatologie, Endokrinologie, Diabetologie Kirrberger Str. 1	66421	Homburg	GERMANY
48	Universitätsklinikum Essen	Medizinisches Zentrum Klinik für Gastroenterologie und Hepatologie Hufelandstr. 55	45122	Essen	GERMANY
49	Universitätsklinikum Essen	Klinik und Poliklinik für Innere Medizin Tumorforschung Hufelandstr. 55	45122	Essen	GERMANY
50	Universitätsklinikum Freiburg	Abteilung für Innere Medizin II Hugstetter Str. 55	79106	Freiburg	GERMANY
51	Universitätsklinikum Hamburg Eppendorf (UKE)	Zentrum für Innere Medizin I. Medizinische Klinik und Poliklinik Martinistr. 52	20246	Hamburg	GERMANY

52	Universitätsklinikum Otto-von Guericke - Magdeburg	Zentrum für Innere Medizin Klinik für Gastroenterologie, Hepatologie und Infektiologie Leipziger Str. 44	39120	Magdeburg	GERMANY
53	Universitätsklinikum Regensburg	Klinik und Poliklinik für Innere Medizin I Franz-Josef-Strauss-Allee 11	93042	Regensburg	GERMANY
54	Hippokration General Hospital of Thessaloniki	50 Papanastasiou Street 54639 Thessaloniki	54639	Thessaloniki	GREECE
55	Papageorgiou General Hospital of Thessaloniki	1st Department of Internal Medicine Peripheral Road 56403 Thessaloniki	56403	Thessaloniki	GREECE
56	THEAGENIO Anticancer Hospital of Thessaloniki	Department of Oncology - Chemotherapy 2, Alex Symeonidi Str.,	540 07	Thessaloniki	GREECE
57	Rabin Medical Center - Beilinson Campus	39 Jabotinski Street	49100	Petach Tikva	ISRAEL
58	Rambam Medical Center	Oncology Department 8, Haaliya Hashniya St. Bat Galim	84801	Haifa	ISRAEL
59	Tel Aviv Sourasky Medical Center	Oncology Institute 6, Weizmann Street	64239	Tel Aviv	ISRAEL

60	A.O. di Padova	Gastroenterologia Dip. Scienze Chirurgiche e Gastroenterologiche Via Giustiniani, 2	35128	Padova	ITALY
61	A.O. San Giuseppe Moscati	Oncologia Medica Via Circumvallazione, 68	83100	Avellino	ITALY
62	A.O.U. di Bologna	Oncologia Medica - Padiglione 2 Dip. Ematologia, Oncologia e Medicina di Laboratorio Policlinico S.Orsola-Malpighi Via Albertoni, 15	40138	Bologna	ITALY
63	A.O.U. di Bologna	Medicina Interna Cardioangiologia ed Epatologia Semeiotica Medica Policlinico S.Orsola-Malpighi Via Albertoni, 14	40138	Bologna	ITALY
64	A.O.U. di Bologna	Medicina Interna Dip. Malattie Apparato Digerente e Medicina Interna Policlinico S.Orsola-Malpighi Via Albertoni, 15	40138	Bologna	ITALY
65	A.O.U. Pisana	Oncologia Medica 1 S.O. Chiara Via Roma, 67	56126	Pisa	ITALY

66	A.O.U. Policlinico Giaccone	Urologia Dip. Medicina Interna Via del Vespro, 129	90127	Palermo	ITALY
67	AUSL Forlì - Emilia Romagna	Oncologia Medica - Padiglione Vallisneri Ospedale Morgagni-Pierantoni Via Forlanini, 34	47100	Forlì	ITALY
68	IRCCS Fond. Ca' Granda Ospedale Maggiore Policlinico	Malattie Apparato Digerente ed Endocrinometabolico - Padiglione Granelli Dip. Medicina Interna 3 Via Francesco Sforza, 35	20122	Milano	ITALY
69	IRCCS IFO Regina Elena	Oncologia Medica A Ospedale Regina Elena Via E. Chianesi, 53	00144	Roma	ITALY
70	IRCCS Ist Clinico Humanitas	Oncologia Medica ed Ematologia Via Manzoni, 56	20089	Rozzano	ITALY
71	IRCCS Istituto Nazionale Tumori	Chirurgia Generale 1 (Epato-gastro-pancreatica) e Trapianto di Fegato Dip. Chirurgia Via G.Venezian, 1	20133	Milano	ITALY
72	IRCCS Policlinico San Matteo	Medicina Interna ed Oncologia Medica Piazzale Golgi, 19	27100	Pavia	ITALY

73	Hospital General de México SS	Dr. Balmis 148 Col. Doctores Delegación Cuauhtémoc	06720	México, D.F.	MEXICO
74	Hospital Regional de Especialidades Nro. 25	5 de Mayo No. 148 1609 poniente - Col. María Luisa	64000	Monterrey	MEXICO
75	Auckland City Hosptial	2 Park Road Grafton	1023	Auckland	NEW ZEALAND
76	Wellington Hospital	Wellington Cancer Centre Private Bag 7902 Riddiford Street Newtown	6001	Wellington South	NEW ZEALAND
77	Akademia Medyczna	Klinika Onkologii, Oddzial Chemioterapii ul. Lakowa 1	61-878	Poznan	POLAND
78	Centrum Onkologii - Instytut im. M.Sklodowskiej-Curie	Klinika Nowotworow Przewodu Pokarmowego Centrum Onkologii ul. W.K. Roentgena 5	02-781	Warszawa	POLAND
79	CSK MSWiA	Klinika Chorob Wewnetrznych i Gastroenterologii ul. Woloska 137	02-507	Warszawa	POLAND
80	Uniwersyteckie Centrum Kliniczne	Klinika Onkologii i Radioterapii ul. Debinki 7	80-952	Gdansk	POLAND
81	Emergency Clinical County Hospital no 1	1, Tabaci Street	200642	Craiova Dolj	ROMANIA
82	Emergency Clinical Municipal Hospital	Medical Oncology Clinic 26, Mihai Viteazu blvd	300223	Timisoara	ROMANIA

83	"Sfantul Spiridon" Emergency Clinical County Hospital	Oncolgy Clinic 1, Independentei blvd	700111	Iasi	ROMANIA
84	Institute of Surgery named after Vishnevsky	Abdominal Surgery Dept. Bolshaya Serpukhovskaya Str 27	113 811	Moscow	RUSSIA
85	Moscow Scintific Clinical Institute named after Vladimirsky	Hepatology Department Schetrina Str 61/2	129110	Moscow	RUSSIA
86	Scientific Research Institute of Emergency n/a Sklifosovsky	Transplantology Center Sukharevskaya sq. 3 bld. 5	129 010	Moscow	RUSSIA
87	State Institute for Medical Doctors Advanced Training	Gastroenterology Dept. Hospitalnaya Sq 2	111 020	Moscow	RUSSIA
88	St. Petersburg State Medical Academy named after Mechnikov	Surgical Clinic no 1 Piskarevsky prospect 47	195 067	St. Petersburg	RUSSIA
89	Ciutat Sanitària i Universitaria de la Vall d'Hebron	Coordinación Oncología, Hematología Clínica y Radioterápica Passeig de la Vall d'Hebrón, 119-129 Edificio General, planta bja	08035	Barcelona	SPAIN
90	Clínica Universitaria de Navarra	Unidad Hepática Avda. Pio XII, 36	31008	Pamplona	SPAIN

91	Hospital Clínic i Provincial de Barcelona	Unidad de cancer hepático C/ Villarroel, 170 Escalera 11, 4ª planta	08036	Barcelona	SPAIN
92	Hospital de Cruces	Servicio Gastroenterología y Hepatología. 1ª planta Pza. de Cruces, s/n	48903	Cruces/Barakaldo	SPAIN
93	Hospital del Mar	Hepatología Paseig Marítim, 27-29	08003	Barcelona	SPAIN
94	Hospital General Universitario de Alicante	Unidad Hepática, planta 4C c/ Pintor Baeza s/n	03010	Alicante	SPAIN
95	Hospital General Universitario de Valencia	Servicio Aparato Digestivo Avda Tres Cruces, s/n Edificio Izquierdo, 3ra. planta	46014	Valencia	SPAIN
96	Hospital Ramón y Cajal	Servicio de Gastroenterología Consultas Externas, planta -1 Ctra. de Colmenar, Km. 9,1	28034	Madrid	SPAIN
97	Hospital Reina Sofía	Unidad Hepática Edificio de Consultas Externas, 1ª planta-izq. Avda. Menéndez Pidal, s/n	14004	Córdoba	SPAIN
98	Hospital Universitario 12 de Octubre	Servicio Oncología Médica Av. de Córdoba, s/n	28041	Madrid	SPAIN

99	Hôpital Cantonal Universitaire de Genève	Unité de sénologie et d'oncogynécologie chirurgicales Rue Gabrielle-Perret-Gentil 4	1211	Genève	SWITZERLAND
100	Universitätsspital Zürich	Departement Innere Medizin Abteilung für Gastroenterologie und Hepatologie Rämistrasse 100	8091	Zürich	SWITZERLAND
101	Bristol Haematology and Oncology Centre	Horfield Road	BS2 8ED	Bristol	UNITED KINGDOM
102	Guy's Hospital	Department of Medical Oncology 3rd Floor, Thomas Guy House St Thomas Street	SE1 9RT	London	UNITED KINGDOM
103	Northern Institute for Cancer Research	Paul O'Gorman Buliding The Medical School University of Newcastle-upon-Tyne Framlington Place	NE2 4HH	Newcastle-upon-Tyne	UNITED KINGDOM
104	Royal Free Hospital	Liver Transplantation and Hepatobiliary Unit Pond Street Hampstead	NW3 2QG	London	UNITED KINGDOM
105	Western Infirmary	Beatson Oncology Centre Dumbarton Road	G11 6NT	Glasgow	UNITED KINGDOM
106	Gabrail Cancer Center	4875 Higbee Avenue NW	44718	Canton	UNITED STATES

107	Henry Ford Health System	Henry Ford Hospital Gastroenterology/ K-7 2799 West Grand Boulevard	48202-2689	Detroit	UNITED STATES
108	Hunter Holmes McGuire Veterans Affairs Medical Center	GI (111N) 1201 Broad Rock Boulevard	23249	Richmond	UNITED STATES
109	Kenmar Research Institute	Oncology Medical Group 201 South Alvarado Street Suite 809	90057	Los Angeles	UNITED STATES
110	Mayo Clinic Hospital	5777 East Mayo Boulevard	85054-4502	Phoenix	UNITED STATES
111	Mount Sinai Medical Center	MSSM-Div.of Liver Diseases Recanati/Miller Transplantation Inst. 11F - 70/ Box 1123 1425 Madison Avenue	10029	New York	UNITED STATES
112	New York-Presbyterian Hospital	Weill Cornell Medical Center Ctr for Liver Dis & Transplantation Box 308 520 East 70th Street	10021	New York	UNITED STATES
113	New York University School of Medicine	Building #VET 10 West 550 First Avenue	10016	New York	UNITED STATES

114	Oregon Health and Science University	Div.of Gastroenterology/Hepatology PV-310 3181 SW Sam Jackson Park Road	97239	Portland	UNITED STATES
115	Stanford Hospital & Clinics	300 Pasteur Drive	94305	Stanford	UNITED STATES
116	St. Louis University Hospital	GI & Hepatology Clin Res Unit 2nd Floor 3545 Lafayette Avenue	63104	St. Louis	UNITED STATES
117	Swedish Health Services	4th Floor 1221 Madison Street	98104	Seattle	UNITED STATES
118	The Methodist Hospital System	Discovery Alliance 6447 Main Street MS-DT801	77030-1502	Houston	UNITED STATES
119	UCLA Medical Center	Hematology/Oncology 10945 LeConte Avenue Suite 3360	90095-7077	Los Angeles	UNITED STATES
120	University of Michigan Health System	3912 Taubman Center 1500 E. Medical Center Drive	48109-0362	Ann Arbor	UNITED STATES
121	University of Pittsburgh Medical Center Health System	UPMC Liver Cancer Center Starzl Transplantation Institute Montefiore Univ. Hosp./ 7- South 3459 Fifth Avenue	15213	Pittsburgh	UNITED STATES

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