## Clinical Study Synopsis

This Clinical Study Synopsis is provided for patients and healthcare professionals to increase the transparency of Bayer's clinical research. This document is not intended to replace the advice of a healthcare professional and should not be considered as a recommendation. Patients should always seek medical advice before making any decisions on their treatment. Healthcare Professionals should always refer to the specific labelling information approved for the patient's country or region. Data in this document or on the related website should not be considered as prescribing advice.
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 | | |
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| Study Sponsor: | Bayer HealthCare AG | |
| Study Number: | 11941 | NCT00492986 |
| Study Phase: | III | |
| Official Study Title: | An open-label, non-comparative, phase-III study of the Raf-kinase inhibitor BAY 43-9006 as a subsequent to first-line therapy in patients with advanced renal cell carcinoma | |
| Therapeutic Area: | Oncology | |
| Test Product | | |
| Name of Test Product: | Sorafenib (Nexavar, BAY43-9006) | |
| Name of Active Ingredient: | Sorafenib tosylate | |
| Dose and Mode of Administration: | Subjects were administered 2 tablets of sorafenib (200 mg tablets) orally bid (twice a day) (i.e., 12-hourly) on a continuous basis. Dosing increases were not permitted. Dose of the study drugs was delayed or reduced in case of clinically significant toxicities that were possibly, probably, or definitely related to the study drug. | |
| Reference Therapy/Placebo | | |
| Reference Therapy: | This was an open-label, non-comparative study; all subjects received the same study drug. | |
| Dose and Mode of Administration: | Not applicable | |
| Duration of Treatment: | Subjects were treated with single-agent sorafenib until any of the following criteria for drug or study discontinuation were reached:<br>• Progression of disease<br>• The subject was unlikely to benefit from further treatment with sorafenib as judged by the Investigator<br>• Intolerable toxicity of the drug<br>• Withdrawal of consent for any reason<br>• Transfer to an alternative sorafenib program or treatment extension protocol<br><br>The Sponsor continued the study until sorafenib was approved by the European Agency for the Evaluation of Medicinal Products (EMEA) and/or Swissmedic for centers in Switzerland. Subjects enrolled in this study at the time sorafenib was approved by the EMEA and/or Swissmedic continued treatment in this study unless they were offered sorafenib free of charge through other means, such as a treatment extension program or commercial drug.<br><br>In Denmark, Italy, Poland, Spain, and the United Kingdom, the end of treatment date for ongoing subjects who were transferred to an extension program or commercial supply was considered the date of transfer to the alternative program. The subjects were followed up within this alternative program and therefore a 30 days safety period of active follow-up was not required within the 011941 protocol. | |
| Studied period: | Date of first subjects' first visit: | 31 OCT 2005 |

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| | Date of last subjects' last visit: | 05 NOV 2008 |
| Premature Study Suspension / Termination: | No | |
| Substantial Study Protocol Amendments: | Amendment no. 2 (dated 20 MAR 2006), was applicable for all countries. It specified the following changes:<br>• Subjects with metastatic brain disease or subjects whose metastatic brain lesions had been surgically removed were enrolled into the study provided they had recovered from any treatment-related toxicity.<br>• Subjects with severe hypersensitivity to sorafenib or any excipients were exluded form the study.<br><br>Amendment no. 3 (dated 05 NOV 2007) was applicable for Denmark, Italy, Poland, Spain, and the United Kingdom. It specified the following changes:<br>• Clarified the end of the study to enable subjects still on treatment to continue to receive sorafenib. Subjects continued receiving single agent sorafenib at the same dose and schedule as in their original study. Following transfer from their original study, subjects continued to be evaluated for safety. | |
| Study Centre(s): | The study was conducted at 33 centers in 11 countries: Germany (10), Belgium (2), France (3), Denmark (1), the Netherlands (1), Sweden (2), Italy (5), Poland (1), Spain (3), the United Kingdom (3), and Switzerland (2). | |
| Methodology: | In this non-comparative, open-label study radiological tumor assessment with computed tomography (CT) or magnetic resonance imaging (MRI) was performed within 28 days prior to start of study drug. The assessment was repeated during sorafenib treatment at intervals in accordance with local standard of care. This radiological evaluation included a CT or MRI of the chest, abdomen, and pelvis. All additional suspected sites of disease were also imaged. Safety assessments included recording of adverse events (AEs), vital signs, and concomitant medication. All drug-related AEs, all National Cancer Institute's Common Terminology Criteria for adverse events (NCI-CTCAE) Version 3.0 Grade 3 or higher AEs, and all serious adverse events (SAEs) regardless of causal relationship to study drug were recorded in this study. During the treatment, subjects visited the study site every month. The end of study visit was 30 days after the last dose of sorafenib. | |
| Indication/ Main Inclusion Criteria: | Indication:<br>Advanced Renal cell Carcinoma (RCC)<br><br>Main Inclusion Criteria:<br>• Subjects with advanced RCC.<br>• Subjects who failed at least one prior systemic established therapy for advanced RCC (e.g., interleukin-2 [IL-2], interferon-α [IFN-α]), or who had been unable to tolerate systemic therapy for advanced RCC, or were deemed by the Investigator to have been unsuited for systemic therapy for advanced RCC.<br>• Subjects who had received prior systemic and local therapies and were completely recovered from acute toxicity (i.e., resolved back to NCI CTCAE version 3.0 Grade 1 or less, or were considered irresolvable), if any, prior to study entry.<br>• Subjects who had an Eastern Cooperative Oncology Group (ECOG) performance status of 0 to 2. | |

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| | • Subjects who did not require other systemic anticancer chemotherapy, immunotherapy (including monoclonal antibodies), signal transduction inhibitors, or hormonal therapy, except for bisphosphonates, while taking sorafenib.<br>• For subjects who had major surgery, the wound had to be completely healed prior to receiving sorafenib treatment (4 weeks). |
| Study Objectives: | Overall:<br>The objective of this study was to make sorafenib available to subjects with advanced RCC who failed prior systemic therapy for advanced disease (i.e., required second-line treatment), and who did not have access to or were not eligible for other clinical trials with sorafenib. In addition, safety data and limited efficacy data were collected. All drug-related AEs, all AEs of NCI CTCAE Version 3.0 Grade 3 or higher, and all SAEs regardless of causal relationship to study drug were recorded in this study. |
| Evaluation Criteria: | Efficacy:<br>• Best overall response according to the Investigator's assessment using procedures following local standard of care and Response Evaluation Criteria for Solid Tumors (RECIST), if possible. Tumor evaluations based on clinical assessment were also allowed.<br>• Progression free survival (PFS)<br>• Time to progression (TTP)<br>• Additional efficacy variables were time to response, duration of response, and duration of stable disease (SD)<br><br>Safety:<br>• All drug-related AEs<br>• All AEs NCI CTCAE Version 3.0 Grade 3 or higher<br>• All serious AEs regardless of causal relationship to study drug<br>• Vital signs (blood pressure, heart rate) and weight |
| Statistical Methods: | Population:<br>The efficacy analysis was performed on the intent-to-treat (ITT) population comprised of subjects who received at least one dose of study drug. In addition, the efficacy analyses of overall best response were provided based on the "evaluable for response" population comprising of all subjects with at least one radiological tumor evaluation at baseline and one after start of study drug and/or a clinical evaluation.<br><br>The population valid for safety comprised of all subjects who received at least one dose of sorafenib and who had at least one safety assessment after start of study drug.<br><br>Efficacy:<br>As this was a non-comparative study, no significant tests were performed.<br><br>Summary statistics (frequency counts and percentages with 95% confidence intervals [CI]) were displayed for the following response categories: complete response (CR), partial response (PR), unconfirmed PR (uPR), SD, and progressive disease (PD) separated by radiological and clinical evaluation. uPR included subjects who had PR |

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| | by a single radiological measurement and no confirmatory assessment.<br><br>Additionally, responses were summarized to confirm overall response (CR, PR), unconfirmed overall response (CR, PR/uPR), and disease control rate (DCR). DCR was defined as CR or PR/uPR or SD for more than a pre-specified time period (8 or 12 weeks).<br><br>PFS time and TTP were analyzed using Kaplan-Meier method. PFS/TTP at 3, 6, and 12 months, median PFS/TTP time with 95% CI and Kaplan-Meier curves were displayed. Additional time-to-event efficacy variables time to response, duration of response, and duration of SD were analyzed in the same way.<br><br>Safety:<br>Incidence rates of all recorded treatment-emergent AEs were summarized by worst grade based on NCI CTCAE Version 3.0. Additionally, listings were provided for all subjects with serious AEs, subjects with AEs that caused permanent discontinuation of study drug, and subjects who died within 30 days of last study drug intake or within 60 days of last known study drug intake (60 days includes subjects for whom the last study drug intake date was unknown).<br><br>Summary statistics were performed on vital signs and weight.<br><br>Subject demographic data and baseline characteristics were analyzed by summary statistics. |
| Number of Subjects: | • 1159 subjects were screened<br>• 1150 received at least one dose of study drug and were included in the ITT population<br>• 1145 subjects were included in the safety population<br>• 1048 subjects were evaluable for response |

Study Results

Results Summary — Subject Disposition and Baseline

A total of 1159 subjects enrolled into this study; of these, 9 subjects did not enter the treatment phase, therefore, 1150 subjects received sorafenib treatment.

Of the 1150 subjects in the ITT population, 858 (75%) were male and White (81%). The mean age was 60.9 years (range: 18 to 84). The mean weight was 75.6 kg (range: 40 to 133). The mean height was 171.8 cm (range: 131 to 198).

Results Summary — Efficacy

This study used an open-label, non-comparative design to collect limited efficacy data on sorafenib treatment from clinical practice in subjects with advanced RCC who were not eligible for, or did not have access to, other clinical trials with sorafenib. Efficacy data were based on Investigators' assessment of clinical and/or radiological findings (using RECIST, if possible).

In total, 1159 subjects were screened and 1150 subjects received at least 1 dose of study drug and were analyzed as ITT population. The reasons for treatment discontinuation were (% of subjects): disease progression (50.9%); AEs (16.4%); switch to commercial drug (10.8%); death (7.5%); switch to an extension protocol no. 12311 (5.3%); withdrawal of consent (4.1%); lost to follow-up (3.8%); non-compliance with study drug (0.6%); investigator’s decision (0.5%); and second malignancy (0.1%).

Analysis of PFS was based on 835 events and analysis of TTP on 717 events, 27.4% of the subjects were censored (ITT population). The median PFS was 202 days (6.6 months) with

95% CI of 186 to 225 days. After 12 months on treatment, 29.2% of all subjects were still progression-free and alive. The median time to disease progression was 241 days (7.9 months) with 95% CI of 220 to 261 days.

The best overall response was provided based on the "evaluable for response" population (N=1048). Although the overall confirmed response rate (CR and PR) was low (4.4%), an overall response regardless of confirmation (including uPR) was reached for 17.4% of all subjects. Most of the subjects showed SD (73.0%) either by radiological evaluation or by clinical judgment only. DCR defined as the percentage of subjects with confirmed CR/PR or uPR or SD maintained for at least 8 or 12 weeks was 85.4% and 77.8%, respectively.

Time to response ranged from 25 to 475 days with a median of 83.5 days (2.7 months). The median duration of response was 308 days (10.1 months) with 95% CI of 211 to 352 days, and the median duration of SD was 244 days (8.0 months) with 95% CI of 224 to 267 days. Both analyses were performed for the ITT population.

Several subgroups were analyzed to detect prognostic factors. Three of them were discussed in the efficacy section: age group <70 vs ≥70 years, pure clear cell vs non-pure clear cell RCC histology, and pre-treatment vs non-pre-treatment with anti-vascular endothelial growth factor (VEGF) (bevacizumab and/or sunitinib). Similar efficacy results were seen in the two age groups. Subjects with non-pure clear cell histology had shorter PFS/TTP and lower response rate than those with pure clear cell histology. Similarly, subjects with prior anti-VEGF therapy had shorter PFS/TTP and lower response rate than those without prior anti-VEGF treatment. However, within this non-comparative trial it was not possible to clarify whether the differences between the subgroups were caused by the respective subject characteristic itself or due to imbalances in other important baseline characteristics or due to the study drug treatment.

Results Summary — Safety

The safety analysis included 1145 subjects who received at least 1 dose of the study drug and had at least 1 safety assessment after starting treatment with the study drug. Mean treatment duration was 8.4 months (±6.8 months) and the mean daily dose was 670.6 mg (±160.7 mg).

AEs (Grade ≥3, drug-related, or serious) were reported by 99% of all subjects. AEs considered by the Investigator to be drug-related were reported for 93.6% of the subjects. The most commonly reported AEs by system organ class were gastrointestinal events (78.2%) and dermatological/skin events (77.2%). The most common AEs by NCI CTCAE term were hand-foot skin reaction (56.3%), diarrhea (55.5%), and fatigue (35.1%). These were also the most frequently reported drug-related AEs.

Although gastrointestinal events were common, they were in general manageable and led only rarely to dose discontinuations. Dermatological toxicities were rarely serious or of high grade and they were amenable to remedial therapy and were generally reversible.

Grade 3 drug-related AEs were reported for 41.2%, Grade 4 for 3.1%, and Grade 5 for 1.0% of the subjects. The most frequently reported AEs of Grade ≥3 considered related to the study drug included: hand-foot skin reaction (13.0%), diarrhea (7.3%), and fatigue (7.1%).

AEs leading to sorafenib discontinuation were reported for 18% of subjects valid for safety. The most common events that led to study drug discontinuation were hand-foot skin reaction (1.7%), fatigue (1.6%), and rash/desquamation (1.5%). A total of 46.9% subjects reported AEs which led to dose reductions, and 44.4% of subjects reported AEs which led to dose interruptions.

SAEs were reported for 517 (45.1%) subjects in total. Of these, 170 subjects (14.8%) had SAEs considered to be drug-related. There were 256 (22%) deaths in total. Most of these,

192 (17%), occurred within 30 or 60 days of receiving the last dose of study drug (60 days included subjects for whom the last study drug intake date was unknown). The most common reason for death was disease progression.

In summary, in both the overall population and the subgroups the data suggest that sorafenib was well tolerated in subjects with advanced RCC. The AEs associated with sorafenib were easily recognizable, manageable, and tolerable.

Conclusion(s)

Renal cell cancer is associated with poor prognosis and few therapeutic options. Previous clinical studies have provided evidence for the activity of sorafenib in RCC. The results from this non-comparative, open-label study demonstrated clinical benefit and meaningful efficacy for a subject population with advanced RCC that was representative of a broader range of RCC subjects in the community. Toxicity and response rates were similar to those reported previously, supporting a favorable safety profile in this subject population.

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| Publication(s): | None | | |
| Date Created or Date Last Updated: | 26 MAR 2012 | Date of Clinical Study Report: | 17 JUL 2009 |

# Investigational Site List

| Marketing Authorization Holder in Germany | |
|---|---|
| **Name** | Bayer Pharma AG |
| **Postal Address** | D-13342<br>Berlin<br>Deutschland |
| **Sponsor in Germany** | |
| **Legal Entity Name** | Bayer HealthCare AG |
| **Postal Address** | D-51368<br>Leverkusen,<br>Germany |

**List of Investigational Sites**

| No | Facility Name | Street | ZIP Code | City | Country |
|---|---|---|---|---|---|
| 1 | Institut Jules Bordet/Jules Bordet Instituut | Institut Jules Bordet/Jules Bordet Instituut<br>Service Oncologie/Dienst Oncologie<br>Boulevard de Waterloo 121 | 1000 | BRUXELLES - BRUSSEL | BELGIUM |
| 2 | UZ Leuven Gasthuisberg | Dienst Oncologie<br>Herestraat 49 | 3000 | LEUVEN | BELGIUM |
| 3 | Aarhus Universitetshospital | Onkologisk Afd<br>Nørrebrogade 44 | 8000 | Århus C | DENMARK |
| 4 | Centre Léon Bérard | Centre Léon Bérard<br>Service de Cancérologie Médicale<br>28 rue Laennec | 69008 | LYON CEDEX | FRANCE |

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| 5 | Hôpital Saint André - Bordeaux | C.H.U Bordeaux - Groupe Hospitalier Saint André-Jean Abadie<br>Hôpital Saint André<br>Service de radiothérapie du Professeur MAIRE<br>1, rue Jean Burguet | 33000 | BORDEAUX | FRANCE |
| 6 | Institut Gustave Roussy - Villejuif | Institut Gustave Roussy<br>Unité immunothérapie<br>114 rue Edouard Vaillant | 94805 | VILLEJUIF | FRANCE |
| 7 | Charité Campus Benjamin Franklin | Medizinische Klinik III (WE 24)<br>Hämatologie, Onkologie und Transfusionsmedizin<br>Hindenburgdamm 30 | 12200 | Berlin | GERMANY |
| 8 | Johannes-Gutenberg-Universität Mainz | III. Medizinische Klinik und Poliklinik<br>Bereich Hämatologie und Onkologie<br>Langenbeckstr. 1 | 55131 | Mainz | GERMANY |
| 9 | Klinikum Darmstadt | Urologische Klinik<br>Grafenstr. 9 | 64276 | Darmstadt | GERMANY |

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| 10 | LMU Klinikum der Universität München - Großhadern | Urologische Klinik und Poliklinik<br>Marchioninistr. 15 | 81377 | München | GERMANY |
| 11 | Medizinische Einrichtungen der Heinrich-Heine-Universität | Urologische Klinik<br>Moorenstr. 5 | 40225 | Düsseldorf | GERMANY |
| 12 | Medizinische Fakultät Carl Gustav Carus | Technische Universität Dresden<br>Klinik und Poliklinik für Urologie<br>Fetscherstraße 74 | 01307 | Dresden | GERMANY |
| 13 | Praxis Hr. Dr. J. Thomalla | Praxis für Hämatologie und Onkologie<br>Nevers-Str. 5 | 56068 | Koblenz | GERMANY |
| 14 | Universitätskliniken des Saarlandes | Klinik für Urologie und Kinderurologie<br>Kirrberger Str. | 66242 | Homburg | GERMANY |
| 15 | Universitätsklinikum Hamburg Eppendorf (UKE) | Klinik und Poliklinik für Innere Medizin<br>Onkologie und Hämatologie<br>Martinistr. 52 | 20251 | Hamburg | GERMANY |
| 16 | Universitätsklinikum Schleswig-Holstein / AÖR | Campus Lübeck<br>Klinik und Poliklinik für Urologie<br>Ratzeburger Allee 160 | 23538 | Lübeck | GERMANY |

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| 17 | A.O. di Perugia | Oncologia Medica<br>Ufficio Operativo Ricerche Cliniche (Piano -1)<br>Località S. Andrea delle Fratte | 06156 | Perugia | ITALY |
| 18 | A.O. di Reggio Emilia | Oncologia Medica<br>Arcispedale Santa Maria Nuova<br>Viale Risorgimento, 80 | 42100 | Reggio Emilia | ITALY |
| 19 | A.O.U. di Modena Policlinico | Centro Oncologico Modenese Policlinico<br>Via Del Pozzo, 71 | 41124 | Modena | ITALY |
| 20 | IRCCS Istituto Nazionale Tumori | Oncologia Medica 3<br>Trattamento Medico Sarcomi Adulto<br>Via G.Venezian, 1 | 20133 | Milano | ITALY |
| 21 | IRCCS Policlinico San Matteo | Medicina Interna ed Oncologia Medica<br>Piazzale Golgi, 19 | 27100 | Pavia | ITALY |
| 22 | Academisch Medisch Centrum Universiteit van Amsterdam | Meibergdreef 9 | 1105 AZ | AMSTERDAM | NETHERLANDS |
| 23 | Wojskowy Instytut Medyczny | Klinika Onkologii CSK MON<br>ul. Szaserow 128 | 04-141 | Warszawa | POLAND |

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| 24 | Ciutat Sanitària i Universitaria de la Vall d'Hebron | Passeig de la Vall d'Hebron, 119-129 | 08035 | Barcelona | SPAIN |
| 25 | Hospital Central de Asturias | Celestino Villamil, s/n | 33006 | Oviedo | SPAIN |
| 26 | Hospital Clínico Universitario San Carlos | C/. Dr. Martín Lagos, s/n | 28040 | Madrid | SPAIN |
| 27 | Karolinska Universitetssjukhuset i Solna | Radiumhemmet<br>Kliniken för onkologi | 171 76 | Stockholm | SWEDEN |
| 28 | Sahlgrenska Universitetssjukhuset | Jubileumskliniken<br>Allmän onkologi | 413 45 | Göteborg | SWEDEN |
| 29 | Hôpital Cantonal Universitaire de Genève | Médicine interne<br>Rue Gabrielle-Perret-Gentil 4 | 1211 | Genève | SWITZERLAND |
| 30 | Universitätsspital Basel | Department Angiology<br>Petersgraben 4 | 4031 | Basel | SWITZERLAND |
| 31 | Royal Marsden Hospital (London) | Department of Medical Oncology<br>1st Floor Mullberry House<br>Fulham Road | SW3 6JJ | London | UNITED KINGDOM |
| 32 | Royal Marsden NHS Trust (Surrey) | Department of Medical Oncology<br>Downs Road | SM2 5PT | Sutton | UNITED KINGDOM |
| 33 | Western Infirmary | Beatson Oncology Centre<br>Cancer Research Campaign<br>Department of Oncology<br>Dumbarton Road | G11 6NT | Glasgow | UNITED KINGDOM |

# Product Identification Information

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| **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