# Clinical Study Report

Version/ Date: Report Final Version 2.0 / 20 February 2013

## OPEN-LABEL PHASE II STUDY OF SORAFENIB IN PATIENTS WITH ADVANCED HEPATOCELLULAR CARCINOMA (HCC) AND CHILD PUGH SCORE B WITH SPECIAL ANALYSIS OF PATIENTS 65 YEARS OR OLDER

| | |
|---|---|
| **Project code:** | SOCS-B |
| **EudraCT:** | 2008-008232-87 |
| **Short title:** | SOCS-B |
| **Investigational substance:** | Sorafenib |
| **Reference substance:** | N/A |
| **Indication:** | Patients with advanced hepatocellular carcinoma and child pugh B |
| **Study phase:** | open-label phase II |
| **Inclusion of first patient:** | 12.11.2009 |
| **End of treatment of last patient:** | 16.01.2012 |
| **Date of final report:** | Final Version 2.0 – 20.02.2013 |

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# Signatures

**Title of the trial:** **OPEN-LABEL PHASE II STUDY OF SORAFENIB IN PATIENTS WITH ADVANCED HEPATOCELLULAR CARCINOMA (HCC) AND CHILD PUGH SCORE B WITH SPECIAL ANALYSIS OF PATIENTS 65 YEARS OR OLDER**

**Trial substance:** Sorafenib

**Trial code:** SOCS-B

The undersigned have read this clinical study report and hereby confirm that, to the best of their knowledge, it accurately describes the conduct and the results of the study.

**LKP in accordance with §40 Of the AMG (German Drug Law)**

22.02.13 _____
Date — Prof. Dr. Eckart Schott

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**Representative of the Sponsor**

11.3.13 _____
Date — Dr. Gerrit Fleige

**Representative of GSO mbH**

19.03.2013 _____
Date — Dr. Anne L. Kranich

# 1 SYNOPSIS

| *Name of the sponsor:*<br><br>Charite Universitätsmedizin Berlin | *Individual study table*<br><br>*Referring to part of the Dossier:*<br><br>*Volume: N/A*<br><br>*Page: N/A* | *(For National Authority Use only)* |
|---|---|---|
| *Name of the finished product:*<br><br>Nexavar | | |
| *Name of the active substances:*<br><br>Sorafenib | | |

**Title of Study:** Open-label phase II study of Sorafenib in patients with advanced hepatocellular carcinoma (HCC) and Child Pugh score B with special analysis of patients 65 years or older. Protocol version 2.3 (22.04.2009), amended in version 2.4 (27.01.2010)

**Investigators:** Prof. Dr. med. E. Schott, Prof. Dr. med. Dr. mult. h.c. H. Blum, PD Dr. med. M. Dollinger, Prof. Dr. med. M. Ebert, Dr. med. T. Ganten, Prof. Dr. med. G. Gerken, Dr. med. A. Hoffmeister/ PD Dr. med. K. Schoppmeyer, Prof. Dr. med. F. Kolligs, Dr. med. B. Krammer-Steiner, Prof. Dr. med. P. Malfertheiner, Dr. med. S. Tebbe, Prof. Dr. med. G. von Wichert, PD Dr. med. R. Wiest

**Study centers:** A total of 15 study centers participated in this trial. Patients were included at 6 study sites (Schott (Charité Berlin), Dollinger (University Hospital Halle), Kolligs (University Hospital Munich), Malfertheiner (University Hospital Magdeburg), Tebbe (Kassel Hospital), von Wichert (University Hospital Ulm)).

**Publication (reference):** The trial was terminated prematurely. No results were published.

| **Studied period (years): 2 years and 2 months**<br>Inclusion of first patient: 12.11.2009<br>End of treatment of last patient: 16.01.2012<br>Due to low recruitment, the study was prematurely terminated. | **Phase of development:**<br>Phase II |
|---|---|

**Trial objectives:**

Primary trial objectives:

- To determine the rate of patients with drug-related toxicity with NCI CTCAE grade ≥ 3

Secondary objectives: determination of

- Time to progression (TPP)
- Progression free survival (PFS)
- Response rate (EASL/RECIST)
- Disease control rate (DCR: CR, PR or SD ≥ 8 weeks as best overall response (BOR)) – EASL/ RECIST
- Overall survival (OS)
- Cumulative dose
- Average daily dose
- Quality of life
- Safety

**Methodology:** Open-label, multi-center phase II

**Number of patients planned:** 112

**Number of patients analyzed:**

| **Number of patients** | **Total** |
|---|---|
| Recruited | 18 |
| Evaluable regarding toxicity | 18 |
| Evaluable regarding efficacy | 13 |

**Diagnosis and main criteria for inclusion:** Patients with proven hepatocellular carcinoma (child pugh B)

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| *Name of the active substances:* Sorafenib | *Page: N/A* | |

not suitable for loco-regional treatment options, resection or liver transplantation could be included in the study. Patients had to have measurable lesions and adequate organ functions.

**Test product, dose and method of administration, batch number:**
Sorafenib (2 × 400 mg/day) p.o. Study medication was prescribed hence no specific batch was used.

**Duration of treatment:** Subjects were treated until progressive disease was documented or unacceptable toxicity occurred

**Reference therapy, dose and method of administration, batch number:** NA. No reference treatment was used as comparison.

**Criteria for evaluation:**

Primary end point:
Determination of the rate of patients with drug-related toxicity with NCI CTCAE grade ≥ 3

Secondary efficacy criteria:
- Determination of time to progression (TPP)
- Determination of progression free survival (PFS)
- Determination of response rate (EASL/RECIST)
- Determination of disease control rate (DCR: CR, PR or SD ≥ 8 weeks as best overall response (BOR)) – EASL/ RECIST
- Determination of overall survival (OS)

Safety
- Evaluation of the incidence and type of adverse event
- Extent of exposure
- Toxicities
- Laboratory investigations

Quality of life
- FACT-Hep questionnaire

**Statistical methods:**
Categorical data were presented in contingency tables with frequencies and percentages. Continuous variables have been summarized with at least the following: frequency: mean, median, standard deviation, minimum, maximum, quartile. Confidence intervals were calculated following exact methods. Time-to-event data were analyzed by Kaplan-Meier-methods.
Safety was analyzed in the ITT population. Adverse events were listed in summary tables that provided numbers and percent of patients with adverse events. Special tables were provided for adverse events of grade III/IV and serious adverse events.
Efficacy analyses were conducted for all patients in the ITT set, the subset IIT (ITT patients evaluable for response), and, if applicable, for patients in the PP set. According to protocol, the primary analysis was performed in the ITT population.
Due to the premature study discontinuation, overall sample size was rather too sparse to perform all pre-planned statistical analyses. Therefore statistical analyses of quality of life as well as all stratified age-group specific analyses have been deleted.

**Summary:** Treatment in this trial was well tolerated. Even though 89% of patients had adverse events of at least CTCAE grade III, the majority of severe and serious adverse events was unrelated to treatment,

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but related to the severity of the underlying disease. Due to the low number of patients, no conclusions can be drawn from the data obtained for efficacy.

Primary end point - rate of patients with drug-related toxicity with NCI CTCAE grade ≥ 3

6 patients (33%,exact 95% Clopper-Pearson test; C.I.: [13%, 59%]) presented with drug related adverse events of NCI-CTCAE ≥ 3. These events were diarrhea, fatigue, syncope (fainting), 2 events of anemia, 2 episodes of GI hemorrhage, hypertension (all grade III), and liver failure (1 event, grade V).

**Efficacy results:**

**Time to progression (TPP):** The median time to progression was 4 months according RECIST and EASL in the ITT, as well as in the subset ITT. The median time to progression was 2 month according RECIST in the per-protocol set and not applicable for EASL due to too few patients being evaluable.

**Progression free survival (PFS):** Patients had a progression-free survival (PFS) of 2 months in the ITT and the per-protocol analysis set, and a PFS of 3 months in the subset ITT analysis set

**Response rate (RR)** No patient achieved a response (complete or partial emission).

**Disease control rate (DCR):** In the ITT, the disease control rate was 39% according RECIST and 33% according to EASL. 7 patients (RECIST) and 6 patients (EASL) had stable disease (SD). No patient achieved a complete or partial remission (CR or PR). In the subset ITT, the disease control rate was 54% according RECIST and 46% according to EASL. 7 patients (RECIST) and 6 patients (EASL) had stable disease (SD). In the per-protocol subset, the disease control rate was 38% according RECIST and EASL. 3 patients (RECIST) and 3 patients (EASL) had stable disease (SD).

**Overall survival (OS):** Patients had a median overall survival of 4 months in the ITT population, 6 months in the subset ITT, and 5 months in the PP analysis set.

**Safety results:**

Overall the treatment was well tolerated. Even though 89% of patients had adverse events of at least CTCAE grade III, the majority of severe and serious adverse events was unrelated to treatment, but related to the severity of the underlying disease. Gastrointestinal adverse events (mainly diarrhea and anorexia) were most common, followed by constitutional symptoms (mostly from fatigue and worsening of constitution), pain, and dermatological adverse events. Most of these events were of mild to moderate severity. The majority of grade III/ IV adverse events were infections, and hemorrhage GI (mainly from esophageal varices).

37 drug related adverse events occurred in 14 patients. Diarrhea was the most frequent drug related adverse event (n=8), while fatigue and weight loss occurred in 4 patients each. Only 6 patients (33%) developed drug related AEs of at least grade III. 2 drug related adverse events affected hemoglobin, 2 drug related adverse events were hemorrhage GI, and 1 drug related adverse event each were diarrhea, fatigue, syncope, hypertension, and liver dysfunction/ failure.

**Date of report:** 20.02.2013