Report Synopsis of Study SIRN (Eudra-CT Number: 2006-006566-42)

Name of Sponsor/Company: Faculty of Medicine delegated to III. Medizinische Klinik und Poliklinik Klinikum der Johannes Gutenberg-Universität Langenbeckstrasse 1 55131 Mainz, Germany	Individual Study Table Referring to Part of the Dossier: na[1] Volume: na Page: na	*(For National Authority Use only)*
Name of Finished Product: Nexavar® (BAY 43-9006)		
Name of Active Substance: Sorafenib		

Title of Study[2]:

Sorafenib in Resected NSCLC (SIRN) – An open-label Phase II Study to Investigate the Efficacy and Safety of Sorafenib as Adjuvant Treatment following Resection of Non-small Cell Lung Carcinoma (NSCLC) in Patients not eligible for Cisplatin-based Adjuvant Chemotherapy (Final Protocol Version 1.5, March 12th, 2007)

Investigators:

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Dr. med. Stefan Guth

Study centre(s): 6 in Germany

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[1] Diese Angabe ist nur bei Einreichung in Zusammenhang mit einem Zulassungsdossier erforderlich.

[2] Es muss klar hervorgehen, dass die letzte Protokollversion einschließlich aller Amendments gemeint ist, die Amendments sind anzugeben und zu identifizieren.

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Name of Active Substance: Sorafenib		
Publication (reference): n.a.		
Studied period (years)[3]: *Date of first enrolment:* October 15th, 2007 *Date of last completed:* July 30th, 2008 Date of LPO is given due to early termination of the trial on July 15th, 2008 Reason for early termination: The study was terminated after enrollment of 7 subjects, as an interim analysis of the ESCAPE trial suggested an inferior outcome for patients with advanced squamous cell carcinoma of the lung treated with carboplatin/paclitaxel, when combined with sorafenib. Although study population and treatment in the ESCAPE trial was not at all comparable to treatment within the SIRN trial, it was felt that patients with squamous cell carcinoma of the lung should not be treated with sorafenib for safety reasons. Under these prerequisites, the SIRN trial was unable to meet its endpoints within the expected time frame, and was hence terminated.	Phase of development: n.a.	

Objectives:

Primary Objective :

To determined progression-free survival (PFS) at 2 years in patients with NSCLC (UICC stages I to III A) treated with Sorafenib following potentially curative surgery of NSCLC.

Secondary Objectives:

- To determined PFS at 3 and 4 years following surgery
- To determined overall survival (assessed after 3 and 4 years)
- To assessed the safety and tolerability of Sorafenib when administered as adjuvant treatment following surgery for NSCLC
- To assessed biomarkers relevant to Sorafenib response and disease state, and their correlation to clinical outcome

Methodology:

This was an open-label, single-armed, multicentric, phase II study of Sorafenib treatment following surgery for NSCLC. The primary

[3] Hier sollen auch Studienunterbrechungen und vorzeitige Studienbeendigungen/Studienabbrüche unter Angabe der Gründe aufgeführt werden.

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hypothesis was to increase the progression-free survival (PFS) of the experimental group in comparison to a historical control group. For sample size calculation a 2 year PFS of 50% was calculated for the historical control group, and a 2 year PFS of 67% was estimated for the intervention group. These estimates are based on the actual PFS and overall survival (OS) of a defined population of 120 NSCLC patients treated at a single institution with surgery alone or surgery followed by adjuvant radiotherapy, which compared favorably to published international results, and the improvement of PFS achieved by 4 cycles of cisplatin/vinorelbine-based cytotoxic chemotherapy in published randomized trials.

Number of patients (planned and analyzed):

Planned sample size: 134 (to obtain 120 evaluable patients)

Due to study termination only 7 patients have been enrolled and anlyzed.

Diagnosis and main criteria for inclusion:

- Patients with histologically confirmed diagnosis of NSCLC pathological stages I, II or III A
- Patients must have completely resected disease and may not be treated with prior chemotherapy. Patients must have fully recovered from surgery prior to initiation of study treatment.
- Adjuvant radiotherapy for stage III A disease is permitted given that the patient has recovered from all radiation-induced toxicities. In those patients, a complete restaging will be performed prior to enrolment into the trial.
- Patients with completely resected NSCLC stage II or III A, who for medical reasons are not eligible for adjuvant chemotherapy consisting of a standard regimen of 4 cycles cisplatin/vinorelbine
- Patients with completely resected NSCLC stage II or III A, who are not willing to undergo adjuvant chemotherapy with 4 cycles of cisplatin/ vinorelbine, are also eligible.
- Age ≥ 18 years
- ECOG performance status ≤ 2
- Normal organ and marrow function defined as: Hematopoetic: absolute neutrophil count >1,500/mm3, platelet count > 100,000/mm3, hemoglobin > 9 g/dL, INR < 1.5 ULN and PTT within normal limits, Hepatic: total bilirubin < 1.5 x ULN, AST or ALT < 2.5 x ULN, Renal: creatinine < 1.5 x ULN
- Women of childbearing potential must have a negative serum pregnancy test performed within 7 days prior to the start of treatment
- Women of childbearing potential and men must agree to use adequate birth contraception prior to study entry and for the duration of study participation. Women and men should use adequate birth control for at least 3 months after the last administration of Sorafenib.
- Written informed consent

Test product, dose and mode of administration, batch number:

Sorafenib (Nexavar®) charge no: BX02ANA

Sorafenib was administered as oral formulation (200 mg tablets) at a dose of 400 mg twice daily starting 28 to 42 days after surgery or surgery plus adjuvant radiotherapy. The dose could be adjusted based on individual toxicities following a predetermined dose reduction schedule.

Duration of treatment:

It was planned to administer the study medication for up to 48 months. However, due to early termination of the trial, maximum treatment duration was 7.5 months in one patient.

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Name of Active Substance: Sorafenib		
Reference therapy, dose and mode of administration, batch number: n.a.		

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Name of Finished Product: *Nexavar® (BAY 43-90069*		
Name of Active Substance: *Sorafenib*		

Criteria for evaluation

Efficacy:

Clinical and radiological assessment of remission status (RECIST criteria).

Safety:

Assessment of clinical toxicities and safety laboratory during scheduled visits at the study centers. All events were reported and graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE Version 3.0). The incidence of treatment interuption and dose reduction were also recorded for all patients.

Statistical methods:

Due to the small number of subjects enrolled in the study, the analysis was only done by subject listings.

Summary – Conclusions

Efficacy results:

Due to early termination of the trial, resulting in enrolment of only 7 subjects and a maximum treatment duration of 7.5 months in one subject, no efficacy analyses were undertaken.

Safety results:

All toxicities and adverse events observed during the trial were in line with the expected toxicities of the study medication sorafenib, which is approved and widely used for the treatment of advanced renal cell carcinoma and hepatocellular carcinoma. There was one serious adverse event, which led to discontinuation of study treatment. This comprised ECG changes consistent with myocardial ischemia; however, relevant myocardial ischemia was ruled out by clinical and laboratory examinations in this subject. Cardiavascular events are amongst the known toxicities of sorafenib. In summary, the results of this study do not change the safety profile of the study medication sorafenib.

Conclusion:

Due to early termination, none of the end points of the study could be addressed. Study treatment was feasible in four of seven subjects until termination of the trial, with a maximum treatment duration of 7.5 months in one patient. Two patients withdrew from the study, and one patient was withdrawn because of a serious adverse event.

I hereby confirm, that the data in the results report were collected properly and are correct.

Date of the report: 26. 10. 2011

Print Name: Prof. Dr. med. Martin Schuler (LKP, according to German Medicinal Act)

Signature: