Clinical Study Report – CSR (Synopse ICH E3)

Study Title:	**A double-blind, placebo-controlled, randomized, multi-centre phase II trial to assess the efficacy of Sorafenib-maintenance therapy in Flt3- ITD positive AML in complete hematological remission after allogenic stem cell transplantation**	
Study Acronym	SORMAIN	
Study Sponsor-ID	KKS-134	
EudraCT No.	2010-018539-16	
CSR Version	V01F	
CSR Date	04-NOV-2019	
	Date	**Signature**
Sponsor Dr. Michael Wittenberg		
Principal Investigator Prof. Dr. Andreas Burchert		
Project-Manager Susanne Harnisch		
Author Dr. Eckhard Bergmann		

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Clinical Study Report (Synopse ICH E3)

1 Name and address of Sponsor/Company

Philipps-University of Marburg, Biegenstraße 10, 35037 Marburg

2 Name of Finished Product

Nexavar® 200mg tablet

3 Name of Active Substance

Sorafenib

4 Individual Study Table: Referring to Part of the Dossier (Volume, Page)

N.A.

5 Title of Study

A double-blind, placebo-controlled, randomized, multi-centre phase II trial to assess the efficacy of Sorafenib-maintenance therapy in Flt3-ITD positive AML in complete hematological remission after allogenic stem cell transplantation – latest Study protocol no.: **V04F, 31.03.2014**. First official protocol version was V02F, 09.03.2012.

Date of approval of competent authority (CA)	25.10.2010	
CA Vorlagen Nummer	**4036508**	
Data of approvals of subsequent changes according to § 10 Para. 1 GCP-V, if applicable:		
Amendment No. 1	approved on	19.03.2012
Amendment No. 2	approved on	28.04.2014
Notification of end of study (§13 (8) GCP-V)	on:	16.11.2018
Date of approval of ethics committee	28.09.2010	
Sign of ethics committee Marburg	138/10 (A)	
Data of approvals of subsequent changes according to § 10 Para. 1 GCP-V, if applicable:		
Amendment No. 1	approved on	09.03.2012
Amendment No. 2	approved on	23.04.2014
Notification of end of study (§13 (8) GCP-V)	on	16.11.2018

Amendment No. 1				
First official version Protocol: V02F (12.09.2010)				
Revision (Version)	**Chapter***	**Description of Changes**	**Effective date**	**Effects on Other Documents**
V02F	p. 8; 1. (DSMC)	Change of DSMC members; The change was necessary because the centers of the previous members joined the trial.	09.03.2012	no
	Inclusion Criteria p 11; 9 and p 26/27; 6.1.2.1. and p. 27/28; 6.1.2.2.	Therapeutic anticoagulation should not be a general exclusion criterion as defined in the previous protocol version. Patients should be proactively monitored for their INR values in case anticoagulation had to be given.	09.03.2012	no

Amendment No. 1				
	p. 14; 2.1. (Flow Chart)	Formal clarification of study processes; no impact on safety or study results	09.03.2012	no
	p. 5/6; p.33; 6.5; p. 51; 14.1; p. 55; 14.10	The study should be enlarged to centers outside Germany. Therefore all German regulatory details were deleted or adapted.	09.03.2012	no
	p.34/35; 6.6.	A patient diary and an additional drug accounting log were added to the study for medication tracking reasons.	09.03.2012	no
	p.36; Punkt 7.1. and S. 22/23; Punkt 5.5. and p. 14; 2.1. (Flow Chart)	e-CRF documentation procedures were facilitated; no impact on safety or study results	09.03.2012	no
	p.37; 7.1.3 and p.40; Table 6	The follow up visits M1 and M5 were completely deleted as they were regarded as obsolete by the CCI and the sponsor.	09.03.2012	no
	p.40; Table 6 and p.42/43; Punkt 9.2.1.	Pregnancy As two Austrian centers had joined the study a monthly pregnancy test obligation for those centers was added to the protocol according to Austrian regulations; A separate pregnancy reporting form (for all centers) was added to the study; According to the previous protocol version pregnancy should have been reported via the SAE form.	09.03.2012	no
	p.44; 9.5. and p.33/32; 6.3. and p.25/26; 6.1.	As Sorafinib is an authorized marked product the SmPC instead of the IB was taken as safety reference document within the study. This has not been clearly stated in the previous protocol version.	09.03.2012	no
	Seite 44/45; 10.1. and 10.2	AE/SAE reporting procedures for ongoing AEs after the end of patient's medical treatment were clarified.	09.03.2012	no
	p46; 10.4.	The causality definitions of AEs were adapted according to the "VIGI S3" tool which has henceforth been used in the study.	09.03.2012	no
	p. 52; 14.3	A family member or acquaintances was no longer accepted as appropriate independent witnesses during informed consent process	09.03.2012	no
> revision lead to protocol version V03 F 2012_01_27 which was accepted by EC on 09.03.2012				

Amendment No. 2				
Revision (Version)	**Chapter***	**Description of and Rationale for Change**	**Effective date**	**Effects on Other Documents**
V03F	*5.1.1 p.44, 11.3*	An interim data inspection should be performed during the first half of 2014 according to the method proposed by Schäfer and Müller (Statist Med 20:3741-3751, 2001), which should take into account all patients included in the SORMAIN trial.The reasons for this additional interim data inspection, were: • The recruitment rate had been much lower than expected. Whereas 200 patients were planned within an accrual period of 24 months, only 45	23.04.2014	no

Amendment No. 2				
		patients had been randomized after 40 months of accrual. • Based on accumulating evidence from controlled trials with AC220 and clinical experience with Sorafenib used outside of clinical studies in the AML indication, it was not considered unlikely that Sorafenib therapy might generate a larger treatment benefit compared to placebo than the hazard ratio of 0.45 implies, which had originally been assumed for the sample size calculation.		
> revision leads to protocol version V04F 2014_03_31 which was accepted by EC on 23.04.2014				

Based on a decision of the TSC (Trial Steering Committee) and DSMC (Data Monitoring and Safety Committee), the study recruitment was prematurely terminated on July 1st, 2016, because of inadequately slow patient recruitment. 200 patients were planned, 83 patients have been finally enrolled.

6 Investigators

Center	**Principal investigator**
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7 Study center(s)

Center-ID	Participating center	Number of recruited patients
01	Universitätsklinikum Gießen u. Marburg GmbH, Standort Marburg Klinik für Hämatologie, Onkologie und Immunologie Baldingerstrasse Germany-35043 Marburg	33
02	Universitätsklinikum Essen Klinik für Knochenmarktransplantation Hufelandstr. 55 Germany-45122 Essen	0
03	Universitätsklinikum Hamburg Interdisziplinäre Klinik und Poliklinik für Stammzelltransplantation Martinistraße 52 Germany-20246 Hamburg	4
04	Universitätsklinikum Münster Medizinische Klinik, Innere Medizin A Albert-Schweitzer-Strasse 3 Germany-48149 Münster	7
05	Klinikum der Johann Wolfgang Goethe-Universität Med. Klinik II, Hämatologie, Onkologie, Rheumatologie, Infektiologie, HIV-Erkrankung	11

Center-ID	Participating center	Number of recruited patients
	Theodor-Stern-Kai 7 Germany-60290 Frankfurt/Main	
06	Universtiätsklinikum Freiburg Innere Medizin I; Hämatologie, Onkologie und Stammzelltransplantation Hugstetter Str. 55 Germany-79106 Freiburg	9
07	Johannes-Gutenberg-Universität III. Medizinische Klinik, Studienzentrale, Bau 302, II. Stock Langenbeckstrasse 1 Germany-55131 Mainz	4
09	Klinikum rechts der Isar III. Medizinische Klinik und Poliklinik Ismaninger Straße 22 Germany-81675 München	1
10	Klinikum Chemnitz gGmbH Klinik für Innere Medizin III Bürgerstraße 2 Germany-09113 Chemnitz	0
11	Stiftung Deutsche Klinik für Diagnostik GmbH Abteilung für Blutstammzell- und Knochenmarktransplantation Aukammallee 33 Germany-65191 Wiesbaden	2
12	Universitätsklinikum Carl Gustav Carus Medizinische Klinik und Poliklinik I Fetscherstraße 74 Germany-01307 Dresden	5
14	Klinikum Augsburg II. Medizinische Klinik Stenglinstr. 2 Germany-86156 Augsburg	2
15	Universitätsklinikum Aachen Hämatologie/Onkologie Pauwelsstr. 30 Germany-52074 Aachen	1
16	Asklepios Klinik St. Georg Abt. Hämatologie, Onkologie & Stammzelltransplantation Lohmühlenstraße 5	2

Center-ID	Participating center	Number of recruited patients
	Germany-20099 Hamburg	
17	Krankenhaus der Elisbethinen Linz GmbH 1. Interne Abteilung - Hämatologie mit Stammzelltransplantation, Hämostaseologie und medizinische Onkologie Fadingerstr. 1 Austria-4020 Linz	1
18	LKH-Univ. Klinikum Graz Univ. Klinik für Innere Medizin, Abt. Hämatologie Auenbruggerplatz 38 Austria-8036 Graz	0
19	Universitätsklinikum Tübingen Medizinische Klinik, Abteilung II Onkologie, Hämatologie, Klinische Immunologie, Rheumatologie, Pulmologie Otfried-Müller-Strasse 10 Germany-72076 Tübingen	1

8 Publication (reference)

First data were presented in December 2018 at the congress American Society of Hematology (ASH 2018). (https://amlglobalportal.com/medical-information/ash-2018-maintenance-therapy-with-sorafenib-in-patients-with-flt3-itd-acute-myeloid-leukemia-sormain-trial)
The main publication is currently in progress.

9 Studied period (years): date of first enrolment, date of last completed, date of database closure

Date of first enrolment: 29.10.2010
Date of last completed: 10.10.2018
Database closure and notification of end of study: 31.10.2018 (database closure); 16.11.2018 (notification of end of study).

10 Phase of development

Phase II

11 Objectives

Primary objective
Relapse free survival (RFS) of Flt3-ITD+ AML patients in complete hematological remission after allo-SCT receiving Sorafenib maintenance therapy versus placebo.

Secondary objectives
1. To compare the median overall survival (OS) of Flt3-ITD+AML patients in CHR after allo-SCT receiving Sorafenib maintenance treatment versus placebo
2. To compare the median RFS and OS of Flt3-ITD+ AMLpatients with and without NPM mutations receiving Sorafenib versus placebo
3. To compare the median RFS and OS of Flt3-ITD+AML patients in CHR after allo-SCT receiving Sorafenib maintenance treatment versus placebo depending on the baseline expression level of Flt3-ITD at diagnosis

4. To compare the toxicity of Sorafenib maintenance versus placebo
5. To longitudinally evaluate biomarkers associated with Sorafenib treatment response and Sorafenib resistance and correlation with RFS and OS
6. To assess safety with type, severity graded by NCI CTC criteria version 4.02.

12 Methodology

Randomized, double-blind, multi-center

13 Number of patients (planned and analyzed)

Planned number of patients: n=200
Analyzed number of patients: n= 83

14 Diagnosis and main criteria for inclusion

Diagnosis:

- FLT3-ITD positive AML after allogeneic-stem-cell transplantation in complete hematological remission

Inclusion criteria:

- Written informed consent
- Age ≥18 years
- ECOG performance ≤ 1
- FLT3-ITD-positive AML
- Complete hematological remission (CHR) after allo-SCT *CHR must be confirmed by bone marrow analysis within 14 days before randomization (CHR criteria are: ≤ 5% marrow blasts, no peripheral blasts, blood platelet count > 100/nl, WBC count > 3 G/L, ANC > 1 G/l)*.
- Allo-SCT with a HLA-identical allo-family donor (FAM) or a matched unrelated donor (MUD) with up to 1 antigen mismatch acceptable (9/10)
- Time point of study treatment start of patients in CHR: between d+60 up to d+100 after allo-SCT
- Adequate organ function: Serum creatinine ≤ 1.5 x upper normal value; ALT, AST, AP ≤ 2.5 x upper normal value; Total bilirubin ≤ 1.5 x upper limit of normal; PT-INR/PTT ≤1.5 x upper limit of normal
- Patients who are being therapeutically anticoagulated with an agent such as Coumadin or Heparin will be allowed to participate in the trial provided that the medical need for anticoagulation is evidence-based (level 1 evidence) and PTINR and PTT values are closely monitored to maintain the therapeutic window.
- Negative serum pregnancy test within seven days prior to firstdose in women of child-bearing potential (WOCBP)
- WOCBP must use a double barrier method of contraception during the study and for 3 months following the last dose of study drug. WOCBP are defined as sexually mature women who have not undergone a hysterectomy or surgical sterilization or who have not been naturally postmenopausal for at least 12 consecutive months (i.e., who has had menses any time in the preceding 12 consecutive months).
- Male subjects whose sexual partners are WOCBP must use a double barrier method of contraception, one of which includes a condom, during the study and for 3 months after the end of treatment.

15 Test product, dose and mode of administration

Product: Sorafenib, 200mg/tablet

Dose: Dosing schedule:

- Dose level 1 (starting dose) : 2 tablets / day (1-0-1)

- Dose level 2 (escalated dose): 3 tablets / day (1-0-2)
- Dose level 3 (targeted dose) : 4 tablets / day (2-0-2)

Dose level 1 will be given for 2 weeks
Dose level 2 applies for 4 weeks
If dose level 2 is well tolerated, the targeted dose will be administered, starting 6 weeks after treatment initiation

Mode of administration: oral; film-coated tablet

16 Duration of treatment

Study medication will be administered up to 2 years or until relapse

17 Reference therapy, dose and mode of administration

Reference product: Placebo

Dose: Dosing schedule:
- Dose level 1 (starting dose) : 2 tablets / day (1-0-1)
- Dose level 2 (escalated dose): 3 tablets / day (1-0-2)
- Dose level 3 (targeted dose) : 4 tablets / day (2-0-2)

Mode of administration: oral; film-coated tablet

18 Criteria for evaluation: Efficacy, Safety

Efficacy criteria:
- Relapse free survival (RFS)
  RFS is defined as time interval from randomization until relapse of AML or death from any cause, which ever occurs first.
  Relapse is defined as any blast appearance in the peripheral blood, in the bone marrow (> 5%) or extramedullary blasts (chloroma). For a patient with no relapse before the end of study follow-up, observation of RFS will be censored at the date of his or her last follow-up examination.
- Overall survival
  Overall survival is defined as time from randomization to the day of death. For a patient who is not known to have died by the end of follow-up, observation of OS will be censored on the date the patient was last known to be alive.

Safety criteria:
Evaluation of the safety of sorafenib versus placebo as prophylactic treatment post SCT.

19 Statistical methods

Kaplan-Meier method, log-rank test, Cox regression, intention to-treat analysis

20 Summary - Conclusions: Efficacy Results, Safety Results, Conclusion

20.1 Efficacy results

After a median follow up of 41.8 months (interquartile range, 24.1 to 42.5), patients randomized to sorafenib had a significantly longer median relapse free survival than those randomized to placebo (not reached vs. 30.9 months). The 2-year relapse free survival was 85.0% (95% CI: 69.5-93.0) in the sorafenib group and 53.3% (95% CI: 36.5-67.5) in the placebo group. The hazard ratio (HR) for relapse or death in the sorafenib arm versus the placebo arm was 0.39 (95% CI: 0.183-0.848; log rank P=0.0135). While the presence of a NPM1 mutation at initial diagnosis positively affected RFS in the sorafenib arm, the FLT3-ITD ratio did not influence the treatment effect. Because early relapses, i.e. within the first 24 months after randomization, occurred more frequently with placebo than with sorafenib (13 versus 5 patients) and because relapses had mainly a fatal outcome (11 versus 3 patients), relapse mortality was significantly higher for patients randomized to the placebo arm (P=0.011). In contrast, non-relapse mortality was not different between the two treatment arms. After a median duration of follow up of 55.1 months, median OS time was not reached in both treatment arms. The hazard ratio (HR) for death from any cause in the sorafenib arm versus the placebo arm was 0.516 (95% CI: 0.239-1.112; log rank P=0.0855). The estimated probability of survival at 30-months (i.e. six months after end of drug/placebo treatment) was 83.3% (95% CI: 0.68-0.91) for sorafenib and 63.6% (95% CI: 0.46-0.76) for placebo, equivalent to a HR for death of 0.447 (95% CI: 0.20-0.97; log rank P=0.0383). Twenty-three of 25 relapsing patients were able to receive relapse therapy. Of these, 20 patients (87%) were treated with sorafenib, 19 patients were treated with chemotherapy (82%) and 7 patients (30.4%) underwent second SCT. Importantly, among the 15 treated relapses in the placebo arm, 13 (87%) received sorafenib as rescue therapy. There was no significant difference in the frequency and types of administration of relapse therapies between the treatment arms.

20.2 Safety results

Sorafenib was generally well tolerated. Dose reductions occurred in 16 of 40 patients in the placebo arm (40%) versus 21 of 43 patients (48.84%) in the sorafenib arm (P=0.78). Study drug discontinuations due to toxicity occurred in 9 patients under sorafenib (20.93%) as compared to two placebo-treated patients (5.00%). The most common ≥3 adverse event (AE) in both treatment groups was acute and/or chronic GvHD, which occurred in 32 of 42 patients (76.8%) in the sorafenib arm and in 23 of 39 patients (59.8%) in the placebo arm (P=0.152). The other common grade ≥3 adverse events (AEs) occurring in ≥ 10% of sorafenib-treated patients were infections in 11 of 42 patients (26.2%), gastrointestinal toxicity in 6 patients (14.3%), electrolyte alterations in 6 patients (14.3%) and skin toxicity in 5 patients (11.9%). In the placebo arm, the common grade ≥3 AEs were infections in 9 patients (23.1%) and gastrointestinal toxicity in 6 patients (15.4%). Only two of sixteen deaths that occurred during the treatment period were unrelated to AML. Both deaths occurred in the placebo arm.

Conclusion:

Sorafenib maintenance therapy in AML patients with *FLT3*-ITD mutation in complete hematological remission after SCT significantly reduces the risk of AML relapse and death.

21 Date of report

04.11.2019