

## Trial Description

### Title

**A double-blind, placebo-controlled, randomized, multi-center 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**

### Trial Acronym

**SORMAIN**

### URL of the trial

[---]\*

### Brief Summary in Lay Language

**The aim of this clinical trial is to investigate the effect of a drug on the relapse in acute myeloid leukaemia after treatment of the patients with chemotherapy and additional stem cell transplantation.**

**Remaining of leukaemia-cells in the bone marrow can lead to relapse, what is tried to prevent by giving oral application of Sorafenib. Sorafenib is an “inhibitor of kinases”, what are a class of proteins that are involved in the growth of cells. One member of this class is the so called Flt3 ITD protein what is the product of a genetic damage which leads to uncontrolled growth of leukaemia-cells.**

**Because Sorafenib inhibits effectively Flt3-ITD, leukaemia-cells but not other blood-cells are eliminated. Therefore only patients who have shown the Flt3-ITD protein are chosen for treatment.**

**Due to the fact that the therapy with Sorafenib is without the adverse event like chemotherapy, it can be realised continuously and so decrease more and more the number of leukaemia-cells. Together with the outcome by the new immune-system given by the transplanted cells the Sorafenib-therapy give hope of a minimised rate of relapse.**

### Brief Summary in Scientific Language

**The aim of this study is the comparison of the relapse free survival (RFS) of Flt3-ITD+ AML patients in complete hematological remission after allo-SCT receiving Sorafenib maintenance therapy versus placebo.**

**The following differences between the Sorafenib and placebo branches are to be investigated: a) the median of Overall survival (OS), b) the mean value of RFS and OS depending on the status of NPM1 mutations, c) the mean value of RFS and OS depending on the level of Flt3 expression at baseline and d) the toxicity.**

**It should proceed a longitudinally examination of biomarkers that are associated with response or resistance for Sorafenib and the correlation of these biomarkers to RFS and OS.**

**The safety of Sorafenib should be analysed in regard to the nature and severity (according to NCI CTC 4.02).**

**Do you plan to share individual participant data with other researchers?**

[---]\*

**Description IPD sharing plan**

[---]\*

**Organizational Data**

- DRKS-ID: **DRKS00000591**
- Date of Registration in DRKS: **2010/10/26**
- Date of Registration in Partner Registry or other Primary Registry: [---]\*
- Investigator Sponsored/Initiated Trial (IST/IIT): **yes**
- Ethics Approval/Approval of the Ethics Committee: **Approved**
- (leading) Ethics Committee Nr.: **138/10 (A) , Ethik-Kommission des Fachbereichs Medizin der Philipps-Universität Marburg**

**Secondary IDs**

- EudraCT-No.  
(for studies acc. to Drug Law): **2010-018539-16**
- BfArM-No.: **4036508**

**Health condition or Problem studied**

- ICD10: **C92.11 - [generalization C92.1: Chronic myeloid leukaemia]**

**Interventions/Observational Groups**

- Arm 1: **Product:**  
**Sorafenib, 200mg / tablet**  
**Mode of administration:**  
**Oral, tablet**  
**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**
  - **Study medication will be administered up to 2 years or until relapse**
- Arm 2: **Product: matching placebo**

**Mode of administration:****Oral, tablet****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**
- **Placebo will be administered up to 2 years or until relapse**

## Characteristics

- Study Type: **Interventional**
- Study Type Non-Interventional: [---]\*
- Allocation: **Randomized controlled trial**
- Blinding: [---]\*
- Who is blinded: **patient/subject, investigator/therapist, caregiver**
- Control: **Placebo**
- Purpose: **Treatment**
- Assignment: **Parallel**
- Phase: **II**
- Off-label use (Zulassungsüberschreitende Anwendung eines Arzneimittels): [---]\*

## Primary Outcome

**Relapse free survival (RFS), 50 events (relapse)**

**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.**

## Secondary Outcome

**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.**

## Countries of recruitment

- **DE Germany**
- **AT Austria**

## Locations of Recruitment

- University Medical Center **Klinik für Hämatologie, Onkologie und Immunologie , Marburg**
- University Medical Center **Klinik für Knochenmarktransplantation, Essen**
- University Medical Center **Interdisziplinäre Klinik und Poliklinik für Stammzelltransplantation, Hamburg UKGM**
- University Medical Center **Medizinische Klinik, Innere Medizin A, Münster**
- University Medical Center **Innere Medizin I; Hämatologie, Onkologie und Stammzelltransplantation, Freiburg im Breisgau**
- Medical Center **Klinikum Rechts der Isar; III. Medizinische Klinik und Poliklinik, München**
- Medical Center **Klinikum Chemnitz gGmbH; Klinik für Innere Medizin III, Chemnitz**
- University Medical Center **Medizinische Klinik und Poliklinik I, Dresden**
- University Medical Center **Klinikum Augsburg; II. Medizinische Klinik, Augsburg**
- University Medical Center **Hämatologie/Onkologie, Aachen**
- Medical Center **Asklepios Klinik St. Georg; Abt. Hämatologie, Onkologie & Stammzelltransplantation, Hamburg**
- University Medical Center **Klinikum der Johann-Wolfgang-Goethe- Universität; Med. Klinik II, Hämatologie, Onkologie, Rheumatologie, Infektiologie, HIV-Erkrankung, Frankfurt a.M.**
- University Medical Center **III. Medizinische Klinik, Studienzentrale, Bau 302, II. Stock, Mainz**
- Medical Center **Stiftung Deutsche Klinik für Diagnostik GmbH; Abteilung für Blustammzell- und Knochenmarktransplantation, Wiesbaden**
- University Medical Center **Medizinische Klinik, Abteilung II Onkologie, Hämatologie, Klinische Immunologie, Rheumatologie, Pulmologie, Tübingen**
- Medical Center **Krankenhaus der Elisabethinen Linz GmbH; 1. Interne Abteilung - Hämatologie mit Stammzelltransplantation, Hämostaseologie und medizinische Onkologie, Linz**

## Recruitment

- Planned/Actual: **Actual**
- (Anticipated or Actual) Date of First Enrollment: **2010/10/29**
- Target Sample Size: **200**
- Monocenter/Multicenter trial: **Multicenter trial**
- National/International: **International**

## Inclusion Criteria

- Gender: **Both, male and female**
- Minimum Age: **18 Years**
- Maximum Age: **no maximum age**

#### Additional Inclusion Criteria

- **Written informed consent**
- **Age  $\geq 18$  y.**
- **ECOG performance  $\leq 1$**
- **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:  $\leq 5\%$  marrow blasts, no peripheral blasts, blood platelet count  $> 100/\text{nl}$ , WBC count  $> 3 \text{ G/L}$ , ANC  $> 1000 \text{ G/l}$ ).**
- **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  $\leq 1.5$  x upper normal value**
  - **ALT, AST, AP  $\leq 2.5$  x upper normal value**
  - **Total bilirubin  $\leq 1.5$  x upper limit of normal**
  - **PT-INR/PTT  $\leq 1.5$  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 PT-INR and PTT values are closely monitored to maintain the therapeutic window.**
  - **Negative serum pregnancy test within seven days prior to first dose 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.**

#### Exclusion criteria

- **Any severe concomitant conditions which make it undesirable for the patient to participate in the study or which could jeopardize compliance with the protocol (such as substance abuse, uncontrolled infection, known HIV, HBV, HCV infection)**
- **Psychiatric disorder that interferes with ability to understand the study and give informed consent, and/or impacts study participation or follow-up.**
- **Cardiac disease: heart failure NYHA III/IV, unstable coronary artery disease (MI more than 6 months prior to study entry is permitted), serious cardiac ventricular arrhythmias requiring anti-arrhythmic therapy (beta-blockers or digoxin are permitted)**
- **Resting blood pressure consistently higher than systolic 150 mmHg and/or diastolic 90 mmHg despite antihypertensive therapy**

- **Patients undergoing renal dialysis**
- **Evidence or history of severe non-leukemia associated bleeding diathesis or coagulopathy**
- **Patients with uncontrolled seizure disorder despite medication**
- **History of organ allograft (except for allogenic SCTX)**
- **Patients with major surgery, open biopsy, or significant traumatic injury within 4 weeks prior to start of first dose of study drug**
- **Serious non-healing wound, ulcer or bone fracture**
- **Known Flt3-kinase inhibitor resistance**
- **Previous Sorafenib therapy**
- **Active (uncontrolled) graft versus host disease GvHD (> grade I) at time of randomization despite the use of adequate therapeutic measures**
- **Investigational drug therapy outside of this trial during or within 4 weeks of study entry**
- **Pregnancy or breast feeding**
- **Allergy to study medication or compositions of excipients in study medication**
- **Secondary allo-SCT**
- **Previous or concurrent cancer curatively treated ≤ 3 years prior to study entry**

## Addresses

### ■ Primary Sponsor

**Philipps-Universität-Marburg (vertreten durch KKS Marburg der Universität Marburg, Karl-von-Frisch-Str.4, 35043 Marburg)  
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35037 Marburg  
Germany**

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E-mail: [---]\*

URL: [---]\*

### ■ Contact for Scientific Queries

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**Klinik für Hämatologie, Onkologie und Immunologie**

### Contact for Public Queries

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### Sources of Monetary or Material Support

■ **Commercial (pharmaceutical industry, medical engineering industry, etc.)**

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**Bayer Schering Pharma**

**51368 Leverkusen**  
**Germany**

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E-mail: [---]\*

URL: [---]\*

### Status

■ Recruitment Status: **Recruiting complete, follow-up complete**

■ Study Closing (LPLV): **2018/10/31**

### Trial Publications, Results and other documents

■ Approval of ethics comm. (mandatory for transfer to Studybox) **Erstvotum EK zur Studie**

■ trial protocol (mandatory for transfer to Studybox) **Studienprotkoll Sormain**

■ Paper **Finale Publikation**

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\* *This entry means the parameter is not applicable or has not been set.*

\*\*\* *This entry means that data is not displayed due to insufficient data privacy clearing.*