Clinical Study Protocol

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

Authors: Prof. Dr. Andreas Burchert, Prof. Dr. A. Neubauer, Susanne Harnisch, Prof. Dr. Konstantin Strauch, Carmen Schade-Brittinger

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Acronym	SORMAIN
Study phase	II
Principal Investigator	Prof. Dr. Andreas Burchert Klinik für Hämatologie, Onkologie und Immunologie Philipps-Universität Marburg, Germany
Sponsor	Philipps-Universität Marburg Biegenstrasse 10 35037 Marburg
Date/Version	Prüfplan V04F-31.03.2014

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Abbreviations:

Allo-SCT	allogenic stem cell transplantation
ALT	alanineamino-transferase
AML	acute myeloid leukemia
ANC	absolute neutrophile count
AP	alkaline phosphatase
AST	aspartat amino-transferase
CHR	complete hematological remission
CMV	cytomegalie virus
Crea	creatinine
CRF	case report form
DLI	donor lymphocyte infusion
DSMC	Data Safety Monitoring Committee
EC	ethics committee
FACS	fluorescence activated cell sorting
FLT3-ITD+	fetal liver type 3 kinase-internal tandem duplication-positive
Flt3-RTK	fetal liver type 3 kinase – receptor tyrosine kinase
G-CSF	granulocyte colony stimulating factor
GvL	graft versus leukemia
GvHD	graft versus host disease
HLA	human leukocyte antigen
ICH-GCP	international conference on harmonisation – good clinical practice
ISF	investigator site file
LKP	coordinating investigator (Leiter der Klinischen Prüfung)
MUD	matched unrelated donor
MI	myocardial infarction
NYHA	New York Heart Association
NPM	nucleophosmin-1 gene
OS	overall survival
PT-INR/PTT	prothrombin time-international ratio/partial thromboplastin time
RFS	relapse free survival
RTK	receptor tyrosine kinase
SAE	serious adverse event
SUSAR	suspected unexpected serious adverse reaction
UAR	unexpected adverse reaction
WBC	white blood cell

Clinical Study Protocol – Signatures

I have read this protocol and agree to execute the study in accordance with all commitments of this protocol, ICH-GCP, the Declaration of Helsinki and the national laws.
I agree to handle all information concerning the study confidentially.

Authorized representative of the sponsor

C. Schade-Brittinger
Carmen Schade-Brittinger

C. Schade-Brittinger 02.04.14
Signature Date

Principle Investigator of the study (LKP)

Prof. Dr. Andreas Burchert

1.4.14
Signature Date

Statistician

Prof. Dr. Konstantin Strauch

K. Strauch 31.03.2014
Signature Date

Clinical Study Protocol – Signatures

I have read this protocol and agree to execute the study in accordance with all commitments of this protocol, ICH-GCP, the Declaration of Helsinki and the national laws.
I agree to handle all information concerning the study confidentially.

Principle Investigator (site)

Name

Signature Date

Deputy Principle Investigator (site)

Name

Signature Date

Co-Investigator (site)

Name

Signature Date

Co-Investigator (site)

Name

Signature Date

Co-Investigator (site)

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Signature Date

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DSMC	Prof. Dr. med. Martin Fey Medizinische Onkologie u. Innere Medizin Universitätsspital Bern, Inselspital, Freiburgstrasse 4, CH-3010 Bern Tel.: +41-31/6324114 Fax: +41-31/3821237 E-mail: martin.fey@insel.ch PD Dr. med. Claudia Baldus Hämatologie, Onkologie Charité, Campus Benjamin Franklin Hindenburgdamm 30 D-12203 Berlin Tel.: +49-(0)30/8445-4922 (o.-2337) Fax: +49-(0)30/8445-4468 E-mail: claudia.baldus@charite.de Heinz Haverkamp Studienzentrale der GHSG Universitätsklinikum Köln (AöR) 50924 Köln Tel.: +49-(0)221/478-88169 Fax: +49-(0)221 478-88188 E-mail: heinz.haverkamp@uk-koeln.de
Serious Adverse Event (SAE) to:	Koordinierungszentrum für Klinische Studien (KKS) Philipps-Universität Marburg Karl-von-Frisch-Strasse 4 35043 Marburg Fax: +49 6421 28-66517 Tel.: +49 6421 28-66553

Further questions concerning study actions to:

Medical advice	Prof. Dr. med. Andreas Burchert (address above)
Producer of study medication	Bayer Vital GmbH Bayer Schering Pharma 51368 Leverkusen, Germany
Molecular diagnostics for Flt3-ITD mutation assessment	Prof. Dr. C. Thiede Labor Molekulare Diagnostik, Medizinische Klinik und Poliklinik I, Universitätsklinikum Carl Gustav Carus Fetscherstr. 74 01307 Dresden Tel: +49 351 458-4680 Fax: +49 351 458-5370 Prof. Dr. med. Dr. phil. T. Haferlach Medizinische Kooperationsgemeinschaft, Innere Medizin, Hämatologie und Internistische Onkologie Max-Lebsche-Platz 31 81377 München Tel:+49 89 99015-0 Fax: +49 89 99015-113 **Alternatively, and if approved by the sponsor, other specialized laboratories may also be permitted to provide the Flt3-ITD diagnostics.**
Labelling and packaging: **Apotheke Dresden**	Klinik-Apotheke Frau Dr. Ina-Maria Klut Universitätsklinikum “Carl Gustav Carus” der Technischen Universität Dresden Fetscherstr. 74 01307 Dresden Tel.: +49 351 458-4625 Fax: +49 351 458-6385 E-mail: Ina-Maria.Klut@uniklinikum-dresden.de

CONTENT

2. *Synopsis*

Study name	A double-blind, placebo-controlled, randomized, multi-centre phase II trial to assess the efficacy and safety of Sorafenib-maintenance therapy in Flt3-ITD positive AML in complete hematological remission (CHR) after allogenic stem cell transplantation (allo-SCT)
Sponsor	Philipps Universität Marburg
Principal Investigator	Prof. Dr. Andreas Burchert
Study design	randomized, double blind, phase II study
Planned study period	Accrual time: 24 months First patient in to last patient out of treatment: 48 months Follow-up: 6 months Study period: 54 months
Interim analysis	• There will be an interim **analysis of safety** after 20 patients have been treated for at least 3 months. • An interim **data inspection** will be performed during the first half of 2014 according to the method proposed by Schäfer and Müller (Statist Med 20:3741-3751, 2001), which will take into account all patients included in the SORMAIN trial so far.
Study 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 objective: 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+ AML patients 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.

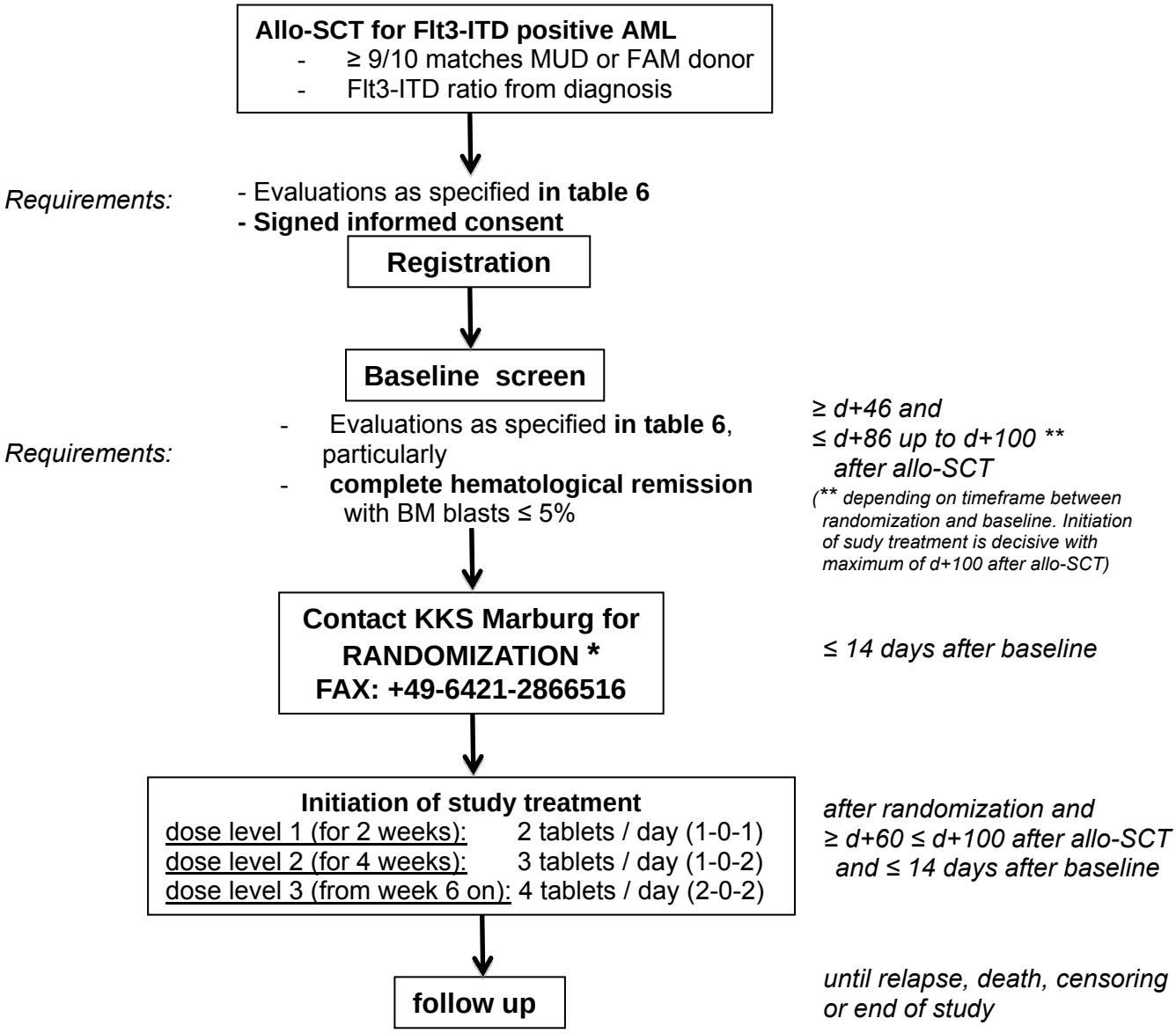
Primary endpoint	**Relapse free survival (RFS), 50 events (relapse)** RFS is defined as time interval from randomization until relapse of AML or death from any cause, which ever occurs first. Relapse is defined as any blast appearance in the peripheral blood, in the bone marrow (> 5%) or extramedullary 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 endpoint	**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.
Planned number of patients	**Total number of patients:** 200
Diagnosis	FLT3-ITD positive AML after allo-SCT in CHR
Criteria for inclusion	• Written informed consent • Age ≥18 y. • 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 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.
Criteria for exclusion	• 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
Investigational therapy: dose/mode of administration/ dosing schedule	**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

Reference (comparator) therapy:	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
Tolerability/safety variable(s)	Safety with type, severity graded by NCI CTC criteria version 4.02
Statistical methods	Kaplan-Meier method, log-rank test, Cox regression, intention-to-treat analysis
Sample size calculation and explanation	Assuming a relapse-free survival rate of 65% with placebo and 82.5% with Sorafenib at two years, corresponding to a hazard ratio of 0.45, a total of 200 patients for both study arms (i.e., 100 per arm) is needed to obtain a power of 80% with the log-rank test at a two-sided alpha of 0.05, allowing for a drop-out rate of 8%.

2.1. *Flow Chart*

2.1.1. *Study eligibility criteria at different time points*



Requirements: - Evaluations as specified **in table 6**

***** Office hours for Randomization:
Monday-Thursday 8.00–16.00h, Friday 08.00–14.00h
FAX: +49-6421-2866516, Tel.: +49-6421-2866456
Randomization will not be possible during public holiday.

3. *Introduction and study background*

3.1. *Disease background*

Acute myeloid leukemia (AML) is the most frequent acute leukemia of adults and has an unfavourable prognosis [1]. Factors, which come along with a poor prognosis are age over 60 years, poor ECOG performance status prior to therapy, secondary AML, a white cell count of more than 20.000 G/l or an elevated lactate dehydrogenase at presentation [2]. Also certain cytogenetic and molecular aberrations are associated with a poor prognosis, e.g. those with particular mutations in the Flt3-receptor thyrosine kinase (RTK) [3]. Flt3 is a type III RTK regulating the hematopoietic progenitor cell homeostasis. The Flt3-RTK activates several conserved pathways, including the Ras/Map-kinase, the phosphoinositide-3-kinase/Akt signaling cascade and Stat-5 [4] [5,6] [7]. Constitutive activation of these pathways occurs through mutations in Flt3, such as those leading to internal tandem duplications in the juxta-membrane domain of the receptor (Flt3-ITD) [8] [9]. The biological consequences of aberrant Flt3-ITD signaling are transformation, resistance to apoptosis, and prevention of differentiation of leukemic blasts in acute myeloid leukemia (AML) [10] [11]. Flt3-ITD can be found in approximately 20% of AML patients and is associated with a poor risk status [12], [13-15] [3]. Therefore, several specific Flt3-inhibitors have been developed and evaluated in clinical trials (for review see ref. Knapper 2007 [16]). However, their overall clinical efficacy in all cases of AMLs must so far be considered as minor (Knapper 2007). The initial treatment of AML consists of two phases. Complete remissions could be achieved after the induction phase in 50% in patients older than 60 years and 70% to 80% in younger patients. To prevent relapse a second phase (consolidation) is applicated either as chemotherapy, autologous or allogeneic stem cell transplantation. Transplantation is more often used in young patients with adverse prognosis as it is true in the case of Flt3-ITD positive AMLs.

3.2. *Investigational product background*

Sorafenib (Nexavar ™) is a novel RAF, Flt3 and VEGFR kinase inhibitor that prevents tumor growth by combining two anticancer activities: inhibition of tumor cell proliferation and tumor angiogenesis.

Sorafenib was developed as an oral cytostatic Raf kinase inhibitor, PDGFR inhibitor and VEGFR-2 (KDR) inhibitor, for the potential treatment of various cancers. It functions by inhibiting the Raf kinase as constituent of the classical mitogen-activated protein kinase (MAPK) signaling cascade [17]. Raf and other members (such as Ras) of this pathway are attractive targets for development of anti-neoplastic agents because their aberrant activity has been heavily implicated in the onset of a variety of cancers. When properly regulated, the classical MAPK (Raf/MEK/ERK) pathway controls a variety of cellular functions such as proliferation, differentiation, and apoptosis. Genetic mutations can, however, lead to overexpression or aberrant activity of a particular MAPK. Furthermore, it is widely known that MAPK hyperactivity can lead to tumorigenesis.

More recently, it has also been shown that Sorafenib is a strong inhibitor of the receptor tyrosine kinase Flt3 that has been implicated in the pathogenesis of AML (see above) [18]. Also, Sorafenib inhibits the activity of VEGF receptors, which are expressed on the surface of AML blasts as well as on the surface of surrounding bone marrow micro-vessels. Micro-vessel density is greatly increased in AML bone marrow and it is possible that by inhibition of VEGF receptors, leukaemia induced neoangiogenesis is targeted, providing a further rationale for the treatment of AML with Sorafenib.

In summary, Sorafenib targets several tyrosine kinases that have been implicated in the pathogenesis of AML, including the classical MAPK pathway, angiogenic VEGF receptors and the receptor tyrosine kinase Flt3.

3.3. *Rationale for the study*

Sorafenib has been approved for the treatment of advanced renal cancer and advanced hepatocellular carcinoma [19]. It inhibits the serine threonine kinase Raf-1, but also the Flt3-RTK, and Flt3-ITD [20], suggesting that it may have a role also in AML [18].

The major rationale for studying Sorafenib in AML was derived from its treatment efficacy in Flt3-ITD positive AML: in a phase I clinical trial on 16 patients with AML Sorafenib was recently found to be particularly active in Flt3-ITD positive patients [20]. Sorafenib induced a complete molecular remission in a Flt3-ITD positive patient after allogenic stem cell transplantation (allo-SCT) [21]. In a cohort of consecutive six Flt3-ITD-positive AML patients single agent Sorafenib led to durable complete molecular remissions in two refractory AML patients post allo-SCT [22]. The efficacy of Sorafenib in refractory / relapsing Flt-3-ITD-positive patients was further supported by a report on additional 13 patients, all of which

showing at least a hematological response to Sorafenib including two complete molecular responders (Metzelder et al, ASH 2009 abstract # 2060).

The poor prognosis of Flt3-ITD positive AMLs mainly results from the high relapse rates rather than induction failure [23,24] [25]. Due to the fact that therapeutic options in relapsing patients after allo-SCT are extremely poor, a selective inhibition of Flt3-ITD positive AML blasts with Sorafenib at the time of complete remission may target residual disease and thus be particularly effective.
Presumably, treatment with Sorafenib in the context of an allo-immune effect (the anti-leukemic graft versus leukemia (GvL) effect) may result in a meaningful synergism leading to a significant improvement of the prognosis of Flt3-ITD AML.

3.4. *Risk-benefit assessment*

Due to a lack of curative treatment alternatives, the prognosis of relapsed Flt3-ITD positive AML after allo-SCT is usually detrimental. Recent data demonstrated a remarkably high therapeutic efficacy of Sorafenib in refractory and relapsed Flt3-ITD positive AML, suggesting that a pre-emptive therapeutic approach after allo-SCT - as planned in this study – may offer to patients the chance to prevent relapse and thus lead to an increased overall survival.
There has been limited experience as to the interference of Sorafenib with GvL / GvHD effects and the toxicity resulting from Sorafenib use in the context of a variety of prophylactic medications routinely taken by transplanted patients after allo-SCT. Casuistic treatment experiences suggest that these adverse events can be managed. However, the overall benefit-risk ratio for patients entering this study seems to be clearly favourable.

4. *Outcome measures*

Aim of this study is to utilize the Flt3-ITD leukemia specific activity of sorafenib after allo-SCT to prevent relapses in the high risk group of patients with Flt3-ITD positive AML.
Toxicity will be evaluated according to toxicity scale Common Terminology Criteria for Adverse Events v4.02 (CTCAE) at http://evs.nci.nih.gov/ftp1/CTCAE
GvHD will be documented using the cGVHD Symptom Tracking Chart on www.asbmt.org (see also Tables 5 and 6 in the appendix)

4.1. Objectives

4.1.1. *Primary objective*

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

4.1.2. *Secondary objectives*

- To compare the median overall survival (OS) of Flt3-ITD+AML patients in CHR after allo-SCT receiving Sorafenib maintenance treatment versus placebo

- To compare the median RFS and OS of Flt3-ITD+ AML patients with and without NPM mutations receiving Sorafenib versus placebo
- 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
- To compare the toxicity of Sorafenib maintenance versus placebo
- To longitudinally evaluate biomarkers associated with Sorafenib treatment response and Sorafenib resistance and correlation with RFS and OS
- To assess safety with type, severity graded by NCI CTC criteria version 4.02.

4.2. Definition of study endpoints

4.2.1. *Primary endpoint*

Relapse free survival (RFS)

RFS is defined as time interval from randomization until relapse of AML or death from any cause, which occurs first. Relapse is defined as any blast appearance in the peripheral blood, in the bone marrow (> 5%) or extra medullary 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.

4.2.2. *Secondary endpoint*

Overall survival (OS)

OS 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.

5. *Study design*

This is a double blind, placebo-controlled, randomized, multi-centre phase II study. Approximately 10 to 20 centres will participate in this study.

5.1. *Study population*

200 patients aged ≥ 18 years with Flt3-ITD positive AML, who have undergone allo-SCT

- for chemotherapy-refractory disease,
- or for consolidation in first or second complete remission

will be treated with either placebo (control group) or Sorafenib (verum group) to maintain a CHR and to prevent hematological relapse.

5.2. *Inclusion criteria*

- Written informed consent
- Age ≥18 y.
- 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 provided that no prior evidence of underlying abnormality in these parameters exists)
- 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.

5.3. *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

5.4. *Registration*

Registration of screened patients will be performed before randomization (flow chart 2.1) in the central database (e-CRF) for patient documentation (see chapter 13.3). This registration is a mandatory condition for randomization. The Patient-ID is combined from the site number (2-digit, starting with 01) and a sequencing number of the patients starting with 01 for each site. The investigator enters at registration only the sequencing number. This unique Patient-ID is used for all documentation on e-CRF and DCF.

5.5. *Randomization*

Randomization will be performed centrally by fax at the

Koordinierungszentrum für klinische Studien (KKS)
Philipps-University Marburg
Karl-von-Frisch-Strasse 4
D-35043 Marburg

Monday-Thursday 8.00–16.00 h
Friday 08.00–14.00 h
FAX: +49(0)6421-28 66516
Tel.: +49(0)6421-286 6456

Randomization will not be possible during public holiday.

The randomization of a registered patient (registration requirements: see 5.4 and flow chart 2.1) can take place, if a registered patient fulfils inclusion/exclusion criteria.
The chance for randomization to the verum group and the placebo group is 1:1.
The KKS reports a package number for the randomized patient back to the centre. The investigator has to note the patient number on the emergency envelope which is already labeled with the corresponding package number, and on the corresponding medication package.

5.6. *Blinding*

Both, subjects and the investigators will be blinded to treatment assignment.
Before inclusion of the first patient, each study centre will obtain sufficient study medication for the first six patients from the pharmacy of the University Dresden. Medication for any patient will be labelled by the Pharmacy Dresden with a package number. The investigator at the centre will have to note the patient number on the designated medication package (s.5.5) after randomization.

5.7. *Unblinding*

Un-blinding may occur for emergency purposes only. Investigators should note that the occurrence of a Serious Adverse Event should not routinely precipitate the immediate un-blinding of the label. In case an adverse event makes it necessary for the treating physician to unblind the study medication, the envelope can be opened - if possible, after prior contact with the study coordinator in Marburg. If this is not feasible, the study coordinator in Marburg must be contacted within 24 hours after un-blinding. The date and the event making it necessary to un-blind the treatment randomization have to be documented in the patient files and in the CRF, on a specific sheet.
After the trial will be ended, envelopes have to be returned to the sponsor.

5.8. *Withdrawal of patients from study treatment*

In accordance with the Declaration of Helsinki, each subject may voluntarily withdraw from the study at any time without giving reasons for this decision. The decision to withdraw from the study treatment must be without any prejudice for the patient.

Study treatment of a patient **may** also be terminated by the investigator for one of the following reasons:

- Severe (S)AE which make it necessary to stop study treatment
- Abnormal laboratory value(s) which make it necessary to stop study treatment
- Abnormal test procedure result(s) which make it necessary to stop study treatment
- Non-compliance with the study protocol
- Physicians decision

Study treatment **has to be** terminated for one of the following reasons:

- Subject withdrew consent
- Relapse of disease
- Pregnancy

If the investigator withdrew the patient prematurely, he has to inform the patient about his decision and has to record the primary reason for the withdrawal in the patient's medical record and on the end of treatment CRF. Safety assessments will be performed at the date of discontinuation and approximately one month after last dose of study drug. Final study evaluations will be done according to the evaluation plan outlined in table 6.

If the patient caused the premature withdrawal, all data before termination may be used for final analysis. After termination they will be followed until end of study or death. Safety assessments will be performed at the date of discontinuation and approximately one month after last dose of study drug. Off study evaluations will be done according to the evaluation plan outlined in table 6.

5.9. *Premature Discontinuation of the study*

5.9.1. *Single centre*

The sponsor, together with the PI, the Competent Authority and the ethical committee (EC) have the right to discontinue this study at any time for reasonable medical or administrative reasons in any single centre. Possible reasons for termination of the study could be but are not limited to:

- Unsatisfactory enrolment with respect to quantity or quality
- Inaccurate or incomplete data collection

- Unexpected accumulation of SAE/AE
- Falsification of records
- Major failure to adhere to the study protocol

5.9.2. *Study as a whole*

The sponsor together with the PI, the Competent Authority and the EC have the right to terminate this clinical study as a whole at any time for reasonable medical or administrative reasons. Any possible premature discontinuation would be documented adequately with reasons being stated, and information would have to be issued according to local requirements (e.g., IRB/EC, regulatory authorities).

6. *Study medication*

6.1. *Sorafenib and Placebo - general aspects*

Sorafenib (Nexavar®) is an oral cytostatic Raf-kinase inhibitor, PDGFR inhibitor, VEGFR-2 (KDR) inhibitor and Flt3 inhibitor. The drug product for supply of clinical trials is a 200mg-coated tablet (calculated as free base Sorafenib). The formulation is presented as an immediate release (IR) dosage form.
For blinding purpose in this controlled clinical trial, corresponding placebo tablets are available.
For more details please refer to the Summary of Product Characteristics (SmPC) of Sorafenib (Nexavar®) in the Investigator's Folder.

6.1.1. *Instructions for storage and handling*

The current retest period for storage at room temperature is 24 months. In addition, the drug substance is insensitive to the influence of light. The tablets are packaged in HDPE bottles, which contain 140 tablets. They should only be stored in the pack provided. The storage temperature should not exceed 25°C.

6.1.2. *Concomitant medications*

6.1.2.1. *Permissible concomitant medication / therapies*

Sorafenib inhibits a variety of liver metabolic enzymes in vitro. Although interaction studies showed no influence on the kinetics of substrates of CYP3A4 (such as midazolam), CYP2D6

(such as dextrometorphane) and CYP2C19 (such as omepazole) making interactions with medications metabolized by these enzymes less likely, the clinical impact of the inhibition of CYP 2B6, CYP2C8/9 by sorafenib may result in increased levels of substrates of these enzymes. A complete list of potential medications can be found at http://medicine.iupui.edu/clinpharm/DDIs/table.aspx (provided by the Indiana University School of Medicine). Sorafenib inhibits P-gp, which could increase levels of the following substrates of P-gp: *Amiodaron, Atorvastatin, Chinin, Chinidin, Ciclosporin, Clarithromycin, Dihydropyridin-Calciumantagonisten, Diltiazem, Erythromycin, Esomeprazol, Grapefruit, Itraconazol, Ketoconazol, Lansoprazol, Methadon, Nefazodon, Nelfinavir, Omeprazol, Pantoprazol, Piperin, Ritonavir, Saquinavir, Simvastatin, Spironolacton, Tacrolimus, Tamoxifen, Verapamil.*

Sorafenib also inhibits glucuronisation enzymes UGT 1A1 and 1A9, which could lead to increased levels of *Estradiol or Propofol*.

However, several of these medications are obligatory standard treatments after allo-SCT (examplary listed in table 1). Since their use could interfere with the pharmacokinetics and -dynamics of sorafenib pro-active monitoring for plasma levels (cyclosporine, tacrolimus), liver toxicity or sorafenib side effects is warranted.

Patients requiring treatment with warfarin should proactively be monitored for their INR values.

Table 1. Standard concomitant medications post allo-SCT that may interfere with sorafenib metabolization and plasma levels

Indication	**Liver Metabolism of sorafenib**	
	unlikely	**possible**
Pneumocystis carinii prophylaxis	• pentamidine inhalation	• trimethoprim-sulfamethoxazole
Antibacterial therapy	• penicillin • cephalosporin antibiotics • betalactam antibiotics • quinolone antibiotics: levofloxacin, ciprofloxacin	• macrolide antibiotics
Antifungal therapy	• caspofungin • amphotericin B (conventional and liposomal preparation)	• 'azole' antifungals (i.e., fluconazole, ketoconazole, itraconazole, voriconazole, posaconazol)
Immune-suppression		• cyclosporine, tacrolimus, mycomofetilphenolate, mTor-inhibitors, cortisone
Anti-viral	• acyclovir, valganciclovir	

Anti-hypertension	• beta-Blocker • amlodipine • furosemid, torasemid • ACE-inhibitors	• Diltiazem, verapamil

(based on known interactions of the indicated drugs with liver metabolizing enzemes of sorafenib, Source: http://medicine.iupui.edu/clinpharm/ddis/table.asp)

6.1.2.2. *Non-permissible concomitant medication / therapies*

- Any other anticancer chemotherapy including cytotoxic, targeted, immunologic, investigational, or antiangiogenic agents other than sorafenib are not allowed.
- There is no clinical information on the effect of CYP3A4 inducers on the pharmacokinetics of sorafenib. Substances that are inducers of CYP3A4 activity (e.g. rifampin, St. John's wort, phenytoin, carbamazepine, phenobarbital, and dexamethasone) are expected to increase metabolism of sorafenib and thus decrease sorafenib concentrations. There are no clinical data evaluating the effect of chronically co-administered CYP3A4 inducers on sorafenib's efficacy. Since there is a possibility of decreased sorafenib efficacy upon chronic co-administration of CYP3A4 inducers with sorafenib, chronic co-administration of CYP3A4 inducers with sorafenib, should be avoided to the extent possible.
- Patients taking narrow therapeutic index medications should be monitored proactively. These medications include phenytoin, quinidine, carbamazepine, phenobarbital, cyclosporin and digoxin.
- St. John's wort containing remedies are not permitted.

6.1.2.3. *Donor lymphocyte infusion*

- **Donor lymphocyte infusions (DLI) are not part of this trial, and are generally not planned,** because there is no experience regarding the potential of Sorafenib to aggravate a graft versus host response in the context of DLI. Sorafenib may alter the activation and function of immunologically relevant cellular sub-fractions and thus the efficacy, tolerability and side effects (elicitation of GvHD) of DLI. DLI may, however, be performed at the discretion of the treating physician.

6.1.2.4. *Growth factors*

The use of myeloid and erythroid growth factors post allo-SCT is generally not planned and any indication should be carefully assessed and reasonable.

6.2. *Sorafenib/placebo - dose modifications and delays*

Sorafenib/placebo therapy will be taken according to defined dose levels:

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)

The starting dose will be dose level 1 in order to allow adaption to the drug and avoid acute toxicities. If after the run-in phase of 2 weeks dose level 1 was well tolerated (no probably related AE´s > grade 1), the next dose level (dose level 2) will be commenced and maintained for the next 4 weeks. If, after this time, dose level 2 was well tolerated the targeted standard dose level (dose level 3) will be administered indefinitely. Dose level 3 is the targeted dose.

6.2.1. *Dose delay and modifications for non-hematological toxicity*

In case of severe toxicities, dose reductions or delays will be required as specified in Table 2. It illustrates dose modifications for all non-hematologic toxicities according to CTCAE Version 4.02 in the CRF, except for skin toxicities, which will be detailed separately below. These recommendations pertain, if the adverse event is considered related to sorafenib.

Table 2: Non-hematologic criteria for dose delay and dose modification of sorafenib (except skin toxicity) [a]

Grade	Dose Delay	Dose modification
0-2	none	No change
3	Interrupt until ≤ grade 2 [b]	Resume with one dose level below last dose level [c]
4	OFF protocol therapy	OFF protocol therapy

a. Excludes nausea/vomiting that has not been pre-medicated, and diarrhea.
b. If no recovery within an up to 28-day delay, treatment will be permanently terminated unless the patient is deriving clinical benefit
c. The dose of study drug may be increased from the reduced dose level stepwise every 4 weeks to dose level 3 if tolerated (no re-appearance of non-hematological toxicity ≥ grade 0-2). In case toxcicity recurs, and repeated dose reductions are required (more than 2), treatment will be indefinitely performed with dose level 1. When this is also not tolerated study treatment will be permanently discontinued.

For the purpose of dose modifications, patients experiencing Hand-Foot syndrome should have their signs and symptoms graded according to the following system (see below). Other skin toxicities will be graded according to CTCAE Version 4.02.

- Grading for Hand-Foot Syndrome

Grade 1
Numbness, dysesthesia/paresthesia, tingling, painless swelling or erythema of the hands and/or feet and/or discomfort, which does not disrupt normal activities.

Grade 2
Painful erythema and swelling of the hands and/or feet and/or discomfort affecting the patient's activities.

Grade 3
Moist desquamation, ulceration, blistering or severe pain of the hands and/or feet and/or severe discomfort, which cause the patient to be unable to work or perform activities of daily living.

According to the grade and incidence of skin toxicity (including rash and hand-foot syndrome) for a given patient, the following dose modification schedule will be followed (see Table 3).

Table 3: Skin Toxicity Criteria for Dose Modification of Sorafenib

Toxicity Grade		Dose modification	Dose level after interruption
Grade 1		Maintain dose level	Institute supportive measures
Grade 2	1st appearance	Interrupt until resolved to grade 0-1	Resume with one dose level below the dose level prior to interruption a
	2nd or 3rd appearance	Interrupt until resolved to grade 0-1	Resume with dose level 1 and maintain indefinitely
	4th appearance	Decision whether to discontinue treatment permanently	
Grade 3	1st appearance	Interrupt until resolved to grade 0-1	Resume with one dose level below the dose level prior to interruption a
	2nd appearance	Interrupt until resolved to grade 0-1	Resume with dose level 1 and maintain indefinitely
	3rd appearance	Decision whether to discontinue treatment permanently	

a For patients who require a dose reduction for grade 2 or 3 rash or hand-foot syndrome, the dose of study drug may be increased subsequently to the targeted dose level after 4 weeks of therapy at the reduced dose without the appearance of rash or hand foot syndrome ≥ grade 1.

Patients with discomfort due to hand foot syndrome may be treated with topical emollients, low potency topical steroids, or urea-containing cream; emoillients and urea cream can be used early as a prophylactic measures to prevent extensive skin toxicity (see also

prophylactic measures [26] [27] [28]. All other grade 3 toxicities related to study drug result in a permanent dose reduction.

- Sorafenib-associated diarrhea

Diarrhea is a common side effect of sorafenib but is usually of low-to-moderate grade. It either resolves while treatment is continued, with appropriate anti-diarrhoic treatments, or once sorafenib is discontinued.

Appropriate prophylactic and/or therapeutic drugs that have been reported to be effective in the treatment of sorafenib-associated diarrhea are loperamide (4 mg after first loose stool, 2 mg after every other loose stool) or racecadotril (Tiorfan®) (one 100mg capsule three times daily). *However, an important differential diagnosis of Sorafenib associated diarrhoea in the context of allo-SCT is intestinal GvHD, which should be histologically confirmed or excluded via endoscopy of the sigmoid / colon*.

- Sorafenib-associated hypertension

The dose modification schedule for treatment emergent **hypertension** during sorafenib dosing should be followed (see table 4). Patients' blood pressure (BP) measurements will be monitored and appropriate treatment to effectively control hypertension under sorafenib-treatment is strongly recommended.

Blood pressure measurements considered out of normal range are diastolic ≥100 mmHg and systolic ≥160 mmHg, or a ≥20 mmHg increase in diastolic measurement if the measurement was previously within normal limits.

Table 4: Management of Treatment-Emergent Hypertension

Grade of Event (NCI-CTCAE V4.02)	**Management/Next Dose**
Grade 1 asymptomatic and transient	Consider increased BP monitoring
Grade 2 asymptomatic and diastolic BP <110 mmHg	Begin anti-hypertensive therapy and continue sorafenib/placebo
Grade 2 symptomatic/persistent OR Diastolic BP ≥110 mmHg OR Grade 3	Sorafenib/placebo should be stopped* until symptoms resolve and diastolic BP returns to ≤100 mmHg. Treat patient with anti-hypertensives and when sorafenib/placebo is restarted, reduce by 1 dose level.** (refer to section 7.3) If diastolic BP not controlled to ≤100 mmHg on therapy, reduce sorafenib/placebo by another dose level and monitor BP closely***
Grade 4 life-threatening	Discontinue protocol therapy

Please note that specific criteria are not completely identical to NCI-CTCAE V4.02 criteria.
* Patients requiring a delay of >28 days should discontinue the study treatment
** May be able to resume full dose later.
*** Patients requiring >2 dose reductions should discontinue the study treatment.

6.2.2. *Dose delay and modifications for hematological toxicity*

There is little experience regarding Sorafenib-induced hematological toxicity after allo-SCT. However, there may be hematological toxicity in the context of a compromised bone marrow reserve, GvHD or subsequent to viral infections, requiring dose delay and modification according to table 5.

Table 5: Hematologic Criteria for Dose Delay and Dose Modification of Sorafenib/Placebo

Toxicity Grade	Dose Delay	Dose Modification
Grade 0-2	Treat on time	No Change
Grade 3	Treat on time	DECREASE one dose level [b]
Grade 4	DELAY [a] until ≤Grade 2	DECREASE one dose level [b]

a If no recovery after 28-day delay, treatment will be discontinued unless patient is deriving clinical benefit
b If more than 2 dose reductions are required, treatment will be discontinued

6.3. *Special precautions with Sorafenib*

Sorafenib is approved for the treatment of renal cell carcinoma in patients after failed cytokine therapy or in those unsuitable for cytokines and for the treatment of hepatocellular carcinoma. Refer to the Summary of product characteristics (SmPC) Nexavar® for more detailed information.

Adverse drug reactions (ADRs) are outlined in the SmPC. If relevant new safety information is identified, the information will be integrated into an update of the SmPC which is done on a regular basis and distributed to all Investigators participating in sorafenib studies.

6.4. *Other conditions during the use of Sorafenib*

If the event **surgical treatment** is required, treatment with sorafenib/placebo should be discontinued 14 days prior to the planned surgery and restarted about 4 weeks after surgery.

6.5. *Labeling und Handling of the medication*

Packaging, labelling and distribution will be performed by the Dresden pharmacy.

The pharmacy of the University Dresden will deliver the products to the centres primary packed in wide-necked plastic bottles (120 ml PE white opaque dosed with Screw cap closure PP/PP white opaque with children proof and sealing insert) containing each 140 Sorafenib film-coated tablets 200 mg and matching placebos. 140 tablets correspond approximately to a drug supply of one month per patient. Each bottle will be pre-labelled with a tear-off label (the product identification of the packed product will be printed on the tear-off part; there will be no printing on the permanent part).
Any centre will receive from the pharmacy Dresden sufficient boxes, containing an initial drug supply of sorafenib and placebo for the first six patients. Afterwards the KKS reorders new medication in the Apotheke Dresden for the patients
The pharmacist will label the bottles according to the national regulations.

Before initiation of the study the pharmacy will be provided with a log, which already contains the package numbers and the corresponding therapy, verum or placebo. Following additional items have to be documented in the log:

- Batch number
- Expiration date of drug
- Centre, where medication was sent to
- Date of shipment

6.6. *Drug accountability in the centre and diary of medication*

In the centre the responsible investigator has to confirm the receipt of the study medication by fax to the pharmacy and to the KKS (needed for randomization). The fax receipt also has to be stored in the study specific file in the pharmacy. Additionally, the centre has to document the receipt of medication in a log and has to document the medication that is released to the patients in another special log, both filed in the ISF (investigator site file).

Empty boxes, medication bottles and unused study medication must be returned to the centre and documented in the drug accountability-log. The log has to be signed and stored in the ISF by the responsible investigators.
Remaining and or expired study medication and empty medication bottles have to be stored up to the monitoring visit where it is counted by the monitor and then disposed in the centres. Each disposal has to be documented and filed in the ISF.

In order to have a screening tool for the investigator each patient will receive a diary of medication that the patient has to complete.

6.7. *Study medication start and discontinuation*

6.7.1. *Start*

Patients in CHR after allo-SCT will receive sorafenib or placebo as a maintenance therapy according to the dosing schedule specified above (s. 6.2).
Treatment will start in CHR as early as possible after allo-SCT, that is, when full hematological recovery has occurred (no peripheral blasts, bone marrow blasts ≤ 5%, white blood cell count> 3G/l, platelets >100G/l), but earliest on day+60 and latest until day+100 after allo-SCT. Treatment will continue for two years or until relapse.

6.7.2. *Discontinuation*

In case of relapse the primary endpoint of this study is reached and study medication has to be stopped immediately.
Treatment of relapse will be left to the discretion of the treating investigator. Investigators should note that sorafenib should not be given after relapse.

7. *Study procedures*

7.1. *Study evaluations*

In this study it will be investigated, whether sorafenib given in the post allo-SCT setting can prevent AML relapse. To enable patient inclusion into the trial a registration screen and a base line screen is required. After a patient has passed registration and baseline screen he will be randomized and start study therapy.

A patient that fails registration or baseline screen will be considered as screening failure and will not be documented in the eCRF.

7.1.1. *Registration*

see section 5.4

7.1.2. *Baseline screen evaluations*

After a patient has been registered, the baseline screening will be performed. The baseline screen is required to ensure that a registered patient fulfils the inclusion and none of the exclusion criteria. This screen should be performed in proximity to the planned study randomization. A bone marrow aspiration must be performed no longer than 14 days before randomization in order to confirm the diagnosis of a CHR. Screening measures at baseline screen are listed below and also summarized in table 6:

- Medical and cancer history
- Physical examination
- Vital signs (heart rate, blood pressure, respiratory rate, temperature)
- Weight, height
- ECOG performance status
- Electrocardiogram
- Echocardiogram
- CBC: RBC, hematocrit, hemoglobin, WBC, differential (recorded in absolute values), reticulocytes, and platelets
- Coagulation: PT, PTT and fibrinogen
- Serum chemistry: sodium, potassium, magnesium calcium, phosphorus, chloride, renal function (BUN, creatinine), uric acid, total bilirubin, direct bilirubin, total protein, albumin, ALT, AST, alkaline phosphatase, LDH, triglycerides, amylase, cholesterol
- Urinalysis
- Pregnancy test (within 7 days before randomization)
- Thyroid profile (fT3, fT4, TSH)
- Bone marrow aspiration for cytological assessment of a CHR (within 14 days before randomization)
- Bone marrow FACS analysis
- Sampling for sorafenib resistance markers and sorafenib blood levels (20 ml heparin Blood, 10ml serum) to be sent to the laboratory of Prof. Dr. A. Burchert, Marburg
- Assessment of concomitant medications

If a registered patient fulfils the in- and exclusion criteria after the baseline screen he/she can be randomized via contacting the KKS Marburg (see 5.5).

7.1.3. *Treatment evaluations (month 0 until month 24)*

Patients will be seen on an outpatient basis according to the schedule outlined in table 6. This table lists all necessary assessments and indicates with an “X” when they have to be performed. All data obtained from these assessments must be supported in the patient’s source documentation. Mandatory follow up visits during the treatment phase are scheduled

at 0.5, 1.5, 3, 4, 6, 8, 10, 12, 15, 18, 21, 24 and 30 months after first dosage, respectively (scheduled time point ± 7 days during first 3 months (0,5 - 3 months) and ± 14 days thereafter).

Treatment ends 24 months after treatment start. The following tests/evaluations have to be performed at this point:

- Physical examination
- Vital signs (heart rate, blood pressure, respiratory rate, temperature)
- Weight, height
- ECOG performance status
- CBC: RBC, hematocrit, hemoglobin, WBC, differential (recorded in absolute values), reticulocytes, and platelets
- Coagulation: PT, PTT and fibrinogen
- Serum chemistry: sodium, potassium, magnesium calcium, phosphorus, chloride, renal function (BUN, creatinine), uric acid, total bilirubin, direct bilirubin, total protein, albumin, ALT, AST, alkaline phosphatase, LDH, triglycerides, amylase, cholesterol
- Thyroid profile (fT3, fT4, TSH)
- Flt3-ITD-PCR from pB
- Sampling for sorafenib resistance markers and sorafenib blood levels (20 ml heparin Blood, 10ml serum) to be sent to the Molecular laboratory of Prof. Dr. A. Burchert, Marburg (see Appendices for laboratory submission sheet)
- Assessment of concomitant medications

7.1.4. *Post study follow up evaluations (month 30 to 42)*

After the treatment phase and post treatment follow up of 6 months, further follow up is planned until month 42 for evaluation of RFS and OS only (only by phone).

7.1.5. *Evaluations in case of relapse*

The KKS Marburg has to be informed and study medication to be stopped immediately, but un-blinding should be avoided in case of a relapse.

All evaluations that have to be performed are indicated in table 6 (M30). The following assessments are critical:

- CBC with manual blood differential and platelet counts (to be faxed to KKS)
- Bone marrow aspirate for cytological assessment of marrow infiltration and FACS analysis
- Peripheral blood molecular genetic analyses for the presence of Flt3-ITD at the MLL in Munich (Prof. Haferlach) or Molecular Laboratory University Dresden (Prof. Thiede) (for sending see 7.2.1)
- Bone marrow and blood sampling for sorafenib resistance markers and sorafenib blood levels (20 ml heparin marrow, 20ml heparin Blood, 10ml serum) to be sent to the laboratory of Prof. Dr. A. Burchert, Marburg (see Appendices for laboratory submission sheet).

7.2. *Molecular Diagnostics*

7.2.1. *Central Flt3-ITD diagnostics*

To fulfil a major registration criterion, the Flt3-ITD ratio from first diagnosis must be available. In order to enable reproducibility and comparability of the Flt3-ITD expression levels, it is important that the Flt3-ITD ratio will be determined at designated centres listed below:

Prof. Dr. C. Thiede
Labor Molekulare Diagnostik, Medizinische Klinik und Poliklinik I, Universitätsklinikum Carl Gustav Carus
Fetscherstr. 74
01307 Dresden
Tel: (0351) 458-4680
Fax: (0351) 458-5370

or:

Prof. Dr. med. Dr. phil. T. Haferlach
Medizinische Kooperationsgemeinschaft, Innere Medizin, Hämatologie und Internistische Onkologie
Max-Lebsche-Platz 31
81377 München
Tel: +49 (0)89 990 15-0
Fax: +49(0)89 990 15-113

Alternatively, and if approved by the sponsor, other specialized laboratories may also be permitted to provide the Flt3-ITD diagnostics as a registration requirement. However, to confirm / establish the Flt3-ITD molecular expression data at first diagnosis it would be appreciated if RNA and/or cDNA from first diagnosis AML samples were submitted to the molecular laboratories listed above at baseline. In this case, please contact the principal investigator of the study before planning these diagnostics (+49(0)6421-58 65611).
After registration, the Flt3-ITD ratio will be performed as part of the protocol at the baseline screen (RNA and/or cDNA from first diagnosis), at the time of relapse respectively at the end of the 6 months follow-up (table 6).
To perform Flt3-ITD diagnostics

- 20 ml heparinized peripheral blood

should be sent to the above mentioned molecular laboratories. Shipment is recommended from Monday through Thursday via 12h express delivery. Please use the forms provided by the choosen laboratory for shipment.

Table 6: Visit evaluation and schedule (scheduled time point ± 7 days during first 3 months (0,5 - 3 months) and ± 14 days thereafter)

	Registration	Baseline Screen	M0.5	M1.5	M3	M4	M6	M8	M10	M12	M15	M18	M21	M24	M30 **or end of study**[l]	M42[m] ±1 week
Flt3-ITD ratio from diagnosis[a]	X															
Signed informed consent	X															
Medical and cancer history		X														
Physical examination		X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Vital signs[b]		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Weight, height[c]		X	X	X	X	X	X	X	X	X	X	X	X	X	X	
ECOG performance status		X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Electrocardiogram		X														
Echocardiogram		X														
CBC+diff, platelets, reticulocytes[d]		X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Coagulation[e]		X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Serum chemistry[f]		X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Urinalysis		X								X				X		
Pregnancy test[g, n]		X														
Thyroid profile		X					X			X				X		
Bone marrow aspiration[h]		X													X[h]	
Bone marrow biopsy[i]		X													X	
Flt3-ITD-PCR from pB[a]		X													X	
Bone marrow FACS analysis[j]		X													X	
Blood and bone marrow sampling[k]		X					X			X		X		X	X	
Concomitant medications		X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Adverse events, continuously until end of study			X	X	X	X	X	X	X	X	X	X	X	X	X	

Months of treatment after first dosing

[a] To be assessed at the “Münchener Leukämie Labor” (Prof. Haferlach) or “Labor für molekulare Diagnostik” of the TU-Dresden (Prof. Thiede) or at another molecular laboratory approved by the sponsor
[b]Vital signs include heart rate, blood pressure (sitting), respiratory rate and temperature
[c]Height performed at screening only
[d] CBC to include; RBC, hematocrit, hemoglobin, WBC, differential (recorded in absolute values), reticulocytes, and platelets
[e] PT, PTT and fibrinogen
[f] sodium, potassium, magnesium, calcium, phosphorus, chloride, renal function (BUN, creatinine), uric acid, total bilirubin, direct bilirubin, total protein, albumin, ALT, AST) and alkaline phosphatase, LDH, triglycerides, cholesterol, albumin, amylase.
[g] Pregnancy test should be performed within 7 days prior to first dose of sorafenib / placebo
[h] Bone marrow aspiration will be performed at baseline and in case of relapse or suspected for i) assessment of blast infiltration by cytology and by FACS and for ii) sampling purposes for later molecular studies of AML blasts in the marrow
[i] A bone marrow biopsy is required in the event of a dry tap or an aspiration that is inadequate for interpretation.
[J] Flow cytometric analysis of bone marrow aspirations will be performed in certified laboratories experienced in flow cytometric detection of AML blasts
[k] 20 ml of Heparin blood and 10ml serum will be shipped within 24 hours of collection to the laboratory of Prof. Dr. A. Burchert, Marburg (see ISF for laboratory submission sheet). 20ml of heparin bone marrow aspirat will be shipped to the same laboratory only in case a biopsy is performed, that is, at baseline and in relapse.
[l] End of study is six months after last protocol treatment. This assessments indicated will also be for patients who discontinue the study for study related AE or abnormal laboratory test or diagnosis of relapse
[m] follow up at month 42 for evaluation of RFS and OS only by phone.
[n] For Austria it is necessary to test monthly.

7.2.2. *Sampling for scientific purposes*

For the investigation of molecular mechanisms of sorafenib resistance development, biomarkers of response, sorafenib plasma levels, and gene regulations associated with study medication, peripheral blood samples (20 ml heparinized blood and 10 ml serum) shall be sent at baseline and every 6 months thereafter (table 6) to Prof. Dr. A. Burchert, Molecular laboratory in Marburg. 20ml of heparin bone marrow will be shipped to the same laboratory only in case a biopsy is performed, that is, at baseline and in relapse. Shipment is recommended from Monday through Thursday via 12h express delivery to

Universitätsklinikum Gießen und Marburg GmbH
Prof. Dr. A. Burchert
Molekularbiologisches Labor
Baldinger Str.
35043 Marburg

A sample accompanying form can be found in the ISF.

8. *Duration of the study and the follow up period*

Assuming an accrual time of 24 months and duration of treatment (of the last included patient) of 24 months the duration of the study will be approximately 48 months. The duration of the follow up period will be 6 months.

- Accrual time: 24 months
- First patient in to last patient out: 48 months
- Follow-up: 6 months
- Study period: 54 months excluding preparation and analysis
- Post study follow up: 12 months

9. *Safety*

In order to comply with the standards for Good Clinical Practice (GCP) it is important that investigators are aware of the different definitions related to adverse events and how to record, report and review each of these specific occurrences.

9.1. *Definition of Adverse Event (AE)*

An Adverse Event (AE) is any untoward medical occurrence in the patient administered a pharmaceutical product that does not necessarily have a causal relationship with this treatment. An AE is therefore described as any unfavourable and unintended sign (including laboratory result), symptom, or disease temporally (timely) associated with the use of a medicinal (investigational) product, whether or not related to the product.
The reporting of abnormal laboratory values should be avoided unless they lead to clinical consequences that are not routine.
Events such as nausea, vomiting or constipation should not be regarded as AE (unless Grade III / IV and worsing of symptoms after treatment start) until day +100 after transplantation.

9.2. *Definition of Serious Adverse Event (SAE)*

A Serious Adverse Event (SAE) is any untoward medical occurrence (whether considered to be related to study drug or not) that occurs at any dose and:

- Results in death or
- Is life-threatening or
- Requires in-patient hospitalization or prolongation of existing hospitalization or
- Results in persistent or significant disability/incapacity or
- Results in congenital abnormality/birth defect.

SAEs will be documented in the patient´s chart and in the CRF. The forwarding of the SAE form will be documented in the ISF. A copy of the SAE will be filed with the investigator site file.

9.2.1. *Other events to be treated as SAEs or treated like SAEs*

This would be exposure to drug during pregnancy/lactation.

In principle, pregnancy and the lactation period are exclusion criteria. In the event of a pregnancy occurring during the course of a study, the subject must be withdrawn from study drug immediately. The Investigator-Sponsor must be notified without delay and the subject followed during the entire course of the pregnancy and postpartum period. This has to be documented by using the pregnancy forms- The signed and dated forms has to be stored in the investigator´s site file by the responsible investigators. Parental and neonatal outcomes must be recorded even if they are completely normal and without AEs. But if a pregnancy fullfill the (serious) adverse criteria, the regular AE or SAE procedure has to be applied.

9.2.2. *Exceptions from SAE-reporting*

a) Hospitalization for diagnostic or regularly therapy as provided in the clinical trial plan

b) Hospitalization that was planned before inclusion of the patient in the study for elective operations or treatment.

c) Hospitalization due to GvHD or coherent treatment

d) Hospitalization for pre-emptive therapy of CMV.

9.3. *Definition of Adverse Drug Reaction (ADR)*

This is defined as any noxious and unintended (harmful or unwanted) response to a medicinal product normally used in man for prophylaxis, diagnosis or therapy of diseases, or for modifications of physiological function, and is suspected to be related to the drug. A suspected ADR is fulfilled, if the causality is judged as possible or probable by the investigator.

9.4. *Definition of Serious Adverse Drug Reaction (SADR)*

This is defined as an adverse drug reaction (ADR) that is serious (see SAE criteria above).

9.5. *Definition of Suspected Unexpected Serious Adverse Drug Reaction*

The definition of a SUSAR is a serious adverse drug reaction or Serious Adverse Events related to Sorafenib, the nature or severity of which is not consistent with the applicable product information and therefore is considered “unexpected” with regard to the valid Summary of Product Characteristics for Sorafenib.

A serious event or drug reaction is not defined as a SUSAR when:

a) It is serious, but expected;
b) It does not fit the definition of a SAE or SADR, whether expected or not.

10. *Recording, reporting and reviewing*

It is the investigators responsibility to maintain an accurate and up to date record of all adverse events/occurrences in patients participating in the clinical trial. This record, including details of nature, onset duration, severity, outcome and any relationship to investigational product, should be made on the relevant documentation as specified below. Medical terminology according to CTCAE Version 4.02 should always be used to describe any event. Investigators should avoid vague terms such as “sick”. For details on assessing causality, see section 10.4 below.

It is the investigators responsibility to review all events occurring at their site and as such, the investigator must ensure that the patients are not compromised. Any appropriate action must be taken to protect the patients whilst ensuring validity of the results.

10.1. *Reporting of Adverse Events*

Adverse events will be reported on CRFs from the time the informed consent is signed, up to and including 30 days following last administration of study drug. In case that a patient has an open AE at the end of the study, it has to be reported until the AE is resolved or got the status unresolvable or the data base is closed. If the patient needs a therapy different from the clinical trial for treatment of the same indication, the reporting of the AE ends at the beginning of this therapy.
The severity of AEs will be graded according to the National Cancer Institute Common Terminology Criteria for AEs (CTCAE) 4.02 for Cancer Clinical Trials.

10.2. *Reporting of Serious Adverse Events*

All SAEs have to be recorded from the time the informed consent is signed, up to and including 30 days following last administration of study drug on the appropriate SAE pages in the CRF. Ongoing SAEs have to be reported every four weeks.
The Investigator must fax or E-mail all serious adverse events (SAEs) to the KKS within 1 working day after awareness of the event. Where possible, a diagnosis rather than a list of symptoms should be given. The Investigator should complete all the details requested including dates of onset, severity, corrective therapies given, outcome and opinion as to whether the adverse event is likely to be drug-related. The Investigator should not wait for full details before making the initial report. Personal data have to be replaced by the trial patient number before forwarding any information.
If the event is fatal or life threatening, the Investigator must fax any relevant follow-up information of the reported SAE to the KKS within additional 8 days. If the reported SAE is not fatal or life threatening, the investigator must fax follow-up information as soon as possible.
In case of death, the Investigator has to supply Principal investigator, KKS, Competent Authority and Ethics Committee with all details requested.

The Principal Investigator will review the SAE again for seriousness and relatedness and assess the SAE for expectedness according to Summary of Product Characteristics (Product Information) or Investigator's Brochure as applicable.

10.3. *Reporting of Suspected Unexpected Serious Adverse Drug Reactions (SUSARs)*

It is the duty of the KKS to report in accordance with legal requirements *fatal or life threatening* SUSARs within 7 calendar days and *non-fatal and non-life threatening* SUSARs within 15 calendar days after receiving first notification of the event to the Ethics Committee, Competent Authorities and all participating investigators.

10.4. *Assessment of causality of adverse events / reactions*

The relationship of adverse events to the medicinal products being studied should be determined according to the classification below:

certain:

- Event or laboratory test abnormality, with plausible time relationship to drug intake
- Cannot be explained by disease or other drugs
- Response to withdrawal plausible (pharmacologically, pathologically)
- Event definitive pharmacologically or phenomenologically (i.e. an objective and specific medical disorder or a recognized pharmacological phenomenon)
- Rechallenge satisfactory, if necessary

probable:

- Event or laboratory test abnormality, with reasonable time relationship to drug intake
- Unlikely to be attributed to disease or other drugs
- Response to withdrawal clinically reasonable
- Rechallenge not required

possible:

- Event or laboratory test abnormality, with reasonable time relationship to drug intake
- Could also be explained by disease or other drugs
- Information on drug withdrawal may be lacking or unclear

unlikely:

- Event or laboratory test abnormality, with a time to drug intake that makes a relationship improbable (but not impossible)
- Disease or other drugs provide plausible explanations

not related:
- no causal relationship

not assessable:
- Report suggesting an adverse reaction
- Cannot be judged because information is insufficient or contradictory
- Data cannot be supplemented or verified

not applicable:
- If any of causal relationship does not make sense (e. g. exposure during pregnancy, overdose, medication error)

unknown:
- no information is available

11. *Statistical Considerations*

11.1. *Description of analysis sets*

Intention to treat set (ITT)

The ITT set includes all patients who were randomized regardless of whether they received treatment or not. Patients will be analysed in the treatment group they were randomized to, regardless of whether they were treated in this group or not.

Per-protocol set (PP)

The PP set includes the patients of the corresponding ITT-set for whom no major protocol violations occurred. A compilation of the major protocol deviations will be generated by the coordinating investigator.

Safety Set

The safety set of the study consists of patients who received at least one dose of sorafenib or placebo and for whom post-dose data are available. Patients will be analysed in the

treatment group they were treated in, regardless of whether they were randomized to this group or not.

11.2. *Power and Sample Size Calculation*

The primary endpoint of the study, relapse-free survival (RFS), is defined as the time interval from randomization until relapse or death from any cause, which ever occurs first. For a patient with none of these events before the end of study follow-up, observation of RFS will be censored at the date of his or her last follow-up examination. It is assumed that the RFS rate after 2 years may be increased from 65% with placebo (Gale et al., Blood 2005; Thiede et al., Blood 2006) to 82.5% with sorafenib, corresponding to a hazard ratio (HR) of 0.45. Comparing the sorafenib with the placebo group by a log-rank test at a two-sided alpha of 5%, 49 observed events are required to obtain a power of 80%. It is important to note that due to a decreasing likelihood of relapses over time, the Kaplan-Meier curve for RFS of Flt3-ITD AML patients after allo-SCT forms a plateau after around 2 years at the above-mentioned values.

Under these assumptions, 184 patients (i.e., 92 per group) are needed in order to observe 49 events after a minimum observation period of 24 months for each patient. The inclusion of a total of 200 patients in the study allows for compensation of a dropout rate of 8%. During the course of the study, it may be decided to adapt the number of included patients. If this is done based on a data inspection (rather than solely on the absolute number of events which occurred so far, irrespective of the study arm), the method for sample-size adaptation in survival trials developed by Schäfer and Müller (Schäfer H, Müller H-H. Modification of the sample size and the schedule of interim analyses in survival trials based on data inspections. Statist Med 2001;20:3741-3751) will be employed which ensures that the type I error risk is not affected. It may also be decided later to add one or more interim analyses using the adaptive method mentioned above, especially if the sample size is increased.

11.3. *Interim analysis*

There will be an interim analysis of safety after 20 patients have been treated for at least 3 months. Numbers of adverse events will be analyzed descriptively as well as in comparison between the two study arms by means of Fisher's exact test. An interim data inspection will be performed during the first half of 2014 according to the method proposed by Schäfer and Müller (Statist Med 20:3741-3751, 2001), which will take into account all patients included in the SORMAIN trial so far. This will offer the study management the chance to adapt the total sample size while keeping the original type I error rate constant, that is, without increasing the risk of a false positive study result. The reasons for this interim data inspection, which

had not been explicitly planned but outlined in the study protocol (V03F, Section 11.2 Power and Sample Size Calculation, p.44) to be decided about later, are twofold:

(1) The recruitment rate has been much lower than expected. Whereas 200 patients were planned to be recruited within an accrual period of 24 months, only 45 patients have been randomized after 40 months of accrual.
(2) Based on accumulating evidence from controlled trials with AC220 and Midostaurin (both are new FLT3-ITD inhibitors) and clinical experience with sorafenib used outside of clinical studies in the AML indication, it is not unlikely that sorafenib therapy might generate a larger treatment benefit compared to placebo than the hazard ratio of 0.45 implies, which was originally assumed for the sample size calculation.

If the interim data inspection, which takes into account all available information regarding relapse or censoring events as well as treatment group allocation of patients, shows indeed a larger treatment difference than originally assumed, the additional number of events required before the final analysis, and hence the sample size, could be reduced. This would enable completion of the SORMAIN trial and a judgement of efficacy in less time and with a smaller number of patients.

According to the method by Schäfer and Müller, the data obtained up to the time point of the interim inspection will be used to calculate the value of the log-rank test statistic. Given that value, the probability of falsely rejecting the null hypothesis of no treatment difference (conditional rejection error probability, CRP) at the originally planned study end point, that is, after a total number of 50 events, will be calculated using the formulae in the above-mentioned paper. The design of the remaining part of the trial can be changed to any other design, that is, to a different number of additional events up to the final analysis, with the log-rank test statistic finally being applied to the additional events and assuming a type I error rate equal to the CRP calculated at the interim inspection. It is allowed to use all information from the interim inspection, such as Kaplan-Meier curves and estimates of the treatment difference (hazard ratio), to recalculate the additional number of events required to obtain a given power, without the total type I error being compromised. It is even possible to apply a group-sequential design to the remaining part of the trial. Alternatively, it can be decided after the interim inspection to leave the trial design unchanged.

The preservation of the pre-specified type I error rate – in this trial a two-sided alpha of 0.05 – is guaranteed when applying the CRP principle if the interim data inspection is used for sample-size adaptation only but not for an interim analysis with the option to reject the null hypothesis of no treatment difference. It is hereby explicitly stated that the envisaged interim inspection will not be used to perform such an analysis, that is, no formal statistical test will be done at that interim time point with the chance to conclude that a significant treatment difference is present. In other words, no alpha will be spent at the interim inspection.

In order to perform the interim data inspection, the trial biostatistician will receive the data regarding relapse and censoring events together with treatment group membership, that is, in a blinded fashion, without any further variables. The Coordinating Centre for Clinical Studies (KKS) Marburg will provide these data with new random ID numbers, such that the biostatistician can use as little information from the interim inspection as possible at later stages of the analysis, maintaining blinding to the largest possible degree. The results of the interim data inspection (log-rank test statistic, CRP given the test statistic, Kaplan-Meier curves, treatment difference in terms of hazard ratio) as well as recalculated power values assuming the CRP and various effect sizes will be communicated by the biostatistician only to the unblinded contact. The unblinded contact will communicate in an unblinded fashion with the DSMC members. The DSMC will decide about whether and how the design of the remaining part of the trial should be changed, e.g. the sample size reduced in case of an unexpectedly large treatment difference, or whether the trial should be stopped due to futility. This decision will be communicated in written form to the unblinded contact and the Steering Committee. If the design is modified, this will be specified in a further protocol amendment. The details of a design modification will be communicated to as few people involved in the performance of the trial as possible, in order to avoid that study personnel might draw conclusions about the observed treatment difference from the decision regarding the change of trial design.

11.4. *Statistical Analysis Plan*

The primary objective, RFS (as defined above), will be analyzed by means of the Kaplan-Meier method as well as the log-rank test at a two-sided alpha of 0.05 to test for differences between the two study arms. Possible sample size modifications or interim analyses will be performed according to the adaptive method by Schäfer and Müller as described in section 11.2.

Secondary endpoint of the study is overall survival (OS), 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. This and other secondary objectives will be analyzed by the Kaplan-Meier method and the log-rank test. Furthermore, RFS and OS will be analyzed by Cox regression in order to account for prognostic factors (Flt3-ITD ratio at diagnosis, treatment with Flt3-inhibitors before allogenic stem cell transplantation, occurrence of chronic GvH). The analysis will be performed according to the intention-to-treat principle.
With regard to safety, numbers of adverse events will be analyzed descriptively as well as in comparison between the two study arms by means of Fisher's exact test.

12. *Efficacy*

12.1. *Response criteria*

Response criteria are defined according to the Revised Recommendations of the International Working Group for Diagnosis, Standardization of Response Criteria, Treatment Outcomes and Reporting Standards for Therapeutic Trials in Acute Myeloid Leukemia [29].

12.2. *Definition of Study Endpoints*

12.2.1. *Primary endpoint*

=> 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.

12.2.2. *Secondary endpoint*

=> Overall Survival (OS)

OS 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.

13. *Quality Assurance*

13.1. *Data Safety Monitoring Committee*

The Safety Committee of this trial will consist of three members of the scientific community not involved in this trial. The committee will be provided with a first safety analysis after 20 patients have been treated for at least 3 months and then yearly thereafter. The safety

meeting will be held by phone conference with the Principal Investigator, KKS and statistician of the trial and review all serious adverse events (SAE), suspected unexpected severe adverse reactions (SUSARS). The Safety committee will give recommendations about the continuation of the trial and/or about necessary trial amendments.

13.2. *Monitoring and inspection by authorities*

The monitoring of the study takes place by the trained staff of the KKS Marburg. Patient recruitment can begin after the initiation visit. During the course of the study each participating centre will be visited for monitoring.

During each of these visits, source data verification will be performed on the basis of a pre-specified sampling plan. The KKS Marburg will generate this plan. Furthermore, at these visits problematic cases will be discussed.

Source data verification will be performed by direct access to the original patient records and the monitoring organization (KKS) guarantees that patient confidentiality will be respected at all times. Participation in this study will be taken as agreement to permit direct source data verification. Data generated at the pre-screening visit are verified against source data only in case the patient enters the study.

In compliance with European regulations/ICH-GCP Guidelines, it is required that the investigator and institution permit authorized representatives of the study central office and the regulatory agency(s) direct access to review the subject's original medical records for verification of study-related procedures and data. Direct access includes examining, analyzing, verifying, and reproducing any records and reports that are important to the evaluation of the study. The investigator is responsible for giving any requested support for any monitoring, inspection or audit visit. The investigator has to be available during these visits.

13.3. *Data Management*

13.3.1. *Data entry*

The investigator is responsible for the performance of the trial in accordance to GCP guidelines and the study protocol as well as the correct data entry to the corresponding electronic case report form (e-CRF). The data of the patients are documented with the EDC (Electronic Data Capture) system MACRO™ which is hosted at KKS Marburg. The data are entered directly via web browser (Microsoft Internet Explorer 6.x or 7.x required or Microsoft Internet Explorer 8.0 run in compatibility mode) to the e-CRF and are transferred via high encryption (SSL 128-bit encryption) to the central database. Therefore, documentation on paper CRF is not necessary.

Detailed requirements for using EDC are specified in an EDC Manual which is part of the ISF.

In order to use the EDC system all staff who are entering and monitoring data are provided with training materials and required documentation by KKS Marburg. For training of data entry KKS provides a test database. All data which are collected during the trial have to be documented in the e-CRF by authorized persons according to the personnel log.
The EDC system has an implemented audit trail. This assures that any documentation and/or changes to database items are traceable anytime. Changes or corrections are permitted to persons who are documented in the TMF and who have access to the system with user specific access rights. This access is documented by KKS Marburg.
Users with monitoring function are not able to enter or change patient's data. They have the possibility to view the data write protected (review function) and they can create SDV marks in case of queries. Discrepancies which appear at data management are forwarded to the monitors or to the site directly.

13.3.2. *Data concealment for electronic transfer*

Every investigator, study nurse, monitor or other person involved in the trial receives his or her personal login data (username and password). Access rights to the database will depend on the group affiliation. Users of the EDC-System MACRO will receive the training materials by the data management of KKS Marburg. Every person who gets access to the system has to fill in a registration form (User-ID request) and has to confirm that they have been adequately trained.

Thus it is guaranteed that only authorized persons (TMF, personal log) have access to the system to enrol patients to the trial. The data are transferred via high encryption (128-bit, SSL) across the internet.

At the end of study, the database will be closed after data cleaning process. This process will be documented according to SOPs of KKS Marburg.
For analysis, the following software will be used:
SAS version 9 or more recent version, as well as statistics software package R (R Development Core Team (2009). R: A language and environment for statistical computing. R Foundation for Statistical Computing, Vienna, Austria. ISBN 3-900051-07-0, URL http://www.R-project.org).

14. *Responsibilities, Ethical Considerations, Confidentiality, Insurance*

14.1. *Investigator's Responsibilities*

The Principal Investigator has more than two years of experience in the conductance of clinical trials.

The investigator shall be responsible for ensuring that the clinical study is performed in accordance with the protocol, the ethical principles that have their origin in the Declaration of Helsinki (World Medical Association Declaration of Helsinki, 1996) as well as with the International Conference on Harmonization of Technical Requirements of Pharmaceuticals for Humans Use (ICH) Note for Guidance on Good Clinical Practice (ICH, Topic E6, 1995) approved July 17, 1996, GCP-Guidelines, the relevant national laws and applicable regulatory requirements. These documents state that the informed consent of the patients is an essential precondition for participation in the clinical study.

14.2. *Patient information*

The consent of the patient to participate in the clinical study has to be given in writing before any study-related activities are carried out. It must be signed and personally dated by the subject after a reasonable decision phase and by the investigator/person designated by the investigator to conduct the informed consent discussion. A subject information sheet in the local language and prepared in accordance with the ICH Note for Guidance on Good Clinical Practice (ICH, Topic E6, 1995) will be provided for the purpose of obtaining informed consent. It will be revised whenever important new information becomes available that may be relevant to the consent of subjects.

In addition to this written information, the investigator or his designate will inform the subject verbally. In doing so, the wording used will be chosen so that the information can be fully and readily understood by laypersons.

Provision of consent will be confirmed in the patient file by the investigator. The signed and dated declaration of informed consent will remain at the investigators' site and must be safely archived by the investigator in the ISF so that the forms can be retrieved at any time for monitoring, auditing and inspection purposes. A copy of the signed and dated information consent should be provided to the subject prior to participation.

14.3. *Witnessed informed consent*

If the subject or legally acceptable representative is unable to read, a reliable and independent witness should be present during the entire informed consent discussion. The

choice of the witness must not breach the subject‘s right to confidentiality. A reliable independent witness is defined as one not affiliated with the institution or engaged in the investigation. A family member or acquaintances are appropriate independent witnesses. After the subject or legally acceptable representative orally consents and has signed, if capable, the witness should sign and personally date the consent form attesting that the information is accurate and that the subject or legally acceptable representative has fully understood the content of the informed consent agreement and is giving true informed consent.

14.4. *Source data and subject files*

The investigator has to keep a written or electronic subject file for every subject participating in the clinical study. In this subject file, the available demographic and medical information of a subject has to be documented, in particular the following: name, date of birth, sex, height, weight, subject history, concomitant diseases and concomitant drug (including changes during the study), statement of entry into the study, study identification, subject number, the date of informed consents, all study visit dates, predefined performed examinations and clinical findings, observed AEs (if applicable), and reason for withdrawal from the study if applicable. It should be possible to verify the inclusion and exclusion criteria for the study from the available data in this file.
It must be possible to identify each subject by using this patient file.
Additionally, any other documents with source data, especially original printouts of data that were generated by technical equipment have to be filed. All these documents have to bear at least subject identification and the printing date printed by the recording device to indicate to which subject and to which study procedure the document belongs. The medical evaluation of such records should be documented as necessary and signed/dated by the investigator.
Computerized subject files will be printed whenever source data verification is performed by the monitor. Printouts must be signed and dated by the investigator, countersigned by the monitor and kept in a safe place.
Data to be recorded directly on the CRFs (i.e. no prior written or electronic record of data) are considered to be source data.

14.5. *Investigator Site File and archiving (ISF)*

The investigator will be provided with an ISF at the start of the study. This file contains all relevant documents necessary for the conduct of the study. This file must be safely archived after termination of the study.

It is the responsibility of the investigator to ensure that the patient-identification sheets are stored for at least 15 years beyond the end of the clinical study. All original patient files must be stored for the longest possible time permitted by the regulations at the hospital, research institute, or practice in question. If archiving can no longer be maintained at the site, the investigator will notify the Investigator-Sponsor.

14.6. *Notification to authorities*

Prior to commencement of the study, the study protocol will be submitted together with its associated documents (patient information, consent form, product information) to the Competent Authority for their favorable opinion. The study will only commence following provision of a written favourable opinion by the regulatory authority. Any substantial amendments to the protocol will be submitted to the Competent Authority.

The investigator shall inform the local authority about termination of the clinical trial. Where the clinical trial has been suspended or interrupted by the sponsor, the sponsor inform the Competent Authority, giving the reasons for suspension or interruption.

14.7. *Ethics Committee or Institutional Review Board*

Prior to commencement of the study, the study protocol will be submitted together with its associated documents (patient information, consent form, product information) to the relevant EC for their favorable opinion.

The study will only commence following provision of a written favourable opinion, documenting the date of the meeting, constitution of the committee and voting members present at the meeting as well as clearly identifying the trial, protocol version, and consent documents reviewed.

Any substantial amendments to the protocol will be submitted to the EC and they will be informed about SUSARs in accordance with national requirements. Additional trial sites may only recruit patients, if the sponsor already obtained approval for the site.

14.8. *Changes to the study protocol*

Changes to, or formal clarifications of the study protocol must be documented in writing.

Major changes to the protocol will be described in a “Substantial Protocol Amendment“.. Any Amendment affecting the subject requires the subjects‘ informed consent prior to implementation.

Changes of administrative or technical nature will be recorded in a document entitled “nonsubstantial amendment“. It will be sent for information to the relevant ECs and to authorities.

Amendments will be signed by all signatories of the protocol. All investigators will acknowledge the receipt and confirm by their signature on the Amendment that they will adhere to the amendment. The signature page will be filed in the Investigator Study File and a copy in the Trial Master File.

14.9. *Confidentiality*

The investigator must ensure that the patient’s encryption is maintained. On documents such as copy of signed informed consent form, Flt3-ITD analysis form, bone marrow and peripheral blood result documenting CHR that are submitted to the KKS, subjects shall be identified by a patient number (first the centre number followed by a consecutive number for each patient ,e.g. 0101) and month and year of birth only (pseudonymized). Documents that are not for submission to the KKS should be kept in strict confidence by the investigator.

14.10. *Patient insurance*

For all patients in this trial, the sponsor has contracted an insurance covering possible damage to the patients at the Gerling Industrie Versicherung AG.

Germany:
HDI-Gerling Industrie Versicherung AG
Vertragsservice Haftpflicht
Am Schönenkamp 45
D-40599 Düsseldorf
Tel: 0211 - 74825404
Fax: 0211 – 7482465
Austria:
HDI-Gerling
Edelsinnstrasse 7-11
Postfach 110
A-1120 Wien
Tel: 050905 – 5010
Email: service@hdi.at

The insurance policy number is: **57 010312 03019**

This insurance covers any damage to health arising from participation in the study up to maximum sum required by law.
In order not to violate the insurance cover, the patient must immediately notify the insurance company or the investigator in case of any damage to health arising from participation in the clinical study.
A copy of the complete insurance terms and conditions will be made available to the patient.

15. *Publication*

The publication policy (also of parts of the study results) should be done in accordance to the principal investigator's instructions. Authorship will be based on the extent of contribution to the study. Publications will list the following co-authors: Coordinating author writing the manuscript (if not the Coordinating investigator); persons who contributed to conception, design, conduct of the trial and analysis of data, representatives of centres reporting at least 10 % of enrolled patients or representatives of the six to ten centres that enrolled most patients; statistician(s) involved in design, analysis or interpretation of data, the KKS, and other persons who significantly contributed to the trial. All authors will review an advanced version of the manuscript. The first publication will be a joint publication of the complete study population.

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17. *APPENDICES*

Table 7) Acute GVHD-Staging (Glucksberg, Storb et al. 1974)

STAGE	SKIN	LIVER	INTESTINAL TRACT
0	no rash	Bilirubin< 2 mg/dl	< 500 ml diarrhoea / d
+	maculopapular rash < 25% of body surface	Bilirubin 2-3 mg/dl	> 500 ml diarrhoea / d
++	maculopapular rash < 25–50% of body surface	Bilirubin 3-6 mg/dl	> 1000 ml diarrhoea / d
+++	Generalised erythroderma	Bilirubin 6-15 mg/dl	> 1500 ml diarrhoea / d
++++	Generalised erythroderma with bullous formation and desquamation	Bilirubin> 15 mg/dl	severe abdominal pain ± ileus

GRADE	DEGREE OF ORGAN INVOLVEMENT
I	• skin rash: + to ++ • no gut involvement • no liver involvement • no decrease in clinical performance
II	• skin rash: + to +++ • gut involvement: + and / or liver involvement • mild decrease in clinical performance
III	• skin rash: ++ to ++++ • gut involvement: ++ to +++ and /or liver involvement ++ to ++++ • marked decrease in clinical performance
IV	• Similar to grade III with − organ involvement ++ to ++++ and − extreme decrease in clinical performance

Table 8) Chronic GvHD-Grading (Shulman, Sullivan et al. 1980)

Chronic GvHD may be defined as *limited* or *extensive* using the following criteria defined by Shulman	
Limited Chronic GvHD	*Either or both criteria must be present:* • Localised skin involvement • Hepatic dysfunction
Extensive Chronic GvHD	*Either:* • Generalised skin involvement ***or*** • Localised skin involvement and / or hepatic dys-function • plus Liver histology showing chronic aggressive hepatitis, bridging necrosis or cirrhosis ***or*** Involvement of eye: Schirmer's test with < 5 mm wetting, ***or*** Involvement of minor salivary glands or oral mucosa demonstrated on labial biopsy

	specimen, ***or*** Involvement of any other target organ (e. g., oeso-phageal abnormalities, polymyositis)