TECHNISCHE UNIVERSITÄT DRESDEN

SAL Study Alliance Leukemia

CLINICAL TRIAL PROTOCOL

Eudra CT Number: **2011-002567-17**

Protocol code: **TUD-MIDOKI-052**

A single-arm phase II trial to assess the efficacy of midostaurin (PKC412) added to standard primary therapy in patients with newly diagnosed c-KIT or FLT3-ITD mutated t(8;21) AML

Short Title: MIDOKIT

Project / Version 2.0

07 February 2012

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A study of the Study Alliance Leukemia (SAL)

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Technical University Dresden

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Approval of the Clinical Trial Protocol:

A single-arm phase II trial to assess the efficacy of midostaurin (PKC412) added to standard primary therapy in patients with newly diagnosed c-KIT or FLT3-ITD mutated t(8;21) AML (TUD-MIDOKI-052)

Eudra CT- Number:	**2011-002567-17**
Version Number:	**2.0**

Sponsor Prof. Dr. G. Ehninger On behalf of the sponsor Coordinating Investigator	Signature	Date Feb 10, 2012
Medical Study-Coordinator Dr. C. Röllig, MSc	Signature	Date 10 Feb 2012
Biometrics/Statistics M. Kramer	Signature	Date 10.02.2012

Original: Trial Master File Copy: ISF

Investigator Statement

Title:	A single-arm phase II trial to assess the efficacy of midostaurin (PKC412) added to standard primary therapy in patients with newly diagnosed c-KIT or FLT3-ITD mutated t(8;21) AML (MIDOKIT)
EudraCT No.:	**2011-002567-17**
Protocol Code:	**TUD-MIDOKI-052**
Coordinating Investigator:	**Prof. Dr. G. Ehninger**

I confirm that I have read the Clinical Trial Protocol and hereby commit myself to adhere to all actions and terms as specified in the relevant sections of the clinical, ethical and general paragraphs.

I confirm that I and my colleagues will abide by the local legislation (in Germany, the German Pharmaceutical Law with the appropriate amendments). I further confirm that the Clinical Trial will be carried out in compliance with the Declaration of Helsinki and ICH-GCP guidelines.

I acknowledge that all confidential information in this document, apart from the evaluation of the Clinical Trial will not be used or circulated without the prior written consent of the Sponsor.

Under my supervision I put copies of this Clinical Trial Protocol and possible updates as well as access to all information regarding the carrying out of this Clinical Trial at the disposal of my colleagues; in particular I will promptly forward all information from the Sponsor in relation to Pharmaceutical Safety (SUSAR) to my colleagues.

I will discuss this Clinical Trial Protocol in detail with my colleagues and ensure that they are comprehensively informed about the trial compound/preparation and the execution of the study.

Furthermore I commit myself not to commence subject enrolment before the approval of the authorities and acceptance by the relevant/responsible Ethics Committee.

Name of the Principal Investigator	Signature	Date

Klinikstempel

Original: Trial Master File Copy: ISF

List of Abbreviations

AE	Adverse Event
AMG	German Drug Law (Arzneimittelgesetz)
ANC	Absolute Neurophil Count
BSA	Body Surface Area
CRA	Clinical Research Associate (Monitor)
CRF	Case Report Form
DMC	Data Monitoring Committee
ESAR	Expected Serious Adverse Reaction
FPFV	First Subject First Visit
GCP-V	German Decree of 09-Aug-2004 on the Use of Good Clinical Practices
GP	General Practitioner
ICH-GCP	ICH Topic E6: Guideline for Good Clinical Practice (GCP)
ISF	Investigator Site File
LPLV	Last Subject Last Visit
LVEF	Left Ventricular Ejection Fraction
MPG	Medicinal Device Law (Medizinproduktegesetz)
MRD	Minimal Residual Disease
PI	Principal Investigator
RTK	Receptor Tyrosin Kinase
SAE	Serious Adverse Event
SAR	Serious Adverse Reaction
SmPC	Summary of Product Characteristics (Fachinformation)
SUSAR	Suspected Unexpected Serious Adverse Reaction
UAR	Unexpected Adverse Reaction
BID	Two times per day
TID	Three times per day
QID	Four times per day

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Synopsis

STUDY TITLE	**A single-arm phase II trial to assess the efficacy of midostaurin (PKC412) added to standard primary therapy in patients with newly diagnosed c-KIT or FLT3-ITD mutated t(8;21) AML**
ABBREVIATED TITLE	MIDOKIT
PROTOCOL CODE	TUD-MIDOKI-052
EUDRACT NUMBER	2011-002567-17
SPONSOR	TECHNISCHE UNIVERSITÄT DRESDEN
PHASE OR MODEL	Phase IIa
INDICATION/ MAIN DIAGNOSIS	newly diagnosed c-KIT or FLT3-ITD mutated t(8;21) AML
RATIONALE	AML patients displaying t(8;21) have a relatively favourable outcome. Nevertheless, only approximately 50% of patients carrying this cytogenetic aberration are alive at 5 years. This suggests that some patients have more aggressive leukemic phenotypes and indicates the need for treatment optimization with novel therapies. The mutated KIT gene as well as the FLT3-ITD mutation have recently been identified as factors most likely to explain the heterogeneous clinical outcomes within the group of t(8;21) AML. The FLT3 and c-KIT genes encode type III receptor tyrosine kinases (RTK) with important and partly redundant functions in early hematopoietic stem cells. Various activating mutations have been described for both genes. For c-KIT, the incidence ranges from 17 to 48% depending on the source population and type of mutations determined. It has been consistently shown that in AMLs with t(8;21), mutated c-KIT is associated with a dramatically increased risk of relapse and reduced overall survival compared to their unmutated counterparts. The FLT3-ITD mutation has a similar negative effect on prognosis in the patient group of t(8;21) mutated AMLs as c-KIT. PKC412 (midostaurin) is known to inhibit the c-KIT RTK activity as well as the FLT3 kinase, both in patients with ITD and TKD mutations. It should therefore be possible to abrogate the negative impact of pathologically increased c-KIT or FLT3-ITD activity on relapse and overall survival by using midostaurin in this patient population. Aim of the proposed clinical trial is to prove the efficacy of midostaurin in c-KIT or FLT3-ITD mutated t(8;21)- AMLs in an open-label one-arm design.
TRIAL OBJECTIVES	To assess the efficacy of tyrosine-kinase inhibitor midostaurin in c-KIT or

	FLT3-ITD mutated t(8;21) AML To assess the efficacy of midostaurin depending on the type of c-KIT mutation	
STUDY DESIGN	single-arm, open label, multicentric	
ENDPOINTS	Primary/Main Endpoint: 2-year Event-free Survival (EFS) Secondary endpoints: Time to relapse (TTR), Cumulative incidence of relapse (CIR), Overall survival (OS), Relapse-free survival (RFS), morphologic and molecular CR rate, incidence of AEs/SAEs, MRD kinetics	
TIMETABLE	Enrolment of first subject (FPFV)*:	*1 May 2012*
	Enrolment of last subject:	*30 April 2016*
	End of trial for last subject (LPLV)*:	*31 May 2018*
	Closing of database	*31 July 2018*
	Conclusion of statistical evaluation:	*1 August 2018*
	Integrated final report:	*30 September 2018*
	Treatment duration per subject:	*16 months*
	Estimated duration of follow-up	*9 months*
	Study duration per subject	*25 months*
	Planned interim analysis:	*none*
	**Study begin/end is generally the first/last visit of the first/last subject*	
SAMPLE SIZE	n = 18 patients	
INVESTIGATIONAL MEDICINAL PRODUCT AND TREATMENT	midostaurin 50 mg (two 25 mg capsules) is given in combination with the second of two induction cycles and in combination with three cycles of high-dose cytarabine (HiDAC) consolidation chemotherapies and maintenance treatment in patients with c-kit or FLT3-ITD positive t(8;21) AML in an open-label one-arm design. The first cycle of induction is not part of the study. <u>Second cycle of induction chemotherapy (7+3 scheme):</u> Cytarabine 100 mg/m^2 days 1-7 Daunorubicin 60 mg/m^2 days 3-5 Midostaurin 50 mg (2 capsules) twice daily days 8-21 <u>Triple consolidation chemotherapy:</u> Cytarabine 3000 mg/m^2 twice daily days 1, 3, 5 Midostaurin 50 mg (2 capsules) twice daily days 8-21	

	Maintenance treatment: Midostaurin 50 mg (2 capsules) twice daily continuously for 12 months
MAIN INCLUSION CRITERIA	1. Diagnosis of c-KIT mutated t(8;21) AML i.e. a. >20% myeloid blasts in bone marrow and/or peripheral blood at initial diagnosis b. Plus cytogenetic diagnosis of aberration t(8;21)/AML1-ETO c. Plus mutation of c-KIT gene (mut-KIT17 or mut-KIT8) or FLT3-ITD mutation or both c-KIT and FLT3-ITD mutations 2. Chemoresponsive disease as determined by early bone marrow assessment on day 14-16 after first cycle of induction therapy with cytarabine in combination with daunorubicine or idarubicine, or mitoxantrone 3. Fit for further intensive chemotherapy 4. Age 18-65 years 5. ECOG performance status of 0-2 6. Life expectancy of at least 12 weeks *[Exact list of inclusion criteria is specified in section 5.3]*
MAIN EXCLUSION CRITERIA	1. Primary refractory or previously relapsed AML 2. Therapy-related AML after prior radiotherapy or chemotherapy 3. Non-eligibility for high-dose cytarabine based consolidation, e.g. intolerance to cytarabine 4. Inability to swallow oral medications *5.* Symptomatic congestive heart failure *6.* Bilirubin >2.5 x upper limit of normal *[Exact list of main inclusion criteria is specified in section 5.3]*
STATISTICAL ANALYSIS	The primary endpoint is a binary variable indicating event-free-survival at 2 years. The nullhypothesis of this trial is that the 2-year-EFS rate is worse or equal to 0.5 under the experimental treatment. The alternate hypothesis is that the 2-year-EFS rate is equal to 0.8 or greater. In an exact single stage phase 2 design, 18 patients have to be enrolled to be able to detect the critical difference in the EFS rates of 0.3 with a power of 80% and a one-sided significance level of 5%. The nullyhpothesis can be rejected if after 2 years, 13 or more patients are without an event. The calculation is based on the exact binomial distribution as described in A'Hern (2001).

Study Evaluations/Visit Schedule

	Screening examination within 7 days before study entry	Day 1of 2nd induction and Day 1 of each consolidation	Day 1-28 of 2nd induction and each consolidation	Remission control†	Start maintenance	During maintenance	Within 14 days after end of maintenance	Follow-up 3, 6+9 months after end of maintenance	Relapse
Screening Examination	X								
Check In- and Exclusion Criteria	X								
Registration	X								
Toxicity Assessment (AE)			X		X				
Toxicity Assessment (SAE)			X		X	Monthly	X	X	
Physical Examination incl. blood pressure, pulse and weight	X	X			X	monthly	X	X	
CBC (incl. differential and plts)	X	X	2x/week	X	X	monthly	X	X	X
Chemistry and Coagulation: Na, K, Ca, Crea, Mg, Urea, ALAT, ASAT, AP, Bili, Total Protein, Albumin, Uric Acid, Glucose, INR, PTT, Fib	X	X	2x/week		X	monthly	X	X	X
fT4, TSH	X								
Urinalysis	X								
Bone marrow cytology	X			X		Q 3 months *		X	X
Bone marrow cytogenetics	X			X		Q 3 months *		X	X
Bone marrow molecular genetics	X			X		Q 3 months *		X	X
EKG (QTc Interval)	X	X	**		**	**			
Chest X-Ray (pa and lateral)	X								
Echocardiography (LVEF)	X								
Beta-HCG pregnancy test	X								
Concomitant Medication			X			X			

† latest day 35 after beginning of each course of chemotherapy
* and in case of suspected or overt relapse for confirmation
** days 1,3,14 of midostaurin during induction 2 and each cycle of consolidation (days 8,10,21 of induction 2 and consolidation) and monthly during maintenance

1 Accountability and Responsibilities

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2 Introduction

2.1 Core-binding factor Acute Myeloid Leukemia and c-KIT/FLT3-ITD mutations

Acute myeloid leukemia (AML) is a very heterogeneous disease with regard to clinical features and acquired microscopic and submicroscopic genetic alterations determining clinical outcome of individual patients [1]. AML patients displaying t(8;21) have a relatively favourable outcome. Nevertheless, only approximately 50% of patients carrying this cytogenetic aberration are alive at 5 years. This suggests that some patients have more aggressive leukemic phenotypes and indicates the need for treatment optimization with novel therapies.

The mutated KIT gene as well as the FLT3-ITD mutation have recently been identified as a factor most likely to explain the heterogeneous clinical outcomes within the group of t(8;21) AML. The FLT3 and *c-KIT* genes encode type III receptor tyrosine kinases (RTK) with important and partly redundant functions in early hematopoietic stem cell. Various activating mutations have been described for both genes.

Different forms of mutations are described for c-KIT, affecting either Exons 8, 9, 11, and 17 [2]. The most common mutations which are also shown to have a negative prognostic impact on patients with AML, are the mutation D816V and D816Y in Exon 17 and mutations in Exon 8. Their incidence ranges from 17 [3] to 48% [4] depending on the source population and type of mutations determined. c-KIT mutations are rarely found in adult AML patients without a core-binding factor (CBF) leukemia [3]. It has been consistently shown that AMLs with t(8;21) with mutated c-KIT are associated with a dramatically increased risk of relapse and reduced overall survival compared to their unmutated counterparts [3,5,6,7].

Together with t(8;21) as one of the two aberrations commonly referred to as CBF leukemias, inv(16) belongs to the group of CBF leukemias. Since it appeared likely that c-KIT mutations might also have a negative prognostic impact in this subgroup of AML, its influence on overall survival was examined by various groups with differing results. Paschka et al. showed a negative impact on survival in c-KIT mutated patients both in t(8;21) and inv(16). Care et al. reported significant differences in relapse rate for patients with inv(16) but no differences in survival [8]. No difference depending on c-KIT mutations in inv(16) were found by Cairoli et al. and Boissel et al. Due to these conflicting results and the higher amount of evidence on the t(8;21) group, only patients with the latter constellation of t(8;21) and c-KIT*mut* will be included in this clinical trial.

The FLT3-ITD mutation has a similar negative effect on prognosis in the patient group of t(8;21) mutated AMLs as c-KIT [3,9]. Our own data, based on a number of 8 FLT3-ITD and 94 FLT3wt patients with t(8;21), confirm the negative prognostic influence on overall survival with a hazard ratio of 3.1 and a p value of 0.042 according to cox regression. Analyses of Kaplan-Meier plots show that

the reduction of overall survival in patients with c-KIT*mut* is mainly due to higher incidence of relapses while in FLT3-ITD patients, primary resistant disease leads to the inferior prognosis during the early course of the disease.

Table 1: Summary of the impact of c-KIT*mut* or FLT3-ITD on overall survival (OS) in patients with t(8;21) AML

Reference	OS
Schnittger 2006 [7]	N=64, HR 6 (med OS 1836/304 days)
Paschka 2006 [6]	N=49, HR 2.4 (med OS 4.4/1.8 years)
Cairoli 2006 [5]	N=36, HR 3.2 (ln0.42/ln0.76 @ 2yrs)
Boissel 2006 [3]	N=6 pts with c-KIT*mut* t(8;21) – no detailed information
Iwanaga 2009 [10] (KIT/ JAK2/ FLT3)	N=44, HR 2.9 (ln0.25/ln0.62 @5 years)
Paschka 2009 (FLT3) [9]	N=146, HR 4.2 (large effect of FLT3)

2.2 Midostaurin (PKC412)

PKC412 is an oral agent that has been shown to inhibit FLT3 kinase potently preclinically in vitro and in vivo, as well as clinically in patients with both ITD and TKD FLT3 mutations (FLT3 mut) both directly and indirectly, PKC412 also potently inhibits multiple other molecular targets thought to be important for the pathogenesis of AML. These targets include VEGFR-1, a VEGF receptor, c-KIT, H- and K-RAS, as well as the multidrug resistant gene, mdr. Of note, the lack of myelosuppression observed in solid tumor patients treated with PKC412 offers the possibility of increased therapeutic efficacy when combined with standard chemotherapy in FLT3mut AML patients without prolonged myelosuppression.

2.2.1 Preclinical Background

PKC412, a staurosporine derivative, is a multitargeted kinase inhibitor, and has been identified as an inhibitor of both mutated and wild type FLT3 kinase. PKC412 potently inhibits recombinant FLT3 kinase using an in vitro kinase assay, and inhibits tyrosine phosphorylation of mutant FLT3, both ITD mutants and D835Y point mutants in vitro. These data suggest that PKC412 directly block the kinase activity of mutant FLT3, thereby interfering with its transforming functions. Expression of a mutant FLT3 receptor (FLT3-ITD or the TKD D835V) in vivo in murine marrow cells results in a lethal myeloproliferative syndrome, which can be successfully cured with the administration of PKC412 [11].

Likewise, PKC412 also inhibits the transforming activity of the mutated KIT protein and the activation of STAT5 by KIT D816V and other mutations [12]. Of 14 known c-KIT mutations, ten confer an interleukin-3 independent growth potential. Growth of All of these can be inhibited with PKC412. The most common c-KIT mutations D816V und D816Y could be inhibited with a remarkably low 50%

inhibitory concentration (IC_{50}) in cell cultures, indicating a high sensitivity of these mutations to the drug. In contrast, D816 mutations are resistant to imatinib [13] [14].

There are additional preclinical features of PKC412 that are noteworthy particularly as relates to the sequence of administration of the drug in the treatment of patients with AML. First, PKC412 has been shown preclinically to be an inhibitor of MDR function. MDR protein function is regulated in part by its phosphorylation, and although PKC412 is not thought to interact directly with the MDR protein, PKC412 indirectly inhibits MDR phosphorylation through an as yet unknown mechanism, possibly PKCenzyme inhibition, therefore inactivating mdr function. There is strong synergy observed when FLT3-mutated cell lines are treated in combination with PKC412 and anthracyclines or cytarabine. This synergy is particularly sequence dependent with cytarabine. PKC given either with, or after cytarabine results in marked synergy. Similarly, synergy is also seen when PKC412 is combined with daunomycin, although no antagonism is observed when PKC412 precedes daunomycin. Identical sequence specific effects were observed using another FLT3 kinase inhibitor, CEP-701, in combinations of daunomycin, cytarabine and 2 other chemotherapy agents frequently used in AML [15]. These observations suggest a class effect of chemotherapy sequence specificity using FLT3 inhibitors, and suggest that the optimal sequence when adding FLT3 inhibitors would be to give chemotherapy first, followed immediately after by the FLT3 inhibitor, with every cycle of chemotherapy.

2.2.2 Clinical Background

PKC412 has been tested in over 400 patients with both solid tumors and hematologic malignancies. Two studies of PKC412 have been performed in patients with AML, the Phase I study 2104 (N=105) and a Phase IB study 2106. The case report of Gotlib et al. showing efficacy of PKC412 in a patient with c-KIT 816V positive systemic mastocytosis provided the first clinical proof-of-principle data [16].

Non-AML Studies: Ph I dose-finding trials in patients with solid tumors concluded that the maximum tolerated single agent dose (MTD) that could be safely administered when administrated to patients in a continuous fashion was 75 mg orally three times per day. No dose limiting toxicity was identified in this study, however, patients could not tolerate a higher dose of 100 mg three times a day, due to excessive, though only Grade 2 nausea and vomiting. PKC412 doses varying from 50 mg bid to 75mg three times a day could be administered in combination with a variety of regimens in patients with solid tumors including 5-FU in colon cancer patients, Taxol and Cisplatinum in non-small cell lung cancer patients, and gemcitabine and Carboplatin. In each study, the dose or rather tolerability limiting toxicity was nausea and vomiting, unresponsive to prophylactic antiemetics. All significant toxicities observed in the combination studies were related either to chemotherapy or disease, and no pattern indicated potentiation of major toxicity by PKC412. Of note, there was no increase in myelosuppression above the levels expected with this chemotherapy regimen. Furthermore, no increase in taxol pharmacokinetic exposure was seen in the lung cancer study, indicating that MDR

interactions of PKC412 on taxol pharmacokinetics are unlikely at the highest tolerable PKC412 dose of 225 mg/m^2.

AML Studies: PKC412 has now been tested in two studies in patients with acute myeloblastic leukemia. As a single agent given continuously, PKC412 has been evaluated in relapsed/refractory patients and in de novo elderly patients with AML (CPKC4122104 core and CPKC4122104E). PKC412 was then evaluated in Study CPKC2106 in combination with standard chemotherapy as a Phase IB trial in first line FLT3 wild type and mutated AML patients less than 60 years of age. In this trial, PKC412 was given in combination with the standard chemotherapy of Daunomycin/Cytarabine induction and HD-ARAC consolidation.

Study 2104:

Study 2104 core was a Phase I study of PKC412 in 20 relapsed, refractory or de novo elderly patients otherwise ineligible for chemotherapy, with documented FLT3 mutated AML Patients received PKC412 at a daily dose of 75 mg three times a day. Fourteen of the 20 patients (70%) had a ≥ 50% decrease in peripheral blood blast counts, and of these, five patients (25%) had a ≥ 50% decrease in bone marrow blast counts. One patient had a prolonged CR for 285 days by Cheson criteria [17]. Autophosphorylation of FLT3 in responding patients blasts was inhibited by >90% by day 3 [18].

Study 2104E (extension) was an amendment to Study 2104 core, designed to include up to an additional 100 patients with either FLT3WT or FLT3mut AML, tested at lower doses of PKC412 at either 50 mg BID or 100 mg BID. Clinical and biologic activity in 35 additional FLT3 mutated patients treated at these doses was comparable to that of patients treated at the higher dose of 75 mg three times a day in Study 2104 Core. FLT3 mutated patients treated at doses of 50 and 100 mg bid had a similar incidence of biologic activity as measured by >50% peripheral blast reduction (61%, 71%) and >50% bone marrow blast reduction (28% and 23%) respectively. One PR was observed in a FLTmut patient treated on 100 mg bid. Of the 57 patients that were FLT3 WT, biological activity was also seen, although less frequently than in FLT3 mutated patients, at 47% and 33% for 50 mg bid and 100mg bid regimens, respectively. No CRs or PRs were observed in the FLT3WT patients.

PKC412 was generally well tolerated. The most common toxicities were Grade 1/2 nausea (48%), vomiting (41%), diarrhea (26%) and fatigue (7%). In Study 2104 Core, there were 2 patients dying of pulmonary failure of unknown etiology. In Study 2104E, there were 2 additional cases of Grade 4 pulmonary edema and/or infiltrates in patients on antifungal azole medications known to be potent CYP3A4 inhibitors; these patients had substantially high PK levels than others without this toxicity. Because of this observation, patients were subsequently no longer allowed on antifungal azoles, and clear chest X rays were made inclusion criteria. Once these changes were implemented, severe pulmonary events with no known aetiology did not occur further.

Although elimination of peripheral blasts was extremely rapid, occurring within a week, the median time to progression in these patients (defined as a doubling of their baseline absolute blast count in

bone marrow) was short, 2-3 months. This early progression was associated both with the emergence of new drug resistant FLT3 mutations [19] as well as a 50-75% decrease in PKC412 pharmacokinetic blood levels by day 28 due to auto induction of its own CYP3A4 metabolism. Thus both mutational and pharmacokinetic mechanisms may be the cause of the short duration of response, despite robust biologic activity when PKC412 is given as a single agent.

Study 2106:

Study 2106 was a Phase IB study of newly diagnosed FLT3WT and FLT3mut AML patients under 60 years of age treated with standard chemotherapy and PKC412 given either sequentially or simultaneously. In this study, DA induction (daunorubicin 60 mg/m^2 d 1-3 and cytarabine 100 mg/m^2/d by IVCI x 7d) and consolidation therapy (cytarabine 3 gm/m^2/3h q 12h, d1,3,5 for 3 cycles) was given with PKC412 to previously untreated FLT3WT and FLT3mut AML patients less than age 60. Results with the original dose schedules of PKC 412 of 100mg po bid from day 8 continuously (arm 1) or day 1 continuously (arm 2) (n=15) or an amended schedule: day 8-21 (arm 1) or day 1-7, 15-21 (arm 2) (n=15) demonstrated safety, but poor tolerability due to nausea and vomiting [20]. However, tolerability was acceptable once the same chemo regimen was given with a reduced dose of PKC412 of 50 mg po bid.

As reported in December 2009, the median ages for the FLT3–wt and FLT3–mut pts were 50 years (range 25–60) and 46 years (range 20–65), respectively. 77% of the FLT3–mut pts displayed normal, 15% adverse and 8% other intermediate cytogenetics compared with 18.5%, 26%, and 26%, respectively, for FLT3-wt (also 18.5% favorable; 11% unknown). Complete response occurred in 32/40 (80%) of all pts (20/27 [74%] of FLT3–wt patients, 12/13 [92%] of FLT3–mut pts). Patients were censored at the last date they were known to be alive with a median post treatment follow-up for FLT3-mut pts of 1059 days and 1086 days for FLT3-wt. Even accounting for their differing cytogenetics and ages, the OS of the FLT3–mut subgroup was expected to be inferior to that of the FLT3–wt subgroup. However, we report that the 1 and 2 year OS for the pts with FLT3–mut AML was 85% and 62%, respectively, and was comparable to that of the FLT3–wt subgroup (81% and 59%, respectively). Although based on small numbers and not stratified for type of FLT3 mutation (TKD, ITD, ITD length, location, or allelic ratio), these long-term results suggest that combination therapy with a FLT3 inhibitor and chemotherapy might be effective enough to obviate the perceived need for allogeneic stem cell transplantation for FLT3–mut AML pts in first complete remission. Moreover, these data support the rationale for the ongoing international phase 3 study of induction, post-remission intensification, and maintenance with midostaurin (50 mg po bid) or placebo [21].

Study CALGB 10603/CTSU C10603

Currently, a phase III randomized controlled trial is evaluating midostaurin in first-line treatment of AML. Results are expected by November 2013.

Clinical Pharmacokinetics in AML patient studies:

Time-dependent pharmacokinetics has been observed following multiple doses in AML patients (Study PKC412 2104 Core and Study 2104E). The mean plasma concentrations of PKC412 decreased 2-4 times following 28 days daily dosing. Because of the declining pattern of PKC412 plasma concentration, it could not be excluded that the low plasma exposure level played a role in the observed early progressions in patients with biologic activity. By administering PKC412 intermittently, either one week on/ one week off, or two weeks on / two weeks off, autoinduction appeared to be reversed, and PKC412 PK levels appeared restored to 50-75% of cycle 1 PK.

In 30 patients studied on Study 2106 at PKC412 100 mg bid, a drug-drug interaction was observed between PKC412 and daunomycin in patients on the simultaneous Arm 2 only. An increase in AUC, t 1/2 and and volume of distribution was observed, along with increased G2 or 3 hyperbilirubinemia in comparison to that of patients on the sequential Arm 1, consistent with an effect on the inhibition of MDR function. Data on daunomycin levels in patients on Arm 2 treated with the lower PKC412 dose of 50 mg is not yet available. There was no drug-drug interaction observed between PKC412 and Cytarabine.

3 Rationale and Objective

3.1 General Design

PKC412 (midostaurin) is known to inhibit the c-KIT RTK activity [22] as well as the FLT3 kinase, both in patients with ITD and TKD mutations. It should therefore be possible to abrogate the negative impact of pathologically increased c-KIT or FLT3-ITD activity on relapse and overall survival by using midostaurin in this patient population. Aim of the proposed clinical trial is to prove the efficacy of midostaurin in c-KIT or FLT3-ITD mutated t(8;21) AMLs.

3.2 Choice of Chemotherapy Regimen

For patients with newly diagnosed AML under 60 years of age, the proposed standard chemotherapy induction regimen is 7+3 cytarabine in combination with antracylins or mitoxantrone. In this trial, all patients with no signs of progression of primary refractory disease after first standard induction treatment as assessed by early bone marrow assessment on day 14-16, will receive a second cycle of induction with daunorubicine and cytarabine (DA 7+3). Consolidation treatment with at least three cycles of high-dose cytarabine (HiDAC) is the current international standard in patients with favourable or intermediate cytogenetic profile [23]. General acceptance of usage of this regimen as the standard for AML chemotherapy in this population predates FDA or European Health Authority approval.

3.3 Choice of PKC412 Regimen

We have chosen to administer PKC412 at 50 mg bid as per the sequential regimen. The choice of the sequential regimen, rather than simultaneous regimen of PKC412 was based on the following considerations: In vitro data suggests that although additive and/or synergistic cytotoxic effects are observed when FLT3 inhibitors are given simultaneously, or after chemotherapy (chemo $\Rightarrow$ PKC412), exposure of cells to FLT3 inhibitors before chemotherapy (PKC412 $\Rightarrow$ chemo) has antagonistic effects on cytotoxicity [24]. Thus the simultaneous regimen would translate into one mimicking an antagonistic interaction, particularly as relates to the effect of earlier doses (e.g. days 1-3) of PKC412 on later doses of cytarabine (e.g. days 4-7).

Recently, data have been published indicating a FLT3-ligand mediated reduction in efficacy of tyrosin-kinase inhibitors when given after chemotherapy instead of parallel to chemotherapy [25]. However, in study 2106, the tolerability of a combined regimen was low with patients mainly suffering from nausea and vomiting, leading to the selection of a sequential application of chemotherapy followed by midostaurin. Furthermore, the results by Sato et al. are derived from in-vitro models and have not been confirmed in a clinical setting yet. Finally, the findings on the influence of tyroskinkinase-receptor ligands on inhibitory efficacy seem to be specific for FLT3 while ligand levels seem to be independent from chemotherapy in the case of the KIT molecule (Mark Levis, personal communication). Since the incidence of c-KIT mutations in t(8;21) AML is much higher than the incidence of FLT3-ITD, the main number of patients will be diagnosed with c-KIT*mut* rather than FLT3-ITD. Considering all arguments, the investigators of this trial have decided to apply the sequential dosing schedule of midostaurin as used in study CALGB 10603/CTSU C10603 (RATIFY).

The MIDOKIT study design also includes a continuous maintenance phase of single agent PKC412 at 50 mg bid for up to an additional 12 months. Standard therapy of adults with AML does not routinely involve a maintenance phase of chemotherapy after completion of consolidation. However, data in the literature [MRD w/FTL3] suggest that minimal residual disease that can be detected in AML patients with FLT3 mutation predicts rapid relapse once chemotherapy is completed. Thus the continued administration of an oral, non-cytotoxic and well-tolerated drug such as PKC412 post chemotherapy might continue to inhibit growth or even kill residual FLT3 mutated blasts present at the end of a routine course of chemotherapy, potentially further prolonging disease-free survival. The use of targeted agents as maintenance therapy to prolong survival has recently been demonstrated in newly diagnosed Ph+ALL patients. Patient survival is significantly improved compared to historical controls when the anti-bcr/abl drug Glivec/Gleevec is given to Ph+ALL patients throughout therapy, from induction to relapse, including a maintenance phase with Glivec alone post completion of chemotherapy [26].

4 Study Plan

4.1 Study Design

This study is planned as a pilot phase-IIa study for the assessment of efficacy and safety. The trial is a one-arm open-label multicentre study.

4.2 Timetable

Enrolment of first subject (FPFV)*:	1 May 2012
Enrolment of last subject:	30 April 2016
End of trial of last subject (LPLV)*:	31 May 2018
Closing of database:	31 July 2018
Completion of statistical analysis:	01 August 2018
Integrated final report:	30 September 2018
Duration of treatment per subject:	16 months
Planned duration of follow-up	9 months
Planned interim analysis or analyses:	none

*Normally, the start/end of the study is defined as the first/last visit of the first/last subject.

4.3 Study Treatment

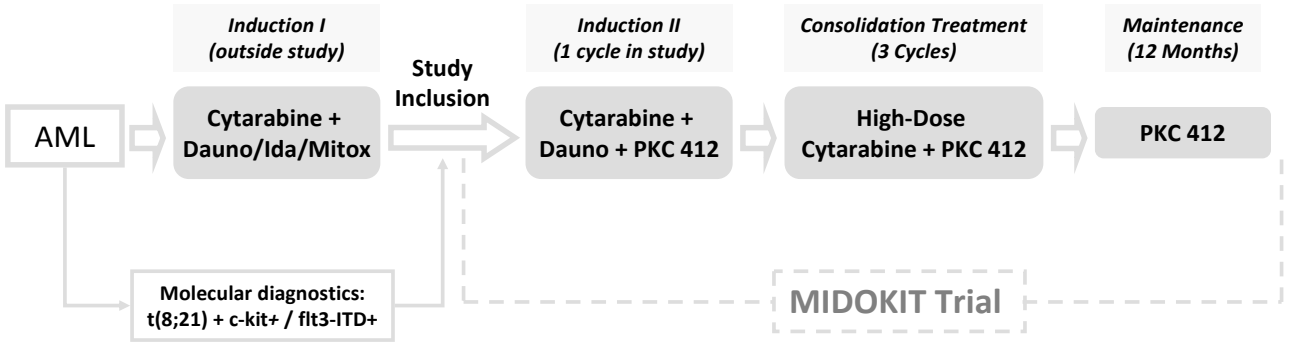
This is a one-arm open-label study, i.e. all included patients will receive the same treatment:

Patients with non-refractory chemo-responsive disease after one cycle of standard 7+3 induction treatment will enter the study before commencing second induction treatment. Standard induction treatment is defined as a seven-day continuous infusion of 100-200 mg/m^2/d plus three doses of daunorubicine, or idarubicine, or mitoxantrone. Chemo-responsive non-refractory disease is defined by reduction of blast count and/or cellularity on the early bone marrow assessment on day 14-16 of the first induction treatment and peripheral blast clearance, i.e. the absence of myeloid blasts in peripheral blood on day 14-16 of the first induction treatment. The first cycle of induction treatment after initial diagnosis is not part of this trial.

After inclusion in the study, patients will receive one cycle of standard DA (days 1-7) in combination with midostaurin treatment (days 8-21). After confirmation of responsive disease and complete remission, patients will continue with three cycles of high-dose cytarabine (HiDAC, days 1, 3, 5) in combination with midostaurin (days 8-21), which shall be administered depending on adequate blood counts and sufficient organ function. After a minimum of 14 days after the last midostaurin application in the last cycle of MidoHiDAC, i.e. earliest on day 36 after the beginning of the last cycle of MidoHiDAC, patients shall commence maintenance treatment. Maintenance treatment consists of 12 cycles with 28 days per cycle, i.e. continuous midostaurin application for a total of 336 days. After a maximum of 12 cycles midostaurin maintenance, patients will be followed up for additional 9 months. If patients stop study treatment or maintenance prematurely, i.e. before having completed 12 cycles of midostaurin maintenance, patients will be followed up until 25 months after study entry.

For details, see section 7

Flow Diagram Study Treatment



4.4 Participating Centres

25 centres are planned in Germany, which must meet the structural and personnel requirements for performing the planned regular study-related investigations. If necessary, additional qualified centres can be included in the performance of the study.

4.5 Number of Study Participants

18 subjects will be enrolled in the study

5 Subject Population and Selection Criteria

5.1 Target Population / Main Diagnosis

Patients diagnosed with a c-KIT and/or FLT3-ITD t(8;21) AML with documented response to standard cytarabine based induction treatment will be treated in this trial.

5.1.1 Gender Distribution

No gender ratio has been stipulated in this study as the results of the preclinical and/or clinical studies did not indicate any difference in the effect of the study treatment in terms of efficacy and safety.

5.2 Inclusion Criteria

- Diagnosis of c-KIT and/or FLT3-ITD mutated t(8;21) AML i.e.
  - >20% myeloid blasts in bone marrow and/or peripheral blood at initial diagnosis
  - Plus cytogenetic diagnosis of aberration t(8;21)/AML1-ETO

    - Plus mutation of c-KIT gene (mut-KIT17 or mut-KIT8) or FLT3-ITD mutation or both c-KIT and FLT3-ITD mutations
- Chemo-responsive disease* as determined by early bone marrow assessment on day 14-16 after first cycle of standard induction therapy with seven-day continuous infusion of 100-200 mg/m^2 cytarabine per day in combination with three doses of daunorubicine, or idarubicine, or mitoxantrone
- Age 18 – 65 years
- Fit for intensive chemotherapy as assessed by
    - Adequate liver and renal function as assessed by the following laboratory requirements to be conducted within 7 days prior to screening:
        - Total bilirubin ≤ 1.5 times the upper limit of normal
        - ALT and AST ≤ 2.5 times upper limit of normal
        - Creatinine ≤ 1.5 times upper limit of normal
    - Adequate cardiac function, i.e. left ventricular ejection fraction (LVEF) of >= 50% as assessed by transthoracal twodimensional echocardiography (“M Mode”) or MUGA scan
- ECOG performance status of 0-2
- Life expectancy of at least 12 weeks
- Subject's written informed consent has been obtained
- Legal capacity (see also exclusion criterion)

* Chemo-responsive non-refractory disease is defined by reduction of blast count and/or cellularity on the early bone marrow assessment on day 14-16 of the first induction treatment and peripheral blast clearance, i.e. the absence of myeloid blasts in peripheral blood on day 14-16 of the first induction treatment.

5.3 Exclusion Criteria

None of the following criteria may be present at the time of registration/screening:

- Primary refractory or previously relapsed AML
- Therapy-related AML after prior radiotherapy or chemotherapy
- Non-eligibility for high-dose cytarabine based consolidation, e.g. intolerance to cytarabine
- Inability to swallow oral medications
- Symptomatic congestive heart failure as defined by left ventricular ejection fraction (LVEF) of ≤50% as assessed by transthoracal twodimensional echocardiography (“M Mode”) or MUGA scan
- Subject without legal capacity who is unable to understand the nature, significance and consequences of the study
- Investigational drug therapy outside of this trial during or within 4 weeks of study entry

- Known or persistent abuse of medication, drugs or alcohol

Women*

- Current pregnancy, nursing period
- Failure to use one of the following safe methods of contraception:
    - Female condoms, diaphragm or coil, each used in combination with spermicides
    - Intra-uterine device
    - Hormonal contraception in combination with a mechanical method of contraception

* Participation of Women

Women can only take part in this study if the risk of becoming pregnant is absolutely minimised. Therefore, only the following conditions are suitable:

— Women who use safe contraception throughout the duration of the study (i.e. from the time of written consent until 4 weeks after the final administration of the study medication) and have a negative pregnancy test one week before study entry
— Surgically sterilised women (tubal ligation, hysterectomy) with a written certificate issued by the treating physician
— Postmenopausal women who have not had a menstrual period for at least 2 years

Women of childbearing potential must be informed during the informed consent procedure that they must not become pregnant during the study (i.e. from the time of written consent until 4 weeks after the final administration of the study medication).

6 Enrolment of Subjects in the Study

6.1 Prerequisites for Enrolment

If a subject appears to be eligible for the study, the investigator will inform the subject or his/her legal representative / authorised agent (for subjects without legal capacity) about the study and ask the subject or the legal representative / authorised agent (for subjects without legal capacity) for his/her written consent (see also section 16/Ethical and Legal Principles).

It is imperative that written consent is obtained prior to any study-specific procedures. The investigator will then record the details of these trial subjects on the lists provided:

- **Enrollment log:** A confidential log of the names of all trial subjects with the identification code* assigned to each subject at the time of enrolment in the clinical trial. With this list, the identity of each subject can be revealed. The list must be kept confidential and must not leave the institution; it

must remain at the study centre and must not be copied or otherwise passed on. Monitors, auditors and representatives of authorities must be allowed to inspect the list on request. The following details will be entered:

* **Subject identification code:** A consecutive number is required for entry in study documents. The acronym MIDOKIT identifies this particular study, the following 3 digits correspond to the number of the centre, the next 2 digits stand for the consecutively screened subjects at the particular centre, for example: MIDOKIT-001-01 (Centre 1, Subject 1).

6.2 Mode of Registration

The subject identification code assigned for the study will be entered on the registration form (“Patientenmeldebogen”) and the questions on inclusion and exclusion criteria on the form (“Checkliste Ein- und Ausschlusskriterien) will be answered. The fully completed form will then be faxed to the SAL central study office (SAL-Studienzentrale Dresden) for registration:

SAL-Studienzentrale

Bereich Klinische Studien der Medizinischen Klinik und Poliklinik I

Universitätsklinikum Carl Gustav Carus, Haus 105

Fetscherstr. 74

01307 Dresden

Fax: +49 (0) 351 / 458 4367

Tel.: +49 (0) 351 / 458 3273

Registration times: Monday to Friday from 8:00 to 16:00

The SAL central study office will review the subject's details on the registration fax. It will then confirm the subject's enrolment in the study by fax. After confirmation, the treatment can be initiated according to the protocol.

6.3 Removal of patients from study

All patients reaching a primary efficacy endpoint of the trial (event) will discontinue study treatment and will be followed up until 25 months after study entry. The following events will lead to discontinuation of study treatment:

- Primary refractory disease, defined as failure to achieve a CR/CRi five weeks after the beginning of the second induction therapy
- Hematological relapse from CR/CRi
- Death from any cause

A patient who withdraws is one who discontinues participation in a clinical study for any reason.
Patients may be withdrawn from the trial for the following reasons:

- At their own request or at the request of their legally acceptable representative
- If, in the investigator's opinion, continuation in the study would be detrimental to the patient's well-being
- At the specific request of the sponsor

Patients must be withdrawn also for the following reasons:

- In case of unacceptable toxicity or progressive disease
- In case of substantial non-compliance with the requirements of the study
- Positive beta-HCG test consistent with pregnancy. Pregnancy will be reported along the same time lines as a serious adverse event
- Use of illicit drugs or other substances that may, in the opinion of the investigator, have a reasonable chance of contributing to toxicity or otherwise skewing results
- Development of an intercurrent illness or situation which would, in the judgment of the investigator, affect assessments of clinical status and study endpoints to a significant degree
- Development of a second cancer that requires treatment
- Patient is lost to follow-up
- Period of > 64 days between the start of the last consolidation cycle and beginning of maintenance treatment
- Interruption in study drug administration for a period longer than 28 consecutive days during maintenance treatment

Relevant visit data will be entered into the CRF, and any unused study medication will be accounted for and returned for all subjects entered into the trial even if for a brief period of time. Subjects who discontinue study treatment will have relevant information completed and recorded in the CRF and medical record. All subjects who discontinue because of adverse events or clinical laboratory abnormalities should be followed up until they recover or stabilize and the subsequent outcome recorded.
In case of premature withdrawal of any cause, all data documented up to the date of withdrawal will be entered into the study analysis.

7 Treatment Plan and Procedure

7.1 Dosage/Dosing Regimen, Drug Administration, and Remission Control

After response to the first cycle of induction treatment has been confirmed in the screening procedures and confirmation for study registration has been given by the SAL central study office, patients will receive one more cycle of induction treatment with MidoDA, followed by a total of three cycles of MidoHiDAC consolidation. Chemo-responsive non-refractory disease is defined by reduction of blast count and/or cellularity on the early bone marrow assessment on day 14-16 of the

first induction treatment and peripheral blast clearance, i.e. the absence of myeloid blasts in peripheral blood on day 14-16 of the first induction treatment. Proof of chemo-responsive, non-refractory disease is required for patient inclusion.

Second cycle of induction: MidoDA

Second induction will commence earliest day 22 after start of the first induction. It is allowed to postpone the second induction course if the patient has an uncontrolled infection or transitory contraindications against chemotherapy. The second course of induction can be started once these problems have been resolved.

MidoDA

Cytarabine	100 mg/m^2 IV over 24 hrs	days 1-7
Daunorubicine	60 mg/m^2 IV over 1 hr	days 3-5
Midostaurin	50 mg/m^2 (2 capsules) p.o. twice daily	days 8-21

Midostaurin 50 mg (two 25 mg capsules) is given twice a day by mouth on days 8-21. Patients should take their doses at approximately the same time each day, and approximately 12 hours should elapse between the morning and evening doses. Each daily dose should be given with food and a glass of water (approx. 240 ml). Patients should be instructed to swallow capsules whole and not chew capsules. If vomiting occurs, no re-dosing is allowed before the next scheduled dose.

For **response assessment**, a bone marrow aspirate (or bone marrow biopsy) must be performed one week after recovery of ANC ≥ 1000/µL and platelets ≥ 100,000/µL to document a complete remission. Remission assessment must be performed latest 35 days after the beginning of second induction, even if ANC or platelets are below the described threshold.

If response assessment shows **< 5%** myeloid blasts, the patient has achieved a CR/CRi and will continue consolidation treatment according to this protocol.

If response assessment reveals **≥ 5%** myeloid blasts, the patient will be classified as primary refractory disease and will discontinue study treatment. Patients who discontinue study treatment will be followed up until 25 months after study entry.

At each bone marrow aspiration, material should be obtained and sent to the central SAL laboratory in Dresden for MRD diagnostics (see section 7.4).

Consolidation treatment: MidoHiDAC

Each consolidation cycle is four weeks in duration, and should begin within two weeks following hematologic recovery (ANC ≥ 1000/µL and platelet count ≥ 50.000/µL), but not sooner than four weeks from the beginning of the previous cycle. If a consolidation cycle is delayed >8 weeks from

the start of the previous course of induction or consolidation due to slow resolution of toxicity or slow recovery of complete blood counts (CBC), please contact the SAL central study office.

MidoHiDAC

Cytarabine	3000 mg/m^2 IV over 3 hrs twice daily	days 1,3,5
Midostaurin	50 mg (2 capsules) p.o. twice daily	days 8-21

High-dose cytarabine (HiDAC) 3000 mg/m^2 will be given by intravenous infusion over 3 hours every 12 hours on days 1, 3, and 5. Serial neurologic evaluation will be performed before and following the infusion of high-dose cytarabine.

It is recommended to administer dexamethasone 0.1% or other corticosteroid ophthalmic solution 2 drops to each eye four times per day to begin 6-12 hours prior to the initiation of the cytarabine infusion and to continue for at least 24 hours after the last cytarbine dose.

Midostaurin 50 mg (two 25 mg capsules) is given twice a day by mouth on days 8-21. Midostaurin is not given from day 22 of the current cycle and day 7 of the next consolidation cycle. Patients should take their doses at approximately the same time each day, and approximately 12 hours should elapse between the morning and evening doses. Each daily dose should be given with food and a glass of water (approx. 240 ml). Patients should be instructed to swallow capsules whole and not chew capsules. If vomiting occurs, no re-dosing is allowed before the next scheduled dose.

For **remission assessment**, a bone marrow aspirate (or bone marrow biopsy) must be performed one week after recovery of ANC ≥ 1000/µL and platelets ≥ 100,000/µL to document a complete remission. Remission assessment must be performed latest 35 days after the beginning of each consolidation cycle, even if ANC or platelets are below the described threshold.

If remission assessment shows **< 5%** myeloid blasts, the patient has a sustained CR/CRi and will continue treatment according to this protocol.

If remission assessment reveals **≥ 5%** myeloid blasts, the patient has a relapse from CR/CRi and will discontinue study treatment. Patients who discontinue study treatment will be followed up until 25 months after study entry.

At each bone marrow aspiration, material should be obtained and sent to the central SAL laboratory in Dresden for MRD diagnostics (see section 7.4).

Three cycles of MidoHiDAC shall be administered depending on adequate blood counts and sufficient organ function.

Midostaurin maintenance

Patients who continue in complete remission (by bone marrow aspiration and blood evaluation) after three cycles of consolidation therapy will receive midostaurin maintenance therapy. If, in the opinion of the investigator, the clinical condition of a patient does not allow a third cycle of MidoHiDAC, the SAL central study office should be contacted for medical advise. If the LKP agrees that the risk of serious adverse events is too high in case of a third MidoHiDAC application, midostaurin maintenance may commence after two cycles of MidoHiDAC.

Prior to initiation of midostaurin maintenance therapy, all significant acute toxicity from consolidation therapy must have resolved to grade 2. Maintenance will begin after hematologic recovery (ANC ≥ 1000/ µL, platelet count ≥50,000/µL) from remission consolidation and no sooner than 14 days after the last midostaurin application in the last cycle of MidoHiDAC, i.e. earliest on day 36 after the beginning of the last cycle of MidoHiDAC. Maintenance treatment must be started before day 64 after the beginning of the last cycle of MidoHiDAC, i.e. patients who cannot start maintenance treatment until 64 days after the beginning of the last cycle of MidoHiDAC will stop study treatment and will be followed up until 25 months after study entry.

Maintenance treatment consists of continuous midostaurin application for 12 cycles with 28 days per cycle:

Midostaurin	50 mg (2 capsules) p.o. twice daily	days 1-28

Start of new maintenance cycle on day 29

Midostaurin 50 mg (two 25 mg capsules) is given twice a day by mouth on days 1-28. Patients should take their doses at approximately the same time each day, and approximately 12 hours should elapse between the morning and evening doses. Each daily dose should be given with food and a glass of water (approx. 240 ml). Patients should be instructed to swallow capsules whole and not chew capsules. If vomiting occurs, no re-dosing is allowed before the next scheduled dose.

For **remission assessment**, a bone marrow aspirate (or bone marrow biopsy) must be performed every three months during maintenance treatment and during follow up including the end-of-study visit 9 months after the end of the 12-month-maintenance period or 25 months after study entry in case of premature discontinuation of study treatment. At each bone marrow aspiration, material should be obtained and sent to the central SAL laboratory in Dresden for MRD diagnostics (see section 7.4).

A suspected relapse during the entire study duration must be confirmed by bone marrow aspiration or biopsy.

Patient follow-up after treatment termination

After a maximum of 12 cycles midostaurin maintenance, patients will be followed up for additional 9 months. If patients stop study treatment or maintenance prematurely, i.e. before having completed 12 cycles of midostaurin maintenance, patients will be followed up until 25 months after study entry.

7.2 Dose Modifications

7.2.1 Midostaurin Dose Modifications

7.2.1.1 Midostaurin induction and consolidation therapy dose modifications for hematologic toxicity

There will be no dose modifications for hematologic toxicity due to midostaurin during induction and consolidation therapy.

7.2.1.2 Midostaurin induction and consolidation therapy dose modifications for non-hematologic toxicity

There will be no dose modifications for any grade 1 or 2 non-hematologic toxicity.

Cardiac Toxicity

- For QTc interval >450 msecs and ≤ 470 msecs, check magnesium and potassium levels and correct any abnormalities. If possible, stop any medications that may prolong the QTc interval. Continue midostaurin at the same dose.
- For QTc interval > 470 msecs and ≤ 500 msecs, check magnesium and potassium levels and correct any abnormalities. If possible, stop any medications that may prolong the QTc interval. Decrease midostaurin to 50 mg once daily for the remainder of the cycle. Resume midostaurin at the initial dose in the next cycle provided that QTc interval improves to ≤ 470 msecs at the start of that cycle. Otherwise continue midostaurin 50 mg once daily.
- For QTc interval > 500 msecs, check magnesium and potassium levels and correct any abnormalities. Hold or interrupt midostaurin for the remainder of the cycle, and, if possible, stop any medications that may prolong the QTc interval. If QTc improves to ≤ 470 msecs just prior to the next cycle, resume midostaurin at the initial dose. If QTc interval is not improved in time to start the next cycle do not administer midostaurin during that cycle. Midostaurin may be held for as many cycles as necessary until QTc improves.
- Missed doses of midostaurin will not be made up.

Pulmonary Toxicity

- For ≥ grade 3 pulmonary infiltrate, interrupt midostaurin for the remainder of the cycle. Resume midostaurin at the same dose when infiltrate resolves to ≤ grade 1.

- Missed doses of midostaurin will not be made up.

Other Non-Hematologic Toxicity

If a patient experiences other grade 3 / 4 non-hematologic toxicity considered at least possibly related to midostaurin, the midostaurin will be interrupted until toxicity resolves to ≤ grade 1. If the toxicity resolves prior to day 21, then restart at same dose to complete current cycle. Missed doses of midostaurin will not be made up.

7.2.1.3 Midostaurin dose modifications for hematologic toxicity during maintenance treatment

In the presence of grade 4 neutropenia during continuation therapy, midostaurin must be held until ANC ≥ 1000/µL. Once ANC ≥ 1000/µL, then resume midostaurin at the previous dose. If neutropenia persists for more than two weeks, then discontinue midostaurin protocol therapy.

7.2.1.4 Midostaurin therapy dose modifications for non-hematologic toxicity during maintenance

Cardiac Toxicity

- For QTc interval >450 msecs and ≤ 470 msecs, check magnesium and potassium levels and correct any abnormalities. If possible, stop any medications that may prolong the QTc interval. Continue midostaurin at the same dose.
- For QTc interval > 470 msecs and ≤ 500 msecs, check magnesium and potassium levels and correct any abnormalities. If possible, stop any medications that may prolong the QTc interval. Decrease midostaurin to 50 mg once daily for the remainder of the cycle. Resume midostaurin at the initial dose in the next cycle provided that QTc interval improves to ≤ 470 msecs at the start of that cycle. Otherwise continue midostaurin 50 mg once daily.
- For QTc interval > 500 msecs, check magnesium and potassium levels and correct any abnormalities. Hold or interrupt midostaurin for the remainder of the cycle, and, if possible, stop any medications that may prolong the QTc interval. If QTc improves to ≤ 470 msecs just prior to the next cycle, resume midostaurin at the initial dose. If QTc interval is not improved in time to start the next cycle do not administer midostaurin during that cycle. Midostaurin may be held for as many cycles as necessary until QTc improves.
- Missed doses of midostaurin will not be made up.
- Dose modifications for QTc are for the remainder of the cycle.

Pulmonary Toxicity

- For ≥ grade 3 pulmonary infiltrate, interrupt midostaurin for the remainder of the cycle. Resume midostaurin at the same dose when infiltrate resolves to ≤ grade 1.
- Missed doses of midostaurin will not be made up.

Other Grade 3 / 4 Non-Hematologic Toxicity

- For other grade 3 / 4 non-hematologic toxicities that are considered to be at least possibly related to midostaurin, interrupt midostaurin. Resume midostaurin at the same dose when toxicity resolves to ≤ grade 2. If midostaurin is held for more than 28 days, then discontinue midostaurin continuation therapy.
- Missed doses of midostaurin will not be made up.

Other Grade 1 / 2 Non-Hematologic Toxicity

- Persistent grade 1 or 2 toxicity during continuation therapy that patients may deem unacceptable may prompt a drug holiday for as many as 28 days. No drug holidays longer than 28 consecutive days will be allowed.
- Missed doses of midostaurin will not be made up.

Daunorubicin Cardiac Toxicity Dose Modifications

Daunorubicin should not be given in case of case any of the following symptoms have a possible relationship according to the investigator's judgement:

- Symptoms of heart failure
- Reduction of the left ventricular ejection fraction below 50%
- Superventricular arrhythmias and/or morphologic changes in the ST period or T wave or low voltage in QRS or prolongation of QT interval

7.2.2 High-Dose Cytarabin Consolidation Therapy Dose Modifications

Contributions of concomitant medications to neurotoxicity should be assessed and other medications discontinued if possible.

For neurotoxicity ≥ grade 2 due to high-dose cytarabine during consolidation therapy, discontinue high-dose cytarabine for the remainder of the cycle. High-dose cytarabine may be considered at the next consolidation therapy cycle with a dose modification from 3 g/m^2 to 2 g/m^2 if the toxicity has resolved to ≤ grade 1.

For a second occurrence of neurotoxicity ≥ grade 2, high-dose cytarabine should be permanently discontinued.

7.2.3 Dose Modifications for Obese Patients

There is no clearly documented adverse impact of treatment of obese patients when dosing is performed according to actual body weight. Therefore, all dosing is to be determined solely by the patient's BSA as calculated from actual weight. This will eliminate the risk of calculation error and the

possible introduction of variability in dose administration. Failure to use actual body weight in the calculation of drug dosages will be considered a major protocol deviation. Physicians who are uncomfortable with administering chemotherapy dose based on actual body weight should not enrol obese patients.

7.3 Concomitant Treatment/Medication

There is no restriction for any medically necessary concomitant treatments or medications. Physicians should be aware that midostaurin is a competitive inhibitor of CYP3A4/5. Studies also show CYP3A4 is the major human p450 enzyme catalyzing biotransformation of midostaurin. Thus, co-administration of drugs which are potent inducers (e.g. phenytoin) or, especially, potent inhibitors (e.g. itraconazole) of this isoenzyme could decrease or increase midostaurin concentrations, and, potentially, decrease the effectiveness or increase toxicity, respectively. A list of agents that may have potential drug interactions is given in appendix 2.

7.4 Study Evaluations

	Screening examination within 7 days before study entry	Day 1of 2nd induction and Day 1 of each consolidation	Day 1-28 of 2nd induction and each consolidation	Remission control†	Start maintenance	During maintenance	Within 14 days after end of maintenance	Follow-up 3, 6+9 months after end of maintenance	Relapse
Screening Examination	X								
Check In- and Exclusion Criteria	X								
Registration	X								
Toxicity Assessment (AE)			X		X				
Toxicity Assessment (SAE)			X		X	Monthly	X	X	
Physical Examination incl. blood pressure, pulse and weight	X	X			X	monthly	X	X	
CBC (incl. differential and plts)	X	X	2x/week	X	X	monthly	X	X	X
Chemistry and Coagulation: Na, K, Ca, Crea, Mg, Urea, ALAT, ASAT, AP, Bili, Total Protein, Albumin, Uric Acid, Glucose, INR, PTT, Fib	X	X	2x/week		X	monthly	X	X	X
fT4, TSH	X								
Urinalysis	X								
Bone marrow cytology	X			X		Q 3 months *		X	X
Bone marrow cytogenetics	X			X		Q 3 months *		X	X
Bone marrow molecular genetics	X			X		Q 3 months *		X	X
EKG (QTc Interval)	X	X	**		**	**			
Chest X-Ray (pa and lateral)	X								
Echocardiography (LVEF)	X								
Beta-HCG pregnancy test	X								
Concomitant Medication			X			X			

† latest day 35 after beginning of each course of chemotherapy
* and in case of suspected or overt relapse for confirmation
** days 1,3,14 of midostaurin during induction 2 and each cycle of consolidation (days 8,10,21 of induction 2 and consolidation) and monthly during maintenance

Molecular and cytogenetic analyses will be done in the central SAL reference laboratory. With each bone marrow aspiration, material for central MRD diagnostics should be obtained and sent to the following address:

Universitätsklinikum Carl Gustav Carus, Medizinische Klinik und Poliklinik I, Hämatologisches Labor Haus 65 a, Fetscherstr. 74, 01307 Dresden, Tel.: 0351/ 458-4251, Fax: 0351/ 458-4367.

For information on results, please contact Prof. Dr. C. Thiede, Tel.: 0351/ 458-5628.

8 Investigational medicinal product: Midostaurin (PKC 412)

8.1 Description of the Investigational medicinal product

The study drug provided is midostaurin 25 mg. The study drug will be supplied by Novartis as soft gelatine capsules, packaged in child-resistant blisters. See Investigator's Brochure for further characteristics, mechanism of action, preclinical activity, side-effects, pharmacokinetics and Phase I studies and results of clinical trials.

8.2 Packaging and Labelling

Novartis is responsible for packaging, labelling, and shipping of study medication via the Drug Distribution Centre. Each blister contains eight (8) capsules and each medication kit contains eight (8) blisters for a total of sixty-four (64) capsules per kit. Each patient shipment will consist of 4 medication kits. Each kit has a 2-part label which looks like this:

labelling: medication kit	Sponsor: TU Dresden, 01062 Dresden, Tel. +49 351 458-4190 CPKC412ADE01T / TUD-MIDOKI-052 EudraCT-Nr. 2011-002567-17 Pat.-Nr. : _____ PKC412 25 mg 8 x 8 Kapseln zum Einnehmen Nach Vorschrift Ihres Arztes einnehmen zwischen 2 und 8 °C lagern Bei einer Lagerung bei Raumtemperatur (nicht über 25°C) innerhalb von 3 Monaten anzuwenden verwendbar bis: MM/YYYY Ch.-B.: XXXX Zur klinischen Prüfung bestimmt Arzneimittel für Kinder unzugänglich aufbewahren Zur Verfügung gestellt von: Novartis Pharma GmbH, D-90327 Nürnberg

labelling: blister	Sponsor: Prof. Dr. G. Ehninger, Universitätsklinikum an der TU Dresden, 01307 Dresden CPKC412ADE01T / TUD-MIDOKI-052 Pat.-Nr. : _____ PKC412 25 mg 8 Kapseln zum Einnehmen Ch.-B.: XXXX Zur klinischen Prüfung bestimmt Zur Verfügung gestellt von: Novartis Pharma GmbH, D-90327 Nürnberg

8.3 Provision, Storage and Dispensing

There will be a central drug distribution by Novartis. Sites are responsible for contacting the Drug Distribution Center to order study drug for individual patients included in this clinical trial. The amount of drug to be requested per shipment is 4 medication kits.

Ordering:

There are no starter supplies. Midostaurin supplies are patient specific. Sites will complete the Drug Request Form available in the ISF, checking the “initial supply” or “resupply” box. The form will be faxed to Novartis, Germany:

Trial Coordinator Novartis Germany

Fax: +49 911 27317 121 (computer fax)

The faxes may be received during regular business hours, Monday-Friday 08:00 am – 05:00 pm.

Storage and Dispensing:

Blister packs should be stored under refrigeration at 2-8°C and protected from light. After dispensing to the patient, midostaurin may be stored at home at room temperature (below 25°C) for as long as three months. Please note that each box of 8 blisters measures 194 mm x 122 mm x 65 mm. Upon opening a blister pack, patients may notice a pungent odor. The odor is due to ethyl thioglycolate that forms when ethanol in the capsules interacts with the thermostabilizer in the foil. The capsules are not affected, and the odor will dissipate.

The investigator will be responsible for ensuring the correct storage and sufficient stocks of the investigational medicinal product at the centre. Where allowed/required, the investigator may/should entrust the investigational medicinal product, in whole or in part, to an appropriate pharmacist (to be designated in advance) or another appropriate individual who is under the supervision of the investigator.

The investigator or a pharmacist, or another appropriate individual who is designated by the investigator, should maintain records of the delivery of the investigational medicinal product, the stocks at the study centre, the use by the individual trial subjects, and the return of unused investigational medicinal products to the sponsor or their disposal. The investigator should ensure that the investigational medicinal product is only used according to this protocol.

- The investigator bears the responsibility for the proper storage in an appropriate place to which unauthorised persons have no access.
- The investigator may only dispense the investigational medicinal product to subjects who have been enrolled in the study. The dispensing of the investigational medicinal product to subjects outside of this clinical trial is not permitted.
- The investigator, or an individual who is designated by the investigator, should explain the correct use of the investigational medicinal product to each trial subject and check at regular intervals that each subject is following the instructions correctly.

8.3.1 Investigational medicinal product Stock Lists (Drug Accountability)

The investigator/pharmacist, or another appropriate individual who is designated by the investigator, should maintain records of the stocks of the investigational medicinal product or its disposal.

- Each delivery will be documented in writing on the forms provided and the forms will be returned to the Drug Distribution Center stated as an acknowledgement of receipt.
- Complete documentation of the whereabouts of the investigational medicinal product (incoming/outgoing) on appropriate forms is mandatory. These records should include dates, quantities, batch numbers, expiry dates (if applicable) and the unique code numbers assigned to the investigational medicinal product and the trial subjects. The investigator should maintain records that document adequately that the subjects received the doses specified by the protocol. These records should be checked against all delivery notes received from Novartis.
- Reasons must be given for stock deficiencies.
- The Investigator is responsible for destroying any unused, partially used and empty investigational medicinal product after the clinical monitor has approved the drug accountability logs. This process should be documented appropriately. A confirmation of the destruction will be sent to the Drug Distribution Center.
- The patients should only receive two medication kits at a time.
- The patients should document the administration of the study drug in a patient diary which will be provided from the sponsor.

8.4 Route of Administration Toxicities and Drug Interactions

8.4.1 Route of Administration

Midostaurin will be administered orally twice daily according to the schedule in the Treatment Plan. Patients should take their daily dose at approximately the same time each day, and separated by approximately 12 hours between the morning and evening doses. Each daily dose should be given with food and a glass of water (approx. 240 ml).

8.4.2 Toxicities

When given as a single agent, doses of up to 300 mg per day (100 mg three times a day) of midostaurin have been used. A dose of 225 mg per day (75 mg three times a day) was originally selected for phase II studies. The adverse events most frequently reported and considered related to midostaurin were nausea, vomiting, and fatigue. In most cases vomiting occurred within an hour of taking midostaurin and subsided when treatment was withdrawn. Treatment with antiemetics was tried with variable success. Other adverse events commonly reported and suspected to be related to midostaurin include headache, and diarrhea. Serious adverse events considered related to midostaurin included diarrhea, vomiting, nausea, anorexia, anemia, leukopenia, elevated liver transaminase levels, and pulmonary edema.

The tolerability (MTD) of midostaurin in combination with chemotherapy is somewhat lower than that seen with single agent midostaurin due to additive toxicity of nausea and vomiting in the combination regimens.

Reversible elevations in transaminases and bilirubin have been reported with midostaurin, including at least three patients with grade 3 elevations at the 50 mg BID dose. To date, there have been no associated pathological changes reported. Transient increase in serum amylase of unknown significance has been observed in four oncology patients. Rash (grad 3 / 4) also was reported in at least one patient.

Pulmonary toxicity including fatal pulmonary events have been described in patients receiving midostaurin. It hast been suggested that pulmonary toxicity may be associated with co-administration of azole antifungal drugs and resultant inhibition of CYP3A4.

Two cases of hyperthyroidism were reported as serious adverse events in two patients treated with midostaurin in combination with imatinib for imatinib-resistant gastrointestinal tumors (GIST). Additionally, there were two adverse events of grade 1 and grade 2 hyperthyroidism as well as six events of asymptomatic thyroid function test lab changes reported in the same study. It is felt that theses events were possibly related to the combination study medication although the mechanism

is not clear. To date, trials with midostaurin monotherapy have not yielded any reports of hyperthyroidism or similarly mentioned thyroid function test abnormalities.

8.4.3 Drug interactions

Midostaurin is metabolized by CYP3A4 to active compounds. As described in section 7.3, potent CYP3A4 inhibitors are thought to represent the most significant potential for drug interactions with midostaurin.

9 Endpoints for the Assessment of Efficacy and Safety

9.1 Efficacy

As pointed out in section 2.1, the reduction of overall survival in patients with c-KITmut is mainly due to a higher incidence of relapses while in FLT3-ITD patients, primary resistant disease leads to the inferior prognosis during the early course of the disease. Since the patient group in this trial consists both of c-KITmut and FLT3-ITD patients, event-free survival seems to be the measure to capture both early treatment failure in FLT3-ITD and later relapse from CR in c-KITmut patients. Therefore, the primary study endpoint will be the event-free-survival (EFS) rate at 2 years. Event-free survival will be defined as the time from inclusion in the study (date of signed informed consent) until either failure to achieve a CR/CRi five weeks after the beginning of the second induction therapy course), or hematological relapse from CR/CRi, or death from any cause. Revised IWG criteria will be used [17].

9.1.1 Complete Remission (CR):

Complete remission is defined as the presence of all of the following:

Peripheral Blood Counts

- Absolute neutrophil count ≥1000/µL.
- Platelet count ≥ 100,000/µL.
- No leukemic blasts in the peripheral blood.
- Transfusion independence for red cells and platelets.

Bone Marrow

- Adequate cellularity for assessment with maturation of all cell lines.
- No Auer rods.
- < 5% blast cells.

No extramedullary leukemia (such as CNS or soft tissue involvement),

9.1.2 Complete Response with incomplete blood count recovery (CRi):

CRi satisfies all CR criteria except platelet counts are < 100,000/µL or ANC < 1,000/µL

9.1.3 Relapse

Any of the following, occurring after either CR or (CRi):

- The reappearance of circulating blast cells on more than one determination
- >5% AML blasts in the bone marrow, not attributable no another cause (e.g. bone marrow regeneration). If there are no circulating blasts, but the marrow contains 5%-20% blasts, a repeat marrow ≥ 1 week later with >5% blasts is necessary to meet the criteria for relapse.
- Development of extramedullary leukemia

9.2 Safety

Laboratory:

The following laboratory parameters will be used for the assessment of safety:

- Complete blood counts (CBC)
- Chemistry and Coagulation
- Urinalysis

Clinical:

- Clinical examination including
- blood pressure
- pulse

ECG and Echocardiography

The ECG recordings for the assessment of safety will be performed as 12-lead standard ECGs. Echocardiography assessment will be done for the determination of LVEF in M-Mode technique.

Further safety examinations

A regular toxicity assessment will be obtained as outlined in the study evaluations (7.4) and in chapter 10. Furthermore, the primary endpoint of this trial, event-free survival is a combined efficacy and safety endpoint and will therefore also be used for the assessment of safety. .

10 Handling of Adverse Events (AEs)

10.1 Definition/Documentation of (Serious) Adverse Events

10.1.1 Definition and Documentation of AEs

An adverse event (AE) is any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and which does not necessarily have a causal

relationship with this treatment. An AE can therefore be any unfavourable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not related to the medicinal (investigational) product. In this context it must be especially stressed that any change in laboratory findings or vital functions, which leads to the discontinuation of the subject's treatment with the investigational medicinal product or to the termination of the clinical trial, must always be documented as an AE.

The investigator will monitor the development of adverse clinical events or pathological laboratory findings until recovery or stabilisation of the subject's condition.

Irrespective of any causal relationship, all adverse events spontaneously reported by the subject or observed by the investigator will be continuously documented in the medical record and on the designated case report form (AE form) during the clinical trial/at each follow-up visit. AEs will be documented from the first administration of study drug up to 30 days after the last administration. Classification of AEs will be done according to the CTC-AE classification, Version 3.0. Suspected relationship of between the AE and the study drug midostaurin or daunorubicin or cytarabine will be documented by the investigator.

10.1.2 Definition and Documentation of SAEs

A **Serious Adverse Event (SAE)** is any untoward medical occurrence that:

- results in the death of the subject,
- is life-threatening,
- requires inpatient hospitalisation of the trial subject or prolongation of existing hospitalisation,
- results in persistent or significant disability/incapacity, or
- is a congenital anomaly/birth defect.

Other conditions which, in the investigator's opinion, may not be immediately life-threatening or result in hospitalisation, but may jeopardise the subject’s safety or may require intervention to prevent one of the other outcomes listed in the definition above, may also be considered serious. Examples of such conditions include: Allergic bronchospasm requiring treatment in an emergency room or at home; Unexpected convulsions (i.e. convulsions which cannot be explained by the underlying illness) that do not result in hospitalisation; Development of drug dependency or drug abuse, etc.

Documentation

All serious AEs (with the exception of the special situation described below) that occur during the study *or within 30 days* after the end of the subject's participation in the study will be documented on the SAE report form provided and the form will be passed on as described in the section below. The

end of the subject's participation in the study is defined as the end of follow up = the end-of-study visit.

10.2 Reporting Requirements for SAEs

10.2.1 Investigator Requirements for Reporting SAEs

All SAEs must be reported by fax to the following address within 24 hours after knowledge:

MIDOKIT-Safety Desk
SAL-Studienzentrale
Fetscherstr. 74
01307 Dresden
Fax: 0351 458 4367
Tel. 0351 458 5222

10.2.2 Sponsor Requirements for Reporting SAEs

SUSARs:

The sponsor's expedited reporting requirements are particularly relevant to suspected unexpected serious adverse reactions (SUSARs). The definition is a combination of the definitions of serious adverse reaction (adverse reaction that results in death, is life-threatening, requires insubject hospitalisation or prolongation of hospitalisation, results in persistent or significant disability/incapacity, causes congenital anomaly/birth defect) and unexpected adverse reaction (an adverse reaction, the nature or severity of which is not consistent with the applicable product information for the investigational medicinal product).

Reporting Requirements:

The sponsor's reporting requirements are divided into **expedited** reporting and reporting that must be performed on request or annually. The sponsor's expedited reporting requirements comprise the following:

- All SUSARs must be reported within 15 days after knowledge (section 13, para. 2 GCP-V),
- All SUSARs that are life-threatening or result in death must be reported within 7 days after knowledge (section 13, para. 3 GCP-V),
- All circumstances requiring a review of the benefit/risk evaluation of the investigational medicinal product must be reported within 15 days after knowledge (e.g. expected serious adverse reaction with unexpected outcome, increased incidence of expected serious adverse reactions, SUSARs after the end of the subject's participation in the clinical trial, events in

connection with the study conduct or the development of the investigational medicinal product which may affect the safety of the trial subjects) (section 13, para. 4 GCP-V).

Study specific reporting exceptions:

Leukemia-associated serious adverse events are excluded from expedited reporting on this protocol, but must be documented in the source data and the CRF. The events excluded from the time lines of expedited reporting are:

- fever resulting from AML progression
- infections resulting from AML progression
- bleeding resulting from AML progression
- hospitalization resulting from AML progression

AML progression is defined by re-appereance of peripheral blood blasts or appereance/ re-appereance of chloromas or an increase in the BM blast count.

The following signs of hematotoxicity/ myelosuppression are intended and expected events during treatment of AML, do therefore not fulfil criteria of adverse events and do not need to be documented as AEs or SAEs:

- leukopenia
- thrombocytopenia
- anemia.

Myelosuppression-associated complications and related hospitalizations must be reported on appropriate pages of the CRF as an adverse event but are excluded from expedited reporting. These complications are:

- fever and infections resulting from leukopenia between the start of each cycle of chemotherapy and day 39 from start
- bleeding resulting from thrombopenia between the start of each cycle of chemotherapy and day 39 from start

In this context only prolonged myelosuppression, i.e. pancytopenia with marrow hypocellularity on day 40 or later from start of last cytotoxic therapy without evidence of leukemia, will require immediate reporting on an SAE form.

Annual Safety Report (ASR):

In addition to the expedited reporting, the sponsor shall submit an annual report **once a year** or on request throughout the clinical trial period, according to section 13, para. 6 GCP-V.

11 Documentation

It is the reasonability of the investigator to perform the clinical study in accordance with the GCP guidelines, the AMG, and the clinical study protocol. All data have to be recorded correctly in the

CRF by authorized persons only. This also includes data of persons that were excluded from the clinical study.

The investigator records the participation of a person at the Participant Identification Log (PIL). This list is meant to identify participating persons at a later point of time. It includes the complete name, the date of birth, and the date of inclusion into the clinical study. The PIL remains in the study centre after the study is finished. In addition, participation in the clinical study has to be recorded in the patient's chart (including study medication, participant number/randomization number, start and end of the clinical study).

It has to be ensured that the person responsible for documentation in the CRF can be identified. Therefore, a list with signatures and abbreviations (site signature log) is kept in the ISF and in the TMF.

11.1 Case report form (CRF)

All data of the participants have to be recorded in the Case Report Forms exclusively designed for the study.

The Case Report Forms are to be filled in only with a **black ballpoint pen**. Corrections are to be conducted in a way, that the original entry stays visible (the use of correcting fluids is not allowed). Corrections have to be signed and dated by the authorized person that has carried them out. Data, that are not available or have not been collected, have to be clearly identified as such (NA or ND). If necessary the reasons should be documented.

The Investigator is responsible for all data of the participant to be documented in the case report form immediately, readably, correctly and according to the patient's chart.

When plausibility and completeness of the CRFs have been verified by the monitor, the original CRFs are sent to SAL-Studienzentrale, a copy stays at the site and has to be stored for 10 years.

11.2 Investigator Site File

The SAL-Studienzentrale Dresden provides the Investigator Site File to the study centre. The ISF includes all documents that are required for the clinical study. During monitoring, the ISF will be checked regularly for completeness and actuality. After the clinical trial is finished or stopped, the ISF has to be stored for 15 years.

11.3 Data Storage

11.3.1 Responsibilities of the Sponsor

As required by law, all important study documents have to be stored by the sponsor for at least 10 years after the clinical trial was finished or stopped.

11.3.2 Responsibilities of the Investigator

All documents that are related to the clinical study and to the distribution of the study medication (e.g. CRFs, written informed consent forms, study medication lists and other relevant material) have to be stored for at least 10 years.

Source data like patients' charts, laboratory analyses, and other original data have to be stored for the longest possible time that is usual practice at the investigator's site.

11.4 Data entry and data management

Data management is performed by SAL-Studienzentrale by means of study software MACRO 3.0. Data are proven by programmed range checks, validity checks, and consistency checks. In addition, a manual/visual data check for medicinal plausibility is done according to GCP guidelines. There might be discrepancies that are to be clarified by means of special forms sent to the investigator's site.

After being filled in by the investigator the query forms are sent back to the data management, where the discrepancies are corrected in the data bank. The query forms are stored together with the CRFs both at the investigator's site and at the data management site.

After the study is finished and before data are analysed, a blinded meeting will be held between the sponsor and statistician. When the database has been declared to be complete and accurate, it will be locked. This procedure has to be documented.

12 Quality Assurance System

During the clinical trial, quality control and quality assurance will be ensured through monitoring, auditing and supervision by the authorities.

12.1 Quality Control (Monitoring)

The study will be monitored to verify that

- the rights and well-being of the trial subjects are protected,
- the reported trial data are accurate, complete and verifiable from source documents.
- the conduct of the clinical trial is in compliance with the currently approved protocol / the currently approved protocol amendment(s), with ICH-GCP and with applicable regulatory requirements.

The investigator will grant the monitor access to the subjects' personal medical records for the verification of the proper documentation of study data. The provisions of the Federal Data Protection Act will be fully observed (the monitor is bound by medical secrecy when comparing the CRFs with the source documents).

All investigators agree that the monitor will visit the centre during and after completion of the study. The investigator must allow sufficient time for these visits, alternatively the monitor may be provided with other trained staff (e.g. so-called co-investigators) for assistance during the visits. The investigator will grant the monitor access to the source documents for the fulfilment of his/her duty.

A monitoring report will be written on each visit. This will document the progress of the clinical trial and give an account of all problems that occurred (e.g. refusal of inspection).

12.2 Source Data Verification (SDV)

Source data verification will be performed in order to verify the accuracy and completeness of the entries on the case report form (CRF) by comparing them with the source data, and to ensure and increase the quality of the data. All data which are subject to SDV must have been entered in the medical record or, in the case of source documents, enclosed with the medical record. The investigators will afford the CRA access to the medical records for the performance of SDV.

Source data as defined by ICH-GCP include data such as hospital records, clinical and office charts, laboratory notes, memoranda, subjects' diaries or evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, copies or transcriptions certified after verification as being accurate copies, microfiches, photographic negatives, microfilm or magnetic media, x-rays, and records kept at the pharmacy, at the laboratories and at medico-technical departments involved in the clinical trial.

12.3 Quality Assurance (Auditing)

According to the ICH-GCP guidelines, audits may be performed according to a quality assurance system. These may be conducted by the sponsor.

13 Biostatistical Planning and Analysis

13.1 Study Design

This trial is designed as a single arm multicentre phase IIa study. The results of the primary endpoint will be compared with historical data from patients with same clinical characteristics. See also section 2.1. The main reason for a one-arm non-randomised design is the rarity of the disease which would cause a very long accrual period in case of a two-arm randomised design. Since the prognosis of the targeted patient population is considerably reduced by the c-KIT or FLT3 mutations, results on midostaurin efficacy should be available within a time period under 10 years. Given the fact that there are various available publications on historical cohorts, it seems justifiable to set up a single-arm study.

13.2 Target Variable/Endpoints

13.2.1 Primary Target Variable

As pointed out in section 2.1, the reduction of overall survival in patients with c-KITmut is mainly due to a higher incidence of relapses while in FLT3-ITD patients, primary resistant disease leads to the inferior prognosis during the early course of the disease. Since the patient group in this trial consists both of c-KITmut and FLT3-ITD patients, event-free survival seems to be the measure to capture both early treatment failure in FLT3-ITD and later relapse from CR in c-KITmut patients. Therefore, the primary study endpoint will be event-free survival (EFS).

Event-free survival rate at 2 years is defined as the time from study inclusion (date of informed consent) until either primary treatment failure or hematologic relapse or death from any cause occurs. Primary treatment failure is defined as the absence of CR/CRi five weeks (35 days) after the start of MidoDA induction treatment.

13.2.2 Secondary Target Variables

- Overall survival = Time from study inclusion (date of informed consent) until death from any cause occurs
- Relapse-free survival = time from documented CR until either relapse or death from any cause, whichever event occurs first
- Time to relapse = Time from study inclusion (date of informed consent) until hematologic relapse
- Toxicity = incidence of AEs
- MRD kinetics = quantitative values of molecular or flow-cytometric disease markers over time

13.3 Sample Size Calculation

The primary endpoint is a binary variable indicating event-free-survival at 2 years. The reference 2-year-EFS rate was obtained from data of the SAL study group including 104 patients with t(8;21). Of the 104 patients, 78 did neither display FLT3-ITD nor c-KITmut. Eight patients were FLT3-ITD positive and 18 patients displayed a c-KIT mutation.

Reference 2-year-EFS rate of a historical cohort: $p0 = 0.5$

Success rate of interest: $p1 = 0.8$

Difference between reference and success rate of interest: $\delta = 0.3$

nullhypothesis: $p \leq p0$

alternate hypothesis: $p \geq p1$

power: 80%

significance level: 5% one sided

The nullhypothesis of this trial is that the 2-year-EFS rate is worse or equal to 0.5 under the experimental treatment. The alternate hypothesis is that the 2-year-EFS-rate is equal to 0.8 or greater. In an exact single stage phase 2 design 18 patients have to be enrolled to be able to detect the critical difference in the EFS-rates of 0.3 with a power of 80% and a one-sided significance level of 5%. The nullyhpothesis can be rejected if after 2 years 13 or more of 18 patients are without an event. The calculation is based on the exact binomial distribution as described in A'Hern [27].

13.4 Definition of Populations Included In the Analyses

All patients included will be analysed. Patients whose 2-year-EFS status cannot be evaluated will be excluded from the primary analysis. Worst case and best case analyses including these patients will be conducted as sensitivity analyses.

13.5 Methods of Analysis

The 2-year-EFS rate and its one sided 95%-confidence interval with the fixed upper bound of 1 will be calculated. If the one sided 95%-confidence interval does not include p0 = 0.5, the experimental treatment is considered effective.

13.6 Interim Analysis

No interim analysis is planned.

14 Data Safety Monitoring Board (DSMB)

The DSMB will consist of three members of the scientific community not involved in this trial. The committee will meet to review study data with the National Coordinating Investigator (LKP) of the trial and review all serious adverse events (SAE), and suspected unexpected severe adverse reactions (SUSARs). Meetings will take place approximately every 4-6 months and will receive monthly SAE listings from the safety database between meetings for review as well. The DSMB will give recommendations about the continuation of the trial and/or about necessary trial amendments.

15 Subsequent Amendments to the Protocol

15.1 Compliance with the Protocol

The investigator should conduct the clinical trial in compliance with this protocol. For this purpose, the document will be signed by the sponsor and the investigator. As a general rule, the investigator should not deviate from the protocol or make amendments to the protocol without the agreement of the sponsor/authority/ethics committee (unless subject safety is at risk, see below).

Any deviations from the approved protocol should be documented and explained by the investigator or an individual who is designated by the investigator.

The investigator may deviate from the protocol or make an amendment to the protocol without prior approval of the ethics committee to eliminate immediate risks to the trial subjects. The deviation or amendment should subsequently be reported to the ethics committee, the sponsor and, if necessary, the competent authority, giving reasons.

15.2 General Amendments to the Protocol

The sponsor can make general amendments to the protocol after the clinical trial has started. These may be of an administrative nature (logistical/administrative amendments) or substantial (subject to approval).

16 Ethical and Legal Principles

16.1 Subject Informed Consent

Before enrolment in the clinical trial, the subject will be informed that participation in the clinical trial is voluntary and that he/she may withdraw from the clinical trial at any time without having to give reasons and without penalty or loss of benefits to which the subject is otherwise entitled.

The treating physician will provide the subject with information about the treatment methods to be compared and the possible risks involved. At the same time, the nature, significance, implications, expected benefits and potential risks of the clinical trial and alternative treatments will be explained to the subject. During the informed consent discussion, the subject will also be informed about the insurance cover that exists and the insured's obligations. The subject will be given ample time and opportunity to obtain answers to any open questions. All questions relating to the clinical trial should be answered to the satisfaction of the subject and/or his/her legal representative. In addition, the subject will be given a "Subject Information Sheet“ which contains all the important information in writing.

The subject's **written** consent must be obtained **before any study-specific tests/treatments**.
For this purpose, the written consent form will be **personally dated and signed** by the trial subject and the investigator conducting the informed consent discussion.

By signing the consent form, the subject agrees to voluntarily participate in the clinical trial and declares his/her intention to comply with the requirements of the clinical trial and the investigator's instructions during the clinical trial. By signing the form, the subject also declares that he/she agrees to the recording of personal data, particularly medical data, for the study, to their storage and codified (“pseudonymised”) transmission to the sponsor, to the competent authority, and further

agrees that authorised representatives of the sponsor Technische Universität Dresden, who are bound to confidentiality, and national or foreign competent authorities may inspect his/her personal data, particularly medical data, which are held by the investigator.

After signing, the subject will be given one copy of the signed and dated written consent form and any other written information to be provided to the subjects.

In the case of substantial amendments, the subject must be informed with an appropriate revised subject information/consent form. Changed study procedures can only be carried out if they have been approved by the competent authority and the leading Ethics Committee, and if the subject has been appropriately informed and has given his/her written consent.

16.2 Ethical and Regulatory Requirements

A favourable opinion from the competent ethics committee and the approval of the competent authority must be obtained before a clinical trial is started:

16.2.1 Ethics Committee/ Competent Authority

Before this clinical trial is started, the sponsor will apply for the following, according to the applicable legal requirements:

- **Favourable opinion from the competent ethics committee´**
- **Approval of the competent supreme federal authority**

16.2.2 Additional Requirements Concerning the Notification of Authorities

The following other notification requirements apply at the start and end of the study (for reporting requirements during the study, see section 10.2.1 (investigator) and 10.2.2 (sponsor):

Notification by the sponsor:

- According to section 67, para. 1 AMG, the sponsor will notify the competent authority and the local authority of the clinical trial before it is started. The notification will include details of the sponsor and details of all investigators, indicating their position as principal investigator or coordinating investigator if necessary.
- According to section 13, para. 8 GCP-V, the sponsor will notify the competent authority, the local authority and the competent ethics committee of the end of the clinical trial within 90 days. If the clinical trial was terminated or suspended by the sponsor, notification will occur within 15 days, giving reasons for the termination or suspension.

Notification by the investigator

- According to section 67, para. 1 AMG, the investigator will notify the competent authority* and the local authority of the clinical trial before it is started. The investigator can assign the task of notification to the sponsor and must document this in an appropriate manner (section 12 (3) GCP-V) data (section 12, GCP-V).
- The investigator will notify the local authority of the end of the clinical trial within 90 days. The investigator can assign the task of notification to the sponsor and must document this in an appropriate manner (section 12 (3) GCP-V).

16.3 Subject/Subject Insurance

Subject insurance (minimum: € 500,000 per subject) according to section 40, para. 1, subpara 8 and para. 3 AMG has been taken out with

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Eisenbahnstr. 1-3, 04315 Leipzig / Germany
policy No: 13 005314-03010

for all subjects participating in the clinical trial.

The investigator, or an individual who is designated by the investigator, will inform the subject of the existence of the insurance, including the obligations arising from it. The trial subjects must be afforded access to insurance documents and provided with a copy of the general conditions of insurance on request.

For further details, see Subject Informed Consent.

16.4 Data Protection and Confidentiality

The trial subjects will be informed of the purpose and extent of the collection and use of personal data, particularly medical data (see section 16.1).

For the protection of these data, organisational measures have been taken to prevent disclosure to unauthorised third parties. For example, the subject data will be captured in pseudonymized form (subject ID No. for the particular study, age at study entry) throughout the documentation and evaluation phase.

17 Study Documents and Filing

17.1 Study Documents/Investigator Site File

The investigator will be given an investigator site file containing all the necessary essential study documents for the initiation of the trial at his/her centre. The essential documents include a list on which the investigator will enter all appropriately qualified persons to whom he/she has delegated important trial-related tasks.

The investigator, or an individual who is designated by the investigator, will be responsible for the maintenance and completeness of the study documents during the clinical trial. At the request of the sponsor, monitor, auditor, ethics committee or competent authority(ies), the investigator shall make available all the requested study-related records for direct access. Essential documents must not be removed permanently.

17.2 Archiving

After completion of the clinical trial, the essential study documents - as defined by section 8 of the Guideline ICH E6 for Good Clinical Practice (GCP) - from clinical trials will be retained at the study centre for a sufficient period so that they will be available for audits and inspections by the authorities.

The investigator will be responsible for the storage. The following retention periods will apply after the completion/termination of the clinical trial:

- The above-mentioned essential documents must be retained for at least 10 years (section13, para. 10 GCP-V); the identification codes of studies submitted for drug approval must be retained for at least 15 years (2001/83/EC).
- The medical records and other source documents must be retained for the longest possible period allowed by the hospital, the institution or the private practice.

The investigator/the institution should take measures to prevent accidental or premature destruction of these documents.

The sponsor will notify the investigator in writing when the study-related essential documents are no longer required.

18 Administrative Agreements

18.1 Financing of the Study

18.1.1 Study Agreeement/Investigator Compensation

According to ICH-GCP 4.9.6, a study agreement on the conduct of the clinical trial and the compensation for conducting the trial will be signed between the sponsor (donor) of the clinical trial and the investigators including their heads of administration (donee).

18.1.2 Reimbursement of Trial Subjects

Trial subjects will not be compensated.

18.2 Study Language

Entries should be made on the case report form and the study forms (ISF) in German language.

18.3 Publication

The right of publication rests primarily with the sponsor, the coordinating investigator and the other investigators involved. All data collected in connection with the clinical trial will be treated in confidence by the sponsor/coordinating investigator and all others involved in the study, until publication. Interim data and final results may only be published (orally or in writing) with the agreement of the sponsor Technische Universität Dresden, the coordinating investigator and the other investigators. This is indispensable for a full exchange of information between the above-named parties, which will ensure that the opinions of all parties involved have been heard before publication. The agreement, which does not include any veto right or right of censorship for any of the parties involved, may not be refused without good reason.

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19 Appendix 1: Relevant Guidelines and Laws

List and reference to websites or copy texts in directly

- Declaration of Helsinki http://www.wma.net/e/policy/b3.htm
- ICH-GCP Guidelines http://www.ich.org
- EMEA Guidelines http://www.emea.eu.int/index/indexh1.htm
- AMG/GCP-V etc.: *http://www.bfarm.de/cln_043/nn_666970/DE/Arzneimittel/klinPr/klin__prf__genehm/gestexte-verordnungen.html*
- Common Terminology Criteria for Adverse Events v3.0 (CTCAE)

  Source: http://ctep.cancer.gov/forms/CTCAEv3.pdf

  A hard copy version of this document is enclosed separately.

20 Appendix 2: Examples of Inducers and Inhibitors of CYP3A4

Inducers*	**Inhibitors****
Carbamazepine	Amiodarone
Ethosuximide	Cimetidine
Dexamethasone	Clarithromycin
Phenobarbitol	Clotrimazole
Phenytoin	Cyclosporin
Primidone	Erythromycin
Rifabutin	Fluconazole (doses >200 mg)
St. John's Wort	Fluoxetine
	Grapefruit Juice
	Indinavir
	Itraconazole
	Ketoconazole
	Metronidazole
	Mibefradil
	Miconazole
	Nefazodone
	Nelfinavir
	Norfloxacin
	Quinine
	Ritonavir
	Saquinavir
	Sertraline
	Zafirlukast

This is not a comprehensive list of inducers and inhibitors of CYP3A4 and is meant only to be used as a guide. This web site may also be consulted http://medicine.iupui.edu/flockhart/table.htm
*Note: Inducers of CYP3A4 may result in rapid metabolism of midostaurin and a decreased clinical effect.
**Note: Inhibitors of CYP3A4 may result in delayed metabolism of midostaurin and increased side effects.