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Thoraxklinik-Heidelberg
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Quizartinib and High-dose Ara-C plus Mitoxantrone in Relapsed/Refractory AML with *FLT3*-ITD

Q-HAM

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Summary

Acute myeloid leukemia (AML) is a clonal malignant disorder which is characterized by the expansion of leukemic blasts in the bone marrow and the peripheral blood, which goes along with a suppression of normal hematopoiesis including granulopoiesis, erythropoiesis and megakaryopoiesis. The prognosis is largely determined by cytogenetic and molecular risk factors, age, performance status and antecedent myelodysplastic syndrome (MDS). With the exception of old and frail patients, most AML patients are eligible for intensive chemotherapy, which is given in curative intent consisting of induction and consolidation therapy. However, despite intensive therapy, the long-term outcome of AML patients remains poor, with less than 30% of patients achieving long lasting remission and even cure. This poor outcome is largely due to refractoriness to induction chemotherapy as well as relapses during and after completion of intensive induction and consolidation therapy. Regarding refractoriness, about 20-30% of AML patients under the age of 60 years and about 50% of older patients fail to attain complete remission (CR) following cytarabine plus anthracycline based standard induction therapy. In addition, patients having achieved CR are at a high risk of relapse, particularly within the first two years after completion of chemotherapy. Allogeneic hematopoietic cell transplantation (allo-HCT) is currently the only treatment strategy to offer the prospect of cure in relapsed/refractory (r/r)-AML; but outcome after allo-HCT is largely determined by the remission state before allo-HCT. With the aim to induce a CR before allo-HCT, salvage chemotherapy regimens are administered in r/r-AML. Typically, these salvage regimens are based on high dose cytarabine (HiDAC), which is frequently combined with either mitoxantrone (HAM regimen) or fludarabin plus idarubicin (idaFLA regimen). However, there is still no commonly accepted standard salvage regimen and overall CR rates remain low with less than one third of the patients achieving a CR. Apart from already known clinical unfavorable prognostic parameters in relapsed AML such as short first CR duration, older age and previous allo-HCT, *FLT3*-ITD has consistently been identified as an unfavorable molecular marker in both relapsed and refractory AML. Recently midostaurin has been approved by the FDA and EMA for the treatment of newly diagnosed AML with activating *FLT3* mutations. But still roughly one quarter of patients, who received midostaurin, was refractory to induction therapy and relapse rate at 2 years exceeded 40%. Thus, new treatment options are urgently needed, particularly in r/r-AML with *FLT3*-ITD.

The oral second-generation bis-aryl urea tyrosine kinase inhibitor quizartinib is very specific for FLT3, has a high capacity for sustained FLT3 inhibition and an acceptable toxicity profile. Furthermore, single agent quizartinib doubled the response rate as compared to standard of care in a randomized study in r/r-AML. Although survival was also improved in this study the difference was only marginal.

In this protocol we evaluate the efficacy of quizartinib in combination with HAM (high-dose cytarabine, mitoxantrone) as compared to historical controls based on the matched threshold crossing approach followed by randomized prophylactic versus MRD-triggered continuation therapy with quizartinib including consolidation (chemotherapy as well as allo-HCT) and maintenance.

Zusammenfassung

Akute myeloische Leukämie (AML) ist eine klonale maligne Erkrankung, die durch leukämische Blasten im Knochenmark und im peripheren Blut sowie der Unterdrückung der normalen Hämatopoese einhergeht. Die Prognose wird maßgeblich durch zytogenetische und molekulare Risikofaktoren, Alter, Allgemeinzustand und vorangegangenes myelodysplastisches Syndrom (MDS) bestimmt. Mit Ausnahme von älteren und gebrechlichen Patienten können die meisten Patienten mit einer intensiven Induktions- und Konsolidierungstherapie in kurativer Absicht behandelt werden. Trotz intensiver Therapie ist die Prognose für AML-Patienten weiterhin schlecht, wobei weniger als 30 % der Patienten eine lang anhaltende Remission erreichen bzw. geheilt werden. Diese schlechten Ergebnisse sind hauptsächlich auf das Nichtansprechen auf die Induktionschemotherpie sowie Rückfälle während und nach Abschluss einer intensiven Induktions- und Konsolidierungstherapie zurückzuführen. Etwa 20 bis 30 % der AML-Patienten unter 60 Jahren und etwa 50 % der älteren Patienten erreichen keine komplette Remission (CR) nach einer Standardinduktionstherapie mit Cytarabin und einem Anthracyclin. Darüber hinaus haben Patienten nach Erreichen einer CR ein hohes Rezidivrisiko, insbesondere innerhalb der ersten zwei Jahre nach Abschluss der Chemotherapie. Die allogene Blutstammzelltransplantation (Allo-HCT) ist derzeit die einzige Behandlungsstrategie mit Aussicht auf Langzeitremissionen bei rezidivierter/refraktärer (r/r)-AML. Das Ergebnis nach der Allo-HCT wird jedoch maßgeblich durch den Remissionszustand vor Allo-HCT bestimmt. Mit dem Ziel, eine CR vor der Allo-HCT zu induzieren, werden Salvage-Chemotherapieschemata bei r/r-AML Patienten verabreicht. Typischerweise basieren diese Salvage-Schemata auf Hochdosis-Cytarabin (HiDAC), das häufig mit Mitoxantron (HAM-Regime) oder Fludarabin plus Idarubicin (IdaFLA-Regime) kombiniert wird. Es gibt jedoch nach wie vor kein allgemein akzeptiertes Standard-Salvage-Schema und die CR-Rate nach diesen Therapien ist insgesamt niedrig, wobei weniger als ein Drittel der Patienten eine CR erreichen. Neben bereits bekannten klinisch ungünstigen prognostischen Parametern bei Patienten mit r/r-AML, wie z. B. kurze erste CR-Dauer, höheres Alter und vorhergehende Allo-HCT, wurde *FLT3*-ITD als ungünstiger molekularer Marker sowohl bei rezidivierten als auch refraktären Patienten identifiziert. Vor kurzem wurde Midostaurin von der FDA und der EMA für die Behandlung von neu diagnostizierter AML mit aktivierenden *FLT3*-Mutationen zugelassen. Trotz Midostaurin sprechen etwa ein Viertel der Patienten nicht auf die Induktionstherapien an und die Rezidivrate liegt nach zwei Jahren bei über 40 %. Daher sind neue Behandlungsmöglichkeiten dringend erforderlich, insbesondere in der r/r-AML mit *FLT3*-ITD.
Der orale zweit Generations Bis-Aryl-Harnstoff-Tyrosinkinase-Inhibitor Quizartinib ist sehr spezifisch für FLT3, führt zu anhaltender FLT3-Hemmung und hat ein akzeptables Toxizitätsprofil. In einer randomisierten Studie zur r/r-AML führte Quizartinib als Monotherapie zu einer Verdopplung der Ansprechrate im Vergleich zur Standardchemotherapie. Quizartinib verbesserte auch signifikant die Überlebensrate in dieser Studie mit allerdings nur einem kleinen Unterschied. Im vorliegenden Protokoll wird die Wirksamkeit von Quizartinib in Kombination mit HAM (Hochdosis-Cytarabin, Mitoxantron) im Vergleich zu historischen Kontrollen auf der Grundlage des Matched-Threshold-Crossing-Ansatzes geprüft. Nach der Salvagetherapie erhalten die Patienten entsprechend der initialen Randomisierung eine prophylaktische versus MRD-gesteuerte Therapie mit Quizartinib in der Konsolidierungs- (Chemotherapie und Allo-HCT) und Erhaltungstherapiephase.

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Protocol Synopsis

Title

Quizartinib and High-dose Ara-C plus Mitoxantrone in Relapsed/Refractory AML with FLT3-ITD

Phase

Phase II

Sponsor

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Medical Faculty
represented in law by Heidelberg University Hospital and its Commercial Director
Mrs. Katrin Erk

Principal Investigator/ Coordinating Investigator (LKP)

Prof. Dr. Richard F. Schlenk

Financing/ Status of the Sponsor

The trial is co-financed by funds of Heidelberg University Hospital and Daiichi Sankyo Europe GmbH. The latter also provides study drug free of charge.

Indication

Acute myeloid leukemia according to WHO 2016 classification

Trial Population - Inclusion Criteria

1. Patients with acute myeloid leukemia according to the 2016 WHO classification (except acute promyelocytic leukemia) who are either
   A) refractory to induction therapy or
   B) relapsed after first line treatment including chemotherapy, autologous and/or allo-HCT (details below).
2. Positive for *FLT3*-ITD (defined as a ratio of mutant to wild-type alleles of at least 0.05; measured within 4 weeks before inclusion)#
3. ECOG performance status ≤ 2. See appendix 18.1
4. Adequate renal function defined as creatinine clearance >50 mL/min (calculated using the standard method for the institution)
5. Discontinuation of prior AML treatment for at least
   - 10 days for cytotoxic agents and
   - 28 days for investigational drug treatment

   before the start of study treatment (except hydroxyurea to control hyperleukocytosis)
6. Age ≥ 18 years and ≤ 75 years
7. Pregnancy and childbearing potential:
   - Non-pregnant and non-nursing women
   - Women of childbearing potential (WOCBP) must have a negative serum or urine pregnancy test within a sensitivity of at least 25 mIU/mL within 48 hours prior to randomization ("Women of childbearing potential" is defined as a sexually active mature woman who has not undergone a hysterectomy or who has had menses at any time in the preceding 24 consecutive months).
   - WOCBP must agree to avoid getting pregnant while on therapy: WOCBP must either commit to continued abstinence from heterosexual intercourse or begin one acceptable method of birth control (IUD, tubal ligation, or partner's vasectomy) during study and 6 months after end of study/treatment.

- Men must use a latex condom during any sexual contact with WOCBP, even if they have undergone a successful vasectomy and must agree to avoid to father a child during study and 6 months after end of study/treatment

8. Signed written informed consent
9. Ability of patient to understand character and consequences of the clinical trial

A) Refractory to induction therapy is defined as no CR, or CRi, or PR (according to standard criteria) [1] after 1 or 2 intensive induction cycles of at least 7 days of cytarabine 100-200mg/m² continuously or an equivalent regimen with cytarabine with total dose not less than 700mg/m² per cycle and 2 days of an anthracycline (e.g. daunorubicin, idarubicin).

B) Relapsed after first line therapy is defined as relapsed AML (according to standard criteria) [1] after a first line therapy including at least one intensive induction and consolidation therapy including (but not limited to) allo-HCT.

Secondary exclusion if *FLT3*-ITD cannot be verified by central testing. Patient already receiving Quizartinib may continue taking it and will be excluded after the first treatment cycle.

Trial Population - Exclusion Criteria

1. Acute promyelocytic leukemia (AML FAB M3 with t(15;17)(q22;q12) / *PML-RARA*)
2. Patients with known CNS leukemia
3. Isolated extramedullary manifestation of AML
4. Patients with a “currently active” second malignancy other than non-melanoma skin cancer. Patients are not considered to have a “currently active” malignancy if they have completed therapy for more than one year and are considered by their physician to be at less than 30% risk of relapse within one year
5. Hyperleukocytosis (leukocytes > 30,000/µl) at the time of study entry. 1)
6. Uncontrolled or significant cardiovascular disease, including any of the following:
   - History of heart failure NYHA class 3 or 4
   - Left ventricular ejection fraction (LVEF) ≤ 40% by echocardiogram (ECHO)
   - History of uncontrolled angina pectoris or myocardial infarction within 12 months prior to screening
   - History of second (Mobitz II) or third degree heart block or any cardiac arrhythmias requiring anti-arrhythmic therapy (beta blockers or digoxin are permitted)
7. Inadequate liver function: ALT and AST ≥ 2.5 x ULN), total bilirubin ≥ 1.5 x ULN; Alkaline phosphatase ≥ 2.5 x ULN. Known liver cirrhosis or history of veno-occlusive disease (VOD) or history of Sinusoidal Obstruction Syndrome (SOS)
8. Known positivity for HIV, active HBV, HCV or hepatitis A infection (active hepatitis B defined by HBs Ag positivity, active hepatitis C defined by positive virus load)
9. Uncontrolled active infection
10. Evidence or history of severe non-leukemia associated bleeding diathesis or coagulopathy
11. within 100 days after allo-HCT
12. clinically relevant Graft-versus-Host-Disease (GvHD) requiring initiation of treatment or treatment escalation within 21 days prior to screening
13. Any one of the following ongoing or in the previous 6 months: congenital long QT syndrome, Torsades de pointes, arrhythmias (including sustained ventricular tachyarrhythmia), right or left bundle branch block and bifascicular block, unstable angina, coronary/peripheral artery bypass graft, cerebrovascular accident, transient ischemic attack or symptomatic pulmonary embolism; as well as bradycardia defined as <50 bpms
14. QTc interval >450 msec using the Fredericia correction (QTcF).
15. Patients known to be refractory to platelet or packed red cell transfusions as per institutional guidelines, or who are known to refuse or who are likely to refuse blood product support.
16. Severe neurologic or psychiatric disorder interfering with ability of giving informed consent
17. Known or suspected active alcohol or drug abuse

18. No consent for registration, storage and processing of the individual disease-characteristics and course as well as information of the family physician about study participation.
19. Pregnancy and lactation
20. History of hypersensitivity to the investigational medicinal product or to any drug with similar chemical structure or to any excipient present in the pharmaceutical form of the investigational medicinal product
21. Prior treatment with quizartinib
-

1) These patients should be treated with hydroxyurea according to routine practice and are only allowed to enter into the study when leukocyte counts of 30,000/µl or below are reached. If hydroxyurea is not sufficient to control hyperleukocytosis, i.v. application of 100mg cytarabine continuously over 24 hours may be discussed with the Principle Investigator or the Medical Coordinator.

Objectives

The primary objectives are

Assess CR and CRi after salvage therapy with Q-HAM according the ELN 2017 criteria [1]

The secondary objectives are

Assess event-free survival (EFS), relapse-free survival (RFS), overall survival (OS), cumulative incidence of relapse (CIR) and death (CID) and patient reported outcomes (PRO) according to continuation therapy strategy (preemptive vs. prophylactic)

Primary Endpoint: CR/CRi

Secondary Endpoints: EFS, RFS, OS, CIR, CID, PRO

Trial Design

In this multicenter, upfront randomized phase II trial, all patients receive quizartinib in combination with HAM (high-dose cytarabine, mitoxantrone) during salvage therapy. Efficacy is assessed by comparison to historical controls based on the matched threshold crossing approach. During consolidation therapy (chemotherapy as well as allo-HCT) patients receive either prophylactic quizartinib therapy or MRD-triggered preemptive continuation therapy with quizartinib according to up-front randomization.

Investigational Medicinal Product

- Quizartinib 20mg tablet

Sample Size

To assess the efficacy with respect to the primary endpoint CR/CRi of Q-HAM during salvage therapy, the sample size required for a fixed design would be a minimum of $n_{fixed}=74$ (assuming a logistic regression is performed at one-sided significance level $\alpha=0.05$, and the aspired power is $1-\beta=0.8$, and number of matching partners per intervention patient is only $M=1$), thus a maximum of $n_1 + n_2^{Max} = 80$ patients will be enrolled. The trial sample size is recalculated based on a conditional power argument in an interim analysis after enrolling n=30 patients and will hence range between n=30 and n=80

Statistical Analysis

A logistic regression model will be applied to assess the Odds Ratio of CR/CRi rate after salvage therapy for patients receiving Q-HAM versus matched controls not receiving Q-HAM. The null hypothesis is that H_0:OR≤1 which is tested against its alternative H_1:OR>1 at a one-sided significance level of α=0.05. The logistic regression analysis will be adjusted for age, high risk cytogenetics (yes/no), and CR1 duration <18 months (yes/no). Due to the adaptive nature of the trial, two separate logistic models will be fitted for the two trial stages and be combined using the inverse normal function approach. Determination of p-values, point and interval estimates will take the adaptive nature of the trial into account. Analysis of the primary endpoint will be based on the full analysis population. Concerning the secondary endpoints: survival and cumulative incidence will be analyzed using a Cox regression model and Kaplan-Meier-Plots, quality of live will be analyzed according to the corresponding guidelines and EORTC recommendations.

Trial Duration and expected Dates

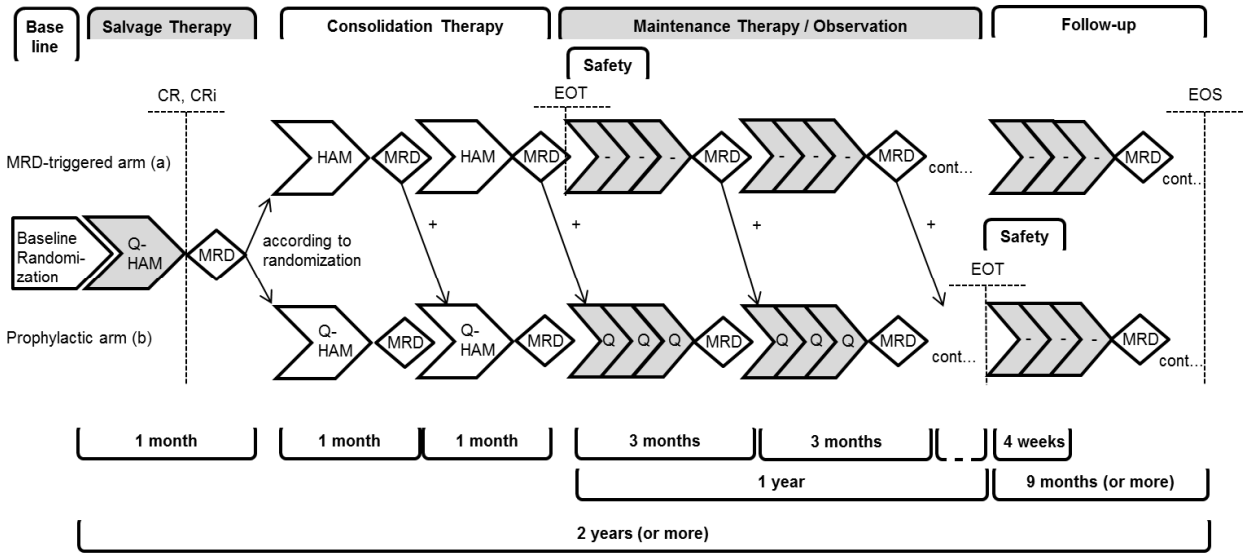
Total trial duration:	5 years (2019-09 – 2024-09)
Duration of the clinical phase:	4 years (2019-09 – 2023-09)
First patient first visit (FPFV):	2020-04
Last patient first visit (LPFV):	2022-04 (FPFV + 2 years)
Last patient last visit (LPLV), End of study (EOS):	2024-04 (LPFV + 2 years)
Trial Report Completed:	2025-04 (LPLV + 1 year)

Trial Schedule

PHASE	BL	ST	ST	ST	ST	CT	CT	CT	CT	M/O	M/O	EOT	SA	FU	EOS
DAY (OF CYCLE)	-14- 0	1	2-3	4-EoC	EoC	1	2-3	4-EoC	EoC	1-27	28		28		
Clinical assessments															
Signs/ symptoms	X			X^{W}	X				X		X	X^{O}	X	X^{3MY}	X
Vital signs	X	X	X^{DA}	X^{W}	X	X^{O}	X^{DA}	X^{W}	X		X	X^{O}	X	X^{3MY}	X
Physical examination	X	X^{O}		X^{W}	X	X^{O}		X^{W}	X		X	X^{O}	X	X^{3MY}	X
ECG	X	X^{O}				X^{O}					X	X^{O}	X	X^{3MY}	
Extramedullary involvement	X				X				X		X^{3M}	X^{O}		X^{3MY}	X
PRO	X				X				X^{2C}		X^{3M}	X^{O}		X^{3MY}	X
ECOG PS	X	X^{O}			X	X^{O}			X		X	X^{O}	X	X^{3MY}	X
Laboratory assessments															
Hematology	X	X^{SL}	$X^{DA,SL}$	$X^{W,SL}$	X	$X^{O,SL}$	$X^{DA, SL}$	$X^{W,SL}$	X		X	X^{O}	X	X^{3MY}	X
Basic blood chemistry	X	$X^{O,SL}$		$X^{W,SL}$	X	$X^{O,SL}$		$X^{W,SL}$	X		X	X^{O}	X	X^{3MY}	X
Ext. b. chemistry & coagulation	X				X				X		X	X^{O}	X	X^{3MY}	X
Local disease assessment	X				X				X		X^{3M}	X^{O}		X^{3MY}	X
Central laboratory assessments															
Sample Collection (BM, PB)	X				X				X		X^{3M}	X^{O}		X^{3MY}	X
MRD & Disease status	X				X				X		X^{3M}	X^{O}		X^{3MY}	X
Treatment															
Quizartinib				X^{DA}				X^{DA}		X^{DA}	X				
SOC: HAM		X	X^{DA}			X	X^{DA}								
Drug Compliance					X				X		X	X^{O}			
Safety															
Concomitant medications	X	X	X^{DA}	X^{W}	X	X	X^{DA}	X^{W}	X		X	X^{O}	X		
AE assessment		X	X^{DA}	X^{W}	X	X	X^{DA}	X^{W}	X		X	X^{O}	X		
Pregnancy test (WOCBP only)	X	X^{O}				X			X^{2C}		X^{3M}	X^{O}	X	X^{1st}	
Screening and Baseline															
Informed consent	X														
Demographics & Family History	X														
Medical/ oncologic history	X														
Genetic Assessment (local)	X														
Genetic Assessment (central)	X														
Cytogenetics	X														
ECHO	X														
Abdominal ultrasound	X														
Urinalysis	X														
Virus diagnostics	X														
Enrollment & Randomization	X														

BL Baseline (within 14 days, incl. ST-D1)
ST Salvage Therapy (1 x 21 days + 21 days optional recovery period)
EoC End of Cycle. Last day including optional recovery period.
CT Consolidation Therapy (2 x 28 days + 14 days optional recovery period)
M/O Maintenance Therapy (prophylactic arm) / Observation (MRD-triggered arm) (12 cycles). For MRD-triggered arm only 3-monthly visits.
EOT End Of Treatment (Within 7 days after or on Last Visit MT)
SA Safety Follow-up (28 days after EOT)
FU Observational Follow-up (3-monthly starting from Last Visit MT until EOS, +/- 7days-window per visit)
EOS End of Study (for all patients: 2 years after LPFV)
O To be **omitted** if already performed within 48 hours
DA To be done **daily.**
W To be done **weekly**, preferably at the same day of the week (e.g. the starting day of the therapy).
1st Only in **1st FU visit**
2C Only in **2nd cycle CT**
3M To be done **3-monthly.**
Y **After 2 years** counted from day 1, visits on site are not mandatory anymore and may be replaced by contacting the treating physician or mailing the questionnaire. In this case, no further samples will be collected.
[ ] optional length in case of needed recovery period
SL Safety lab, values not captured in eCRF
Note See chapter 7.2 for a **day by day schedule**. **Further details** are given below.

Flow Chart & Study Narrative



Baseline & ST: Salvage Therapy	Baseline can be done within 14 days prior to day 1 ST and on day 1 ST. All patients are randomized upfront and receive one cycle Q-HAM **salvage therapy**. All patients achieving CR or CRi are allocated according to **randomization** to either (a) MRD-triggered arm or (b) prophylactic arm treatment with quizartinib. If a prolonged recovery phase is needed, the EoC-visit is moved to the end of the recovery phase. *(Duration: one cycle á 21 days followed by up to 3 weeks recovery period if needed, 22-42 days in total)* All patients who do not achieve CR or CRi do not receive any further trial medication. The last visit of the ST counts as **EOT**. All those patients are directly allocated to the **observational follow-up (FU)** including the **safety follow-up** at day 28 after EOT. In case of MRD positivity, a cross over to the prophylactic arm is also possible directly after Savage Therapy.
CT: Consolidation Therapy	During **consolidation therapy** patients allocated to **MRD-triggered arm (a)** receive one cycle of HAM and are further allocated based on the MRD-results assessed by flow cytometry with a cut of level of 0.1%: if the MRD is negative they remain in the MRD-triggered arm for another cycle, whereas MRD positive patients have to move to the prophylactic arm. All patients randomized to **(b) prophylactic arm** will receive quizartinib irrespective of the MRD results (MRD results are provided by the central MRD laboratory). During CT patients may be discharged at D4. If a prolonged recovery phase is needed, the EoC-visit is moved to the end of the recovery phase. *(Duration: two cycles á 28 days each followed by up to two weeks recovery period if needed, 56-84 days in total)*
M/O: Maintenance Therapy/ Observation	During the **maintenance therapy**/ **observation** no treatment will be given in the **MRD-triggered arm (observation only);** MRD positive patients have to move to the prophylactic arm**.** Quizartinib will be given as single-agent therapy in the **prophylactic arm**. The dose of quizartinib is increased during maintenance therapy (see ch. 6.3, page 36). The maintenance therapy will be continued for up to 12 cycles and consist of monthly visits (approximately one year). All patients in the **MRD-triggered arm** have only 3-monthly visits within SOC. *(Duration: four times three cycles á 28 days, 48 weeks in total)*
EOT	In the MRD-triggered arm end of treatment (EOT) is determined by the end of consolidation therapy. In the prophylactic arm the last administration of quizartinib determines EOT.
Safety & FU: Observational Follow-up	The maintenance therapy is followed by a safety follow-up of 28 days counted from EOT for all patients from the prophylactic arm. After EOT all patients are followed within the observational follow-up, which consist of 3-monthly regular visits within SOC starting from EOT. For all patients of the MRD-triggered arm the safety follow-up starts after the last visit of the last cycle of CT. Their observational follow-up continues seamlessly. The observational follow-up will be performed until EOS (see below). All visits may be done within a +/-7days time window. (Duration: roughly 9 months or more)
EOS	Two years after the first visit of the last patient (LPFV) is the end of study (EOS) date for all included patients. If the last included patient died before that date, EOS will be when the last patient being included and alive has been followed for at least 730 days (2 years) counting from this patient's day 1.
Endpoints	The primary endpoint is collected after one cycle of Q-HAM at day 22. The secondary endpoints are collected continuously and during the last study visit (EOS).

Allo-HTC and Treatment Deviances	The **anticipated standard treatment course for the prophylactic arm** consist of one cycle salvage therapy, two cycles consolidation therapy and 12 cycles maintenance therapy. Maintenance therapy may be initiated earlier (after salvage or first consolidation therapy based on patients' individual needs) by the treating physician without need to exclude the respective patient from the trial. The patient continues the standard trial schedule at the next possible cycle. **Allo-HCT is allowed at any time after Salvage Therapy and maintenance therapy may be given starting the earliest at day 30 and the latest at day 100 after transplant according to initial randomization.**

Study Procedures

Clinical assessments	
Signs/ symptoms	Standardized assessment of all organ systems
Vital signs	At baseline only: height (in cm). At baseline and at the start of every new cycle: weight (in kg), temperature (in degree Celsius) and blood pressure/pulse, Every visit: Vital status. In case of death: date and cause.
Physical examination	Inspection, abdominal, cardiac and lung auscultation, palpation of the abdomen and lymph node sites, neurological examination.
ECG	One 12-lead electrocardiogram
Extramedullary involvement	Assessment of extramedullary disease status by tumor imaging (yes/no). In case of initial extramedullary involvement in patients with hematological response (complete or partial response), the extramedullary status has to be re-evaluated at the time of bone marrow evaluation according to ELN recommendations (see appendix 18.2). Baseline tumor imaging will be accepted within 2 weeks prior to the start of treatment.
PRO	Patient Reported Outcomes (PRO) will be assessed by questionnaires of the EORTC Quality of Life Item Library (core questionnaire QLQ-C30, fatigue module QLQ-FA12, and selected symptom items), as well as the Pittsburgh Sleep Quality Index (PSQI), the Patient Health Questionnaire for Anxiety and Depression (PHQ-4), and the Functional Assessment of Cancer Therapy - cognitive function scale (FACT-cog). In addition, patient-reported information on personal traits and experiences will be collected at baseline. The paper based questionnaires will be mailed or handed out at the study site.
ECOG Performance status	See appendix 18.1.
Local laboratory assessments	
General timing	Samples for hematology, blood chemistry and coagulation are to be taken at all time points as shown by the Trial Schedule (page **Fehler! Textmarke nicht definiert.**).Only values at time points of MRD assessments and during Safety Follow-up (SA) are captured in the eCRF. Values of other time points are collected for safety reasons (regarding documentation see below "safety laboratory")
Hematology	RBC, WBC, hemoglobin level, hematocrit, platelet count, blood differential in case of leukocytes ≥ 1 G/L
Basic blood chemistry	Sodium, potassium, calcium, creatinine, uric acid
Extended blood chemistry and coagulation	Lactate dehydrogenase (LDH), Alanine amino transferase (ALT), aspartate amino transferase (AST), alkaline phosphatase (AP), gamma glutamyl transferase (GGT), bilirubin total, direct bilirubin in case of elevated total bilirubin, PTT + INR
Safety laboratory	Laboratory values that are collected for safety reasons only are not captured as such in the eCRF. If significantly deviating from normal range, and/or assessed by the investigator as clinically relevant, results of safety lab investigations are to be documented as adverse events (AEs) on the appropriate forms of the eCRF.
Local Disease assessment	Disease Status assessments to be done according to 2017 European Leukemia Net (ELN) criteria (see appendix 18.2). The local disease assessment determines all immediate treatment decisions but may be outvoted by central disease assessment in case of contradictory results. Upon treatment failure or relapse, treatment is discontinued and the respective patient is followed within the regular Follow-up.
Central laboratory assessments	

<table>
<tr><td>Sample Collection (BM, PB)</td><td>Collection of bone marrow aspirates (EDTA, Heparin), unstained bone marrow slides, peripheral blood (Heparin) and peripheral blood smears. Samples must be shipped at the day of collection. For details see instruction for sending biomaterial form.
See chapter 7.4.2 page 46 for more details.
Bone marrow aspiration will be performed at baseline and for remission assessment after each chemotherapy cycle and every 3 months during maintenance therapy and follow-up.
A bone marrow biopsy (histology) is intended in all patients at time of study inclusion.
During baseline, sample collection for local and central assessment may be taken simultaneously provided the ICF has been signed already.</td></tr>
<tr><td>MRD & Disease status</td><td>Central Assessment of MRD by flow cytometry according to 2017 European Leukemia Net (ELN) criteria (see appendix 18.2).
Upon treatment failure or relapse, treatment is discontinued and the respective patient is followed within the regular Follow-up. In case of contradictory results, the central disease status outvotes the local disease assessment for final analysis.</td></tr>
<tr><td>Treatment</td><td></td></tr>
<tr><td>Quizartinib</td><td>See ch. 6.3, page 36.</td></tr>
<tr><td>SOC: HAM</td><td>See ch. 6.3, page 36.</td></tr>
<tr><td>Drug Compliance</td><td>Dates of drug intake and all missed doses must be recorded.
Bottles (empty or containing unused tables) and dosing diaries are returned.</td></tr>
<tr><td>Safety</td><td></td></tr>
<tr><td>Concomitant medications</td><td>Concomitant medications have to be reported in the respective case report form (CRF) pages, including supportive care drugs and drugs used for treating AEs or chronic diseases.</td></tr>
<tr><td>AE assessment</td><td>Events have to be documented and recorded continuously. Patients must be followed for AEs up to 28 days after last study drug administration (safety follow up) or until all drug-related toxicities have been resolved, whichever is later, or until the investigator assesses AEs as “chronic” or “stable”. However, if the patient commences alternative anti-cancer therapy <28 days after the last dose of study drug administration, the AE reporting period will end at the time the new treatment is started. Each AE must be reported only once per cycle, indicating the worst CTC (Version 5.0) grade. If an event stops and later restarts within the same cycle, all occurrences must be reported. A specific procedure for definition and reporting of SAEs is described in chapter 9.</td></tr>
<tr><td>Pregnancy test (WOCBP only)</td><td>For WOCBP, a pregnancy test with sensitivity of at least 25 mIU/mL must be performed at baseline ≤ 48 hours prior to patient inclusion).
In addition, WOCBP and male patients must be counseled to avoid getting pregnant or to father a child within 6 months after the last application of therapy.</td></tr>
<tr><td>Screening and Baseline</td><td>Screening can be accomplished over one or multiple visits over a 2-week period (14 days), unless specifically noted otherwise (i.e., cytogenetics).
If needed, Baseline examinations may be performed on ST day 1, given all inclusion criteria are met and the patient signed the informed consent.
Baseline day 0 and ST day 1 may be on the same day.

The following table lists all baseline actives with the respective time frames:
<table>
<tr><th>Days</th><th>Examination</th></tr>
<tr><td>0</td><td>Examinations to be done at day of inclusion: vital signs, physical examination, ECOG, hematology, clinical chemistry & coagulation, PRO, sample collection for central assessments</td></tr>
<tr><td>-2-0</td><td>Pregnancy test</td></tr>
<tr><td>-14-0</td><td>ECG, ECHO, abdominal ultra sound, virus diagnostics, extramedullary involvement, urinalysis
Genetic assessment (central),</td></tr>
<tr><td>-28-0</td><td>Genetic assessment (local), cytogenetics</td></tr>
</table>
Patients may be re-screened if they did not pass all eligibility criteria.</td></tr>
<tr><td>Informed consent</td><td>Every patient must date and sign the informed consent to participate in this trial. Protocol specific tests or procedures not considered standard of care can only be done after the patient has agreed on trial participation and signed the Informed Consent document. The Informed Consent document may be signed maximally up to 14 days prior to initiation of treatment. Upon screening a screening number (Scr-No) is assigned. In case of re-screening patients must re-consent but will keep their screening number.</td></tr>
<tr><td>Demographics & Family History</td><td>Demographics: Sex, year of birth, ethnicity
Family History: Cases of tumor diseases (hematological and solid tumors) in first grade family members (parents, siblings, children)</td></tr>
</table>

Medical/ oncologic history	Date of first diagnosis, detailed information on diagnosis of AML including karyotype and molecular profiling according to ELN recommendations [1] Date of first CR and date of relapse in relapsed patients. Details on prior AML-therapy. Medical history on concomitant diseases, prior exposure to toxic agents, prior malignancy including therapy, information on smoking.
Genetic Assessment (local)	Local assessment of *FLT3*-ITD for screening purposes. To be done within 4 weeks before screening visit. Relevant for inclusion.
Genetic Assessment (central)	Central assessment of *FLT3*-ITD. Samples must be collected at baseline.
Cytogenetics	Cytogenetics performed locally by R-banding or G-banding analysis
ECHO	Echocardiography at baseline and thereafter at investigator's discretion
Abdominal ultrasound	Abdominal ultrasound at baseline and thereafter at investigator's discretion
Urinalysis	pH, glucose, proteins (qualitative, dipstick accepted): at baseline and at investigator's discretion during treatment.
Virus diagnostics	HBsAg, anti-HBs, anti-HBc, anti-HCV IgG, Anti-HAV IgM. In case of positive anti-HCV IgG Hep C virus load, HIV test at baseline and thereafter at investigator's discretion.
Enrollment & Randomization	The investigator is requested to sign the request for enrollment form in the eCRF. This signature guarantees that eligibility criteria are met and a unique patient ID (PAT-ID) will be assigned. Randomization is carried out by the responsible investigator online. The random-number (Rand-No) will be assigned.

Abbreviations

AE	Adverse Event
AESI	Adverse events of special interest
ALT	Alanine Amino Transferase, also known as SGPT
allo-HCT	Allogeneic hematopoietic cell transplantation
AMG	German Drug Law (Deutsches Arzneimittelgesetz)
AML	Acute myeloid leukemia
AST	Aspartate Amino Transferase, also known as SGOT
AP	Alkaline Phosphatase
bid	bi-daily
CI	Confidence Interval
CID	cumulative incidence of death
CIR	cumulative incidence of relapse
CR	Complete Remission
CRi	Complete Remission with incomplete hematological recovery
(e)CRF	(electronic) Case Report Form
CRP	CR with incomplete platelet recovery
CTCAE	Common Toxicity Criteria for Adverse Events
CV	Coefficient of variation DMC Data Monitoring Committee
EC	Ethics Committee
ECG	Electrocardiogram
EFS	Event-free Survival
ELN	European LeukemiaNet
EMA	European Medicines Agency
EOS	End of Study
EOT	End of Treatment
FDA	Food and Drug Administration
FPFV	First Patient First Visit
FPLV	Fist Patient Last Visit
GCP	Good Clinical Practice
GCP-V	GCP-Verordnung
GGT	Gamma Glutamyl Transferase
GMP	Good Manufacturing Practice
IB	Investigator´s Brochure
ICH	International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use
IIT	Investigator Initiated Trial
IMP	Investigational Medicinal Product
INN	International Nonproprietary Name
ISF	Investigator Site File
ITT	Intention To Treat
KKS	Coordination Center for Clinical Trials (Koordinierungszentrum für Klinische Studien)
LDH	Lactate dehydrogenase
LKP	Coordinating Investigator according to AMG (Leiter der Klinischen Prüfung)
LPFV	Last Patient First Visit
LPLV	Last Patient Last Visit
NYHA	New York Heart Association classification
OS	Overall Survival
PAT-ID	Patient ID
P-gp	p-gylocoprotein
p. o.	per os/ per oral/ orally
PR	Partial Remission
PRO	Patient Reported Outcomes
QoL	Quality of Life
QTc	Corrected QT interval
QTcF	Corrected QT interval using Fridericia Formula
Rand-No	Random number, assigned during randomization
RBC	Red Blood Cell
RFS	Relapse free survival
SAE	Serious Adverse Event
Scr-No	Screening Number, assigned upon screening
SDV	Source Data Verification
SGPT	→ ALT
SGOT	→ AST
SOS	Sinusoidal Obstruction Syndrome
SUSAR	Suspected Unexpected Serious Adverse Reaction
TMF	Trial Master File
UKHD	Heidelberg University Hospital
ULN	Upper Limit of Normal
VOD	Veno-occlusive disease
WBC	White Blood Cell
WHO	World Health Organization

1 Introduction

1.1 Current Acute Myeloid Leukemia (AML) treatment

Acute Myeloid Leukemia (AML) is a clonal malignant disorder which is characterized by the expansion of leukemic blasts in the bone marrow and the peripheral blood, which goes along with a suppression of normal hematopoiesis including granulopoiesis, erythropoiesis and thrombopoiesis. The prognosis is largely determined by cytogenetic and molecular risk factors, age, performance status and antecedent myelodysplastic syndrome (MDS) or myeloproliferative neoplasm (MPN) [1][2][3][4]. With the exception of old and frail patients, most AML patients are eligible for intensive chemotherapy, which is given in curative intent consisting of induction and consolidation therapy[1][5][6]. However, despite intensive therapy, the long-term outcome of AML patients remains poor, with less than 30% of patients achieving long lasting remission and even cure [5][7]. This poor outcome is largely due to refractoriness to induction chemotherapy as well as relapses during and after completion of intensive induction and consolidation therapy. Regarding refractoriness, about 20-30% of AML patients under the age of 60 years and about 50% of older patients fail to attain complete remission (CR) following cytarabine plus anthracycline based standard induction therapy [8][9][10]. However, patients having achieved CR are at a high risk of relapse, particularly within the first two years after completion of chemotherapy [11]. Allogeneic hematopoietic cell transplantation (allo-HCT) is currently the only treatment strategy to offer the prospect of cure in relapsed/refractory (r/r-)AML. Outcome of allo-HCT is heavily influenced by the remission state before allo-HCT [10][11]. With the aim to induce a CR before allo-HCT, salvage chemotherapy regimens are administered in r/r-AML. Typically, these salvage regimens are based on high dose cytarabine (HiDAC), which is frequently combined with either mitoxantrone (HAM regimen) or fludarabin plus idarubicin (idaFLA regimen) [12]. However, there is still no commonly accepted standard salvage regime and overall CR rates are low [12]. Apart from already known clinical unfavorable prognostic parameters in relapsed AML, such as short first CR duration, older age and previous allo-HCT, internal tandem duplications of the FMS-related tyrosine kinase 3 (*FLT3*-ITD) have consistently been identified as an unfavorable molecular marker in both relapsed and refractory AML [10][11][12]. Recently, midostaurin has been approved by the FDA and EMA for the treatment of newly diagnosed AML with activating *FLT3* mutations [13][14]. However, still roughly one quarter of patients in the midostaurin arm of the study was refractory to induction therapy and relapse rate at 2 years excited 40% [13]. Thus, new treatment options are urgently needed particularly for r/r-AML with *FLT3*-ITD.

1.2 FLT3 Mutations in AML

Activating mutations of *FLT3,* resulting in the constitutive activation of this receptor tyrosine kinase, are among the most frequent molecular abnormalities in AML and are present in about 30% of newly diagnosed patients [15][16]. FLT3 is a member of the class III receptor-tyrosine kinase family and has an established role in normal growth and differentiation of hematopoietic precursor cells [17]. Following ligand binding, the FLT3 receptor dimerizes at the plasma membrane, leading to a conformational change in its activation loop that allows adenosine triphosphate (ATP) access to the FLT3 active site. This is followed by autophosphorylation and activation of numerous downstream signaling pathways [18][19][20]. Mutations of the *FLT3* gene lead to ligand-independent activation and dysregulation of downstream pathways such as PI3K/AKT, MAPK/ERK and STAT5 [21][22][23]. These pathways inhibit apoptosis and differentiation, and promote proliferation. The frequency of mutated *FLT3* in AML, its location on the cell surface and its association with an adverse prognosis make it an attractive target [24].

1.2.1 Internal tandem duplications

The most common *FLT3* mutations are ITDs, which occur in roughly 20-30% of all AML patients, particularly in cytogenetically normal AML [25][26], but also in APL with t(15;17)(q22;q12) and AML with t(6;9)(p23;q34). Its incidence is associated with age: whereas it can only rarely be found in children, its incidence is highest in adults up to the age of 60 years and declines in older patients

[6]. Clinically, *FLT3*-ITD mutations are associated with a high white blood cell count, a high percentage of myeloid blast cells in the peripheral blood and bone marrow, and a more frequent diagnosis of *de novo* rather than secondary AML [21][27].

In cytogenetically normal AML the presence of an ITD is associated with an increased relapse rate and reduced OS as compared to wild type *FLT3* [27][28][29], even after allogeneic hematopoietic stem cell transplantation (allo-HCT) [30][31]. *FLT3*-ITD is also a negative prognostic factor for survival in patients with either refractory or relapsed AML as they have a poor response to salvage therapy [10][11][32][33].

Regarding specific ITD characteristics, the size of these duplications varies widely, typically ranging from 3 to over 100 base pairs (bps) with a median of 48 bps [34]. In addition, size and ITD insertion site in the *FLT3* gene seem to be correlated in that the more 3' the insertion site the longer the ITD is [34]. The impact of the size on outcome is still unclear with some publications stating no impact on outcome [35] [36] whereas one publication found that short ITDs may impart an unfavorable outcome [37]. Nevertheless, most publications stated that longer ITDs correlate with lower complete response (CR) rates and shorter OS and event-free survival (EFS) [38][39][40].

The ITD insertion site within the *FLT3* gene has been shown to be an important prognostic factor [34]. About 3 quarters of *FLT3*-ITDs occur in the juxtamembrane domain (JMD) whereas one quarter in the tyrosine kinase domain 1 (TKD1) of the *FLT3* gene, in particular in the beta1-sheet [34]. In cell culture analyses, a prototypic *FLT3*-ITD with insertion site in the β2-sheet of the TKD1 (*FLT3*-ITD627E) mediated phosphorylation of FLT3 and STAT5, suggesting that non-JMD *FLT3*-ITD mutations confer constitutive activation of the receptor [41]. Additionally, *FLT3*-ITD627E induced transformation of hematopoietic 32D cells and led to a lethal myeloproliferative disease in a syngeneic mouse model. Insertions in the beta 1-sheet of TKD1 may introduce a greater instability into the protein structure and may therefore be associated with a pronounced adverse prognosis [34][41].

Besides the insertion site, further prognostic and predictive impact has been shown for the allelic ratio, which is quantified by GeneScan analysis using DNA fragment analysis [42][43]. This method is a semi-quantitative assessment of the *FLT3*-ITD allelic ratio, expressing the allelic ratio as a percentage of the area under the curve for *FLT3*-ITD divided by the area under the curve for wild-type *FLT3*. According to different publications the distribution of the allelic ratio varies widely [34][35][40][43][44]. Therefore, the question arises where the optimal cut-off value should be to distinguish patients with high versus low allelic ratio. Currently, there is still a lack of consensus on clinically relevant cut-offs between high/low allelic ratios, which might be due to different methodologies of testing that had been applied. Nevertheless, there is a clear association of an inferior OS and EFS in patients with higher allelic ratios [34][39][43][45]. Besides, the allelic ratio with a cut-off value of 0.5 to distinguish high versus low allelic ratio has entered the risk classification system of the ELN [1]. In addition, as AML evolves from diagnosis to relapse, the allelic ratio seems to increase [46][47]. However, in a small proportion of relapses *FLT3*-ITD was no longer detectable [48][49].

1.2.2 Point mutations of the tyrosine kinase domain

Approximately 5%–10% of AML patients harbor point mutations within exon 20 of the *FLT3* gene (*FLT3*-TKD) [23]. TKD mutations most frequently occur at codon 835 where a tyrosine residue replaces aspartic acid, stabilizing the activation loop in the ATP–bound configuration and promoting activation [50]. Other point mutations include for instance N676D, I836S and Y842C in the TKD1 and TKD2 domains, respectively [51]. The prognostic significance of *FLT3*-TKD is discussed controversial [15][45][50][52][53][54][55]. Nevertheless, TKD mutations can occur after treatment with TKI as a mechanism of resistance, thus implicating an adverse prognosis [56][57][58].

1.2.3 Treatment without FLT3 inhibitors

In younger patients with newly diagnosed AML considered suitable for intensive induction therapy, the combination of an anthracycline and cytarabine ("7+3" regimen) remains the standard of care also for patients with activating *FLT3* mutations [7]. However, higher allelic ratios were associated with lower CR-rates after induction therapy [43] bringing up the question of dose-intensification in these patients [59][60]. In older adults a substantial proportion of patients cannot tolerate intensive induction chemotherapy; in these cases other less intensive regimens may be used including low dose cytarabine [61] or hypomethylating agents (e.g. azacitidine or decitabine) [62] [63]. Based on the assessment of the risk-benefit ratio (i.e., non-relapse mortality/morbidity vs. reduction of relapse risk) alloHCT from matched-related or unrelated donor in early first CR is the treatment option for patients with intermediate and adverse risk genetics. In addition, allo-HCT has been shown to improve outcomes in *FLT3*-ITD AML, particular in patients with a high allelic ratio [31][43][64][65].

1.2.4 New therapies targeting FLT3

In the last decade, numerous small molecule FLT3-tyrosine kinase inhibitors (TKIs) have been developed to disrupt oncogenic signalling. Most compete for the ATP binding site in the active domain of the kinase, inhibiting protein phosphorylation [66].

Early TKI inhibitors, rather than being specifically designed to target FLT3, had multiple targets including KIT, PDGFR, VEGFR, and JAK2 [67]. Several agents have shown evidence of modest antileukemic activity as monotherapy including midostaurin (phase IIb) [68], linifanib (phase I) [69], semaxanib (phase II) [70][71], tandutinib [72], and KW-2449 (preclinical) [73]. However, responses were typically short-lived and mostly partial remissions.

Moreover, it has been suggested that the responsiveness to FLT3 TKIs seems to depend on the *FLT3* allelic ratio [47]. In an *in vitro* analysis, six different FLT3 inhibitors (lestaurtinib, midostaurin, quizartinib, KW-2449, sorafenib, and sunitinib) were examined for potency against mutant and wild-type *FLT3*, as well as for cytotoxic effect against a series of primary blast samples obtained from *FLT3*-ITD mutated AML patients. Relapsed samples and samples with a high allelic ratio were more likely to be responsive to cytotoxicity from FLT3 inhibition as compared to the samples obtained at diagnosis or those with a low allelic ratio [47]. Therefore, it has been hypothesized that patients with newly diagnosed *FLT3*-mutant AML might be less likely to respond to highly selective FLT3 inhibition [47]. However, the results probably indicate that the presence of a *FLT3*-ITD with even a low allelic ratio cannot be excluded altogether from prognostic risk stratification.

Midostaurin is currently the only TKI that has demonstrated convincingly superior results as compared to standard intensive therapy in younger *FLT3*-mutated newly diagnosed AML patients for all survival end points including overall survival [13]. Midostaurin affects multiple targets including c-Kit, PDGFR as well as FLT3 [74]. In a phase I-II trial midostaurin 50 mg orally 2x/d given for 14 days was safely combined with standard induction therapy of daunorubicin and cytarabine in patients with newly diagnosed AML and a CR-rate of 80% could be achieved [75]. These encouraging results provided rational to move on to a randomized phase III trial (CALGB 10603 (RATIFY). The trial was activated in May 2008 and recruitment of over 700 younger adult *FLT3*-mutated, including *FLT3*-ITD and *FLT3*-TKD, AML patients (18-<60 years) was finally achieved in October 2011. The study scheme consisted of the addition of midostaurin or placebo to standard intensive 7+3 induction chemotherapy as well as 4 cycles of high-dose cytarabine (HiDAC) as consolidation therapy. In all patients, maintenance therapy of one year with midostaurin or placebo according to initial randomization was intended. Although not specifically mandated, alloHCT was performed in first CR in 23% of the overall study cohort. The combination of midostaurin to intensive chemotherapy significantly improved OS in younger adults with *FLT3*-mutated AML with a hazard ratio of 0.78 (95%-CI: 0.63-0.96, p-value: 0.009), translating into a median OS of 74.7 months for the midostaurin arm (range, 31.5 months-not reached) as compared to 25.6 months for the placebo-arm (range, 18.6-42.9 months), respectively. Interestingly, this improvement was regardless of the *FLT3* mutational status (either ITD or TKD) or the *FLT3*-ITD allelic ratio [13]. Midostaurin (Rydapt®) is now approved for the treatment of AML in newly diagnosed patients who are *FLT3*-mutation-positive in combination with chemotherapy in Europe and US. Based on a phase-II follow-up study of the RATIFY trial in AML patients (age

18 to 70 years) with *FLT3*-ITD evaluating midostaurin in combination with intensive induction-, consolidation- including allo-HCT and maintenance-therapy in all patients the approval was extended to older patients aged between 60 and 70 years [76].

1.2.5 Quizartinib a potent FLT3 inhibitor

The oral second-generation bis-aryl urea inhibitor quizartinib is very specific for FLT3 tyrosine kinase, has a high capacity for sustained FLT3 inhibition and an acceptable toxicity profile [77]. In a phase II study (n=333) quizartinib demonstrated particular efficacy in patients with *FLT3*-ITD mutations (n=248) who were relapsed or refractory to 2nd-line, salvage chemotherapy or relapsed after allo-HCT [78]. The response to single agent quizartinib in *FLT3*-ITD positive patients was overall 50.4% (125/248), 56% in patients with r/r-AML with the first year of first-line therapy and 46% after allo-HCT. A subsequent phase II study recruited 76 patients with *FLT3*-ITD mutations, with r/r-AML after either one second line therapy or allo-HCT. Patients were randomized to single agent quizartinib 30 mg/day (Group A) or 60 mg/day (Group B) given as single agent orally during 28-day continuous treatment cycles, until relapse, intolerance or proceeding to allo-HCT. The response rate was 61% in Group A and 71% in Group B.. In addition, 32% of patients in Group A and 42% in Group B could be successfully bridged to allo-HCT [79]. Recently, first results of the randomized study in relapsed (with duration of first CR of 6 months or less)/refractory AML have been reported comparing single agent Quizartinib (n=245) to investigator's choice (n=122) [80]. In this setting single agent quizartinib improved significantly OS (hazard ratio 0.76 (95% CI 0.58-0.98; stratified log-rank test, 1-sided P=0.0177). Median OS was 27 weeks (95% CI 23.1-31.3) and 20.4 weeks (95% CI 17.3-23.7) for patients treated with quizartinib and investigator's choice, respectively. Estimated OS probability at one year was 27% for the Quizartinib and 20% for investigator's choice. Although quizartinib was superior compared to investigator's choice, results may be improved when quizartinib is combined with intensive chemotherapy. Feasibility of combination therapy with quizartinib and chemotherapy has been shown in several phase-II trials [81][82] leading to a double blinded, randomized phase III study of quizartinib with induction and consolidation chemotherapy and as maintenance in patients with newly diagnosed *FLT3*-ITD AML (ClincalTrials.gov identifier: NCT02668653) [83].

1.2.6 Clinical Experience with Quizartinib

As of 24 January 2017, a total of 1215 subjects received quizartinib in 16 studies including 743 patients and 472 healthy volunteers. A brief summary of previous studies is given below. Please refer to the most recent IB for additional information [84].

In the first in human Phase 1 study, CP0001, quizartinib was administered with intermittent dosing (14 days on drug followed by 14 days rest) from 12 mg to 450 mg and continuous dosing at 200 mg and 300 mg for 28 days in 76 patients with r/r-AML, regardless of *FLT3*-ITD mutation status [77]. Plasma taken from subjects and assayed in an in vitro plasma inhibitory assay (PIA) showed rapid and durable inhibition of FLT3 phosphorylation as early as 2 hours after the first dose. The overall response rate was 53% in *FLT3*-ITD (+) and 14% in *FLT3*-ITD (-) patients [77].

The response rate observed in Study CP0001 was confirmed in the Phase 2 study, AC220-002, of single agent quizartinib in relapsed or refractory AML. In this Phase 2 study a total of 333 patients were enrolled in 2 cohorts; Cohort 1 included patients 60 years or older who were relapsed or refractory to 1 line of therapy and Cohort 2 included patients 18 years or older who were relapsed or refractory to salvage therapy or relapsed after allo-HCT. In Cohort 1, the composite complete remission (CRc) rate was 57% in *FLT3*-ITD (+) patients with a median survival of 25.3 weeks [84][85]. Cohort 2 showed a CRc rate of 46% in *FLT3*-ITD (+) patients with a median survival of 24.0 weeks [84]. Importantly, 35% of Cohort 2 *FLT3*-ITD (+) patients were bridged to allo-HCT [86].

The maximum tolerated dose (MTD) determined in the Phase 1 study, CP0001, was 200 mg continuous daily dosing [77]. However, in the Phase 2 Study (AC220-002) 35% of patients experienced Grade 3 QT prolongation at the 200 mg dose and therefore the dose was reduced. A single case of Grade 4 QT prolongation, Torsades de Pointes, was reported in the AC220-002

Study in a patient with pneumonia, atrial fibrillation, taking concomitant medications known to cause QT prolongation [87]. No deaths related to QT prolongation have been reported [84].

A Phase 2b Study (2689-CL-2004) was subsequently conducted, which enrolled 76 patients with *FLT3*-ITD (+) AML randomized to 60 mg or 30 mg daily, to examine efficacy and toxicity at these lower doses. Both males and females were randomized at each dose. The study showed that the CRc rate was similar at both lower doses and to that observed in the earlier Study AC220-002 (Table 1) [88]. QT prolongation was dose-dependent and was substantially reduced at the lower doses (Table 2).

Table 1: Summary of the Efficacy Findings Across all 5 Daily Doses Studied in the Phase 2 Program

Study	**2689-CL-2004**		**AC220-002**		
Quizartinib Dose	**30 mg (N=38)**	**60 mg (N=38)**	**90 mg (N=57)**	**135 mg (N=67)**	**200mg (N=12)**
CRc rate	47%	47%	47%	45%	42%
Partial Remission rate	13%	24%	25%	28%	50%

CR=complete remission; CRc=composite complete remission (CR+CRp+CRi); CRi=CR with incomplete neutrophil recovery; CRp=CR with incomplete platelet recovery. [88]

Table 2: Summary of the QTcF Findings Across all 5 Daily Doses Studied in the Phase 2 Program

Study	**2689-CL-2004**		**AC220-002**		
Quizartinib Dose	**30 mg (N=38)**	**60 mg (N=36)[a]**	**90 mg (N=57)**	**135 mg (N=67)**	**200mg (N=12)**
Maximum value of QTcF (msec)					
>480 to ≤500 (Grade 2)	5%	14%	21%	13%	33%
>500 (Grade 3)	5%	3%	21%	15%	42%
Maximum change in QTcF from baseline (msec)					
≤30	50%	44%	9%	9%	0%
>30 to ≤60	47%	36%	46%	51%	8%
>60	5%	19%	46%	39%	92%

QTcF=QT interval corrected with Fridericia's formula; a:Two subjects in the 60 mg/day group were randomized but never treated with quizartinib. [89]

Common adverse events (AEs) observed in the Phase 1 and 2 studies included gastrointestinal disorders (nausea, diarrhea, and vomiting), hematologic disorders (anemia, neutropenia, and thrombocytopenia), febrile neutropenia, fatigue, and QT prolongation.

Although hematologic toxicity is associated with underlying disease, safety reports from Study AC220-002 in AML indicate delayed recovery or continued suppression of absolute neutrophil counts (ANC) and platelets as a consequence of continued treatment with quizartinib [84].

There are insufficient data to exclude the risk of phototoxicity/photosensitivity reactions due to quizartinib. Excessive exposure to sunlight and other Ultra Violet (UV) light exposure should be avoided. Patients should be advised to contact the Investigator if they develop a rash or exaggerated sunburn in exposed areas of skin.

1.2.6.1 Clinical Pharmacology

The tablet formulation, which is used in this Phase 2 study, exhibited comparable relative bioavailability to the solution formulation which was administered in the earlier Phase 1 and 2 studies. In a relative bioavailability study (AC220-014) in fasting, healthy volunteers and oral administration of a single 60 mg dose (2x30 mg tablets) of quizartinib, the median time to maximum plasma concentration (Tmax) was 4 (minimum, 2; maximum; 8) hours for quizartinib and 8 (minimum, 4; maximum; 48) hours for AC886 (the major active metabolite of quizartinib, with similar potency to the parent molecule, quizartinib). The geometric mean (coefficient of variation [CV] %) terminal half-life was 64.9 (75%) hours and 53.5 (40%) hours for quizartinib and AC886, respectively.

Quizartinib and AC886 showed dose-proportional increases in area under the concentration vs time curve (ng•h/mL) (AUC) and maximum plasma concentrations (Cmax) over the tested dose range of 30 to 90 mg [84].

Following a single-oral dose of [^{14}C]-quizartinib, 76.3% of total radioactivity was recovered in feces with only 1.6% recovered in urine 14 days after dosing (AC220-006). Excretion of radioactivity was still ongoing at study completion at Day 14, mainly in feces. AC886 was the only major circulating metabolite and is formed by cytochrome P450 (CYP3A4) [84].

In a Phase 2b study, 2689-CL-2004, in which AML patients receiving multiple doses of quizartinib at 30 mg/day or 60 mg/day, steady-state was reached by Day 15 for both quizartinib and AC886, consistent with the terminal half-life of approximately 3 days observed in healthy subjects. Geometric means (CV%) of the metabolite to parent ratios (Area under the concentration versus time curve (ng•h/mL) from the time 0 to 24 hours [AUC0-24]) were 0.40 (124%) and 0.35 (91.0%) for 30 mg/day and 60 mg/day, respectively, on Day 1 and were 0.52 (123%) and 0.54 (138%) for 30 mg/day and 60 mg/day, respectively, on Day 15.

Previous analysis evaluated QT interval corrected with Fridericia's formula (QTcF) prolongation (change from baseline in QTcF [ΔQTcF]) and concentration relationship with pharmacokinetics (PK) and electrocardiogram (ECG) data collected from Study 2689-CL-2004, where ΔQTcF was derived from the differences of QTcF at the time of interest and QTcF at the predose. This analysis did not include circadian dependent changes in QTcF. An updated analysis was performed by incorporating circadian rhythm using a non-linear mixed effect model. The covariates evaluated were quizartinib and AC886 plasma concentrations and sex. QTcF changes with circadian rhythm and is linearly dependent on quizartinib plasma concentrations. AC886 plasma concentrations and sex are not significant covariates for the QTcF prolongation. This updated model was used to predict QTcF prolongation at steady state geometric mean Cmax normalized to 40 mg. The analysis predicted that administration of 40 mg/day quizartinib with dose reduction to 20 mg/day for the subjects on strong CYP3A4 inhibitors resulted in the upper 90% confidence interval (CI) of ΔQTcF less than 17 msec.

A drug-drug interaction study assessing the effect of strong and moderate CYP3A4 inhibitors on quizartinib PK showed that concomitant ketoconazole, a strong CYP3A4 inhibitor, and concomitant fluconazole, a moderate CYP3A4 inhibitor, resulted in an increase in quizartinib area under the concentration versus time curve (ng•h/mL) from the time of dosing extrapolated to infinity (AUC0-inf) values, approximately 2-fold and 1.2-fold, respectively. Additionally, concomitant ketoconazole and concomitant fluconazole resulted in an increase in predicted quizartinib Cmax at steady state after repeat daily dosing, approximately 2-fold and 1.2-fold, respectively.

A drug-drug interaction (DDI) study was conducted with the proton pump inhibitor lansoprazole. Healthy subjects were randomized to receive quizartinib 30 mg alone or lansoprazole 60 mg administered once daily for 5 days with a single dose of quizartinib 30 mg administered on day 5. A weak PK drug-drug interaction was observed between quizartinib and lansoprazole. Cmax and AUC decreased 14% and 5%, respectively, for quizartinib. However, the decrease in quizartinib exposure is not considered to be clinically significant. Other types of gastric pH modifiers (e.g. antacids and H2 antagonists) are also not expected to have a clinically significant DDI with quizartinib.

A food-effect study involving single-dose administration of a 30-mg tablet of quizartinib to healthy volunteers under fasting conditions or with a high-fat meal indicated that AUC was increased by

approximately 8% while the 90% CI of the Cmax ratio of fed to fasting condition was contained within the 80 to 125% interval. This increase in exposure is not clinically significant, and therefore quizartinib can be taken with or without food. However, food did prolong the time to peak concentrations, time to maximum plasma concentration (Tmax), by approximately 2 hours.

1.2.6.2 Combination Studies with Induction Chemotherapy

Study 2689-CL-0005 is a Phase 1, open-label, multiple-dose, dose-escalation study in patients with newly diagnosed AML [*FLT3*-ITD (+) or *FLT3*-ITD (-)]. The treatment and follow-up phase of the study has been completed.

The dose escalation was conducted using a modified 3+3 design, where 6 patients were enrolled at each dose level. The patients were given cytarabine 200 mg/m^2 × 7 days and daunorubicin 60 mg/m^2 × 3 days (7+3) for induction and high dose intermittent cytarabine 3 g/m^2 every 12 hours on Days 1, 3, and 5 for consolidation. Quizartinib was administered daily for either 7 or 14 days, starting at Day 4 of induction and/or consolidation chemotherapy. Patients were allowed to proceed directly to allo-HCT after achieving a response or receive further quizartinib as maintenance therapy after consolidation if they were not transplant eligible. Three dose levels were tested; 60 mg × 7 days, 60 mg × 14 days, and 40 mg × 14 days. Through May 31, 2013 18 patients were enrolled in the study. The median age of the patients was 43 years (minimum, 22; maximum, 60). Of those, 16 were *FLT3*-ITD mutated. At 60 mg × 7 days, one of the 6 patients had a dose limiting toxicity (DLT, grade 3 hyponatremia). At 60 mg × 14 days, 2 of the 6 patients had a DLT (Grade 3 QT corrected [QTc] prolongation and Grade 4 pericarditis) which exceeded the pre-specified criteria. Thus, 40 mg × 14 days was then explored. At 40 mg × 14 days, 1 of the 6 patients had a DLT (Grade 3 constrictive pericarditis). The most common (20%) treatment related AEs were nausea (42%), diarrhea (32%), anemia (26%), febrile neutropenia (26%), neutropenia (21%), fatigue (21%), pyrexia (21%) and thrombocytopenia (21%). The most common (10%) Grade 3 or 4 treatment-related AEs were febrile neutropenia (26%), thrombocytopenia (21%) anemia (21%), neutropenia (21%), leukopenia (16%), and nausea (11%). The maximum tolerated dose was identified as 40 mg for 14 days or 60 mg for 7 days [84][90].

The AML18 pilot quizartinib dose-escalation study was an Investigator-sponsored study conducted in the UK that enrolled newly diagnosed (*FLT3* [+] and *FLT3* [-]) AML patients greater than 60 years old [84]. Quizartinib was administered with standard chemotherapy comprised daunorubicin, cytarabine, and etoposide [82]. Six cohorts with escalating doses of quizartinib (60 mg, 90 mg or 135 mg based on doses used in the Phase 2 AC220-002 study with quizartinib) for 7 or 14 days were planned. If 60 mg was not tolerated dose de-escalation to 40 mg for 7 or 14 days was allowed. Because of the presumed increased sensitivity in females to QTc prolongation, each cohort required a minimum of 3 females. The day of safety evaluation was on completion of the chemotherapy in course 2.

Fifty-five patients with a median age of 69 years (minimum, 62; maximum, 87) were enrolled, of whom 48 were evaluable. Four patients were *FLT3*-ITD (+). Thirteen patients (4 males, 9 females) entered Cohort 1 (60 mg for 7 days). No DLTs were seen in males, but 3 DLTs occurred in females (all grade 4: 1 cardiac (myocardial infarction), 1 hypokalemia; 1 mucositis). Thus, this cohort exceeded tolerability for female. Eight patients (all males) entered Cohort 2 (60 mg for 14 days), where 4 DLTs (all grade 3; 3 QTc prolongation, 1 appetite loss) were seen. Thus, this cohort exceeded tolerability for males [82].

In the 40 mg for 14 day cohort, there was 1 DLT (hematological) of 5 evaluable males and 0 of 8 evaluable females. Induction death (death within 30 days) occurred in 3/46 (6.5%) evaluable patients. CR was achieved in 33/42 (79%; including all 4 *FLT3*-ITD [+]) of patients evaluable for CR. Overall median time to neutrophil and platelet count recovery (neutrophils to 1000/mm^3; platelets to 100 000/mm^3) was prompt (28 and 22 days post Course 1; 22 and 19 days post Course 2, respectively). None of the patients received an allo-HCT.

Based on data from these 2 clinical studies, quizartinib is predicted to be tolerated and provide sufficient clinical benefit administered in patients as 40 mg dose once daily.

1.3 Trial Rationale/ Benefit- Risk Assessment

Despite intensive therapy, the long-term outcome of AML patients remains poor, with less than 30% of patients achieving long lasting remission [1][2]. This poor outcome is largely due to refractoriness to induction chemotherapy [10] as well as relapses during and after completion of intensive induction and consolidation therapy [11]. Regarding refractoriness, about 20-30% of AML patients under the age of 60 years and about 50% of older patients fail to attain CR following cytarabine plus anthracycline based standard induction therapy. Patients having achieved CR are at high risk of relapse, particularly within the first two years after completion of chemotherapy, with 50-60% of AML patients under the age of 60 years and up to 90% of older patients [12]. Allo-HCT is currently the only treatment strategy to offer the prospect of cure in r/r-AML; but outcome after allo-HCT is largely determined by the remission status before allo-HCT [12]. Consistently, *FLT3*-ITD has been identified as an unfavorable molecular marker in both relapsed and refractory AML. Patients with refractory disease exhibiting a *FLT3*-ITD have despite an allo-HCT a 1.5 (range 1.2-1.7) higher probability of death [10]. In patients with relapse disease exhibiting an *FLT3*-ITD, the situation is even worse with dramatic low probability achieving a CR and a survival below 20% after 3 years [11]. In contrast, studies in r/r-AML with single agent second generation FLT3 inhibitors show high efficacy in terms of remission induction but not long term survival [78][91]. Results from first-line treatment trials indicate that combination of chemotherapy with FLT3 inhibitors is safe [13][76][81][82][83] and effective in terms of improving long term outcome [13][76]. Thus, to evaluate the combination of salvage chemotherapy with Quizartinib in r/r-AML appears as a logic consequence in terms of efficacy and safety.

1.3.1 Consideration of SARS-CoV-2 Pandemic

Acute myeloid leukemia is a medical/hematological urgency. Without treatment 50% of the patients die within 3 months and survival after one year is below 5%. Therefore, all patients are treated immediately whenever possible. In addition, despite intensive chemotherapy most relapsed/refractory patients die of their disease. Hence, there is a high medical need to improve outcome in this patient population. This can only be achieved, if patients are treated within clinical studies and this applies as well during the SARS-CoV-2 pandemic.

1.4 Reference Committees

1.4.1 Data Monitoring Committee (DMC)

Before start of the trial a DMC is assembled. The DMC is composed of three independent experts, assessing the progress and safety data. The mission of the DMC is to ensure the ethical conduct of the trial and to protect the safety interests of patients in this trial.

The DMC meets regularly. Based on its review, the DMC provides the sponsor with recommendations regarding trial modification, continuation or termination.

Further details including DMC members are specified in the DMC charter.

2 Trial Objectives

2.1 Primary Objective

Assess CR and CRi after salvage therapy with Q-HAM according the ELN 2017 criteria [1]

The endpoints are described chapter 10.2.

2.2 Secondary Objectives

Assess event-free survival (EFS), relapse-free survival (RFS), overall survival (OS), cumulative incidence of relapse (CIR) and death (CID) and patient reported outcomes (PRO) according to continuation therapy strategy (preemptive vs. prophylactic)

The endpoints are described chapter 10.2.

3 Trial Design

In this multicenter, upfront randomized phase II trial, all patients receive quizartinib in combination with HAM (high-dose cytarabine, mitoxantrone) during salvage therapy. Efficacy is assessed by comparison to historical controls based on the matched threshold crossing approach. During consolidation therapy (chemotherapy as well as allo-HCT) patients receive either prophylactic quizartinib therapy or MRD-triggered preemptive continuation therapy with quizartinib according to up-front randomization.

See chapter 6.3 for the details on the administration schedule.

See chapter “Trial Schedule” on page 13 for a detailed narrative of the trial schedule.

4 Trial Duration

Study duration and expected dates are indicated below. Recruitment is estimated to take 2 years. Each patient stays at least 2 years in the study. The overall duration of the trial is expected to be approximately 5 years with 4 years clinical phase. The actual starting date, overall duration and recruitment may vary.

See Trial Schedule on page 13 for detailed information on overall and individual duration.

Trial Duration and expected Dates

Total trial duration:	5 years (2019-09 – 2024-09)
Duration of the clinical phase:	4 years (2019-09 – 2023-09)
First patient first visit (FPFV):	2020-04
Last patient first visit (LPFV):	2022-04 (FPFV + 2 years)
Last patient last visit (LPLV), End of study (EOS):	2024-04 (LPFV + 2 years)
Trial Report Completed:	2025-04 (LPLV + 1 year)

5 Selection of Patients

5.1 Number of Patients, Recruitment and Drop-out rates

As described in section 10.3, 80 patients have to be enrolled in the clinical trial. Following a 1:1 randomization 40 patients are allocated to each arm.

Recruitment and treatment of patients is performed in 20 or more centers to recruit the intended number of patients. Expecting a number of at least 4 eligible patients per year and center, 2 years are required to recruit the intended number of patients.

5.2 General Criteria for Patients’ Selection

This clinical trial can fulfill its objectives only if appropriate patients are enrolled. The following eligibility criteria are designed to select patients for whom protocol treatment is considered appropriate. All relevant medical and non-medical conditions should be taken into consideration when deciding whether this protocol is suitable for a particular patient. Any questions regarding a patient’s eligibility should be discussed with the Coordinating Investigator or the Medical Coordinator.

General: Older patients with relapsed/refractory AML who are eligible for intensive therapy may be included.

Sex: AML has been shown to be slightly more frequent in males. However, outcome has not been shown to be related to sex. Neither the pharmacokinetic nor the pharmacodynamic data of the IMP showed a correlation with sex.

Ethnicity: AML has been shown to occur in all ethnicities without impact on outcome after correction for confounding co-variables. Neither the pharmacokinetic nor the pharmacodynamic data of IMP showed a correlation with ethnicity.

Patients entirely depending on the sponsor or investigator must not be included in this study.

5.3 Inclusion Criteria

1. Patients with acute myeloid leukemia according to the 2016 WHO classification (except acute promyelocytic leukemia) who are either
   A) refractory to induction therapy or
   B) relapsed after first line treatment including chemotherapy, autologous and/or allo-HCT (details below).
2. Positive for *FLT3*-ITD (defined as a ratio of mutant to wild-type alleles of at least 0.05; measured within 4 weeks before inclusion)#
3. ECOG performance status ≤ 2. See appendix 18.1
4. Adequate renal function defined as creatinine clearance >50 mL/min (calculated using the standard method for the institution)
5. Discontinuation of prior AML treatment for at least
   - 10 days for cytotoxic agents and
   - 28 days for investigational drug treatment

   before the start of study treatment (except hydroxyurea to control hyperleukocytosis)
6. Age ≥ 18 years and ≤ 75 years
7. Pregnancy and childbearing potential:
   - Non-pregnant and non-nursing women
   - Women of childbearing potential (WOCBP) must have a negative serum or urine pregnancy test within a sensitivity of at least 25 mIU/mL within 48 hours prior to randomization ("Women of childbearing potential" is defined as a sexually active mature woman who has not undergone a hysterectomy or who has had menses at any time in the preceding 24 consecutive months).
   - WOCBP must agree to avoid getting pregnant while on therapy: WOCBP must either commit to continued abstinence from heterosexual intercourse or begin one acceptable method of birth control (IUD, tubal ligation, or partner's vasectomy) during study and 6 months after end of study/treatment.
   - Men must use a latex condom during any sexual contact with WOCBP, even if they have undergone a successful vasectomy and must agree to avoid to father a child during study and 6 months after end of study/treatment
8. Signed written informed consent
9. Ability of patient to understand character and consequences of the clinical trial

A) Refractory to induction therapy is defined as no CR, or CRi, or PR (according to standard criteria) [1] after 1 or 2 intensive induction cycles of at least 7 days of cytarabine 100-200mg/m² continuously or an equivalent regimen with cytarabine with total dose not less than 700mg/m² per cycle and 2 days of an anthracycline (e.g. daunorubicin, idarubicin).

B) Relapsed after first line therapy is defined as relapsed AML (according to standard criteria) [1] after a first line therapy including at least one intensive induction and consolidation therapy including (but not limited to) allo-HCT.

Secondary exclusion if *FLT3*-ITD cannot be verified by central testing. Patient already receiving Quizartinib may continue taking it and will be excluded after the first treatment cycle.

5.4 Exclusion Criteria

1. Acute promyelocytic leukemia (AML FAB M3 with t(15;17)(q22;q12) / *PML-RARA*)
2. Patients with known CNS leukemia

3. Isolated extramedullary manifestation of AML
4. Patients with a “currently active” second malignancy other than non-melanoma skin cancer. Patients are not considered to have a “currently active” malignancy if they have completed therapy for more than one year and are considered by their physician to be at less than 30% risk of relapse within one year
5. Hyperleukocytosis (leukocytes > 30,000/µl) at the time of study entry. 1)
6. Uncontrolled or significant cardiovascular disease, including any of the following:
    - History of heart failure NYHA class 3 or 4
    - Left ventricular ejection fraction (LVEF) ≤ 40% by echocardiogram (ECHO)
    - History of uncontrolled angina pectoris or myocardial infarction within 12 months prior to screening
    - History of second (Mobitz II) or third degree heart block or any cardiac arrhythmias requiring anti-arrhythmic therapy (beta blockers or digoxin are permitted)
7. Inadequate liver function: ALT and AST ≥ 2.5 x ULN), total bilirubin ≥ 1.5 x ULN; Alkaline phosphatase ≥ 2.5 x ULN. Known liver cirrhosis or history of veno-occlusive disease (VOD) or history of Sinusoidal Obstruction Syndrome (SOS)
8. Known positivity for HIV, active HBV, HCV or hepatitis A infection (active hepatitis B defined by HBs Ag positivity, active hepatitis C defined by positive virus load)
9. Uncontrolled active infection
10. Evidence or history of severe non-leukemia associated bleeding diathesis or coagulopathy
11. within 100 days after allo-HCT
12. clinically relevant Graft-versus-Host-Disease (GvHD) requiring initiation of treatment or treatment escalation within 21 days prior to screening
13. Any one of the following ongoing or in the previous 6 months: congenital long QT syndrome, Torsades de pointes, arrhythmias (including sustained ventricular tachyarrhythmia), right or left bundle branch block and bifascicular block, unstable angina, coronary/peripheral artery bypass graft, cerebrovascular accident, transient ischemic attack or symptomatic pulmonary embolism; as well as bradycardia defined as <50 bpms
14. QTc interval >450 msec using the Fredericia correction (QTcF).
15. Patients known to be refractory to platelet or packed red cell transfusions as per institutional guidelines, or who are known to refuse or who are likely to refuse blood product support.
16. Severe neurologic or psychiatric disorder interfering with ability of giving informed consent
17. Known or suspected active alcohol or drug abuse
18. No consent for registration, storage and processing of the individual disease-characteristics and course as well as information of the family physician about study participation.
19. Pregnancy and lactation
20. History of hypersensitivity to the investigational medicinal product or to any drug with similar chemical structure or to any excipient present in the pharmaceutical form of the investigational medicinal product
21. Prior treatment with quizartinib

1) These patients should be treated with hydroxyurea according to routine practice and are only allowed to enter into the study when leukocyte counts of 30,000/µl or below are reached. If hydroxyurea is not sufficient to control hyperleukocytosis, i.v. application of 100mg cytarabine continuously over 24 hours may be discussed with the Principle Investigator or the Medical Coordinator.

5.5 Reproduction Guidelines

In this study, male patients who are able to father children and female patients who are of childbearing potential will receive quizartinib that has been associated with teratogenic risk. Patients who are, sexually active and at risk for pregnancy with their partner(s) must agree to use at least 1 highly effective form of contraception throughout the study and for at least 6 months after the last dose of investigational product. Male patients must additionally use a condom to

prevent potential transmission of investigational product in seminal fluid. The investigator or his or her designee, in consultation with the patient, will confirm that the patient has selected at least 1 appropriate method of contraception for the individual patient and his/her partner(s) from the list of permitted contraception methods (see below) and will confirm that the patient has been instructed in their consistent and correct use. At time of inclusion, the investigator or designee will inform the patient of the need to use at least 1 highly effective method of contraception consistently and correctly and document the conversation, and the patient's affirmation, in the patient's medical file. In addition, the investigator or designee will instruct the patient to call immediately if the selected contraception method is discontinued or if pregnancy is known or suspected in the patient or partner(s).

Highly effective methods of contraception are those that, alone or in combination, result in a failure rate of less than 1% per year when used consistently and correctly (i.e., perfect use) and include the methods described in Table 3.

Table 3: Methods of Birth Control

Highly effective (failure rate <1% if used consistently and correctly), low user dependency	**Highly effective (Failure rate <1% if used consistently and correctly), high user dependency**
• Progestogen only contraceptive implant • Intrauterine hormone releasing system (IUS) • Intrauterine device (IUD) • Bilateral tubal occlusion	Combined hormonal contraception (estrogen and progestogen) • Oral • Intravaginal • Transdermal • Injectable
Vasectomized partner: A vasectomized partner is a highly effective form of contraception provided they are the sole male partner of the WOCBP and the absence of sperm has been confirmed. If not an additional highly effective method of contraception should be used	Progestogen only hormonal contraception • oral • injectable

5.6 Criteria for Withdrawal & Discontinuation of Study Drug

In accordance with the Declaration of Helsinki and other applicable regulations, a patient has the right to withdraw consent from study procedures or to discontinue the study drug at any time and for any reason without prejudice to his or her future medical care by the Investigator or at the Study Center.

5.6.1 Reasons for Permanent Discontinuation of Study Drug

Quizartinib will be permanently discontinued for any of the following reasons:

- Adverse Event:
  - Intolerable AE related to quizartinib, including Grade 4 QTcF prolongation;
  - Any clinical AE or abnormal laboratory test result indicating, in the Investigator's opinion, that continued quizartinib dosing is not in the patient's best interest;
- Unacceptable toxicity dictating cessation of treatment
- Changes in medical status of the patient such that the investigator believes that patient safety will be compromised or that it would be in the best interest of the patient to stop treatment
- Refractory disease after salvage therapy

- Relapse
- Institution of nonprotocol specified AML therapy (prophylactic intrathecal therapy and DLI are permitted);
- Pregnancy
- At any time at request of the participant
- Patient withdrawn from study for any reasons

Investigators should contact the Medical Coordinator if they want to permanently discontinue quizartinib for reasons other than those listed above. Permanent discontinuations of quizartinib including the reason must be recorded. In case of questions regarding continuation of quizartinib, the Investigator should consult with the Medical Coordinator and/or Coordinating Investigator.

Patients permanently discontinuing the study drug (partial withdrawal, see5.6.2.1) are followed using the procedures described for the Safety and Observational Follow-up (see Trial schedule page 13) and have their EOT visit scheduled immediately.

5.6.2 Withdrawal from Study

The duration of subject participation in the study will prematurely terminated if one of the following occurs:

- Patient's death
- Study closure or termination
- Patient's withdrawal of consent from study participation (see 5.6.2.1)
- Investigator withdraws the patient from study (see 5.6.2.2)
- Patient lost to follow-up (see 5.6.2.4)

If a patient is withdrawn from the study, the Investigator will complete and report the observations as thoroughly as possible up to the date of withdrawal including the date of last treatment and the reason for withdrawal. All patients who are withdrawn from the study should complete protocol-specified withdrawal procedures.

5.6.2.1 Withdrawal of Consent from Study Participation

Only patients who refuse all of the following procedures will be considered to have withdrawn consent from study participation:

1. Treatment with study drug (partial withdrawal)
2. Attendance at study visits and or follow-up visits per protocol (complete withdrawal)

If the patient refuses the above mentioned procedures, the Investigator should personally speak to the patient. If medically indicated, efforts should be made to continue participation and thus treatment or at least within the Follow-up. The reason of withdrawal should be asked for and documented.

If the patient withdraws consent for disclosure of future information (e.g. complete withdrawal), no further evaluations are allowed to be performed and no additional data can be collected. The sponsor may retain and continue to use any data collected before such withdrawal of consent.

5.6.2.2 Investigator withdraws a patient from study

The investigator may withdraw a patient from the study in the following cases:

- Non-compliance by the patient with protocol requirements to an extend that may impact the scientific integrity of the study

Investigators should contact the Medical Coordinator if they want to withdraw a patient from the study.

5.6.2.3 Violation of inclusion criteria FLT3-ITD

If *FLT3*-ITD cannot be verified by central testing the patient has to be withdrawn from the study and replaced. Patients receiving Quizartinib within the first treatment cycle may continue until completion of the first cycle.

5.6.2.4 Patients Lost to Follow-up

The Investigator will make every effort not to have any patients Lost to Follow-up. If a patient is potentially Lost to Follow-up (e.g. missed study visits, unable to be contacted by phone), the Investigator will make every effort to contact the patient before the patient is declared Lost to Follow-up. Patients will not be classified as Lost to Follow-up unless all actions have been exhausted and documented.

5.6.3 Handling of Withdrawals and Permanent Discontinuation of Study Drug

- In all cases, the reason for withdrawal / discontinuation must be recorded in the case report form (CRF) and in the patient's medical records.
- Unresolved AEs should be followed.
- Patients discontinuing the study drugs and patients withdrawn from the study are not to be excluded from analyses. They must be taken into account appropriately during analyses to prevent biased results.

5.6.4 Replacement of Patients

Randomized patients who do not receive salvage therapy with the IMP quizartinib for any reasons will be replaced. All patients receiving at least one dose of the IMP quizartinib must not be replaced.

5.6.5 Premature Closure of the Clinical Trial or a Single Center

The trial can be prematurely closed or suspended by the Sponsor after consulting the Coordinating Investigator. The Ethics Committee (EC) and the competent higher regulatory authorities must then be informed. Furthermore, the Ethics Committee(s) and competent higher regulatory authorities themselves may decide to stop or suspend the trial.

Should the trial be closed prematurely, all trial material (completed, partially completed, and blank CRFs, IMP and other material) must be returned to the Sponsor or treated according to Sponsor notice.

All involved investigators have to be informed immediately about a cessation/ suspension of the trial. The decision is binding to all trial centers and investigators.

The Sponsor after consulting the Coordinating Investigator has the right to close a center, at any time, in case of:

- Non-compliance with the protocol
- Poor data quality
- No recruitment in 6 months
- Potential danger for study participants
- Danger for the scientific integrity of the trial

5.7 Prior and Concomitant Illnesses

Relevant illnesses present at the time of informed consent are regarded as concomitant illnesses and will be documented on the appropriate pages of the case report form (CRF). Included are conditions that are seasonal, cyclic, or intermittent (e.g. seasonal allergies; intermittent headache).

Abnormalities which appear for the first time or worsen (intensity, frequency) during the trial are adverse events (AEs) and must be documented on the appropriate pages of the CRF.

5.8 Background Medication

As background therapy the patients receive high dose cytarabine (HiDAC) combined with mitoxantrone (HAM regimen) during salvage and consolidation therapy.

See chapter 6.3 for the details on the administration schedule.

5.9 Prior and Concomitant Medication / Non-Drug Treatment

All concomitant medications and treatments must be recorded in the CRF. Any prior treatment received within 28 days prior to study entry (including hematopoietic growth factor receptor agonists: erythropoietin, granulocyte colony stimulating factor (G-CSF), romiplostim, eltrombopag) will be recorded in the CRF.

Every concomitant treatment, blood products, any transfusion (red blood cells or platelets), growth factors, as well as interventions, required by the patients during the active study treatment (and up to 28 days following last study drug administration or until initiation of another anti-cancer treatment) and the reason for its administration must be recorded on the CRF.

All concomitant medications the patient receives must be reviewed by the Investigator prior to enrollment.

5.9.1 Restricted or Prohibited Concomitant Medications

Subjects may not receive concomitant chemotherapy, immunotherapy, radiotherapy, transplant, or any ancillary therapy for AML that is not specified in the protocol, or that is considered to be investigational (i.e., used for non-approved indication(s) and in the context of a research investigation) while on quizartinib. Donor lymphocyte infusion (DLI) after allo-HCT is permitted.

Medications associated with QT/QTc prolongations are prohibited (see list in appendix 19.1). Exceptions are made for antibiotics, antivirals, and antifungals that are used as standard of care for the prevention or treatment of infections or if the Investigator believes that beginning therapy with a potentially QTc-prolonging medication (such as anti-emetic) is vital to an individual patient's care while on study. In that case additional ECG monitoring is performed at the commencement of such a medication or from when there is an increase in its dosage.

See Section 6.2 for guidelines on monitoring and managing QTc prolongation.

Strong CYP3A4 inhibitors should be avoided if possible but may be given with a corresponding dose reduction for quizartinib (see chapter 6.3.1). There are no restrictions for moderate or weak CYP3A4 inhibitors (see list in appendix 19.2).

Strong or moderate CYP3A4 inducers must not be used (see list in appendix 19.3).

If quizartinib is co-administered with drugs that are substrates of P-gp, increased concentrations of the substrate drugs are possible and caution should be exercised.

6 Investigational Medicinal Products

6.1 Quizartinib

6.1.1 General Information

Investigational medicinal product:

Drug Code:	AC220
International Nonproprietary Name (INN):	**Quizartinib**
ATC code, if officially registered:	n.a.
Pharmaceutical formulation:	20 mg coated tablets
Route of administration:	Orally
Storage conditions:	HDPE bottles with child-resistant caps. Store up to 25ºC, do not freeze.
Manufacturer / Importer:	Daiichi Sankyo Europe GmbH
License Number	Not yet approved

6.1.2 Summary of Quizartinib Product Profile

Quizartinib is a Class III receptor tyrosine kinase (RTK) inhibitor exhibiting highly potent and selective inhibition of FLT3. Quizartinib is currently being studied as a treatment for AML.

Complete information for Quizartinib is laid down in the Investigator Brochure (IB) [84].

6.1.3 Warning and Precautions

6.1.3.1 Risk of QT Interval Prolongation

Quizartinib can prolong the QT/QTc interval. QT/QTc interval prolongation increases the risk for ventricular arrhythmias.

Quizartinib should be used with caution in patients who have or who are at significant risk of developing prolongation of QT. Concomitant administration of quizartinib with strong CYP3A4 inhibitors may increase the plasma concentration of quizartinib and therefore may increase the risk of QTc prolongation. For concomitant administration dose reduction of quizartinib is required (see chapters 6.2 and 6.3.1).

Close monitoring of the QTcF interval is advisable and a baseline ECG is scheduled prior to initiating therapy with quizartinib. Electrolyte abnormalities (hypomagnesemia, hypokalemia, and hypocalcemia) should be corrected prior to quizartinib administration and should be kept within upper normal range and should be closely monitored during therapy especially in subjects with congestive heart failure, bradyarrhythmias, and receiving concomitant drugs known to prolong the QT interval, including Class Ia and III antiarrhythmics [84].

Complete information for Quizartinib is given in the Investigator Brochure (IB) [84].

See Section 6.2 for guidelines on monitoring and managing QTc prolongation.

6.1.3.2 Differentiation syndrome (DS)

Quizartinib can cause terminal differentiation of AML blast cells in patients with relapsed or refractory disease, which may be associated with the development of differentiation syndrome and may be life-threatening or fatal if not treated. Symptoms of differentiation syndrome are dyspnea, fever, peripheral edema, hypotension, weight gain, pleuro-pericardial effusion, acute renal failure, musculoskeletal pain, and hyperbilirubinemia. Less commonly, DS might present with pulmonary hemorrhage or acute febrile neutrophilic dermatosis. It is important to promptly

recognize the signs and symptoms of differentiation syndrome and implement appropriate treatment. Patients with suspected differentiation syndrome should promptly start treatment with systemic glucocorticoids and hemodynamic monitoring until improvement.

Complete information for Quizartinib is given in the Investigator Brochure (IB) [84].

6.1.3.3 Myelosuppression

Concomitant administration of quizartinib with strong CYP3A4 inhibitors may increase the plasma concentration of quizartinib and therefore may increase the risk of myelosuppression. If administered concomitantly, a dose reduction of quizartinib is required (see chapters 6.2 & 6.3.1).

Treatment with quizartinib can cause Grade 3/4 thrombocytopenia, neutropenia and anemia. [84].

Complete information for quizartinib is given in the Investigator Brochure (IB) [84].

6.1.4 Known Adverse Drug Reactions

Adverse reactions with quizartinib from studies to date include general disorders (e.g. pyrexia and fatigue), gastrointestinal disorders (e.g., nausea, diarrhea, and vomiting), hematologic disorders (e.g., anemia, neutropenia, and thrombocytopenia), QTc prolongation, Torsades de Pointes, neutrophilic dermatosis/differentiation syndrome/pyoderma gangrenosum and the consequences of cytopenias including increased risk of infection and bleeding. Infections and bleeding resulting from cytopenias may be severe and may result in fatal outcome [84].

Serious AEs of myelosuppression (e.g. neutropenia, bone marrow hypocellularity, lymphocytopenia, anemia, thrombocytopenia, and pancytopenia) have been observed which may result in infections or hemorrhage. Resulting infections (particularly, but not exclusively, fungal and other opportunistic infections, Gram negative bacterial infections, and bacteremia/septicemia/sepsis) or hemorrhage (e.g. epistaxis, hemoptysis, melena, gastrointestinal bleeding, and hemorrhage intracranial) may be severe, including fatal outcome. Reports of infection have often been in the context of neutropenia, fever or both [84].

Quizartinib is associated with QTc prolongation in a dose dependent manner. The incidence of QTcF > 500 msec was 3 to 5% among subjects receiving 30 to 60 mg quizartinib daily, 15 to 17% among subjects receiving 90 to 135 mg daily, and 35% among 17 subjects receiving 200 mg daily. Subjects who have experienced severe QTc prolongation while receiving quizartinib have typically been asymptomatic [84].

A list of adverse drug reactions reported in long term clinical studies is given in appendix 18.4.

Complete information for quizartinib is given in the Investigator Brochure (IB) [84].

6.2 QTcF Prolongation

Subjects taking quizartinib who experience QTcF prolongation >480 msec should be managed according to the guidelines below:

QTcF >480 msec ≤500 msec

- Electrolytes (potassium, calcium, and magnesium) should be checked and supplementation given to correct any values outside the normal range; Concomitant

medications should be reviewed to identify and, if appropriate, discontinue any medication with known QT prolonging effects.
- The dose of quizartinib will be reduced by at least 50%without interruption of dosing.
- Following dose reduction, the quizartinib dose may be resumed at the previous level in the next cycle if the QTcF has decreased to within 30 msec of baseline or <450 msec but subject must be monitored closely for QT prolongation for the first cycle at the increased dose.

QTcF >500 msec

- Electrolytes (potassium, calcium, and magnesium) should be checked and supplementation given to correct any values outside the normal range; Concomitant medications should be reviewed to identify and, if appropriate, discontinue any medication with known QT prolonging effects.
- Quizartinib dosing will be interrupted for up to 14 days. If QTcF returns to within 30 msec of baseline or <450 msec within 14 days, quizartinib administration may be resumed at a reduced dose.
- If QTcF >500 msec occurs during the Induction or Consolidation Phases, and if no cause other than quizartinib can be identified, then during the Maintenance Phase, the dose of quizartinib cannot be escalated to 60 mg/day.

QTcF >500 msec or >60 msec change from baseline, and Torsade de pointes or polymorphic ventricular tachycardia or signs/symptoms of serious arrhythmia

- Quizartinib dosing will be permanently discontinued.

6.2.1 Managing QTc Prolongation

Electrolytes (potassium, calcium, and magnesium) should be checked and supplementation given to correct any values outside the normal range; Concomitant medications should be reviewed to identify and, if appropriate, discontinue any medication with known QT prolonging effects.

Patients who experience >480 msec QTcF prolongation and undergo dose interruption and/or reduction must be monitored closely with ECGs, performed twice weekly for the first week of the QTcF prolongation and then weekly thereafter until the QTcF prolongation is resolved.

6.3 Dosage Schedule & Treatment plan

Salvage therapy:

Arm	IMP	Drug	Administration	Days
All		Cytarabine	18-60yrs: 3g/m² twice-daily, i.v. 3h >-60yrs: 1g/m² twice-daily, i.v. 3h	1,2,3
All		Mitoxantrone	10mg/m², i.v. 30min	2,3
All	Yes	Quizartinib	40mg, orally, (20mg if on strong CYP3A4 inhibitor)	4-21

Consolidation therapy (up to 2 cycles):

Arm	IMP	Drug	Administration	Days
All		Cytarabine	18-60yrs: 3g/m² twice-daily, i.v. 3h >-60yrs: 1g/m² twice-daily, i.v. 3h	1,2,3
All		Mitoxantrone	10mg/m², i.v. 30min	2,3

PROP.	Yes	Quizartinib	40mg, orally (20mg if on strong CYP3A4 Inhibitor)	4-21

PROP = prophylactic arm

Maintenance therapy (up to 12 cycles):

Arm	IMP	Drug	Administration	Days
PROP.	Yes	Quizartinib	Cycle 1, Days 1-28: 40mg, orally (20 mg if on strong CYP3A4 inhibitor) Starting from Cycle 2, Day 1: 60mg, orally (20 mg if on strong CYP3A4 inhibitor)	1-28

PROP = prophylactic arm

With the 1st day of the second cycle of maintenance therapy the dose of quizartinib can be raised to 60mg) if the average QTcF of the triplicate ECGs is ≤450 msec on Cycle 1, Day 28. Once the dose is increased to 60 mg/day, the subject may continue on this dose as long as dose reduction is not needed.

6.3.1 Dosage Adjustment & Interruptions

Every effort should be made to administer the study drug treatment according to the planned dose and schedule.

In the event of significant toxicity, dosing must be interrupted, delayed and/or reduced by at least 50%. [84]. In the event of unresolved or severe toxicities, administration should be interrupted. In the event of multiple toxicities, dose modification should always be based on the worst toxicity observed. Patients must be instructed to notify investigators at the first occurrence of any adverse symptom/s.

Investigators should consult the Medical Coordinator and/or Coordinating Investigator in case of dosage adjustments and interruptions.

6.3.1.1 Dose modifications for co-administration with strong CYP3A4 inhibitors

Strong CYP3A4 inhibitors should be avoided if possible but may be given with a corresponding dose reduction for quizartinib as follows:

"For subjects receiving a concomitant strong CYP3A4 inhibitor, the dose of quizartinib will be reduced as follows:

- Salvage Therapy and Consolidation Phases: The dose of quizartinib will be reduced from 40 mg/day to 20 mg/day
- Maintenance Phase: The dose of quizartinib will be reduced from 40 mg/day to 20 mg (eg, Cycle 1, Days 1 to 28), or from 60 mg to 20 mg (Cycle 2, Day 1 onward).

Once the strong CYP3A4 inhibitor is discontinued, the dose of quizartinib is resumed at the full dose when the inhibitor is withdrawn. No washout is required for the strong CYP3A4 inhibitor before increasing the dose of quizartinib back to the full dose.

6.3.2 Administration of Quizartinib

Quizartinib is administered orally as tablet.

6.4 Drug Supplies, Formulation, Labelling and Storage

6.4.1 General aspects

Quizartinib is supplied by Daiichi Sankyo Europe GmbH as 20 mg tablets for oral administration. Supplies are labeled according to local regulatory requirements.

Supplies of the IMP have to be obtained by sending an order form to Daiichi Sankyo Europe GmbH and in copy to the NCT Trial Center. The required amount of investigational medicinal product will be shipped to the study sites by Daiichi Sankyo Europe GmbH. A pre-requisite for shipment is the full regulatory approval of the study site.

The participating centers keep an account of the trial medication and acknowledge the receipt of all shipments of the trial medication. Adequate records on receipt, use, return, loss, or other disposition of medication must be maintained. A specific drug accountability form either supplied or approved by the Sponsor has to be used to provide drug accountability information. Information describing study drug supplies and their disposition, patient by patient, must be provided, signed by the Investigator and returned to the NCT clinical trials office. Requisite data includes relevant dates, quantities, batches or code numbers, and patient identification for patients who received trial product.

The investigator keeps accurate records of the quantities of trial medication dispensed, used, and returned by each patient. The documentation has to include date of dispensary, pseudonymized patient ID, batch/ serial numbers or other identification of trial medication. At the end of the trial, all unused trial medication and all medication containers will be destroyed and this process will take place and will be documented at the participating site. Trial medication that may no longer be used (e.g. expiry date passed) may be destroyed before the end of the trial. If destruction of trial medication at the site is not possible, it may be sent to the sponsor for destruction It will be assured that a final report of the drug accountability is prepared and maintained by the investigator in the Investigator's site file.

All trial medication must be kept in a locked area with access restricted to designated trial staff. The trial medication must be stored dry and in accordance with manufacturer's instructions. Deviations from the storage requirements, including any actions taken, must be documented and reported to the sponsor. Once a deviation is identified, the investigational product must be quarantined and not used until the sponsor provides documentation of permission to use the investigational product.

Any excursions from the product label storage conditions should be reported upon discovery. The site should actively pursue options for returning the product to labeled storage conditions, as soon as possible. Deviations from the storage requirements, including any actions taken, must be documented and reported to the sponsor.

Once a temperature excursion is identified, the investigational product must be quarantined and not used until the sponsor provides documentation of permission to use the investigational product. Specific details regarding information the site should report for each excursion, will be provided to the site.

Site staff instructs patients on the storage requirements for take home medications and how to report temperature excursions.

The IMP is not allowed to be used outside the context of this protocol. Under no circumstances should the Investigator or site personnel supply study product to other investigators or clinics, or allow the supplies to be used other than as directed by this protocol.

6.4.2 Quizartinib: handling by the patient

Quizartinib is packaged in high-density polyethylene (HDPE) bottles with child-resistant caps and should be handled with care. Each bottle will contain enough medication for one cycle of daily dosing, plus an additional amount to cover the time between site visits (if applicable). Patients

should be instructed to keep their medication in the bottles provided and not transfer it to any other containers and return the bottles to the site at the next study visit. Site personnel must ensure that patients clearly understand the directions for self-medication.

Investigational product should be dispensed by an appropriately qualified and experienced member of the study staff (e.g. physician, nurse, physician's assistant, practitioner or pharmacist) as allowed by local, state, and institutional guidance.

6.5 Compliance

All patients maintain patient dosing diaries throughout the study which records the date of administration and all regular, missed, changed or delayed doses as well as any occurring adverse events.

Patients are required to return all bottles, unused study drug and the patient dosing diary, at each cycle and at End of Treatment visit for compliance assessment and drug accountability. The number of tablets returned by the patient at the end of the cycle will be counted, documented and recorded.

7 Trial Methods

7.1 Registration and Randomization

There are three IDs to differentiate

Name	Abbreviation	Usage / Generation
Screening Number	Scr-No	Usage at the site only. To track the screened patients
Patient ID	PAT-ID	Study wide ID for each unique patient. To be assigned automatically by the eCRF. Primary identifier. Contains ID of the site.
Random Number	Rand-No	Study wide number for each unique patient. Assigned during randomization.

A site specific screening number (Scr-No) is allotted to each screened patient. The informed consent has to be signed prior to any trial-related procedures.

Each patient meeting all inclusion criteria must be registered. Registration must occur prior to any trial-related procedures or initiation of therapy. Patients are registered through the eCRF and the unique patient ID (PAT-ID) will be assigned manually. In case of technical failures or unavailability of the web-based system, a fax-based registration can be used.

After registration in the eCRF, the patient is randomized into one of the study arms and receives a randomization number (Rand-No) using the PAT-ID.

The patient-identification list at the study centers should contain Pat-ID and Rand-No.

Patients withdrawn from the trial retain their already assigned identification codes and numbers. New patients must always be allotted to new identification codes.

For assistance, call the NCT Clinical Trials Office and or the Data Management (see page 2).

7.1.1 Randomization procedure

Eligible patients are allocated to one of the two treatment arms in a 1:1 ratio via randomization using a centralized web-based tool (randomizer.at). Randomization is performed stratified according to previous treatment with midostaurin.

The treatment arms are the

a. MRD-triggered arm and the
b. prophylactic arm.

7.2 Description of Study Visits

The description of study visits is given as a comprehensive table. In case of conflicts, the trial schedule on Trial Schedule on page 13 must be used. The description of each procedure can be found on page 15. All study phases are described on page 14.

Q-HAM: Working Sheet Phase	Baseline	Salvage Therapy									
	BL	ST One cycle									
Day (of Cycle) , [] = optional	-14 - 0	1	2-3	4	8	15	[22]	[29]	[36]	[42]	EoC
Visit Window (+/-days)					3	3	3	3	3	3	3
Clinical assessments											
Signs/symptoms	X			X	X	X	X	X	X	X	X
Vital signs	X	X	X	X	X	X	X	X	X	X	X
Physical examination	X	X^{O}		X	X	X	X	X	X	X	X
ECG	X	X^{O}									
Extra medullary involvement	X										X
PRO	X										X
ECOG PS	X	X^{O}									X
Laboratory assessments											
Hematology	X	X^{SL}	X^{SL}	X^{SL}	X^{SL}	X^{SL}	X^{SL}	X^{SL}	X^{SL}	X^{SL}	X
Basic blood chemistry	X	X^{OSL}		X^{SL}	X^{SL}	X^{SL}	X^{SL}	X^{SL}	X^{SL}	X^{SL}	X
Extended blood chemistry and coagulation	X										X
Local disease assessment	X										X
Central laboratory assessments											
Sample collection (BM, PB)	X										X
MRD & Disease status	X										X
Treatment											
Quizartinib				X (d4-d21)							
SOC: HAM		X	X								
Drug Compliance											X
Safety											
Concomitant medications	X	X	X	X	X	X	X	X	X	X	X
AE assessment		X	X	X	X	X	X	X	X	X	X
Pregnancy test (WOCBP only)	X	X^{o}									
Screening and Baseline											
Informed consent	X										
Demographics & Family History	X										
Medical/oncologic history	X										
Cytogenetics	X										
Genectic assessment (local)	X										
Genectic assessment (central)	X										
ECHO	X										
Abdominal ultrasound	X										
Urinalysis	X										
Virus diagnostics	X										
Enrollment & Randomization	X										

Legend
O = To be omitted if already performed within 48h
3M = To be done 3-monthly; during FU counting from EOT, +/-7 days
Y = After 2 years counted from day 1, visits on site are not mandatory anymore
[ ] = optional visits in case of needed recovery period
...

Q-HAM: Working Sheet Phase	Consolidation Therapy										Consolidation Therapy									
	CT Cycle 1										CT Cycle 2									
Day (of Cycle) , [] = optional	1	2-3	4	8	15	22	[28]	[35]	[42]	EoC	1	2-3	4	8	15	22	[28]	[35]	[42]	EoC
Visit Window (+/-days)				3	3	3	3	3	3	3				3	3	3	3	3	3	3
Clinical assessments																				
Signs/symptoms										X										X
Vital signs	X^{O}	X	X	X	X	X	X	X	X	X	X^{O}	X	X	X	X	X	X	X	X	X
Physical examination	X^{O}		X	X	X	X	X	X	X	X	X^{O}		X	X	X	X	X	X	X	X
ECG	X										X									
Extra medullary involvement										X										X
PRO																				X
ECOG PS	X^{O}									X	X^{O}									X
Laboratory assessments																				
Hematology	X^{OSL}	X^{SL}	X^{SL}	X^{SL}	X^{SL}	X^{SL}	X^{SL}	X^{SL}	X^{SL}	X	X^{OSL}	X^{SL}	X^{SL}	X^{SL}	X^{SL}	X^{SL}	X^{SL}	X^{SL}	X^{SL}	X
Basic blood chemistry	X^{OSL}		X^{SL}	X^{SL}	X^{SL}	X^{SL}	X^{SL}	X^{SL}	X^{SL}	X	X^{OSL}		X^{SL}	X^{SL}	X^{SL}	X^{SL}	X^{SL}	X^{SL}	X^{SL}	X
Extended blood chemistry and coagulation										X										X
Local disease assessment										X										X
Central laboratory assessments																				
Sample collection (BM, PB)										X										X
MRD & Disease status										X										X
Treatment																				
Quizartinib			X (d4-d21)										X (d4-d21)							
SOC: HAM	X	X									X	X								
Drug Compliance										X										X
Safety																				
Concomitant medications	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
AE assessment	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Pregnancy test (WOCBP only)	X										X									X
Screening and Baseline																				
Informed consent	**...**																			
Demographics & Family History	EoC = end of cycle: either day 22 as planned or day 29, 36 or 42 in case of a recovery period.																			
Medical/oncologic history	SL = Safety lab, values not captured in eCRF																			
Cytogenetics																				
Genectic assessment (local)	**Note**																			
Genectic assessment (central)	During Observation (MRD-triggered arm) only 3-monthly visits.																			
ECHO	EoC = end of cycle: either day 28 as planned or day 35 or 42 in case of a recovery period.																			
Abdominal ultrasound																				
Urinalysis																				
Virus diagnostics		Version																		
Enrollment & Randomization		20210406 Trial Shedule Q-HAM v1_6.xlsx																		

Q-HAM: Working Sheet	Maintenance Therapy											
Phase	M/O Cycle 1		M/O Cycle 2		M/O Cycle 3		M/O Cycle 4		M/O Cycle 5		M/O Cycle 6	
Day (of Cycle) , [] = optional	1-27	28	1-27	28	1-27	28	1-27	28	1-27	28	1-27	28
Visit Window (+/-days)		2		2		2		2		2		2
Clinical assessments												
Signs/symptoms		X		X		X		X		X		X
Vital signs		X		X		X		X		X		X
Physical examination		X		X		X		X		X		X
ECG		X		X		X		X		X		X
Extra medullary involvement						X						X
PRO						X						X
ECOG PS		X		X		X		X		X		X
Laboratory assessments												
Hematology		X		X		X		X		X		X
Basic blood chemistry		X		X		X		X		X		X
Extended blood chemistry and coagulation		X		X		X		X		X		X
Local disease assessment						X						X
Central laboratory assessments												
Sample collection (BM, PB)						X						X
MRD & Disease status						X						X
Treatment												
Quizartinib	X	X	X	X	X	X	X	X	X	X	X	X
SOC: HAM												
Drug Compliance						X						X
Safety												
Concomitant medications		X		X		X		X		X		X
AE assessment		X		X		X		X		X		X
Pregnancy test (WOCBP only)		X		X		X		X		X		X
Screening and Baseline												
Informed consent												
Demographics & Family History												
Medical/oncologic history												
Cytogenetics												
Genectic assessment (local)												
Genectic assessment (central)												
ECHO												
Abdominal ultrasound												
Urinalysis												
Virus diagnostics												
Enrollment & Randomization												

Note
During Observation (MRD-triggered arm) only 3-monthly visits.

Q-HAM: Working Sheet	/ Observation (M/O)											
Phase	M/O Cycle 7		M/O Cycle 8		M/O Cycle 9		M/O Cycle 10		M/O Cycle 11		M/O Cycle 12	
Day (of Cycle) , [] = optional	1-27	28	1-27	28	1-27	28	1-27	28	1-27	28	1-27	28
Visit Window (+/-days)		2		2		2		2		2		2
Clinical assessments												
Signs/symptoms		X		X		X		X		X		X
Vital signs		X		X		X		X		X		X
Physical examination		X		X		X		X		X		X
ECG		X		X		X		X		X		X
Extra medullary involvement						X						X
PRO						X						X
ECOG PS		X		X		X		X		X		X
Laboratory assessments												
Hematology		X		X		X		X		X		X
Basic blood chemistry		X		X		X		X		X		X
Extended blood chemistry and coagulation		X		X		X		X		X		X
Local disease assessment						X						X
Central laboratory assessments												
Sample collection (BM, PB)						X						X
MRD & Disease status						X						X
Treatment												
Quizartinib	X	X	X	X	X	X	X	X	X	X	X	X
SOC: HAM												
Drug Compliance						X						X
Safety												
Concomitant medications		X		X		X		X		X		X
AE assessment		X		X		X		X		X		X
Pregnancy test (WOCBP only)		X		X		X		X		X		X
Screening and Baseline												
Informed consent												
Demographics & Family History												
Medical/oncologic history												
Cytogenetics												
Genectic assessment (local)												
Genectic assessment (central)												
ECHO												
Abdominal ultrasound												
Urinalysis												
Virus diagnostics												
Enrollment & Randomization												

Note
During Observation (MRD-triggered arm) only 3-monthly visits.

Q-HAM: Working Sheet	End of Treatment	Safety FU	Observational FU		End of Study
Phase	EOT	28d after EOT	3-monthly FU	3-monthly FU	EOS
Day (of Cycle) , [] = optional			until 2 years	after 2 years	LPLV or prior
Visit Window (+/-days)		2			
Clinical assessments					
Signs/symptoms	X^{O}	X	X^{3M}	X^{3MY}	X
Vital signs	X^{O}	X	X^{3M}	X^{3MY}	X
Physical examination	X^{O}	X	X^{3M}	X^{3MY}	X
ECG	X^{O}	X	X^{3M}	X^{3MY}	
Extra medullary involvement	X^{O}		X^{3M}	X^{3MY}	X
PRO	X^{O}		X^{3M}	X^{3MY}	X
ECOG PS	X^{O}	X	X^{3M}	X^{3MY}	X
Laboratory assessments					
Hematology	X^{O}	X	X^{3M}	X^{3MY}	X
Basic blood chemistry	X^{O}	X	X^{3M}	X^{3MY}	X
Extended blood chemistry and coagulation	X^{O}	X	X^{3M}	X^{3MY}	X
Local disease assessment	X^{O}		X^{3M}	X^{3MY}	X
Central laboratory assessments					
Sample collection (BM, PB)	X^{O}		X^{3M}	X^{3MY}	X
MRD & Disease status	X^{O}		X^{3M}	X^{3MY}	X
Treatment					
Quizartinib					
SOC: HAM					
Drug Compliance	X^{O}				
Safety					
Concomitant medications	X^{O}	X			
AE assessment	X^{O}	X			
Pregnancy test (WOCBP only)	X^{O}	X	X^{1st}		
Screening and Baseline					
Informed consent					
Demographics & Family History					
Medical/oncologic history					
Cytogenetics					
Genectic assessment (local)					
Genectic assessment (central)					
ECHO					
Abdominal ultrasound					
Urinalysis					
Virus diagnostics					
Enrollment & Randomization					

Note
Pregnancy test (WOCBP only) only at first FU-visit.

The whole table is available as separate working sheet upon request from the NCT Trial Center.

7.3 Allogeneic Hematopoietic Stem Cell Transplantation (up to 180 Days after Transplant Date)

Subjects are permitted to undergo allo-HCT. Allo-HCT is allowed at any time after Salvage Therapy.

Quizartinib should be discontinued at least 7 days before the start of a conditioning regimen. From the time of allo-HCT up through the end of the allo-HCT period (up to 180 days after the date of transplant), the Investigator will contact the transplant unit regularly (ideally every 4 weeks) for the following information:

- Determine if the subject has experienced a relapse and collect BM and PB reports;
- Review and document all conditioning regimens the subject has received;
- Review and document the date and type of transplant (matched related donor (10/10), matched unrelated donor (10/10), haploidentical donor) the subject has received;
- Review and document the type of donor and HLA matching (HLA-A, HLA-B, HLA-C, HLA-DR, HLA-DQ);
- Review and document the development of acute and chronic GVHD;
- Record engraftment failures;
- Record transplant related mortality and death of any reason.

Maintenance therapy may be given starting the earliest at day 30 and the latest at day 100 after transplant according to initial randomization.

From the time of allo-HCT until start of maintenance therapy with quizartinib no AEs will be recorded.

7.4 Methods of Data and Sample Collection

7.4.1 Data Collection and Handling

All findings including clinical and laboratory data are documented by the investigator or an authorized member of the study team in the patient's medical record and in the electronic case report form (eCRF). The investigator at the clinical site is responsible for ensuring that all sections of the eCRF are completed correctly and that entries can be verified against source data. The eCRF has to be filled out according to the specified eCRF Completion Guidelines. The correctness of entries in the eCRF will be confirmed by dated signature of the responsible investigator. Patient-reported outcomes and QoL will be collected on paper-based CRFs set up with the TELEFORM® system (Cardiff). CRFs will be scanned, verified in the system and written to an electronic database.

All data are reported pseudonymized.

Data entry to the eCRF has to be done within 7 days. Queries have to be answered within 14 days.

7.4.2 Sample Collection and Handling

The following samples are collected:

Bone marrow	Peripheral blood
• 4 unstained bone marrow slides • Bone marrow aspirate, 20 ml, Heparin	• 2 peripheral blood smears • Peripheral blood, Heparin (40 ml at baseline, 10 ml during all following visits)

• Bone marrow aspirate, 10 ml, EDTA (first pull if feasible) • At baseline only: bone marrow biopsy in formalin* • At baseline only: Bone marrow aspirate, 10 ml, EDTA additionally (20ml in total)

The samples will be collected during the following days:

- At baseline (1)
- After salvage therapy (2)
- After each cycle consolidation therapy (3,4)
- After each third cycle maintenance therapy (5,6,7)
- At the end of treatment (EOT) (8)
- Every 3 months during observational follow-up for up to 2 years after day 1 or longer (9-12,+X)
- At the end of study (EOS)

All samples are shipped to the Central MRD Laboratory (see responsibilities, page 2).

Transport is done by courier service or a similar operator providing the needed transport conditions at the day of sample collection. Until shipment the samples may be stored at room temperature (max 22°C).

* Samples for references histology are shipped from the Central MRD laboratory Heidelberg to Prof. Claudia Wickenhauser, Pathological Institute, University Hospital Halle.

7.5 Measurement of Efficacy Parameters

7.5.1 Monitoring of Measurable Residual Disease

Bone marrow aspirate and peripheral blood are analyzed at the Central MRD Laboratory. Sampling dates are described in chapter 7.4.2. In parallel, MRD will be evaluated in an explorative manner using a molecular biological approach.

7.5.2 Bone Marrow Aspirate and Hematology

Bone marrow aspirate and hematology (complete blood cell count [CBC] including red blood cells, platelets, white blood cells with differential cell counts) are performed for disease assessment.

The response to treatment will be evaluated using standard criteria defined by the ELN (European LeukemiaNet) Recommendation (see Appendix 18.2) [1].

Sampling dates are described in chapter 7.4.2.

7.5.3 Relapse-free Survival

Relapse-free survival follow-up is performed every three months (quarterly) during regular follow-up visits starting from maintenance therapy until EOS.

7.5.4 Quality of Life

Quality of life is assessed using paper based questionnaires of the EORTC Quality of Life Item Library (core questionnaire QLQ-C30, fatigue module QLQ-FA12, and selected symptom items), as well as the PSQI (sleep), the PHQ-4 (anxiety and depression), and the FACT-cog (cognitive function), which are handed out at the study site or mailed to the patients at regular intervals.

7.6 Measurement of Safety Parameters

7.6.1 Adverse Events

Assessment of AEs will include the type, incidence, severity (graded by the NCI CTCAE version 5.0) timing (date and time), seriousness, and relatedness. Additional information regarding AE and Serious AE (SAE) reporting is provided in chapter 9.

7.6.2 Laboratory Safety Assessments

Hematology, blood chemistry, coagulation and urinalysis assessments will be drawn at the time points described in the Trial Schedule and will be analyzed at local laboratories. Laboratory certificates and normal ranges with units must be provided to the LKP.

Laboratory values that are collected for safety reasons only are not captured as such in the eCRF. If significantly deviating from normal range, and/or assessed by the investigator as clinically relevant, results of safety lab investigations are to be documented as adverses events (AEs) on the appropriate forms of the eCRF (see Section 9.1.1).

Applicable reminders to the investigators will be included in the eCRF (i.e. at time points when safety lab investigations are stipulated by the study protocol, investigators will be requested to review lab results and consider if representing AEs or not).

7.7 Measurement of Further Parameters

Pharmacokinetics and pharmacodynamics will not be analyzed.

7.7.1 Pregnancy Testing

For female patients of childbearing potential, a serum or urine pregnancy test, with sensitivity of at least 25 mIU/mL, will be performed prior to study therapy. Following a negative pregnancy result at screening, appropriate contraception must be commenced and a further negative pregnancy result will then be required at the baseline visit before the patient may receive the investigational product. Pregnancy tests will also be routinely repeated at every cycle during the active treatment period, at the end of study treatment, and additionally whenever one menstrual cycle is missed or when potential pregnancy is otherwise suspected. In the case of a positive confirmed pregnancy, the patient will be withdrawn from administration of study drug combination and enter into the Follow-up phase. Additional pregnancy tests may also be undertaken if requested by Institutional Review Boards (IRBs)/Ethic Committees (ECs) or if required by local regulations.

8 Ancillary and Post Trial Care

For all patients in the prophylactic arm, treatment ends after the 12th cycle of maintenance therapy (EOT).

For all patients randomized to the MRD-triggered arm, who did not cross-over in the prophylactic arm, treatment ends after the 2nd cycle of consolidation therapy (EOT).

After EOT patients are routinely followed-up and treated regarding standard of care according to the discretion of the treating physician.

The period of observation (and the study) ends for all patients when the last patient being included and alive has been followed for at least 730 days (2 years) counted from this patient's day 1 (EOS).

8.1 Study Alliance Leukemia (SAL)

All investigators are highly encouraged to registers their AML-patients at the SAL (Study alliance Leukemia) registry, which facilitates access to further clinical AML-trials and collects structured follow-up data. For further information please refer to https://www.sal-aml.org/ or contact:

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9 Assessment of Safety

9.1 Specification of Safety Parameters

9.1.1 Adverse Events

According to GCP, an adverse event (AE) is defined as follows: Any untoward medical occurrence in a patient administered a pharmaceutical product and which does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable 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.

An AE may be:

- New symptoms/ medical conditions
- New diagnosis
- Changes of laboratory parameters which is judged as clinically significant by the investigator
- Intercurrent diseases and accidents
- Worsening of medical conditions/ diseases existing before inclusion into the trial
- Recurrence of disease
- Increase of frequency or intensity of episodical diseases.

If an AE shows an undulating course of intensity, it must be reported only once per cycle, indicating the highest CTCAE (Version 5.0) grade. If an event stops and later restarts within the same cycle, all occurrences must be reported.

During allo-HCT no AEs will be recorded (see ch. 7.3). In case of start of maintenance therapy with Quizartinib after allo-HCT, AE reporting restarts.

A pre-existing disease or symptom will not be considered an adverse event unless there will be an untoward change in its intensity, frequency or quality. This change will be documented as AE by an investigator.

Surgical procedures themselves are not AEs; they are therapeutic measures for conditions that require surgery. The condition for which the surgery is required may be an AE. Planned surgical measures permitted by the clinical trial protocol and the condition(s) leading to these measures are not AEs, if the condition leading to the measure was present prior to inclusion into the trial.

AEs are classified as "non-serious" or "serious".

9.1.2 Serious Adverse Event

A serious adverse event (SAE) is one that at any dose:

- Results in death
- Is life-threatening (the term life-threatening refers to an event in which the patient was at risk of death at the time of event and not to an event which hypothetically might have cause death if it was more severe)
- Requires patient hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability/ incapacity or
- Results in a congenital anomaly/ birth defect.
- Is medically significant (e.g. suspected transmission of an infectious agent via medicinal product). Moreover there are other situations - such as important medical events that may not be immediately life threatening or result in death or hospitalization but may jeopardize the patient or may require intervention to prevent one of the other outcomes listed above.

9.1.3 Expectedness

An 'unexpected' adverse event is one the nature or severity of which is not consistent with the applicable product information, i.e. Reference Safety Information (IB). Furthermore, reports which add significant information on specificity or severity of a known adverse reaction are counted as 'unexpected' events.

9.1.4 Suspected Unexpected Serious Adverse Reaction (SUSAR)

SAEs that are both suspected, i.e. possibly related to IMP, and 'unexpected', i.e. the nature and/ or severity of which is not consistent with the applicable product information are to be classified as Suspected Unexpected Serious Adverse Reactions (SUSARs).

In case if either the investigator, who primarily reported the SAE, or the second assessor classifies the SAE as 'suspected' (i.e. 'Yes: There is a reasonable possibility that the IMP caused the AE', see below) and the SAE is also 'unexpected', it will be categorized as a SUSAR.

All SUSARs are subject to an expedited reporting to the responsible ethics committee(s), the competent authority (BfArM) and to all participating investigators.

9.2 Period of Observation and Documentation

All AEs reported by the patient or detected by the investigator will be collected during the trial, and must be documented on the appropriate pages of the CRF. AEs must also be documented in the patient's medical records. Whenever possible, the Investigator will record the main diagnosis instead of the signs and symptoms normally included in the diagnoses.

In this trial, all AEs that occur after the **baseline screening visit** (or as soon as the medical history of the patient has been examined) will be documented on the pages provided in the CRF. The period of observation ends **28 day after the last administration of the IMP** (Quizartinib) in the prophylactic arm and **28 day after conclusion of consolidation therapy** in the MRD-triggered arm. In both arms no AEs will be documented after **beginning of another chemotherapy**. **No AEs/SAEs will be documented in the time between allo-HCT and beginning of maintenance treatment with the IMP** (Quizartinib). All patients who have AEs, whether considered associated with the use of the trial medication or not, must be monitored to determine the outcome. The clinical course of the AE will be followed up until resolution or normalization of changed laboratory parameters or until it has changed to a stable condition.

Ongoing AEs will be followed up until resolution or normalization of changed laboratory parameters or until it has changed to a stable condition.

9.2.1 Grading of AEs

The grading of AEs in this trial will be carried out on the basis of the 5-grade scale defined in the CTCAE version 5.0.

Grade 1: Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.

Grade 2:	Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental ADL*
Grade 3:	Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care ADL**.
Grade 4:	Life-threatening consequences; urgent intervention indicated.
Grade 5:	Death related to AE

A Semi-colon indicates 'or' within the description of the grade. Activities of Daily Living (ADL) *Instrumental ADL refer to preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc. **Self-care ADL refer to bathing, dressing and undressing, feeding self, using the toilet, taking medications, and not bedridden.

The grading of all AEs listed in the CTCAE v5.0 will be based on the information contained therein. The grading of all other AEs, i.e. those which are not listed in the CTCAE will be performed by a responsible investigator.

mild:	temporary event which is tolerated well by the patient.
moderate:	event which results in discomfort for the patient and impairs his/ her normal activity.
severe:	event which results in substantial impairment of normal activities of patient.

9.2.2 Coherence between AEs and the IMP

The Investigator must provide an assessment of causal relationship of each of the clinical trial IMPs to each AE according to the following scale:

Y (Yes)	There is a reasonable **possibility** that the IMP/s caused the AE.
N (No)	There is no reasonable possibility that the IMP/s caused the AE and other causes are more probable.

9.2.3 Outcome of AEs

The outcome of an AE at the time of the last observation will be classified as:

Recovered/ resolved	All signs and symptoms of an AE disappeared without any sequels at the time of the last interrogation.
Recovering/ resolving	The intensity of signs and symptoms has been diminishing and/ or their clinical pattern has been changing up to the time of the last interrogation in a way typical for its resolution.
Not recovered/ not resolved	Signs and symptoms of an AE are mostly unchanged at the time of the last interrogation.
Recovered/ resolved with sequel	Actual signs and symptoms of an AE disappeared but there are sequels related to the AE.
Fatal	Resulting in death. If there are more than one AE only the adverse event leading to death (possibly related) will be characterized as 'fatal'.
Unknown	The outcome is unknown or implausible and the information cannot be supplemented or verified.

9.2.4 Action taken with the IMP/ Background Medication

The action taken with IMP will be assigned to one of the following categories:

Dose not changed	No change in the dose of IMP.

Dose reduced	Reduction in the dose of IMP.
Temporary discontinuation	Temporary discontinuation of IMP.
Dose increased	Increase in the dose of IMP.
Drug withdrawn	Discontinuation of IMP.
Unknown	The information is unknown or implausible and it cannot be supplemented or verified.
Not applicable	The question is implausible (e.g. the patient is dead).

This also applies to any given background medication

9.2.5 Countermeasures

The term 'Countermeasures' refers to the specific actions taken to treat or alleviate adverse events or to avoid their sequels. The following categories will be used to categorize the countermeasures to adverse events:

None	No action taken
Drug treatment	Newly-prescribed medication or change in dose of a medication
Others	Other countermeasures, e.g. an operative procedure

9.3 Reporting of Serious Adverse Events by Investigator

All SAEs must be reported by the investigator to the KKS Heidelberg (on behalf of sponsor) within 24 hours after the SAE becomes known using the 'Serious Adverse Event' form. The initial report must be as complete as possible, including details of the current illness and (serious) adverse event as well as an assessment of the causal relationship between the event and the trial medication. The reporting will be performed by faxing of a completed 'SAE Form' to the KKS Heidelberg (fax number: see responsibilities, page 2).

9.4 Expedited Reporting

SUSARs are to be reported to the ethics committee(s), regulatory authorities (BfArM) and to all participating investigators within regulative defined timelines, i.e. they are subject to an expedited reporting.

All SAEs are forwarded by e-mail immediately (not later than 24 hours after receipt) by the responsible person at the KKS Heidelberg to the Coordinating Investigator or the Medical Coordinator in order to perform a second assessment. The Coordinating Investigator or the Medical Coordinator fills out a 'Second Assessment Form' for each SAE and return it by e-mail (see responsibilities, page 2) to the KKS Heidelberg within 48 hours.

The 'Second Assessment Form' contains the following information:

I) Assessment of relationship between SAE and IMP
II) Assessment of expectedness of SAE (derived from IB)
III) Assessment of relationship between SAE and the underlying disease
IV) Statement if the benefit/ risk assessment for the trial did change as a result of SAE.

The expedited reporting is carried out by the KKS Heidelberg. Only SUSARs occurring after administration of IMP will undergo expedited reporting.

9.5 Emergency Treatment

During and following a patient's participation in the trial, the investigator should ensure that adequate medical care is provided to a patient for any AE, including clinically significant laboratory values. The investigator should inform a patient when medical care is needed for intercurrent illness(es) of which the investigator becomes aware.

9.6 Adverse Events of Special Interest

Adverse events of special interest (AESI) are to be reported to the KKS Heidelberg within 24 hours after investigator's awareness using the 'SAE Form'.

In this AESI are defined as following events:

- QTc prolongation, torsades de pointes, and other ventricular arrhythmias
- Combined elevation of aminotransferases and bilirubin

9.6.1 QTc Prolongation, Torsades de Pointes, and Other Ventricular Arrhythmias

Subjects who experience >480 msec QTcF prolongation and undergo dose interruption and/or reduction must be monitored closely with ECGs, performed twice weekly for the first week of the QTcF prolongation and then weekly thereafter until the QTcF prolongation is resolved, as described in section 6.2.1

QTcF prolongation ≥ Grade 3, either serious or non-serious and whether or not causally related to the IMP, must be recorded as AE in eCRF system within 24 hours of awareness with the Investigator's assessment of seriousness, causality, and a detailed narrative. The same information must be provided on the 'SAE Form'.

9.6.2 Combined Elevations of Aminotransferases and Bilirubin

Combined elevations of aminotransferases and bilirubin, either serious or non-serious and whether or not causally related to the IMP, meeting the laboratory criteria of a potential Hy's Law case [ALT or AST ≥3 x ULN with simultaneous TBL ≥2 x ULN] should always be recorded as an AE within 24 hours of awareness, with the Investigator's assessment of seriousness, causality, and a detailed narrative. The same information must be provided on the 'SAE Form'.

9.7 Deaths

All deaths that occur during the study must be reported as follows:

- Death which are clearly a result of disease progression should be documented in the eCRF but should not be reported as an SAE.
- In cases death is not due (or not clearly due) to progression of the disease under study, the AE causing death must be reported to the KKS Heidelberg within 24 hours after the death becomes known using the "SAE Form". The report should contain a comment regarding the co-involvement of progression of disease, if appropriate, and should assign main and contributory causes of death.

Deaths with an unknown cause have to be always reported as a SAE.

9.8 Pregnancy

9.8.1 Maternal exposure

If a patient becomes pregnant during the course of the study, study treatment has to be discontinued immediately. The outcome of any conception occurring from the date of the first dose until 3 month after the last dose should be followed up and documented.

Pregnancy itself is not regarded as an adverse event unless there is a suspicion that the investigational product under study may have interfered with the effectiveness of a contraceptive medication. Congenital abnormalities/birth defects and spontaneous miscarriages should be reported and handled as SAEs. Elective abortions without complications should not be handled as AEs. The outcome of all pregnancies (spontaneous miscarriage, elective termination, ectopic pregnancy, normal birth or congenital abnormality) should be followed up and documented even if the patient was withdrawn from the study.

If any pregnancy, suspected pregnancy, or positive pregnancy test occurs in the course of the study, it must immediately be reported to the KKS Heidelberg (on behalf of sponsor) by fax using a 'Pregnancy Reporting Form'.

All pregnancies should be followed up and documented, even if the patient was withdrawn from the study, until its outcome (spontaneous miscarriage, elective termination, ectopic pregnancy, normal birth or congenital abnormality). The outcome must be notified immediately by the investigator to the KKS Heidelberg (on behalf of sponsor) within 24 hours of first knowledge as a follow-up to the initial report.

For any event during the pregnancy, which meets a seriousness criterion, the investigator will also follow the procedures for reporting SAEs (complete and send the SAE form to the KKS Heidelberg by fax within 24 hours of the investigator's knowledge of the event).
All neonatal deaths that occur within 30 days of birth should be reported, without regard to causality, as SAEs. In addition, any infant death at any time thereafter that the investigator suspects as related to the exposure to the IMP should also be reported to the KKS Heidelberg by fax within 24 hours of the investigators' knowledge of the event.

The KKS Heidelberg (on behalf of sponsor) informs appropriately Daiichi Sankyo representatives within one working day from the date the KKS, is aware of the pregnancy related SAE.

9.8.2 Paternal exposure

Male patients should refrain from fathering a child or donating sperm during the study and for 6 months following the last dose.

Pregnancy of the patient's partners is not considered to be an adverse event. However, the outcome of all pregnancies (spontaneous miscarriage, elective termination, ectopic pregnancy, normal birth or congenital abnormality) should if possible be followed up and documented.

The outcome of any conception occurring from the date of the first dose until 3 months after the last dose should be followed up and documented.

10 Statistical Considerations

10.1 Research Hypothesis

H_0: The CR/CRi rate after salvage therapy for patients receiving Q-HAM is lower or equal as compared to matched controls not receiving Q-HAM; i.e. OR≤1

H_1: The CR/CRi rate after salvage therapy for patients receiving Q-HAM is higher as compared to matched controls not receiving Q-HAM; i.e. OR>1

10.2 Analysis Variables

10.2.1 Primary Endpoints

- **Composite remission**, defined as the proportion of patients experiencing a CR/CRi after salvage therapy.

10.2.2 Secondary Endpoints

- **Event-free survival (EFS)** defined as the time from randomization to time until one of the following events, whichever occurs first: a) failure to obtain complete remission (CR) or

complete remission with incomplete hematological recovery (CRi) after Q-HAM salvage therapy, b) relapse from CR/CRi or c) death from any cause. Patients without an applicable event are censored on the last date of follow-up.

- **Overall survival (OS)** defined as the time from randomization to time of death from any cause. Patients without event are censored on the last date of follow-up. [time frame: up to LPLV]

- **Relapse-free survival (RFS)** defined as the time from achievement of a CR/CRi after salvage therapy to time of recurrence of the disease or death from any cause, whatever occurs first. Patients without event are censored at the last date of follow-up.

- **Cumulative incidence of relapse (CIR)** defined as time from achievement of a CR/CRi after salvage therapy to time of recurrence of the disease whereby death from any cause is a competing event.

- **Cumulative incidence of deaths (CID)** defined as the time from achievement of a CR/CRi after salvage therapy to death from any cause whereby recurrence of the disease is a competing event.

- **Quality of Life & Patient-Reported Outcomes (PRO)**

    - **Health-related quality of life (QoL)** will be calculated as the new EORTC QLQ-C30 Summary Score recommended by the EORTC Quality of Life Group, which has been recently developed and evaluated [92]. In addition, the EORTC QLQ function and symptom scores will be calculated according to the actual EORTC Scoring Manual [93].

    - **Fatigue** will be calculated from the EORTC QLQ-FA12 according to the EORTC Scoring Manual [93].

    - **Sleep problems** will be calculated from the PSQI according to the corresponding scoring guidelines [94].

    - **Perceived cognitive impairments** and **impact of cognitive changes** will be calculated from the FACT-cog according to the corresponding scoring manual.

    - **Anxiety** will be calculated from the PHQ-4 according to the corresponding scoring manual [95].

    - **Depression** will be calculated from the PHQ-4 according to the corresponding scoring manual [95].

10.2.3 Safety Endpoints

The safety endpoints within the study are periodically assessed and include the following:

- rate of early/hypoplastic deaths,
- In patients achieving BM blast count of <5%: rate of neutropenia or thrombopenia CTC Grade 3/4 for more than 42 days in the absence of further antineoplastic treatment.

10.3 Sample Size Considerations

10.3.1 Choice and description of Matched-threshold crossing design

For the selection of historical controls, a matched-threshold crossing design [12][96][97][106] will be used. The latter is a novel approach to enhance the classic single-arm trial design by including matched control patients. This design overcomes common disadvantages of single-armed and small randomized studies as described in Gan et al. [98], since the expected outcome of the observed study population can be adjusted based on the matched controls with a comparable distribution of known prognostic and predictive factors. Furthermore, balanced treatment groups lead to stable statistical models.

The proposed adaptive design consists of two stages with an interim analysis after the first stage. For the first stage, n_1 intervention patients are recruited into the trial. At the interim analysis, historical control patients are matched to the enrolled intervention patients with regard to known prognostic and predictive factors. The treatment effect of the intervention as compared to the control group is then estimated based on the enrolled intervention patients and the selected historical control patients. There are two options regarding the second stage of the trial:

1. in case the estimated treatment effect is below a pre-specified threshold, the trial is stopped for futility
2. in case the estimated treatment effect is above a pre-specified threshold, the sample size for the second stage of the trial n_2 is recalculated to obtain a sufficiently high conditional power based on the results of the interim analysis and the trial continues to the second stage with the recalculated sample size n_2.

In the proposed design, matched control patients will be drawn from two large IPD meta-analyses datasets of r/r-AML patients (“historical control”) [10][11] after inclusion of the n_1 patients of the first stage. For matching, the variables age and high risk cytogenetics are used in refractory patients and additionally CR1 duration <18 months in relapsed patients. After the enrolment of n_1=30 patients, the *a priori* unknown matching rate and the number of matched controls per patient *M* in the intervention group are determined at the interim analysis using an iterative procedure [97]. A (non-binding) interim stop for futility is done in case the odds ratio, estimated using a logistic regression model adjusting for the matching parameters, does not exceed a threshold of OR_{stop}=1.3. If the trial continues to a second stage, a sample size recalculation is performed using a conditional power argument taking number of matched partners and observed treatment effect into account. In the final analysis, historical control patients are also matched to the patients from the second stage, and the p-values from the two stages are combined using the inverse normal approach and tested at a one-sided significance level of α=0.05.

10.3.2 Sample Size Calculation

Based on the assumptions regarding response rates in treatment and control patients, it is assumed that an OR of 0.3/0.7=2.33 can be achieved under the alternative hypothesis (see chapter 1).

For the proposed trial, the number of patients to be enrolled in the first stage is set to n_1=30, and the futility threshold is set to OR_{stop} =1.3. In case this futility threshold is crossed, the minimal number of patients enrolled in the second trial stage is set to n_2^{Min}=10, while the maximal number to be enrolled is n_2^{Max} =50. The sample size required for a fixed design would be a minimum of n_{fixed}=74. This sample size is obtained when assuming a logistic regression is performed at a one-sided significance level α=0.05, and the aspired power is 1-β=0.8, and number of matching partners per intervention patient is only M=1.Thus a maximum of $n_1 + n_2^{Max}$ = 80 intervention patients will be enrolled. Simulation studies show that the proposed adaptive design ensures strict control of the type I error rate and achieves comparable expected sample sizes and power under H_1 as compared to a respective fixed design approach with the same number of matched controls [97]. Furthermore, the number of expected patients under H_0 is generally smaller than compared

to a design with fixed sample size (see Table 4). The chosen futility threshold of OR_{stop}=1.3 both yields a sufficiently high probability to continue the trial under the point alternative OR=2.33 and a sufficiently high probability to stop the trial in case there is no treatment effect (i.e. OR=1). Point and interval estimates of the treatment effect will take the adaptive nature of the trial into account (see 10.5.4 for details).

Table 4: Expected sample sizes depending on the number of matched controls together with power and stopping probabilities

Expected sample sizes, power, and stopping probabilities of the proposed adaptive two-stage design in comparison to a fixed design with respect to number of matched control patients *M* based on 100.000 simulated studies:

Number of matched control patients *M*	Required sample size for fixed design n_{fixed}	Expected sample size for adaptive MTC-design under H_0	Expected sample size for adaptive MTC-design under H_1	Power of adaptive MTC-design	Probability to stop the trial at interim under H_0	Probability to continue the trial at interim under H_1
1	74	46.38	65.30	0.7453	0.6649	0.8783
2	55	42.97	54.85	0.7934	0.7108	0.8949
3	48	41.21	50.51	0.8013	0.7335	0.9003
4	45	40.46	48.43	0.8088	0.7387	0.9078
5	43	40.08	47.28	0.8131	0.7406	0.9124

Assumptions: α=0.05 (one-sided), 1-β=0.8 for fixed design, π_T=0.50 under H_1, π_T=0.30 under H_0, π_C=0.30 (under both H_0 and H_1), n_1=30, n_2^{Min}=10, n_2^{Max}=50, OR_{stop}=1.3, n_{fixed} was calculated using the formula by Hsieh et al. [99].

Given the approval of midostaurin by EMA, the proportion of patients with previous midostaurin during first line therapy is expected to be about 50%. A total maximum sample size of 80 patients allows for meaningful subset analyses according to midostaurin pretreatment.

10.4 Analysis Populations

10.4.1 Full Analysis Population (ITT)

The Full Analysis Population will include all randomized patients with treatment groups assigned in accordance with the randomization scheme, who received at least one day of Quizartinib treatment. Patients who were randomized but did not subsequently receive treatment are excluded from the Full Analysis Population.

All enrolled patients who have finished at least one cycle of the study medication and who are evaluable for the primary endpoint are included in the response assessment analysis set and are analyzed according to the ITT principle.

10.4.2 Per Protocol (PP) Population

The Per Protocol Population patients comprises all patients from the FAP population without important/major protocol deviations. Definition of important protocol deviations are given in the statistical analysis plan (SAP).

10.4.3 Safety Population

All enrolled patients who have received at least one dose of quizartinib are subject to the safety analysis. Details of the safety analysis are specified in the statistical analysis plan (SAP).

10.5 Statistical Methods

10.5.1 General Considerations

Details of the interim and final analysis will be specified in a statistical analysis plan (SAP), which will be finalized and approved prior to study activation.

10.5.2 Demographic and other Baseline Characteristics

Descriptive statistics of the baseline characteristics will be generated across all treated patients as well as for matched control patients in order to assess the homogeneity between the enrolled patients and the historical cohort.

- Categorical baseline characteristics, like sex, history of cancer, performance status (ECOG), relevant previous anticancer treatment, AML entity according to WHO 2016 classification, concomitant illness at trial initiation, and concomitant treatment maintained, will be summarized by frequency tables.
- Summary statistics will be provided for quantitative variables like age, weight, laboratory values.

10.5.3 Interim Analysis

An interim analysis is planned after 30 patients are evaluable for the primary endpoint, which is defined as response after salvage therapy (see chapter 10.2.1).

The analysis will be performed by means of a logistic regression model adjusting for the variables treatment (Q-HAM/no Q-HAM), age, high risk cytogenetics (yes/no), and CR1 duration <18 months(yes/no). In case the futility threshold for the odds ratio of OR_{stop} =1.3 is crossed, the minimal number of patients enrolled in the second trial stage is set to n_2^{Min}=10, while the maximal number to be enrolled is n_2^{Max} =50. If the trial continues to a second stage, a sample size recalculation is performed in order to achieve a sufficiently high conditional power to reject the null hypothesis taking number of matched partners *M*, the matching rate, and the observed treatment effect into account. The treatment effect assumed for the second stage sample size calculation will be the originally assumed effect of 2.33.

The futility threshold is set to OR_{stop} =1.3. In case this futility threshold is crossed (estimated OR > 1.3), enrolment of the study will continue as planned. In case the futility threshold is not crossed (estimated OR ≤ 1.3), the trial will be continued as planned, but no additional patients will be enrolled.

The interim analysis is performed immediately after response assessment of the 30th patient. Results of the interim analysis will be presented to the Data Monitoring Committee (DMC) who will advise the Steering Committee of the trial to either terminate or to continue the trial.

10.5.4 Analysis of the Primary Endpoint

Composite remission rate (CRR)

A logistic regression model will be applied to assess the Odds Ratio of CR/CRi rate after salvage therapy for patients receiving Q-HAM versus matched controls not receiving Q-HAM. The null hypothesis is that H_0:OR≤1 which is tested against its alternative H_1:OR>1 at a one-sided significance level of α=0.05. The logistic regression analysis will be adjusted for age, high risk cytogenetics (yes/no), and CR1 duration <18 months(yes/no). Due to the adaptive nature of the trial, two separate logistic models will be fitted for the two trial stages. The one-sided p-values from the two stages, p_I and p_{II} will then be combined using the inverse normal function approach [100]with equal weights for the two stages. Thus, H_0 will be rejected if the combined one-sided p-value p_{Total} is below 0.05. The matched control patients used for the first trial stage will not be re-used when the matched control patients for the second trial stage are determined in order to

ensure type I error rate control. The adaptively weighted maximum likelihood (AWML) estimator proposed by [101], which takes the adaptive nature of the trial into account, will be used to estimate the combined odds ratio of the two stages in order to ensure unbiased estimates with a low root mean square error [97]. 90% confidence intervals for the OR will be provided by means of a repeated confidence interval, as proposed by Wassmer & Brannath [102] for designs which use the inverse normal combination method, will be used for interval estimation. In case the trial does not proceed to the second stage, maximum likelihood estimates based on the first trial stage will be used. Analysis of the primary endpoint will be primarily done based on the Full Analysis Population. Additionally, a PP analysis will be performed.

10.5.5 Analysis of the Secondary Endpoints

Cumulative Incidence (cumulative incidence of relapse, cumulative incidence of deaths)

Cumulative incidences of relapses and deaths will be analyzed according to Gray 1988 taking their competing nature into account [103]. Cumulative incidence plots will be provided.

Survival Analysis (Event-free survival, Relapse-free survival, Overall Survival)

The method of Kaplan and Meier will be used to estimate the distributions of EFS, RFS and OS. Cox proportional hazards regression will be used to examine the influence of covariates on EFS/RFS/OS if deemed clinically relevant.

Analysis of Patient Reported Outcomes (PRO)

The scales will be scored and analyzed according to the corresponding EORTC guidelines. The Quality of Life subscales and single item sub-scores will be summarized by the mean, standard deviation, median, minimum and maximum, and plotted by time. The change from baseline for all domains will be examined descriptively.

Safety Analysis

The assessment of safety will be based mainly on the frequency of adverse events (see chapter 9) and on the number of laboratory values that fall outside of pre-determined ranges and/or show prominent worsening from baseline during the study phase. Adverse events will be summarized by presenting the number and percentage of patients having any adverse events or serious adverse events, and having each individual adverse event, and by determining and summarizing the maximum individual toxicity grade (over all forms of toxicity) for each treatment cycle during the study phase. Furthermore, the most common AEs (those occurring in at least 10% of the treatment group) will be determined. Any other information collected (e.g. severity or relatedness to study drug) will be summarized as appropriate. Laboratory data will be summarized by presenting summary statistics of raw data and change from baseline values. Incidence rates will be summarized along with two-sided Wilson score 95% confidence intervals and analyzed by (descriptive) chi-squared tests.

10.5.6 Patients' disposition and other analyses

- Patients' disposition and reasons for ending the study will be presented in frequency distribution tables and individual data listing.
- Individual data will be presented in listings.

10.5.7 Handling of Missing Data

For patients with incomplete follow-up, time to last follow-up date will be used as the censoring time in the analysis of time-to-event data. Otherwise, no imputation of missing data will be conducted.

11 Data Management

11.1 Data Collection

The data collection is performed using an eCRF. Data collection using the eCRF can only be done by authorized persons. All study data are password-protected. The eCRF provides several checks for completeness and consistency. Each entry or change of data will be tracked with name and exact date. When data has been entered, reviewed, edited and Source Data Verification (SDV) performed according to the monitoring plan, the investigator will be notified to sign the eCRF electronically as per agreed project process, and data will be locked to prevent further editing. A copy of the eCRF will be archived at the study site.

All data collected as stipulated by the study protocol including clinical and laboratory data (with regard to documentation of safety laboratory data see sections 7.6.2) are documented by the investigator or an authorized member of the study team in the patient's medical record and in the eCRF. The investigator is responsible for ensuring that all sections of the eCRF are completed correctly and that entries can be verified by source data. The eCRF has to be filled out according to the specified eCRF Completion Guidelines.

PRO questionnaires are paper-based, are completed by patients and serve as source data. Upon completion questionnaires are mailed back to the project management and transferred to the central unit for Quality of Life & Patient-Reported Outcomes (see section responsibilities). The questionnaires are then recorded using the TELEFORM® system (Cardiff) and undergo a computer assisted manual verification. Derived data sets, combining eCRF and PROs data are produced at interim and at EOT.

The link between the questionnaires and the CRF is maintained by a combination of a unique number for each questionnaire and the patient-ID (PAT-ID) which is recorded in the eCRF.

11.2 Data Handling

Data entries undergo an automated check for plausibility and consistency. In case of implausibility, 'warnings' will be produced. A responsible investigator will be obliged either to correct the implausible data or to confirm its authenticity, and to give appropriate explanation. If not corrected, the data will be flagged, enabling a convenient check of all questionable entries. A responsible monitor will check all flagged data and will generate questions (“queries”) that will be sent back to the responsible investigator. The investigator will have to resolve all 'discrepancies'.

Further checks for plausibility, consistency, and completeness of data will be performed during and after completion of the study. Queries will be generated on the basis of these checks, combined with a visual control by a responsible monitor/data manager.

All missing data or inconsistencies will be reported back to the sites and clarified by the responsible investigator. If no further corrections are to be made in the trial database it will be declared closed and used for statistical analysis.

All data management activities will be done according to the current Standard Operating Procedures (SOPs).

11.3 Storage and Archiving of Data

According to §13 of the German GCP-Regulation all important trial documents (e.g. CRFs) will be archived for at least 10 years after the trial termination if no longer archiving period is defined by the sponsor.

The investigator(s) will archive all trial data (source data and Investigator Site File (ISF) including Patient Identification List and relevant correspondence) according to the section 4.9 of the ICH Consolidated Guideline on GCP (E6) and to local law or regulations. The Patient Identification List will be archived for at least 15 years after trial termination.

If the investigator relocates, retires, or for any reason withdraws from the study, the NCT Trial Center should be prospectively notified. The study records must be transferred to an acceptable designee, such as another investigator, another institution, or to the NCT Trial Center. The investigator must obtain CIs written permission before disposing of any records, even if archiving requirements have been met.

12 Ethical and Legal Aspects

12.1 Good Clinical Practice

The procedures set out in this trial protocol, pertaining to the conduct, evaluation, and documentation of this trial, are designed to ensure that all persons involved in the trial abide by Good Clinical Practice (GCP) and the ethical principles described in the current version of the Declaration of Helsinki. The trial will be carried out in keeping with local legal and regulatory requirements.

12.2 Patient Information and Informed Consent

Before being admitted to the clinical trial, the patient must consent in written form to participate after the nature, scope, and possible consequences of the clinical trial have been explained in a form understandable to him or her. The original personally signed and dated Informed Consent Form must be kept on file by the investigator(s), and documented in the case report form.

A copy of the signed informed consent document must be given to the patient. The documents must be in a language easily understandable to the patient and must clearly state who informed the patient, which is confirmed by the dated signature of the responsible investigator

If new safety information results in significant changes in the risk/benefit assessment, or if changes are made in the protocol, the consent form should be reviewed and updated if necessary. All patients (including those already being treated) should be informed of the new information and must give their written informed consent to continue the study.

12.3 Confidentiality

The data obtained in the course of the trial will be treated pursuant to the General Data Protection Regulation (EU-DSGVO, EU 2016/679) and the Data Protection Law of the Federal State (Landesdatenschutzgesetz), and the § 40 (2a) AMG.

During the clinical trial, patients will be identified solely by means of an individual identification code (Patient ID). Storage of trial findings on a computer will be done in accordance with local data protection law and will be handled in strictest confidence. For protection of these data, organizational procedures are implemented to prevent distribution of data to unauthorized persons. The appropriate regulations of local data legislation will be fulfilled in its entirety.

The patient consents in writing to relieve the investigator from his/her professional discretion in so far as to allow inspection of original data for monitoring purposes by health authorities and authorized persons (inspectors, monitors, auditors). Authorized persons (clinical monitors, auditors, inspectors) may inspect the patient-related data collected during the trial, ensuring the data protection law.

The investigator will maintain a patient identification list (Patient IDs with the corresponding patient names) to enable records to be identified.

Patients who did not consent to circulate their pseudonymized data will not be included into the trial.

12.4 Responsibilities of Investigator

The Coordinating Investigator should ensure that all persons assisting with the trial are adequately informed about the protocol and any amendments, the trial treatments, and their trial-related duties and functions.

The Coordinating Investigator should maintain a list of investigators and other appropriately qualified persons to whom he or she has delegated significant trial-related duties (Log of Staff).

The investigator(s) should support monitoring, auditing and inspections.

12.5 Approval of Trial Protocol and Amendments

Before the start of the trial, the trial protocol, informed consent document, and any other appropriate documents will be submitted to the independent Ethics Committee (EC) as well as to the competent federal authority (BfArM). A written favorable vote of the EC and an (implicit) approval by the competent higher federal authority are a prerequisite for initiation of the clinical trial. The statement of EC should contain the title of the trial, the trial code, the trial site, and a list of reviewed documents. It must mention the date on which the decision was made and must be officially signed by a committee member.

Before the first patient is enrolled in the trial, all ethical and legal requirements must be met. All planned substantial changes (see §10, (1) of German GCP-Regulation) will be submitted to EC and the competent higher federal authority in writing as amendments. They have to be approved by the EC and the competent higher federal authority.

The Coordinating Investigator or the NCT Trial Center, and if applicable the investigator(s) will keep a record of all communication with the EC and the regulatory authorities.

12.6 Continuous Information to Independent Ethics Committee

Pursuant to the German Drug Law (AMG) and the GCP Regulation, the EC and the competent higher federal authority will be informed of all suspected serious unexpected adverse reactions (SUSARs) and all AEs resulting in death or being live-threatening which occur during the trial. Both institutions will be informed in case the benefit-risk assessment did change or any others new and significant hazards for patients' safety or welfare did occur. Furthermore, a report on all observed serious adverse events (SAEs) will be submitted once a year (Development Safety Update Report (DSUR)).

The EC and the regulatory authorities must be informed of the end of the trial. They will be provided with a summary of trial results within one year after the end of clinical phase (LPLV).

12.7 Notification of Regulatory Authorities

The local regulatory authorities as responsible for each particular investigator and the competent higher federal authority will be informed before the beginning, during and at the end of the trial according to §67 AMG and §13 GCP-V. NCT Trial Center is obliged to notify his/ her local regulatory authority and the competent higher federal authority according §67 AMG and §12 (1, 2, 6) GCP-V.

12.8 Registration of the Trial

Prior to the beginning of the clinical phase (FPFV) the coordinating investigator will register the trial at a public accessible clinical trial register having the status of a primary register according to the International Clinical Trials Registry Platform (ICTRP) and correspondingly is listed at the International Clinical Trials Registry Platform of the World Health Organization (WHO, http://www.who.int/ictrp/en/). The requirements are fulfilled by the European Clinical Trials Register and submission of EMA Module 1 (Clinical Trial Application Form).

12.9 Insurance

According to § 40 AMG, the sponsor has to subscribe to an insurance policy which covers in its terms and provisions its legal liability for injuries caused to participating persons. The insurance policy also covers any damage done to the patient, even if the harm done arises out of strictly following the procedures described in this protocol and abiding as applicable law and professional standards. The insurance was taken out at HDI Global SE (insurance policy number: 5701031003018, registration number: 14012019106, maximum limit: € 500.000 per participating person).

Additionally an accident insurance was taken out at SV Sparkassenversicherung (insurance policy number: 50079192101, client number: 0 040 622 983-8, maximum limit: € 100.000 per participating person). This insurance policy covers any damage to the patient that arises from accidents on the direct way between the patients' place of residence and the respective trial center.

Any impairment of health which might occur in consequence of trial participation must be notified to the insurance companies. The patient is responsible for notification. The insured person must agree to help clarify the cause and the extent of damage with all appropriate measures. He is also obliged to take measures himself to reduce damage as much as possible. During the conduct of the trial, the patient must not undergo other clinical treatment except for cases of emergency. The patient is bound to inform the investigator immediately about any adverse events and additionally drugs taken. The terms and conditions of the insurance must be delivered to the patient.

The insurance company has to be informed about all amendments that could affect patients' safety, and must also receive the actual version of the informed consent.

13 Quality Assurance

13.1 Monitoring

Monitoring is done by personal visits from a clinical monitor and by centralized monitoring according to the monitoring plan. The investigator must allow the monitor to verify all essential documents and must provide support at all times to the monitor. Monitoring will be done in a risk based manner.

By frequent communications (e-mails, letters, telephone, fax), the site monitor and the central monitor will ensure that the trial is conducted according to the protocol and to regulatory requirements.

13.2 Inspections/ Audits

Regulatory authorities and an auditor authorized by the sponsor may request access to all source documents, CRF, and other trial documentation. Direct access to these documents must be guaranteed by the investigator, who must provide support at all times for these activities.

14 Agreements

14.1 Financing of the Trial

The study is supported by Daiichi Sankyo Europe GmbH. Study drug will be provided free-of-charge by Daiichi Sankyo Europe GmbH.

The funding organizations did not influence the study design nor will they influence the results of this trial.

14.2 Declaration of Interests

Before the start of the trial, the investigator will disclose to the sponsor any proprietary or financial interests he or she might hold in the sponsors/ a funding company, in the investigational product(s), or any commercial organization being involved in the clinical trial. The investigator has

also to confirm that he/she has not entered into any financial arrangement whereby the value of compensation paid could affect the outcome of the clinical trial.

The investigator agrees to update this information in case of significant changes.

14.3 Dissemination Policy

14.3.1 Access to data

After the trial has been completed and published, it is planned to make trial data available for re- and meta-analyses. We will look for an appropriate repository at the end of the trial [104].

14.3.2 Reports

The biostatistician will prepare the final trial report together with the Coordinating Investigator within 12 months after the end of the study (database lock).

Interim safety reports (DSURs) will be prepared by the pharmacovigilance officer together with the Coordinating Investigator in accordance with legally required timeframes; data reconciliation will be carried out where necessary and possible together with the data management of the NCT Trial Center based on already available CRF-AE data.

14.3.3 Publication

All information concerning the trial is confidential before publication.

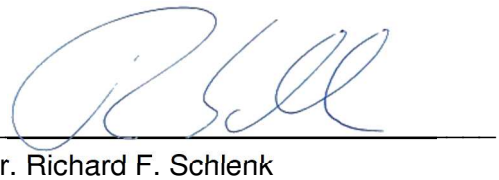
Trial results will be published in medical peer-reviewed journals.

15 Signatures

The present trial protocol was subject to critical review and has been approved in the present version by the persons undersigned. The information contained is consistent with:

- The current benefit-risk assessment of the investigational medicinal product
- Moral, ethical, and scientific principles governing clinical research as set out the principles of GCP and in the applicable version of Declaration of Helsinki.

The investigator will be supplied with details of any significant or new finding, including relevant safety information relating to treatment with the investigational medicinal product.

Date: 6.4.2021 Signature: 

Prof. Dr. Richard F. Schlenk

Coordinating Investigator (LKP) according to § 40 German Drug Law (AMG) and

on behalf of sponsor

16 Declaration of Investigators

I have read the above trial protocol and confirm that it contains all information to conduct the clinical trial. I pledge to conduct the clinical trial according to the protocol.

I will enroll the first patient only after all ethical and regulatory requirements are fulfilled. I pledge to obtain written consent for trial participation from all patients before enrolment.

I know the requirements for accurate reporting of serious adverse events, and I pledge to document and notify such events as described in the protocol.

I pledge to retain all trial-related documents and source data as described.

I agree that my personal data in the role as investigator as well as the data of the study site may be published and/or submitted to the local authorities and/or ethical committees and/or registries in order to adequately report this clinical trial in accordance with the respective laws and regulations (e.g. §42b & §67 AMG and §12.1 GCP-V).

Trial Site:

Date	Name (Prüfer):	Signature:

Date	Name (Stellvertreter):	Signature:

Please return this page with all signatures to the following recipients:

Project Management: by email to Q-HAM@nct-heidelberg.de or by fax to 0221 56-5863

Monitor: by email to your respective monitor

- Friederike.Dominick@med.uni-heidelberg.de or
- Wiebke.Wagner@med.uni-heidelberg.de

or by fax to 06221 56-33508

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This protocol has been written using information from the following study protocols:

- “A PHASE 3, DOUBLE-BLIND, PLACEBO-CONTROLLED STUDY OF QUIZARTINIB ADMINISTERED IN COMBINATION WITH INDUCTION AND CONSOLIDATION CHEMOTHERAPY, AND ADMINISTERED AS MAINTENANCE THERAPY IN SUBJECTS 18 TO 75 YEARS OLD WITH NEWLY DIAGNOSED FLT3-ITD (+) ACUTE MYELOID LEUKEMIA AC220-A-U302 (QuANTUM-First)”. Version 2.0. EudraCT: 2015-004856-24

18 Appendixes

18.1 *ECOG & Karnofsky Performance Status*

ECOG		Karnofsky	
Score	**Description**	**Score**	**Description**
0	Fully active, able to carry on all pre-disease performance without restriction	**100**	Normal, no complaints, no evidence of disease.
		90	Able to carry on normal activity; minor signs or symptoms of disease.
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light housework, office work	**80**	Normal activity with effort; some signs or symptoms of disease.
		70	Cares for self, unable to carry on normal activity or do active work.
2	Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about more than 50% of waking hours.	**60**	Requires occasional assistance, but is able to care for most of his/her needs.
		50	Requires considerable assistance and frequent medical care.
3	Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.	**40**	Disabled, requires special care and assistance.
		30	Severely disabled, hospitalization indicated. Death not imminent
4	Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.	**20**	Very sick, hospitalization indicated. Death not imminent
		10	Moribund, fatal processes progressing rapidly

18.2 Response Criteria for Acute Myeloid Leukemia

Category	Definition	Comment
Response		
CR without minimal residual disease (CR_{MRD-})	If studied pretreatment, CR with negativity for a genetic marker by RT-qPCR, or CR with negativity by MFC	Sensitivities vary by marker tested, and by method used; therefore, test used and sensitivity of the assay should be reported; analyses should be done in experienced laboratories (centralized diagnostics)
Complete remission (CR)	Bone marrow blasts <5%; absence of circulating blasts and blasts with Auer rods; absence of extramedullary disease; ANC ≥1.0 × 10^9/L (1000/μL); platelet count ≥100 × 10^9/L (100 000/μL)	MRD^+ or unknown
CR with incomplete hematologic recovery (CR_i)	All CR criteria except for residual neutropenia (<1.0 × 10^9/L [1000/μL]) or thrombocytopenia (<100 × 10^9/L [100 000/μL])	
Morphologic leukemia-free state (MLFS)	Bone marrow blasts <5%; absence of blasts with Auer rods; absence of extramedullary disease; no hematologic recovery required	Marrow should not merely be "aplastic"; at least 200 cells should be enumerated or cellularity should be at least 10%
Partial remission (PR)	All hematologic criteria of CR; decrease of bone marrow blast percentage to 5% to 25%; and decrease of pretreatment bone marrow blast percentage by at least 50%	Especially important in the context of phase 1-2 clinical trials
Treatment failure		
Primary refractory disease	No CR or CR_i after 2 courses of intensive induction treatment; excluding patients with death in aplasia or death due to indeterminate cause	Regimens containing higher doses of cytarabine (see Table 8) are generally considered as the best option for patients not responding to a first cycle of 7+3; the likelihood of responding to such regimens is lower after failure of a first
Death in aplasia	Deaths occurring >7 d following completion of initial treatment while cytopenic; with an aplastic or hypoplastic bone marrow obtained within 7 d of death, without evidence of persistent leukemia	
Death from indeterminate cause	Deaths occurring before completion of therapy, or <7 d following its completion; or deaths occurring ≥7 d following completion of initial therapy with no blasts in the blood, but no bone marrow examination available	
Response criteria for clinical trials only		
Stable disease	Absence of CR_{MRD-}, CR, CR_i, PR, MLFS; and criteria for PD not met	Period of stable disease should last at least 3 mo
Progressive disease (PD)*,†	Evidence for an increase in bone marrow blast percentage and/or increase of absolute blast counts in the blood: • >50% increase in marrow blasts over baseline (a minimum 15% point increase is required in cases with <30% blasts at baseline; or persistent marrow blast percentage of >70% over at least 3 mo; without at least a 100% improvement in ANC to an absolute level (>0.5 × 10^9/L [500/μL], and/or platelet count to >50 × 10^9/L [50 000/μL] nontransfused); or • >50% increase in peripheral blasts (WBC × % blasts) to >25 × 10^9/L (>25 000/μL) (in the absence of differentiation syndrome)†; or • New extramedullary disease	Category mainly applies for older patient given low-intensity or single-agent "targeted therapies" in clinical trials In general, at least 2 cycles of a novel agent should be administered Some protocols may require blast increase in 2 consecutive marrow assessments at least 4 wk apart; the date of progression should then be defined as of the first observation date Some protocols may allow transient addition of hydroxyurea to lower blast counts "Progressive disease" is usually accompanied by a decline in ANC and platelets and increased transfusion requirement and decline in performance status or increase in symptoms
Relapse		
Hematologic relapse (after CR_{MRD-}, CR, CR_i)	Bone marrow blasts ≥5%; or reappearance of blasts in the blood; or development of extramedullary disease	
Molecular relapse (after CR_{MRD-})	If studied pretreatment, reoccurrence of MRD as assessed by RT-qPCR or by MFC	Test applied, sensitivity of the assay, and cutoff values used must be reported; analyses should be done in experienced laboratories (centralized diagnostics)

ANC, absolute neutrophil count; IDH, isocitrate dehydrogenase; MLFS, morphologic leukemia-free state; WBC, white blood cell.

*The authors acknowledge that this new provisional category is arbitrarily defined; the category aims at harmonizing the various definitions used in different clinical trials.

†Certain targeted therapies, for example, those inhibiting mutant IDH proteins, may cause a differentiation syndrome, that is, a transient increase in the percentage of bone marrow blasts and an absolute increase in blood blasts; in the setting of therapy with such compounds, an increase in blasts may not necessarily indicate PD.

Source: Döhner H, Estey E, Grimwade D, et al. Diagnosis and management of AML in adults: 2017 ELN recommendations from an international expert panel. Blood 2017;129(4):424–447. [1]

18.3 WHO myeloid neoplasm and acute leukemia classification

WHO myeloid neoplasm and acute leukemia classification [105]

Acute myeloid leukemia (AML) and related neoplasms

- AML with recurrent genetic abnormalities
  - AML with t(8;21)(q22;q22.1);*RUNX1-RUNX1T1*
  - AML with inv(16)(p13.1q22) or t(16;16)(p13.1;q22);*CBFB-MYH11*
  - APL with *PML-RARA*
  - AML with t(9;11)(p21.3;q23.3);*MLLT3-KMT2A*
  - AML with t(6;9)(p23;q34.1);*DEK-NUP214*
  - AML with inv(3)(q21.3q26.2) or t(3;3)(q21.3;q26.2); *GATA2*, *MECOM*
  - AML (megakaryoblastic) with t(1;22)(p13.3;q13.3);*RBM15-MKL1*
  - *Provisional entity: AML with BCR-ABL1*
  - AML with mutated *NPM1*
  - AML with biallelic mutations of *CEBPA*
  - *Provisional entity: AML with mutated RUNX1*
- AML with myelodysplasia-related changes
- Therapy-related myeloid neoplasms
- AML, NOS
  - AML with minimal differentiation
  - AML without maturation
  - AML with maturation
  - Acute myelomonocytic leukemia
  - Acute monoblastic/monocytic leukemia
  - Pure erythroid leukemia
  - Acute megakaryoblastic leukemia
  - Acute basophilic leukemia
  - Acute panmyelosis with myelofibrosis
- Myeloid sarcoma
- Myeloid proliferations related to Down syndrome
  - Transient abnormal myelopoiesis (TAM)
  - Myeloid leukemia associated with Down syndrome

18.4 Incidences of Adverse Drug Reactions in Long-Term Clinical Studies [84]

ADRs	Events	2689-CL-2004	AC220-002
		Quizartinib doses: 30 mg and 60 mg daily	Quizartinib doses: 90 mg and 135 mg (confirmatory; total TEAE)
		N= 74 %	N= 271 %
Blood and Lymphatic system disorders†*	Febrile neutropenia Anemia Thrombocytopenia Neutropenia Pancytopenia	33.8 36.5 23.0 8.1 0	38.0 32.5 17.7 12.9 4.4
General Disorders and administrative site conditions †	Pyrexia Fatigue Asthenia	33.8 28.4 6.8	32.1 31.0 19.9
GI Disorders †	Abdominal pain Nausea Vomiting Diarrhea	23.0 36.5 32.4 31.1	11.8 53.1 39.1 39.1
Infections & Infestations†*	Most frequent types of infections are shown here, but all types of infections may occur (including bacteremia and sepsis including bacterial, fungal, and opportunistic infections) and may be severe, including fatal outcome Reports of infection have often been in the context of neutropenia, fever, or both.		
	Pneumonia Septic shock Sepsis/Escherichia sepsis UTI Herpes/oral herpes Oral candidiasis	14.9 4.1 2.7 4.1 4.1 0	14.8 2.6 2.2 7.4 2.6/7.0 6.3
Bleeding†* and Bruising	Bleeding and bruising may occur from any site as a result of cytopenias, and may be severe, including fatal outcome.		
	Epistaxis Hematoma Mouth hemorrhage Hematuria GI hemorrhage Melena Hemoptysis Vaginal hemorrhage Cerebral hemorrhage	13.5 2.7 2.7 4.1 4.1 4.1 4.1 1.4 1.4	19.6 9.6 6.6 5.5 4.1 2.6 2.2 2.2 1.5
QTc prolongation†	Δ QTcF > 60 msec Grade 3 / 4**	12.2 4.1	39.1 16.6
Torsades de Pointe		0	<1
Skin and subcutaneous tissue disorders†	Acute febrile neutrophilic dermatosis (Sweet's Syndrome)	1.4	3.0

GI = gastrointestinal; QTcF = corrected QT interval using the Fridericia's formula; TEAE = treatment-emergent adverse event; UTI = urinary tract infection.
† indicates events that may be serious
* indicated events that may be fatal

** QTcF prolongation: Grade 3/4: value >500 msec
Source: 2689-CL-2004, Table 14.3.1.9 and 14.3.6.11; AC220-002, Table 14.3.2.2.1 and 14.3.9.3.1, preliminary data.

19 QT Prolonging Medications and CYP3A4 Inhibitors/Inducers

This appendix lists medications that potentially prolong QT/QTc and medications and foods that are common inhibitors/inducers of CYP3A4. These lists should not be considered all inclusive. Consult individual drug labels for specific information on a compound's propensity to prolong QT/QTc and/or inhibit/induce CYP3A4

19.1 Potential QT/QTc Prolonging Drugs

Potential QT/QTc Prolonging Drugs	Generic Drug Name
Class IA antiarrhythmics	Quinidine, procainamide, disopyramide
Class IC antiarrhythmics	Flecainide, propafenone, moricizine
Class III antiarrhythmics	Sotalol, bretylium, ibutilide, dofetilide
Antipsychotics	Thioridazine, mesoridazine, chlorpromazine, prochlorperazine, trifluoperazine, fluphenazine, perphenazine, pimozide, risperidone, ziprasidone, lithium, haloperidol
Tricyclic/tetracyclic antidepressants	Amitriptyline, desipramine, doxepin, dosulepin, hydrochloride, imipramine, maprotiline
Selective serotonin and norepinephrine reuptake inhibitors (SSNRIs)	venlafaxine
Macrolide antibiotics	azithromycin, erythromycin, clarithromycin, dirithromycin, roxithromycin, tulathromycin
Fluoroquinolone antibacterials	moxifloxacin, gatifloxacin
Azole antifungals	ketoconazole, fluconazole, itraconazole, posaconazole, voriconazole
Antimalarials	amodiaquine, atovaquone, chloroquine, doxycycline, halofantrine, mefloquine, proguanil, primaquine, pyrimethamine, quinine, sulphadoxine
Antiprotozoals	pentamidine
Antiemetics	droperidol, dolasetron, granisetron, ondansetron
Antiestrogens	tamoxifen
Immunosuppressants	tacrolimus

Source: Protocol AC220-A-U302, V2

19.2 CYP3A4 Inhibitors

Inhibitor Type	Generic Drug Name	Allowance
Strong	boceprevir, clarithromycin, conivaptan, grapefruit, grapefruit juice, indinavir, itraconazole, ketoconazole, lopinavir, mibefradil, nefazodone, nelfinavir, posaconazole, ritonavir, saquinavir, telaprevir, telithromycin, voriconazole	Use should be avoided if possible. If necessary for subject care a dose reduction of quizartinib is required.
Moderate	amprenavir, aprepitant, atazanavir, ciprofloxacin, crizotinib, darunavir, diltiazem, erythromycin, fluconazole, fosamprenavir, imatinib, verapamil	Use allowed. No requirement for quizartinib dose reduction.
Weak	alprazolam, amiodarone, amlodipine, atorvastatin, bicalutamide, cilostazol, cimetidine, cyclosporine, fluoxetine, fluvoxamine, ginkgo, goldenseal, isoniazid, lapatinib, oral contraceptives, nilotinib, pazopanib, ranitidine, ranolazine, ticagrelor, tipranavir, zileuton	Use allowed. No requirement for quizartinib dose reduction

Source: Protocol AC220-A-U302, V2

19.3 CYP3A4 Inducers

Inducer Type	Generic Drug Name	Allowance
Strong	avasimibe, carbamazepine, phenytoin, rifampin, St. John's wort	Use prohibited while on quizartinib.
Moderate	bosentan, efavirenz, etravirine, modafinil, nafcillin	Use prohibited while on quizartinib.
Weak	amprenavir, aprepitant, armodafinil, clobazam, echinacea, pioglitazone, prednisone, rufinamide, vemurafenib	Use allowed.

Source: Protocol AC220-A-U302, V2