NOVARTIS

Oncology Global Development Unit

PKC412 (Midostaurin)

Clinical Protocol CPKC412E2301 / NCT03512197

A phase III, randomized, double-blind study of chemotherapy with daunorubicin or idarubicin and cytarabine for induction and intermediate dose cytarabine for consolidation plus midostaurin (PKC412) or chemotherapy plus placebo in newly diagnosed patients with FLT-3 mutation negative acute myeloid leukemia (AML)

Document type	Oncology Clinical Trial Protocol (Clean)
EUDRACT number	2017-003540-21
Version number	01 (Amended Protocol)
Development phase	III
Document status	Final
Release date	08-Jun-2018

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Template version 06-Apr-2017

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List of abbreviations

ADR	Adverse Drug Reaction
AdSM	Advanced systemic mastocytosis
AE	Adverse Event
AESI	Adverse event of special interest
AHNMD	Associated hematologic non-mast cell lineage disorder
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
AML	Acute myeloid leukemia
ANC	Absolute Neutrophil Count
APL	acute promyelocytic leukemia
AR	Allelic Ratio
ASM	Aggressive systemic mastocytosis
AST	Aspartate aminotransferase
ATC	Anatomical Therapeutic Chemical
AUC	Area under the curve
AV	Atrioventricular
BCRP	Breast cancer resistant protein
BCS	Biopharmaceutics classification system
BM	Bone Marrow
BMA	Bone marrow aspirate
BSA	Body Surface Area
CABG	Coronary artery bypass graft
CALGB	Cancer and Leukemia Group B
CBF	Core binding factor
CID	Cumulative incidence of death
CIR	Cumulative incidence of relapse
CIVI	Continuous intravenous infusion
CMO&PS	Chief Medical Office and Patient
CMV	Cytomegalovirus
CNS	Central Nervous System

CPO	Country Pharma Organization
CR	Complete remission
CRi	Morphologic complete remission without hematopoietic recovery
eCRF	Electronic Case Report/Record Form; the term CRF can be applied to either EDC or Paper
CRO	Contract Research Organization
CSF	Cerebrospinal fluid
CSR	Clinical study report
CSR addendum	An addendum to Clinical Study Report (CSR) that captures all the additional information that is not included in the CSR
CTCAE	Common Terminology Criteria for Adverse Events
CV	Coefficient of variation
CYP3A4	cytochrome P450 3A4 enzyme
DILI	Drug-induced liver injury
DFS	Disease-free survival
DMC	Data Monitoring Committee
EBV	Epstein-Barr Virus
EC	Ethic committee
ECG	Electrocardiogram
ECHO	Echocardiogram
ECOG	Eastern Cooperative Oncology Group
EDC	Electronic Data Capture
EDD	Expected Delivery Date
EFS	Event-free survival
ELN	European LeukemiaNet
EOT	End of Treatment
EQ-5D	EuroQol- 5 Dimension
EQ VAS	EQ visual analogue scale
FAB	French American British
FACT-G	Functional assessment of cancer therapy-general
FACT-Leu	Functional assessment of cancer therapy-leukemia
FAS	Full analysis set

[redacted]

FDA	Food and drug administration
FGFR	Fibroblast growth factor receptor
FLT3	FMS-like tyrosine kinase
FLT-3 MN (SR<0.05)	FLT-3 Mutation Negative (FLT-3 mutant to wild type signal ratio below the 0.05 clinical cut-off
FLT3-WT	FLT3 wild type
GGT	Gamma-glutamyltransferase
GI	Gastrointestinal
HIV	Human Immunodeficiency Virus
HR	Hazard Ratio
HSCT	Hematopoietic Stem Cell Transplantation
HSV	Herpes simplex virus
IB	Investigator's Brochure
ICF	Inform consent form
ICH	International Conference on Harmonization
ICMJE	International Committee of Medical Journal Editors
IDAC	Intermediate dose of Ara-C/Cytarabine
IEC	Independent Ethics Committee
IN	Investigator notification
INR	International Normalized Ratio
IRB	Institutional Review Board
IRT	Interactive Response Technology that includes Interactive Voice Response System and Interactive Web Response System
ITD	Internal Tandem duplication
IUD	Intrauterine Device
IUS	Intrauterine System
I.V	Intravenous(ly)
IWG	International Working Group
LAIP	Leukemia-Associated ImmunoPhenotypes
LFT	Liver function tests
LPLV	Last patient last visit
LLOQ	Lower limit of quantitation

[redacted]

LVEF	Left Ventricular Ejection Fraction
MAR	Missing-at-random
MCL	Mast cell leukemia
MDS	Myelodysplastic Syndrome
MedDRA	Medical dictionary for regulatory activities
MFC	multi-parameter flow cytometry
MI	Myocardial Infarction
MMRM	Mixed models for repeated measures
MR	Minor Response
MRD	Minimal/Measurable Residual Disease
MRP2	Multi-drug resistance associated protein 2
MUGA	Multigated Acquisition Scan
NCA	Non-compartmental analysis
NCCI	National Comprehensive Cancer Network
NCI	National cancer institute
[redacted]	[redacted]
NOEL	number of observable effect level
OS	Overall Survival
PAS	Pharmacokinetic Analysis Set
PD	Pharmacodynamic
PDGFR	Platelet-derived growth factor receptor
P-gp	P-glycoprotein
PHI	Protected Health Information
[redacted]	[redacted]
PK	Pharmacokinetic
PML-RARA	Promyelocyte Leukemia - Retinoic Acid Receptor Alpha Rearrangement
p.o.	per os/by mouth/orally
PopPK	Population pharmacokinetic analysis
PPS	Per-Protocol Set
PR	Partial remission
PRO	Patient reported outcome
PT	Prothrombin time

[redacted]

aPTT	activated partial thromboplastin time
QT/QTcF	QT interval/QT interval corrected with Fridericia's formula
RATIFY	Randomized AML Trial In FLT3+ patients <60 Years (Study A2301)
REB	Research Ethics Board
RT	Radiotherapy
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SC	Steering Committee
SD	Standard deviation
SDAC	Standard dose of Ara-C/Cytarabine
SM	Systemic Mastocytosis
SR	Signal Ratio
SS	Safety set
SSD	Study specification document
SUSAR	Suspected unexpected serious adverse reations
TBIL	Total bilirubin
TdP	Torsades de Pointes
TKD	Tyrosine Kinase Domain
ULN	Upper limit of normal
VAP	Validation and planning
VAS	Visual analogue scale
VEGFR	Vascular endothelial growth factor
WBC	White blood cell
WHO	World Health Organization

Glossary of terms

Assessment	A procedure used to generate data required by the study
Biologic Samples	A biological specimen including, for example, blood (plasma, serum), bone marrow, saliva, tissue, urine, stool, etc. taken from a study subject or study patient
Cycles	Number and timing or recommended repetitions of therapy are usually expressed as number of days (e.g.: 28 days)
Enrollment	Point/time of patient entry into the study; the point at which informed consent must be obtained (i.e. prior to starting any of the procedures described in the protocol)
FLT3-Mutation Negative (MN)	For the purpose of this study FLT3-MN is defined as the absence of ITD mutation and absence of TKD activating mutation at codons D835 and I836 in the FLT3 gene (FMS-like tyrosine kinase 3 gene), based on mutant to wild type signal ratio below the 0.05 clinical cutoff.
Investigational drug	The study treatment whose properties are being tested in the study; this definition is consistent with US CFR 21 Section 312.3 and is synonymous with “investigational new drug.”
Investigational treatment	Drug whose properties are being tested in the study as well as their associated placebo and active treatment controls (when applicable). This also includes approved drugs used outside of their indication/approved dosage, or that are tested in a fixed combination. Investigational treatment generally does not include other study treatments administered as concomitant background therapy required or allowed by the protocol when used in within approved indication/dosage
Medication number	A unique identifier on the label of each study treatment package which is linked to one of the treatment groups of a study
Other study treatment	Any drug administered to the patient as part of the required study procedures that is not included in the investigational treatment
Subject number (Subject No.)	A unique identifying number assigned to each patient/subject/healthy volunteer who enrolls in the study
Period	A subdivision of the study timeline; divides stages into smaller functional segments such as screening, induction, consolidation, post-consolidation, follow-up for efficacy or survival.
Personal Data	Subject information collected by the Investigator that is transferred to Novartis for the purpose of the clinical trial. This data includes subject identifier information, study information and biological samples.
Randomization number	A unique treatment identification code assigned to each randomized patient, corresponding to a specific treatment arm assignment
Stop study participation	Point/time at which the patient came in for a final evaluation visit or when study treatment was discontinued whichever is later
Study treatment	Midostaurin or placebo in sequential combination with daunorubicin/idarubicin and cytarabine induction, in sequential combination with intermediate dose cytarabine consolidation, and as single agent post-consolidation therapy.
Study treatment discontinuation	Point/time when patient permanently stops taking study treatment for any reason
Treatment group	A treatment group defines the dose and regimen of the combination.
Variable	Identifier used in the data analysis; derived directly or indirectly from data collected using specified assessments at specified timepoints.
Withdrawal of consent	Withdrawal of consent from the study occurs only when a subject does not want to participate in the study any longer, and does not allow any further collection of personal data

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Protocol summary:

Title	A phase III, randomized, double-blind study of chemotherapy with daunorubicin or idarubicin and cytarabine for induction and intermediate-dose cytarabine for consolidation plus midostaurin (PKC412) or chemotherapy plus placebo in newly diagnosed patients with FLT3-mutation negative acute myeloid leukemia (AML)
Brief title	A global study of the efficacy and safety of midostaurin + chemotherapy in newly diagnosed patients with FLT3-MN AML
Sponsor and clinical phase	Novartis, Phase III
Investigation type	Drug
Study type	Interventional
Purpose and rationale	The purpose of this study is to confirm the preliminary evidence from early clinical trials that midostaurin may provide clinical benefit not only to AML patients with the FLT3-mutations but also in FLT3-MN (SR<0.05) AML (FLT3 mutant to wild type signal ratio below the 0.05 clinical cut-off). This study will evaluate the efficacy and safety of midostaurin in combination with daunorubicin or idarubicin and cytarabine for induction and intermediate-dose cytarabine for consolidation, and midostaurin single agent post-consolidation therapy in newly diagnosed patients with FLT3-MN (SR<0.05) AML.
Primary objective(s) and key secondary objective	Primary Objective: To determine if the addition of midostaurin to standard induction and consolidation therapy, followed by single agent post-consolidation therapy improves event-free survival (EFS) in patients with newly diagnosed FLT3-MN (SR<0.05) AML. Key Secondary Objective: To determine if the addition of midostaurin to standard induction and consolidation therapy, followed by single agent post-consolidation therapy improves overall survival (OS) in patients with newly diagnosed FLT3-MN (SR<0.05) AML.
Secondary objectives	Objective 1: To compare the rate of complete remission (CR + CRi with adequate blood count recovery) in the two treatment groups. Objective 2: To compare the percentage of patients who reached MRD negative status in the two treatment groups. Objective 3: To compare the percentage of patients with MRD negative status in the post-consolidation phase in the two treatment groups. Objective 4: To compare the time to MRD negative status bone marrow between the two treatment groups. Objective 5: To compare disease-free survival (DFS), as well as the cumulative incidence of relapse (CIR) and cumulative incidence of death (CID) in the two treatment groups. Objective 6: To compare the time to CR or CRi with adequate blood count recovery in the two treatment groups. Objective 7: To compare the time to neutrophil recovery in the two treatment groups. Objective 8: To compare the time to platelet recovery in the two treatment groups. Objective 9: To assess the safety and tolerability of midostaurin in combination with chemotherapy and as monotherapy during post-consolidation. Objective 10: To further characterize the pharmacokinetics of midostaurin, CGP52421 and CGP62221. Objective 11: To assess the impact of midostaurin on health related quality of life and AML symptom reduction.
[redacted]	[redacted]

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	[redacted]
Study design	This is a multi-center, multinational, randomized, double-blind Phase III study using a group sequential design with two interim analyses. The primary endpoint is EFS as per investigator assessment and is defined as the time from randomization to failure to achieve CR or CRi with adequate blood count recovery (i.e., neutrophils ≥1.0 x 10^9/L and platelets ≥50 x 10^9/L) in induction phase, relapse from CR or CRi with adequate blood count recovery or death due to any cause whichever occurs first. Overall survival (OS) is the key secondary endpoint and is defined as the time from randomization to death due to any cause. OS will be hierarchically tested if the EFS shows significant improvement in the second interim analysis or in the final analysis. Patients will be stratified according to Age (<60 vs. ≥ 60 years) Patients within each stratum will be randomized in a 1:1 ratio into one of two treatment arms: Midostaurin + chemotherapy or Placebo + chemotherapy The study will consist of the following phases: Screening/randomization phase: Patients having signed informed consent will be screened for eligibility criteria. Patients will start treatment with chemotherapy at day 1 and will be randomized at day 8. Induction phase: All patients will receive at least one cycle of induction therapy with continuous infusion cytarabine and daunorubicin or idarubicin (induction 1). Patients not achieving CR or CRi with adequate blood count recovery after Induction 1 will receive a second cycle with intermediate-dose cytarabine and daunorubicin or idarubicin (induction 2). Patients not achieving CR or CRi with adequate blood recovery after induction 2 will discontinue study treatment and will be followed for survival. Patients achieving CR or CRi with adequate blood count recovery after induction 2 will enter the consolidation phase. Consolidation phase : Patients achieving CR or CRi with adequate blood count recovery after induction with one or two cycles will proceed to consolidation therapy with either 3 or 4 cycles of intermediate-dose cytarabine, or to Hematopoietic Stem Cells Transplantation (HSCT) with or without preceding consolidation cycles. Post-consolidation phase: Patients achieving CR or CRi with adequate blood count recovery at the end of the consolidation phase will receive 12 cycles (28 days/cycle) of continuous therapy with midostaurin or placebo twice daily at 50 mg. Patients who underwent HSCT after achieving CR or CRi with adequate blood count recovery will receive midostaurin or placebo twice daily 50 mg post-transplant therapy, continuously, for up to 12 cycles (28 days/cycle). Post HSCT post-consolidation therapy will begin >30 days but not later than 100 days following HSCT. Follow-up phase:

[redacted]

	All patients enrolled to the study will be followed through the treatment period and until relapse/treatment failure, thereafter for start of new line of therapy and survival.
Population	The study will include 502 adult (male and female) patients ≥ 18 years with newly diagnosed FLT3-MN (SR<0.05) AML.
Inclusion criteria	Patients eligible for inclusion in this study have to meet all of the following criteria: Diagnosis of AML (≥20% blasts in the bone marrow based on World Health Organization (WHO) 2016 classification). Patients with acute promyelocytic leukemia APL with a PML-RARA rearrangement are not eligible. Suitability for intensive induction chemotherapy in the judgment of the investigator based on patient's performance status and comorbidities Documented absence of an internal tandem duplication (ITD) and tyrosine kinase domain (TKD) activating mutation at codons D835 and I836 in the FLT3 gene, with clinical cutoff of 0.05 mutant to wild type signal ratio. Age ≥ 18 years Laboratory values that indicate adequate organ function assessed locally at the screening visit: Aspartate aminotransferase (AST) ≤ 3 times upper limit of normal (ULN) Alanine aminotransferase (ALT) ≤ 3 times ULN Serum total bilirubin ≤ 1.5 times ULN, except in the setting of isolated Gilbert syndrome Estimated (by Cockcroft-Gault) creatinine clearance ≥ 30ml/min Written informed consent
Exclusion criteria	Patients eligible for this study must not meet any of the following criteria: Central nervous system (CNS) leukemia Therapy-related secondary AML Isolated extramedullary leukemia Prior therapy for leukemia or myelodysplasia with the following exceptions: Emergency leukapheresis Emergency treatment for hyperleukocytosis with hydroxyurea or low-dose cytarabine for ≤ 7 days Cranial radiotherapy (RT) for CNS leukostasis (one dose only) Hematopoietic Growth factor/cytokine support Other supportive therapy including antibiotics at the discretion of the investigator AML after antecedent myelodysplasia (MDS) with prior cytotoxic treatment (e.g., azacytidine or decitabine) Any investigational agent within 30 days or 5 half-lives, whichever is greater Prior treatment with a FLT3 inhibitor Strong CYP3A4/5 enzyme inducing drugs (see Appendix 1) unless they can be discontinued or replaced prior to enrollment. Any other known disease or concurrent severe and/or uncontrolled medical condition that could compromise participation in the study. Abnormal chest X-ray with corresponding clinical symptoms or findings that indicate an active infection, or other pulmonary conditions that are currently clinically significant. Intestinal malabsorption Known human immunodeficiency virus (HIV) infection or active viral hepatitis Cardiovascular abnormalities, including any of the following: History of myocardial infarction (MI), angina pectoris, coronary artery bypass graft (CABG) within 6 months prior to starting study treatment Clinically uncontrolled cardiac arrhythmias (e.g., ventricular tachycardia), complete left bundle branch block, high-grade atrioventricular (AV) block (e.g., bifascicular block, Mobitz type II and third degree AV block) Uncontrolled congestive heart failure

[redacted]

	Left ventricular ejection fraction of <50% Poorly controlled hypertension Pregnant or nursing (lactating) women Women of child-bearing potential, defined as all women physiologically capable of becoming pregnant, unless they are using highly effective methods of contraception during dosing and for at least 4 months after stopping medication. Sexually active males unless they use a condom during intercourse Unwillingness or inability to comply with the protocol. Known hypersensitivity to midostaurin, cytarabine or idarubicin / daunorubicin or to any of the excipients of midostaurin/placebo, cytarabine or idarubicin / daunorubicin.
Investigational and reference therapy	Midostaurin or placebo in sequential combination with daunorubicin/idarubicin and cytarabine induction, in sequential combination with intermediate dose cytarabine consolidation, and as single agent post-consolidation therapy. Treatment switching is not an option in this trial.
Efficacy assessments	Efficacy assessment will be determined by the following parameters: Blast count in bone marrow, peripheral blood specimens (platelet count, neutrophils and blasts), evaluation of extramedullary disease and assessment of red blood cell and platelet transfusion. Entry of response evaluations in the case report form (CRF) will be according to the International Working Group (IWG) criteria for AML (Cheson et al., 2003, ELN 2017 / Döhner et al 2017) as per investigator assessment. The response to treatment and relapse will not require confirmation by a repeated test. Response assessment will be done at the following time points: End of each induction cycle, end of each consolidation cycle, every cycle during post-consolidation phase and every 3 months during follow-up phase. Patients moving to HSCT will have a response assessment documented before start of HSCT. Patients with CRi without adequate blood count recovery at end of each cycle, will have a response assessment performed (for a maximum of 2-3 additional weeks) upon blood recovery. Moreover, disease assessment will be performed any time in case of suspected relapse. For details please see Section 7.2.1.
Safety assessments	Safety assessment will include AEs with severity, relationship to study treatment and seriousness, physical examination, Eastern cooperative oncology group (ECOG) PS, vital signs, 12-lead electrocardiogram (ECG), local measurements of QTc≥480ms will be centrally verified on a copy of a high quality recording that includes time and voltage scales, multigated acquisition scan (MUGA), echocardiogram (ECHO) and laboratory assessments including hematology, chemistry, coagulation and urinalysis
Other assessments	PK parameters Plasma concentrations of midostaurin and its active metabolites CGP62221 and CGP52421 [redacted] Patient reported outcome assessment using EuroQol- 5 Dimension (EQ-5D), Functional assessment of cancer therapy-general (FACT-G) with FACT-leukemia (FACT-Leu) [redacted]

[redacted]

Statistical methods and data analyses	Populations: The Full Analysis Set (FAS) comprises all patients to whom study drug has been assigned by randomization. According to the intent to treat principle, patients will be analyzed according to the treatment and stratum they have been assigned to during the randomization procedure. The Safety Set (SS) includes all patients who received at least one dose of study treatment starting at day 1, were randomized and took at least one dose of midostaurin or placebo. Patients will be analyzed according to the study treatment received, where treatment received is defined as the randomized treatment if the patient took at least one dose of that treatment. Primary efficacy and key secondary endpoints: EFS and OS are the primary and key secondary endpoints, respectively. Therefore, family wise type I error rate associated with efficacy analyses for testing EFS and OS will be controlled by using hierarchical testing procedure. Event Free Survival (EFS): The study is designed to test the following statistical hypothesis for EFS using a stratified log-rank test (stratified according to randomization stratification factor of age (<60 vs. ≥ 60 years)) at the one-sided 2.5% level of significance: H_{01}: $\theta_1 \geq 1$ vs. H_{a1}: $\theta_1 < 1$ Where θ_1 is the hazard ratio (Midostaurin treatment arm vs. placebo arm) of EFS. The primary efficacy endpoint EFS will be analyzed at the interim looks and final look of a group sequential design based on the FAS population according to the treatment group patients were randomized and the strata they were assigned at randomization (i.e. age < 60 vs. >=60 years). EFS will be estimated using the Kaplan-Meier method. The median EFS along with 95% confidence intervals will be presented by treatment group. Under the proportional hazards assumption, a test based on the stratified log-rank test provides an asymptotically equivalent result as that of the stratified Cox regression model which will be used to estimate the hazard ratio (HR) of EFS, along with 95% confidence interval (using the same strata information as above). The final analysis will be performed when there are approximately 285 EFS events. Two interim analyses will be performed when approximately 114 and 214 of the 285 EFS events (approximately 40% and 75% information fraction respectively) have been documented. These analyses are expected to take place around 12 and 20 months respectively from the date of first patient randomized in the study assuming an increasing recruitment rate to reach 30 patients / month in month 6. The primary intent of the first interim analysis is to allow the study to stop early for lack of efficacy (futility). There is no intent to carry out an analysis to declare superior efficacy at the time of the first interim analysis. At least, 283 patients (56%) are expected to be randomized at the time of the interim futility analysis, i.e., when approximately 114 EFS events have occurred. The 2nd interim analysis will allow the study to stop early for outstanding efficacy. The 2nd interim analysis will only be carried out after all patients have been randomized. A user-defined gamma spending function (γ = -1.2) will be used as a beta-spending function to determine the non-binding futility boundary at the time of the 1st interim analysis. The futility boundary at the first interim is calculated as hazard ratio of 0.97. The observed (i.e., nominal) p-value has to be greater than p=0.44 (one-sided) to conclude futility. Since the observed number of EFS events at the interim analyses may not exactly be equal to the planned number of events, the futility boundary will need to be re-calculated (or updated) based on the actual number of observed events. Therefore, the observed p-value (or Z-test statistic) at the first interim analysis will be compared with the updated futility boundary. A Haybittle-Peto stopping boundary will be used for efficacy interim and final EFS analyses (Peto et al 1976). At the second interim analysis, the observed p-value has to be less than p=0.0001 (i.e. HR<0.601) in order to conclude superior efficacy. If the study continues, the final analysis will be performed when approximately 285 EFS events have been documented or 5 years after the end of the study treatment for the last patient whichever occurs first. The final analysis criteria will be determined based

[redacted]

on the actual number of events observed such that the overall significance level across all analyses is maintained at 0.025. It is estimated that the observed hazard ratio (HR) needs be less than 0.793 to declare statistical significance at the final EFS analysis.

The following table represents the operational characteristics of this design. These are based on simulations in the software package East version 6.4. The following are a few key operational characteristics: The cumulative probability to detect an efficacious treatment by the primary analysis is 90%; while the cumulative probability of erroneously detecting a non-efficacious treatment by the final analysis is 2.4%. If the null hypothesis is true then cumulative probability to stop the trial at the first interim analysis for lack of efficacy is 55.8%.

Hazard ratio	Analysis	Average sample size	EFS (information fraction)	Average Time (months)	Simulated cum. Prob stop due to	
					Efficacy	Futility
0.675	IA 1	282	114 (40%)	11.9	0.0149*	0.025
	IA 2	502	223 (78%)	20	0.1983	NA
	FA	502	285 (100%)	38.8	0.900	NA
0.8375	IA1	264	123 (43%)	11.3	0.0003*	0.213
	IA2	502	240 (84%)	20	0.009	NA
	FA	502	285 (100%)	31	0.312	NA
1.0	IA1	249	114 (40%)	10.8	0	0.558
	IA2	502	255 (89%)	20	0.0001	NA
	FA	502	285 (100%)	26.5	0.024	NA

*Although the probability to stop for efficacy at IA1 is provided, there is no intent to stop for efficacy at IA1.

Overall Survival (OS):

OS is the key secondary endpoint. A hierarchical testing procedure will be adopted and analysis of OS will be performed only if the primary null hypothesis for EFS is rejected. The analysis of OS will be based on FAS following a separate group-sequential plan.

Two interim analyses and a final analysis for OS may be performed in this study. A Haybittle-Peto boundary (Peto et al 1976), independent of the Haybittle-Peto boundary used for EFS, along with the testing strategy outlined below will be used to maintain the overall type I error probability. Timing of two interim OS analyses will be at the same time as the second interim and final EFS analyses. The OS analysis will compare midostaurin+chemotherapy with placebo+chemotherapy (H_{02}: $\theta_2 \geq 1$ vs. H_{a2}: $\theta_2 < 1$ Where θ_2 is the hazard ratio (midostaurin treatment arm vs. placebo arm) of OS). The median OS in the control treatment arm is expected to be around 30 months. It is hypothesized that midostaurin treatment arm will result in a 28.6% reduction in the hazard rate for overall survival (corresponding to an increase in median survival by 12 months (from 30 to to 42 months) under the exponential model assumption). If the true hazard ratio is 0.714, a total of 278 deaths are needed to be observed to have 80% power at an one-sided overall 2.5% level of significance to reject the null hypotheses (HR≥1) using a log-rank test and a 3-look group sequential design. Under the assumptions mentioned above, approximately 79 and 190 survival events (28% and 68% information fraction respectively) are expected to occur at the time of the first and second interim OS analysis, respectively. The final analysis for OS will be conducted when 278 deaths have occurred.

It is estimated that these 278 deaths will be observed at approximately 64 months from the date of first patient to be randomized.

The following table provides expected time at which interim and final analyses for EFS and OS will be performed. These estimates are based on the assumptions used for determining the study design:

[redacted]

Analysis	Expected number of randomized patients	Number of events EFS (information fraction)	OS** (information fraction)	Expected time*** (month)
EFS First interim	283	114 (40%)	-	12
Second EFS interim/first OS interim	502	223 (78%)	79 (28%)	20
EFS final/Second OS interim	502	285 (100%)	190 (68%)	39
OS final	502	-	278 (100%)	64

** Analyses performed in case EFS is significant

*** Expected time after FPFV.

The interim analyses for EFS and the first interim analysis of OS will be performed by an independent statistician.

Results from the EFS interim analysis will not be communicated to clinical team, the study steering committee (SC) or any party involved in the study conduct (apart from the independent statistician and independent data monitoring committee (DMC) members) or external parties including Health Authority and investigators until EFS is found to be significant or study needs to be terminated due to safety or lack of efficacy. Unblinded results from the OS interim analysis will not be communicated to clinical team or any party involved in the study conduct (apart from the independent statistician and DMC members) or external parties, until OS is found to be significant or until the final OS analysis or the study needs to be terminated due to any cause. Note that the DMC will also conduct regular safety looks which may include on-study deaths.

Other secondary endpoints:

Other secondary efficacy variables include CR or CRi with adequate blood count recovery rate, DFS, Cumulative Incidence of Relapse (CIR), and Cumulative Incidence of Death (CID). The assessment of these endpoints will be based on the IWG for AML (Cheson et al 2003, ELN 2017 / Döhner et al 2017), per investigator assessment.

CR or CRi with adequate blood count recovery rates will be analyzed using Cochran-Mantel-Haenszel test based on strata at randomization. Estimated CR or CRi with adequate blood count recovery rates along with corresponding 95% confidence intervals will be presented by treatment group.

Median DFS, Time to CR or CRi with adequate blood count recovery, Cumulative Incidence of Relapse (CIR) and Cumulative Incidence of Death (CID) along with corresponding 95% confidence intervals will be presented by treatment group.

The rate of CR or CRi with adequate blood count recovery and time to CR or CRi with adequate blood count recovery will be analyzed based on the FAS. However, DFS, Cumulative Incidence of Relapse (CIR) and Cumulative Incidence Death (CID) will be analyzed based on data from responders (CR or CRi with adequate blood count recovery) in the FAS. Assessment of relapse from CR or from CRi with adequate blood count recovery, DFS, Cumulative Incidence of Relapse (CIR), and Cumulative Incidence of Death (CID) will not consider whether a patient received HSCT.

The median time to platelet and to neutrophil recovery along with their corresponding 95% confidence intervals will be presented by treatment group.

In addition safety, pharmacokinetic, patient reported outcome (PRO) data will be analyzed. For PRO, The FACT-Leu will be scored. For each treatment group, calculated score and change from baseline will be analyzed. Effects of treatment on overall HRQL will be assessed.

Sample size

The assumption of median EFS of 12.0 months for the control treatment arm for sample size calculations is based on available data for patients with FLT-MN Hoenekopp (Bacher et al 2008). It is expected that treatment with test treatment arm will result in a

[redacted]

	37.5% reduction in the hazard rate (corresponding to an increase in median PFS from 12.0 months to 17.8 months under the exponential model assumption. If the true hazard ratio is 0.675, a total of 285 EFS events are required to have 90% power at an one-sided overall 2.5% level of significance to reject the null hypothesis (HR=1) using a log-rank test and a 3-look group sequential design with Haybittle-Peto boundary to determine efficacy boundary and gamma spending function (γ = -1.2) to determine the non-binding futility boundary. Considering a recruitment period of approximately 20 months assuming an increasing recruitment rate to reach 30 patients / month in month 6, 502 patients will need to be randomized to the two treatment arms in a 1:1 ratio. Assuming about 10% patients will be lost to follow-up for EFS, a total of 502 patients will need to be randomized. Given the above assumptions, it is estimated that the 285th EFS event will be observed at approximately 39 months from the date of first patient randomized in the study. The sample size calculation was conducted with software package East 6.4. For details of the statistical methods, please see section 10.
Key words	PKC412, midostaurin, cytarabine, daunorubicin, idarubicin, acute myeloid leukemia, FLT3-MN (SR<0.05), combination treatment, induction failure, event free survival, measurable residual disease.

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Amendment 1 (08-Jun-2018)

Amendment rationale

At the time of this protocol amendment, patients have not yet been enrolled in the trial.

Due to the implementation of the Global Data Protection Regulation (GDPR) on 25-May-2018, corresponding changes have been made to the ICF and protocol.

Additional text has been added to the screening section in order to clarify that at sites that also participate in the CPKC412A2220 (A2220) trial (aiming at patients with FLT3 mutated AML), patients who are screened in the A2220 trial and confirmed to be FLT3 mutation negative (SR<0.05) may be offered the opportunity to join the E2301 trial provided they also meet all other inclusion criteria. As the majority of patients diagnosed with AML are FLT3 mutation negative, this will allow that a considerable number of patients, who have gone through complex screening procedures and who would remain without study treatment, can be offered the opportunity to be treated within the E2301 clinical trial.

Further text has been added to outline that blood will be taken to collect information on some enzyme activity (pharmacogenomic analysis) to understand how the drug is broken down, and to address a Regulatory Authority request.

Additional changes were implemented based on Health Authority recommendations.

Changes to the protocol

Minor typos and grammatical errors were updated throughout the protocol.

1. List of Abbreviations updated.
2. Glossary of terms: Updated ‘Personal data’ and ‘withdrawal of consent’ to coincide with GDPR guidelines.
3. All: Correction of typos and formatting to include Pgp to P-gp, 109/L to 10^9. Bone marrow samples ‘on’ day 21-28 changed to “between” day 21-28. Updated to CTCAE version 5.0.
4. Section 2.2.2: Analyses of OS updated ‘indicates’ to ‘suggests’.
5. Section 4.2.2: Updated timing for Study treatment interruption before HSCT.
6. Section 4.4: Clarified the time to End of study.
7. Section 4.5: Further defined early termination.
8. Section 5.3: Exclusion criterion #16 updated.
9. Section 5.3: Exclusion criterion #18 added ‘Known hypersensitivity to IMP’.
10. Section 6.1.1.1: Clarification on study drug characteristics.
11. Section 6.3.2 and Table 6.2: Clarified dose modifications.
12. Table 6.2: Dose modifications for idarubicin included.
13. Section 6.4.2: Permitted Concomitant medication updated.
14. Table 7.1 and Table 7.6: Cytogenetics updated to reflect new AML testing guidelines.
15. Table 7.1: Update 30 day follow up assessments.

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16. Section 7.1.2: Screening section updated to capture inclusion of A2220 FLT3 mutation negative patients and to clarify the sample collection and timing of AML diagnosis.
17. Section 7.1.2.2: Clarification on FLT3 data collection.
18. Section 7.1.3: Updated duration of each cycle length.
19. Section 7.1.5: Withdrawal of consent updated to align with GDPR.
20. Section 7.2.2.1: Physical exam definition updated.
21. Section 7.2.2.5 and 11.3: Fertility information updated.
[redacted]
23. Section 7.2.4 and Table 7.11: Biomarker tests clarified.
24. Section 10.5.2.2: MRD negative status updated.
25. Section 10.5.4 and Table 10-1: Updated pharmacokinetics and PK parameters.
26. References: Addition of 'Thiede et al 2002' citation.
27. Appendix 1: Prohibited concomitant medication updated for clarity.

Changes to specific sections of the protocol are shown in the track changes version of the protocol using ~~strike through red font for deletions~~ and red underlined for insertions.

IRBs/IECs

A copy of this amended protocol will be sent to the Institutional Review Board (IRBs)/Independent Ethics Committee (IECs) and Health Authorities.

The changes described in this amended protocol require IRB/IEC approval prior to implementation.

The changes herein affect the Informed Consent. Sites are required to update and submit for approval a revised Informed Consent that takes into account the changes described in this protocol amendment.

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1 Background

1.1 Overview of disease pathogenesis, epidemiology and current treatment

Acute myeloid leukemia (AML) is one of the most common types of leukemia in adults. It is a heterogeneous disease that is characterized by the presence of acquired mutations as well as cytogenetic and epigenetic alterations that influence disease prognosis. Risk stratification in AML is evolving as a consequence of characterizing cytogenetic abnormalities and mutational profiling, and the latter is especially important in patients lacking karyotypic abnormalities (Döhner et al 2017).

Currently, the most generally recognized approach to classifying AML and predicting its prognosis considers the (co)occurrence of specific cytogenetic abnormalities together with mutations such as NPM1, FLT3-ITD and CEBPA. However other mutations such as DNMT3A and TP53 are also increasingly recognized to impact clinical outcome (Papaemmanuil et al 2016; Arber et al 2016). The European LeukemiaNet (ELN) guidelines have provided updated recommendations for prognostic determination (Döhner et al 2017). Favorable prognosis AML includes that with FLT3-ITD^{low} allelic ratio or FLT3-ITD-negative genotype combined with a NPM1-mutation, or the presence of core binding factor (CBF) alterations. Adverse prognosis is associated with karyotypes such as monosomy 5 or monosomy 7, NPM1-WT genotype with FLT3-ITD^{high} allelic ratio, or the t(6;9) or t(9;22) translocations, among others. The remainder is classified as intermediate risk disease. For the complete ELN risk groups including all genetic and genomic risk markers please refer to the 2017 guidelines (Döhner et al 2017).

Approximately 30% of patients with newly diagnosed AML have an activating mutation in the FLT3 gene, usually either an ITD mutation, in approximately 20% of AML patients, or an activating point mutation in the activating loop of the TKD, approximately 6-8% of AML patients) (Kayser and Levis 2014); rarely, both occur in the same leukemia. The FLT3 gene encodes a protein in the class III tyrosine kinase receptor family, and it serves a key role in the proliferation and differentiation of normal hematopoietic progenitor cells. FLT3-ITD mutations, particularly when they are present at a high allelic ratio relative to FLT3-MN (FLT3-wildype), are associated with poor prognosis (Kottaridis et al 2001, Bacher et al 2008, Thiede et al 2002, Pratcorona et al 2013). In patients with newly diagnosed AML, the complete remission (CR) rates in patients with FLT3 mutations are generally similar, or only slightly lower, than in those without FLT3 mutations. However, FLT3-ITD mutations have been shown to be associated with inferior DFS and OS, with a higher risk of relapse (Kottaridis et al 2001, Bacher et al 2008, Thiede et al 2002). The prognostic significance of the FLT3-TKD mutation has not been consistent in reports.

Initial therapy for AML in younger patients (<60 years) to induce remission has changed little in the past three decades, and for patients with an adequate performance status it frequently comprises the “7 + 3” remission induction regimen with daunorubicin and cytarabine, followed by high dose cytarabine for remission consolidation. The 5-year survival rate with

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this approach is 30 to 40% in patients under the age of 60 years, and less than 15% in older patients (Stone et al 2005).

Patients with poor prognostic features of AML are recommended to enroll into clinical trials and/or to undergo HSCT following achievement of remission with standard induction chemotherapy (Schiller 2014). Significant improvements in OS and DFS for AML patients harboring FLT3-ITD mutations have been reported with allo-HSCT compared to chemotherapy or autologous HSCT (DeZern et al 2011, Brunet et al 2013), especially for patients with high FLT3-ITD allelic ratios (Schlenk et al 2014). However, these patients remain at high risk of relapse post-HSCT compared to patients without FLT3-ITD mutations, with a higher 2-year relapse incidence (30% vs 16%; p=0.006) and lower leukemia free survival (58% vs 71%; p=0.04), respectively (Brunet et al 2012).

The ability to delay or prevent relapses in transplant candidates who experience complete remission could allow more eligible patients to undergo a HSCT. This benefit of a longer time window in remission would particularly apply to those patients who require an unrelated donor, because 3 to 6 months is generally required for the donor search alone. In addition, midostaurin may reduce the rate of relapses after HSCT. Overall, these effects may contribute to a longer EFS and OS. In AML patients with mutated FLT3 the interim analysis of a study that investigates the safety and efficacy of post-transplant treatment with midostaurin suggest an improved EFS when comparing with historical controls.

1.2 Introduction to investigational treatment(s) and other study treatment(s)

1.2.1 Overview of Midostaurin

Midostaurin (Rydapt®, PKC412, CGP41251) is an orally bioavailable staurosporine analog with potent activity against both ITD- and TKD-mutant as well as against FLT3-MN, and these observations informed the decision to pursue its development in patients with FLT3-mutated AML. In addition, it inhibits other molecular targets including several isoforms of protein kinase C, KIT, vascular endothelial growth factor receptor (VEGFR-2), platelet-derived growth factor receptor (PDGFR), fibroblast growth factor receptor (FGFR), and multi-drug resistance gene products, which are thought to be important for the pathogenesis of AML or its sensitivity to standard therapies. Furthermore, midostaurin inhibits kinases with mutations that confer resistance to other tyrosine kinase inhibitors such as imatinib.

The anti-proliferative effects of midostaurin were demonstrated in *in vitro* assays with cells expressing FLT3-ITD or FLT3-TKD mutations (Weisberg et al 2002). Synergistic inhibitory activity of midostaurin in combination with daunorubicin or cytarabine was observed in AML patient cell lines. Moreover, a related FLT3 inhibitor provided enhanced but sequence dependent cell cytotoxicity when administered simultaneously with or immediately following cytarabine, and the combinatorial activity of the FLT3 inhibitor with daunorubicin was also demonstrated (Levis et al 2004).

The potential clinical activity of midostaurin in patients with FLT3-Wildtype AML is supported by enzymatic and cell-based studies. Midostaurin potently inhibits the activity of the purified FLT3-MN tyrosine kinase with an IC50 of 19.8 nM, and it binds to the purified

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FLT3-MN kinase with a dissociation constant of 11 nM. Midostaurin inhibits the proliferation of the M07e leukemia cell line (FLT3-MN) with an IC50 of 183 ± 16 nM (Novartis internal data). Moreover, midostaurin inhibits protein tyrosine phosphorylation of FLT3-MN-expressing Ba/F3 hematopoietic cells stimulated with FLT-ligand at midostaurin doses in the range of 0.01-1 μM (Weisberg et al 2002).

1.2.1.1 Non-clinical experience

Pharmacokinetics and drug metabolism in animals

The oral absorption of [^{14}C]midostaurin in all species was moderate to high, and the bioavailability was low to moderate. Given midostaurin's low aqueous solubility (<0.001 mg/mL) and its high absorption in human (>90%), midostaurin is classified as a Biopharmaceutics classification system (BCS) II drug. In rats, dogs and rabbits, the total systemic plasma clearance (0.24 - 0.98 L/h/kg) and the volume of distribution at steady state (1.20 - 3.77 L/kg) were moderate. The half-life was relatively short in animals (3.2-7.3 h). In human the apparent terminal half-life was relatively long (~20 h) following a single oral dose.

Radioactivity derived from [^{14}C]midostaurin was extensively distributed into tissues in the rat. The concentrations in most tissues were higher than that in blood. Radioactivity crossed the blood brain barrier. After multiple doses, the radioactivity in tissues was 2-10-fold higher than that after a single dose. [^{14}C]midostaurin showed a high protein binding in the rat, dog and human (>98-99%). The protein binding was independent of concentration in animals. In human, a concentration dependent increase in fraction unbound was observed over a concentration range of 100-20,000 ng/mL. The two major metabolites of midostaurin, [^{14}C]CGP52421 and [^{3}H]CGP62221, showed a similar plasma protein binding to midostaurin.

Midostaurin was extensively metabolized in the rat, dog, rabbit and human. The primary biotransformation pathways observed included hydroxylation, O-demethylation, N-demethylation and amide hydrolysis. The major circulating components were midostaurin and CGP52421 (two epimers) in all species. CGP62221 (the O-demethylation product) was also a major human circulating metabolite and detectable in the dog and rabbit. The total recovery of radioactivity was high in the rat, rabbit, dog and human (81.5% - 99.4%). In all these species, radioactivity was mainly excreted via fecal excretion. Renal excretion was apparently very minor (<4%).

Based on recombinant enzymes and human liver microsomes, the CYP3A4 is the major enzyme involved in midostaurin oxidative metabolism. Midostaurin, CGP52421 and CGP62221 were found to inhibit the following cytochromes *in-vitro*: CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2D6, CYP2E1 and CYP3A4. It also induces the following cytochromes: CYP1A2, CYP2C8, CYP2C9, CYP2B6 and CYP3A4. The results of the net effect model suggest that an impact of midostaurin and/or CGP52421 and CGP62221 is expected on the following CYP: CYP3A4, CYP2C8 and CYP2B6.

In vitro experiments demonstrated as well that midostaurin, CGP52421 and CPG62221 can potentially inhibit P-glycoprotein (P-gp) inhibitor with an IC_{50} value of 1.7 μM, breast cancer resistant protein (BCRP) (IC50=0.23 μM) and OATP1B1 (IC50=1.25 μM). Thus, its concomitant use with P-gp, BCRP or OATP1B1 substrates could lead to clinical drug-drug

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interactions. Midostaurin drug transport inhibition experiments indicated that midostaurin is not likely to be a substrate of P-gp, multi-drug resistance associated protein 2 (MRP2), and is not actively taken up into the liver.

Preclinical toxicology

Midostaurin has been extensively evaluated in various *in vitro* systems and *in vivo* models. Studies relevant to clinical dosing of midostaurin include repeat dose toxicology studies with durations of up to 52 weeks, genetic toxicology, reproductive and developmental toxicity, juvenile toxicity and safety pharmacology studies. Additional toxicology studies have been performed with the combination of midostaurin and daunorubicin/cytarabine. No carcinogenicity studies have been performed.

Overall, the effects of treatment with midostaurin observed in the toxicology studies have been essentially limited to those expected from an inhibitor of cell proliferation. The no observable effect level (NOEL) in the 12-month toxicity studies was 3 mg/kg in rat and 1 mg/kg in dog. In-vitro and in-vivo mutagenicity tests revealed no genotoxicity. There was no teratogenic effect noted from embryo-fetal development studies in rats and rabbits. Developmental toxicity was seen at 10 mg/kg or higher. NOEL for fertility and general reproductive toxicity was defined at 30 mg/kg.

Treatment with midostaurin at doses ≥3 mg/kg in dogs and ≥10 mg/kg in rats at durations up to 12 months was associated with effects on proliferating tissues, especially the intestine (mucosal alteration), testes (degenerated spermatogonia), and bone marrow (hypocellularity). The effect on the bone marrow was accompanied by hematological changes (decreased total white cells, lymphocytes and erythrocytic parameters).

Please, refer to the Investigators Brochure for additional information.

1.2.1.2 Clinical experience

Clinical pharmacokinetics

PK characteristics

Midostaurin is a BCL class II compound with good absorption and poor solubility. Two of its metabolites demonstrated pharmacological activities (CGP52421 and CGP62221). Following multiple doses, the PK of midostaurin and CGP62221 was time-dependent with an initial increase observed the first week followed by a decline of concentrations until reaching a steady-state on D28. CGP52421 concentrations do not appear to decline significantly as for midostaurin and CGP62221. Midostaurin is rapidly absorbed after oral administration, with peak plasma concentrations observed at 1-3 hours post dose. Midostaurin has an apparent volume of distribution of 95 L and is highly bound to protein, including albumin, alpha-glycoprotein and lipoprotein, with a free fraction of about 2%.

Midostaurin is predominantly metabolized by CYP3A4 into two major active circulating metabolites, CGP62221 (via *O*-demethylation) and CGP52421 (via hydroxylation). The major circulating components in plasma are CGP52421, CGP62221 and midostaurin, accounting for 38, 28, and 22% of area under the curve AUC0-168h, respectively. The compound related materials are mainly distributed to plasma, and minimally to red blood cells. The median

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terminal half-lives of midostaurin-, CGP62221 and CGP52421 in plasma are approximately 20.5, 32.3 and 471 hours, respectively. The midostaurin mean apparent plasma clearance (CL/F) was 2.4-3.1 L/h in healthy subjects. In AML and advanced systemic mastocytosis (SM) patients, popPK estimates for clearance of midostaurin at steady-state was 5.9 L/h and 4.4 L/h, respectively. The Human Mass Balance study results indicated that faecal excretion is the major route of excretion (78% of the dose), and mostly as metabolites (73% of the dose), while unchanged midostaurin accounts for 3% of the dose. Only 4% of the dose is recovered in urine.

Drug-drug interactions

Strong CYP3A4 inhibitors

Overall, strong CYP3A4 inhibitors increase exposure of midostaurin. The potential impact of these agents on the pharmacokinetics of midostaurin was assessed across the midostaurin clinical program since many of these agents are commonly used as standard of care antifungal prophylaxis in patients with AML.

In the Phase 3 study A2301, a high proportion of patients received a strong CYP3A4 inhibitor mostly during induction chemotherapy (62%), and using routine antifungal prophylaxis. Patients receiving concomitant strong CYP3A4 inhibitors had 1.44-fold higher exposure to midostaurin compared to patients not receiving strong CYP3A4 Inhibitors. However, increases in midostaurin exposure following co-administration of strong CYP3A4 inhibitors were off-set by reductions in exposure to the active metabolites, resulting in relatively small changes in the exposure to the sum of active moieties at steady state, consisting of 1.22 fold higher exposure in patients receiving strong CYP3A4 inhibitors. Analysis of the grade 3-4 AEs demonstrated that although differences were noted between patients treated with strong CYP3A4 inhibitors compared to those without, there was no definite pattern. For example, for patients treated with strong CYP3A4 inhibitors, a slightly higher incidence of sepsis and febrile neutropenia was observed; yet patients who did not receive strong CYP3A4 inhibitors had a slightly higher incidence of neutropenic infection Nevertheless, different approaches were taken to further assess the impact of strong CYP3A4 inhibitors on the PK of midostaurin. In a pooled analysis across advanced systemic mastocytosis (AdSM) and AML patients receiving midostaurin as single –agent therapy, there was maximum of 2.7-fold increase of midostaurin exposure (Cmin) at steady state upon co-administration with strong CYP3A4 inhibitors. When exposure to the sum of active moieties was compared, the geometric mean Cmin increased by 76% upon co -administration with CYP3A4 inhibitors. In Study A2104E2, AML patients who were concomitantly administered the strong CYP3A4 inhibitor itraconazole (n=7) with midostaurin 50 mg (twice daily) in the combination arm had a 2.09 -fold increase in midostaurin Cmin at steady state compared to when they received midostaurin 50 mg twice daily alone, CGP52421, CGP62221 and the sum of the active moieties were increased by 16%, 33% and 18% respectively. A similar finding was confirmed through popPK analysis for AML patients.

Of note, in the Phase III Study A2301, no dose-reduction of midostaurin/placebo was recommended with concomitant strong CYP3A4 inhibitors. Based on these data, no dose adjustment is required when midostaurin is co-administered with CYP3A4 inhibitors. However, caution should be advised when administering medicinal products that are strong

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inhibitors of CYP3A4 concomitantly with midostaurin, and alternative therapeutics that do not strongly inhibit CYP3A4 activity should be considered. In situations where satisfactory therapeutic alternatives do not exist -for example with the use of routine antifungal prophylaxis with azole antifungals during induction/consolidation chemotherapy for AML, patients should be closely monitored due to the potential for increase in exposure.

Strong CYP3A4 inducers: In the healthy volunteer study A2110, midostaurin concentrations decreased by approximately 10-fold (90% decrease) when co-administered with rifampicin, a CYP3A4 inducer. In the single-agent midostaurin studies D2201, A2213 and A2104E1, there were no difference in plasma Cmin between patients who received CYP3A4 inducers and those who did not for any of the active moieties or sum of active moieties. Of note, none of the patients were administered a strong CYP3A4 inducers at least 7 days prior to a PK sample. Therefore, concomitant administration of medicinal products that are strong inducers of CYP3A4 with midostaurin should be avoided, and alternative therapeutics that do not strongly induce CYP3A4 should be considered.

CYP3A4 induction related to midostaurin administration: The PK of a single dose of midazolam (sensitive CYP3A4 probe substrate) was not affected in a clinically meaningful manner following four dosing days of midostaurin administration in healthy subjects (Study A2112). The geomean Cmax and AUCinf of midazolam decreased by 9% and 5%, respectively. However, it cannot be excluded that midostaurin may be an inducer of CYP3A4, as the dose of midazolam was administered only after four dosing days of midostaurin and not at steady state. Based on a physiologically-based PK analysis, the simulated results indicate that the midazolam geometric mean ratio of AUC could be reduced by 25% at steady-state levels of midostaurin, as compared to the value observed in Study A2112 (Day 8).

Medicinal products with a narrow therapeutic range that are CYP3A4 substrates should be used with caution when administered concomitantly with midostaurin, and may need dose adjustment to maintain optimal exposure.

Clinical efficacy in AML

Irrespective of activating mutations of FLT3 which are present in 30%, FLT3 is constitutively overexpressed in 70% or more of AML patients. As detailed in section 1.2.1 the potential clinical activity of midostaurin in patients with FLT3-MN AML is supported by enzymatic and cell-based studies (Weisberg et al 2002). Accordingly, some of the early clinical trials with midostaurin in AML included not only patients with FLT3 mutated AML but also patients with FLT3-MN AML.

The [CPKC412A2104-E1] phase II trial evaluated midostaurin (single agent) in patients with AML or high-risk MDS with either FLT3-mutated or FLT3-MN disease. Among the 57 patients with FLT3-MN disease who were enrolled and were evaluable for efficacy, the best response was MR in nine (15.8%) patients, and blast reduction (with or without MR) was observed in 23 (40.4%) patients. The results overall indicated evidence of clinical activity and also supported the evaluation of midostaurin in combination with standard chemotherapy in patients with previously untreated AML. In the [CPKC412A2104-E2] phase II trial in the same patient population, midostaurin was either dose escalated or combined with itraconazole to pharmacologically enhance drug exposure.

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Of note, one patient in the [CPKC412A2104-E2] trial with FLT3-MN AML who was enrolled in the midostaurin+itraconazole arm obtained a minor response with blast reduction from Day 8 to Day 205, PR on Day 261, and obtained a CR on Day 324. The duration of response was 1320 days. Both midostaurin and itraconazole were administered until Day 1362, and the patient subsequently discontinued the study due to unsatisfactory therapeutic effect.

The [CPKC412A2106] phase IB trial evaluated midostaurin administered sequentially or concomitantly with daunorubicin and cytarabine in 69 patients with AML. Among patients treated at 50 mg twice daily, 11/13 (84.6%) patients with FLT3 mutation positive AML and 16/27 (59.3%) patients with FLT3-MN AML obtained a CR. The median time to CR was similar in FLT3-mutated and FLT3-MN patients Kaplan–Meier OS probabilities at 1 and 2 years, respectively, were 0.85 (95% CI: 0.65–1.0) and 0.62 (95% CI: 0.35–0.88) in patients with FLT3-mutated AML, and 0.78 (95% CI: 0.62–0.93) and 0.52 (96% CI: 0.33–0.71) in patients with FLT3–WT AML. Kaplan–Meier DFS probabilities at 1 year for FLT3-mutated and FLT3–WT patients were 0.50 (95% CI: 0.22–0.78) and 0.60 (95% CI: 0.39–0.81), respectively.

The Cancer and Leukemia Group B10603 (CALGB10603) ([CPKC412A2301], RATIFY) trial, hereafter referred to as Study [A2301], enrolled patients in North America and Europe < 60 years of age with newly diagnosed FLT3-mutated acute myeloid leukemia (AML), Midostaurin combined with standard induction and consolidation therapy following by single agent midostaurin continuation was compared to placebo plus chemotherapy. Study [A2301] is a randomized, double-blind, multi-center, placebo-controlled Phase III study conducted in 717 in patients with newly diagnosed FLT3 mutation positive (ITD or TKD) AML according to WHO criteria. The primary efficacy endpoint was OS non-censored at the time of HSCT, and the key secondary endpoint was EFS non-censored at the time of HSCT. The study met its primary endpoint; a significant improvement in OS was demonstrated with a HR of 0.77 (95% CI: 0.629, 0.953), corresponding to a 23% reduction in risk of death in favor of the midostaurin arm. The result was statistically significant with a p-value of 0.0078 at a one-sided alpha of 0.0239. Because the OS primary analysis was statistically significant, the key secondary endpoint EFS was tested in a confirmatory setting. The median EFS was 8.2 months for patients in the midostaurin arm compared to 3.0 months for patients in the placebo arm (HR=0.78; 95% CI 0.662, 0.930); this was statistically significant (p=0.0024) at a one-sided alpha level of 0.025. Subgroup analysis demonstrated that the benefit in OS and EFS was of similar magnitude for FLT3 ITD mutated patients with low allelic ratio (allelic ratio AR < 0.7) compared to high allelic ratio (> 0.7). In addition the OS & EFS benefit for FLT3 TKD mutated patients, who have disease prognosis closer to wild type patients also showed a similar benefit compared to FLT3 ITD with AR > 0.7, suggesting that the observed treatment benefit may not only be driven by the action on the FLT3 mutated AML clones but midostaurin may have activities on FLT3 WT AML.

Based on data from the [A2301] study, midostaurin has been approved by US food and drug administration (FDA) for the treatment of patients with newly diagnosed FLT3 mutated AML, in combination with standard cytarabine and daunorubicin induction and cytarabine consolidation.

The multi-kinase inhibitor sorafenib inhibits FLT3 and other kinases. In a phase III evaluation of sorafenib versus placebo added to standard chemotherapy in patients with newly diagnosed

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AML, patients with either FLT3-MN or FLT3-mutated AML were enrolled. Although full quantitative information about mutation subgroups has not been presented publicly, an analysis in which patients with FLT3-ITD mutations were excluded showed that increases in EFS and RFS remained statistically significant; however, an analysis of patients with FLT3-MN disease was not reported (Röllig et al 2015). These data suggest that multikinase inhibition may be useful in AML more broadly and not just among patients with FLT3-mutated AML.

Summary of safety in clinical studies

Midostaurin has been extensively studied in both oncology and non-oncology indications as well as in a large number of healthy volunteers over the past two decades. Taken together, midostaurin has been evaluated in an extensive clinical program including more than 1800 subjects, including one large, placebo-controlled study of midostaurin in combination with chemotherapy in FLT3-mutated AML, two Phase 2 studies in advanced SM, nine Phase 1-2 studies conducted in various indications, and 11 clinical pharmacology studies

The safety profile of midostaurin is well characterized, with predictable, primary gastrointestinal (nausea, vomiting) events and cytopenias that are generally manageable with the use of anti-emetic therapy and dose adjustment/temporary interruption.

The largest portion of the midostaurin clinical safety experience has been in two indications:

- As a single agent in patients with AdSM [formerly aggressive systemic mastocytosis (ASM) or mast cell leukemia (MCL) with or without an associated hematologic non-mast cell lineage disorder (AHNMD)]
- In combination with standard chemotherapy in patients with newly diagnosed FLT3-mutated AML

When administered to AML patients in combination with standard “7+3” chemotherapy in the pivotal phase III [A2301] trial, most of the AEs, AEs suspected to be related to study drug, serious adverse events (SAEs) and AEs leading to discontinuation occurred at similar frequencies in both midostaurin and placebo control groups. The most frequent adverse events reported in the combination setting included predominantly cytopenias (thrombocytopenia, anemia, neutropenia) and gastrointestinal events (nausea, vomiting) compared with patients receiving midostaurin monotherapy, as expected from the known toxicities of the backbone “7+3” chemotherapy regimen.

In Study [A2301], the safety profile (overall) for both the midostaurin and placebo groups was consistent. The median duration of exposure to midostaurin and placebo was 42.0 days (range 2-576 days) and 34.0 days (range 1-465 days), respectively. As expected, the most frequent grade 3/4 AEs in both groups were related to myelosuppression (neutropenia, anemia, thrombocytopenia, febrile neutropenia) and occurred in nearly all patients during the induction/consolidation phases. The addition of midostaurin did not prolong the time to platelet or neutrophil recovery in the induction and consolidation phases.

The most frequent non-hematologic grade 3/4 AEs in the midostaurin group were infections (device-related), diarrhea, and exfoliative dermatitis; and for the placebo arm, hypokalemia, diarrhea, and pneumonia. AEs were generally balanced between the two arms, with the exception of exfoliative dermatitis and transaminase elevations, which occurred more

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frequently in midostaurin-treated patients. Please refer to the Investigators Brochure for additional information.

2 Rationale

2.1 Study rationale and purpose

The available preclinical and clinical evidence suggesting a potential clinical activity of midostaurin in patients with FLT3-MN AML is summarized in Section 1.2.

A [A2301] subgroup analysis compared the benefit in OS and EFS in patients with different ratios of FLT3-mutated and FLT3-MN (allelic ratio). This subgroup analysis demonstrated that the benefit in OS and EFS was of similar magnitude for FLT3 ITD mutated patients with low allelic ratio (AR < 0.7 and AR < 0.5) compared to high allelic ratio (≥ 0.7). In addition the OS and EFS benefit for FLT3 TKD mutated patients, who have disease prognosis closer to wild type patients also showed a similar benefit compared to FLT3 ITD with AR ≥ 0.7, suggesting that the observed treatment benefit may not be driven by FLT3-inhibition alone but could be driven by other factors, such as the inhibition of the tyrosine-kinase activity of overexpressed FLT3-MN. Midostaurin is an ATP-competitive inhibitor of multiple kinases including FLT3, KIT, protein kinase C, VEGFR, PDGFR and FGFR. These are molecular targets implicated in the pathogenesis of AML and a variety of other diseases. The relative contribution to efficacy of the different mechanisms of action of midostaurin is currently not fully understood.

The efficacy of currently available treatments is dissatisfying in both, AML with FLT3-mutated as well as FLT3-MN AML. Despite multiple attempts, little improvement of the available therapy for AML was achieved during several decades of preclinical and clinical research. Approximately 35% to 40% of patients younger than 60 years of age may obtain long-term survival with current forms of treatment. However, there is a wide variation in outcome among genetically distinguishable subsets of the disease, with some subtypes having a notoriously poor outcome such as patients with genetic abnormalities that indicate adverse prognosis like monosomies, complex cytogenetic abnormalities, p53 mutations, RUNX1 mutations, ASXL1 mutations and others. Also, in older patients, the overall prognosis has remained highly unsatisfactory. E.g. a clinical study of intensive chemotherapy in 998 older patients with a median age of 71 years (range, 65–89 years) demonstrated a CR rate of 45%, a death rate in induction of 29% and a median survival of 5.4 months. The 1- and 2-year survival rates were 30% and 16%, respectively (Kantarjian et al 2006). Thus; there is an urgent unmet need for therapeutic improvements.

This study is designed to confirm the preliminary evidence from early clinical trials that midostaurin may provide clinical benefit not only to AML patients with the FLT3-mutation but also in FLT3-MN (SR<0.05) AML. If midostaurin is active in this subgroup, patients could derive clinical benefit in multiple ways. For example, a higher CR rate or a longer remission time that would widen the time window to search for an allogeneic HSCT donor or midostaurin may prolong the time in remission and overall survival in patients with and without HSCT. This study will also allow an increase in the preliminary understanding of the

prognostic potential of MRD assessments during treatment and follow-up and may contribute to the standardization of the required assays.

2.2 Rationale for the study design

The efficacy of midostaurin at a dose of 50 mg twice daily in combination with the 7+3 chemotherapy regimen for induction and with intermediate-dose cytarabine for consolidation will be evaluated in a 1:1 randomized double-blind study using placebo plus chemotherapy as a comparator. The justification for randomization is that it will provide the most robust assessment of safety and efficacy of midostaurin in this patient population when used in combination with frequently used standard chemotherapy regimens. Randomization will be stratified according to age (<60 vs. ≥60 years).

After completion of consolidation therapy or after allogeneic HSCT, patients will receive post-consolidation therapy with midostaurin/placebo alone for twelve 28-day cycles.

2.2.1 Midostaurin post-consolidation therapy in AML: disease considerations

The incorporation of post-consolidation therapy in the study is based on high incidence of relapse after the completion of induction and consolidation chemotherapy. Additionally, in the [A2301] study, there was a trend for a reduction in the rate of relapses during the maintenance phase, followed by a peak of early relapse observed among patients who discontinued or completed 12 cycles of midostaurin continuation therapy [A2301] (see Section 2.4, below). This observation is consistent with the mechanistic observation that midostaurin, effective at blast reduction in the relapsed refractory setting, may play a role, through its blast reduction of preventing the reappearance of clinical disease after the completion of consolidation treatment with intensive induction chemotherapy. The selection of a 12-month period of midostaurin/placebo post-consolidation was deemed appropriate based on the considerable risk of relapse during this period even among patients who remained in CR through the induction and consolidation treatment phases. The 12-month duration is also consistent with the safety experience with single-agent midostaurin.

In summary, patients who still have measurable residual disease experience rapid relapse once chemotherapy is completed. Thus, the continued administration of an oral, non-cytotoxic drug such as midostaurin after completion of chemotherapy might continue to inhibit the outgrowth or even eliminate residual leukemic blasts that are present at the end of a routine course of chemotherapy, potentially prolonging DFS. The observation of anti-leukemic activity when midostaurin was used as a single agent in patients with relapsed/refractory FLT3-mutated and FLT3-MN AML provided a supporting rationale.

2.2.2 Benefit of midostaurin post-consolidation therapy

Data from Study [A2301] in patients with FLT3-mutated AML suggest that single agent post-consolidation therapy for 12 cycles was an important factor in the overall success of the study. However, A2301 evaluated patients with AML with FLT3 mutations and the results of 2301 cannot be extrapolated to AML with FLT3-MN (SR<0.05). The results of MRD measurements during the post-consolidation phase of Study [E2301] may support the

[redacted]

hypothesis that post-consolidation treatment with midostaurin in AML with FLT3-MN (SR<0.05) is effective as well.

In A2301, the analysis of OS (non-censored for HSCT) from the start of the post-consolidation phase shows a survival benefit for patients treated with midostaurin compared to placebo (HR=0.802, 95% CI: 0.504, 1.276). This analysis included 205 patients (120 patients in the midostaurin arm, and 85 patients in the placebo arms). A comparison of baseline demographic and disease characteristics for these patients did not identify any imbalance between the midostaurin and placebo groups that would have influenced the OS assessment. Of note, the study was not sufficiently powered to test for statistical significance [AML Summary of Clinical Efficacy-Section 3.2.5].

The OS Kaplan-Meier curves show clear separation between midostaurin and placebo during the first 18 months after start of post-consolidation, before getting closer together. This is consistent with the data below for DFS, which suggest a protective effect during the 12 months of midostaurin post-consolidation therapy.

To determine the treatment benefit whilst on post-consolidation therapy, DFS was analyzed for the subset of patients who entered the post-consolidation phase in CR (194 patients; 115 in the midostaurin arm and 79 in the placebo arm). Patients were censored at the end of the 12-month post-consolidation phase. In this analysis, the HR was 0.714 (95% CI 0.430, 1.184), showing benefit for midostaurin post-consolidation therapy over placebo.

Taken together, the analyses of OS from the start of post-consolidation and DFS during post-consolidation are consistent, and suggest a treatment benefit of post-consolidation therapy. Of note, the observations above do not follow a secondary randomization and rely on few events, so conclusions must be drawn cautiously.

2.2.2.1 Safety and tolerability of midostaurin post-consolidation therapy

When the post-consolidation phase (single agent midostaurin or placebo) was assessed separately, a difference in the type and severity of adverse drug reactions (ADRs) was observed compared to the phases of combined treatment with chemotherapy i.e. induction and consolidation phase. The overall incidence of ADRs during the post-consolidation phase was generally lower. ADR during the post-consolidation phase with at least ≥5% difference between the midostaurin and placebo arms were: nausea (46.4% vs 17.9%), hyperglycaemia (20.2% vs 12.5%), vomiting (19% vs 5.4%) and lymphopenia (16.7% vs 8.9%). Most of the hematological abnormalities reported occurred during the induction and consolidation phase when the patients received midostaurin or placebo in combination with chemotherapy. The most frequent grade 3/4 hematological abnormalities reported in patients during the post-consolidation phase with midostaurin and placebo respectively were absolute neutrophil count decrease (20.8% vs 18.9%) and leukopenia (7.5% vs 5.9%). Overall, ADRs reported during the post-consolidation phase were of mild to moderate intensity and led to very few discontinuations (8.1% for midostaurin arm and 5.4% for placebo arm). The median duration of exposure in the post-consolidation phase was the same in both treatment groups (336 days) [Study A2301-Table 12-2], demonstrating the tolerability of midostaurin monotherapy following chemotherapy for previously untreated AML.

[redacted]

2.3 Rationale for dose and regimen selection

The recommended dose of midostaurin 50 mg twice daily combined sequentially with intensive standard chemotherapy for AML was established in the clinical trials described in Section 2.4.

The currently approved midostaurin dosing regimen in FLT3 positive AML patients during the induction/consolidation cycles is 50 mg twice daily at day 8 – 21, i.e., the midostaurin regimen that was evaluated in [A2301]. In E2301, midostaurin will be dosed at 50 mg twice daily from day 8 to 48h prior to the first day of the subsequent cycle of chemotherapy. The reasons for this change are detailed below.

An exposure-response analysis of the pivotal study [A2301] showed a positive relationship of dose intensity of midostaurin with efficacy endpoints including complete response rates in cycle 1, EFS and OS. Although a modest increase of the probability of grade 3/4 clinically notable adverse events was observed there was no relationship between an increased midostaurin exposure with the frequency of study drug discontinuation. Hence a higher exposure with midostaurin was associated with an increased efficacy as measured with clinically relevant endpoints but not at the expense of a clinically concerning increase of adverse events. No association of the plasma exposures of midostaurin, the pharmacologic active metabolites CGP62221 and CGP52421 with the duration of neutropenia was found. Most importantly an increased exposure with the active metabolite CGP62221 was associated with an increased survival. Further considering that CGP62221 is a stronger inhibitor of mutated as opposed to wild type FLT3 a higher exposure with midostaurin in AML without FLT3 mutation is expected to be clinically beneficial in this indication.

The proposed longer midostaurin dosing regimen is being used in study ADE02 (newly diagnosed AML with FLT3 mutation). The analysis of interim ADE02 results from the first 245 patients enrolled (median age: 53.6 years old, range 20 – 69) showed that an increased dose intensity of midostaurin can be safely achieved by increasing the number of dosing days per treatment cycle compared to the [A2301] trial. Overall the safety and tolerability of the treatment in ADE02T was very similar compared to [A2301]. Most importantly, the rate of death in patients up to 60 years old during induction and consolidation therapy was low in both trials (death during induction therapy was 3.4% and 3% in [A2301] and ADE02T respectively). Therefore, in order to further optimize the risk-benefit relationship of the treatment of AML without FLT3 mutation the same dosing regimen of midostaurin will be applied in E2301 as was used in ADE02T.

2.4 Rationale for choice of combination drugs

For patients with newly diagnosed AML regardless of cytogenetic and molecular markers (except acute promyelocytic leukemia), and who are judged to be fit, the most frequently used therapy has been the '7 + 3' remission induction regimen with cytarabine and daunorubicin, followed by high dose cytarabine for remission consolidation. Studies showed that modifications of the components of the chemotherapy regimen and their timing and dosing resulted in little incremental benefit for patients of all risk categories, including patients with and without FLT3-mutations. Therefore, minor modifications or variants of this standard treatment approach that better reflect the existing variants of current standard of care and that

[redacted]

are not expected to jeopardize the treatment homogeneity in the study are allowed such as replacement of daunorubicin with an equivalent dose of idarubicin or the omission of a second induction chemotherapy cycle in patients who achieved CR already with the first induction cycle. Significant improvements in OS and DFS for AML patients have been reported with HSCT compared to consolidation chemotherapy (Kayser et al 2010, DeZern et al 2011). Therefore, patients in this study are allowed to undergo allogeneic or autologous HSCT at any time after induction therapy and can thereafter resume treatment with the study drug during the post-consolidation phase of the study.

Midostaurin will be administered sequentially with chemotherapy during each induction and consolidation treatment cycle. Midostaurin will be dosed at 50 mg twice daily. Study [CPKC412A2106] showed that in combination with chemotherapy the 50 mg twice daily. midostaurin dose was better tolerated than was the 100 mg twice daily. dose, and the sequential regimen was better tolerated than was concomitant administration. The safety of intensive chemotherapy combined with midostaurin was confirmed in the phase III study A2301 as described in section 1.2.1.2. Moreover, in a leukemia cell culture model a related FLT3 tyrosine kinase inhibitor was shown to synergize with cytarabine when administered following this chemotherapy but antagonized anti-leukemic cytotoxicity when administered before cytarabine (Levis et al 2004).

Data suggest that the detection of measurable residual disease in AML patients predicts rapid relapse once chemotherapy is completed. The continued administration of an oral, non-cytotoxic drug such as midostaurin following chemotherapy might continue to inhibit growth or even kill residual blasts present at the end of a routine course of chemotherapy, potentially prolonging DFS (Ivey et al). Studies [CPKC412A2104], [CPKC412A2104E1] and [CPKC412A2104E2] showed that midostaurin has single agent activity in relapsed or refractory AML even in FLT3-MN cases.

In addition, the analysis of [A2301] study suggests a protective effect against relapse during the 12 months of midostaurin continuation therapy and a contribution to the sustained overall survival benefit. More details are summarized in section 2.2.2. To determine the treatment benefit whilst on maintenance therapy, DFS was analyzed for the subset of patients who entered the maintenance phase in CR (194 patients; 115 in the midostaurin arm and 79 in the placebo arm). Patients were censored at the end of the 12-month maintenance phase. In this analysis, the HR was 0.714 (95% CI 0.430, 1.184), showing benefit for midostaurin maintenance therapy over placebo. DFS after completion of the maintenance phase was analyzed using the subset of patients who remained in CR after completing the maintenance phase. The DFS events (all relapses) in the midostaurin arm occurred early (primarily within the first 6 months after stopping therapy), whereas in the placebo arm, the events were more distributed over time. The findings show that even after the completion of maintenance therapy, the risk of disease relapse is substantial and it is supportive of the hypothesis that continued suppression of leukemic cell clones that survived induction and consolidation therapy is important even after completion of cytotoxic chemotherapy administration. The observations above do not follow a secondary randomization and rely on few events, so conclusions must be drawn cautiously. However, taken together, the analyses of OS from the start of maintenance, DFS during maintenance, and DFS after maintenance, are consistent, and indicate a clear treatment benefit of maintenance therapy in AML with mutated FLT-3.

[redacted]

Similarly, suppression of the kinase activity in residual leukemic blasts in AML with non-mutated but overexpressed FLT3 during 12 month maintenance treatment with midostaurin may improve the DFS after completion of the induction and consolidation therapy. During the maintenance phase patients will be followed in 3-months intervals for MRD as well as 3 months after completion of the maintenance therapy. Since a strong relationship between the presence of MRD and subsequent relapse was demonstrated in several studies in AML MRD might be a surrogate marker of the likelihood of relapse during and after maintenance and quantitative changes of MRD may indicate effectiveness of maintenance therapy.

It has been demonstrated that allogeneic HSCT does not cure all patients with AML with or without mutated FLT3 as MRD may persist and relapses occur at substantial frequencies (Christopeit et al 2014). The interim analysis of a single arm study in AML FLT3-mutated demonstrated that midostaurin can be safely administered after allogeneic transplant. Patients received midostaurin during induction, consolidation and after transplant. EFS at 2 years after start of treatment was substantially improved from 25% to 34.6% compared to historical controls. The relative contribution of each phase of treatment (induction, consolidation if applicable, HSCT and post-consolidation) could not be determined (PKC412ADE02T Interim Study Report June 2016, on file). In this study patients can start post-consolidation treatment after allogeneic HSCT and recovery from the procedure. MRD measurements during and after post-consolidation treatment may help to determine whether midostaurin can reduce the residual leukemic disease load in MRD-positive patients after allogeneic transplant and convert the MRD status to negative and/or reduce the rate of molecular and hematologic relapses in MRD-negative transplanted patients. Such findings would support the hypothesis that midostaurin after allogeneic HSCT could ultimately result in a longer DFS after transplant.

The study design will assess the use of midostaurin in combination with standard remission induction chemotherapy, with intermediate dose cytarabine during consolidation, and as a single agent during 12 cycles of post-consolidation therapy. Patients who have AML without a FLT3 mutation (neither ITD nor TKD per clinical cut-off SR<0.05) will be randomly assigned in a 1:1 ratio to midostaurin or placebo arm.

Patients will be treated with one or two cycles of remission induction therapy with cytarabine and daunorubicin or idarubicin, followed by sequential midostaurin or placebo. Patients who demonstrate a CR or CRi with adequate blood count recovery (neutrophils $\geq 1.0 \times 10^9$/L and platelets $\geq 50 \times 10^9$/L) will receive in consolidation therapy three or four cycles of intermediate-dose cytarabine chemotherapy with sequential midostaurin/placebo as assigned. If a patient continues to be in remission, post-consolidation therapy for up to twelve 28-day cycles will be administered with midostaurin/placebo as assigned. Patients who receive HSCT can stay in the study and will start midostaurin/placebo post-consolidation therapy but will interrupt midostaurin during the procedure and recovery.

The safety of the chemotherapy regimen combined with midostaurin was demonstrated in the [A2301] study (Stone et al 2017). This study will comprise the first randomized placebo-controlled evaluation of safety and efficacy of midostaurin chemotherapy regimen in FLT-MN AML.

[redacted]

2.5 Rationale for choice of comparators drugs

Midostaurin will be added to the 7+3 standard combination regimen with daunorubicin (or idarubicin) and cytarabine for induction and intermediate dose cytarabine for consolidation. Because no standard treatment that combines chemotherapy with a kinase inhibitor exist, placebo added to the standard chemotherapy 7+3 will serve as comparator.

2.6 Rationale for MRD assessment

MRD in AML refers to the presence of leukemic cells at a sensitivity of detection below the threshold of conventional morphologic methods. Patients who experience a CR or CRi according to morphologic assessments (<5% blasts in the bone marrow), can potentially still harbor a large number of leukemic cells in the bone marrow (up to 10^{10}) which can confer a poor outcome. Detection of MRD (usually <0.1% bone marrow blasts) has shown prognostic relevance in several studies (Terwijn et al 2013; Ivey A et al, 2016), indicating that depth of leukemic clearance should be considered as a relevant prognostic endpoint in AML. The most frequently used methods for MRD assessment in AML include multi-parameter flow cytometry (MFC) to detect abnormal immunophenotypes and PCR assays to detect molecular alterations, including NPM1 mutations or genomic translocations (Hourigan CS et al, 2017). While molecular methods are generally more sensitive than MFC, they are currently only suitably to monitor MRD in the subset of patients harboring those genomic aberrations (40-60% of all patients). In contrast, MFC is suitable for MRD monitoring in ~90% of all AML patients, making it the most adequate technology currently available to test the prognostic impact of MRD status in this trial.

MRD will be assessed during and after treatment using MFC for secondary endpoint, to determine the treatment benefit of midostaurin. Flow cytometry assessments for leukemia-associated immunophenotypes (LAIP) will be used to monitor MRD at a sensitivity of 0.1% in bone marrow aspirates. [redacted]

Monitoring of MRD will be performed at baseline, during treatment (including induction, consolidation and post-consolidation), post treatment and at relapse to sensitively assess the depth and duration of response and to provide prognostic information on risk of relapse.

[redacted]

[redacted]

2.8 Risk and benefit

The data available for midostaurin in AML, taken from early stage single agent and combination trials, indicated a favorable benefit-risk profile. This was confirmed in the randomized phase III [A2301] trial, which met its primary endpoint of overall survival, whereby patients receiving midostaurin had a 23% reduced risk of death compared to the placebo arm. The secondary endpoints of CR rate, EFS and DFS were all superior in the midostaurin arm, with generally balanced toxicities and no impact of midostaurin treatment on time to hematologic recovery, infections or bleeding. The challenge in evaluating toxicities with this compound is separating out those associated with background chemotherapy seen in patients in trials, multiple concomitant medications or confounding factors due to complications of underlying disease. Pooled data from completed studies indicated gastrointestinal events, consisting of nausea, vomiting and diarrhea are the most prevalent adverse events, and the most common causes for drug discontinuation. These events tended to be grades 1 or 2, and resolved upon discontinuing study medication. The data thus demonstrate a positive benefit-risk balance for midostaurin in combination with standard

[redacted]

chemotherapy followed by 12 months of continuation therapy in patients with FLT3-mutated AML.

This study E2301 may demonstrate similar benefits as seen in [A2301], i.e., prolongation of the overall survival, event free survival and disease free survival compared to standard therapy. Since there is no other approved FLT3-inhibitor available for AML with FLT3WT current standard intensive induction and consolidation chemotherapy with or without HSCT is the relevant alternative treatment for comparison of the benefit and risks of the study treatment. Moreover it is regarded unlikely that the safety and tolerability of Midostaurin in AML with FLT3-MN (SR<0.05) AML will significantly differ from those observed in [A2301] in FLT3-mutated AML. The risks of the study treatment during induction and consolidation are expected to reflect mainly those associated with the chemotherapy backbone and to be similar compared to standard chemotherapy as was seen in the [A2301] trial. During the post-consolidation phase with midostaurin monotherapy the adverse events expected to be observed more frequently compared to placebo are mainly grade 1 or 2 gastrointestinal events, including nausea, vomiting and diarrhea and the most common causes for drug discontinuation. Overall it appears plausible that the risk profile associated with the study treatment in patients with AML with FLT3-MN (SR<0.05) will not be significantly different from the risks in AML-mutated.

No diagnostic procedures that are different from those in standard of care will be performed in E2301.

Appropriate eligibility criteria as well as specific dose modification and stopping rules, are included in this protocol. Recommended guidelines for prophylactic or supportive management of study-drug induced adverse events are provided in Section 6.3. The risk to subjects in this trial may be minimized by compliance with the eligibility criteria and study procedures, as well as, close clinical monitoring, dose reduction recommendations for toxicity, stopping rules and supportive therapy according to clinical standard of care. For the most current overview of known risks refer to the latest Investigator's Brochure. There may be unforeseen risks which could be serious. In the large Phase III study [A2301] in FLT3-mutated AML, midostaurin at a dose of 50 mg twice daily was overall well tolerated in combination

In summary, the collectively available clinical data support a positive benefit risk assessment addressing important unmet medical needs in in patients with AML-FLT3-MN (SR<0.05).

[redacted]

3 Objectives and endpoints

Objectives and related endpoints are described in Table 3-1 below.

Table 3-1 Objectives and related endpoints

Objective	Endpoint	Analysis
Primary		Refer to Section 10.4
To determine if the addition of midostaurin to standard induction and consolidation therapy, followed by single agent post-consolidation therapy improves EFS in patients with newly diagnosed FLT3-MN (SR<0.05) AML.	EFS is defined as the time from randomization to failure to obtain a CR or CRi with adequate blood count recovery in induction, relapse after CR or CRi with adequate blood count recovery or death due to any cause, whichever occurs first as assessed by the investigator.	
Key secondary		Refer to Section 10.5.1
To determine if the addition of midostaurin to standard induction and consolidation therapy, followed by single agent post-consolidation therapy improves OS in patients with newly diagnosed FLT3-MN (SR<0.05) AML.	Overall survival is defined as the time from randomization to date of death due to any cause.	
Other secondary		
To compare CR + CRi with adequate blood count recovery rate in the two treatment groups.	CR and CRi with adequate blood count recovery rate according to the International Working Group (IWG) for AML (Cheson et al 2003, ELN 2017 / Döhner et al 2017) as per investigator assessment.	Refer to Section 10.5.2.1
To compare the percentage of patients who reached MRD negative status in the two treatment groups.	Percentage of patients with MRD negative status.	Refer to Section 10.5.2.2

[redacted]

Objective	Endpoint	Analysis
To compare the percentage of patients with MRD negative status in the post-consolidation phase in the two treatment groups.	Percentage of patients with MRD negative status during post-consolidation phase	
To compare the time to MRD negative bone marrow between the two treatment arms in the two treatment groups.	Number of days from date of randomization to first documented MRD-	
To compare DFS, as well as the Cumulative Incidence of Relapse (CIR) and Cumulative Incidence of Death (CID) in the two treatment groups.	DFS, as measured from the date of first CR or CRi with adequate blood count recovery to relapse or death from any cause, whichever occurs first. CIR is defined for patients with CR or CRi with adequate blood count recovery: time from achieving CR or CRi with adequate blood count recovery until onset of relapse. Patients without relapse are censored at the last adequate response assessment. Patients who died without relapse are counted as a competing cause of failure. CID is defined for patients with CR or CRi with adequate blood count recovery: time from achieving CR or CRi with adequate blood count recovery until death. Patients who did not die are censored at the last contact date. Patients who relapsed are counted as a competing cause of failure.	Refer to Section 10.5.2.1
To compare the time to CR or CRi with adequate blood count recovery in the two treatment groups.	Number of days from date of randomization to first documented CR or CRi with adequate blood count recovery.	Refer to Section 10.5.2.1
To compare the time to neutrophil recovery in the two treatment groups.	Number of days from the first day of a chemotherapy cycle to first day neutrophils ≥0.5 x 10^9/L. Number of days from day 1 of commencing induction therapy to first day neutrophils ≥1.0 x 10^9/L.	Refer to Section 10.5.2.2

[redacted]

Objective	Endpoint	Analysis
To compare the time to platelet recovery in the two treatment groups.	Number of days from the first day of a chemotherapy cycle to first day platelets ≥50 x 10^9/L. Number of days from day 1 of commencing induction therapy to first day platelets ≥100 x 10^9/L.	
To assess the safety and tolerability of midostaurin in combination with chemotherapy and as monotherapy during post-consolidation.	Frequency/severity of AEs, and laboratory abnormalities.	Refer to Section 10.5.3
To further characterize the pharmacokinetics of midostaurin, CGP52421 and CGP62221.	Plasma concentrations and pharmacokinetic parameters for midostaurin, CGP52421 and CGP62221.	Refer to Section 10.5.4
To assess the impact of midostaurin on health related quality of life and AML symptom reduction.	Change from baseline score for each time point for the FACT-Leu and the EQ5D-5L (visual analogue scale (VAS)) by treatment arm.	Refer to Section 10.5.5
[redacted]	[redacted]	[redacted]
[redacted]		[redacted]
[redacted]	[redacted]	
[redacted]	[redacted]	
[redacted]	[redacted]	[redacted]
[redacted]		

Objective	Endpoint	Analysis
[redacted]	[redacted]	[redacted]

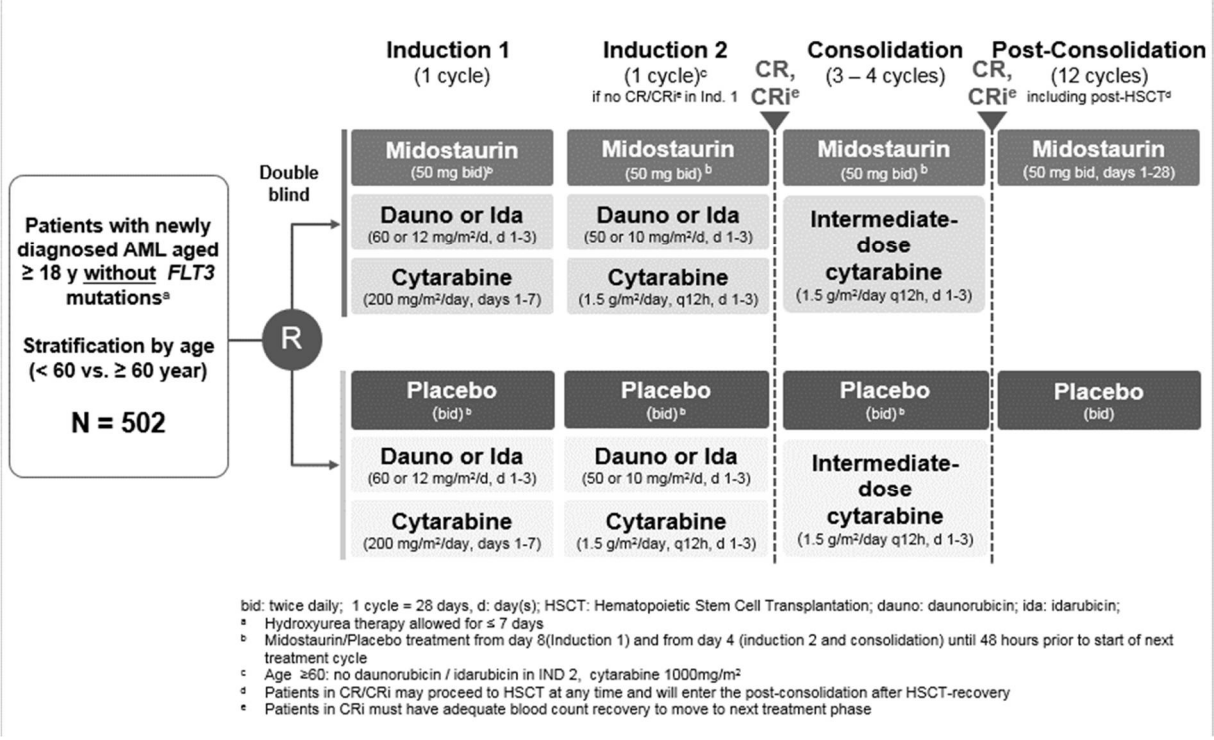
[redacted]

4 Study design

4.1 Description of study design

This is a randomized, double-blind, multi-center, placebo-controlled phase III study of midostaurin (PKC412) or placebo in combination with idarubicin/daunorubicin and cytarabine for induction therapy, intermediate-dose cytarabine for consolidation therapy, followed by post-consolidation therapy with midostaurin or placebo in adult patients with newly diagnosed FLT3-MN (SR<0.05) AML, i.e., FLT3 mutant to wild type signal ratio below the 0.05 clinical cut-off. The study is designed to evaluate the efficacy and safety of midostaurin combined with intensive chemotherapy in this indication. 502 adult patients with newly diagnosed AML demonstrating FLT3-MN (SR<0.05) as determined by a Novartis designated laboratory will be enrolled at approximately 150-180 sites worldwide.

Figure 4-1 Study Design



Eligible and consented patients are allowed to start with the 7+3 chemotherapy immediately after the unequivocal diagnosis of AML; the day of the first dose of chemotherapy is defined as Day 1.

Patients will be tested for the absence of FLT3-ITD and FLT-TKD mutations, using a validated clinical trial assay in a Novartis designated laboratory. Absence of mutation is defined as ITD and TKD activating mutations at codons D835 and I836 in the FLT3 gene, below the clinical cutoff of 0.05 mutant to wild type signal ratio.

[redacted]

Patients with confirmed FLT3-MN (SR<0.05) AML will be randomly assigned 1:1 to midostaurin or placebo by using a stratified randomization according to age (<60 vs. ≥60 years), Patients will be randomized on Day 8, i.e., the day of the first dose of midostaurin or placebo. Patients with a FLT3 mutation or with an unknown FLT3 mutation status by study Day 8 will be considered as molecular screening failures and cannot be randomized.

Provided that FLT3-MN (SR<0.05) status has been confirmed, patients meeting all other eligibility criteria will start the administration of midostaurin or placebo on Day 8.

4.2 Study phase (details of dosing in section 6)

The study contains three treatment phases:

- Induction treatment phase
- Consolidation treatment phase and,
- Post-consolidation treatment phase

A patient has to meet the following criteria to continue with the next treatment phase:

- A patient achieves CR at end of any treatment phase OR patient achieves CRi at end of any treatment phase **with adequate blood count recovery** defined as the following:
  - Complete Recovery in neutrophil count (≥1 x 10E9/L)
  - Minimal recovery in platelet count (≥50 x 10E9/L)

Of note, a patient not meeting the above criteria up to 93 days after start of induction phase is considered as "*induction failure*". For details please see Section 7.2.1.1.

The planned duration of an induction and consolidation cycle is 28 days. Upon adequate blood count recovery after day 28, midostaurin is stopped immediately (e.g., the evening dose of midostaurin or placebo on that day is not taken). Forty-eight hours thereafter is Day 1 (and start of chemotherapy) of the next cycle (Induction 2, Consolidation 1-4). At the end of the last consolidation cycle, i.e., prior to start of the post-consolidation cycle 1, midostaurin or placebo will not be interrupted. The duration of each post-consolidation cycle is 28 days.

4.2.1 Induction phase

All patients will receive at least one cycle of induction therapy with continuous infusion cytarabine and idarubicin/daunorubicin. Patients not achieving CR nor CRi with adequate blood count recovery after induction 1 will receive a second cycle with intermediate-dose cytarabine and daunorubicin/idarubicin (the latter only in patients under 60 years of age).

Daunorubicin may be replaced by an equivalent dose of idarubicin.

The dose of idarubicin would be one fifth of the planned daunorubicin dose. Midostaurin will start on day 8 of the first induction cycle and last until 48 hours before the start of the next chemotherapy cycle which is either a second induction or the first consolidation cycle.

Patients achieving CR or CRi with adequate blood count recovery with induction cycle 1 will go directly to consolidation therapy (4 cycles) without a second cycle of induction therapy. Patients who do not achieve CR nor CRi with adequate blood count recovery with one cycle

of induction will receive a second induction cycle with intermediate dose cytarabine and daunorubicin/idarubicin.

Patients achieving CR or CRi with adequate blood count recovery with 2 cycles of induction will go directly to consolidation therapy (3 cycles).

Patients not achieving CR nor CRi with adequate blood count recovery after induction 2 (i.e. up to 93 days after start of induction phase) will discontinue study treatment and will be followed for survival.

4.2.2 Consolidation phase

Patients achieving CR or CRi with adequate blood count recovery after induction with one or two cycles of induction therapy will proceed to consolidation therapy with either 3 or 4 cycles of intermediate-dose cytarabine respectively, or to HSCT with or without preceding consolidation cycles. Patients may undergo transplantation at the discretion of the Investigator (refer to 2017 ELN and 2016 National Comprehensive Cancer Network (NCCI) recommendations). In patients who are treated with allogeneic HSCT instead of consolidation therapy or after start of consolidation therapy the conditioning regimen and management after transplantation will be according to local institutional standards. Study treatment will be interrupted at least 48 hours before the initiation of the transplant conditioning regimen. Patients with transplantation and recovery from the procedure will not receive further cycles of consolidation treatment but receive post-consolidation treatment with study drug. They can start the post-consolidation therapy not earlier than 30 days after transplant but not later than 100 days after transplant.

Patients will receive midostaurin (two 25 mg capsules) or placebo (2 capsules) twice daily orally from day 4 until 48 hours prior to the start of the next consolidation cycle.

4.2.3 Post-consolidation phase

After adequate blood count recovery following the final cycle of consolidation therapy, patients will receive 12 cycles (28 days/cycle) of continuous therapy with midostaurin or placebo twice daily at 50 mg.

Patients who underwent HSCT after achieving CR or CRi with adequate blood count recovery will receive midostaurin or placebo 50 mg twice daily as post-consolidation therapy, continuously, for up to 12 cycles (28 days/cycle). Post HSCT post-consolidation therapy will begin >30 days but not later than 100 days following HSCT.

4.2.4 Follow-up phase

Patients who discontinue study treatment will continue to have response assessments performed every 12 weeks until documented relapse, and thereafter will be followed every 3 months for survival except those who are lost to follow-up. Data on anti-neoplastic therapies will be collected as well.

[redacted]

4.3 Timing of interim analyses and design adaptations

Two interim analyses are planned when approximately 114 and 214 of the 285 EFS events targeted for the primary analysis (approximately 40% and 75% information fraction, respectively) have been documented. The first interim analysis is planned for a futility assessment. The study can be stopped for efficacy at the second interim analysis. These analyses are expected to take place around 12 and 20 months, respectively, from the date of first patient randomized in the study assuming an increasing recruitment rate to reach 30 patients/month 6 months after start of the study. Please refer to Section 10.7 for detailed information.

4.4 Definition of end of study

The end of study will occur when approximately 278 deaths have been documented (it is estimated that these 278 deaths will be observed at approximately 64 months from the date of randomization of the first patient) or 5 years after the end of the study treatment for the last patient whichever occurs first. At this time, the final OS analysis will be performed. All patients will remain in treatment, post-treatment or survival follow-up until the data cut-off date and all available data up to this cut-off date will be analyzed.

4.5 Early study termination

The study may be terminated at any time for any reason by Novartis. This may include reasons related to the benefit/ risk assessment of participating in the study, practical reasons (including slow enrollment), or for regulatory or medical reasons. In taking this decision to terminate, Novartis will always consider the subject's welfare and safety. Should this be necessary, patients should be seen as soon as possible for the End of Treatment (EOT) visit, and assessments for EOT as described in Section 7 should be performed for discontinued or withdrawn patients. The investigator may be informed of additional procedures to be followed in order to ensure that adequate consideration is given to the protection of the patient's interests. The investigator will be responsible for informing institutional review boards (IRBs) and/or ethics committees (ECs) of the early termination of the trial.

In the event that the study is terminated prematurely, e.g., due to futility or overwhelming efficacy, patients still receiving study treatment and who, according to investigator assessment, continue to benefit from the treatment, will be offered to complete study treatment as per protocol.

5 Population

5.1 Patient population

The study population will be comprised of male and female patients ≥ 18 years of age with newly diagnosed FLT3-MN (SR<0.05) (no ITD in the juxtamembrane domain or TKD activating mutation as defined in inclusion criteria) AML who are deemed by the investigator to be suitable for treatment with intensive induction and consolidation chemotherapy.

[redacted]

All data for the Inclusion/Exclusion criteria must be verifiable in the patient's source documents.

5.2 Inclusion criteria

Patients eligible for inclusion in this study have to meet **all** of the following criteria:

1. Diagnosis of AML (≥20% blasts in the bone marrow based on WHO 2016 classification). Patients with APL with PML-RARA are not eligible.
2. Suitability for intensive induction chemotherapy in the judgment of the investigator
3. Documented absence of an ITD and TKD activating mutation at codons D835 and I836 in the FLT3 gene, as determined by analysis in a Novartis designated laboratory using a validated clinical trial assay with clinical cutoff of 0.05 mutant to wild type signal ratio.
4. Age ≥ 18 years
5. Laboratory values that indicate adequate organ function assessed locally at the screening visit:
   - AST ≤ 3 times ULN
   - Alanine aminotransferase (ALT) ≤ 3 times ULN
   - Serum total bilirubin ≤ 1.5 times ULN, unless in case of hyperbilirubinemia due to an isolated Gilbert syndrome
   - Estimated (by Cockcroft-Gault) creatinine clearance ≥ 30ml/min
6. Written informed consent must be obtained prior to any screening procedures.

5.3 Exclusion criteria

Patients eligible for this study must not meet **any** of the following criteria:

1. Central nervous system (CNS) leukemia
2. Therapy-related secondary AML
3. Isolated extramedullary leukemia
4. Prior therapy for leukemia or myelodysplasia with the following exceptions:
   a. Emergency leukapheresis
   b. Emergency treatment for hyperleukocytosis with hydroxyurea or low-dose cytarabine for ≤ 7 days
   c. Cranial RT for CNS leukostasis (one dose only)
   d. Hematopoietic Growth factor/cytokine support
   e. Other supportive therapy including antibiotics at the discretion of the investigator
5. AML after antecedent myelodysplasia (MDS) with prior cytotoxic treatment (e.g., azacytidine or decitabine)
6. Any investigational agent within 30 days or 5 half-lives, whichever is greater, prior to Day 1. An investigational agent is defined as an agent with no approved medical use in adults or in pediatric patients.
7. Prior treatment with a FLT3 inhibitor (e.g., midostaurin, quizartinib, sorafenib)
8. Strong CYP3A4/5 enzyme inducing drugs (see Appendix 1) unless they can be discontinued or replaced prior to enrollment.

[redacted]

9. Any other known disease or concurrent severe and/or uncontrolled medical condition (e.g., cardiovascular disease including congestive heart failure or active uncontrolled infection) that could compromise participation in the study.
10. Abnormal chest X-ray with corresponding clinical symptoms or findings that indicate an active infection, or other pulmonary conditions that are currently clinically significant.
11. Impairment of gastrointestinal (GI) function or GI disease that might alter significantly the absorption of midostaurin.
12. Known confirmed diagnosis of HIV infection or active viral hepatitis (testing is not mandatory to exclude these viral infections).
13. Cardiovascular abnormalities, including any of the following:
    - History of MI, angina pectoris, CABG within 6 months prior to starting study treatment
    - Clinically uncontrolled cardiac arrhythmias (e.g., ventricular tachycardia), complete left bundle branch block, high-grade AV block (e.g., bifascicular block, Mobitz type II and third degree AV block)
    - Uncontrolled congestive heart failure
    - Left ventricular ejection fraction of <50%,
    - Poorly controlled hypertension
14. Pregnant or nursing (lactating) women
15. Women of child-bearing potential, defined as all women physiologically capable of becoming pregnant, unless they are using highly effective methods of contraception during dosing and for at least 4 months after stopping medication. Highly effective contraception methods include:
    - Total abstinence (when this is in line with the preferred and usual lifestyle of the subject). Periodic abstinence (e.g., calendar, ovulation, symptothermal, post-ovulation methods) and withdrawal are not acceptable methods of contraception
    - Female sterilization (have had surgical bilateral oophorectomy with or without hysterectomy), total hysterectomy, or tubal ligation at least six weeks before taking study treatment. In case of oophorectomy alone, only when the reproductive status of the woman has been confirmed by follow up hormone level assessment
    - Male sterilization (at least 6 months prior to screening). The vasectomized male partner should be the sole partner for that subject
    - Use of oral, injected or implanted hormonal methods of contraception or placement of an intrauterine device (IUD) or intrauterine system (IUS), or other forms of hormonal contraception that have comparable efficacy (failure rate <1%), for example hormone vaginal ring or transdermal hormone contraception.
    - Midostaurin may reduce the effectiveness of hormonal contraceptives; therefore, females using systemically active hormonal contraceptives should add a barrier method of contraception.

    Women are considered post-menopausal and not of child bearing potential if they have had 12 months of natural (spontaneous) amenorrhea with an appropriate clinical profile (i.e., age appropriate, history of vasomotor symptoms) or have had surgical bilateral

[redacted]

oophorectomy (with or without hysterectomy), total hysterectomy, or tubal ligation at least six weeks ago. In the case of oophorectomy alone, only when the reproductive status of the woman has been confirmed by follow up hormone level assessment is she considered not of child bearing potential.

16. Sexually active males unless they use a condom during intercourse while taking the drug during treatment, and for at least 4 months after stopping treatment and should not father a child in this period. A condom is required to be used also by vasectomized men as well as during intercourse with a male partner in order to prevent delivery of the drug via semen.
17. Unwillingness or inability to comply with the protocol.
18. Known hypersensitivity to midostaurin, cytarabine or daunorubicin/idarubicin or to any of the excipients of midostaurin/placebo, cytarabine or daunorubicin /idarubicin.

6 Treatment

6.1 Study treatment

In this study, the term "Study drug" refers to midostaurin/placebo labeled as PKC412/placebo provided as 25 mg capsules which are packaged in blister packs and supplied by Novartis as double-blind supplies.

The term "Study treatment" will indicate treatment with daunorubicin/idarubicin, cytarabine, or midostaurin/placebo.

Induction chemotherapy will start on Day 1 and the randomization and treatment start with midostaurin/placebo will be done on Day 8 when (molecular) eligibility has been confirmed based on the absence of a FLT3 mutation as determined by a Novartis designated laboratory. If the patient does not have FLT3 test results qualifying for eligibility by Day 8 then the patient will be considered as a molecular screening failure and cannot be randomized.

6.1.1 Dosing regimen

On Day 1 of study treatment, the first dose of induction chemotherapy will be administered.

Daunorubicin/ idarubicin and cytarabine are approved drugs and will be sourced either according to local practice or centrally. Please refer to the Package Insert for complete guidelines for administration and for safety monitoring guidelines.

The dosage of daunorubicin/idarubicin and cytarabine will be adjusted based on body surface area (BSA) calculated before administration. To calculate BSA, the height at baseline and weight on the first day of the respective treatment cycle will be used.

Dose modification for obese patients:

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

[redacted]

6.1.1.1 Treatment regimen:

First Induction:

- **Cytarabine** 200 mg/m^2/day will be administered by continuous intravenous infusion (CIVI) on Days 1-7 (168 hour infusion).
- **Daunorubicin** 60 mg/m^2/day ***or*** **idarubicin** 12 mg/m^2/day will be administered intravenously by IV push (IVP) or short (30 minutes) infusion on Day 1-3.
- **Study drug (midostaurin** 50 mg [two 25 mg capsules] or **placebo** [2 capsules]) will be administered twice per day by mouth from Day 8 until 48 hrs prior to the start of next cycle (i.e. the morning of Day 27 if hematopoiesis recovers timely (cycle length of 28 days) or later if the cycle needs to be prolonged for blood count recovery). Patients should take their doses at approximately the same time each day, and approximately 12 hours should elapse between the morning and evening doses. On days that PK samples are obtained, the patient should take study drug during the clinic visit after the pre-dose PK sample and prior to post-dose PK samples, when instructed by the study staff. Each daily dose should be given with food and a glass of water (~240 mL). Patients should be instructed to swallow capsules whole and not chew capsules. If vomiting occurs, no re-dosing is allowed prior to the next scheduled dose. The soft capsules should be removed from the blister pack only shortly prior to administration. The capsules may have an unpleasant odor, which disappears a few seconds after the blister foil is opened.

A bone marrow aspiration will be performed in all patients between Day 21-28 to determine the need for a second induction cycle. If the bone marrow aspirate is insufficient to make a determination of remission, then the bone marrow assessment should be repeated after about one week.

A disease assessment will be performed at the end of induction 1 based on bone marrow and peripheral blood assessments. If the response is CR or CRi with adequate blood recovery the patient will proceed to the consolidation phase. If the response is CRi without adequate blood count recovery, the patient will continue to be treated with Midostaurin/Placebo and observed up to 2 weeks to get the platelet ≥50 x 10^9/L and neutrophil ≥1 x 10^9/L (i.e., adequate blood count recovery) to be able to move to consolidation. In such cases a response assessment will be performed at day 42 (28 days plus the time window of 2 weeks for adequate blood count recovery)

If patients after induction 1 therapy still show ≥5% blasts (i.e., no CR or CRi) in their D21-D28 bone marrow, then they require a second induction treatment. Dosing of midostaurin/placebo should be stopped immediately after knowledge of ≥5% blasts persistence. 48 hours thereafter the second induction treatment should start.

Of note, Physicians should consider earlier bone marrow exams in patients whose peripheral blood counts are not recovering or recovering in an unexpectedly slow manner.

Second Induction:

Patients who still have more than ≥5% blasts in their bone marrow **(no CR or CRi)** after induction cycle 1 require a second induction treatment. Dosing of midostaurin/placebo should be stopped immediately. 48 hours thereafter the second induction treatment should start.

[redacted]

- **Intermediate-dose cytarabine** (IDAC) 1500 mg/m^2 will be administered by intravenous infusion over 3 hours every 12 hours on Day 1 to 3. Serial neurologic evaluations will be performed before and following the infusion of intermediate-dose cytarabine. **For patients of age 60 years or older at the time of study entry a dose of 1000 mg/m^2 will be administered.**
- **Daunorubicin** 50 mg/m^2/day ***or*** **idarubicin** 10 mg/m^2/day will be administered intravenously by IV push (IVP) or short (30 minute) infusion on Day 1-3 **for patients <60 years** only**. Patients ≥ 60 years at the time of study entry will not be given daunorubicin *or* idarubicin**
- **Study drug (midostaurin** 50 mg [two 25 mg capsules] or **placebo** [2 capsules]) will be administered twice per day by mouth from Day 4 until 48 hrs prior to start of next cycle (i.e. the morning of Day 27 if hematopoiesis recovers timely (cycle length of 28 days) or later if the cycle needs to be prolonged for blood count recovery).).

A bone marrow aspiration will be performed in all patients between Day 21-28 to determine if the patient can move to consolidation phase. If the response is CR, the patient will proceed immediately after Day 28 to the consolidation phase. If the response is CRi without adequate blood count recovery, the patient will continue to be treated with Midostaurin/Placebo and observed 3 additional weeks for an adequate blood recovery to be able to move to consolidation. If no adequate blood count recovery will be achieved after these 3 additional weeks, the patient will be discontinued from treatment and followed for survival. Otherwise, the patient will move to consolidation. A response assessment will be performed at day 49 (28 days plus the time window of 3 weeks for adequate blood count recovery).**Patients who failed to achieve CR or CRi with adequate blood count recovery after a second induction will be discontinued from protocol** therapy and followed for survival and post-study-treatment therapies **(Section 7.1).**

Consolidation (3 or 4 cycles)

Patients achieving a CR or CRi with adequate blood count recovery after induction 1 will receive 4 cycles of consolidation therapy with midostaurin/placebo + chemotherapy.

Patients achieving a CR or CRi with adequate blood count recovery only after induction 2 will receive 3 cycles of consolidation therapy with midostaurin/placebo and chemotherapy.

A bone marrow examination must be performed at each cycle of the consolidation phase to evaluate for relapsed AML.

- **Intermediate-dose cytarabine** (IDAC) 1500 mg/m^2 will be administered by intravenous infusion over 3 hours every 12 hours on Days 1 to 3. Serial neurologic evaluations will be performed before and following the infusion of intermediate-dose cytarabine. **For patients of age 60 years or older at the time of study entry a dose of 1000 mg/m^2 will be administered .**
- **Study drug (midostaurin** 50 mg [two 25 mg capsules] or **placebo** [2 capsules]) will be administered twice per day by mouth on Days 4 until 48 hrs prior to start of next consolidation cycle (i.e. the morning of Day 27 if hematopoiesis recovers timely (cycle length of 28 days) or later if the cycle needs to be prolonged for blood count recovery). .

[redacted]

Post-consolidation therapy (12 cycles)

Patients who maintain CR or CRi with adequate blood recovery (by bone marrow aspirate/biopsy and peripheral blood evaluation) after completing consolidation therapy will receive 12 cycles (28 days/cycle) of midostaurin/placebo post-consolidation therapy.

Prior to initiation of midostaurin/placebo post-consolidation therapy, all significant acute toxicity from consolidation therapy must have resolved to <grade 2 or be stable except alopecia of any grade. Midostaurin/placebo post-consolidation therapy will begin after partial platelet recovery (platelets ≥ 50,000/μL) from remission consolidation.

- **Study drug (midostaurin** 50 mg [two 25 mg capsules] or **placebo** [2 capsules]) will be administered twice per day by mouth for 28 consecutive days. Patients should take their doses at approximately the same time each day, and approximately 12 hours should elapse between the morning and evening doses. On days that PK samples are obtained, the patient should take midostaurin/placebo during the clinic visit after the pre-dose PK samples and prior to post-dose PK samples, when instructed by the study staff.

Hematopoietic stem cell transplantation

Patients who underwent HSCT after achieving CR or CRi with adequate blood count recovery will receive midostaurin or placebo 50 mg twice daily as post-consolidation therapy, continuously, for up to 12 cycles (28 days/cycle). Post HSCT post-consolidation therapy will begin >30 days following HSCT and adequate blood count recovery but not later than 100 days following HSCT.

Table 6-1 Dose and treatment schedule

Study phase	Study treatments	Pharmaceutical form and route of administration	Dose	Frequency and/or Regimen
Induction 1	Cytarabine	CIVI	200 mg/m^2/day	Day 1-7 (168 hour infusion)
	Daunorubicin	Intravenously by IV push or short (30 minute) infusion	60 mg/m^2/day (irrespective of age)	Day 1-3
	Or Idarubicin	Intravenously by IV push or short (30 minute) infusion	12 mg/m^2/day (irrespective of age)	Day 1-3
	Midostaurin/ Placebo	Capsules for oral use	50 mg/dose	Twice daily on Day 8 until 48 hrs before start of next cycle (i.e. the last dose of Midostaurin/Placebo to be administered in the morning of Day 27 if the cycle

[redacted]

Study phase	Study treatments	Pharmaceutical form and route of administration	Dose	Frequency and/or Regimen
				length is 28 days or later if the cycle needs to be prolonged for blood count recovery).
Induction 2 for patients without CR/CRi with adequate recovery after Induction 1	Cytarabine	Intravenously over 3 hours	1500 mg/m^2/dose for pts <60 years 1000 mg/m^2/dose for pts ≥60 years	12-hour intervals on Day 1-3
	Daunorubicin ***Or*** Idarubicin **No daunorubicin or Idarubicin for pts ≥60 years**	Intravenously by IV push or short (30 minute) infusion Intravenously by IV push or short (30 minute) infusion	50 mg/m^2/day 10 mg/m^2/day	Day 1-3 Day 1-3
	Midostaurin/ Placebo	Capsules for oral use	50 mg/dose	Twice daily on Day 4 until 48 hrs before start of next cycle (i.e. the last dose of Midostaurin/Placebo to be administered in the morning of Day 27 if the cycle length is 28 days or later if the cycle needs to be prolonged for blood count recovery)
Consolidation phase	Cytarabine	Intravenously over 3 hours	1500 mg/m^2/dose for pts <60 years 1000 mg/m^2/dose for pts ≥60 years	12-hour intervals on Day 1-3

[redacted]

Study phase	Study treatments	Pharmaceutical form and route of administration	Dose	Frequency and/or Regimen
	Midostaurin/ Placebo	Capsules for oral use	50 mg/dose	Twice daily on Day 4 until 48 hrs before start of next chemotherapy cycle (i.e. the last dose of Midostaurin/Placebo to be administered in the morning of Day 27 if the cycle length is 28 days or later if the cycle needs to be prolonged for blood count recovery)
Post-consolidation phase	Midostaurin/ Placebo	Capsules for oral use	50 mg/dose	Twice daily for 28 consecutive days of each 28-day treatment cycle up to 12 cycles No interruption between post-consolidation cycles required

6.1.2 Ancillary treatments

Not applicable.

6.1.3 Rescue medication

Not applicable.

6.1.4 Guidelines for continuation of treatment

See Section 6.3

6.1.5 Treatment duration

The treatment consists of 3 treatment phases and the maximum planned duration of treatment is 17 cycles. Planned durations of each treatment phase are:

- **Induction phase**: 1 or 2 cycles (daunorubicin/idarubicin, cytarabine and midostaurin/placebo). The maximum length of the first induction cycle is 43 days (28 days plus potentially up to 14 additional days for adequate blood count recovery plus 1 day prior to the start of the next cycle. Patients not achieving CR or CRi after Induction 1 will

[redacted]

get a second cycle of Induction. The maximum length of the second induction cycle is 50 days (28 days plus potentially up to 21 additional days for adequate blood count recovery plus 1 day prior to the start of the next cycle).

- **Consolidation phase**: Patients who achieved CR or CRi with adequate blood count recovery after induction 1 therapy will receive 4 cycles of consolidation (intermediate-dose cytarabine and midostaurin/placebo). Patients achieving CR or CRi with adequate blood count recovery only after induction 2 therapy will receive 3 cycles of consolidation. One cycle length is planned to be 28 days whereas the maximum length of each consolidation cycle is 50 days (28 days plus potentially up to 21 additional days for adequate blood count recovery plus 1 day prior to the start of the next cycle).
- **Post-consolidation phase** : 12 cycles (midostaurin/placebo). Each cycle is 28 days.

Patients may be discontinued from treatment prior to completion of study therapy for reasons of unacceptable toxicity, induction failure, relapse from CR/CRi with adequate blood count recovery, withdrawal of consent, failure to abide by the protocol, or at the discretion of the investigator.

6.2 Dose escalation guidelines

Not applicable.

6.3 Dose modifications

6.3.1 Dose modification and dose delay

For patients who do not tolerate the protocol-specified dosing schedule, dose interruptions and/or reductions are either recommended or mandated in order to allow patients to continue the study treatment.

These dose modifications are summarized in Table 6-2. Deviations to mandatory dose interruptions and/or reductions are not allowed. Permanent treatment discontinuation is mandatory for specific events indicated as such in Table 6-2.

These dose changes must be recorded on the appropriate CRF.

Study drug (midostaurin/placebo)

Table 6-2 describes toxicities (i.e., adverse drug reactions), laboratory values, or other assessments that require interruption or dose modification of study drug. Whether an AE that is not considered to be caused by the study treatment requires modifications needs to be assessed by the investigator. The need for modification in case of non-drug related AEs depends on the type of these AEs.

During induction and consolidation therapies, modifications must be done in case of non-hematologic toxicities, i.e., ADRs (pulmonary, cardiac or other non-hematologic toxicities).

During post-consolidation therapy, modifications must be done in case of hematologic and non-hematologic toxicities (pulmonary, cardiac or other non-hematologic toxicities).

If interruptions occur, missed doses of study drug will not be made up.

[redacted]

Study drug interruptions of greater than 28 consecutive days will require discontinuation from study treatment, unless the patient undergoes HSCT as in that case the drug interruption can be longer than 28 consecutive days (please refer to section 6.1.1 for more detailed information).

Cytarabine

Doses will be modified only during the consolidation phase with intermediate-dose cytarabine and in case of neurotoxicity, hematology and non-hematology toxicity. Please refer to Table 6-2.

Idarubicin/ Daunorubicin

Doses will be modified during induction phase in case of hepatotoxicity, hematology and non-hematology toxicity. Please refer to Table 6-2.

[redacted]

Table 6-2 Criteria for dose reduction/interruption and re-initiation of midostaurin/placebo, daunorubicin/idarubicin and cytarabine treatment for adverse drug reactions

Dose modifications for midostaurin/placebo	
Hematologic toxicities	
During induction and consolidation cycles During post-consolidation cycles	No dose modifications are required for hematologic toxicity due to midostaurin/placebo during induction and consolidation therapy. In the presence of grade 4 neutropenia during post-consolidation therapy, midostaurin/placebo must be held until Absolute Neutrophil Count (ANC) ≥ 1.0 x 10^9/L. Once ANC ≥ 1.0 x 10^9/L, then resume midostaurin/placebo at the previous dose. If neutropenia persists for more than two weeks, then discontinue midostaurin/placebo protocol therapy.
Non-Hematologic toxicities:	
• **Pulmonary toxicities**	
During induction, consolidation and post-consolidation cycles	**For ≥ grade 3 pulmonary infiltrate**, midostaurin/placebo must be interrupted for the remainder of the cycle. Resume midostaurin/placebo at the same dose when infiltrate resolves to ≤ grade 1. **Missed doses of midostaurin/placebo will not be made up.** If there is no improvement after 28 days, the patient must be discontinued from study drug.
• **Cardiac Toxicity**	
During induction, consolidation and post-consolidation cycles	• **For QTcF interval > 470 ms and ≤ 500 ms**, check magnesium and potassium levels and correct any abnormalities. If possible, stop any medications that may prolong the QTcF interval. Decrease midostaurin/placebo to 50 mg once daily for the remainder of the cycle. Resume midostaurin/placebo at the initial dose in the next cycle provided that QTcF interval improves to ≤ 470 ms at the start of that cycle. Otherwise continue midostaurin/placebo 50 mg once daily. • **For QTcF interval > 500 ms and/or QTcF prolongation >60 ms from baseline,** check magnesium and potassium levels and correct any abnormalities. Hold or interrupt midostaurin/placebo for the remainder of the cycle, and, if possible, stop any medications that may prolong the QTcF interval. If QTcF improves to ≤ 470 ms just prior to the next cycle, resume midostaurin/placebo at the initial dose. If QTcF interval is not improved to ≤ 470 ms in time to start the next cycle, midostaurin/placebo may be held up to 28 days. If there is no improvement after 28 days, the patient must be discontinued from study drug.
• **Other Non-Hematologic toxicity**	

[redacted]

During induction and consolidation cycles	• **Grade 1/2:** No dose modifications for any grade 1 or 2 non-hematologic toxicity. • **Grade 3/4**: If a patient experiences **other grade 3/4 non-hematologic toxicity considered related to midostaurin/placebo,** midostaurin/placebo will be interrupted until toxicity resolves to ≤ grade 1. If the toxicity resolves prior to day 21, then restart at same dose to complete current cycle. Missed doses of midostaurin/placebo will not be made up. A study drug interruption in excess of 28 days will require discontinuation of study treatment.
During post-consolidation cycles	• Grade 1/2: **Persistent grade 1 or 2 toxicity during post-consolidation therapy** that patients deem to be unacceptable may prompt a study drug interruption for as long as 28 days. A study drug interruption in excess of 28 days will require discontinuation of study treatment. • Grade 3/4: For other **grade 3/4 non-hematologic toxicities that are considered to be related to midostaurin/placebo,** interrupt midostaurin/placebo. Resume midostaurin/placebo at the same dose when toxicity resolves to ≤ grade 2. If midostaurin/placebo is held for more than 28 days, then discontinue midostaurin/placebo post-consolidation therapy.
Dose modifications for intermediate-dose cytarabine (IDAC) induction 2 if applicable and consolidation therapy	
During Induction 2 if applicable and consolidation cycles	Dose reduction according to institutional guidelines except in case of neurotoxicity dose modifications as below: Contributions of concomitant medications to neurotoxicity should be assessed and other medications discontinued if possible. For neurotoxicity ≥ grade 2 due to intermediate-dose cytarabine, discontinue cytarabine for the remainder of the cycle. Intermediate-dose cytarabine may be considered at the next consolidation therapy cycle with a dose modification from 1500mg/m2 to 1000mg in patients <60 years of age and from 1000mg/m2 to 600mg/mg2 in patients ≥60 of age if the toxicity has resolved to ≤ grade 1. For a second occurrence of neurotoxicity ≥ grade 2, intermediate-dose cytarabine should be permanently discontinued.

[redacted]

Dose modifications for daunorubicin		
	Dose reduction according to institutional guidelines except in case of hepatotoxicity dose modifications as below:	
During induction cycles	**Total Bilirubin (mg/dL)**	**% daunorubicin dose to administer**
	≤ 1.2	100%
	> 1.2 – ≤ 3.0	75% (25% dose reduction)
	> 3.0	50% (50% dose reduction)
Dose modifications for idarubicin		
	Dose reduction according to Prescribing Information:	
	Idarubicin should not be administered if the serum bilirubin level exceeds 5 mg/100 ml. In patients with hepatic and/or renal impairment, a dose reduction of idarubicin should be considered.	
Patients with serum creatinine concentrations of greater than 3 mg/dL should receive 50% of the usual daily daunorubicin dose.		
All dose modifications should be based on the worst preceding toxicity. Common Toxicity Criteria for Adverse Events (CTCAE Version 5.0)		

[redacted]

6.3.2 Dose adjustments for QTcF prolongation

In case of QTcF >500 ms, (or QTcF prolongation >60 ms from baseline)

1. Assess the quality of the ECG recording and the QT value and repeat if needed
2. Interrupt study treatment
3. Determine the serum electrolyte levels (in particular hypokalemia, hypomagnesemia). If abnormal, correct abnormalities before resuming study drug treatment.
4. Review concomitant medication associated with QT prolongation, including drugs with a "Known", "Possible", or "Conditional risk of Torsades de Pointes", and drugs with the potential to increase the risk of study drug exposure related QT prolongation
5. Check study drug dosing schedule and treatment compliance
6. Consider collecting a time-matched PK sample, and record time and date of last study drug intake.
7. Note that measurements of QTcF ≥480ms shall be centrally verified on a copy of the original high quality recording that includes time and voltage scales

After confirming ECG reading at site, if QTcF > 500 ms

- Interrupt study treatment
- Repeat ECG and confirm ECG diagnosis by a cardiologist
- If QTcF confirmed > 500 ms:
  - Correct electrolytes, eliminate culprit concomitant treatments, and identify and address clinical conditions that could potentially prolong the QT
  - Consult with a cardiologist (or qualified specialist)
  - Increase cardiac monitoring as indicated, until the QTcF returns to ≤ 470 ms.
- After resolution to ≤ 470 ms, consider re-introducing treatment at reduced dose, and increase ECG monitoring for the next treatment(s):
  - If QTcF remains ≤ 500 ms after dose reduction, continue planned ECG monitoring during subsequent treatment
  - If QTcF recurs > 500 ms after dose reduction, discontinue patient from study drug.

6.3.3 Follow-up for toxicities

Please refer to IB for AEs of special interest.

6.3.3.1 Follow up on potential drug-induced liver injury (DILI) cases

Patients with transaminase increase combined with total bilirubin (TBIL) increase may be indicative of potential DILI, and should be considered as clinically important events.

The threshold for potential DILI may depend on the patient's baseline AST/ALT and TBIL value; patients meeting any of the following criteria will require further follow-up as outlined below:

- For patients with normal ALT and AST and TBIL value at baseline: AST or ALT > 3.0 x ULN combined with TBIL > 2.0 x ULN

[redacted]

- For patients with elevated AST or ALT or TBIL value at baseline: [AST or ALT > 2 x baseline AND > 3.0 x ULN] OR [AST or ALT > 8.0 x ULN], combined with [TBIL > 2 x baseline AND > 2.0 x ULN]

Medical review needs to ensure that liver test elevations are not caused by cholestasis, defined as ALP elevation > 2.0 x ULN with R value < 2 in patients without bone metastasis, or elevation of ALP liver fraction in patients with bone metastasis.

Note: (The R value is calculated by dividing the ALT by the ALP, using multiples of the ULN for both values. It denotes whether the relative pattern of ALT and/or ALP elevation is due to cholestatic ($R \leq 2$), hepatocellular ($R \geq 5$), or mixed ($R > 2$ and < 5) liver injury).

In the absence of cholestasis, these patients should be immediately discontinued from study drug treatment, and repeat liver function testing (LFT) as soon as possible, preferably within 48 hours from the awareness of the abnormal results. The evaluation should include laboratory tests, detailed history, physical assessment and the possibility of liver metastasis or new liver lesions, obstructions/compressions, etc.

1. Laboratory tests should include ALT, AST, albumin, creatine kinase, total bilirubin, direct and indirect bilirubin, gamma-glutamyl transferase (GGT), prothrombin time (PT)/international normalized ratio (INR) and alkaline phosphatase.
2. A detailed history, including relevant information, such as review of ethanol, concomitant medications, herbal remedies, supplement consumption, history of any pre-existing liver conditions or risk factors, should be collected.
3. Further testing for acute hepatitis A, B, C or E infection and liver imaging (e.g. biliary tract) may be warranted.
4. Obtain PK sample, as close as possible to last dose of study drug, if PK analysis is performed in the study.
5. Additional testing for other hepatotropic viral infection (cytomegalovirus (CMV), Epstein-Barr virus (EBV) or herpes simplex virus (HSV)), autoimmune hepatitis or liver biopsy may be considered as clinically indicated or after consultation with specialist/hepatologist.

All cases confirmed on repeat testing meeting the laboratory criteria defined above, with no other alternative cause for LFT abnormalities identified should be considered as “medically significant”, thus, met the definition of SAE (Section 8.2.1) and reported as SAE using the term “potential drug-induced liver injury”. All events should be followed up with the outcome clearly documented.

6.4 Concomitant medications

Administration of certain concomitant medications may lead to the requirement for subject to be discontinued. Such cases should be discussed with the sponsor on a case by case basis.

6.4.1 Permitted concomitant therapy

Supportive therapy including prophylactic antibiotic and antifungal treatments, transfusions, growth factors etc. will be administered at the discretion of the investigators according to standard of care.

[redacted]

The patient must be told to notify the investigational site about any new medications he/she takes after the start of the study drug. All medications (other than study drug) and significant non-drug therapies (including physical therapy, herbal/natural medications and blood transfusions) administered during the study must be listed on the Prior or Concomitant non-drug therapies/procedures CRF.

6.4.2 Permitted concomitant therapy requiring caution and/or action

Strong CYP3A4 inhibitors should be used with caution due to potential increase in midostaurin exposure. Alternative medicinal products that do not strongly inhibit CYP3A4 activity should be considered. In situations where satisfactory therapeutic alternatives do not exist, patients should be closely monitored for midostaurin-related toxicity.

Based on in vitro data, midostaurin and its active metabolites may have the potential to inhibit P-glycoprotein (P-gp), BCRP, and OATP1B1. Midostaurin, CGP62221 and CGP52421 can potentially induce the following CYPs: CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP3A4 and inhibit the following ones: CYP1A2, CYP2C8, CYP2C9, CYP2D6, CYP2E1, CYP3A4/5. In absence of clinical data medicinal products with a narrow therapeutic range that are substrates of these CYPs should be used with caution when administered concomitantly with midostaurin, and may need dose adjustment to maintain optimal exposure.

Therefore medicinal products with a narrow therapeutic range that are substrates of CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2D6, CYP2E1, CYP3A4/5, P-gp, BCRP or OATP1B1 should be used with caution when administered concomitantly with midostaurin and may need dose adjustment to maintain optimal exposure.

A list of strong CYP3A4 inhibitors, substrates with narrow therapeutic index for CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, CYP2E1, CYP3A and P-gp and substrates of BCRP and OATP1B1 is available in Appendix 1.

6.4.3 Prohibited concomitant therapy

Strong CYP3A4 inducers: Concomitant use of midostaurin/placebo with strong inducers of CYP3A4 should be avoided. Strong CYP3A4 inducers decrease exposure of midostaurin and its active metabolites (CGP52421 and CGP62221). In a study in healthy subjects, coadministration of the strong CYP3A4 inducer rifampicin (rifampin, 600 mg daily) to steady state with a single dose of midostaurin decreased midostaurin Cmax by 73% and -AUC_{inf} by 96% in average, respectively. CGP62221 exhibited a similar pattern. The mean AUC_{last} of CGP52421 decreased by 60%. In absence of clinical data, the impact of strong CYP3A4 inducers on midostaurin exposure at steady-state was investigated based on physiologically-based PK models. Exposure was predicted to be decreased by 60%.

A list of strong inducers of CYP3A4 is available in Appendix 1.

Other prohibited concomitant medications: If concomitant administration of drugs with a "known risk of torsades de pointes (TdP)" is required and cannot be avoided, then the study drug must be interrupted. If, based on the investigator assessment and clinical need, study treatment is resumed, close ECG monitoring is advised. Note that measurements of QTc≥480ms shall be centrally verified on a copy of a high quality recording that includes time and voltage scales.

[redacted]

If during the course of the study, concomitant administration of a drug with ¨Possible risk of TdP ¨ or ¨Conditional risk of TdP¨ is required, based on the investigator assessment and clinical need, study treatment may be continued with close ECG monitoring to ensure patient safety. A list of drugs associated with QT prolongation and/or TdP is available online at [www.qtdrugs.org].

As far as possible avoid co-administering drugs with a "Known", "Possible", or "Conditional" risk of TdP during the course of the study:

- If concomitant administration of drugs with a "Known risk of TdP" is required and cannot be avoided, study drug must be interrupted. If, based on the investigator assessment and clinical need, study treatment is resumed, close ECG monitoring is advised.
- If during the course of the study, concomitant administration of a drug with ¨Possible risk¨ or ¨Conditional risk of TdP¨ is required, based on the investigator assessment and clinical need, study treatment may be continued under close ECG monitoring to ensure patient safety.

A list of drugs associated with QT prolongation and/or TdP is available online at [www.qtdrugs.org]

6.4.4 Use of Bisphosphonates (or other concomitant agents)

Not Applicable.

6.5 Patient numbering, treatment assignment or randomization

6.5.1 Patient numbering

Each patient is identified in the study by a Subject Number (Subject No.), that is assigned when the patient is first enrolled for screening and is retained as the primary identifier for the patient throughout his/her entire participation in the trial. The Subject No. consists of the Center Number (Center No.) (as assigned by Novartis to the investigative site) with a sequential subject number suffixed to it, so that each subject is numbered uniquely across the entire database. Upon signing the informed consent form, the patient is assigned to the next sequential Subject No. available to the investigator through the Clinical Data Management System interface.

The investigator or designated staff will contact Interactive Response Technology (IRT) and provide the requested identifying information for the patient to register them into IRT. Once assigned, the Subject No. must not be reused for any other subject and the Subject No. for that individual must not be changed, even if the patient is re-screened. If the patient fails to be randomized or start treatment for any reason, the reason will be entered into the Disposition page.

IRT must be notified within 2 days that the patient was not randomized.

6.5.2 Treatment assignment or randomization

Patients will be assigned to one of the 2 treatment arms, midostaurin or placebo (Section 4.1 and Section 6.1) in a ratio of 1:1.

[redacted]

Randomization will be stratified by age (<60 versus ≥60 years).

The randomization numbers will be generated using the following procedure to ensure that treatment assignment is unbiased and is concealed from patients and investigator staff. A patient randomization list will be produced by the IRT provider using a validated system that automates the random assignment of patient numbers to randomization numbers. These randomization numbers are linked to the different treatment arms, which in turn are linked to medication numbers. A separate medication randomization list will be produced by or under the responsibility of Novartis Drug Supply Management using a validated system that automates the random assignment of medication numbers to medication packs containing each of the study treatments.

On study Day 8, all patients who fulfill all inclusion/exclusion criteria, including demonstrated FLT3-NM AML as confirmed by a Novartis-designated laboratory, and who have begun induction chemotherapy will be randomized via IRT to one of the treatment arms. The investigator or delegate will call or log on to the IRT and confirm that the patient fulfills all the inclusion/exclusion criteria. The IRT will assign a randomization number to the patient, which will be used to link the patient to a treatment arm and will specify a unique medication number for the first package of study drug to be dispensed to the patient. The randomization number will not be communicated to the caller.

6.5.3 Treatment blinding

Patients, investigators, site personnel, study team members, and anyone involved in the study conduct will remain blinded to the identity of the study drug from the time of randomization until database lock for the EFS analysis.

Randomization data will be kept strictly confidential until the time of unblinding and will not be accessible to anyone involved in the conduct of the study except for the independent biostatistician who will perform the interim analysis and the bioanalyst to avoid the unnecessary analysis of placebo samples. The identity of the study drug will be concealed by the use of study drug (midostaurin or placebo) that is identical in packaging, labeling, schedule of administration, appearance, and odor. Confidentiality of randomization data is required to limit the occurrence of potential bias arising from the influence that the knowledge of treatment may have on the recruitment and allocation of patients.

Unblinding of study drug assignment will only occur in the case of patient emergencies (Section 8.3), at the time of the interim analysis (see Section 10.7), for regulatory reporting purposes and at the conclusion of the study.

In rare cases when unblinding occurs because of emergency patient management, the actual treatment arm will not be communicated to any Novartis employee involved in the trial conduct in order to maintain their blinded status.

6.6 Study drug preparation and dispensation

The investigator or responsible site personnel must instruct the patient or caregiver to take the study drugs as per protocol. Study drug(s) will be dispensed to the patient by authorized site personnel only. All dosages prescribed to the patient and all dose changes during the study must be recorded on the appropriate CRF.

[redacted]

Study drug provided is midostaurin 25 mg and matching placebo control. Study drug will be supplied by Novartis as capsules and will be packaged in child-resistant blisters. Each blister pack contains eight capsules, and each medication kit contains eight blisters for a total of sixty-four capsules per kit.

Study treatment provided is daunorubicin/ idarubicin and cytarabine. They will be procured locally according to local practice and regulation, or supplied by Novartis (or its designee).

Table 6-3 Dispensing and preparation

Study treatments	Dispensing	Preparation
Midostaurin or Placebo	Capsules including instructions for administration are dispensed by study personnel on an outpatient basis. Patients will be provided with adequate supply of study drug for self-administration at home until at least their next scheduled study visit.	Not applicable
Daunorubicin or Idarubicin	Not applicable	Refer to product information
Cytarabine	Not applicable	Refer to product information

6.6.1 Study treatment packaging and labeling

Study drug: midostaurin/placebo:

Midostaurin/placebo will be provided as global clinical blinded supply and will be packed and labeled under the responsibility of Novartis Drug Supply Management.

Labels for midostaurin/placebo will comply with the legal requirements of each country and will include storage conditions and a unique medication number (corresponding to study treatment and strength). Responsible site personnel will identify the study drug package(s) to be dispensed by the medication number(s) assigned by IRT to the patient. Site personnel will add the subject number on the label. The label has 2-parts (base plus tear-off label); immediately before dispensing the package to the patient, site personnel will detach the outer part of the label from the package and affix it to the patient's source document.

Chemotherapy: daunorubicin/idarubicin and cytarabine:

Daunorubicin/idarubicin and cytarabine will be procured locally according to local practice and regulation, or supplied by Novartis (or its designee).

6.6.2 Drug supply and storage

Study treatments must be received by designated personnel at the study site, handled and stored safely and properly, and kept in a secured location to which only the investigator and designated site personnel have access. Upon receipt, the study treatment should be stored according to the instructions specified on the drug labels and in the Investigator's Brochure for midostaurin/placebo or the package insert for daunorubicin/idarubicin and cytarabine.

These instructions should be made clear to the patient for storage and self-administration of midostaurin/placebo at home.

[redacted]

Site staff will be responsible for managing re-supplies for the chemotherapy (daunorubicin/idarubicin and cytarabine)

Midostaurin/placebo will be managed by IRT system.

Table 6-4 Supply and storage of study treatments

Study treatments	Supply	Storage
Midostaurin/Placebo	Centrally supplied by Novartis	Refer to study drug label
Daunorubicin/Idarubicin Cytarabine	Procured locally according to local practice and regulation, or supplied by Novartis (or its designee).	Refer to local product information

6.6.3 Study drug compliance and accountability

6.6.3.1 Study drug compliance

Compliance will be assessed by the investigator and/or study personnel at each patient visit, and information provided by the patient and/or caregiver will be captured in the Drug Accountability Form. This information must be captured in the source document at each patient visit.

6.6.3.2 Study drug accountability

The investigator or designee must maintain an accurate record of the shipment and dispensing of study treatment in a drug accountability log. Drug accountability will be noted by the field monitor during site visits and at the completion of the study. Patients will be asked to return all unused study treatment and packaging on a regular basis, at the end of the study or at the time of study treatment discontinuation.

At study close-out, and, as appropriate during the course of the study, the investigator will return all used and unused study treatment, packaging, drug labels, and a copy of the completed drug accountability log to the Novartis (or Contract Research Organization (CRO)) monitor or to the Novartis address provided in the investigator folder at each site.

6.6.3.3 Handling of other study treatment

Not applicable.

6.6.4 Disposal and destruction

The study drug supply can be destroyed at the local Novartis facility, Drug Supply group or third party, as appropriate. Arrange for drug supply to be destroyed at the site only if permitted by local regulations and authorized by Novartis in a prior agreement.

Drug supplies will be destroyed only after the approval of monitor and after the completion of drug accountability reconciliation.

[redacted]

7 Visit schedule and assessments

7.1 Study flow and visit schedule

Table 7-1 lists all of the assessments and indicates with an "X", the visits when they are performed. All data obtained from these assessments must be supported in the patient's source documentation.

The table indicates which assessments produce data to be entered into the clinical database (D) or remain in source documents only (S) ("Category" column). No CRF will be used as a source document.

Allowed visit windows are specified as follows:

- Screening assessments listed below, must occur within 14 days prior to Day 1 as per Table 7-1.
- During each induction and consolidation cycle, PK and ECG assessments must be performed on the specified day. Local measurements of QTc≥480ms will be centrally verified on a copy of a high quality recording that includes time and voltage scales.
- All other assessments should not exceed a 5 day window to take into account scheduling over public holidays if not explicitly specified otherwise.

Every effort should be made to follow the schedule outlined in Table 7-1.

[redacted]

Table 7-1 Visit evaluation schedule

A: Screening until end of consolidation phase

	Category	Protocol Section	Screening Phase	Induction Phase Cycle 1 -2													End of Induction Phase / EOT	Prior to each cycle of Consolidation phase	Consolidation Phase/HSCT Cycle 1-4									End of Consolidation Phase / EOT
Visit name	D		SCR	INDUCTION C1-C2													IND DISPOSITION		CONSOLIDATION C1- C4									CON DISPOSITION
Day of cycle			-14 to -1	1	2	3	4	5	7	8	11	15	18	21	24	27	28			1	2	3	4	8	11	15	17	21	27	28	
Informed consent																														
Obtain study Informed Consent	D		x																											
IRT																														
Registration	D		x																											
Randomization: I1, D8: when FLT3 mutation status is confirmed	D									x I 1																				

[redacted]

	Category	Protocol Section	Screening Phase	Induction Phase Cycle 1 -2													End of Induction Phase / EOT	Prior to each cycle of Consolidation phase	Consolidation Phase/HSCT Cycle 1-4										End of Consolidation Phase / EOT
Visit name	D		SCR	INDUCTION C1-C2													IND DISPOSITION		CONSOLIDATION C1- C4										CON DISPOSITION
Day of cycle			-14 to -1	1	2	3	4	5	7	8	11	15	18	21	24	27	28			1	2	3	4	8	11	15	17	21	27	28	
Patient history																														
Diagnosis	D		x																											
Disease history	D		x																											
Demography	D		x																											
Inclusion/ exclusion criteria	D		x																											
Eligibility checklist I1,D8	D		x							x																				
FLT3 mutation status	D		x																											
Cytogenetics	D		x																											
Medical History	D		x																											

[redacted]

	Category	Protocol Section	Screening Phase	Induction Phase Cycle 1 -2													End of Induction Phase / EOT	Prior to each cycle of Consolidation phase	Consolidation Phase/HSCT Cycle 1-4									End of Consolidation Phase / EOT
Visit name	D		SCR	INDUCTION C1-C2													IND DISPOSITION		CONSOLIDATION C1- C4									CON DISPOSITION
Day of cycle			-14 to -1	1	2	3	4	5	7	8	11	15	18	21	24	27	28			1	2	3	4	8	11	15	17	21	27	28	
Prior antineoplastic medications	D		x																										
Prior/ concomitant medications and procedures including blood transfusions.	D		x	Continuous																									

[redacted]

	Category	Protocol Section	Screening Phase	Induction Phase Cycle 1 -2														End of Induction Phase / EOT	Prior to each cycle of Consolidation phase	Consolidation Phase/HSCT Cycle 1-4										End of Consolidation Phase / EOT
Visit name	D		S C R	INDUCTION C1-C2														IND DISPOSITION		CONSOLIDATION C1- C4										CON DISPOSITION
Day of cycle			-14 to -1	1	2	3	4	5	7	8	11	15	18	21	24	27	28			1	2	3	4	8	11	15	17	21	27	28	
Physical examination (7.2.2.1)																														
Performance status	D	7.2.2.4	x	x														x (at EOT)	x					x					x	x (at EOT)
Height	D	7.2.2.3	x																											
Weight	D	7.2.2.3	x	x														x (at EOT)		x										x (at EOT)
Vital signs	D	7.2.2.2	x	x						x		x		x			x	x (at EOT)	x	x				x		x		x	x	x (at EOT)
Physical examination	S	7.2.2.1	x	x			x			x	x	x	x	x	x		x	x (at EOT)	x	x				x		x		x	x	x (at EOT)
Lab assessments (see Table 7-5)																														
Hematology	D	7.2.2.5.1	x	x			x			x	x	x	x	x	x	x		x (at EOT)	x	x				x		x		x	x	x (at EOT)
Chemistry B: Tot Bilirubin only	D	7.2.2.5.2	x	x	x B	x B				x		x		x				x (at EOT)	x	x				x		x		x		x (at EOT)

[redacted]

	Category	Protocol Section	Screening Phase	Induction Phase Cycle 1 -2													End of Induction Phase / EOT	Prior to each cycle of Consolidation phase	Consolidation Phase/HSCT Cycle 1-4									End of Consolidation Phase / EOT
Visit name	D		S C R	INDUCTION C1-C2													IND DISPOSITION		CONSOLIDATION C1- C4									CON DISPOSITION
Day of cycle			-14 to -1	1	2	3	4	5	7	8	11	15	18	21	24	27	28			1	2	3	4	8	11	15	17	21	27	28	
Coagulation	D	7.2.2.5.3	x	x						x		x		x			x												
Other hepatic tests in case of suspected DILI	D	6.3.3.1		If clinically indicated																									
Urinalysis dipstick and sediment	D	7.2.2.5.4	x	If clinically indicated															If clinically indicated										
Serum (S) or Urine (U) Pregnancy test	S	7.2.2.5.5	x S	x U													x (U at EOT)	x U											x (U at EOT)
Imaging/other assessments																													
Chest X-ray	D	7.2.2.6	x	If clinically indicated																									
ECG (Table 7-7)	D	7.2.2.7.1	x							x I1	x I1			x I1				x (at EOT)					x			x			x (at EOT)
Cardiac	D	7.2.	x	If clinically indicated																									

[redacted]

	Category	Protocol Section	Screening Phase	Induction Phase Cycle 1 -2													End of Induction Phase / EOT	Prior to each cycle of Consolidation phase	Consolidation Phase/HSCT Cycle 1-4									End of Consolidation Phase / EOT
Visit name	D		SCR	INDUCTION C1-C2													IND DISPOSITION		CONSOLIDATION C1- C4									CON DISPOSITION
Day of cycle			-14 to -1	1	2	3	4	5	7	8	11	15	18	21	24	27	28			1	2	3	4	8	11	15	17	21	27	28	
MUGA/ ECHO		2.7.2																											
Efficacy/ disease assessments (see Section 7.2.1 for details)																													
Microscopic peripheral blood exam incl. full differential count	D		x												x (and up to 2 and 3 weeks after day 28 for induction1 and 2 respectively for patients in CRi without adequate blood count recovery)		x (at time of relapse)									x (and up to 3 weeks after day 28 for patients in CRi without adequate blood count recovery)	x (at time relapse)

[redacted]

	Category	Protocol Section	Screening Phase	Induction Phase Cycle 1 -2													End of Induction Phase / EOT	Prior to each cycle of Consolidation phase	Consolidation Phase/HSCT Cycle 1-4										End of Consolidation Phase / EOT
Visit name	D		SCR	INDUCTION C1-C2													IND DISPOSITION		CONSOLIDATION C1- C4										CON DISPOSITION
Day of cycle			-14 to -1	1	2	3	4	5	7	8	11	15	18	21	24	27	28			1	2	3	4	8	11	15	17	21	27	28	
Microscopic exam of bone marrow aspirate/ biopsy for morphology & bone marrow differential count	D		x											x				x (at time of relapse)										x		x (at time of relapse)
Extramedullary disease assessment (physical exam and CNS symptom assessment)	D		x											x														x		x
Investigator assessment of Disease Response	D													x (and up to 2 and 3 weeks after day 28 for induction1 and 2 respectively for patients in CRi				x	x									x (and up to 3 weeks after day 28 for patients in		x

[redacted]

	Category	Protocol Section	Screening Phase	Induction Phase Cycle 1 -2													End of Induction Phase / EOT	Prior to each cycle of Consolidation phase	Consolidation Phase/HSCT Cycle 1-4										End of Consolidation Phase / EOT
Visit name	D		S C R	INDUCTION C1-C2													IND DISPOSITION		CONSOLIDATION C1- C4										CON DISPOSITION
Day of cycle			-14 to -1	1	2	3	4	5	7	8	11	15	18	21	24	27	28			1	2	3	4	8	11	15	17	21	27	28	
														without adequate blood count recovery)													CRi without adequate blood count recovery)			
BMA for Flow cytometry MRD	D		x											x				x (at time of relapse)										x (C1 only)		x (at time of relapse)
Safety																														
Adverse events	D	8.1	x	Continuous																										
Pharmaco kinetics																														
PK sampling (Tables 7-8 & 7-9)	D	7.2.3								x I 1	x I 1	x I 1	x I 1	x I 1								x C 1 & 3				x C 1 & 3				

[redacted]

	Category	Protocol Section	Screening Phase	Induction Phase Cycle 1 -2													End of Induction Phase / EOT	Prior to each cycle of Consolidation phase	Consolidation Phase/HSCT Cycle 1-4									End of Consolidation Phase / EOT
Visit name	D		SCR	INDUCTION C1-C2													IND DISPOSITION		CONSOLIDATION C1- C4									CON DISPOSITION
Day of cycle			-14 to -1	1	2	3	4	5	7	8	11	15	18	21	24	27	28			1	2	3	4	8	11	15	17	21	27	28	
[redacted]																														

[redacted]

	Category	Protocol Section	Screening Phase	Induction Phase Cycle 1 -2													End of Induction Phase / EOT	Prior to each cycle of Consolidation phase	Consolidation Phase/HSCT Cycle 1-4									End of Consolidation Phase / EOT
Visit name	D		S C R	INDUCTION C1-C2													IND DISPOSITION		CONSOLIDATION C1- C4									CON DISPOSITION
Day of cycle			-14 to -1	1	2	3	4	5	7	8	11	15	18	21	24	27	28			1	2	3	4	8	11	15	17	21	27	28	
Biomarkers (7.2.4) (for detailed biomarker collection plan, please refer to Table 7-11)																													
BMA for DNA, and RNA analysis (MRD [redacted])	D		x											x			x (at time of relapse)										x (C1 only)		x (at time of relapse)
Whole blood for DNA and RNA analysis (MRD [redacted])	D		x											x			x (at EOT)										x (C1 and C3)		x (at EOT)

[redacted]

	Category	Protocol Section	Screening Phase	Induction Phase Cycle 1 -2													End of Induction Phase / EOT	Prior to each cycle of Consolidation phase	Consolidation Phase/HSCT Cycle 1-4									End of Consolidation Phase / EOT
Visit name	D		SCR	INDUCTION C1-C2													IND DISPOSITION		CONSOLIDATION C1- C4									CON DISPOSITION
Day of cycle			-14 to -1	1	2	3	4	5	7	8	11	15	18	21	24	27	28			1	2	3	4	8	11	15	17	21	27	28	
[redacted]																														
Patient reported outcomes																														
FACT-G with FACT-Leu EQ-5D-5L	D	7.2.6	x	x													x (at EOT)	x											x (at EOT)

[redacted]

	Category	Protocol Section	Screening Phase	Induction Phase Cycle 1 -2													End of Induction Phase / EOT	Prior to each cycle of Consolidation phase	Consolidation Phase/HSCT Cycle 1-4										End of Consolidation Phase / EOT
Visit name	D		SCR	INDUCTION C1-C2													IND DISPOSITION		CONSOLIDATION C1- C4										CON DISPOSITION
Day of cycle			-14 to -1	1	2	3	4	5	7	8	11	15	18	21	24	27	28			1	2	3	4	8	11	15	17	21	27	28	
Disposition	D		x														x													x
IRT																														
Dispensation Midostaurin/ Placebo	D						x (I 2 only)			x (I 1 only)												x								
Treatment Discontinuation	D																x (at EOT)													x (at EOT)
Study treatment administration																														
Midostaurin / Placebo	D						**Induction 1:** Continuous twice daily **Day 8** until 48 hrs prior to start of next cycle **Induction 2**: Continuous twice daily **Day 4** until 48 hrs prior to start of next cycle												Continuous twice daily **Day 4** until 48 hrs prior to start of next cycle										
Daunorubicin/ Idarubicin **I 2 <60 years only**	D	6.1		x	x	x																								
Cytarabine	D	6.1		x	x	x	x I 1	x I 1	x I 1										x	x		x								

[redacted]

B: End of consolidation phase until end of study

	Category	Protocol Section	Prior to 1st cycle of post-consolidation Phase	Post-consolidation Phase Cycle 1-12		End of post-consolidation Phase /EoT	30 day safety follow up	Post treatment follow up (until 5 years after the last day of study treatment of the last patient, failure, relapse or death whichever occurs first)	Survival follow up (until 5 years after last day of study treatment of the last patient)
Visit name	D			Post-Consolidation C1-C12					
Day of cycle				1	15				
Patient history									
Prior/concomitant medications and procedures including blood transfusions.	D		continuous						
Antineoplastic therapies after discontinuation of study treatment	D						x	Every 3 months	Every 3 months
Transplant after discontinuation of study treatment	D						x	Every 3 months	Every 3 months
Physical examination									
Performance status	D	7.2.2.4	x	x		x	x		
Weight	D	7.2.2.3	x	x		x			
Vital signs	D	7.2.2.2	x	x		x	x		

[redacted]

	Category	Protocol Section	Prior to 1st cycle of post-consolidation Phase	Post-consolidation Phase Cycle 1-12		End of post-consolidation Phase /EoT	30 day safety follow up	Post treatment follow up (until 5 years after the last day of study treatment of the last patient, failure, relapse or death whichever occurs first)	Survival follow up (until 5 years after last day of study treatment of the last patient)
Visit name	D			Post-Consolidation C1-C12					
Day of cycle				1	15				
Physical examination	S	7.2.2.1	x	x		x	x		
Lab assessments (see Table 7-5)									
Hematology	D	7.2.2.5.1	x	x	x (C1 and C2 post-consolidation only **if** no grade 2 or higher anemia, thrombocytopenia, or neutropenia)	x		Every 3 months until relapse	
Chemistry	D	7.2.2.5.2	x	x		x			
Other hepatic tests in case of suspected DILI	D	6.3.3.1	If clinically indicated						
Urinalysis dipstick and sediment	D	7.2.2.5.4		If clinically indicated					

[redacted]

	Category	Protocol Section	Prior to 1st cycle of post-consolidation Phase	Post-consolidation Phase Cycle 1-12		End of post-consolidation Phase /EoT	30 day safety follow up	Post treatment follow up (until 5 years after the last day of study treatment of the last patient, failure, relapse or death whichever occurs first)	Survival follow up (until 5 years after last day of study treatment of the last patient)
Visit name	D			Post-Consolidation C1-C12					
Day of cycle				1	15				
Urine Pregnancy test	S	7.2.2.5.5		x		x	x		
Imaging/other assessments									
Chest X-ray	D	7.2.2.6	If clinically indicated						
ECG (Table 7-6)	D	7.2.2.7.1	x	x (C 2 to C 12)		Completion of C12 or at EOT	x		
Cardiac MUGA/ECHO	D	7.2.2.7.2	If clinically indicated				x		
Safety									
Adverse events	D	8.1	Continuous						
Pharmacokinetics									
PK sampling (see Tables 7-8 & 7-9)	D	7.2.3	x	C4, C7, C10		Completion of C12			

[redacted]

	Category	Protocol Section	Prior to 1st cycle of post-consolidation Phase	Post-consolidation Phase Cycle 1-12		End of post-consolidation Phase /EoT	30 day safety follow up	Post treatment follow up (until 5 years after the last day of study treatment of the last patient, failure, relapse or death whichever occurs first)	Survival follow up (until 5 years after last day of study treatment of the last patient)
Visit name	D			Post-Consolidation C1-C12					
Day of cycle				1	15				
Biomarkers (7.2.4) (for detailed biomarker collection plan, please refer to Table 7-11)									
Bone marrow aspirate for DNA and RNA analysis (MRD [redacted])	D		x	C4, C7, C10		Completion of C12/ at relapse		3 months after end of post-consolidation therapy and at relapse	
Whole blood for DNA and RNA analysis (MRD [redacted])	D		x	C4, C7, C10		Completion of C12/ at EOT		Every 3 months during years 1 and 2 and then yearly	
[redacted]									

[redacted]

	Category	Protocol Section	Prior to 1st cycle of post-consolidation Phase	Post-consolidation Phase Cycle 1-12		End of post-consolidation Phase /EoT	30 day safety follow up	Post treatment follow up (until 5 years after the last day of study treatment of the last patient, failure, relapse or death whichever occurs first)	Survival follow up (until 5 years after last day of study treatment of the last patient)
Visit name	D			Post-Consolidation C1-C12					
Day of cycle				1	15				
Efficacy/ disease assessments (see Section 7.2.1 for details)									
Microscopic peripheral blood exam incl. full differential count	D		x	C1-C12		Completion of C12/ at relapse		Every 3 months until relapse and when clinically indicated	
Microscopic exam of Bone marrow aspirate/ biopsy for morphology & Bone marrow differential count	D		x	C4, C7, C10		Completion of C12/ at relapse		3 months after end of post-consolidation therapy and at relapse and when clinically indicated	
Extramedullary disease assessment (physical exam and	D		x	C1-C12		Completion of C12/ at relapse		3 months after end of	

[redacted]

	Category	Protocol Section	Prior to 1st cycle of post-consolidation Phase	Post-consolidation Phase Cycle 1-12		End of post-consolidation Phase /EoT	30 day safety follow up	Post treatment follow up (until 5 years after the last day of study treatment of the last patient, failure, relapse or death whichever occurs first)	Survival follow up (until 5 years after last day of study treatment of the last patient)
Visit name	D			Post-Consolidation C1-C12					
Day of cycle				1	15				
CNS symptom assessment)								post-consolidation therapy and at relapse and when clinically indicated	
Investigator assessment of Disease Response	D		x	C1-C12		Completion of C12/ at relapse		Every 3 months until relapse or death	
BMA for flow cytometry MRD	D		x	C4, C7, C10		Completion of C12/ at relapse		3 months after end of post-consolidation therapy and at relapse	

[redacted]

	Category	Protocol Section	Prior to 1st cycle of post-consolidation Phase	Post-consolidation Phase Cycle 1-12		End of post-consolidation Phase /EoT	30 day safety follow up	Post treatment follow up (until 5 years after the last day of study treatment of the last patient, failure, relapse or death whichever occurs first)	Survival follow up (until 5 years after last day of study treatment of the last patient)
Visit name	D			Post-Consolidation C1-C12					
Day of cycle				1	15				
Patient reported outcomes									
FACT-G with FACT-Leu EQ5D-5L	D	7.2.6		x		x	x	Every 6 months for the first 2 years and then yearly	
[redacted]									
Disposition	D					x		x	
IRT									
Dispensation Midostaurin/ Placebo	D			x					
Treatment Discontinuation	D					x			
Study treatment administration									

[redacted]

	Category	Protocol Section	Prior to 1st cycle of post-consolidation Phase	Post-consolidation Phase Cycle 1-12		End of post-consolidation Phase /EoT	30 day safety follow up	Post treatment follow up (until 5 years after the last day of study treatment of the last patient, failure, relapse or death whichever occurs first)	Survival follow up (until 5 years after last day of study treatment of the last patient)
Visit name	D			Post-Consolidation C1-C12					
Day of cycle				1	15				
Midostaurin/ Placebo	D			continuous twice daily (from D1 to D28)					
Follow-up									
Efficacy Follow-up	D							every 3 months	
Survival Follow-up	D								every 3 months

[redacted]

7.1.1 Molecular pre-screening

Not applicable

7.1.2 Screening

Written informed consent must be obtained prior to any screening procedures. Screening assessments to confirm eligibility into the study should be performed as per visit evaluation schedule between Day-14 and Day-1. Serum pregnancy test must be conducted within 72 hours prior to start of study treatment and must be confirmed negative before the first dose of study treatment. ECG should be obtained within 3 days prior to start of study treatment. Local measurements of QTc≥480ms will be centrally verified on a copy of a high quality recording that includes time and voltage scales.

As part of screening procedures, a bone marrow aspirate or a whole blood sample will be collected and shipped immediately to a Novartis designated laboratory for FLT3 mutation assessment. In case both sample types are collected/available, FLT3 screening will be preferentially performed only on the bone marrow sample; and the peripheral blood sample will be banked for future testing.

Assessments done within four days prior to Day 1 (start of chemotherapy) as per local practice or under a local protocol, prior to signing the study specific informed consent form and start of screening for the study, will not have to be repeated and results can be used for the study. At the discretion of the investigator, the final diagnosis of AML by bone marrow aspirate can be confirmed after the informed consent form has been signed for the study.

In some specific cases (and with Novartis' prior approval), the FLT3 status may have been determined prior to screening in a Novartis validated laboratory. In such cases, this previously obtained FLT3 result will be used for the study. Part of the remaining bone marrow sample should be provided to Novartis for further analyses defined in the protocol. [redacted]

At sites that also participate in the CPKC412A2220 (A2220) trial (aiming at patients with FLT3 mutated AML), patients who are screened in the A2220 trial and confirmed to be FLT3 mutation negative (SR<0.05) may be offered the opportunity to join the E2301 trial provided they also meet all other inclusion criteria. To allow this, patients screened as part of A2220 trial may be offered to sign E2301 informed consent at the same time as the one for A2220. Screening, baseline and the start of the first induction cycle will be performed under the A2220 protocol. All information obtained during that period will then be used for the E2301 trial, samples collected under the A2220 trial would be used for further E2301 assessments. Some additional assessments will have to be performed for the E2301 trial, such as MRD flow cytometry and ePROs. Patients are only considered for the E2301 trial if, under the A2220 protocol, they are treated with the "RATIFY regimen" (i.e., daunorubicin or idarubicin/ cytarabine dosing regimen as described for the E2301 trial) during the first induction cycle and are FLT3-MN.

Re-screening is not allowed, and a patient who does not meet all inclusion/exclusion criteria will be considered to be a screen failure and cannot be randomized.

[redacted]

7.1.2.1 Eligibility screening

Dosing with chemotherapy may begin while FLT3 mutation results are pending. FLT3 mutation results from the central laboratory must be received by Day 8 and will be used to determine if the subject is eligible for randomization and to receive midostaurin/placebo.

Following registering in the IRT for screening, patient eligibility will be checked once all screening procedures are completed (except FLT3 status). The eligibility check will be embedded in the IRT system.

Please refer and comply with detailed guidelines in the IRT manual.

7.1.2.2 Information to be collected on screening failures

A patient who signs an informed consent but fails to begin chemotherapy for any reason will be considered as a screen failure. The reason for not being started on chemotherapy will be entered on the Disposition CRF. The demographic information, informed consent, and Inclusion/Exclusion CRF must also be completed for Screen Failure patients. FLT3 data will be collected for all patients including screen failures. No other data will be entered into the clinical database for patients who are screen failures, unless the patient experienced a Serious Adverse Event during the Screening Phase (see Section 8 for SAE reporting details). If the patient fails to be randomized, the IRT must be notified within 2 days of the screen fail that the patient was not randomized.

Information to be collected on patients who failed to be randomized

Patients who are determined to have a positive or unknown FLT3 mutation status at Day 8 of the 1st cycle of induction will not be randomized and will then be discontinued from the study.

In addition to data collected at screening, the reason for not being randomized will be entered on the disposition CRF, and AEs/SAEs will also be collected, if applicable.

No other data will be collected for those patients.

7.1.2.3 Patient demographics and other baseline characteristics

The data to be collected on subject characteristics at screening includes:

- Diagnosis and extent of cancer (WHO and French American British (FAB) classification)
- Demography (Age, gender, race and ethnicity, or as allowed by local regulations)
- Cytogenetics
- Medical history
- Prior antineoplastic medications
- Prior and concomitant medications

Assessments to be performed at screening/baseline include:

- Physical examination (i.e., performance status Eastern Cooperative Oncology Group (ECOG), height, weight, vital signs)
- Extramedullary involvement

[redacted]

- Laboratory assessments (i.e., hematology, chemistry, coagulation, urinalysis, serum pregnancy test)
- Cardiovascular assessments (i.e., ECG; ECHO or MUGA)
- Chest x-ray
- Assessment of disease (in blood and bone marrow)
- Biomarker assessments in blood and bone marrow (for FLT3 mutation status [redacted])

7.1.3 Treatment period

Patients will be assigned on Cycle 1 Day 8 of induction therapy to midostaurin or placebo using a stratified randomization according to age.

- Study treatment will begin on Day 1 of Cycle 1 with chemotherapy: daunorubicin from Day 1 to Day 3 and cytarabine from Day 1 to Day 7. Study treatment will continue on Day 8 with midostaurin/placebo until 48 hours prior to start of next cycle.
- Chemotherapy and midostaurin/placebo will be administered as indicated in Table 7-1 and until the subject experiences any of the following: persistent disease, relapse as determined by investigator, unacceptable toxicity that precludes further treatment, pregnancy, start of non-protocol anti-cancer therapy, discontinuation at the discretion of the Investigator or patient, loss to follow-up, death, or study termination by the Sponsor.

Visit frequency

- Induction phase cycle 1: most assessments will be scheduled once or twice per week until hematology recovery. This cycle may be longer than 28 days (until hematology recovery occurs), and the assessments will be performed accordingly but cannot be longer than 43 days (28 days plus up to 14 additional days for blood count recovery) in total. If the patient has evidence of persistent leukemia on a bone marrow evaluation at the end of the first induction cycle, then a second cycle of induction therapy will be administered.
- Induction phase cycle 2: assessments will be the same as for Cycle 1, except for the PK [redacted] and study drug dispensation. The maximum length of induction cycle 2 is 50 days (28 days plus up to 21 additional days for blood count recovery). For details of assessments in induction Cycles 1 and 2, refer to Table 7-1.
- Patients who achieve a CR or CRi with adequate blood count recovery will continue with consolidation therapy for 3 to 4 cycles with a maximum length of 50 days (28 days plus up to 21 additional days for blood count recovery) each. Patients achieving CR/CRi with adequate blood count recovery after induction cycle 1 will have 4 cycles of consolidation therapy and patients achieving CR or CRi with adequate blood count recovery after the second cycle of Induction will have 3 cycles of consolidation therapy.
- Patients who remain in CR or CRi with adequate blood count recovery after consolidation therapy will begin post-consolidation therapy for up to 12 cycles of 28 days each. Post-consolidation therapy will begin immediately (i.e. up to 48 hours) after the last dose of midostaurin/placebo during the last cycle of consolidation therapy and no later than 50 days after the start of the last consolidation cycle. Patients who remain in remission after 12 cycles of post-consolidation therapy will continue in post-treatment follow-up.

[redacted]

- Patients in CR or CRi with adequate blood count recovery may proceed to HSCT and will enter the post-consolidation phase within 48 hours after the end of the consolidation phase.

Time windows for scheduling assessments

- Every effort should be made to follow the schedule of assessments as described in the protocol and especially during the induction and consolidation cycles for PK and ECG assessments.
- All other assessments have a ± 5 days window, unless otherwise indicated.
- Patients who discontinue study treatment must have an End of Treatment (EOT) visit performed ≤ 7 days after stopping study treatment.

7.1.4 Discontinuation of study treatment

Patients may voluntarily discontinue from the study treatment for any reason at any time. If a patient decides to discontinue from the study treatment, the investigator should make a reasonable effort (e.g., telephone, e-mail, letter) to understand the primary reason for this decision and record this information in the patient's chart and on the appropriate CRF pages. They may be considered withdrawn if they state an intention to withdraw, fail to return for visits, or become lost to follow-up for any other reason.

The investigator may discontinue study treatment for a given patient if he/she believes that continuation would be detrimental to the patient's well-being.

Study treatment must be discontinued under the following circumstances:

- Emergence of specific adverse events or laboratory abnormalities under some circumstances outlined in Section 6.3.
- Failure to achieve CR or CRi with adequate blood count recovery in induction or relapse from CR or CRi with adequate blood count recovery.
- Pregnancy (pregnancy will be followed for outcome)
- Any other protocol deviation that results in a significant risk to the patient's safety

The appropriate personnel from the site and Novartis will assess whether study treatment should be discontinued for any patient whose treatment code has been broken inadvertently for any reason.

Patients who discontinue study treatments should NOT be considered withdrawn from the study. They should return for the assessments indicated in Section 7.2.1. If they fail to return for these assessments for unknown reasons, every effort (e.g., telephone, email, and letter) should be made to contact them as specified in Section 7.1.9.

For patients who discontinue treatment for reasons other than documented failure to achieve CR or CRi with adequate blood count recovery in induction phase or relapse from CR or CRi with adequate blood recovery, death, loss to follow-up, or withdrawal of consent, will continue to be followed for efficacy assessment and survival.

The investigator (or designee) must also contact the IRT to register the patient's discontinuation from study treatment.

[redacted]

7.1.4.1 Replacement policy

Not applicable

7.1.5 Withdrawal of consent

Subjects may voluntarily withdraw consent to participate in the study for any reason at any time. Withdrawal of consent occurs only when a subject:

- Does not want to participate in the study anymore, and
- Does not allow further collection of personal data

In this situation, the investigator should make a reasonable effort (e.g. telephone, e-mail, letter) to understand the primary reason for the subject's decision to withdraw his/her consent and record this information.

Study treatment must be discontinued and no further assessments conducted, and the data that would have been collected at subsequent visits will be considered missing.

Further attempts to contact the subject are not allowed unless safety findings require communicating or follow-up.

All efforts should be made to complete the assessments prior to study withdrawal. A final evaluation at the time of the subject's study withdrawal should be made as detailed in the assessment table.

Novartis will continue to keep and use collected study information (including any data resulting from the analysis of a subject's samples until their time of withdrawal) according to applicable law.

For US and Japan: All biological samples not yet analyzed at the time of withdrawal may still be used for further testing/analysis in accordance with the terms of this protocol and of the informed consent form.

For EU and RoW: All biological samples not yet analyzed at the time of withdrawal will no longer be used, unless permitted by applicable law. They will be stored according to applicable legal requirements.

7.1.6 Follow up for safety evaluations

All patients must have safety evaluations for 30 days, after the last dose of study treatment (including cytarabine, daunorubicin/idarubicin or midostaurin/placebo).

Data collected should be added to the Adverse Events CRF and the Concomitant Medications CRF.

7.1.7 Follow up for efficacy evaluations

Patients who discontinue study treatment for reasons other than death, failure to achieve CR or CRi with adequate blood count recovery in the induction phase or relapse from CR or CRi with adequate blood count recovery will continue to have post-treatment assessments as outlined in Section 7.1 until relapse or death.

During this phase, the following data will be collected:

[redacted]

- Antineoplastic therapy/transplantation after discontinuation of treatment: every 3 months including start of new line, best response, and relapse date etc...

The following assessments will be performed:

- Physical examination for extramedullary disease assessment, blood samples for hematology [redacted]: every 3 months
- Bone marrow aspirate/biopsy for disease assessment [redacted]: after first 3 months after completion of post-consolidation therapy and at relapse.
- Questionnaires (EQ5D-5L, FACT with FACT-Leu) [redacted] every 6 months during the first two years and then yearly.

Patients will be followed in post-treatment follow up until relapse or end of study, whichever occurs first.

7.1.8 Survival follow up

Patients will enter the survival follow-up phase once they complete the safety follow up period (30 days after the last dose of midostaurin/placebo) in case of induction failure or have relapse during post-treatment follow-up. Patients will then be contacted by telephone every 3 months +/- 2 weeks or have a visit to follow up on their survival status. Any new antineoplastic medications that have been started since the last contact date will also be collected during these phone calls or visits.

7.1.9 Lost to follow-up

For patients whose status is unclear because they fail to appear for study visits without stating an intention to withdraw consent, the investigator should show "due diligence" by contacting the patient, family or family physician as agreed in the informed consent and by documenting in the source documents steps taken to contact the patient, e.g. dates of telephone calls, registered letters, etc. A patient should not be considered lost to follow-up until due diligence has been completed. Patients lost to follow up should be recorded as such on the appropriate Disposition CRF.

7.2 Assessment types

7.2.1 Efficacy assessments

Efficacy assessments will be performed according to the IWG criteria for AML (Cheson et al 2003, ELN 2017 / Döhner et al 2017). The investigator assessment will be used for the efficacy analyses. Response criteria in AML are described in Table 7-2:

Table 7-2 Response classification in AML at a given evaluation time (Cheson 2003, ELN 2017 / Döhner et al 2017)

Response category	Definition#
Complete remission (CR)	Bone marrow < 5% blasts no blasts with Auer rods

[redacted]

Response category	Definition[#]
	Peripheral blood neutrophils ≥ 1.0 x 10^9/L platelets ≥ 100 x 10^9/L no blasts No evidence of extramedullary disease (such as CNS or soft tissue involvement). Transfusion independent (see Section 7.2.1.6).
Complete remission with incomplete hematologic recovery (CRi)	Bone marrow < 5% blasts no blasts with Auer rods Peripheral blood[#] neutrophils < 1.0 x 10^9/L and/or platelets < 100 x 10^9/L no blasts No evidence of extramedullary disease (such as CNS or soft tissue involvement). **CRi with adequate blood count recovery is defined as the following:** Bone marrow < 5% blasts no blasts with Auer rods Peripheral blood[#] Neutrophils >= 1.0 x 10^9/L and 50 x 10^9/L <=platelets < 100 x 10^9/L no blasts No evidence of extramedullary disease (such as CNS or soft tissue involvement).
Partial remission (PR)	Bone marrow < 5% blasts AND presence of blasts with Auer rods OR ≥ 50% decrease from baseline in blasts in bone marrow AND blast count in bone marrow is 5% to 25% Peripheral blood neutrophils ≥ 1.0 x 10^9/L platelets ≥ 100 x 10^9/L no blasts No transfusion of neutrophils/platelets within 2 days preceding the assessment (see Section 7.2.1.6).
No Response	Failure to attain the criteria needed for any response categories or relapse

[redacted]

Response category	Definition#
Relapse from CR or CRi	Only in patients with a CR or CRi with adequate blood count recovery. Any of the following: Reappearance of blasts in peripheral blood OR ≥ 5% blasts in bone marrow OR (Re-)appearance of extramedullary disease
Unknown	In case the response assessment was not done or the assessment was incomplete.

If not defined otherwise, all of the criteria apply.

Response assessment will be performed by investigator between Day 21-28 of each cycle of the induction, the consolidation and the post-consolidation phases. Response assessment will be re-performed for patients achieving CRi without adequate blood count recovery up to 3 weeks after day 28 of each cycle. Moreover, patient can be assessed any time if clinically indicated.

Treatment failure includes patients who failed to achieve a CR or CRi with adequate blood count recovery up to the end of induction cycle 2. The following categories will only be assessed in case of induction treatment:

Category	Definition
Primary refractory disease	No CR nor CRi with adequate blood count recovery after 2 cycles of induction treatment; excluding patients with death in aplasia or death due to indeterminate cause
Death in aplasia	Deaths occurring ≥7 days following completion of induction therapy while cytopenic; with an aplastic or hypoplastic bone marrow obtained within 7 days of death, without evidence of persistent leukemia (< 5% blasts in bone marrow, no Auer rods in blasts and/or no extramedullary disease)
Death from indeterminate cause	Deaths occurring before completion of therapy, or ,<7 d following its completion; or deaths occurring ≥7 d following completion of induction therapy with no blasts in the blood, but no bone marrow examination available

Induction therapy

Between Day 21-28 of the first induction cycle, a bone marrow aspirate/biopsy will be performed to determine the presence of residual leukemia (≥ 5% blasts) according to the International Working Group (IWG) criteria for AML (Cheson et al 2003, ELN 2017 / Döhner et al 2017). If the Day 21-28 bone marrow aspirate/biopsy shows <5% blasts and the response assessment is CR or CRi without adequate blood count recovery, then it is not necessary to repeat bone marrow aspiration/biopsy while patient is under platelet and/or neutrophil recovery but a new blood count assessment will be performed to determine if the patient has achieved CR or CRi with adequate blood count recovery to be able to move to consolidation phase. If the response is CRi without adequate blood count recovery between Day 21-28, the cycle will be prolonged up to two weeks for blood count recovery (i.e. day 42). If the patient has reached CR or CRi with adequate blood count recovery, the patient will be

able to move to consolidation phase. Otherwise, the patient will receive a second cycle of induction therapy.

If a patient receives a second course of induction therapy, a bone marrow aspiration/biopsy between Day 21-28 of the second induction cycle will be performed to determine if the patient has achieved CR or CRi with adequate blood count recovery. If the response is CRi without adequate blood count recovery between Day 21-28, the cycle will be prolonged up to three weeks for blood count recovery. If no adequate blood count recovery is reached, the patient will be considered as treatment failure and will be discontinued from study treatment and followed for survival and post treatment therapies. Otherwise, the patient will move to consolidation phase. Of note, the bone marrow results obtained between Day 21-28 can be used retrospectively to determine response level by Day 49 (Day 28 plus 3 weeks).

Therefore, the maximum duration of the induction phase cannot exceed 93 days: 28 days (planned duration of cycle 1) + 14 days (i.e. 2 weeks for blood count recovery period)) + plus 1 day prior to the start of the next cycle + 28 days (planned duration of cycle 2) + 21 days (i.e. 2 weeks blood count recovery period)) + plus 1 day prior to the start of the next cycle.

7.2.1.1 Consolidation therapy:

A bone marrow and blood count examination will be performed to evaluate for continued remission (CR or CRi with adequate blood count recovery) between Day 21-28 of each cycle of consolidation. For each cycle, if the patient achieves CR or CRi with adequate blood count recovery up to 3 weeks after day 28 of each cycle, the patient will receive the next treatment cycle. Of note, the bone marrow results obtained between Day 21-28 can be used retrospectively to determine response level by day 49 (Day 28 plus 3 weeks).

7.2.1.2 Post-Consolidation therapy:

A bone marrow examination will be performed to evaluate for continued remission (CR or CRi with adequate blood count recovery) prior the start of the post-consolidation therapy, at the start of Cycle 4, Cycle 7 and Cycle 10, and at the end of Cycle 12 of post-consolidation therapy or at any time at suspected relapse.

7.2.1.3 Post-treatment follow-up:

A bone marrow examination will be performed to evaluate for continued remission (CR or CRi with adequate blood count recovery) 3 months after completion of post-consolidation therapy. A bone marrow examination will also be performed at any time of relapse.

7.2.1.4 Assessment of minimum residual disease (MRD) in bone marrow

For the purpose of the secondary MRD endpoint, MRD will be assessed by flow cytometry, since this technology can be used for the large majority of AML patients. Assessments will be performed at baseline during treatment phases indicated in Table 7-1 and 7-3. Patients with leukemic blasts below 0.1% will be considered as MRD-negative based on leukemia-associated immunophenotype (LAIP). [redacted]

[redacted]

[redacted]

Table 7-3 Flow cytometry MRD sample collection plan

Sample Type	Volume/visit	Visit	Time Point
Bone Marrow Samples			
Bone Marrow Aspirate for flow cytometry MRD analysis	6ml* *First BMA pull should be used for this assessment	Screening	Anytime
		Induction Phase 1 Day 21-28	Pre-dose
		Induction Phase 2 Day 21-28	Pre-dose
		Consolidation phase C1 Day 21-28	Pre-dose
		Prior to 1st cycle of Post-consolidation Phase	Pre-dose
		Post-consolidation Phase C4 Day 1	Pre-dose
		Post-consolidation Phase C7 Day 1	Pre-dose
		Post-consolidation Phase C10 Day 1	Pre-dose
		Completion of Post-consolidation Phase C12 Day 28	Pre-dose
		At relapse (at any phase of the study)	Anytime
		Post treatment Follow Up: 3 months after end of post-consolidation therapy, and at relapse	Anytime

7.2.1.5 Extramedullary disease assessment

Extramedullary involvement is to be assessed at baseline and at each visit for response assessment. Presence or absence and physical location of extramedullary disease is to be captured in the CRF.

Extramedullary disease is to be assessed via physical examination, cerebrospinal fluid (CSF) assessment in case of symptoms suggestive of meningeosis leukemica, and if clinically appropriate relevant imaging techniques. In case of extramedullary disease at baseline or (re-) appearance during the study, the lesions should be considered for confirmation by imaging or biopsy if technically and/or clinically feasible.

7.2.1.6 Evaluation of transfusion dependency

Information on transfusion dependency will be assessed at baseline as well as during the course of the trial for all patients. Transfusion of blood products will be recorded in a separate module of the CRF. The type of transfusion, start and end date as well as the volume of blood product will be captured at each visit with hematologic assessment.

[redacted]

A period of at least 2 days without any transfusion has been taken as a convention to define the status of transfusion independence to assess a CR or CRi with adequate blood count recovery. A patient who has received a blood transfusion within 2 days preceding a response assessment (i.e. CR) will be considered transfusion dependent at the time of this response assessment.

7.2.2 Safety and tolerability assessments

Safety will be monitored by assessing physical examination, performance status, laboratory examinations, ECGs, Echo/MUGA as well as collecting of the adverse events at every visit. Local measurements of QTc≥480ms shall be centrally verified on a copy of the original high quality recording that includes time and voltage scales. For details on AEs collection and reporting, refer to Section 8.

More frequent examinations may be performed at the investigator's discretion, if clinically indicated.

7.2.2.1 Physical examination

Significant findings that were present prior to the signing of informed consent must be included in the Medical History page on the patient's CRF. Significant new findings that begin or worsen after informed consent must be recorded on the Adverse Event page of the patient's CRF.

Physical examination will be performed as described in Table 7-1 and will include the examination of general appearance, skin, neck (including Thyroid), eyes, ears, nose, throat, lungs, heart, abdomen, anus, back, lymph nodes, extremities, vascular and neurological assessments.

Information about the physical examination must be present in source documents at the study site. Significant findings that were present prior to the signing of informed consent must be included in the Medical History CRF. Significant new findings that begin or worsen after informed consent must be recorded on the Adverse Events CRF.

7.2.2.2 Vital signs

Vital signs include blood pressure (supine position preferred), pulse measurement, and body temperature and will be measured at screening and at subsequent time points as specified in Table 7-1. Data on vital signs will be tabulated and listed, notable values will be flagged.

7.2.2.3 Height and weight

Height in centimeters (cm) will be measured at screening.

Body weight (to the nearest 0.1 kilogram [kg] in indoor clothing, but without shoes) will be measured at screening and at subsequent time points as specified in Table 7-1.

7.2.2.4 Performance status

ECOG Performance status scale will be performed as described in the Table 7-1. More frequent examinations may be performed at the investigator's discretion, if medically indicated. ECOG performance status scale will be used as described in the Table 7-4.

[redacted]

Table 7-4 ECOG performance status scale

Score	Performance Status
0	Fully active, able to carry on all pre disease performance without restriction
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature ,light housework, office 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
3	Capable of only limited self-care, confined to bed or chair more than 50% of waking hours
4	Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair
5	Dead

[redacted]

7.2.2.5 Laboratory evaluations

Table 7-5 Clinical laboratory parameters collection plan

Test Category	Test Name
Hematology (Local)	Hgb, white blood cell (WBC) with differential (including basophils, eosinophils, lymphocytes, monocytes, neutrophils, bands, metamyelocytes, myelocytes, promyelocytes blasts), atypical cells (e.g. LUC, erythroblasts), platelets
Biochemistry (Local)	Albumin, alkaline phosphatase, ALT, AST, LDH, calcium, magnesium, phosphorous, sodium, potassium, creatinine, total bilirubin, direct bilirubin, total cholesterol, BUN/urea, uric acid, amylase, lipase, glucose
Coagulation (Local)	International normalized ratio (INR), activated partial thromboplastin time (aPTT)
Urinalysis (Local)	Dipstick examination includes specific gravity, pH, glucose, protein, blood, bilirubin, ketones and WBC as clinically indicated
Other hepatic tests in case of suspected DILI (Local)	GGT, alkaline phosphatase, other tests for diagnosis of acute hepatitis A, B, C or E infection or testing for hepatotropic viral infection or autoimmune hepatitis
Pregnancy Test (Local)	Pregnancy test in serum (at screening) and urine

Clinical laboratory analyses are to be performed by the local laboratory (at the investigational' site) according to the schedule of assessments and collection plan outlined respectively in Table 7-1 and Table 7-3. Novartis must be provided with a copy of the local laboratory's certification and a tabulation of the normal ranges and units of each parameters collected in the CRF. Any changes regarding normal ranges and units for laboratory values assessed during the study must be reported via an updated tabulation indicating the date of revalidation. Additionally, if at any time a patient has laboratory parameters obtained from a different laboratory, Novartis must be provided with a copy of the certification and a tabulation of the normal ranges and units for this laboratory as well. The investigator is responsible for reviewing all laboratory reports for patients in the study and evaluating any abnormalities for clinical significance.

At any time during the study, abnormal laboratory parameters which are clinically significant and require an action to be taken with study treatment (e.g.; require dose modification and/or interruption of study treatment, lead to clinical symptoms or signs, or require therapeutic intervention), whether specifically requested in the protocol or not will be recorded on the Adverse Events CRF. Laboratory data will be summarized using the CTCAE version 5.0. Additional laboratory evaluations are left to the discretion of the investigator.

7.2.2.5.1 Hematology

Hematology tests are to be performed by the local laboratory according to the schedule of assessments and collection plan outlined respectively in Table 7-1 and Table 7-6.

More frequent hematology testing may also be performed as medically necessary. Additional results from unscheduled hematology lab evaluations should be recorded on the appropriate unscheduled visit CRF.

[redacted]

Table 7-6 Standard hematologic diagnostics

Sample Type	Blood volume/visit	Visit	Time Point
Bone marrow by biopsy/aspirate smears for cytomorphology including differential count	6 -8 bone marrow smears	Screening	
		Induction Phase 1 Day 21-28	
		Induction Phase 2 Day 21-28	
		Consolidation Phase C1 Day 21-28	
		Consolidation Phase C2 Day 21-28	
		Consolidation Phase C3 Day 21-28	
		Consolidation Phase C4 Day 21-28	
		Consolidation Phase (at time of relapse)	
		Prior to 1st cycle of post-consolidation Phase	
		Post-consolidation Phase C4 Day 1	
		Post-consolidation Phase C7 Day 1	
		Post-consolidation Phase C10 Day 1	
		Completion of Post-consolidation Phase C12 Day 28	
		Post-consolidation Phase (at relapse)	
		Post treatment Follow Up: 3 months after end of post-consolidation therapy and at relapse	
Peripheral blood smears for cytomorphology including microscopic differential count	2 peripheral blood smears	Screening	
		Induction Phase 1 Day 21-28	
		Induction Phase 2 Day 21-28	
		Consolidation Phase C1 Day 21-28	
		Consolidation Phase C2 Day 21-28	
		Consolidation Phase C3 Day 21-28	
		Consolidation Phase C4 Day 21-28	
		Consolidation Phase (at time of relapse)	
		Prior to 1st cycle of post-consolidation Phase	
		Post-consolidation Phase C2 Day 1	
		Post-consolidation Phase C3 Day 1	
		Post-consolidation Phase C4 Day 1	
		Post-consolidation Phase C5 Day 1	
		Post-consolidation Phase C6 Day 1	
		Post-consolidation Phase C7 Day 1	
		Post-consolidation Phase C8 Day 1	

[redacted]

Sample Type	Blood volume/visit	Visit	Time Point
		Post-consolidation Phase C9 Day 1	
		Post-consolidation Phase C10 Day 1	
		Post-consolidation Phase C11 Day 1	
		Post-consolidation Phase C12 Day 1	
		Completion of Post-consolidation Phase C12 Day 28	
		Post-consolidation Phase (at relapse)	
		Post treatment Follow Up, every 3 months until relapse and when clinically indicated	
Bone marrow for conventional metaphase cytogenetics	5 mL (minimum)	Screening	
Bone marrow for immunophenotyping	5mL	Screening	
Bone marrow (preferably trephine) biopsy for histology and immunohistology	1-2 cm trephine	Screening (mandatory)	
		Optional in parallel to all bone marrow (BM) aspiration for cytomorphology (e.g., for the purpose of immunohistochemically supported blast counting)	

7.2.2.5.2 Clinical chemistry

Clinical chemistry tests are to be performed by the local laboratory according to the schedule of assessments and collection plan outlined respectively in Table 7-1 and Table 7-5.

More frequent clinical chemistry testing may also be performed as medically necessary. Additional results from unscheduled chemistry lab evaluations should be recorded on the appropriate unscheduled visit CRF.

It should be noted in the patient's CRF if the patient was fasting as the time of blood sampling.

7.2.2.5.3 Coagulation

Coagulation analyses (INR and aPTT) are to be performed by the local laboratory according to the schedule of assessments and collection plan outlined respectively in Table 7-1 and Table 7-5.

7.2.2.5.4 Urinalysis

Dipstick analysis (includes specific gravity, pH, glucose, protein, blood, bilirubin, ketones and WBC) is to be performed by the local laboratory at screening and during treatment phase if clinically indicated.

[redacted]

Abnormal findings will be followed up with a microscopic analysis and/or additional assessments as clinically indicated.

7.2.2.5.5 Pregnancy and assessments of fertility

Women of child-bearing potential will have serum pregnancy tests at screening. During the treatment phases, the absence of pregnancy will be confirmed by urine pregnancy test prior to the first dose of study treatment (at day 1 during induction, prior to each consolidation cycle and Day 1 during post-consolidation cycles).

Urine pregnancy tests will be required to be performed as well as at the End of Treatment visit and at 30-day Safety follow up visit. Every effort must be made for the women of child bearing potential to return to the site for the final pregnancy test. However if the patient is unable to return then the patient will administer the urine pregnancy test at home using the kit provided. For all pregnancy test performed at home, the site personnel will follow up with the patient via telephone call to collect the date and the test results and document the information in the patient's source documents.

Women of child-bearing potential will be instructed to contact the site immediately at any time during the study (on treatment or during follow-up) should they have a positive pregnancy test.

Male patients treated with idarubicin, daunorubicin or cytarabine should receive appropriate advice on the risk of infertility and the option of sperm conservation. Midostaurin may impair both male and female fertility and this should be communicated to the patients.

7.2.2.6 Radiological examinations

Chest X-ray will be collected at baseline and during the study if clinically indicated.

7.2.2.7 Cardiac assessments

7.2.2.7.1 Electrocardiogram (ECG)

A standard triplicate 12 lead ECG each 2 min apart will be performed according to the relevant Visit Evaluation Schedule (Table 7-1 and Table 7-7).

[redacted]

Table 7-7 Local ECG assessment monitoring schedule

	Day	Time	ECG Type
Screening	-3 to -1	Pre-dose	12 Lead
Induction Phase 1	Day 8, Day 11, Day 21	Pre-dose (before PK) Post-dose at 3 hours ± 0.5 hour (before PK)	12 Lead
Consolidation Phase, each cycle	Day 4, Day 17	Pre-dose (before PK) Post-dose at 3 hours ± 0.5 hour (before PK)	12 Lead
Prior to 1st cycle of post-consolidation		Pre-dose (before PK)	12 Lead,
Post-consolidation, cycle 2 to cycle 12	Day 1	Pre-dose (before PK)	12 Lead
Post-consolidation, cycle 12 or at EOT (at any phase of the study)	Day 28	Pre-dose (before PK) Anytime	12 Lead 12 Lead
Unscheduled sample		Anytime when clinically indicated	12 Lead

Interpretation of the tracing must be made by a qualified physician and documented on the CRF. Each ECG tracing should be labeled with the study number, patient initials (where regulations permit), subject number, date, and kept in the source documents at the study site. Clinically significant abnormalities present at screening should be reported on the Medical History CRF.

Standard 12 lead ECG recording will be performed after the patient has been resting for approximately 10 min prior to each ECG collection time point indicated in Table 7-7 and prior to PK samples. Local measurements of QTc≥480ms shall be centrally verified on a copy of the original high quality recording that includes time and voltage scales.

Dose adjustments in case of QT prolongation should be performed per Section 6.3.

Clinically significant ECG abnormalities present at screening should be reported on the Medical History CRF. New or worsened clinically significant findings occurring after informed consent must be recorded on the Adverse Events CRF.

7.2.2.7.2 Cardiac imaging - MUGA (multiple gated acquisition) scan or echocardiogram

Cardiac Imaging will be performed at screening, at the 30 day Safety Follow Up Visit and whenever clinically indicated. LVEF needs to be measured and reported at each cardiac imaging. Any clinically relevant abnormalities will be reported on the medical history or AE page as applicable.

7.2.2.7.3 Cardiac enzymes

Not applicable.

[redacted]

7.2.3 Pharmacokinetics

Serial PK samples will be collected in all patients to assess the plasma concentrations of midostaurin, CGP52421 and CGP62221. To allow a proper description of midostaurin, CGP52421 and CGP62221 pharmacokinetics additional PK samples will be collected in a subset of the first 60 patients randomized into the trial. Therefore there will be approximately 30 patients receiving midostaurin and contributing to the PK analysis. A detailed description of the sample collection is provided in Table 7-8. In this subset of patients, non-compartmental PK parameters will be derived as described in Section 10.5.4.

The PK samples in the other patients will be collected according to the sampling scheme described in Table 7-9.

The whole set of concentrations will also be further analyzed using a population PK approach (Section 10.5.4).

Table 7-8 Pharmacokinetic blood collection log for Midostaurin, CGP52421 and CGP62221 – Full PK collection (N=60)

Dose Reference ID (2)	PK Sample number	Cycle (Period number)	Study day for each cycle	Time(1)	Blood volume (mL)
1	101	Induction 1 Cycle 1*	8	Pre-dose	3
1	102	Induction 1 Cycle 1*	8	1h	3
1	103	Induction 1 Cycle 1*	8	Post-dose 3hrs +- 0.5 hrs	3
1	104	Induction 1 Cycle 1*	8	6h	3
1/ 111(3)	105	Induction 1 Cycle 1*	8	12h (prior to the evening dose of Midostaurin/ Placebo)	3
2/201	106	Induction 1 Cycle 1	11	Pre-dose	3
2	107	Induction 1 Cycle 1	11	Post-dose 3hrs +- 0.5 hrs	3
3/301	108	Induction 1 Cycle 1	15	Pre-dose	3
4/401	109	Induction 1 Cycle 1	18	Pre-dose	3
5/501	110	Induction 1 Cycle 1	21	Pre-dose	3
5	111	Induction 1 Cycle 1	21	Post-dose 3hrs +- 0.5 hrs	3
6/601	112	Consolidation, cycle 1	4	Pre-dose	3
6	113	Consolidation Cycle 1	4	Post-dose 3hrs +- 0.5 hrs	3

[redacted]

Dose Reference ID (2)	PK Sample number	Cycle (Period number)	Study day for each cycle	Time(1)	Blood volume (mL)
7/701	114	Consolidation, cycle 1	17	Pre-dose	3
7	115	Consolidation, cycle 1	17	Post-dose 3hrs +- 0.5 hrs	3
8/801	116	Consolidation, cycle 3	4	Pre-dose	3
8	117	Consolidation, cycle 3	4	Post-dose 3hrs +- 0.5 hrs	3
9/901	118	Consolidation, cycle 3	17	Pre-dose	3
9	119	Consolidation, cycle 3	17	Post-dose 3hrs +- 0.5 hrs	3
10/1001	120	Prior to 1st of Post-consolidation, cycle 1		Pre-dose [redacted]	3
11/1101	121	Post-consolidation, cycle 4	1	Pre-dose	3
11	122	Post-consolidation, cycle 4	1	Post-dose 3hrs +- 0.5 hrs	3
12/1201	123	Post-consolidation, cycle 7	1	Pre-dose	3
13/1301	124	Post-consolidation, cycle 10	1	Pre-dose	3
14/1401	125	End of Post-consolidation, cycle 12	28	Pre-dose	3
Total volume					
Unscheduled samples					
NA	100x	NA	NA	Unscheduled	

*: When medically feasible full blood sample to be collected

(1): When PK is collected at the same time point as ECG, ECG should be done first.

(2): Dose reference ID: The first number refers to the administration at the day, the second number refers to the administration the day before (The information has to be collected) with an exception on Day 1 (see below).

(3) The first number refers to the administration on Day 1 morning dose, the second number refers to the administration on Day 1 evening dose.

Unscheduled blood samples will be uniquely, sequentially numbered 1001, 1002, …

[redacted]

Table 7-9 Pharmacokinetic blood collection log for Midostaurin, CGP52421 and CGP62221 – Sparse PK collection

Dose Reference ID (2)	PK Sample number	Cycle (Period number)	Study day for each cycle	Time(1)	Blood volume (mL)
1	201	Induction 1 Cycle 1*	8	Pre-dose	3
1	202	Induction 1 Cycle 1*	8	Post-dose 3hrs +- 0.5 hrs	3
2/201	203	Induction 1 Cycle 1	11	Pre-dose	3
2	204	Induction 1 Cycle 1	11	Post-dose 3hrs +- 0.5 hrs	3
3/301	205	Induction 1 Cycle 1	15	Pre-dose	3
4/401	206	Induction 1 Cycle 1	18	Pre-dose	3
5/501	207	Induction 1 Cycle 1	21	Pre-dose	3
5	208	Induction 1 Cycle 1	21	Post-dose 3hrs +- 0.5 hrs	3
6/601	209	Consolidation, cycle 1	4	Pre-dose	3
6	210	Consolidation Cycle 1	4	Post-dose 3hrs +- 0.5 hrs	3
7/701	211	Consolidation, cycle 1	17	Pre-dose	3
7	212	Consolidation, cycle 1	17	Post-dose 3hrs +- 0.5 hrs	3
8/801	213	Consolidation, cycle 3	4	Pre-dose	3
8	214	Consolidation, cycle 3	4	Post-dose 3hrs +- 0.5 hrs	3
9/901	215	Consolidation, cycle 3	17	Pre-dose	3
9	216	Consolidation, cycle 3	17	Post-dose 3hrs +- 0.5 hrs	3
10/1001	217	Prior to 1st of Post-consolidation, cycle 1		Pre-dose [redacted]	3
11/1101	218	Post-consolidation, cycle 4	1	Pre-dose	3
12/1201	219	Post-consolidation, cycle 7	1	Pre-dose	3

[redacted]

Dose Reference ID (2)	PK Sample number	Cycle (Period number)	Study day for each cycle	Time(1)	Blood volume (mL)
13/1301	220	Post-consolidation, cycle 10	1	Pre-dose	3
14/1401	221	End of Post-consolidation, cycle 12	28	Pre-dose	3
Total volume					
Unscheduled samples					
NA	200x	NA	NA	Unscheduled	

*: When medically feasible full blood sample to be collected
(1): When PK is collected at the same time point as ECG, ECG should be done first.
(2): Dose reference ID: The first number refers to the administration at the day, the second number refer to the administration the day before (The information has to be collected)
Unscheduled blood samples will be uniquely, sequentially numbered 2001, 2002, …

Detailed instructions for the collection, handling, and shipment of PK samples will be provided in a separate document.

[redacted]

7.2.3.1 Analytical method

Plasma concentrations of midostaurin and its active metabolites CGP62221 and CGP52421 will be measured using a validated liquid chromatography-tandem mass spectrometry (LC-MS/MS) assay with a lower limit of quantification (LLOQ) of approximately 10.0 ng/mL. Concentrations below the LLOQ will be reported as 0.00 ng/mL and missing samples will be labeled accordingly.

[redacted]

7.2.4 Biomarkers

[redacted]

Table 7-11 Biomarker sample collection plan

Sample Type	Blood volume/visit	Visit	Time Point
Samples for Molecular Screening			
Bone Marrow Aspirate for FLT3 mutational testing *	2 mL	Screening (eligibility confirmation)	Anytime, as early as possible after patient signed ICF
Peripheral Blood for FLT3 mutational testing *	6 mL	Screening (eligibility confirmation)	Anytime, as early as possible after patient signed ICF
***A bone marrow aspirate or a whole blood sample will be collected. In case both sample types are collected/available, FLT3 screening will be preferentially performed only on the bone marrow sample; and the peripheral blood sample will be banked for future testing**			
Bone Marrow Samples			
Bone Marrow Aspirate for RNA, DNA (MRD and [redacted])	6 mL	Screening	Anytime
		Induction Phase 1 Day 21-28	Pre-dose
		Induction Phase 2 Day 21-28	Pre-dose
		Consolidation phase C1 Day 21-28	Pre-dose
		Prior to 1st cycle of Post-consolidation Phase	Pre-dose

[redacted]

Sample Type	Blood volume/visit	Visit	Time Point
		Post-consolidation Phase C4 Day 1	Pre-dose
		Post-consolidation Phase C7 Day 1	Pre-dose
		Post-consolidation Phase C10 Day 1	Pre-dose
		Completion of Post-consolidation Phase C12 Day 28	Pre-dose
		At relapse (at any phase of the study)	Anytime
		Post treatment Follow Up: 3 months after end of post-consolidation therapy, and at relapse	Anytime
Blood Samples			
Peripheral Blood for RNA and DNA analysis (MRD [redacted])	16 mL	Screening	Anytime
		Induction Phase C1 Day 21-28	Pre-dose
		Induction Phase C2 Day 21-28	Pre-dose
		Consolidation Phase C1 Day 21-28	Pre-dose
		Consolidation Phase C3 Day 21-28	Pre-dose
		Prior to 1st cycle of Post-consolidation Phase	Pre-dose
		Post-consolidation Phase C4 Day 1	Pre-dose
		Post-consolidation Phase C7 Day 1	Pre-dose
		Post-consolidation Phase C10 Day 1	Pre-dose
		Completion of Post-consolidation Phase C12 Day 28	Pre-dose
		EOT (at any phase of the study)	Anytime
		Every 3 months during years 1 and 2 and then yearly	Anytime
[redacted]			

[redacted]

[redacted]

7.2.4.1 Additional biomarker assessments

[redacted]

7.2.6 Patient reported outcomes

Two questionnaires will be used in this study to capture PROs: Functional Assessment of Cancer Therapy-Leukemia (FACT-Leu) and EQ-5D-5L. Brief description of each questionnaire is given in the sections below.

The patient should be given the questionnaire(s) to be completed at the scheduled visit before other clinical assessments are conducted. Questionnaires should be completed in the language the respondent is most familiar with, at the scheduled visit before the patient sees the investigator for clinical assessments. The patient should be given sufficient space and time to complete the questionnaire.

[redacted]

Reason for missing data at scheduled visit will also be captured ('patient refused due to poor health', 'patient refused (unrelated to health), 'study staff felt patient was too ill', 'patient missed appointment', 'other reasons').

Data from both questionnaires will be captured electronically using dedicated devices. Instructions for operating the devices will be available to each study site. In addition detailed instructions relating to the administrative procedures of the questionnaires will be provided to the sites in a separate document. Patient's refusal to complete all or any part of a questionnaire should be documented in the study data capture system.

FACT-Leu

The FACT-Leu is a questionnaire to assess the quality of life in patients with leukemia. It consists of a general quality of life instrument (FACT-G) and a condition specific module Leu. The FACT-Leu is a fully validated QOL questionnaire applicable for patients with leukemia and includes a module which assesses specific concerns of patients with leukemia. The FACT-G has 27 statements that patients will need to endorse on a five-point scale (not at all, a little, somewhat, quite a bit, very much). The statements cover five subscales (Physical Well-Being, Social/Family Well-Being, Emotional Well-Being, Functional Well-Being and Additional Concerns). The Leu module consists of 17 statements patients need to endorse on an identical five-point scale. The recall period is "Past 7 days", and the questionnaire requires approximately 5 minutes to complete.

EQ-5D-5L

The EQ-5D is a widely used, self-administered questionnaire designed to assess health status in adults. The EQ-5D-5L essentially consists of 2 pages: the EQ-5D descriptive system and the EQ visual analogue scale (EQ VAS). The descriptive system comprises five dimensions: mobility, self-care, usual activities, pain/discomfort and anxiety/depression. Each dimension has 5 levels: no problems, slight problems, moderate problems, severe problems and extreme problems.

Patients rate each of these items: no problems, slight problems, moderate problems, severe problems and extreme problems. A composite health index is then defined by combining the levels for each dimension. The second section of the questionnaire measures self-rated (global) health status utilizing a vertically oriented visual analogue scale where 100 represents the "best possible health state" and 0 represents the "worst possible health state." Respondents are asked to rate their current health by placing a mark along this continuum. The recall period is "today," and the questionnaire requires approximately 5 minutes to complete.

8 Safety monitoring and reporting

8.1 Adverse events

8.1.1 Definitions and reporting

An adverse event is defined as the appearance of (or worsening of any pre-existing) undesirable sign(s), symptom(s), or medical condition(s) that occur after patient's signed informed consent has been obtained.

[redacted]

Abnormal laboratory values or test results occurring after informed consent constitute adverse events only if they induce clinical signs or symptoms, are considered clinically significant, require therapy (e.g., hematologic abnormality that requires transfusion or hematological stem cell support), or require changes in study medication(s).

Adverse events that begin or worsen after informed consent should be recorded in the Adverse Events CRF. Conditions that were already present at the time of informed consent should be recorded in the Medical History CRF. Adverse event monitoring should be continued for at least 30 days following the last dose of study treatment. Adverse events (including lab abnormalities that constitute AEs) should be described using a diagnosis whenever possible, rather than individual underlying signs and symptoms. When a clear diagnosis cannot be identified, each sign or symptom should be reported as a separate Adverse Event.

Adverse events will be assessed and graded according to the CTCAE version 5.0.

If CTCAE grading does not exist for an adverse event, the severity of mild, moderate, severe, and life-threatening, death related to the AE corresponding respectively to Grades 1 - 5, will be used. Information about any deaths (related to an Adverse Event or not) will also be collected through a Death form.

The occurrence of adverse events should be sought by non-directive questioning of the patient during the screening process after signing informed consent and at each visit during the study. Adverse events also may be detected when they are volunteered by the patient during the screening process or between visits, or through physical examination, laboratory test, or other assessments. As far as possible, each adverse event should be evaluated to determine:

1. The severity grade (CTCAE Grade 1-5)
2. Its duration (start and end dates)
3. Its relationship to the study treatment (related, not related)
4. Action taken with respect to study treatment (dose increased, dose not changed, dose reduced, drug interrupted, drug withdrawn, unknown, not applicable)
5. Whether medication or therapy was given (no concomitant medication/non-drug therapy, concomitant medication/non-drug therapy)
6. Whether it is serious, where a SAE is defined as in Section 8.2.1 and which seriousness criteria have been met
7. Outcome (not recovered/not resolved, recovered/resolved, recovered/resolved with sequelae, fatal, unknown)
8. If the event worsens, the event should be reported a second time in the CRF noting the start date when the event worsens in toxicity. For grade 3 and 4 adverse events only, if improvement to a lower grade is determined a new entry for this event should be reported in the CRF noting the start date when the event improved from having been Grade 3 or Grade 4.

All adverse events should be treated appropriately. If a concomitant medication or non-drug therapy is given, this action should be recorded on the Adverse Event CRF.

Once an adverse event is detected, it should be followed until its resolution or until it is judged to be permanent, and assessment should be made at each visit (or more frequently, if

necessary) of any changes in severity, the suspected relationship to the study treatment, the interventions required to treat it, and the outcome.

Treatment failure or relapse (including fatal outcomes), if documented by use of appropriate method should not be reported as a serious adverse event.

Adverse events separate from relapse or treatment failure will be reported as per usual guidelines used for such events with proper attribution regarding relatedness to the drug.

8.1.2 Laboratory test abnormalities

8.1.2.1 Definitions and reporting

Laboratory abnormalities that constitute an AE in their own right (are considered clinically significant, induce clinical signs or symptoms, require concomitant therapy or require changes in study treatment), should be recorded on the AEs CRF. Whenever possible, a diagnosis, rather than a symptom should be provided (e.g. anemia instead of low hemoglobin). Laboratory abnormalities that meet the criteria for Adverse Events should be followed until they have returned to normal or an adequate explanation of the abnormality is found. When an abnormal laboratory or test result corresponds to a sign/symptom of an already reported adverse event, it is not necessary to separately record the lab/test result as an additional event.

Laboratory abnormalities, that do not meet the definition of an adverse event, should not be reported as adverse events. A Grade 3 or 4 Event (severe) as per CTCAE does not automatically indicate a SAE unless it meets the definition of serious as defined below and/or as per investigator's discretion. A dose hold or medication for the lab abnormality may be required by the protocol in which case the lab abnormality would still, by definition, be an adverse event and must be reported as such.

8.1.3 Adverse events of special interest

Adverse events of special interest (AESI) are defined as events (serious or non-serious) which are ones of scientific and medical concern specific to Midostaurin, for which ongoing monitoring and rapid communication by the investigator to the sponsor should be appropriate. Such events may require further investigation in order to characterize and understand them.

AESI are defined on the basis of an ongoing review of the safety data. AESI are discussed in detail in the Investigator Brochure.

8.2 Serious adverse events

8.2.1 Definitions

Serious adverse event (SAE) is defined as one of the following:

- Is fatal or life-threatening
- Results in persistent or significant disability/incapacity
- Constitutes a congenital anomaly/birth defect
- Is medically significant, i.e., defined as an event that jeopardizes the patient or may require medical or surgical intervention to prevent one of the outcomes listed above

[redacted]

- Requires inpatient hospitalization or prolongation of existing hospitalization,
- Note that hospitalizations for the following reasons should not be reported as serious adverse events:
  - Routine treatment or monitoring of the studied indication, not associated with any deterioration in condition
  - Elective or pre-planned treatment for a pre-existing condition that is unrelated to the indication under study and has not worsened since signing the informed consent
  - Social reasons and respite care in the absence of any deterioration in the patient's general condition
- Note that treatment on an emergency outpatient basis that does not result in hospital admission and involves an event not fulfilling any of the definitions of a SAE given above is not a serious adverse event.

8.2.2 Reporting

To ensure patient safety, every SAE, regardless of suspected causality, occurring after the patient has provided informed consent and until at least 30 days after the patient has stopped study treatment must be reported to Novartis within 24 hours of learning of its occurrence.

Any additional information for the SAE including complications, progression of the initial SAE, and recurrent episodes must be reported as follow-up to the original episode within 24 hours of the investigator receiving the follow-up information. An SAE occurring at a different time interval or otherwise considered completely unrelated to a previously reported one should be reported separately as a new event.

Any SAEs experienced after the 30 day safety evaluation follow-up period should only be reported to Novartis if the investigator suspects a causal relationship to the study treatment.

Information about all SAEs is collected and recorded on the Serious Adverse Event Report Form; all applicable sections of the form must be completed in order to provide a clinically thorough report. The investigator must assess and record the relationship of each SAE to each specific study treatment (if there is more than one study treatment), complete the SAE Report Form in English, and submit the completed form within 24 hours to Novartis. Detailed instructions regarding the SAE submission process and requirements for signatures are to be found in the investigator folder provided to each site.

Follow-up information is submitted in the same way as the original SAE Report. Each re-occurrence, complication, or progression of the original event should be reported as a follow-up to that event regardless of when it occurs. The follow-up information should describe whether the event has resolved or continues, if and how it was treated, whether the blind was broken or not, and whether the patient continued or withdrew from study participation.

If the SAE is not previously documented in the Investigator's Brochure or Package Insert (new occurrence) and is thought to be related to the Novartis study treatment, an oncology Novartis Chief Medical Office and Patient Safety (CMO&PS) department associate may urgently require further information from the investigator for Health Authority reporting. Novartis may need to issue an Investigator Notification (IN), to inform all investigators involved in any study with the same drug that this SAE has been reported. Suspected Unexpected Serious Adverse

[redacted]

Reactions (SUSARs) will be collected and reported to the competent authorities and relevant ethics committees in accordance with Directive 2001/20/EC or as per national regulatory requirements in participating countries.

8.3 Emergency unblinding of treatment assignment

Emergency unblinding should only be undertaken when it is essential for effective treatment of the patient. Most often, study treatment discontinuation and knowledge of the possible treatment assignments are sufficient to treat a study patient who presents with an emergency condition. Emergency code breaks are performed using the IRT. When the investigator contacts the IRT to unblind a patient, he/she must provide the requested patient identifying information and confirm the necessity to unblind the patient. The investigator will then receive details of the drug treatment for the specified patient and a fax confirming this information. The system will automatically inform the Novartis monitor for the site and the Study Lead that the code has been broken.

It is the investigator's responsibility to ensure that there is a procedure in place to allow access to the IRT in case of emergency. The investigator will inform the patient how to contact his/her backup in cases of emergency when he/she is unavailable. The protocol number, study treatment name if available, subject number, and instructions for contacting the local Novartis country pharma organization (CPO) (or any entity to which it has delegated responsibility for emergency code breaks) will be provided to the patient in case emergency unblinding is required at a time when the investigator and backup are unavailable. However, if a mechanism is already in place to ensure that the investigator and/or back-up can always be reached in case of emergency then the procedure above is not required.

The appropriate personnel from the site and Novartis will assess whether study treatment should be discontinued for any patient whose treatment code has been broken inadvertently for any reason.

8.4 Pregnancies

To ensure patient safety, each pregnancy occurring while the patient is on study treatment must be reported to Novartis within 24 hours of learning of its occurrence. The pregnancy should be followed up to determine outcome, including spontaneous or voluntary termination, details of the birth, and the presence or absence of any birth defects, congenital abnormalities, or maternal and/or newborn complications.

Pregnancy should be recorded on a Clinical Trial Pregnancy Form and reported by the investigator to the oncology Novartis CMO&PS. Pregnancy follow-up should be recorded on the same form and should include an assessment of the possible relationship to the study treatment for any pregnancy outcome. Any SAE experienced during pregnancy must be reported on the SAE Report Form.

Pregnancy outcomes should be collected for the female partners of any males who took study treatment in this study. Consent to report information regarding these pregnancy outcomes should be obtained from the mother.

[redacted]

If pregnancy occurs in a patient in the study, the **study treatment must be discontinued**, though the patient may stay in the study and follow the assessments, if she wishes to do so. All assessments that are considered as a risk during pregnancy must not be performed. The patient may continue all other protocol assessments.

Follow up of the pregnancy (female patient or female partner of patient) should be according to the following schedule:

- Tracking of pregnancy cases occurs until after Expected Delivery Date (EDD) for all prospective pregnancy cases received from clinical studies (including pregnancies where the patient was exposed to placebo or comparator and pregnancies due to the conduct of the study).
- EDD +1 month (mandatory for all cases). Requesting the pregnancy outcome and other clinically relevant pregnancy data or changes in data.
- EDD+2 month (mandatory if no answer is obtained after request at EDD+1 month). A reminder letter for the outcome.
- The follow up at EDD+3 months is mandatory for all cases of live birth. Information on the status of the baby 3 months after delivery and information on any development issue or abnormality that would not be seen at birth must be collected.
- The follow up at EDD+12 months is mandatory for all cases of live birth. Information on the status of the baby 12 months after delivery and information on any development issue or abnormality that would not be seen at birth must be collected.

If the pregnancy case is lost to follow-up (e.g. no response after 3 attempts) this information must be transferred to the Safety Desk of the CPO.

8.5 Warnings and precautions

No evidence available at the time of the approval of this study protocol indicated that special warnings or precautions were appropriate, other than those noted in the provided Investigator Brochure. Additional safety information collected between IB updates will be communicated in the form of Investigator Notifications. This information will be included in the patient informed consent and should be discussed with the patient during the study as needed.

8.6 Data Monitoring Committee

This study will institute a DMC which will function independently of all other individuals associated with the conduct of this clinical trial, including the site investigators participating in the study. The DMC will be constituted prior to the randomization of the first patient. The DMC will be responsible to review safety data approximately every 6 months (after the first randomized patient has started study treatment). The DMC will also be responsible to review efficacy and safety data, in the conduct of the interim analysis as defined in the protocol. This includes but does not limit the role of the DMC to evaluate these data and to provide recommendations to the sponsor to continue, modify or stop the study early.

It is expected that the DMC will consist at a minimum of two physicians with appropriate disease area qualifications and one statistician. There will be a meeting with the DMC

describing their roles and responsibilities and discussing potential data format and process issues prior to the finalization of DMC charter and the interim analysis plan.

It is envisioned that the DMC may make five types of recommendations, namely:

- No safety or efficacy issues, ethical to continue the study as planned
- Serious safety concerns precluding further study treatment, regardless of efficacy
- Overwhelming evidence for efficacy making further participation in the study unethical
- Overwhelming evidence for futility, recommend stopping the study.
- Recommendation to continue the study but proposing an amendment to the protocol (e.g., incorporate an additional safety assessments)

If the study is recommended to continue by the DMC, no details about the results of the current interim analysis will be revealed prior to the next scheduled analysis.

8.7 Steering Committee

The Steering Committee (SC) will be established comprising investigators participating in the trial and will not include the independent safety committee or the Novartis representatives from the Clinical Trial Team.

The SC will ensure transparent management of the study according to the protocol through recommending and approving modifications as circumstances require. The SC will review protocol amendments as appropriate. Together with the clinical trial team, the SC will also develop recommendations for publications of study results including authorship rules. The details of the role of the SC will be defined in a SC charter. The SC will not have access to un-blinded trial data prior to the primary analyses.

9 Data collection and management

9.1 Data confidentiality

Information about study subjects will be kept confidential and managed under the applicable laws and regulations. Those regulations require a signed subject authorization informing the subject of the following:

- What protected health information (PHI) will be collected from subjects in this study
- Who will have access to that information and why
- Who will use or disclose that information
- The rights of a research subject to revoke their authorization for use of their PHI.

In the event that a subject revokes authorization to collect or use PHI, the investigator, by regulation, retains the ability to use all information collected prior to the revocation of subject authorization. For subjects that have revoked authorization to collect or use PHI, attempts should be made to obtain permission to collect follow-up safety information (e.g. has the subject experienced any new or worsened AEs) at the end of their scheduled study period.

The data collection system for this study uses built-in security features to encrypt all data for transmission in both directions, preventing unauthorized access to confidential participant

[redacted]

information. Access to the system will be controlled by a sequence of individually assigned user identification codes and passwords, made available only to authorized personnel who have completed prerequisite training.

Subject Age will be recorded in the eCRF to establish that the subject satisfies protocol age requirements and to enable appropriate age-related normal ranges to be used in assessing laboratory test results.

9.2 Site monitoring

Before study initiation, at a site initiation visit or at an investigator's meeting, Novartis personnel (or designated CRO) will review the protocol and CRFs with the investigators and their staff. During the study, the field monitor will visit the site regularly to check the completeness of patient records, the accuracy of entries on the CRFs, the adherence to the protocol to Good Clinical Practice, the progress of enrollment, and to ensure that study treatment is being stored, dispensed, and accounted for according to specifications. Key study personnel must be available to assist the field monitor during these visits.

The investigator must maintain source documents for each patient in the study, consisting of case and visit notes (hospital or clinic medical records) containing demographic and medical information, laboratory data, electrocardiograms, and the results of any other tests or assessments. All information recorded on CRFs must be traceable to source documents in the patient's file. The investigator must also keep the original signed informed consent form (a signed copy is given to the patient).

The investigator must give the monitor access to all relevant source documents to confirm their consistency with the CRF entries. Novartis monitoring standards require full verification for the presence of informed consent, adherence to the inclusion/exclusion criteria and documentation of SAEs. Additional checks of the consistency of the source data with the CRFs are performed according to the study-specific monitoring plan.

9.3 Data collection

For studies using Electronic Data Capture (EDC), the designated investigator staff will enter the data required by the protocol into the eCRF. The eCRFs have been built using fully validated secure web-enabled software that conforms to 21 CFR Part 11 requirements. Investigator site staff will not be given access to the EDC system until they have been trained. Automatic validation programs check for data discrepancies in the eCRFs and, allow modification or verification of the entered data by the investigator staff.

The investigator must certify that the data entered into CRF are complete and accurate and that entry and updates are performed in a timely manner.

ECG data will be collected via 12-lead ECG machines and the data will be recorded on the CRF.

PK [redacted] samples (including FLT3 analytics) drawn during the course of the study will be shipped by the site to a Novartis designated laboratory for sample management and/or analysis.

[redacted]

PRO data must be recorded by patients onto the electronic tablet device maintained at the study site. Paper questionnaires as back-up might be allowed to use in exceptional cases.

9.4 Database management and quality control

For studies using eCRFs, Novartis personnel (or designated CRO) will review the data entered by investigational staff for completeness and accuracy. Electronic data queries stating the nature of the problem and requesting clarification will be created for discrepancies and missing values and sent to the investigational site via the EDC system. Designated investigator site staff are required to respond promptly to queries and to make any necessary changes to the data.

Concomitant treatments and prior medications entered into the database will be coded using the WHO Drug Reference List, which employs the Anatomical Therapeutic Chemical classification system. Medical history/current medical conditions and adverse events will be coded using the Medical dictionary for regulatory activities (MedDRA) terminology.

In terms of samples and/or data (e.g. [redacted] PK) that will be processed centrally the results will be sent electronically to Novartis.

PRO data will be entered into an electronic diary by the patient. The system will be supplied by a vendor(s), who will also manage the database. The database will be sent electronically to Novartis personnel.

Randomization codes and data about all study treatments dispensed to the patient and all IRT assigned dosage changes will be tracked using an Interactive Response Technology. The system will be supplied by a vendor(s), who will also manage the database. The data will be sent electronically to Novartis personnel.

At the conclusion of the study, the occurrence of any emergency code breaks will be determined after return of all code break reports and unused drug supplies to Novartis personnel (or designated CRO). The occurrence of any protocol violations will be determined. After these actions have been completed and the data has been verified to be complete and accurate, the database will be declared locked and the treatment codes will be unblinded and made available for data analysis. Authorization is required prior to making any database changes to locked data, by joint written agreement between the Global Head of Oncology Biostatistics, Global Head of Data Management and the Global Head of Clinical Development.

After database lock, the investigator will receive copies of the patient data for archiving at the investigational site.

10 Statistical methods and data analysis

The final EFS analysis will be performed by Novartis. The interim analyses for the EFS and the first interim analyses for OS if EFS statistically significant will be performed by an independent external statistician and an independent external programmer (CRO not involved with the conduct of the study). The second OS interim analysis at the time of the final EFS analysis will be performed by Novartis study team if the final analysis of EFS is statistically

[redacted]

significant. Investigators and patients will be kept blinded at the patient level in case the trial continues.

The final EFS analysis will be conducted at the time when approximately 285 EFS events have been observed. The final OS analysis will be performed when there are approximately 278 deaths documented. The safety analysis will be performed approximately every 6 months by the iDMC and at the time of EFS or OS analyses.

10.1 Analysis sets

10.1.1 Full Analysis Set

The Full Analysis Set (FAS) comprises all patients to whom study drug has been assigned by randomization. According to the intent to treat principle, patients will be analyzed according to the treatment and stratum they have been assigned to during the randomization procedure.

10.1.2 Safety set

The Safety Set (SS) includes all patients who received at least one dose of study treatment starting at day 1 and being randomized with at least one dose of Midostaurin or placebo. Patients will be analyzed according to the study treatment received, where treatment received is defined as the randomized treatment if the patient took at least one dose of that treatment. Patients who started therapy at day 1 but discontinued prior to randomization at day 8 will be listed separately.

10.1.3 Per-Protocol set

The Per-Protocol Set (PPS) consists of a subset of the patients in the FAS who are compliant with requirements of the study protocol (i.e., without any major protocol deviation). Protocol deviations leading to exclusion from the PPS will be justified and specified in the study Specification Document (SSD) and Statistical Analysis Plan (SAP) documents prior to database lock.

10.1.4 Pharmacokinetic analysis set

Pharmacokinetic Analysis Set for all (PAS-all)

The Pharmacokinetic analysis set for all (PAS-all) includes all subjects in the safety set, and provide at least one evaluable PK concentration.

For a concentration to be evaluable:

- Dosing information must be properly documented (data and time of administration)
- the planned dose of midostaurin must be taken prior to sampling,
- For pre-dose samples: no vomiting within 4 hours after the midostaurin dose prior to sampling, the sample is collected before the next dose administration.
- For post-dose samples: no vomiting within 4 hours after midostaurin dosing

The PAS-all will be the primary population used for all pharmacokinetic analyses using trough concentration data.

[redacted]

Pharmacokinetic analysis set for full PK profile (PAS-full)

The Pharmacokinetic analysis set for full PK profiles (PAS-full) includes all subjects in the PAS-all, who provide an evaluable PK profile. A profile is considered evaluable if all of the following conditions are satisfied:

- Subject receives the planned first dose of midostaurin on C1D8 of Induction therapy
- Subject did not vomit within 4 hours of the first dose of midostaurin on C1D8 of Induction therapy
- Subject provides at least one primary PK parameter (Cmax, AUC0-t)

The PAS-full will be the primary population used for all pharmacokinetic analyses based on full PK profile data.

Protocol deviations leading to exclusion from the PAS-all and PAS-full will be justified and specified in the study Validation and Planning (VAP) and Statistical Analysis Plan (SAP) documents.

10.2 Patient demographics/other baseline characteristics

Baseline demographics and disease characteristics data will be summarized descriptively by treatment group for the FAS. Qualitative data, such as gender, race, etc., will be presented as frequencies and percentages. Quantitative data, such as age, height, etc., will be summarized as mean, standard deviation, median, minimum, and maximum.

10.3 Treatments (study treatment, concomitant therapies, compliance)

Data on the study treatment administration will be summarized by treatment group in the safety set. The duration of treatment and relative dose intensity of each of the components of study treatment will be summarized using descriptive statistics.

Concomitant medications and significant non-drug therapies prior to and after the start of the study treatment will be listed and summarized according to the Anatomical Therapeutic Chemical (ATC) classification system, by treatment group.

Any prior concomitant medications or significant non-drug therapies starting and ending prior to the start of study treatment will be summarized and listed by treatment group.

10.4 Primary objective

The primary objective of this study is to determine if the addition of midostaurin to standard induction and consolidation therapy, followed by single agent post-consolidation therapy improves EFS in patients with newly diagnosed FLT3-MN (SR<0.05) AML.

- The primary endpoint is EFS as per investigator assessment and is defined as the time from the date of randomization to failure to obtain CR or CRi with adequate blood count recovery in induction, relapse after CR or CRi with adequate blood count recovery, or death due to any cause, whichever occurs first.

[redacted]

10.4.1 Statistical hypothesis, model, and method of analysis

The study is designed to test the following statistical hypothesis for EFS using a stratified log-rank test (stratified according to randomization stratification factor of age (<60 vs. ≥ 60 years)) at the one-sided 2.5% level of significance:

$$H_{01}: \theta_1 \geq 1 \text{ vs. } H_{a1}: \theta_1 < 1$$

Where θ_1 is the hazard ratio (Midostaurin treatment arm vs. placebo arm) of EFS.

The primary efficacy endpoint EFS will be analyzed at the interim looks and final look of a group sequential design based on the FAS population according to the treatment group patients were randomized and the strata they were assigned at randomization (i.e. age < 60 vs. >=60 years). EFS will be estimated using the Kaplan-Meier method. The median EFS along with 95% confidence intervals will be presented by treatment group.

Under the proportional hazards assumption, a test based on the stratified log-rank test provides an asymptotically equivalent result as that of the stratified Cox regression model which will be used to estimate the hazard ratio (HR) of EFS, along with 95% confidence interval (using the same strata information as above).

10.4.2 Handling of missing values/censoring/discontinuations

In the primary analysis, a patient who had not an EFS event at the date of the analysis cut-off would have his/her EFS censored at the time of the last adequate response assessment before the cut-off date.

A patient who failed to achieve CR or CRi with adequate blood count recovery in induction, would have his/her EFS event due to induction failure documented at the date of randomization.

EFS events documented after the initiation of HSCT or new anti-neoplastic therapy will be considered as EFS event for the primary EFS analysis.

If an EFS event is observed after two or more missing or non-adequate response assessments, then EFS will be censored at the last adequate response assessment before the EFS event. If an EFS event is observed after a single missing or non-adequate response assessment, the actual date of event will be used.

An adequate response assessment is considered any disease assessment indicating response status apart from “unknown” or “not done”.

10.4.3 Supportive analyses

A supportive analysis on the primary efficacy variable using a stratified Cox’s proportional hazards model adjusting for time dependent covariates such as SCT and MRD and other potential prognostic factors will be performed. Other potential prognostic factors will be specified in the SAP document prior to database lock.

Subgroup analyses based on age and gender etc. will be performed. There will be sensitivity analyses for the EFS (e.g., using different censoring techniques, per protocol set analysis, etc...). More details on these will be available in SAP.

[redacted]

10.5 Secondary objectives

The key secondary objective is to determine if the addition of midostaurin to standard induction and consolidation therapy, followed by single agent post-consolidation therapy improves OS in patients with newly diagnosed FLT3-MN (SR<0.05) AML.

Other secondary efficacy objectives are to compare CR or CRi with adequate blood count recovery rate, MRD, DFS, Cumulative Incidence of Relapse (CIR), Cumulative Incidence of Disease (CID) and health-related quality of life and symptoms of AML in patients treated with midostaurin in combination with daunorubicin or idarubicin/cytarabine versus those treated with placebo in combination with daunorubicin or idarubicin/cytarabine.

The secondary safety/PK objective is to assess safety, pharmacokinetic of midostaurin in combination with daunorubicin or idarubicin/cytarabine versus placebo in combination with daunorubicin or idarubicin/cytarabine.

Population and grouping for the analyses

The secondary efficacy variables will be analyzed using the FAS. For all safety analyses, the safety set will be used. Subgroup analyses will be performed by age (<60 versus ≥60 years) , ELN risk group (Favorable/ Intermediate/ Adverse) etc.... All listings and tables will be presented by treatment group.

10.5.1 Key secondary objective(s)

The key secondary objective of the study is to determine if the addition of midostaurin to standard induction and consolidation therapy, followed by single agent post-consolidation therapy improves OS in patients with newly diagnosed FLT3-MN (SR<0.05) AML.

OS is defined as the time from date of randomization to date of death due to any cause. If a patient is not known to have died, survival will be censored at the date of last contact. No censoring will be done in case of HSCT.

Assuming proportional hazards model for OS, the following statistical hypothesis for OS will be tested using a stratified log-rank test (stratified according to randomization stratification factor of age) at the one-sided 2.5% level of significance:

$$H_{02}: \theta_2 \geq 1 \text{ vs. } H_{a2}: \theta_2 < 1$$

Where θ_2 is the hazard ratio (Midostaurin treatment arm vs. placebo arm) of OS.

The analyses for OS will be based on the FAS population according to the treatment group patients were randomized and the strata they were assigned at randomization.

The final OS analysis will not be performed at the time point of the final EFS analysis, but after additional follow up. Therefore, a three-look design is considered for OS following a separate group-sequential plan.

The OS will be hierarchically tested in the following way:

1. The first potential time point for OS analysis will be at the time of the 2nd EFS interim analysis, where approximately 79 deaths are expected. If EFS is statistically significant at this stage, OS will also be tested. If OS is not statistically significant at this stage, the 2nd

[redacted]

OS analysis will be planned at approximately 190 deaths (i.e. at time of EFS final analysis). If OS is not statistically significant at this stage, a final analysis is planned at approximately 278 deaths have been recorded.

2. If EFS is not statistically significant at the time of the interim analysis of EFS, then OS will not be tested at the time of the interim analyses of EFS. If EFS is statistically significant at the time of the final analysis of EFS, then OS will also be tested. If OS is not statistically significant at this stage, the final analysis for OS is planned at approximately 278 deaths have been recorded.
3. If EFS is not statistically significant at the final analysis, then OS will not be tested.

The type I error probability will be controlled by using a separate Haybittle-Peto boundary independent of the one used for the primary efficacy analysis of EFS at 2.5% level of significance. This guarantees the protection of the overall level $\alpha = 2.5\%$ (one-sided) across the two hypotheses and the repeated testing of the OS hypotheses in the interim and the final analyses.

OS will be estimated using the Kaplan-Meier method. The median OS along with 95% confidence intervals will be presented by treatment group. The stratified Cox regression model will be used to estimate the HR of OS, along with 95% confidence interval. All OS analyses will be based on the FAS.

10.5.2 Other secondary efficacy objectives

10.5.2.1 CR/CRi rate, Time to CR or CRi with adequate blood count recovery, Disease Free survival (DFS), Cumulative Incidence of Relapse (CIR) and Cumulative Incidence of Death (CID)

Other secondary efficacy variables include CR or CRi with adequate blood count recovery rate, DFS, CIR and CID. The assessment of these endpoints will be based on the IWG criteria for AML (Cheson et al 2003, ELN 2017 / Döhner et al 2017) as per investigator assessment.

CR/CRi with adequate blood count recovery rate will be analyzed using Cochran-Mantel-Haenszel test based on strata at randomization. Estimated CR/CRi rate along with corresponding 95% confidence intervals will be presented by stratum and overall, and by treatment group.

Time to CR or CRi with adequate blood count recovery is defined as the time from randomization to CR or CRi with adequate blood count recovery whichever occurs first. Patients without experiencing CR, CRi with adequate blood count recovery will be censored according to the following events:

- Patients experiencing induction failure will be censored at maximum follow-up (i.e. date of FPFV to date of LPLV used for the analysis).
- Patients not experiencing induction failure and who did not die (any cause) will be censored at their last adequate response assessment date which is different from “unknown” or “not done”.

[redacted]

DFS is defined as the time from CR or CRi with adequate blood count recovery to relapse or death due to any cause. Patient who did not relapse nor die will be censored at the last adequate response assessment.

DFS will be estimated using the Kaplan-Meier method. The median DFS along with 95% confidence intervals will be presented by treatment group. The stratified Cox regression will be used to estimate the HR of DFS, along with 95% confidence interval.

Cumulative Incidence of Relapse (CIR) is defined for patients with CR or CRi with adequate blood count recovery and is time from achieving the CR or CRi with adequate blood count recovery until the onset of relapse from CR or CRi with adequate blood recovery. Patients without relapse are censored at the last adequate response assessment. Patients who died without relapse are counted as a competing cause of failure.

Cumulative Incidence of Relapse (CIR) will be estimated using the Kaplan-Meier method. The median CIR along with 95% confidence intervals will be presented by treatment group. The stratified Cox regression will be used to estimate the HR of CIR, along with 95% confidence interval.

Cumulative Incidence of Death (CID) is defined for all patients achieving CR or CRi with adequate blood count recovery measured from the date of achievement of CR or CRi until the date of death due to any reason. Patients not known to have died are censored on the last contact date. Patients who experienced relapse are counted as a competing cause of failure.

CID will be estimated using the Kaplan-Meier method. The median CID along with 95% confidence intervals will be presented by treatment group. The stratified Cox regression will be used to estimate the HR of CID, along with 95% confidence interval.

The rate of CR/CRi with adequate blood count recovery will be analyzed based on the FAS. However, DFS, Cumulative Incidence of Relapse (CIR) and Cumulative Incidence of Death (CID) will be analyzed based on data from responders (CR or CRi with adequate blood count recovery) in the FAS. Assessment of relapse from CR or CRi with adequate blood count recovery, DFS, CIR and CID will not consider whether a patient received HSCT.

10.5.2.2 MRD negative status

The percentage of patients with MRD negative bone marrow will be summarized along with exact 95% CI by treatment group and by treatment phase. Importantly, comparisons of the MRD levels between the end of the consolidation phase during the post-consolidation phase will be performed by treatment groups.

The time to MRD negative status is defined as the time from randomization to first occurrence of MRD negativity. Patients without reaching MRD negative status level will be censored according to the following events:

- Patients experiencing induction failure will be censored at maximum follow-up (i.e. date of FPFV to date of LPLV used for the analysis).
- Patients not experiencing induction failure and who did not die (any cause) will be censored at their last adequate MRD assessment.

[redacted]

Moreover, the kinetics of MRD levels will be displayed in terms of boxplot by over time for each treatment phase.

10.5.2.3 Time to neutrophil/platelet recovery

The time to neutrophil recovery will be assessed for the following criteria:

- Number of days from start of treatment to the first day neutrophils $\geq 0.5 \times 10^9$/L
- Number of days from start of treatment to the first day neutrophils $\geq 1.0 \times 10^9$/L.

Similarly, the time to platelet recovery will be assessed for the following criteria:

- Number of days from start of treatment to the first day platelets $\geq 50 \times 10^9$/L
- Number of days from start of treatment to the first day platelets $\geq 100 \times 10^9$/L.

Moreover, the time to adequate blood count recovery will be assessed as:

- Number of days from start of treatment to the first day platelets $\geq 50 \times 10^9$/L and the first day neutrophils $\geq 1.0 \times 10^9$/L.

In addition, data on transfusion will be summarized by treatment group.

The median time to platelet and to neutrophil recovery along with their corresponding 95% confidence intervals will be presented by treatment group.

10.5.3 Safety objectives

10.5.3.1 Analysis set and grouping for the analyses

For all safety analyses, the safety set will be used. All listings and tables will be presented by treatment group.

The overall observation period will be divided into three mutually exclusive segments:

1. Pre-treatment period: from day of patient's informed consent to the day before first dose of study treatment
2. On-treatment period: from day of first dose of study medication to 30 days after last dose of study medication
3. Post-treatment period: starting at day 31 after last dose of study medication.

The safety summary tables will include only assessments collected within 30 days after study treatment discontinuation and assessments prior to the data cut-off date for ongoing patients, unless otherwise specified.

All data, regardless of observation period, will be listed and assessments collected in the pretreatment and post-treatment period will be flagged in all the listings.

10.5.3.2 Adverse events (AEs)

Summary tables for AEs will include only AEs that started or worsened during the on-treatment period, the ***treatment-emergent*** AEs.

The incidence of treatment-emergent adverse events (new or worsening from baseline) will be summarized by system organ class and or preferred term, severity (based on CTCAE grades version 5.0), type of adverse event, relation to study treatment

[redacted]

Serious adverse events, non-serious adverse events during the on-treatment period will be tabulated.

All deaths (on-treatment and post-treatment) will be summarized.

All AEs, deaths and serious adverse events (including those from the pre and post-treatment periods) will be listed and those collected during the pre-treatment and post-treatment period will be flagged.

AESI will be analyzed. Such categories consist of one or more well-defined safety events which are similar in nature and for which there is a specific clinical interest in connection with the investigational treatment(s).

AESI will be defined at the project level and may be regularly updated based on emergent data. For each specified AESI, number and percentage of patients with at least one event part of the AESI will be reported.

10.5.3.3 Laboratory abnormalities

Grading of laboratory values will be assigned programmatically as per national cancer institute (NCI) CTCAE [version 5.0]. The calculation of CTCAE grades will be based on the observed laboratory values only, clinical assessments will not be taken into account.

CTCAE Grade 0 will be assigned for all non-missing values not graded as 1 or higher.

For laboratory tests where grades are not defined by CTCAE 5.0, results will be categorized as low/normal/high based on laboratory normal ranges.

The following by-treatment summaries will be generated separately for hematology, biochemistry and urinary laboratory tests

- Worst post-baseline CTCAE grade (regardless of the baseline status). Each patient will be counted only once for the worst grade observed post-baseline.
- Shift tables using CTCAE grades to compare baseline to the worst on-treatment value
- For laboratory tests where CTCAE grades are not defined, shift tables using the low/normal/high/(low and high) classification to compare baseline to the worst on-treatment value.
- Listing of all laboratory data with values flagged to show the corresponding CTCAE grades and the classifications relative to the laboratory normal ranges.

In addition to the above mentioned tables and listings, other exploratory analyses, for example figures plotting time course of raw or change in laboratory tests over time or box plots may be specified in the SAP

10.5.3.4 Other safety data

ECG values and Vital signs will be listed and summarized by treatment group.

ECG

- Listing of ECG evaluations for all patients with at least one abnormality.

[redacted]

Change from baseline (QTcF and Vital signs)

- Shift table baseline to worst on-treatment result.
- Table with descriptive statistics at baseline, one or several post-baseline time points and change from baseline to this/these post-baseline time points.

10.5.3.5 Supportive analyses for secondary objectives

Subgroup analyses will be provided for specific secondary variables based on age, gender, race, etc. will be performed as appropriate, more details will be provided in the SAP.

10.5.4 Pharmacokinetics

Plasma concentrations: Plasma concentrations will be summarized by treatment part and time point. Summary statistics will include n (number of values to be reported), arithmetic and geometric mean, median, SD, CV, and geometric CV, minimum and maximum. Concentrations below the LLOQ will be treated as zero in summary statistics except for geometric mean. Zero concentrations will not be included in the geometric mean calculation. For Tmax, the median and range will be provided.

Non-compartmental analysis (NCA): PK parameters for midostaurin and the active metabolites will be determined using non-compartmental method(s) using Phoenix WinNonlin (Version 6.4 or later- Certara L.P.) for the patients who had full PK sampling on Cycle 1 Day 8 of the induction therapy.

Concentration data from patients who underwent sparse sampling only will be analyzed where possible, and relevant NCA parameters determined.

PK parameters listed in Table 10-1 will be estimated and reported, when feasible (dependent on sampling scheme, and validity of samples).

AUC0-t and Cmax are defined as primary parameters (contributing to PAS-full definition).

All PK parameters will be determined when possible. In addition, and when feasible, analysis of data from all subjects (frequently and less frequently sampled) for PK parameters at steady state (Table 10-1) will be performed.

NCA PK parameters and all concentrations will be summarized and reported. Summary statistics will include n (number of values to be reported), arithmetic and geometric mean, median, SD, CV, geometric CV, minimum and maximum.

Population pharmacokinetic (PopPK) analysis: the PK samples of the PAS-all will be analyzed using a population PK approach. Comparisons of new data with predicted exposures from existing models will be provided through visual predictive checks (VPCs). Further details of the analysis as well as the results will be reported in a stand-alone analysis plan and report independent of this clinical study report. In addition, comparisons of individual predicted patient parameters with those observed will be conducted and reported in the CSR. Further details will be provided in the SAP.

Exposure-response analyses for relevant efficacy endpoints (including CR, CRi with adequate blood count recovery and EFS, plus investigation of further endpoints such as MRD) and safety endpoints (including QT and AEs) will be further discussed as appropriate in the SAP.

[redacted]

Table 10-1 Noncompartmental pharmacokinetic parameters

AUC0-t	The AUC from time zero to a measurable concentration sampling time (t) (mass x time x volume-1). Note: as the last sampling time is at 12 h, AUC0-12h will be determined after the first dose
AUClast	The AUC from time zero to the last measurable concentration sampling time after the first dose (tlast) (mass x time x volume^{-1})
Cmax	The maximum (peak) observed plasma, blood, serum, or other body fluid drug concentration after the first dose administration (mass x volume^{-1})
Cmin	Minimal observed pre-dose concentration (when feasible)
C3h	Concentration at 3 hours post-dose (when feasible)
Tmax	The time to reach maximum (peak) plasma, blood, serum, or other body fluid drug concentration after single dose administration (time)

[redacted]

10.5.5 Patient-reported outcomes

Responses to the FACT-Leu and EQ5D-5L, will be generated in accordance with the respective scoring manual.

A table of decomposition of patients will be created at each visit depicting the 'number of patients in the analyses', 'patients died', 'patients achieved CR/CRi', 'patient refused data due to poor health', 'patient refused (unrelated to health), 'study staff felt patient was too ill', 'patient missed appointment', 'other reasons').

Descriptive statistics (mean, standard deviation, median, minimum, and maximum) will be used to summarize the scored scales at each scheduled assessment time point for the FACT-Leu and EQ5D-5L (VAS) by treatment arm. Additionally, change from baseline in the scores at the time of each assessment will be summarized. Patients with an evaluable baseline score and at least one evaluable post baseline score during the treatment period will be included in the change from baseline analyses.

Mixed models for repeated measures (MMRM) will be used to estimate the treatment effect on the FACT-Leu scores over time. MMRM are commonly used to analyze longitudinal data from randomized trials under the missing-at-random (MAR) assumption. The MMRM will

[redacted]

include fixed-effect covariates for treatment, study visit (time), and interaction of treatment and time; other fixed covariates may include baseline score and randomization stratification factors. A subject-specific random effect will be included in the model. Change from baseline score will serve as the dependent variable. Least squares estimates and accompanying 95% CIs for change scores by study arm and visit will be presented. As a sensitivity analysis to the MMRM, pattern-mixture models will be used to examine the missing mechanism and explore the plausibility of the MAR assumption.

Analysis will be carried out for all patients as well as excluding those received HSCT.

[redacted]

[redacted]

[redacted]

10.7 Interim analyses

10.7.1 Event free survival (EFS)

The efficacy analyses will be based on FAS and are event driven. The final EFS analysis will be performed when there are approximately 285 EFS events. Two interim analyses will be performed when approximately 40% and 75% of 285 EFS events have occurred.

These analyses are expected to take place around 12 and 20 months respectively from the date of first patient randomized in the study assuming an increasing recruitment rate to reach 30 patients / month in month 6. The primary intent of the first interim analysis is to allow the study to stop early for lack of efficacy (futility). There is no intent to carry out an analysis to declare superior efficacy at the time of the first interim analysis. At least, 283 patients (56%) are expected to be randomized at the time of the interim futility analysis, i.e., when approximately 114 EFS events have occurred. The 2nd interim analysis will allow the study to stop early for outstanding efficacy. The 2nd interim analysis will only be carried out after all patients have been randomized.

A user-defined gamma spending function (γ = -1.2) will be used as a beta-spending function to determine the non-binding futility boundary at the time of the 1st interim analysis. The futility boundary at the first interim is calculated as hazard ratio of 0.97. The observed (i.e., nominal) p-value has to be greater than p=0.44 (one-sided) to conclude futility. Since the observed number of EFS events at the interim analyses may not exactly be equal to the

[redacted]

planned number of events, the futility boundary will need to be re-calculated (or updated) based on the actual number of observed events. Therefore, the observed p-value (or Z-test statistic) at the first interim analysis will be compared with the updated futility boundary.

A Haybittle-Peto stopping boundary will be used for efficacy interim and final EFS analyses (Peto et al 1976). At the second interim analysis, the observed p-value has to be less than p=0.0001 (i.e. HR<0.601) in order to conclude superior efficacy. If the study continues, the final analysis will be performed when approximately 285 EFS events have been documented or 5 years after the end of the study treatment for the last patient whichever occurs first. The final analysis criteria will be determined based on the actual number of events observed such that the overall significance level across all analyses is maintained at 0.025. It is estimated the the observed HR needs to be less than 0.80 to declare statistical significance at the final EFS analysis.

Table 10-2 represents the operational characteristics of this design. These are based on simulations in the software package East version 6.4. The following are a few key operational characteristics: The cumulative probability to detect an efficacious treatment by the primary analysis is 90%; while the cumulative probability of erroneously detecting a non-efficacious treatment by the final analysis is 2.4%. If the null hypothesis is true then cumulative probability to stop the trial at the first interim analysis for lack of efficacy is 55.8%.

[redacted]

Table 10-2 Simulated cumulative probabilities to stop for efficacy or futility by the 1st interim (IA1), the 2nd interim (IA2) or the final EFS (FA) analyses

Hazard ratio	Analysis	Average sample size	Average Time (months)	Simulated cum. prob. stop due to	
				Efficacy	Futility
0.675	IA 1	282	11.9	0.0149	0.025
	IA 2	502	20	0.1983	NA
	FA	502	38.8	0.900	NA
0.8375	IA1	264	11.3	0.0003	0.213
	IA2	502	20	0.009	NA
	FA	502	31	0.312	NA
1.0	IA1	249	10.8	0	0.558
	IA2	502	20	0.0001	NA
	FA	502	26.5	0.024	NA

* In the middle of H_0 and H_A; cum. prob.: cumulative probability

Note: Simulation is performed with software package [East version 6.4] with number of simulations = 10,000 and randomization seed =2301. The interim analyses for EFS will be performed by an independent statistician. Results from EFS interim analysis will not be communicated to clinical team or any party involved in the study conduct (apart from the independent statistician and DMC members) until EFS is found to be significant or study needs to be terminated due to safety or lack of efficacy.

10.7.2 Key secondary endpoint: Overall survival (OS)

OS will be compared between the two treatment groups, provided the primary endpoint EFS is statistically significant favoring the active treatment group. A hierarchical testing procedure will be adopted and the statistical tests for OS will be performed only if the primary efficacy endpoint EFS is statistically significant.

Three analyses are planned for OS; at the time of the interim and final EFS analyses (provided EFS is significant), at which point a total of approximately 79 and 190 deaths are expected (28% and 68% information fraction respectively) and a final OS analysis when approximately 278 deaths are expected (expected 64 months from date of first patient to be randomized).

A Haybittle-Peto boundary as implemented in East version 6.4 (Peto et al 1976) , independent of the Haybittle-Peto boundary used for EFS, along with the testing strategy outlined below will be used to maintain the overall type I error probability. This guarantees the protection of the (2.5%) overall level of significance across the two hypotheses and the repeated testing of the OS hypotheses in the interim and the final analysis (Glimm 2010).

The trial allows for the stopping of the study for a superior OS result, provided the primary endpoint EFS has already been shown to be statistically significant favouring the test

[redacted]

treatment group. Further, the exact nominal p-values that will need to be observed to declare statistical significance at the time of these analyses for OS will depend on the number of OS events that have been observed at the time of these analyses and the α for OS already spent at the time of earlier analyses. Given the hierarchical testing strategy of EFS and OS, the design concerning OS analyses will have the following characteristics based on simulations in software package [East 6.4]. The probabilities shown in Table 10-3 are conditional probabilities (conditional on EFS being statistically significant) not marginal probabilities.

Table 10-3 Simulated probabilities to stop for efficacy on overall survival at 2nd EFS interim (1st OS interim (IAOS1)), final EFS (2nd OS interim (IAOS2)) analysis or final OS analysis (FAOS)

Hazard ratio	Analysis	Average sample size	Average Time (months)	Simulated cum. prob. stop due to Efficacy
0.714	IAOS1	502	20	0.010
	IAOS2	502	38	0.074
	FAOS	502	64	0.799
0.857	IAOS1	502	20	0.0018
	IAOS2	502	35	0.0050
	FAOS	502	58	0.327
1.0	IAOS1	502	20	0
	IAOS2	502	34	0.0001
	FAOS	502	54	0.026

* Probabilities are reported as if OS was tested alone, regardless the testing strategy with EFS. The true probabilities should take into account the probability of EFS at each look.

Note: Simulation is performed with software package [East 6.4] with number of simulations = 10,000 and randomization seed =2301.

At the time of interim analysis for EFS, an interim analysis for the key secondary endpoint of OS will be performed by an independent statistician. Unblinded results from the interim analysis for EFS and corresponding interim analysis for OS will not be communicated to the Sponsor's clinical team or to any party involved in the study conduct (apart from the independent statistician and DMC members) until the DMC has determined that either (i) EFS analysis has crossed the pre-specified boundary for efficacy, or (ii) the study needs to be terminated due to any cause including futility or safety reasons. Further details will be described in the DMC Charter.

At the time of the primary analyses, both EFS and interim OS analysis will be performed by the Sponsor's clinical team. Investigators and patients will remain blinded to study treatment and all patients will continue to be followed for OS until the final analysis (or earlier if OS reaches statistical significance at any of the interim analyses).

[redacted]

10.8 Sample size calculation

The assumption of median EFS of 12.0 months for the control treatment arm for sample size calculations is based on available data for patients with FLT-MN (Bacher et al 2008). It is expected that treatment with test treatment arm will result in a 37.5% reduction in the hazard rate (corresponding to an increase in median EFS from 12.0 months to 17.8 months under the exponential model assumption).

If the true hazard ratio is 0.675, a total of 285 EFS events are required to have 90% power at an one-sided overall 2.5% level of significance to reject the null hypothesis (HR≥1) using a log-rank test and a 2-look group sequential design with Haybittle-Peto boundary to determine efficacy boundary and gamma spending function (γ = -1.2) to determine the non-binding futility boundary. Considering a recruitment period of approximately 20 months assuming an increasing recruitment rate to reach 30 patients / month in month 6, 502 patients will need to be randomized to the two treatment arms in a 1:1 ratio. Assuming about approximately 10% patients will be lost to follow-up for EFS, a total of 502 patients will need to be randomized. Given the above assumptions, it is estimated that the 285th EFS event will be observed at approximately 40 months from the date of first patient randomized in the study. The sample size calculation was conducted with software package [East 6.4].

10.9 Power for analysis of key secondary endpoint

OS will be compared between the two treatment groups, provided that the primary endpoint EFS is statistically significant. Based on available data (Gale et al 2008), the median OS in the control treatment arm is expected to be around 30 months. It is hypothesized that Midostaurin treatment arm will result in a 28.6% reduction in the hazard rate for overall survival (corresponding to an increase in median survival by 12 months (from 30 to 42 months) under the exponential model assumption). If the true hazard ratio is 0.714, a total of 278 deaths are needed to be observed to have 80% power at an one-sided overall 2.5% level of significance to reject the null hypotheses (HR≥1) using a log-rank test and a 3-look group sequential design conditionally to a significant improved EFS before or at the same time of analyses testing OS. Based on the same number of patients that are planned to be enrolled in this study to detect the primary endpoint, it is estimated that these 278 deaths will be observed at approximately 64 months from the date of first patient to be randomized. Therefore the estimated time for the final OS evaluation is expected to be approximately 24 months after the final EFS analysis have been conducted. The power calculation was conducted with software package [East 6.4].

11 Ethical considerations and administrative procedures

11.1 Regulatory and ethical compliance

This clinical study was designed, shall be implemented and reported in accordance with the international conference on harmonization (ICH) Harmonized Tripartite Guidelines for Good Clinical Practice (GCP), with applicable local regulations (including European Directive 2001/20/EC and US Code of Federal Regulations Title 21), and with the ethical principles laid down in the Declaration of Helsinki.

[redacted]

11.2 Responsibilities of the investigator and IRB/IEC/REB

The protocol and the proposed informed consent form must be reviewed and approved by a properly constituted Institutional Review Board/Independent Ethics Committee/Research Ethics Board (IRB/IEC/REB) before study start. Prior to study start, the investigator is required to sign a protocol signature page confirming his/her agreement to conduct the study in accordance with these documents and all of the instructions and procedures found in this protocol and to give access to all relevant data and records to Novartis (or CRO) monitors, auditors, Novartis Clinical Quality Assurance representatives, designated agents of Novartis, IRBs/IECs/REBs and regulatory authorities as required.

11.3 Informed consent procedures

Eligible patients may only be included in the study after providing written (witnessed, where required by law or regulation), IRB/IEC/REB-approved informed consent

Informed consent must be obtained before conducting any study-specific procedures (i.e. all of the procedures described in the protocol). The process of obtaining informed consent should be documented in the patient source documents. The date when a subject's Informed Consent was actually obtained will be captured in their CRFs.

Novartis will provide to investigators, in a separate document, a proposed informed consent form (ICF) that is considered appropriate for this study and complies with the ICH GCP guideline and regulatory requirements. Any changes to this ICF suggested by the investigator must be agreed to by Novartis before submission to the IRB/IEC/REB, and a copy of the approved version must be provided to the Novartis (or CRO) monitor after IRB/IEC/REB approval.

Women of child bearing potential should be informed that taking the study medication may involve unknown risks to the fetus if pregnancy were to occur during the study and agree that in order to participate in the study they must adhere to the contraception requirement for the duration of the study. Male patients treated with idarubicin, daunorubicin or cytarabine should receive appropriate advice on the risk of infertility and the option of sperm conservation. Midostaurin may impair both male and female fertility and this should be communicated to the patients. If there is any question that the patient will not reliably comply, they should not be entered in the study.

Additional consent form

Not applicable.

11.4 Discontinuation of the study

Novartis reserves the right to discontinue this study under the conditions specified in the clinical study agreement. Specific conditions for terminating the study are outlined in Section 4.4.

11.5 Publication of study protocol and results

Novartis is committed to following high ethical standards for reporting study results for its innovative medicine, including the timely communication and publication of clinical trial results, whatever their outcome. Novartis assures that the key design elements of this protocol will be posted on the publicly accessible database, e.g., www.clinicaltrials.gov before study start. In addition, results of interventional clinical trials in adult patients are posted on www.novartisclinicaltrials.com, a publicly accessible database of clinical study results within 1 year of study completion (i.e., last patient last visit (LPLV)), those for interventional clinical trials involving pediatric patients within 6 months of study completion.

Novartis follows the International Committee of Medical Journal Editors (ICMJE) authorship guidelines (www.icmje.org) and other specific guidelines of the journal or congress to which the publication will be submitted

Authors will not receive remuneration for their writing of a publication, either directly from Novartis or through the professional medical writing agency. Author(s) may be requested to present poster or oral presentation at scientific congress; however, there will be no honorarium provided for such presentations.

As part of its commitment to full transparency in publications, Novartis supports the full disclosure of all funding sources for the study and publications, as well as any actual and potential conflicts of interest of financial and non-financial nature by all authors, including medical writing/editorial support, if applicable.

For the Novartis Guidelines for the Publication of Results from Novartis-sponsored Research, please refer to www.novartis.com.

11.6 Study documentation, record keeping and retention of documents

Each participating site will maintain appropriate medical and research records for this trial, in compliance with Section 4.9 of the ICH E6 GCP, and regulatory and institutional requirements for the protection of confidentiality of subjects. As part of participating in a Novartis-sponsored study, each site will permit authorized representatives of the sponsor(s) and regulatory agencies to examine (and when required by applicable law, to copy) clinical records for the purposes of quality assurance reviews, audits and evaluation of the study safety and progress.

Source data are all information, original records of clinical findings, observations, or other activities in a clinical trial necessary for the reconstruction and evaluation of the trial. Examples of these original documents and data records include, but are not limited to, hospital records, clinical and office charts, laboratory notes, memoranda, subjects' diaries or evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, copies or transcriptions certified after verification as being accurate and complete, microfiches, photographic negatives, microfilm or magnetic media, x-rays, and subject files and records kept at the pharmacy, at the laboratories, and medico-technical departments involved in the clinical trial.

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Data collection is the responsibility of the clinical trial staff at the site under the supervision of the site Principal Investigator. The study CRF is the primary data collection instrument for the study. The investigator should ensure the accuracy, completeness, legibility, and timeliness of the data reported in the CRFs and all other required reports. Data reported on the CRF, that are derived from source documents, should be consistent with the source documents or the discrepancies should be explained. All data requested on the CRF must be recorded. Any missing data must be explained. For electronic CRFs an audit trail will be maintained by the system.

The investigator/institution should maintain the trial documents as specified in Essential Documents for the Conduct of a Clinical Trial (ICH E6 Section 8) and as required by applicable regulations and/or guidelines. The investigator/institution should take measures to prevent accidental or premature destruction of these documents.

Essential documents (written and electronic) should be retained for a period of not less than fifteen (15) years from the completion of the Clinical Trial unless Sponsor provides written permission to dispose of them or, requires their retention for an additional period of time because of applicable laws, regulations and/or guidelines.

11.7 Confidentiality of study documents and patient records

The investigator must ensure anonymity of the patients; patients must not be identified by names in any documents submitted to Novartis. Signed informed consent forms and patient enrollment log must be kept strictly confidential to enable patient identification at the site.

11.8 Audits and inspections

Source data/documents must be available to inspections by Novartis or designee or Health Authorities.

11.9 Financial disclosures

Financial disclosures should be provided by study personnel who are directly involved in the treatment or evaluation of patients at the site - prior to study start.

12 Protocol adherence

Investigators ascertain they will apply due diligence to avoid protocol deviations. Under no circumstances should the investigator contact Novartis or its agents, if any, monitoring the study to request approval of a protocol deviation, as no authorized deviations are permitted. If the investigator feels a protocol deviation would improve the conduct of the study this must be considered a protocol amendment, and unless such an amendment is agreed upon by Novartis and approved by the IRB/IEC/REB it cannot be implemented. All significant protocol deviations will be recorded and reported in the CSR.

12.1 Amendments to the protocol

Any change or addition to the protocol can only be made in a written protocol amendment that must be approved by Novartis, Health Authorities where required, and the IRB/IEC/REB.

Only amendments that are required for patient safety may be implemented prior to IRB/IEC/REB approval. Notwithstanding the need for approval of formal protocol amendments, the investigator is expected to take any immediate action required for the safety of any patient included in this study, even if this action represents a deviation from the protocol. In such cases, Novartis should be notified of this action and the IRB/IEC at the study site should be informed according to local regulations but not later than 10 working days.

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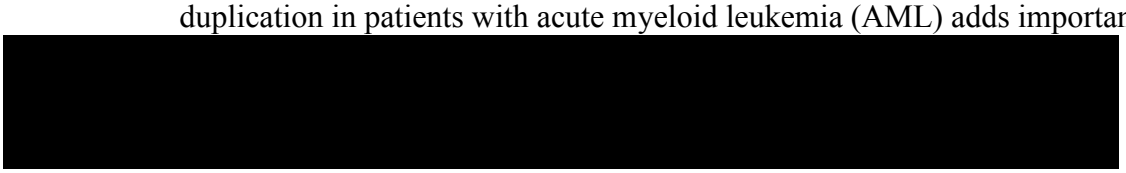

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14 Appendices

14.1 Appendix 1 – Concomitant medications

The following lists are not comprehensive and are only meant to be used as a guide. The lists are based on the Novartis PK Sciences' guidance, Drug-Drug Interaction and Co-Medication Considerations (v07, release date: Jan 2018), which was compiled from the Indiana University School of Medicine's P450 Drug Interaction Table (http://medicine.iupui.edu/clinpharm/ddis/main-table/) and supplemented with the FDA Draft Guidance for Industry, Drug Interaction Studies – Study Design, Data Analysis, and Implications for Dosing and Labeling (February 2012) (http://.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm292362.pdf), and the University of Washington's Drug Interaction Database (http://www.druginteractioninfo.org/).

For current lists of medications that may cause QT prolongation and/or torsades de pointes (TdP), refer to the CredibleMeds® website (www.qtdrugs.org/). Please contact the medical monitor with any questions.

14.1.1 List of prohibited medications

Strong inducers of CYP3A4	carbamazepine, enzalutamide, lumacaftor, phenobarbital, phenytoin, rifabutin, rifampicin (rifampin), mitotane, St. John's wort (Hypericum perforatum)[1]
Medications with a known risk for QT prolongation[2]	amidarone, anagrelide, arsenic trioxide, astemizole, azithromycin, chloroquine, chlorpromazine, cilostazol, cisapride, citalopram, clarithromycin, disopyramide, dofetilide, domperidone, donepezil, dronedarone, droperidol, erythromycin, escitalopram, flecainide, fluconazole, gatifloxacin, halofantrine, haloperidol, ibutilide, levofloxacin, levomepromazine, levosulpiride, methadone, moxifloxacin, ondansetron, oxaliplatin, papaverine HCl (intra-coronary), pentamidine, pimozide, procainamide, propofol, quinidine, roxithromycin, sevoflurane, sotalol, sulpiride, sultopride, terlipressin, terodiline, thioridazine, vandetanib

[1] Herbal product

[2] The list provided is as of January 2018.Check https www crediblemeds.org/healthcare-providers/drug-list for the most updated list.

14.1.2 Permitted medications to be used with caution

Strong inhibitors of CYP3A	ombitasvir/paritaprevir/dasabuvir/ritonavir (Viekira Pak)[1], indinavir/ritonavir[1], tipranavir/ritonavir[1], ritonavir, cobicistat, indinavir, ketoconazole, troleandomycin, telaprevir, danoprevir/ritonavir[1], elvitegravir/ritonavir[1], saquinavir/ritonavir[1], lopinavir/ritonavir[1], itraconazole, voriconazole, mibefradil, posaconazole, telithromycin, grapefruit juice[2], conivaptan, nefazodone, nelfinavir, idelalisib, boceprevir, atazanavir/ritonavir[1], darunavir/ritonavir[1]
Substrates with narrow therapeutic index (NTI)	
CYP1A2	theophylline, tizanidine (also sensitive)
CYP2B6	No substrate with narrow therapeutic index known.
CYP2C8	paclitaxel
CYP2C9	(S)-warfarin
CYP2C19	(S)-mephenytoin (also sensitive)

[redacted]

CYP2E1	No substrate with narrow therapeutic index known.
CYP3A	alfentanil, cyclosporine, dihydroergotamine, ergotamine, fentanyl, sirolimus, tacrolimus
Transporter substrates	
NTI substrates of P-gp[3]	cyclosporine, digoxin, fentanyl, paclitaxel, sirolimus, tacrolimus
BCRP substrates	atorvastatin daunorubicin, doxorubicin, hematoporphyrin, imatinib, methotrexate, mitoxantrone, pitavastatin, rosuvastatin, SN-38 (irinotecan), ethinyl estradiol, simvastatin, sulfasalazine, sofosbuvir, topotecan, sulfasalazine, tenofovir, topotecan.
OATP1B1 substrates (including OATP1B3, and OATP2B1 substrates)	aliskiren, ambrisentan, anacetrapib, atenolol, asunaprevir, atrasentan, atorvastatin, bosentan, bromociptine, caspofungin, cerivastatin, celiprolol, danoprevir, digoxin, docetaxel, eliglustat, epangliflozin, ezetimibe, fimasartan, fexofenadine, fluvastatin, glyburide, maraviroc, methotrexate, sn-38, rosuvastatin, saquinavir, simvastatin acid, paritaprevir, pitavastatin, pravastatin, repaglinide, rosuvastatin, simvastatin, valsartan, olmesartan, telmisartan, montelukast, ticlopidine, thyroxine

[1] Combination ritonavir-boosted regimens are listed here in the DDI memo as strong CYP3A inhibitors (to avoid potential confusion), even though some are considered moderate CYP3A inhibitors in the UW DDI Database.

[2] The effect of grapefruit juice varies widely among brands and is concentration-, dose-, and preparation-dependent. Studies have shown that it can be classified as a “strong CYP3A inhibitor” when a certain preparation was used (e.g., high dose, double strength) or as a “moderate CYP3A inhibitor” when another preparation was used (e.g., low dose, single strength).

[3] These drugs have both a narrow therapeutic index and an *in vivo* DDI outcome partly ascribed to P-gp inhibition or induction that exceeds 20% change in AUC.

[redacted]

14.2 Appendix 2 – FACT-Leu questionnaire

FACT-Leu (Version 4)

Below is a list of statements that other people with your illness have said are important**. Please select one number per line to indicate your response as it applies to the past 7 days.**

	PHYSICAL WELL-BEING	**Not at all**	**A little bit**	**Some-what**	**Quite a bit**	**Very much**
GP1	I have a lack of energy	0	1	2	3	4
GP2	I have nausea	0	1	2	3	4
GP3	Because of my physical condition, I have trouble meeting the needs of my family	0	1	2	3	4
GP4	I have pain	0	1	2	3	4
GP5	I am bothered by side effects of treatment	0	1	2	3	4
GP6	I feel ill	0	1	2	3	4
GP7	I am forced to spend time in bed	0	1	2	3	4

	SOCIAL/FAMILY WELL-BEING	**Not at all**	**A little bit**	**Some-what**	**Quite a bit**	**Very much**
GS1	I feel close to my friends	0	1	2	3	4
GS2	I get emotional support from my family	0	1	2	3	4
GS3	I get support from my friends	0	1	2	3	4
GS4	My family has accepted my illness	0	1	2	3	4
GS5	I am satisfied with family communication about my illness	0	1	2	3	4
GS6	I feel close to my partner (or the person who is my main support)	0	1	2	3	4
Q1	*Regardless of your current level of sexual activity, please answer the following question. If you prefer not to answer it, please mark this box* ☐ *and go to the next section.*					
GS7	I am satisfied with my sex life	0	1	2	3	4

[redacted]

Please select one number per line to indicate your response as it applies to the <u>past 7 days</u>.

	EMOTIONAL WELL-BEING	**Not at all**	**A little bit**	**Some-what**	**Quite a bit**	**Very much**
GE1	I feel sad	0	1	2	3	4
GE2	I am satisfied with how I am coping with my illness	0	1	2	3	4
GE3	I am losing hope in the fight against my illness	0	1	2	3	4
GE4	I feel nervous	0	1	2	3	4
GE5	I worry about dying	0	1	2	3	4
GE6	I worry that my condition will get worse	0	1	2	3	4

	FUNCTIONAL WELL-BEING	**Not at all**	**A little bit**	**Some-what**	**Quite a bit**	**Very much**
GF1	I am able to work (include work at home)	0	1	2	3	4
GF2	My work (include work at home) is fulfilling	0	1	2	3	4
GF3	I am able to enjoy life	0	1	2	3	4
GF4	I have accepted my illness	0	1	2	3	4
GF5	I am sleeping well	0	1	2	3	4
GF6	I am enjoying the things I usually do for fun	0	1	2	3	4
GF7	I am content with the quality of my life right now	0	1	2	3	4

[redacted]

Please select one number per line to indicate your response as it applies to the <u>past 7 days</u>.

	ADDITIONAL CONCERNS	**Not at all**	**A little bit**	**Some-what**	**Quite a bit**	**Very much**
BRM3	I am bothered by fevers (episodes of high body temperature)	0	1	2	3	4
P2	I have certain parts of my body where I experience pain	0	1	2	3	4
BRM2	I am bothered by the chills	0	1	2	3	4
ES3	I have night sweats	0	1	2	3	4
LEU1	I am bothered by lumps or swelling in certain parts of my body (e.g., neck, armpits, or groin)	0	1	2	3	4
TH1	I bleed easily	0	1	2	3	4
TH2	I bruise easily	0	1	2	3	4
HI12	I feel weak all over	0	1	2	3	4
BMT6	I get tired easily	0	1	2	3	4
C2	I am losing weight	0	1	2	3	4
C6	I have a good appetite	0	1	2	3	4
An7	I am able to do my usual activities	0	1	2	3	4
N3	I worry about getting infections	0	1	2	3	4
LEU5	I feel uncertain about my future health	0	1	2	3	4
LEU6	I worry that I might get new symptoms of my illness	0	1	2	3	4
BRM9	I have emotional ups and downs	0	1	2	3	4
LEU7	I feel isolated from others because of my illness or treatment	0	1	2	3	4

[redacted]

14.3 Appendix 3 – EQ-5D-5L questionnaire

Health Questionnaire

English version for the USA

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[redacted]

Under each heading, please check the ONE box that best describes your health TODAY

MOBILITY

I have no problems walking ❑
I have slight problems walking ❑
I have moderate problems walking ❑
I have severe problems walking ❑
I am unable to walk ❑

SELF-CARE

I have no problems washing or dressing myself ❑
I have slight problems washing or dressing myself ❑
I have moderate problems washing or dressing myself ❑
I have severe problems washing or dressing myself ❑
I am unable to wash or dress myself ❑

USUAL ACTIVITIES *(e.g. work, study, housework, family or leisure activities)*

I have no problems doing my usual activities ❑
I have slight problems doing my usual activities ❑
I have moderate problems doing my usual activities ❑
I have severe problems doing my usual activities ❑
I am unable to do my usual activities ❑

PAIN / DISCOMFORT

I have no pain or discomfort ❑
I have slight pain or discomfort ❑
I have moderate pain or discomfort ❑
I have severe pain or discomfort ❑
I have extreme pain or discomfort ❑

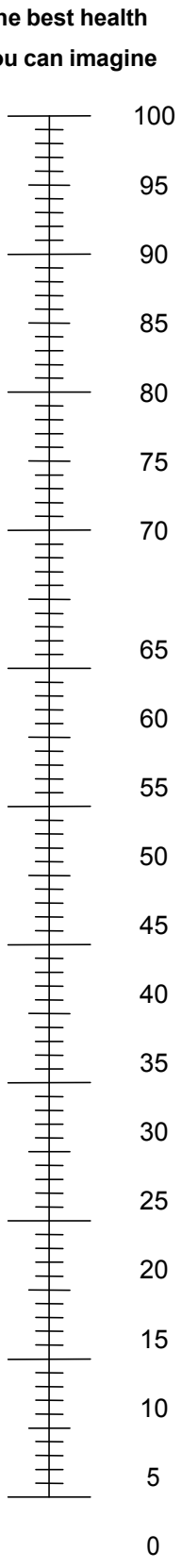
ANXIETY / DEPRESSION

I am not anxious or depressed ❑
I am slightly anxious or depressed ❑
I am moderately anxious or depressed ❑
I am severely anxious or depressed ❑
I am extremely anxious or depressed ❑

[redacted]

- We would like to know how good or bad your health is TODAY.
- This scale is numbered from 0 to 100.
- 100 means the best health you can imagine.
  0 means the worst health you can imagine.
- Mark an X on the scale to indicate how your health is TODAY.
- Now, please write the number you marked on the scale in the box below.

YOUR HEALTH TODAY = ☐



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