NOVARTIS

Oncology Clinical Development & Medical Affairs

PKC412, MIDOSTAURIN

Protocol CPKC412AUS23 / NCT01883362

A Phase II, randomized trial of standard of care, with or without midostaurin to prevent relapse following allogeneic hematopoietic stem cell transplantation in patients with FLT3-ITD mutated acute myeloid leukemia

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List of abbreviations

AE	Adverse event
ALT	Alanine aminotransferase/glutamic pyruvic transaminase/GPT
AML	Acute Myeloid Leukemia
ASM	Aggressive Systemic Mastocytosis
AST	Aspartate aminotransferase/glutamic oxaloacetic transaminase/GOT
BR	Blast reduction
b.i.d.	*bis in die* / twice a day
BM	Bone Marrow
CBC	Complete Blood Count
CRF	Case Report/Record Form
CR	Complete Remission/Response
CRO	Contract Research Organization
CSR	Clinical Study Report
CTCAE	Common Terminology Criteria for Adverse Events v4.0
CYP3A4	Cytochrome P 450 3A4
DLT	Dose Limiting Toxicity
DNA	Deoxyribonucleic acid
DSE&E	Drug Safety and Epidemiology
DFS	Disease Free Survival
eCRF	Electronic Case Report/Record Form
ECG	Electrocardiogram
FLT3-ITD	fms-like tyrosine kinase 3, internal tandem duplication
FAS	Full Analysis Set
GVHD	Graft versus host disease
HSCT	Hematopoietic Stem Cell Transplant
HR	Hazard Ratio
ICH	International Conference on Harmonization
IEC	Independent Ethics Committee
IRB	Institutional Review Board
IWRS	Interactive Web Response System
kg	Kilograms
KM	Kaplan-Meier
MA	Medical Affairs
MCL	Mast cell leukemia
MDS	Myelodysplastic syndrome
mg	Milligrams
[redacted]	[redacted]
MTD	Maximum Tolerated Dose
MUGA	Multi Gated Acquisition scan
NRM	Non-relapse mortality
OS	*Overall Survival*

[redacted]

p.o.	*per os*/by mouth/orally
PPS	*Per Protocol Set*
PD	Pharmacodynamics
PFS	Progression Free Survival
PHI	Protected Health Information
Pgp	P-glycoprotein
PK	Pharmacokinetics
PR	Partial Response
REB	Research Ethics Board
RFS	Relapse Free Survival
SS	Safety Set
SAE	Serious adverse event
SOP	Standard Operating Procedure
SOC	Standard of Care
TD-PCR	Tandem Duplication Polymerase Chain Reaction
t.i.d.	Three times per day
TKD	Tyrosine Kinase Domain
TRM	Treatment Related Mortality
ULN	Upper limit of normal
WT	Wild-type

Glossary of terms

Assessment	A procedure used to generate data required by the study
Cohort	A group of newly enrolled patients treated at a specific dose and regimen (i.e. treatment group) at the same time
Cycles	Number and timing or recommended repetitions of therapy are usually expressed as number of days, for this study cycles are 28 days in length
Complete Remission	Patients are considered to be in Complete Remission (CR) when the following levels are detected in the Peripheral Blood (PB); ANC ≥ 1000/uL; Platelet count ≥ 100K and no circulating leukemic myeloblasts in peripheral blood and Bone Marrow (BM) has adequate cellularity, BM blast count ≤ 5% and no auer rods detected
Dose level	The dose of drug given to the patient (total daily or weekly etc.)
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)
Investigational drug	The study drug, midostaurin in this case, 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. 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
Other study treatment	Any drug administered to the patient as part of the required study procedures that was not included in the investigational treatment
Patient Number	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, baseline, titration, washout, etc.
Premature patient withdrawal	Point/time when the patient exits from the study prior to the planned completion of all study treatment administration and/or assessments; at this time all study treatment administration is discontinued and no further assessments are planned, unless the patient will be followed for progression and/or survival
Randomization number	A unique treatment identification code assigned to each randomized patient, corresponding to a specific treatment arm assignment
Relapse	Recurrence of disease (≥ 5% blasts in peripheral blood or bone marrow) applies to patient transplanted after achieving a complete remission and for whom relapse of disease can be recorded.
Study treatment	Includes any drug or combination of drugs in any study arm administered to the patient (subject) as part of the required study procedures, including placebo and active drug run-ins. In specific examples, it is important to judge investigational treatment component relationship relative to a study treatment combination; study treatment in this case refers to the investigational and non-investigational treatments in combination.

[redacted]

Study treatment discontinuation	Point/time when patient permanently stops taking study treatment for any reason; may or may not also be the point/time of premature patient withdrawal
Variable	Identifier used in the data analysis; derived directly or indirectly from data collected using specified assessments at specified timepoints

Amendment 2

Amendment rationale

This study is actively enrolling in 23 centers with 35/60 patients enrolled to date. Based on feedback from various investigators the decision was made to change the inclusion criteria. The changes proposed in this amendment will primarily influence the eligibility criteria for this study changing the eligibility from age 18-60 to age 18-70 years. There were additional changes to dose interruption, visit schedule, [redacted] IRC and drug destruction.

Changes to the protocol

Administrative and Formatting changes are present throughout the document.

Throughout the document the D30-100 time points were amended to specify that D30-100 is from time of HSCT, "Day 30-100 Post HSCT"

Section 5.2: Inclusion Criteria:

Change to inclusion criteria 1: Age changed from between 18 and 60 to "between 18 and 70 years of age"

Section 5.3: Exclusion Criteria:

Updated language in exclusion criteria 10: "Patient requires treatment with (a) strong CYP3A4 inhibitors other than those required for GVH or infection prophylaxis or treatment or (b) moderate or strong CYP3A4 inducer regardless of prophylaxis or treatment."

Section 6.2: Update Criteria for interruption and re-initiation of Midostaurin treatment

Updated Nausea and Vomiting language from:

Grade 2	If this develops despite use of standard anti-emetic therapy, hold midostaurin for 3 days (6 doses) and resume midostaurin as tolerated;
Grade 3 or 4	If this develops despite use of prophylactic anti-emetic therapy, hold midostaurin until recovery to Grade 2 (or at least 3 days) then restart. If this is felt to be related to study drug and the re-challange results in a subsequent Grade 3 or 4 toxicity then the patient should be discontinued from treatment.

Updated Nausea and Vomiting language to:

Grade 2	If this develops despite use of prophylactic anti-emetic therapy, hold midostaurin for 3 days (6 doses) and resume midostaurin as tolerated
Grade 3 or 4	If this develops despite use of prophylactic anti-emetic therapy, hold midostaurin until recovery to Grade 2 (or at least 3 days) then restart. If this is felt to be related to study drug and the re-challange results in a subsequent Grade 3 or 4 toxicity then the midostaurin dose may be reduced (e.g from 50mg b.i.d to 25mg b.i.d). In the event of additional toxicity requiring dose modification refer to "Grade 3 or 4 - Other adverse events (Non-Hematologic) below.

Section 6.3.1: Added language referencing "the dose modification table"

[redacted]

Section 6.4.2.2: Concomitant anti-infective prophylaxis and treatment:

Corrected the language to allow use of the suggested prophylaxis and spelling errors. Gramatical changes applied.

Section 6.6.4: Disposal and destruction:

Updated language to, "The study drug supply should be destroyed at the designated Novartis facility or third party, as appropriate. On site disposal or destruction is permitted upon Novartis review and agreement with the local policy/SOP."

Table 7-1: Visit evaluation schedule

Updated language to allow CT scan, Chest x-ray/CT Scan

Removed, [redacted]

Section 7.2.2.6: Radiological examinations

Updated language to allow CT scan: "A screening chest image; Chest x-ray (CXR) or CT scan must be performed to assess study eligibility. If a CXR or CT scan was done within 14 days of screening assessments then it does not need to be repeated."

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

Added: "Cycle 3, 6 and at the EOT visit"

Table 7-7: ECG collection plan

Removed, "placebo"

Table 7-8: Routine pharmacokinetic blood collection log

Removed, "Unscheduled"

[redacted]

Section 8.8: Independent Review committee

Updated language to allow for additional patients at the discretion of the IRC

Section 9.4: Database management and quality control

Removed language, "by joint written agreement between US Oncology Medical Affairs Franchise [redacted] and the US Oncology Medical Affairs Franchise [redacted]."

Amendment 1

Amendment rationale

This trial is in study start-up with 14 sites opened and 3 patients have been randomized into the study. During the study start-up phase, feedback has been received from various investigators and EC/IRBs on areas where clarifications/Amendments could be made to the protocol - these have been incorporated in the current amendment.

The changes proposed in this amendment will influence the eligibility criteria, drug supply and storage, data monitoring and capturing, addition of assumption for study size calculation and change of study steering committee to independent review committee.

Changes to the protocol

Administrative and Formatting changes are present throughout the document.

Glossary of Terms:

Update definition of relapse to include 5% blasts in peripheral blood or bone marrow

Section 2.2, 2.4 and 4.1:

Deleted “Comparative” or “Comparator” language throughout the document. This trial is not a comparative trial.

Section 2.3 and 4.1:

Replaced “Study Steering Committee” with “Independent Review Committee”

Section 3: Objective and End Points

Table 3-1:

[redacted]

Section 5.1: Patient Population

Addition of “Enrollment criteria will be evaluated at both Visit 1 (screening) and Visit 2 (C1D1), prior to randomization.”

Section 5.2: Inclusion Criteria:

Addition to inclusion criteria 4: “Peripheral blood”

Addition to inclusion criteria 7:

“Patients must have received a myeloablative conditioning regimen prior to HSCT. The following regimens are considered to be myeloablative. Alternative myeloablative regimens must be approved by Novartis prior to enrollment.”

[redacted]

"Busulfan dosing based on individual PK parameters is allowed as long as myeloablative dosing is used (e.g., target AUC at least 4000 μM x min for 4 days).

Section 5.3: Exclusion Criteria

Addition to Exclusion criteria 3:

"haploidentical or cord blood"

Addition to Exclusion criteria 4:

"uncontrolled diabetes and chronic active pancreatitis"

Deletion from Exclusion criteria 6 and added as separate criteria:

"Patients with any pulmonary infiltrate including those suspected to be of infectious origin (unless resolves to ≤ Grade 1 within screening timeframe)"

Addition to Exclusion criteria 8:

"(For GVHD prophylaxis refer to Section 6.4.1.2)"

Addition to Exclusion criteria 9:

"GVHD related biopsy"

Updated Exclusion criteria 15:

Changed 3 to "5" months for male contraception.

Section 6.3.1: Dose modification and dose delay

Updated this language ". It is anticipated that dose interruption will be common during the early post-transplant period and the intent is to allow time to assess whether events are due to midostaurin, GVHD or other causes and to allow patients to remain on study."

Addition to Table 6-2:

Pulmonary Infiltrates	
Grade 3 or 4	Pulmonary infiltrate interruption of midostaurin for the remainder of the cycle until the infiltrate resolves to ≤ grade.

Deletion from other adverse events (Non-Hematologic): "if the toxicities occurred in the first 2 months of treatment. Patients who tolerate this resumption of 50 mg b.i.d dose may remain on this dose."

Addition to table notes: "Investigator discrection to continue study drug (midostaurin) may be used for the following if it is felt that the AE is not study drug related:

Cytopenias, AST/ALT elevation, Nausea or Vomiting. All of other AEs require dose modification per Table 6-2."

Section 6.4: Concomitant medications

Addition of "Sorafenib" to prohibited drugs

Section 6.4.2.1:

Title updated to **"Concomitant medications with potential for CYP3A4 interactions"**

[redacted]

Deleted this language "Midostaurin is primarily metabolized by CYP3A4 enzymes. Drugs which are substrates of CYP3A4 only (not inhibitors nor inducers) are not likely to interact with midostaurin. The recommendation is to avoid the co-administration of a **strong CYP3A4 inhibitor** or a **strong or moderate CYP3A4 inducer** with midostaurin."

Section 6.4.2.1.1 and 6.4.2.1.3: Updated with study codes

Section 6.4.2.1.2:

Deleted "strong" from title

Addition of "Moderate CYP3A4 inhibitors: Caution should be exercised for patients receiving moderate CYP450 3A4 inhibitors. A list of moderate CYP450 3A4 can be found on:

http://medicine.iupui.edu/clinpharm/ddis/main-table/"

Section 6.4.2.1.4:

Deleted this information from other section and updated here

Section 6.6.1: Study drug packaging and labelling:

Addition of "The drug should be stored in the blister pack until use and no further preparation of the study drug is needed."

Deleted due to duplication of information already captured in subcategories Section 6.6

"Midostaurin will be provided as soft gelatin capsules to be taken orally. No further preparation of the study drug is needed. Two capsules of midostaurin 25 mg should be taken orally twice a day and a sufficient amount of study drug has to be dispensed to the patient at each visit.

Important: The storage conditions for study drug have to be maintained as described on the medication label."

Section 6.6.2: Drug supply and storage

Addition to storage "Do not store above 25° C"

Section 6.6.4: Disposal and destruction

Addition to disposal language "Patients must return any remaining capsules should to the clinical site for proper disposal. Contact of the product with the skin should be avoided."

Section 7.1: Study flow and visit schedule

Changes in Table 7-1

Screening labs must be drawn within 14 days before randomization instead of 21 days before randomization.

Addition of physical exam to be performed in cycle1 Day 3 visit.

[redacted]

Deletion of optional gene expression sample to be taken at Day 30 -100, C6D1 and C12D1

Updated language to "Study Drug dispensation and review"

[redacted]

Addition of "archived stored frozen mononuclear cells/DNA" from Historical samples.

Section 7.1.1: Screening

Updated Gene Expression language to [redacted]

Patients are only required to complete failed assessments as long as the patient is re-screened within 14 days of the initial screening and have met eligibility by Day 60

Section 7.1.1.2: Information to be collected on screening failures

Updated language to ". All data for screen failures are entered into the IWRS system, including the reason for not being started on treatment"

Addition of "All screen failure data from the IWRS will be exported to a SAS dataset for final data review and archiving."

Section 7.1.3.2: Study Evaluation Completion (SEC)

Updated language from Disease progression to "Relapse"

Table 7-4: Bone marrow collection plan

Updated language from Historical to "Results from initial diagnosis required for eligibility"

Section 7.2.2.5: Laboratory evaluations

Updated screening laboratory test should be drawn with 14 days of study entry instead of 7 days

Table 7-6: Local clinical laboratory parameters collection plan

Serum "Lipase and Amylase" to be included in labs (chemistry) to be drawn at regular visits

Addition of "All efforts should be made to collect the labs prior to dosing. Fasting is not required for them."

Section 7.2.2.5.1: Pregnancy and assessments of fertility

Updated child bearing potential language here are per exclusion criteria no. 14

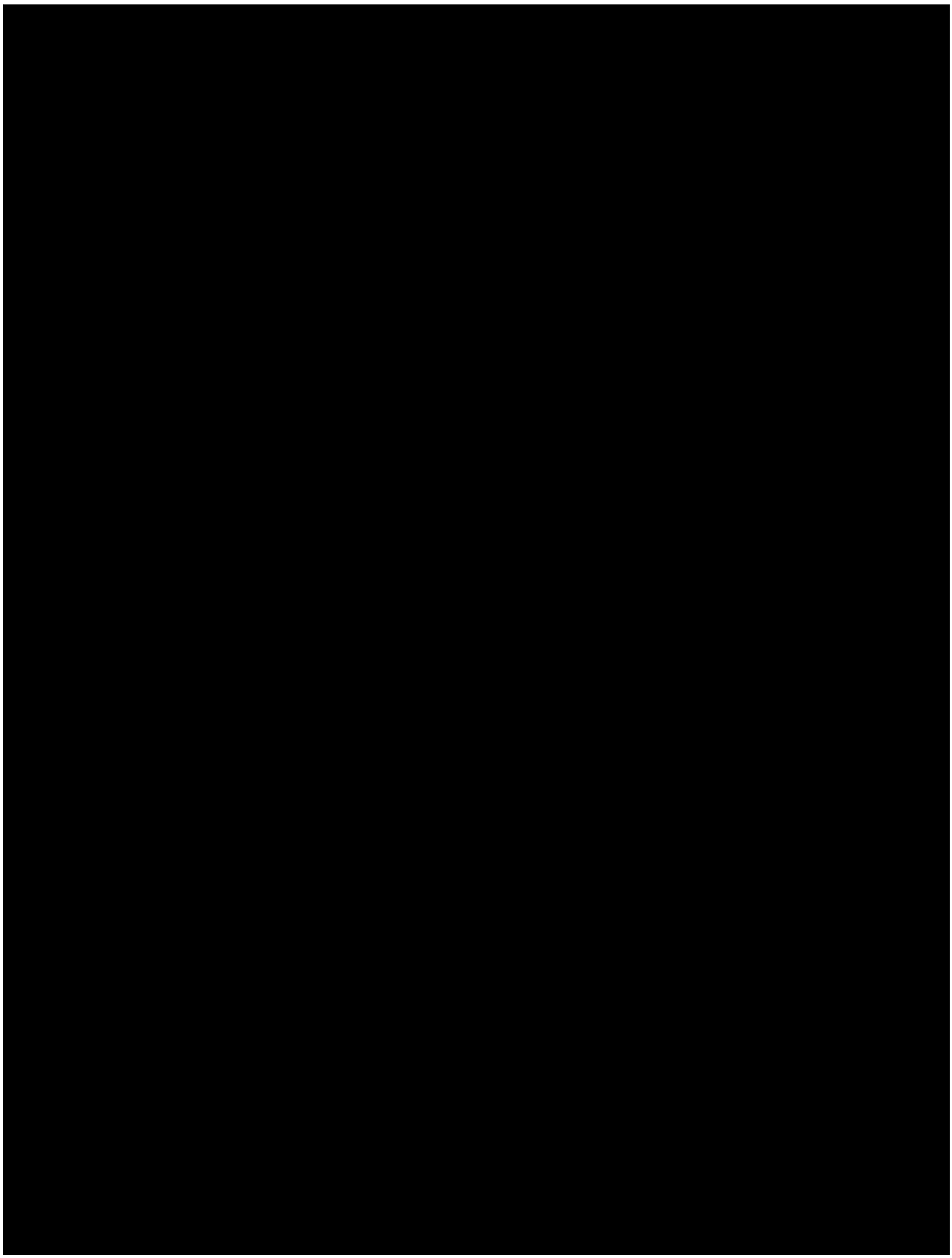
Section 7.2.2.6: Radiological examinations

Addition of "If a CXR was done within 14 days of screening assessments then it does not need to be repeated"

Section 7.2.4.1: Central determination of FLT3 ITD status

Deletion of "Both results will be used in the analysis. If the results are discordant, the results will be summarized" and updated in Section 10.5.4

[redacted]



[redacted]

Section 8.4: Pregnancy prevention requirements

Addition of this new title here and added a link for these requirements

Section 8.8: Independent Review committee

Updated independent review committee members selection criteria to those transplant expert physicians who are not participating in the trial

Section 10.5.4: Biomarkers

Addition of "The FLT3 results from the centralized assay using archived material will be compared to the local result, and differences will be described

In addition, the clinical outcome of RFS and DFS based on the FLT3 ITD result from the centralized assay compared to the local FLT3 ITD status will also be described."

[redacted]

Section 10.8: Sample size calculation

Addition of sample size calculation assumption

"The sample size for the trial was chosen 30 patients per treatment arm to get separate estimates of the primary endpoint relapse free survival"

"If the two arms were compared, the following gives the power that could be achieved under 2 scenarios of relapse rate with 30 patients per treatment arm.

Scenario 1: Assuming a 30% relapse rate in the SOC arm

Scenario 2: Assuming a 50% reduction with midostaurin (experimental arm)

i.e., 15% relapse rate in the experimental arm, a sample size of 30 patients in each arm will detect the reduction with 71% power. This calculation is based on one-sided type I error rate of 20%. The power would be 81% if we assume relapse rate to be even lower at 12% keeping everything else the same."

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.

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. In addition, if 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 amended protocol.

[redacted]

Protocol summary:

Protocol number	CPKC412AUS23
Title	A Phase II, randomized trial of standard of care, with or without midostaurin to prevent relapse following allogeneic hematopoietic stem cell transplantation in patients with FLT3-ITD mutated Acute Myeloid Leukemia
Brief title	Study to prevent relapse in FLT3-ITD mutated AML patients treated with standard of care (SOC) with or without midostaurin (PKC412) post allogeneic hematopoietic stem cell transplant.
Sponsor and Clinical Phase	Novartis
Investigation type	Drug
Study type	Interventional
Purpose and rationale	To determine if the addition of midostaurin (PKC412) to Standard of Care (SOC) therapy reduces relapse in FLT3-ITD mutated AML patients receiving allogeneic hematopoietic stem cell transplantation.
Primary Objective(s)	To determine if the addition of midostaurin to standard of care (SOC) therapy reduces relapse after at least 18 months of follow-up following allogeneic HSCT in FLT3-ITD mutant AML patients in first complete remission (CR1)
Secondary Objectives	• To evaluate disease free survival (DFS) • To evaluate relapse free survival (RFS) all along the study • To evaluate non-relapse mortality (NRM) • To evaluate overall survival (OS) • To evaluate safety and tolerability of midostaurin in patients FLT3-ITD AML in the post-transplant setting • To evaluate pharmacokinetics (PK) of midostaurin • To assess FLT3-ITD mutation status centrally in archived material from diagnosis (if available) including the mutant:wild type ratio
[redacted]	
Study design	This is a randomized, open label Phase II study to investigate the efficacy and safety of 50mg twice daily midostaurin in patients with FLT3 ITD mutated AML after HSCT.
Population	60 patients, randomized to Standard of Care +/- Midostaurin; (30 patients per treatment arm) Male and Female patients, aged 18 to ≤ 70 years old, FLT3-ITD mutated AML patients receiving allogeneic hematopoietic stem cell transplantation

[redacted]

Inclusion criteria	• Patients must be between 18 and 70 years of age • Patients must have an ECOG Performance Status of ≤ 2 • Patients must have a documented Unequivocal diagnosis of AML according to WHO 2008 classification (>20% blasts in the bone marrow and/or peripheral blood), excluding M3 (acute promyelocytic leukemia). • Patients must have a documented FLT3 ITD mutation, determined by local laboratory for eligibility (historical tissue will be requested for central analysis confirmation) • Patients who have undergone allogeneic HSCT in CR1 from a matched related or matched unrelated donor. All of the following criteria must also be met: HLA typing to include available 8/8 or 7/8 allele HLA matched donor (at A,B,C, DRB1) Single allelic mismatch allowed • Patients who received one of the following conditioning regimens Alternative regimens must be approved by Novartis prior to enrollment: **Busulfan*/Fludarabine (Bu/Flu)** Busulfan (16 mg/kg PO or 12.8 mg/kg IV) Fludarabine (120-180 mg/m2) **Fludarabine / Melphalan (Flu/Mel)** Fludarabine (120-180 mg/m2) Melphalan (≤ 150 mg/m2) **Busulfan*/Cyclophosphamide (Bu/Cy)** Busulfan (16 mg/kg PO or 12.8 mg/kg IV) Cyclophosphamide (120 mg/kg) **Cyclophosphamide/Total Body Irradiation (Cy/TBI)** Cyclophosphamide (120 mg/kg) TBI (1200-1420 cGy) * Note: Busulfan dosing based on individual PK parameters is allowed as long as myeloablative dosing is used (e.g., target AUC at least 4000μM x min for 4 days) • Recovery of counts by day 42 and able to start midostaurin by day 60 post-HSCT (first dose of midostaurin to start no earlier than 28 days post-HSCT); ANC >1000μL, platelets ≥20,000 without platelet transfusion • Patients must have the following laboratory values: AST and ALT ≤ 3 x Upper Limit of Normal (ULN) Serum Bilirubin ≤ 3 x ULN Serum Creatinine ≤ 2.5 x ULN
Exclusion criteria	• Patients whom have failed prior attempts at allogeneic HSCT • Patients who have received an autologous transplant, haploidentical or cord blood. • Patients with Acute GVHD Grade III-IV • Patients with any other known concurrent severe/and or uncontrolled medical condition (expect carcinoma in-situ), which could compromise participation in the study (e.g. uncontrolled infection, uncontrolled diabetes, chronic active pancreatitis) • Patients with a known confirmed diagnosis of HIV infection or active viral hepatitis.

[redacted]

	• Impaired cardiac function including any of the following: -Screening ECG with a QTc > 450 msec. If QTc > 450 and electrolytes are not within normal ranges, electrolytes should be corrected and then the patient rescreened for QTc. -Patients with congenital long QT syndrome -History or presence of sustained ventricular tachycardia -Any history of ventricular fibrillation or torsades de pointes -Bradycardia defined as HR. < 50 bpm -Right bundle branch block + left anterior hemiblock (bifascicular block) -Patients with myocardial infarction or unstable angina < 6 months prior to starting study -Congestive Heart Failure NY Heart Association class III or IV -Patients with an ejection fraction < 45% assessed by MUGA or ---ECHO within 21 days prior to starting study cycle 1 (of midostaurin or control group) • Patients with any pulmonary infiltrate including those suspected to be of infectious origin (unless resolves to ≤ Grade 1 within screening timeframe) • Antineoplastic chemotherapy or radiotherapy, within 21 days prior to study cycle 1. • Patients who have had any surgical procedure, excluding central venous catheter placement or other minor procedures (e.g. skin biopsy) within 14 days prior to study cycle 1. • Patient requires treatment with strong CYP3A4 inhibitors or moderate or strong CYP3A4 inducers other than those required for GVH or infection prophylaxis or treatment • Known sensitivity to study drug(s) or class of study drug(s) • Participation in a prior investigational study within 30 days prior to enrollment or within 5-half lives of the investigational product, whichever is longer • Pregnant or nursing (lactating) women, or women of child-bearing potential, must use highly effective methods of contraception during dosing and for 30 days after treatment period • Sexually active males unless they use a condom during intercourse while taking drug and for 5 months after stopping midostaurin medication. They should not father a child in this period. A condom is required to be used also by vasectomized men in order to prevent delivery of the drug via seminal fluid. • Not able to understand and to comply with study instructions and requirements
Investigational and reference therapy	Midostaurin (PKC412)
Efficacy assessments	• Relapse Free Survival (RFS), • Disease Free Survival (DFS), • Overall Survival (OS)

[redacted]

Safety assessments	• Adverse Events (AEs) • Physical examination • Vital Signs and weight • Performance status • Laboratory evaluations • ECGs • Non-Relapse Mortality (NRM)
Other assessments	• Pharmacokinetics (PK) of midostaurin • FLT3-ITD mutation status in archived material from diagnosis • [redacted] • [redacted] • [redacted]
Data analysis	The primary efficacy criterion is the relapse free survival (RFS). The primary objective is related to the Kaplan-Meier estimate at 18 months. Efficacy variables will be analyzed using Kaplan-Meier and Cox methods. For more details refer to Section 10.4.2. Safety endpoints will be assessed using descriptive statistics.
Key words	acute myeloid leukemia, FLT3-ITD; midostaurin; PKC412; allogeneic stem cell transplant; hematopoietic stem cell transplantation (HSCT)

[redacted]

1 Background

1.1 Overview of acute myeloid leukemia, epidemiology and current treatment

Acute myeloid leukemia (AML) is a malignant disorder of immature hematopoietic cells. It is characterized by differentiation arrest and malignant proliferation of clonal myeloid precursors of the bone marrow. AML represents about 30% of the forms of adult leukemia and the incidence is estimated at 13,000 new cases per year in the U.S. and incidence increases with age. The American Cancer Society also estimates the number of deaths due to AML as 9,000 per year. (American Cancer Society 2011)

The diagnostic workup of acute leukemia is multifaceted and may include bone marrow biopsy, flow cytometry, cytogenetics, and gene mutation analysis. The 2008 WHO classification categorizes myeloid leukemia into numerous subtypes and prognostic groups. The presence of abnormal cytogenetics, or the presence of leukemia-associated gene mutations (FLT3, NPM1, CEPBA) are important prognostic indicators. (Estey 2010) Treatment approaches in AML vary for patients with APL (M3) but have remained relatively unchanged for the past three decades for all other types of AML.

Combination chemotherapy regimens commonly used in treatment of non-APL AML have typically included induction with an anthracycline and nucleoside analog. Complete remission (CR) rates of 65-90% in younger AML patients can be observed with daunorubicin or idarubicin given in conjunction with cytarabine for one to two cycles. (Ravandi 2007) Recently, higher doses of daunorubicin have shown better results in younger AML patients although this benefit did not extend to the FLT3 ITD patients (Fernandez 2009). Consolidation therapy typically involves high dose cytarabine and duration is debated although typically includes three to four cycles of post-remission therapy. (Estey 2010) Despite the high CR rate, the majority of adults with AML will relapse within 3 years with only 40-45% of younger patients achieving cure. (Burnett 2011) There are subsets of AML patients with very poor outcomes, including intermediate or poor risk by cytogenetics or molecular analysis. In such cases, approaches including stem cell transplantation (HSCT) are recommended in CR1. (NCCN Guidelines v1.2012, Estey 2010)

1.1.1 FMS-like tyrosine kinase 3 mutations

The FMS-like tyrosine kinase 3 (FLT3) belongs to the group of class III receptor tyrosine kinases. It belongs to a family of important signaling receptors that include c-KIT, c-FMS, and PDGFR. FLT3 is a growth factor receptor involved in hematopoietic cell growth and differentiation. FLT3 receptor and its ligand (FL) also play an important role in survival and self-renewal of early hematopoietic progenitors, monocytic precursors and in lymphoid development. Activation of FLT3 results in receptor auto-phosphorylation leading to downstream signaling of the RAS/MAPK, JAK/STAT5, and PI3K/AKT pathways. In normal bone marrow (BM), FLT3 is expressed on progenitor cells and regulates stem cell proliferation. As hematopoietic progenitor cells differentiate and mature, FLT3 expression is normally lost.

[redacted]

In AML, signaling of FLT3 pathway is often activated and leads to malignant blast cell proliferation, in part due to over expression of FLT3 receptor in leukemia cells. However, a major research advance was the identification of mutations occurring in the FLT3 gene in AML patients. It is the most common somatic mutation identified in AML, with an incidence of about 25% (Kindler 2010, Kottaridis 2001). Two major types of FLT3 gene mutation have been identified: 1) internal tandem duplication (ITD) and 2) tyrosine kinase domain (TKD) point mutations (PM) and ITDs make up a majority of FLT3 mutations in newly diagnosed patients (Thiede 2002). These duplications are the result of 3 to > 400 base pairs inserted into the receptor in-frame (Schnittger 2002). The ITDs promote ligand-independent FLT3 receptor dimerization and signal activation, culminating in cellular proliferation (Kiyoi 1998, Hayakawa 2000).

The presence of FLT3-ITDs has been found in certain studies to be the strongest predictor of patient outcome (Kottaridis 2001, Kiyoi 1999). AML patients harboring FLT3 ITD mutations are characterized by certain pretreatment features like higher levels of white blood cell counts and blood and bone marrow blasts (Frohling 2002, Thiede 2002). FLT3 ITD has been reported consistently as an unfavorable prognostic marker for relapse-free (RFS) and overall survival (OS) (Kottaridis 2001, Frohling 2002, Thiede 2002, Gale 2008). In a study of 854 AML patients, an ITD was present in 27% of the patients. Although presence of FLT3 mutation did not impact CR rate, long term clinical outcomes varied based on the presence of FLT3 ITD. The relapse rate at 5 years was 64% in patients with the mutation versus 44% in those without. Disease free survival at 5 years was 30% compared to 46% in patients without a mutation and overall survival of 32% compared to 44% of patients without the mutation. (Kottaridis 2001)

Furthermore, additional factors of the FLT3 ITD mutation may impact outcome, including size of the base pair insertion, higher allelic ratio (mutant: wild-type FLT3) and insertion site (Stirewalt 2006, Thiede 2002, Kayser 2009) As details of FLT3 ITD mutations continue to be evaluated, it remains clear that AML with a FLT3 ITD mutation results in higher relapse, shorter DFS and shorter OS which has led to an increased focus on HSCT in CR1 in this group.

1.1.2 Allogeneic hematopoietic stem cell transplantation in AML

It has long been recognized that despite achieving CR, undetectable leukemic cells are often present leading to relapse in most patients and post remission treatment is warranted. Post remission treatment options include intensive conventional chemotherapy (often high dose cytarabine), prolonged maintenance treatment, or intensive therapy followed by autologous or allogeneic hematopoietic stem cell transplantation (HSCT). Patients with high-risk AML are typically evaluated for HSCT early as the chance of long-term cure with chemotherapy alone is low. Allogeneic HSCT is a highly effective treatment for AML, with improved progression free survival (PFS) and OS for patients with intermediate and high-risk disease. (Yanada 2005, Estey 2011)

In the subset of patients with FLT3 ITD mutations whom achieve complete remission, outcomes of HSCT have so far only been reported in three large retrospective analyses. The MRC group compared outcomes in FLT3 ITD+ and FLT3 ITD- patients (Gale 2005) This intent to treat analysis (donor versus no donor) failed to show a statistically significant

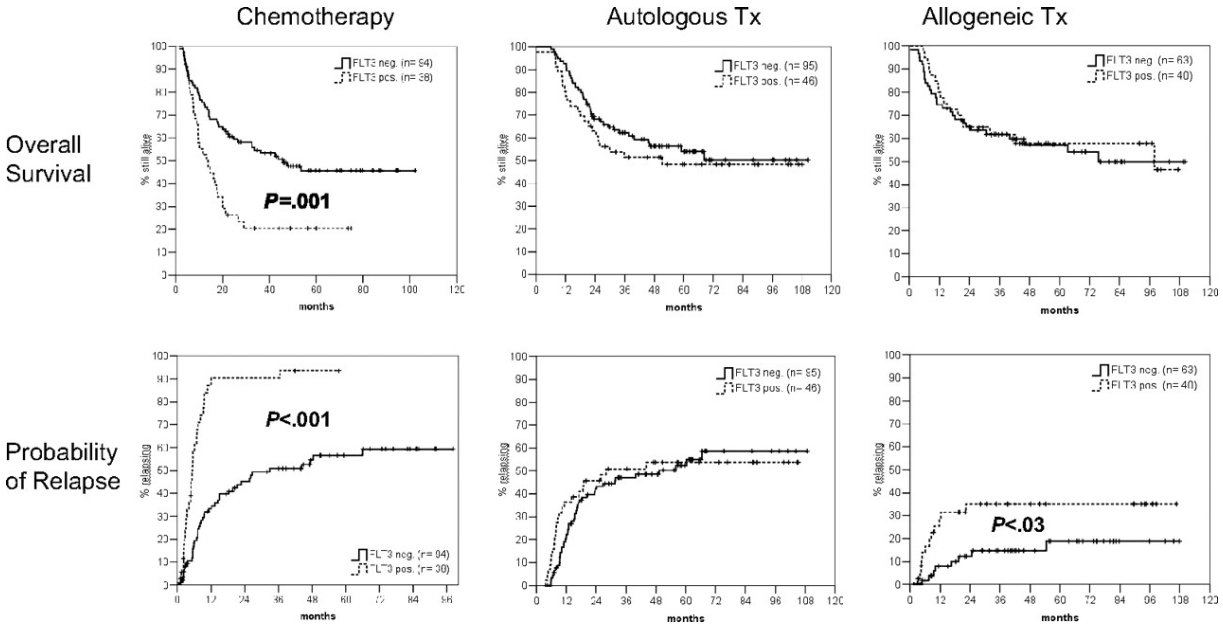
[redacted]

difference between HSCT and no HSCT in FLT3 ITD patients; however the small sample size of 35 FLT3 ITD allograft patients limits the power in the analysis (Gale 2005, Gale 2007). The observed OS in the allograft patients at 5 years was 58% and 44% in the FLT3 ITD- and ITD+ groups, respectively. The rate of relapse over 5 years was 31% in FLT3 ITD+ and 25% in FLT3 ITD- patients whom were allograft recipients.

An AMLSG analysis also compared outcomes for patients with FLT3 ITD versus FLT3 wild type (WT) in groups given post-remission chemotherapy, autologous HSCT or allogeneic HSCT. (Bornhauser 2007) The 376 younger, intermediate risk patients included 176 patients with FLT3 ITD. Overall, there were 103 matched sibling allogeneic transplants, 141 autologous transplants and 132 chemotherapy recipients without transplant. Kaplan Meier analyses show that transplant increased OS in the FLT3 ITD+ patients to similar levels as FLT3 WT patients who underwent allogeneic or autologous transplant (approximate median OS 72 months for allogeneic and 36 months for autologous). The group of FLT3 ITD patients whom received chemotherapy had a much shorter OS than FLT3 WT. While this study shows benefit with HSCT in FLT3 ITD, the OS is double that of other literature reports in FLT3 WT AML. Discussions amongst researchers point to likely exclusion of early TRM and/or censoring the early relapse events in FLT3 ITD which could introduce bias and magnify the difference between the arms (Schlenk 2008, Bornhauser 2007, Meshinchi 2006). Following allogeneic HSCT, relapse occurred in about 35% of patients in the FLT3 ITD group (N=40) which was much higher than in the FLT3 wild type (N=60) patients at a median follow-up of 53 months. (Bornhauser 2007)

[redacted]

Figure 1-1 Probability of overall survival and relapse according to post remission therapy

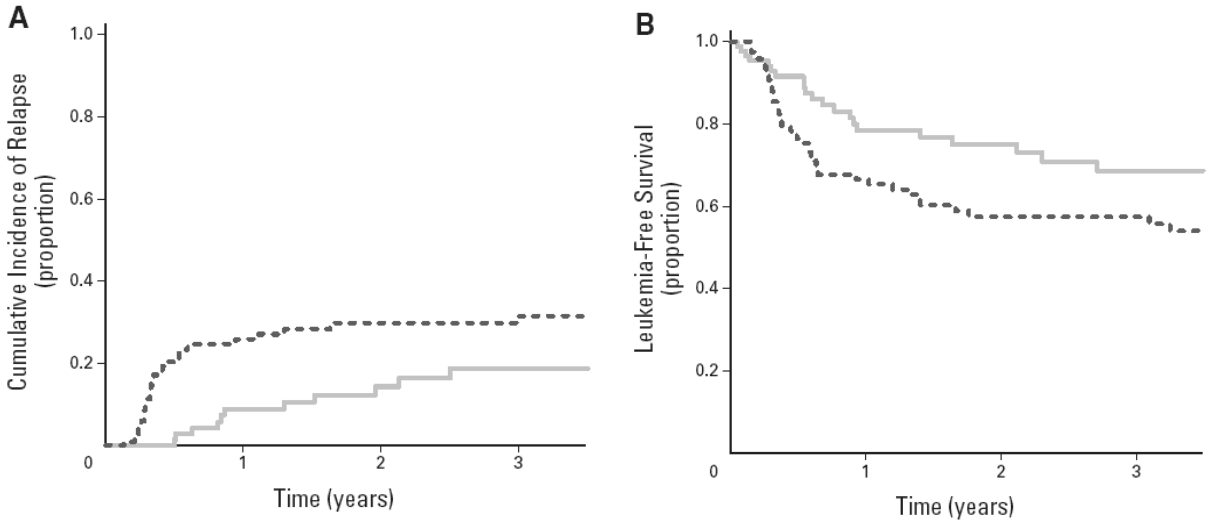


Probability of overall survival and relapse according to postremission therapy. After a median follow-up of 53 months for surviving patients, the probability of overall survival and relapse (from remission) are shown for patients having received either chemotherapy (n = 132), autologous transplant (n = 141), or allogeneic transplant (n = 103) as postremission therapy. Tx indicates transplantation. (Bornhauser 2007)

These findings were corroborated by data recently published from the EBMT group. Of 206 patients whom underwent matched sibling or matched unrelated HSCT with myeloablative conditioning, FLT3 ITD was observed in 120 (58%) patients. This is the largest group of FLT ITD patients undergoing allogeneic transplant and was the most clearly defined patient group of the three retrospective analyses. The incidence of relapse at two years was higher in the FLT3 ITD positive group at a rate of 30% compared to 16% in the negative group. Disease free survival was also negatively impacted by FLT3 positive status (DFS at 2 years of 58% vs. 71% in FLT3 ITD negative) (Brunet 2012). Despite the intervention of HSCT, patients with FLT3 ITD relapsed at a much higher rate than patients without the mutation. Most relapses in the FLT3 ITD group occurred by 18 months after HSCT. Despite differences in the three retrospective analyses, they report a similarly high rate of relapse of 30-35% in patients with FLT3 ITD undergoing allogeneic HSCT.

[redacted]

Figure 1-2 Outcome after allogeneic transplantation in first CR for patients with AML and normal cytogenetics according to the presence or absence of FLT3-ITD



Outcome after allogeneic transplantation in first CR for patients with AML and normal cytogenetics according to the presence (dashed line) or absence (solid line) of ITD of *FLT3* gene. (A) Estimated probability of 2 years of cumulative incidence of relapse; (B) leukemia-free survival after transplantation at 2 years. (Brunet 2012)

Due to the poor prognosis conferred with a FLT3 ITD mutation, many centers are prioritizing allogeneic HSCT for these patients who remain at high risk for relapse. (Levis 2011, Van den Brink 2010) New treatments which could improve relapse rates after HSCT would be a significant benefit. Clinical trials are now launching to understand whether maintenance therapy targeting FLT3 ITD shortly after allogeneic transplantation can delay or prevent relapse in this high risk subset of AML patients (Metzelder 2009, Sora 2011, Levis 2010).

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

1.2.1 Overview of midostaurin

Midostaurin is an inhibitor of several protein kinase C (PKC) isoforms, of the tyrosine kinase of the vascular endothelial growth factor receptor (VEGFR) and most importantly of the class III tyrosine protein kinases FLT3 (fms-like tyrosine kinase-3) and KIT which are involved in hematopoiesis and play a key role in certain hematopoietic disorders. Midostaurin binds to the catalytic domain of these kinases and inhibits the signaling of the respective growth factors in cells and results in growth arrest. The anti-proliferative effects of midostaurin were easily detectable in FLT3-ITD, FLT3-TKD and FLT3 WT cells (Weisberg 2002, Barry 2007). Midostaurin has also been found to revert the P-glycoprotein (Pgp) mediated MDR (multidrug resistance) phenotype by inhibiting the function of Pgp (Utz 1998).

Midostaurin is currently in Phase II/Phase III clinical development including:

[redacted]

- Two phase II single arm single agent studies in patients with aggressive systemic mastocytosis / Mast Cell Leukemia
- One phase III randomized, double-blind study (CALGB 10603; RATIFY) in patients with FLT3-mutated AML.

1.2.1.1 Clinical experience

1.2.1.1.1 Pharmacokinetic and pharmacodynamic data

The clinical pharmacology of midostaurin has been extensively studied in healthy volunteers as well as patients with AML and diabetes mellitus (Yin 2008; Stone 2012). Midostaurin is rapidly absorbed following oral administration with peak plasma concentrations observed 1-3 hours post-dose. Upon daily oral dosing, midostaurin concentrations accumulated in a time linear manner in the first 3-8 days. Thereafter, the PK becomes non-linear with an apparent large increase in CL/F. This relatively high apparent oral clearance necessitates a high dosing rate (e.g. bid administration) to maintain target drug levels in the long term. Midostaurin concentrations reach steady-state after 28 days of daily dosing. (Yin 2008) In vitro studies have shown that midostaurin, CGP62221, and CGP52421 inhibit mutant FLT3 at low nanomolar concentrations, with IC50s of 10-36 nM, 26 nM and 584nM, respectively. (Manley 2003; Stone 2012)

Midostaurin is predominantly metabolized by CYP3A4 iso-enzymes to form two major, pharmacologically active metabolites which may contribute to *in vivo* activity: CGP62221 (half-life ~ 30 hours, comparable to midostaurin's half-life of ~25 hours) and CGP52421 (half-life of ~28 days). Phase I studies in healthy volunteers evaluated the effects of a strong CYP3A4 inhibitor (ketoconazole) and a strong CYP3A4 inducer (rifampin) on concentrations of midostaurin and its metabolites and the effect of midostaurin on midazolam (a sensitive CYP3A4 substrate). Concomitant administration with strong CYP3A4 inhibitors or inducers significantly alters midostaurin concentrations. Midostaurin does not cause a drug-drug interaction with CYP3A4 substrates.

For additional pharmacokinetic information, please refer to the Investigators Brochure.

1.2.1.1.2 Overview of efficacy with midostaurin

Midostaurin has demonstrated activity in patients with relapsed or refractory AML/myelodysplastic syndrome (MDS) in Studies CPKC412A2104 (2104) and CPKC412A2104E1 (2104E1). In Study 2104E1, the rate of BR (blast reduction) for the efficacy population (n=92) was 71% in FLT3-mutant patients and 42% in FLT3-WT patients. One partial response (PR) occurred in a FLT3-mutant patient on the 100 mg b.i.d. dose regimen. Both doses levels evaluated in this trial (50 mg b.i.d., and 100 mg b.i.d.) were well tolerated; the toxicity profiles and response rates were similar for the two doses of midostaurin. The results suggest that midostaurin has hematologic activity in both FLT3-mutant and wild-type patients. The degree of clinical activity observed supports further studies in earlier stage disease and that combine midostaurin with other agents such as chemotherapy especially in FLT3-mutant AML (Fischer et al 2010).

[redacted]

Preliminary data from the phase Ib, CPKC412A 2106 (2106), study of midostaurin in combination with standard daunorubicin and cytarabine therapy in patients with newly diagnosed AML patients indicate that midostaurin at 50 mg p.o. b.i.d. can be given with tolerable side effects in this patient population (Stone 2012). Efficacy data for the 50 mg b.i.d. population was presented at the American Society of Hematology (ASH) in 2009. The investigator assessment of Complete response (CR) occurred in 32/40 (80%) of all patients (20/27 [74%] of FLT3–WT patients, 12/13 [92%] of FLT3–mutant patients). One and 2 year overall survival (OS) for the patients with FLT3–mutant AML was 85% and 62%, respectively, and was comparable to that of the FLT3–WT subgroup (81% and 59%, respectively). This data was based on small numbers and not stratified for type of FLT3 mutation (TKD, ITD, or allelic ratio) (Stone 2009). This study supported the ongoing double blind, placebo controlled, phase III study, CPKC412A2301 (CALGB 10603, Ratify), in newly diagnosed FLT3 mutated AML. Enrollment in that trial is complete (N=717) and awaiting the Overall Survival (OS) events required for final analysis.

In addition to the AML programs described above, an ongoing single arm, phase II study, CPKC412D2201 (2201) in aggressive systemic mastocytosis / mast cell leukemia has completed enrollment with stage I (N=40) and extension (N=40) to determine the efficacy and safety of 100 mg twice daily oral midostaurin as a single agent. The Overall Response Rate, per Valent criteria, for stage I is 60% (24/40 eligible patients) including a major response rate of 52.5%. (Gotlib 2012)

1.2.1.1.3 Overview of safety with midostaurin

Overall, approximately 1746 subjects have received midostaurin including ~650 patients with AML / MDS. In AML patients, doses of up to 600 mg per day have been given, but the 50 mg twice daily dose is recommended based upon reaching the IC50 and showing acceptable tolerability. Safety data in AML are based upon three studies: monotherapy in FLT3 mutated patients (2104 Core; N=20), monotherapy in relapsed AML or ineligible for chemotherapy (2104E1; N=95) and front-line combination therapy with daunorubicin and cytarabine (2106; N=69). (Stone 2005, Fischer 2010, Stone 2012). Data from the maintenance phase of the Phase III (2301, CALGB 10603 Ratify) study would also be very informative but the ongoing trial remains blinded at this time. Single agent safety data from 2104E1 will be discussed.

In study 2104E1, patients were randomized to receive midostaurin at doses of 50 mg b.i.d. or 100 mg b.i.d. Of the patients enrolled, 73% were relapsed/refractory and 61% were greater than 60 years of age. Six patients had previously undergone HSCT. Midostaurin was generally well tolerated at both dose levels. All 95 patients experienced at least one AE regardless of relationship to study drug. The most frequent events were grades 1 or 2 nausea (61%; Grade 3 was 1%), vomiting (49%; Grade 3 was 1%), diarrhea (44%; Grade 3 or 4 was 5%), fatigue (38%; Grade 3 was 3%), pyrexia (35%; Grade 3 was 7%) and dyspnea (29%; Grade 3 or 4 9%). The most commonly reported grade 3 / 4 AEs were febrile neutropenia (21%), thrombocytopenia (19%), neutropenia (12%), anemia (13%) and pneumonia (12%). [Inv Brochure ed 16, Table 6-20] The decreases observed in the hematology parameters were as expected for this patient population. Only one patient discontinued treatment due to a hematologic abnormality (grade 3 febrile neutropenia). The majority of new or worsened biochemistry abnormalities were of CTC grade 1-2. There were grade 3 or 4 abnormalities in

[redacted]

AST/ALT in 13% patients (2 were Grade 4, both receiving 100 mg b.i.d.), amylase 7% and albumin 5%. The full table of newly occurring or worsening hematology and chemistry abnormalities is shown in the Investigators Brochure Version 16. [Tables 6-21 and 6-22]

SAEs were reported for 71 (75%) patients and most commonly included: febrile neutropenia (20 patients), pneumonia (17 patients), pyrexia (13 patients), dyspnea (8 patients), thrombocytopenia (7 patients) and anemia (6 patients). The incidence of SAEs was similar for both dose groups. SAEs were mostly considered to be due to disease progression. Eighteen (19%) patients had SAEs that were considered related to study drug, with grade 3/4 anemia and thrombocytopenia being the most frequently reported.

In 2011, a pooled safety analysis was performed using data available from 14 solid tumor or AML/MDS studies. Trials included combinations with 5-FU, paclitaxel, gemcitabine, carboplatin, cisplatin, daunorubicin, and cytarabine. The pooled analysis included 542 subjects (213 with AML/MDS) and the most common drug related toxicities (> 20%) in these phase I/II trials were nausea, vomiting and diarrhea, general disorders / administration site, nervous system disorders (including headache, dizziness, syncope), metabolism and nutrition disorders, and decreased appetite. AEs occurring less frequently (10-19%) included fatigue, headache, anemia, AST/ALT elevations, thrombocytopenia and constipation. (Investigators Brochure, ed 15) In the pooled analysis, frequencies of cardiac events were consistent with the investigated populations.

A Phase I trial evaluated the effect of midostaurin on the QTc interval in healthy volunteers in a thorough QTc study. The mean maximum change from baseline (QTcF) for midostaurin compared with placebo demonstrated a lack of QTcF prolongation effects. (DelCorral 2012) This trial evaluated midostaurin and the short acting metabolite but could not investigate effects of the long-acting metabolite at steady state. The long acting metabolite information cannot be attained from a healthy volunteer study thus will be provided from the CALGB 10603 (Ratify) dataset.

Overall, AEs suspected to be related to midostaurin treatment were mostly Grade 1 and 2 gastrointestinal events requiring little or no intervention. These were considered related to midostaurin, as the frequency increased at higher dose levels. At the 100mg twice daily dose in AML patients with chemotherapy, patients discontinued treatment more frequently due to nausea and vomiting despite addition of antiemetic therapy which contributed to selection of a 50mg twice daily dose which was found to be well tolerated. In addition to prophylactic anti-emetics, administering the doses with meals can reduce gastrointestinal AEs. These AEs are most common in the early cycles of administration. In the ongoing ASM/MCL studies, patients are tolerating the 100 mg twice daily dose for up to 4 years; however, prophylactic anti-emetics are given to all patients.

2 Rationale

2.1 Study rationale and purpose

Midostaurin is an oral agent that has been shown to inhibit FLT3 kinase in preclinical in vitro and in vivo studies, as well as clinically in patients with both ITD and TKD FLT3 mutations (FLT3mut). Both directly and indirectly, midostaurin also potently inhibits multiple other

[redacted]

molecular targets thought to be important for the pathogenesis of AML. These targets include VEGFR-1, a VEGF receptor; c-kit; H- and K-ras; as well as the multidrug resistant gene, MDR. Midostaurin, a staurosporine derivative, has been identified as an inhibitor of both mutated and wild type FLT3 kinase. Midostaurin potently inhibits recombinant FLT3 kinase in an in vitro kinase assay, and inhibits tyrosine phosphorylation of mutant FLT3, both ITD mutants and D835Y point mutants in vitro. These data suggest that midostaurin directly blocks the kinase activity of mutant FLT3, thereby interfering with its transforming functions. Expression of a mutant FLT3 receptor (FLT3-ITD or the TKD D835Y) in vivo in murine marrow cells results in a lethal myeloproliferative syndrome which can be successfully cured with the administration of midostaurin. (Weisberg 2002)

2.2 Rationale for the study design

This is a phase II, randomized, open label trials of standard of care, with or without midostaurin to prevent relapse following allogeneic hematopoietic stem cell transplantation (HSCT) in patients with FLT3-ITD acute myeloid leukemia. The intent of this study is to evaluate whether the addition of midostaurin to standard of care (SOC) following allogeneic HSCT improves Relapse Free Survival (RFS) in FLT3-ITD AML patients in first complete remission (CR1). This trial will not be powered to detect a difference between the two arms. Powering of the trial is not feasible considering the rare nature of FLT3-ITD mutant AML receiving a HSCT. With a 22-25% FLT3-ITD mutation rate and approximately 25% rate of HSCT, estimated from the ongoing Phase III study (2301, CALGB 10603 Ratify), more than 1050 newly diagnosed AML patients would need to be evaluated to identify 60 patients undergoing HSCT in CR1. The control arm, SOC, in this study provides the first prospective set of subjects treated at the same centers in the same timeframe which will allow an estimate of treatment effect which can be used to design a larger trial. There are no published sets of prospective, FLT3-ITD AML outcomes after transplantation.

2.3 Rationale for dose and regimen selection

Patients receiving midostaurin on this trial will receive 50mg b.i.d for 28 consecutive days of each cycle.

In adults, the maximum tolerated dose (MTD) of the single agent was 75 mg t.i.d. in relapsed AML. Preliminary PK/PD analysis from this study showed that the plasma level of midostaurin seems to be well above the IC50 value for FLT3 ITD/D835 inhibition. (Stone 2005) In this study, it was also demonstrated that single agent treatment up to 100 mg b.i.d. was most tolerable. Doses of at least 50 mg b.i.d. still demonstrated presence of blast activity.

In relapsed/refractory AML patients, average trough concentrations observed at the 50- and 100-mg doses showed that steady-state levels of midostaurin and the metabolites reached the 50% inhibitory concentration. This supports a minimum dose of 50 mg twice daily in FLT3 mutated AML. (Fischer 2010). Currently the 100 mg b.i.d. dose is only used in Aggressive Systemic Mastocytosis patients which targets c-KIT rather than FLT3.

In order to achieve IC50 values at steady state and allow the most tolerable dosing, the dose for patients receiving midostaurin on this trial will be 50mg b.i.d daily. For patients unable to

[redacted]

tolerate the proposed dose, dose adjustments are outlined in Section 6.3. An Independent Review committee (IRC) will additionally review safety information after 10, 20, and 30 patients, regardless of treatment assignment, have completed at least 3 cycles or discontinued.

2.4 Rationale for choice of drugs

All patients on study will receive Standard of Care (SOC) therapy and half of these patients will be randomized to receive midostaurin in addition to this. Currently, SOC therapy varies per treating institution in the post HSCT setting but includes anti-infective prophylaxis and treatment and GVHD prophylaxis and treatment.

A placebo will not be used in this trial. While a placebo was considered, it can limit enrollment which is already expected to be the largest challenge for the trial. In addition, the primary endpoint of the trial is relapse and clinical relapse in patients with AML is not expected to be impacted by the open label design. The frequency of relapse assessments is the key component and is the same for both arms.

All SOC treatment while on study must be captured for all patients on the Concomitant Medications / Significant Non-drug Therapies eCRF page.

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 of care (SOC) therapy reduces relapse after at least 18 months of follow-up following allogeneic HSCT in FLT3-ITD mutant AML patients in first complete remission (CR1)	Relapse Free Survival (RFS) is defined as the time from transplant to relapse or death due to the disease 18 months post transplant	
Key secondary		Refer to Section 10.5.
To evaluate disease free survival (DFS)	DFS is defined as the time from transplant to relapse or death from any cause	
To evaluate relapse free survival (RFS) all along the study	Relapse Free Survival (RFS) is defined as the time from transplant to relapse or death due to the disease	
To evaluate non-relapse mortality (NRM)	NRM is calculated from the date of transplant to date of patient death due to reasons other than relapse/progressive AML.	
To evaluate overall survival (OS)	OS is defined as the time from transplant to the date of death from any cause	
To evaluate safety and tolerability of midostaurin in patients with FLT3 –ITD AML in the post-transplant setting	Safety will be assessed by the Common Toxicity Criteria for Adverse Events (CTCAE) version 4.0. Incidence of adverse events (AEs), serious adverse events (SAEs), changes from baseline in clinically notable changes in vital signs and CTC grading for laboratory results (hematology, blood chemistry, ECGs) will be reported.	
To evaluate pharmacokinetics (PK) of midostaurin in the post-transplant	PK concentration-steady state levels	
To assess FLT3-ITD mutation status centrally in archived material from diagnosis, if available	FLT3-ITD mutation status, including the mutant:wild type ratio	

[redacted]

Objective	Endpoint	Analysis
[redacted]		

4 Study design

4.1 Description of study design

This is a randomized, open label Phase II study to investigate the efficacy and safety of twice daily midostaurin in patients with FLT3 ITD AML after HSCT.

Patients will be treated with the Standard of Care (SOC) treatment with or without (+/-) midostaurin in a 1:1 randomization. All patients who have engrafted and recovered counts by day 42 after HSCT will be eligible for randomization no later than 60 days after transplant (may occur as early as day 28 post transplant), regardless of treatment assignment. Based on other tyrosine kinase inhibitor data, it is anticipated that starting midostaurin shortly after transplant will offer the best chance to improve relapse rates. Most relapses after transplant in FLT3-ITD patients occur by day 100 so an earlier treatment start (days 28 to 60) is targeted in this trial. Midostaurin will be given at a dose of 50mg twice daily continuously in cycles of 4 weeks (28 days) each for up to 12 cycles or disease relapse or withdrawal due to any cause, whichever occurs earlier.

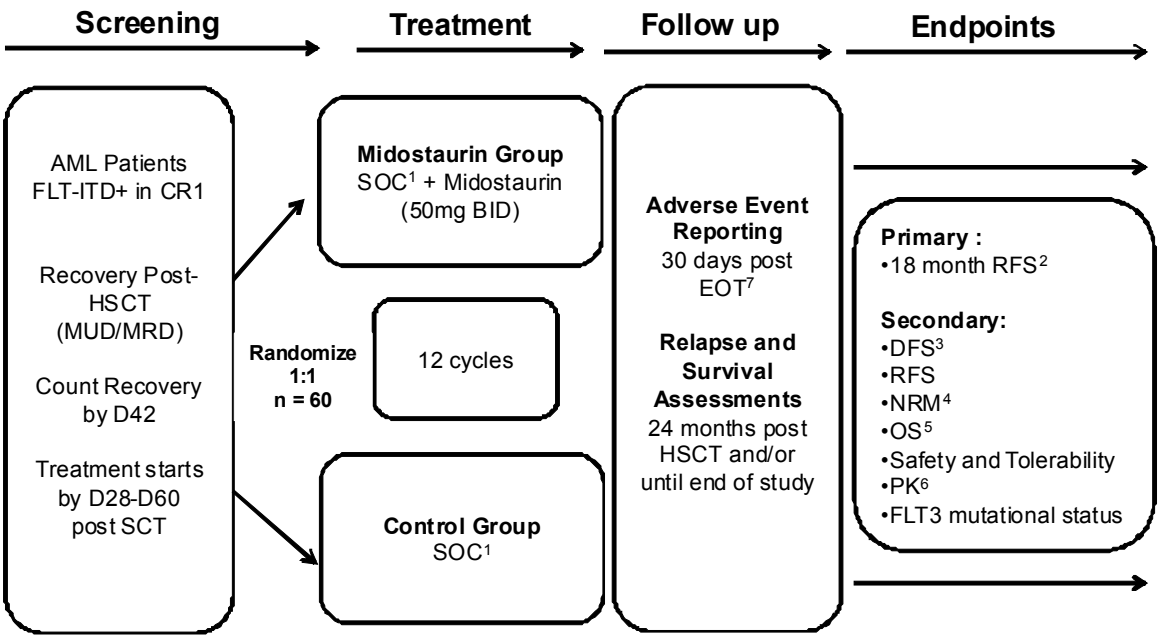
Patient visits will occur monthly for one year during the Treatment Phase (Cycles 1-12). Visits will continue in the Follow-up Phase thru 24 months post HSCT. Hematology Lab Panels will be collected every two months to assess relapse in addition to survival status. Patients that have not relapsed, died or withdrawn at 24 months will be asked to provide quarterly hematology panels until the study ends.

The study will end when all patients have been followed for 24 months post HSCT, unless all patients have died or withdrawn from the study prior to this time point. Prior to database lock, an additional OS and RFS update will be requested for all living patients.

Patients will have bone marrow aspirate performed early (between days 30 and 100 post-HSCT), at Cycle 6, at Cycle 12, at relapse or more frequently if clinically indicated. All patients will begin treatment, regardless of treatment assignment, upon recovery of counts as listed in the eligibility criteria. Patients who do not meet recovery eligibility criteria by day 42 post allogeneic HSCT will not be eligible for this trial. Safety will be evaluated by an independent review committee after 10, 20, and 30 patients, regardless of treatment arm, have completed at least 3 cycles or discontinued. An independent review committee of 3 to 5 study investigators will review safety information to include (but not limited to) adverse events, serious AEs, lab parameters, bone marrow results [redacted].

[redacted]

Figure 4-1 Study design



[1]Standard of Care (SOC), [2]Relapse Free Survival (RFS), [3]Disease Free Survival, [4]Non Relapse Mortality, [5]Overall Survival, [6] Pharmacokinetics, [7]End of Treatment

4.2 Definition of end of the study

The study will end when all planned patients have either been followed for 24 months post HSCT, died or have withdrawn from the study. Prior to database lock, an additional OS and RFS update will be requested from all living patients.

4.3 Early study termination

The study can be terminated at any time for any reason by Novartis. Should this be necessary, the patient should be seen as soon as possible and the same assessments should be performed as described in Section 7.1.3 for a prematurely withdrawn patient. 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 IRBs and/or ECs of the early termination of the trial.

5 Population

5.1 Patient population

Patients with acute myeloid leukemia (AML) must have documented FLT3-ITD mutation and have undergone allogeneic HSCT in first complete remission (CR1) to be eligible to enter the study.

Sixty (60) patients will be enrolled during the study. The investigator or his/her designee must ensure that all patients who meet the following inclusion/exclusion criteria are offered

enrollment into the study. Enrollment criteria will be evaluated at both Visit 1 (screening) and Visit 2 (C1D1), prior to randomization.

Patients enrolled in this study are not permitted to participate in additional parallel investigational drug or device studies. Patients who have completed the study may not be re-enrolled for a second course of treatment.

5.2 Inclusion criteria

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

Written informed consent must be obtained prior to any screening procedures. If consent cannot be expressed in writing, it must be formally documented and witnessed, ideally via an independent trusted witness.

1. Patients must be between 18 and 70 years of age
2. Patient must give written informed consent
3. Patients must have an ECOG Performance Status of ≤ 2
4. Patients must have a documented Unequivocal diagnosis of AML according to WHO 2008 classification (>20% blasts in the bone marrow and/or peripheral blood), excluding M3 (acute promyelocytic leukemia).
5. Patients must have a documented FLT3 ITD mutation, determined by local laboratory for eligibility (historical tissue will be requested for central analysis confirmation)
6. Patients who have undergone allogeneic HSCT in CR1 from a matched related or matched unrelated donor. All of the following criteria must also be met:
   - HLA typing to include available 8/8 or 7/8 allele HLA matched donor (at A,B,C, DRB1) Single allelic mismatch allowed
7. Patients must have received one of the following conditioning regimens prior to HSCT. Alternative regimens must be approved by Novartis prior to enrollment:

   Busulfan*/Fludarabine (Bu/Flu)

   Busulfan (16 mg/kg PO or 12.8 mg/kg IV)

   Fludarabine (120-180 mg/m2)

   Fludarabine / Melphalan (Flu/Mel)

   Fludarabine (120-180 mg/m2)

   Melphalan (≤ 150 mg/m2)

   Busulfan*/Cyclophosphamide (Bu/Cy)

   Busulfan (16 mg/kg PO or 12.8 mg/kg IV)

   Cyclophosphamide (120 mg/kg)

   Cyclophosphamide/Total Body Irradiation (Cy/TBI)

   Cyclophosphamide (120 mg/kg)

   TBI (1200-1420 cGy)

   * Note: Busulfan dosing based on individual PK parameters is allowed as long as myeloablative dosing is used (e.g., target AUC at least 4000μM x min for 4 days)
8. Recovery of counts by day 42 and able to start Standard of Care +/- midostaurin by day 60 post-HSCT (first dose of midostaurin to start no earlier than 28 days post-HSCT)

[redacted]

- ANC >1000 perμL, platelets ≥20,000 perμL without platelet transfusion

9. Patients must have the following laboratory values:
   - AST and ALT ≤ 3 x Upper Limit of Normal (ULN)
   - Serum Bilirubin ≤ 3 x ULN
   - Serum Creatinine ≤ 2.5 x ULN

5.3 Exclusion criteria

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

1. Patients whom have failed prior attempts at allogeneic HSCT
2. Patients who have received an autologous transplant, haploidentical or cord blood.
3. Patients with Acute GVHD Grade III-IV
4. Patients with any other known concurrent severe/and or uncontrolled medical condition (expect carcinoma in-situ), which could compromise participation in the study (e.g. uncontrolled infection, uncontrolled diabetes, chronic active pancreatitis)
5. Patients with a known confirmed diagnosis of HIV infection or active viral hepatitis.
6. Impaired cardiac function including any of the following:
   - Screening ECG with a QTc > 450 msec. If QTc > 450 and electrolytes are not within normal ranges, electrolytes should be corrected and then the patient rescreened for QTc.
   - Patients with congenital long QT syndrome
   - History or presence of sustained ventricular tachycardia
   - Any history of ventricular fibrillation or torsades de pointes
   - Bradycardia defined as HR. < 50 bpm
   - Right bundle branch block + left anterior hemiblock (bifascicular block)
   - Patients with myocardial infarction or unstable angina < 6 months prior to starting study
   - Congestive Heart Failure NY Heart Association class III or IV
   - Patients with an ejection fraction < 45% assessed by MUGA or ECHO within 21 days prior to starting study cycle 1 (of midostaurin or control group)
7. Patients with any pulmonary infiltrate including those suspected to be of infectious origin (unless resolves to ≤ Grade 1 within screening timeframe)
8. Antineoplastic chemotherapy or radiotherapy, within 21 days prior to study cycle 1 (For GVHD prophylaxis refer to Section 6.4.1.2)
9. Patients who have had any surgical procedure, excluding central venous catheter placement or other minor procedures (e.g. skin biopsy/GVHD related biopsy) within 14 days prior to study cycle 1
10. Patient requires treatment with (a) strong CYP3A4 inhibitor other than those required for GVH or infection prophylaxis or treatment or (b) moderate or strong CYP3A4 inducer regardless of prophylaxis or treatment
11. Known sensitivity to study drug(s) or class of study drug(s)

[redacted]

12. Participation in a prior investigational study within 30 days prior to enrollment or within 5-half lives, if known, of the investigational product, whichever is longer.
13. Pregnant or nursing (lactating) women, where pregnancy is defined as the state of a female after conception and until the termination of gestation, confirmed by a positive hCG laboratory test within 48 hours of beginning study treatment.
14. 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 3 months after treatment completion. 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) 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). For female subjects on the study the vasectomized male partner should be the sole partner for that subject.
    - Combination of any two of the following (a+b or a+c, or b+c):
    a. Use of oral, injected or implanted hormonal methods of contraception or other forms of hormonal contraception that have comparable efficacy (failure rate <1%), for example hormone vaginal ring or transdermal hormone contraception.
    b. Placement of an intrauterine device (IUD) or intrauterine system (IUS)
    c. Barrier methods of contraception: Condom or Occlusive cap (diaphragm or cervical/vault caps) with spermicidal foam/gel/film/cream/vaginal suppository

In case of use of oral contraception women should have been stable on the same pill for a minimum of 3 months before taking study treatment.

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 (e.g. age appropriate, history of vasomotor symptoms).

15. Sexually active males unless they use a condom during intercourse while taking drug and for 5 months after stopping midostaurin medication. They should not father a child in this period. A condom is required to be used also by vasectomized men in order to prevent delivery of the drug via seminal fluid.
16. Not able to understand and to comply with study instructions and requirements

6 Treatment

6.1 Study treatment

Study Treatment refers to the treatment assigned upon randomization;

- Standard of Care (SOC) or
- Standard of Care (SOC) with midostaurin.

[redacted]

Study drug refers to any Novartis investigational drug(s) being used for an unapproved indication. For this study, the term "Study drug" refers to midostaurin (PKC412) supplied in 25 mg soft gelatin capsules which are packaged in blister packs.

6.1.1 Midostaurin dosing regimen

Table 6-1 Dose and drug schedule

Study drug	Pharmaceutical form and route of administration	Dose	Frequency and/or Regimen
Midostaurin (PKC412)	25mg Soft gelatin capsule; oral administration	50mg (2 x 25mg) capsules)	Twice Daily (28 day cycles)

The standard dose of midostaurin is listed in Table 6-1 and should be followed unless patients meet criteria for dose modifications Section 6.3.

6.1.2 Treatment duration

The treatment phase is defined as Cycles 1 – 12. Patients will be randomized to SOC +/- midostaurin. Patients receiving midostaurin will receive study drug for 12 cycles (max) or until patient experiences unacceptable toxicity, disease progression and/or treatment is discontinued at the discretion of the investigator or withdrawal of consent, whichever comes first.

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 adjustments are permitted in order to allow the patient to continue the study treatment as listed in Table 6-2.

The toxicities listed will require treatment interruption of midostaurin treatment until recovery to ≤ Grade 2 or for a maximum of up to 21 consecutive days (a modification to this rule for nausea/vomiting is noted below). In addition, dosing interruption is allowed to up to 1 week at a time to assess if it is related to GVHD or midostaurin. It is anticipated that dose interruption will be common during the early post-transplant period and the intent is to allow time to assess whether events are due to midostaurin, GVHD or other causes and to allow patients to remain on study. Patients may be re-challenged per the dose modification table. Any patient requiring a longer delay than 21 days will be discontinued from the study.

Until durable engraftment has occurred, cytopenias may require transfusion support and/or growth factors and are permitted as per standard of care. If the cytopenia(s) are not considered related to midostaurin, the cause should be documented and dose holding and reduction of midostaurin is not required. If the cytopenia(s) is determined to be possibly attributable to midostaurin, the dose modification guidelines should be followed.

[redacted]

Dose adjustments are required for patients taking concomitant strong CYP3A4 inhibitors with midostaurin, refer to Section 6.4.2 for details.

These changes must be recorded on the Dosage Administration Record eCRF.

Table 6-2 Criteria for interruption and re-initiation of midostaurin treatment

Recommended dose modifications for CPKC412AUS23	
Investigations (Hematologic)	
Neutropenia (ANC)	
Grade 4 (ANC < 500/mm3)	First event, hold midostaurin dose until recovery to Grade 2 then restart at 50mg b.i.d
	Second event, hold midostaurin until recovery to Grade 2, then restart at 25mg b.i.d for 2 weeks and then re-escalate to 50mg b.i.d as tolerated
	Third event, patient should be discontinued if neutropenia is attributable to midostaurin
Febrile Neutropenia	
Grade 4	First event, hold midostaurin dose until recovery to Grade 2 then restart at 50mg b.i.d
	Second event, hold midostaurin until recovery to Grade 2, then restart at 25mg b.i.d for 2 weeks and then re-escalate to 50mg b.i.d as tolerated
	Third event, patient should be discontinued if neutropenia is attributable to midostaurin
Thrombocytopenia	
Platelet count < 15,000/mL	First event, hold midostaurin dose until recovery to ≥ 20,000 per microliter then restart at 50mg b.i.d
	Second event, hold midostaurin dose until recovery to ≥ 20,000 per microliter then restart at 25mg b.i.d for 2 weeks and then re-escalate to 50mg b.i.d as tolerated
	Third event, patient should be discontinued if other causes for the thrombocytopenia cannot be determined
Other Hematologic Adverse Events	
Grade 3 or 4	If a patient has not recovered from a new or worsening grade 3 or 4 hematologic toxicity (suspected relationship to midostaurin) to grade ≤ 2 within 21 days, he/she must be discontinued from the study.

[redacted]

Recommended dose modifications for CPKC412AUS23	
Investigations (Hepatic)*	
Bilirubin, AST or ALT	
Grade 3 (> 3.0 - 10.0 x ULN) related to midostaurin (rather than VOD, GVH)	If alternate causes of liver dysfunction have been managed, but liver dysfunction persists, hold midostaurin until recovery to Grade 2 then restart.
	If this is felt to be related to study drug and the re-challenge results in a subsequent Grade 3 or 4 elevation, then patient should be discontinued from treatment.
Pulmonary Infiltrates	
Grade 3 or 4	Pulmonary infiltrate interruption of midostaurin for the remainder of the cycle until the infiltrate resolves to ≤ grade.
Investigation (Gastro intestinal)	
Nausea or Vomiting	
Grade 2	If this develops despite use of prophylactic anti-emetic therapy, hold midostaurin for 3 days (6 doses) and resume midostaurin as tolerated; e.g. reduce the dose to 25mg b.i.d; if the event continues hold for 3 days (6 doses), resume at 25mg qd. If the event continues the patient should be discontinued from treatment,
Grade 3 or 4	If this develops despite use of prophylactic anti-emetic therapy, hold midostaurin until recovery to Grade 2 (or at least 3 days) then restart at 50mg b.i.d. If this is felt to be related to study drug and the re-challange results in a subsequent Grade 3 or 4 toxicity then the midostaurin dose may be reduced to 25mg b.i.d (50mg/day). In the event of additional toxicity requiring dose modification refer to “Grade 3 or 4 -Other adverse events (Non-Hematologic) below.

[redacted]

Recommended dose modifications for CPKC412AUS23	
Other adverse events (Non-Hematologic)	
Grade 3 or 4	If a patient has recovered to ≤ Grade 2 within 21 days of interrupting treatment, the midostaurin dose will be reduced to 25mg b.i.d (50mg/.day). In the event of additional toxicity requiring dose modification, further dose reductions of midostaurin below 25mg b.i.d (50mg/day) will not be allowed. If the patient tolerates the lower dose of midostaurin (25 mg b.i.d) and considering the nature of the PK profile of midostaurin (concentration drops following multiple doses), a dose increase back to 50mg b.i.d may be attempted as tolerated. If a patient has not recovered from any grade 3 or 4 non-hematologic toxicity to < Grade 2 within 21 days of interrupting treatment (with the exception of the dose modification stated above for Grade 2-4 nausea and vomiting) will be discontinued from the study.
QTc Prolongation	Refer to Table 7-7.
All dose modifications should be based on the worst preceding toxicity. Common Toxicity Criteria for Adverse Events (CTCAE Version 4.0)	
Investigator discrection to continue study drug (midostaurin) may be used for the following if it is felt that the AE is not study drug related: Cytopenias, AST/ALT elevation, Nausea or Vomiting. All of other AEs require dose modification per Table 6-2.	

[redacted]

6.3.2 Follow-up for toxicities

Patients whose treatment is interrupted or permanently discontinued due to an adverse event or clinically significant laboratory value must be followed at least once a week during drug-hold and be followed for 4 weeks, and subsequently at 4-week intervals, until resolution or stabilization of the event, whichever comes first. If a patient requires a dose delay of > 21 days from the intended day of the next scheduled dose, then the patient must be discontinued from the study. However, the patient will continue to be followed for toxicity as previously described. All patients will be followed for adverse events and serious adverse events for 30 days following the end of study treatment period.

For collection of survival data, the status of all patients who discontinue study treatment will be followed through 24 months. Patients that have not relapsed, died or withdrawn at 24 months will be followed until the study ends.

The study will end when all patients have been followed for 24 months post HSCT, unless all patients have died or withdrawn from the study prior to this time point. Prior to database lock, an additional OS and RFS update will be requested for all living patients.

6.3.3 Anticipated risks and safety concerns of the study drug

Appropriate eligibility criteria as well as specific dose modification and stopping rules are included in this protocol. Recommended guidelines for prophylactic or supportive treatment for expected toxicities, including management of study-drug induced adverse events, i.e., nausea and vomiting are provided in Section 6.4.1.1.1. Refer to preclinical toxicity and or clinical data found in the Investigator's Brochure.

6.4 Concomitant medications

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 taken within 28 days prior to randomization and all concomitant medications/therapies must be recorded on the Concomitant/Non-Drug Therapy eCRF.

Other anticancer agents including chemotherapy, radiation therapy, or biologic response modifiers, e.g. FLT3 inhibitors (including sorafenib), are not permitted prior to relapse. Donor Lymphocyte Infusion (DLI) is not allowed except for viral specific Cytotoxic T Cells (CTLs) or low dose CTLs for EBV lymphoproliferative disorders (i.e., DLI for worsening chimerism is not allowed prior to relapse). No other investigational drug is allowed during the study.

6.4.1 Permitted concomitant therapy

6.4.1.1 Supportive care

In general, the use of any concomitant medication/therapies deemed necessary for patient supportive care and safety are permitted provided they are documented in the patient records.

Based on preclinical investigations demonstrating that midostaurin is an inhibitor of P-gp though not a good substrate, the interaction between midostaurin and P-gp subtrate,

[redacted]

daunorubicin was studied in the clinical study [CPKC412A2106]. The pharmacokinetics of daunorubicin did not show any notable modification when coadministered with midostaurin.

6.4.1.1.1 Anti-emetic treatment with midostaurin

Nausea and vomiting are commonly reported in studies with midostaurin administration. These events are more frequent during combination therapy and are dose-dependent.

Prophylaxis for the prevention of nausea and vomiting is highly recommended. The kind and dose of anti-emetic drug should be chosen as per investigator discretion. Patients may be given ondansetron hydrochloride or granisetron. Other anti-emetics such as metoclopramide, methotrimeprazine, cyclizine, prochlorperazine or tropisetron may be used at the discretion of the investigator.

Since nausea (and in some cases vomiting) may still occur 1-3 hours after the dose, additional anti-emetics after midostaurin dosing may be required. In these cases, promethazine (phenergan), prochlorperazine (compazine), lorazepam (ativan) or other anti-emetics can be used ½ hour to 1 hour after study drug as per investigator discretion.

If patients suffer from Grade 3 or 4 severe nausea and/or vomiting, refer to Section 6.3.

6.4.1.1.2 Anti-diarrhetic treatment with midostaurin

For the management of diarrhea, oral loperamide can be administered. An initial dose of 4 mg followed by 2 mg every 4 hours or after every unformed stool (maximum of 16 mg/day) is suggested. However, the kind and dose of anti-diarrheal should be chosen per investigator discretion.

6.4.1.2 Prophylaxis and treatment management of GVHD and systemic immunosuppressive medications

As per standard of care, GVHD prophylaxis regimens are recommended (e.g., mycophenolate mofetil, cyclosporine, methotrexate, tacrolimus, sirolimus) and should follow standard of care at your institution.

If patients develop active GVHD, standard of care per your institution should be followed and steroids are permitted. While some of these medications are substrates of CYP3A4, midostaurin has minimal impact on CYP3A4 substrates (see Section 1.2.1.1.1 and Section 6.4.2 on PK). The recommendation is to avoid the co-administration of a strong CYP3A4 inhibitor or a strong and moderate CYP3A4 inducer with midostaurin. Levels of cyclosporine, tacrolimus, sirolimus or cyclosporine should be monitored closely, as per standard of care.

6.4.1.3 Contraceptives with midostaurin

Women must avoid breast-feeding during study treatment, and all women of childbearing potential will be required to employ a highly effective method of birth control which is defined as a birth control which results in a low failure rate (i.e. less than 1% per year) when used consistently and correctly. This has to be employed for the duration of the study and for 3 months post study because of the long half-life of the metabolite, CGP52421.

[redacted]

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 3 months of midostaurin 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) 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). For female subjects on the study the vasectomized male partner should be the sole partner for that subject.
- **Combination of any two of the following (a+b or a+c, or b+c):**
  a. Use of oral, injected or implanted hormonal methods of contraception or other forms of hormonal contraception that have comparable efficacy (failure rate <1%), for example hormone vaginal ring or transdermal hormone contraception.
  b. Placement of an intrauterine device (IUD) or intrauterine system (IUS)
  c. Barrier methods of contraception: Condom or Occlusive cap (diaphragm or cervical/vault caps) with spermicidal foam/gel/film/cream/vaginal suppository

In case of use of oral contraception women should have been stable on the same pill for a minimum of 3 months before taking study treatment.

Sexually active males unless they use a condom during intercourse while taking drug and for 5 months after stopping midostaurin medication. They should not father a child in this period. A condom is required to be used also by vasectomized men in order to prevent delivery of the drug via seminal fluid.

6.4.2 Permitted concomitant therapy requiring caution and/or action

6.4.2.1 Concomitant medications with potential for CYP3A4 interactions

6.4.2.1.1 Midostaurin can be impacted by CYP3A4 inhibitors and inducers:

Midostaurin is a sensitive substrate of CYP3A4 [CPKC412A2109]; [CPKC412A2110],. This indicates that the pharmacokinetics of midostaurin may be influenced by drugs that are inducers or inhibitors of CYP3A4.

6.4.2.1.2 Interactions with inhibitors of Cytochrome P450 3A4

In a healthy volunteer drug-drug interaction study where midostaurin was co-administrated with the potent CYP450 3A4 inhibitor ketoconazole, the exposure of midostaurin increased by 10-fold (90% confidence interval 7.4-14.5) [CPKC412A2109]. Based on the above data, administration of concomitant strong CYP3A4 inhibitors with midostaurin should be avoided and alternative therapeutics which does not strongly inhibit CYP450 3A4 activity should be considered. If there are no other treatment options for the patient (i.e life-threatening infection), a compensatory reduction in the dose of midostaurin is warranted.

[redacted]

The dose adjustment of midostaurin is aimed to achieve similar exposure to the range observed of midostaurin 50mg twice daily without the strong inhibitor. As a result, a dose reduction of 7-fold based on the lower bound of the confidence interval of the ratio of [AUC midostaurin with ketoconazole/AUC midostaurin without ketoconazole] is recommended [CPKC412A2109]. Hence the prescribed dose reduction during the time of a concomitant strong CYP3A4 inhibitor (see list below) is midostaurin 25 mg every other day.

If the strong CYP3A4 inhibitor is discontinued, approximately 2 to 3 days should elapse before increasing the midostaurin dose back to the dose prior to initiation of the strong CYP3A4 inhibitor.

Strong CYP3A4 inhibitors: clarithromycin, telithromycin, troleandomycin, indinavir, lopinavir, nelfinavir, ritonavir, saquinavir, tipranavir, itraconazole, ketoconazole, posaconazole, voriconazole, boceprevir, telaprevir, cobicistat, conivaptan, nefazodone.

Moderate CYP3A4 inhibitors: Caution should be exercised for patients receiving moderate CYP450 3A4 inhibitors. A list of moderate CYP450 3A4 can be found on:

http://medicine.iupui.edu/clinpharm/ddis/main-table/

6.4.2.1.3 Interactions with moderate and strong inducers of Cytochrome P450 3A4

In a healthy volunteer drug-drug interaction study where midostaurin was co-administrated with the potent CYP450 3A4 inducer rifampicin, the Cmax and AUC of midostaurin decreased by 73% and 94%, respectively [CPKC412A2110]. To avoid sub-therapeutic exposure to midostaurin, moderate or potent CYP450 3A4 inducers should not be coadministered.

Strong CYP3A4 inducers: avasimibe, carbamazepine, mitotane, phenobarbital, phenytoin, rifabutin, rifampin (rifampicin), St. John's wort (hypericum perforatum);

Moderate CYP3A4 inducers: bosentan, efavirenz, etravirine, genistein, modafinil, nafcillin, ritonavir, talviraline, thioridazine, tipranavir.

6.4.2.1.4 Midostaurin not expected to affect the pharmacokinetics of other CYP3A4 substrates:

Midostaurin, administered as a single dose or in multiple doses, did not appear to affect the concentrations of midazolam or its metabolite 1'-hydroxymidazolam [CPKC412A2112]. As a result, midostaurin is neither a CYP3A4 inhibitor nor a CYP3A4 inducer in vivo in humans at clinically relevant conditions. Therefore, midostaurin is not expected to affect the pharmacokinetics of other CYP3A4 substrates.

6.4.2.2 Concomitant anti-infective prophylaxis and treatment

It is highly recommended to avoid concomitant strong CYP3A4 inhibitors (e.g., ketoconazole, itraconazole, voriconazole, posaconazole). The suggested antifungal regimens from a drug metabolism perspective is described below:

Prophylaxis

Fluconazole (moderate CYP3A4 inhibitor)

Micafungin

[redacted]

If a patient requires active treatment for a fungal or mold infection and and the only treatment options is an azole that is a strong CYP3A4 inhibitorthen the suggested agents from a drug metabolism and safety perspective include:

Treatment

Voriconazole

Posaconazole

These are both strong CYP3A4 inhibitors and will likely increase midostaurin concentrations, therefore, if there are no other treatment options to treat the infection, a dose reduction of midostaurin is required.See details in Section 6.4.2. With intra-patient variability with regard to CYP3A4 inhibition and midostaurin pharmacokinetics, the suggested approach is to avoid strong CYP3A4 inhibitors unless there are no treatment alternatives.

6.5 Patient numbering, treatment assignment or randomization

6.5.1 Patient numbering

Each patient is identified in the study by a **9-digit Subject Number** (Subject No.), that is assigned when the patient is first presented 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 **4-digit center number** (Center No.) (as assigned by Novartis to the investigative site) with a sequential **5-digit patient 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 Interactive Web Response System (IWRS). Once assigned to a patient, a patient number will not be reused. If the patient fails to be assigned to treatment for any reason, the reason for not being assigned to treatment will be captured through the IWRS system. Patients cannot be re-randomized.

6.5.2 Treatment assignment or randomization

This is a randomized (1:1) two-arm, open-label study with standard of care with or without (+/-) midostaurin 50mg twice daily for up to 12 cycles.

The two arms will be: (1) Standard of Care and (2) Standard of Care plus midostaurin.

The randomization numbers will be generated using the following procedure to ensure that treatment assignment is unbiased. A patient randomization list will be produced by the Interactive Web Response Technology (IWRS) 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.

After all assessments have been completed, all patients who fulfill all inclusion/exclusion criteria will be randomized via IWRS on C1D1 to one of the treatment arms. The investigator or his/her delegate will call or log on to the IWRS and confirm that the patient fulfills all the inclusion/exclusion criteria. The IWRS will assign a randomization number to the patient, which will be used to link the patient to a treatment arm. The randomization number will be communicated by the IWRS confirmation via email, to the investigator and or delegate for patient designation to the trial.

[redacted]

6.5.3 Treatment blinding

Not applicable – Open label treatment

6.6 Study drug preparation and dispensation

Midostaurin will be administered by twice daily oral dosing of 50 mg (i.e. 4 capsules of midostaurin 25 mg in two divided doses) beginning on Day 1 and should be administered with water following breakfast and dinner. Previous studies have shown midostaurin to be better tolerated (with respect to short term nausea and vomiting) if taken following meals. Patients should be instructed to swallow capsules whole and not chew capsules. An interval of approximately 12 hours between doses is preferred. If vomiting occurs, no re-dosing is allowed before the next scheduled dose. If a dose of midostaurin is missed by the patient, the dose should not be made up and the patient should only take the next scheduled dose.

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 Dosage Administration Record eCRF.

Table 6-3 Preparation and dispensing

Study treatments	Dispensing	Preparation
Midostaurin (PKC412)	Gelatin capsules including instructions for administration are dispensed by study personnel on an outpatient basis. Patients will be provided with adequate supply of study treatment for self-administration at home until at least their next scheduled study visit.	Midostaurin is packaged in blister packs. Midostaurin should not be removed from the blister pack until the patient is ready to take the scheduled dose. Upon opening a blister pack, patients may notice a pungent odor but will dissipate.

6.6.1 Study drug packaging and labeling

Midostaurin will be supplied by Novartis as soft gelatin capsules to be taken orally. The study drug will be provided as open label bulk and packed in child resistant blisters. The drug should be stored in the blister pack until use and no further preparation of the study drug is needed. Upon opening a blister pack, patients may notice a pungent odor. The odor is due to ethyl thioglycolate that forms when ethanol in the capsules interacts with the thermostabilizer in the foil. The capsules are not affected, and the odor will dissipate. Each capsule contains 25 mg of midostaurin. Medication labels will comply with the legal requirements of each country and be printed in the local language.

One component of the packaging has a 2-part label. Immediately before dispensing study drug to the patient, investigator staff will detach the outer part of the label from the packaging and affix it to the source document (Drug Label Form) containing that patient's unique patient number.

[redacted]

Table 6-4 Packaging and labeling

Study drug	Packaging	Labeling (and dosing frequency)
Midostaurin (PKC412)	25mg soft gelatin capsules in child resistant blisters	Labeled as PKC412 25mg Study treatment packaging has a 2-part label.

6.6.2 Drug supply and storage

Study drug (Midostaurin) 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 drug** should be stored according to the instructions specified on the drug labels. Do not store above 25° C.

Table 6-5 Supply and storage of study treatments

Study treatment	Supply	Storage
Midostaurin (PKC412)	Centrally supplied by Novartis	Do not store above 25° C.

6.6.3 Study drug compliance and accountability

6.6.3.1 Study drug compliance

The data that will be collected on study drug and other therapy use will provide information about drug exposure. These data should correspond to the information requested on the eCRFs entitled Dosage Administration Record (used for midostaurin administration only); Concomitant Medications; any other eCRFs specific to the project and/or patient diaries.

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.

Compliance will be assured by administrations of the study drug under the supervision of investigator or his/her designee, and will be verified by determinations of **PKC412 and two metabolites** in the plasma.

6.6.3.2 Study drug accountability

The investigator or designee must maintain an accurate record of the shipment and dispensing of study drug 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 drug and packaging on a regular basis, at the end of the study or at the time of study drug discontinuation.

6.6.3.3 Handling of other study treatment

Not applicable.

[redacted]

6.6.4 Disposal and destruction

Patients must return any remaining capsules should to the clinical site for proper disposal. Contact of the product with the skin should be avoided.

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

The study drug supply should be destroyed at the designated Novartis facility or third party, as appropriate. On site disposal or destruction is permitted upon Novartis review and agreement with the local policy/SOP.

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.

No CRF will be used as a source document.

[redacted]

Table 7-1 Visit evaluation schedule

	Protocol Section 7.2 (if applicable)	**Screening**	**Cycle 1**			**Day 30 – Day 100 Post HSCT**	**Subsequent Cycles (2-12)** **Refer to Section for Frequency*	**End of study treatment (EoT)**	**Follow up**	**Survival follow up**	**Study Completion Evaluation**
Visit Number		**1**	**2**	**3**	**4**		**5-15**	**16 (777)**	**501, 502 etc**	**701,701, etc**	**778**
Day of cycle		-14 to -1	1	3	15		1	Last	n/a	n/a	n/a
Obtain Informed Consent		X									
IWRS/IRT		X	X	X	X		X	X	X	X	X
Randomization			X								
Patient history		X									
Demography		X									
Inclusion/exclusion criteria		X	X								
Relevant medical history/current medical conditions		X									
Diagnosis and extent of cancer		X									
Prior antineoplastic therapy		X									
Prior concomitant medications		X									
Safety											
Serious Adverse Events		X	X	X	X	X	X	X	30 Days Post EOT		
Adverse events			X	X	X	X	X	X	30 Days Post EOT		
Concomitant Medications			X	X	X	X	X	X			
Physical examination	7.2.2.1.	X	X	X	X		X	X			
Vital signs	7.2.2.2.	X	X	X	X		X	X			
Height	7.2.2.3.	X						X			
Weight	7.2.2.3.	X	X		X		X	X			

[redacted]

	Protocol Section 7.2 (if applicable)	Screening	Cycle 1			Day 30 – Day 100 Post HSCT	Subsequent Cycles (2-12) *Refer to Section for Frequency	End of study treatment (EoT)	Follow up	Survival follow up	Study Completion Evaluation
Visit Number		**1**	**2**	**3**	**4**		**5-15**	**16 (777)**	**501, 502 etc**	**701,701, etc**	**778**
Day of cycle		-14 to -1	1	3	15		1	Last	n/a	n/a	n/a
Performance status	7.2.2.4.	X	X					X			
Laboratory assessments	7.2.2.5.	X	X		X		X	X			
Hematology	7.2.2.5.	X	X		X		X	X	X		
Chemistry	7.2.2.5.	X	X		X		X	X			
Urinalysis	7.2.2.5.	X									
Coagulation	7.2.2.5.	X									
Thyroid (T4 and TSH)	7.2.2.5.	X					C2D1, C6D1 and C12D1	X	30 Days Post EOT		
Pregnancy	7.2.2.5.1.	X	X								
Imaging											
Chest x-ray/CT Scan	7.2.2.6.	X									
ECG	7.2.2.7.1.	X	X	X			X	X			
MUGA/ECHO	7.2.2.7.2.	X					C3 and C6	X			
Pharmacokinetics											
PK Sampling (study maintenance)	7.2.3.1.		X		X		X				
[redacted]											
Biomarkers	7.2.4.										
Central Determination of FLT3-ITD	7.2.4.1.	X									
[redacted]											
GVHD assessment	[redacted]		X	X	X		X	X			

[redacted]

	Protocol Section 7.2 (if applicable)	**Screening**	**Cycle 1**			**Day 30 – Day 100 Post HSCT**	**Subsequent Cycles (2-12)** **Refer to Section for Frequency*	**End of study treatment (EoT)**	**Follow up**	**Survival follow up**	**Study Completion Evaluation**
Visit Number		**1**	**2**	**3**	**4**		**5-15**	**16 (777)**	**501, 502 etc**	**701,701, etc**	**778**
Day of cycle		-14 to -1	1	3	15		1	Last	n/a	n/a	n/a
Study Drug dispensation and review			X	X	X		X	X			
SOC Study Drug administration			X	X	X		X	X			
Bone marrow	7.2.4.1. [redacted]					X	C6D1 and C12D1				
Archived stored frozen mononuclear cells / DNA		X-historical									

[redacted]

7.1.1 Screening

Patients will be eligible to screen for this study 28 days post-HSCT. The trial Informed consent, which includes the [redacted] sample Informed Consent must be signed prior to any screening procedures begin. Patients should be randomized onto the trial within 14 days from date of screening; randomization will occur after all assessments have been completed on C1D1.

Patients that do not meet eligibility criteria at initial screening, but have met eligibility criteria by Day 60 post HSCT may be eligible to enroll onto study. Patients are only required to complete failed assessments as long as the patient is re-screened within 14 days of the initial screening and have met eligibility by Day 60.

7.1.1.1 Eligibility screening

Following registering in the IWRS for screening, patient eligibility will be checked once all screening procedures are completed. The eligibility check will be embedded in the IWRS system. Please refer and comply with detailed guidelines in the IWRS manual.

7.1.1.2 Information to be collected on screening failures

Patients who sign an informed consent but fail to be started on treatment for any reason will be considered a screen failure. All data for screen failures are entered into the IWRS system, including the reason for not being started on treatment Screen failure data will not be entered into the clinical database unless the patient experienced a Serious Adverse Event during the Screening Phase (see Section 8 for SAE reporting details). All screen failure data from the IWRS will be exported to a SAS dataset for final data review and archiving.

The reasons for screen failures may include the following:

- Unacceptable medical history/concomitant diagnosis
- Intercurrent medical event
- Unacceptable laboratory value(s)
- Unacceptable test procedure result(s)
- Did not meet diagnostic/severity criteria
- Unacceptable use of excluded medications/therapies
- Subject withdrew consent

7.1.1.3 Patient demographics and other baseline characteristics

Baseline patient data pertaining to demographic information and relevant medical history related to study indication should be documented accordingly in the eCRFs to include, but not limited to the following information:

- Date of birth
- Age
- Sex
- Race
- Relevant medical history and if active at start of study

[redacted]

Date of diagnosis
Performance status
FLT3-ITD mutation status
Any additional mutation information, if known
Cytogenetics
Date of first Complete Remission (CR1)
Date of Transplant

A detailed history of **all** prior antineoplastic therapies, such as medications for treatment of leukemia must be recorded on the eCRF including:

Medication name/ Non-drug therapy
Dose
Start/End date
Best response

Additionally all other medications and significant non-drug therapies taken within **28 days before first dose is administered** must be recorded on the eCRF page and updated on a continual basis if there are any new changes to the medication. Medications include physician prescribed, over-the-counter medications, vitamins, and herbal and alternative therapies. Information to be collected on concomitant medications/significant non-drug therapies will include the following:

Medication/Non-drug therapy trade name
Reason for medication
Start/End date and if continuing at time of examination

In addition to the general demographic and relevant medical history information, study specific information will be collected during the screening period as indicated in the assessment schedule (Table 7-1) in order to determine eligibility of the patient.

7.1.2 Treatment and study period

The treatment period for all patients regardless of treatment assignment is defined as Cycles 1 – 12.

For the treatment period patients will be randomized to SOC +/- midostaurin. Patients receiving SOC + midostaurin will receive midostaurin for 12 cycles (max) or until patient experiences unacceptable toxicity, relapse, death and/or treatment is discontinued at the discretion of the investigator or withdrawal of consent, whichever comes first.

It is likely that patients receiving SOC may have already began this treatment prior to randomizing onto the trial as part of his/her post HSCT standard of care treatment regimen. Any medications that began prior to the randomization/treatment period will be captured in the medical history and subsequently captured on the Concomitant Medication page during the treatment period. If the medication is still being taken at the end of the treatment phase, the medication should be recorded as ongoing.

Patient visits will occur monthly for one year during the Treatment Period (Cycles 1-12). Patients will continue in the Follow-up Phase and have assessments for at least 24 months

[redacted]

post HSCT. Hematology Lab Panels will be collected on average every two months between Follow up assessments to evaluate relapse in addition to survival status.

Patients that have not relapsed, died or withdrawn at 24 months will be asked to provide quarterly hematology panels until the study ends.

The study will end when all patients have either been followed for 24 months post HSCT, unless all patients have died or have withdrawn from the study. Prior to database lock, an additional OS and RFS update will be requested from all living patients.

Table 7-2 Treatment visit frequency and windows

Visits	Frequency	Window
Cycle 1	D1, 3 and 15	+/- 1 day
Cycles 2-12	Monthly, D1	+/- 5 days
End of Treatment (EOT)	SOC: C12 D28 or at first relapse or discontinuation from the study SOC + Midostaurin: C12 D28 or at time of midostaurin treatment discontinuation	+/- 7 days

7.1.3 End of treatment visit including study completion and premature withdrawal

7.1.3.1 End of Treatment (EOT)

Patients **may** voluntarily withdraw from the study or be dropped from it at the discretion of the investigator at any time.

- In the SOC arm, the End of Treatment (EOT) is considered as the end of cycle 12, the date of first relapse or the date of discontinuation, whichever occurs first.
- In the SOC + Midostaurin arm, the EOT is defined as the last study drug (midostaurin) intake.

At the time patients discontinue study treatment; a visit should be scheduled as soon as possible, an End of Treatment (EOT) Phase eCRF page should be completed, giving the date and primary reason for a patient's premature withdrawal from the study

Patients may be withdrawn from treatment if any of the following occur:

- Adverse events
- Abnormal laboratory values
- Abnormal test procedure result
- Subject withdrew consent
- Lost to follow up
- Administrative problems
- Death
- Relapse

[redacted]

- Treatment duration competed as per protocol
- Protocol deviation

At minimum, patients who discontinue study drug/from the study, including those who refuse to return for a final visit will be contacted for safety evaluations during 30 days following the end of treatment.

Patients who discontinue study treatment also should return for relapse and follow up assessments at visits and should not be considered withdrawn from the study. If patients refuse to return for these visits or are unable to do so, every effort should be made to contact them or a knowledgeable informant by telephone to determine the patients relapse and/or survival status.

7.1.3.2 Study Evaluation Completion (SEC)

If a patient discontinues study treatment, but continues study assessments, the patient remains on study until such time as he/she completes protocol criteria for ending study assessments. At that time, the reason for study completion should be recorded on the Study Evaluation Completion CRF (SEC) page. End of treatment/Premature withdrawal visit is not considered as the end of the study.

The reasons for study evaluation completion may include, but not limited to the following:

Subject withdrew consent
Lost to follow-up
Administrative problems
Death
Relapse
Protocol Deviation
Follow up phase completed as per protocol

7.1.4 Follow up for survival and RFS

Patients should be followed up until the end of the study. The study will end when all patients have been followed up for at least 24 months, relapsed, died or have withdrawn consent. For all living patients, an additional OS and RFS update will be requested prior to database lock.

All patients must have safety evaluations 30 days after the last dose of midostaurin for patients in the SOC+ midostaurin arm. For patients in the SOC arm, all patients must have safety evaluations 30 days after the end of Cycle 12/first relapse/withdrawal, whichever comes first.

During Follow up, patients will be asked to have a hematology panel every 2 months thru 24 months post HSCT. This date will be calculated from the date of transplant. If a patient prematurely discontinues from the treatment phase prior to completing Cycle 12, patients will be asked to have a hematology panel every 2 months from the EOT visit until 24 months post HSCT as outlined in Table 7-1.

Hematology Lab Panels will be collected every two months between Follow up visits to assess relapse in addition to survival status. Patients that have not relapsed, died or withdrawn

[redacted]

at 24 months will be asked to provide quarterly hematology panels until the study ends. For all living patients, an additional OS and RFS update will be requested prior to database lock.

The assessment schedule is outlined in Table 7-3.

Table 7-3 Follow up assessment frequency and windows

Time Point	Assessment	Window
Patients that prematurely discontinue from treatment phase prior to completion of Cycle 12 • Every 2 months from EOT until 24 months post HSCT	• Survival • Hematology Panel • Bone Marrow (BM) at investigator's discretion	+/- 14 days
Patients that complete Cycle 12 • Every 2 months from EOT until 24 months	• Survival • Hematology Panel • BM at investigator's discretion	+/- 14 days
Patients that have not relapsed at 24 months • Quarterly until the last patient has been followed for 24 months	• Survival • Hematology Panel	+/- 21 days
Relapse	• Hematology Panel • BM	+/- 14 days

Patients lost to follow up should be recorded as such on the eCRF. For patients who are lost to follow-up, the investigator should show "due diligence" by documenting in the source documents steps taken to contact the patient, e.g., dates of telephone calls, registered letters, etc.

7.2 Assessment types

7.2.1 Efficacy assessments

- Complete Response (CR) is when the following levels are detected in the Peripheral Blood (PB); ANC ≥ 1000/uL; Platelet count ≥ 100K and no circulating leukemic myeloblasts in peripheral blood and Bone Marrow (BM) has adequate cellularity, BM blast count ≤ 5% and no auer rods detected.
- Relapse following complete response is defined as reappearance of leukemic blasts in the peripheral blood or finding more than 5% blasts in the bone marrow.
- Relapse Free Survival (RFS) assesses the clinical benefit of remaining in remission free from relapse or death due to the disease. It is defined as the time from transplant to relapse or death due to the disease.
- Disease Free Survival (DFS) assesses the clinical benefit of remaining in remission free from relapse or death from any cause. It is defined as the time from transplant to relapse or death from any cause. This is aligned with Novartis AML guidance and FDA guideline on endpoints (Clinical Trial Endpoints for the Approval of Cancer Drugs and Biologics, 2007). If a patient has more than one event (e.g. relapse and death) then the earliest date will be taken into account.
- Overall Survival (OS) is defined as the time from transplant to death from any cause.

[redacted]

7.2.1.1 Bone marrow aspirate and biopsy

Bone Marrow will be collected at the time points listed in Table 7-4 to assess Efficacy [redacted] endpoints.

Table 7-4 Bone marrow collection plan

Procedure	Screening/During Treatment Period	During Follow up
Bone Marrow	Results from Initial diagnosis required for eligibility Between D30 – 100 **Post HSCT** Cycle 6 Cycle 12	Relapse and/or investigator discretion

The BM aspirates are collected in EDTA tubes and are processed at the local laboratory as per institutional procedures. If required in case of inspirable bone marrows, core biopsy should be performed.

For response assessment it is required that bone marrow assessment and the corresponding blood assessment (CBC) is done within a 5 day window.

7.2.2 Safety and tolerability assessments

The assessment of safety will be based mainly on the frequency of Adverse Events (AEs), on the number of laboratory values summarized by CTCAE grades and non-relapse mortality (NRM).

Summary statistics will be provided for data from other tests (e.g. electrocardiogram or vital signs) and any other information collected will be listed as appropriate.

All AEs recorded during the study will be summarized by treatment arm. The incidence of treatment-emergent AEs (new or worsening from baseline) will be summarized by primary system organ class, preferred term, severity (based on CTCAE grades), type of AE and relationship to the study drug. Deaths reportable as SAEs and nonfatal SAEs will be listed by patient and tabulated by type of AE.

For further details on AE collection and reporting, refer to Section 8.

All assessments must be drawn **PRIOR** to administration of study treatment (of that day).

Non-relapse mortality assesses the other causes of death not due to disease or relapse (e.g., late toxicity due to GVHD). It is calculated from the date of transplant to the date of patient death due to reasons other than relapse.

7.2.2.1 Physical examination

A physical examination must be performed at the screening visit, Day 1 and 15 of Cycle 1, Day 1 of each subsequent cycle, and on the day of discontinuation/end of treatment (EOT).

Information about the physical examination must be present in the source documentation at the study site.

Significant findings that were present prior to the signing of informed consent must be included in the Medical History page on the patient's eCRF. Significant new findings that

[redacted]

begin or worsen after informed consent must be recorded on the Adverse Event page of the patient's eCRF.

7.2.2.2 Vital signs

Vital signs include temperature, respiratory rate, blood pressure and pulse and will be taken in the sitting position. Vitals will be measured at Screening, Cycle 1 Day 1, 3, 15, Day 1 of each subsequent cycle and at End of Treatment (EOT)

Information about vital signs must be recorded in the source document at the study site. Significant findings present prior to the start of study drug must be in the Relevant Medical History/ Current Medical Conditions eCRF. Significant finding made after the start of study drug which meet the definition of an adverse event must be recorded on the Adverse Event eCRF.

7.2.2.3 Height and weight

Height in centimeters (cm) and body weight (to the nearest 0.1 kilogram [kg] in indoor clothing, but without shoes) will be measured. Height will be measured at Screening and on the day of discontinuation/end of treatment (EOT). Weight will be measured at Screening, Day 1 and 15 of Cycle 1, Day 1 of each subsequent cycle, and on the day of discontinuation/end of treatment (EOT).

7.2.2.4 Performance status

ECOG Performance Status will be assessed at Screening, Day 1 of Cycle 1 and at End of Treatment (EOT).

Table 7-5 ECOG Performance Status

Grade	ECOG
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, e.g., light house work, office work
2	Ambulatory and capable of all selfcare but unable to carry out any work activities. Up and about more than 50% of waking hours
3	Capable of only limited selfcare, confined to bed or chair more than 50% of waking hours
4	Completely disabled. Cannot carry on any selfcare. Totally confined to bed or chair
5	Dead

7.2.2.5 Laboratory evaluations

Frequency of evaluations must be performed according to the Visit Schedule and Assessment, Table 7-1, and parameters outlined in Local Clinical laboratory parameters collection plan Table 7-6. Analyses and assessments are to be done locally and results transcribed to the eCRF. When abnormal laboratory values or test results constitute an adverse event (i.e., induces clinical signs/symptoms or requires therapy) they must be recorded on the Adverse Events eCRF.

[redacted]

All laboratory values must be drawn **PRIOR** to randomization / first dose of study drug. Every effort should be made to obtain screening laboratory values 14 days prior to study entry and these need then not be repeated at study entry if performed within 14 days of the initial dose of midostaurin. All other laboratory evaluations must be performed within +/- 48 hours of a study visit.

If administration of midostaurin is interrupted due to ≥ Grade 3 non-hematologic laboratory parameters, refer to Section 6.3, for instructions.

Table 7-6 Local clinical laboratory parameters collection plan

Test Category	Test Name	Screening/During Treatment	During Follow-up
Hematology	Total white blood cell count with differential (neutrophil count including bands, lymphocyte, monocyte, eosinophil, basophil/mast cell, % and absolute blast count, and early myeloid forms), hemoglobin, hematocrit, platelet count and reticulocyte count.	Screening Cycle 1 D1,15 Cycle 2-12; D1 EOT	Refer to Table 7-3 after EOT
Chemistry	Albumin, Alkaline phosphatase, ALT (SGPT), AST (SGOT), Bicarbonate, Calcium, Chloride, Creatinine, Creatine kinase, Sodium, Potassium, phosphorus, magnesium, glucose, Direct Bilirubin, Indirect Bilirubin, Total Bilirubin, Total Cholesterol, LDL, HDL, Total Protein, Triglycerides, Blood Urea Nitrogen (BUN) or Urea, Uric Acid, Lipase and Amylase.	Screening Cycle 1 D1,15 Cycle 2-12; D1 EOT	Refer to Table 7-3 after EOT
Urinalysis	Macroscopic Panel (Dipstick) (Color, Bilirubin, Blood, Glucose, Ketones, Leukocytes esterase, Nitrite, pH, Protein, Specific Gravity) Any significant findings on dipstick will be followed up with a microscopic evaluation where bacteria, WBC, RBC sediments will also be measured. Microscopic Panel (Red Blood Cells, White Blood Cells, Bacteria, and additional findings)	Screening or more frequent if clinically indicated.	n/a
Coagulation	Prothrombin time (PT), International normalized ratio [INR]), Partial thromboplastin time (PTT) or Activated partial thromboplastin time (APTT)	Screening or more frequent if clinically indicated	n/a
Thyroid	T4 [free], TSH	Screening, C2D1, C6D1, C12D1 or more frequent if clinically indicated	30 Days after end of treatment (EOT)
Note: All efforts should be made to collect the labs prior to dosing. Fasting is not required.			

[redacted]

7.2.2.5.1 Pregnancy and assessments of fertility

All women of childbearing potential must have a negative serum or urine pregnancy test ≤ 48 hours prior to administration of midostaurin on Day 1 of Cycle 1.

Women considered Post-menopausal and **not** of childbearing potential if they have had 12 months of natural (spontaneous) amenorrhea with an appropriate clinical profile (e.g. age appropriate, history of vasomotor symptoms).

Note: Barrier contraceptives must be used throughout the study in both sexes.

7.2.2.6 Radiological examinations

A screening chest image; Chest x-ray (CXR) or CT scan must be performed to assess study eligibility. If a CXR or CT scan was done within 14 days of screening assessments then it does not need to be repeated.

7.2.2.7 Cardiac assessments

7.2.2.7.1 Electrocardiogram (ECG)

A standard 12 lead ECG will be performed

- at screening
- at Cycle 1: Day 1 (pre-dose)
- at Cycle 1: Day 3
- at Cycles 2-12: Day 1
- End of Treatment (EOT) or Treatment Discontinuation

Currently the effect of midostaurin on QTc interval prolongation is not fully characterized. Therefore, all patients experiencing a post baseline prolonged QTc interval must have potassium and magnesium checked and any electrolytes imbalances corrected. Additionally, the investigator should consider the risk benefit of any concomitant medications that may prolong the QTc interval. For the purpose of this trial, the correction formula according to Fredericia, i.e. QTc**F** is being referred to - wherever QTc is mentioned.

The baseline ECG QTc interval must be less or equal than 450 ms.

[redacted]

Table 7-7 ECG collection plan

QTc Interval	Action
ECG > 450msec	If the ECG shows a QTc interval greater than 450 msecs at screening or during the trial, triplicates should be performed, one minute apart to confirm the finding (after replacement of any electrolyte imbalance). If 2/3 or 3/3 of the ECGs confirm the QT prolongation (i.e. QTc interval > 450 msecs) the patient must not be included into the trial.
> 450 msecs and ≤ 470 msecs	Check magnesium and potassium levels and correct any abnormalities. If possible, stop any medications that may prolong the QTc interval. Continue midostaurin at the same dose.
QTc interval > 470 msecs and ≤ 500 msecs,	Check magnesium and potassium levels and correct any abnormalities. If possible, stop any medications that may prolong the QTc interval. Decrease midostaurin to 25 mg twice daily for the remainder of the cycle/or for 2 weeks. Resume midostaurin at the initial dose in the next cycle provided that QTc interval improves to ≤ 470 msecs.
> 500 msecs	Check magnesium and potassium levels and correct any abnormalities. Hold or interrupt midostaurin for the remainder of the cycle, and, if possible, stop any medications that may prolong the QTc interval. If QTc improves to ≤ 470 msecs just prior to the next cycle, resume midostaurin at the initial dose. If QTc interval is not improved in time to start the next cycle do not administer midostaurin during that cycle.

Interpretation of the tracing must be made by a qualified physician and documented on the ECG eCRF page. Each ECG tracing should be labeled with the study number, patient initials (where regulations permit), patient number, date, and kept in the source documents at the study site. Clinically significant abnormalities present when the patient signed informed consent should be reported on the Medical History eCRF page. Clinically significant findings must be discussed with Novartis prior to enrolling the patient in the study. New or worsened clinically significant findings occurring after informed consent must be recorded on the Adverse Events eCRF page.

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

An echocardiogram or MUGA scan must be performed

- at screening prior to Day 1
- at Cycle 3, 6
- at the EOT visit

The baseline left ventricular ejection fraction (LVEF) must be > 45% for eligibility and the patient must not meet the criteria for congestive heart failure NYHA classification grade III or IV to be eligible for the trial.

The modality chosen at screening (echocardiogram or MUGA) must remain constant throughout the study. These assessments may be repeated at the investigator's discretion if there are signs or symptoms of cardiotoxicity through the study between the above mentioned time-points.

[redacted]

Should the investigator consider that there is an EF decrease which is clinically relevant, Novartis must be informed. The study drug must be withheld. A discussion will take place with the sponsor to determine the necessary steps to be taken to safeguard the patient.

7.2.3 Pharmacokinetics (PK)

Blood samples for pharmacokinetic assessment will be collected only for patients receiving midostaurin.

Routine PK blood collection will be completed at each visit; [redacted]

7.2.3.1 Routine pharmacokinetic (PK) blood collection

Trough blood samples must be taken prior to midostaurin administration, refer to Table 7-8 for collection schedule. A pharmacokinetic collection applies only to patients randomized to the midostaurin treatment arm.

Patients are instructed to bring their medication with them during their weekly visits and not to eat prior to their visit. After the trough/pre-dose PK samples are collected on the visit day, patients will then be instructed to take midostaurin following food intake.

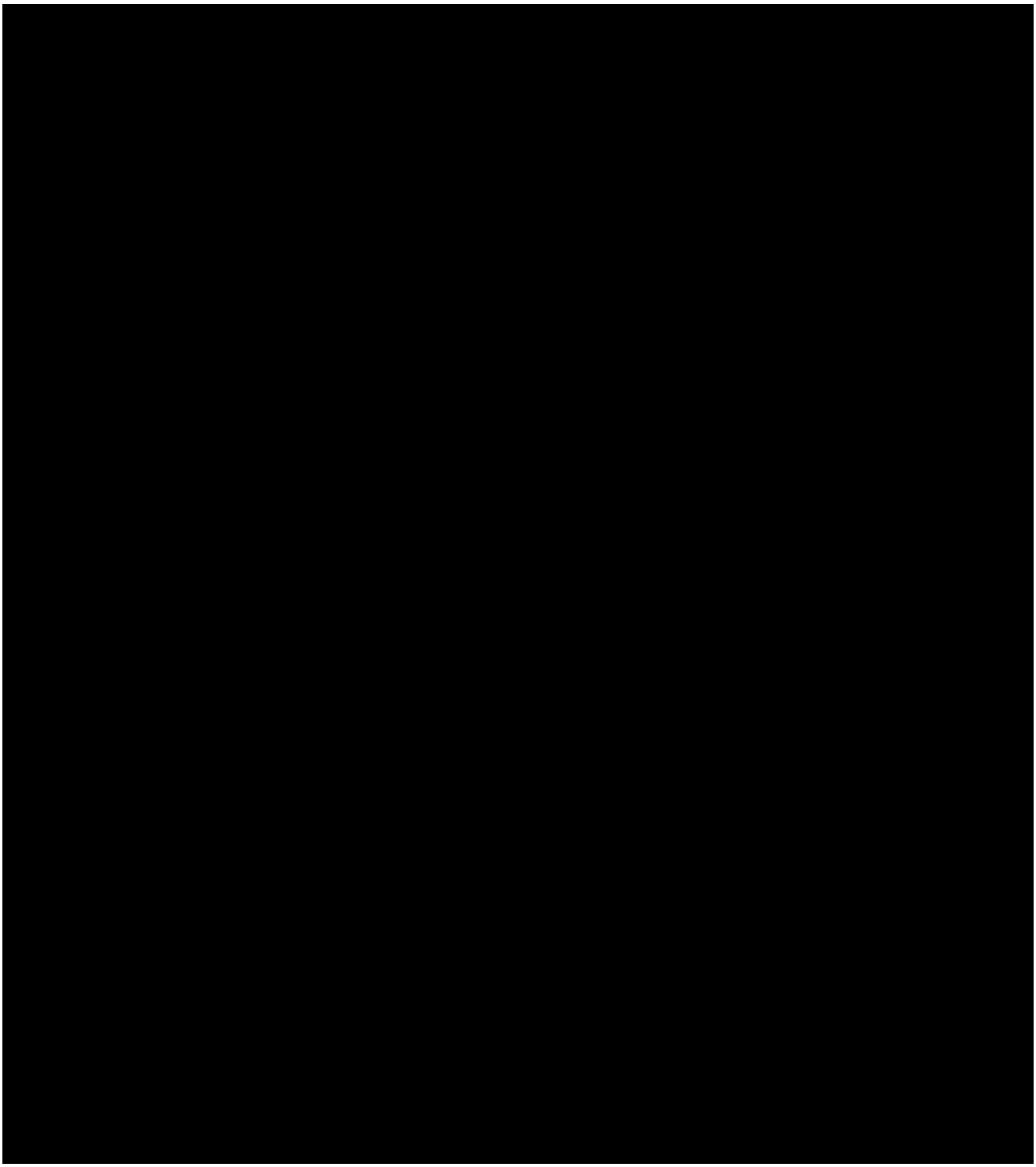
The collection date and time of all samples must be documented on the Routine PK blood collection eCRF page in addition to the date and time of dosing.

Refer to the CPKC412AUS23 Laboratory Manual for detailed instructions for the collection, handling, and shipment of PK samples.

Table 7-8 Routine pharmacokinetic blood collection log

Treatment Period or Cycle	Day	Scheduled Time Point	PK Sample No	Sample Volume
1	1	Pre-dose/0h	101	3 mL
1	15	Pre-dose/0h	102	3 mL
2	1	Pre-dose/0h	103	3 mL
3	1	Pre-dose/0h	104	3 mL
4	1	Pre-dose/0h	105	3 mL
5	1	Pre-dose/0h	106	3 mL
6	1	Pre-dose/0h	107	3 mL
7	1	Pre-dose/0h	108	3 mL
8	1	Pre-dose/0h	109	3 mL
9	1	Pre-dose/0h	110	3 mL
10	1	Pre-dose/0h	111	3 mL
11	1	Pre-dose/0h	112	3 mL
12	1	Pre-dose/0h	113	3 mL

[redacted]

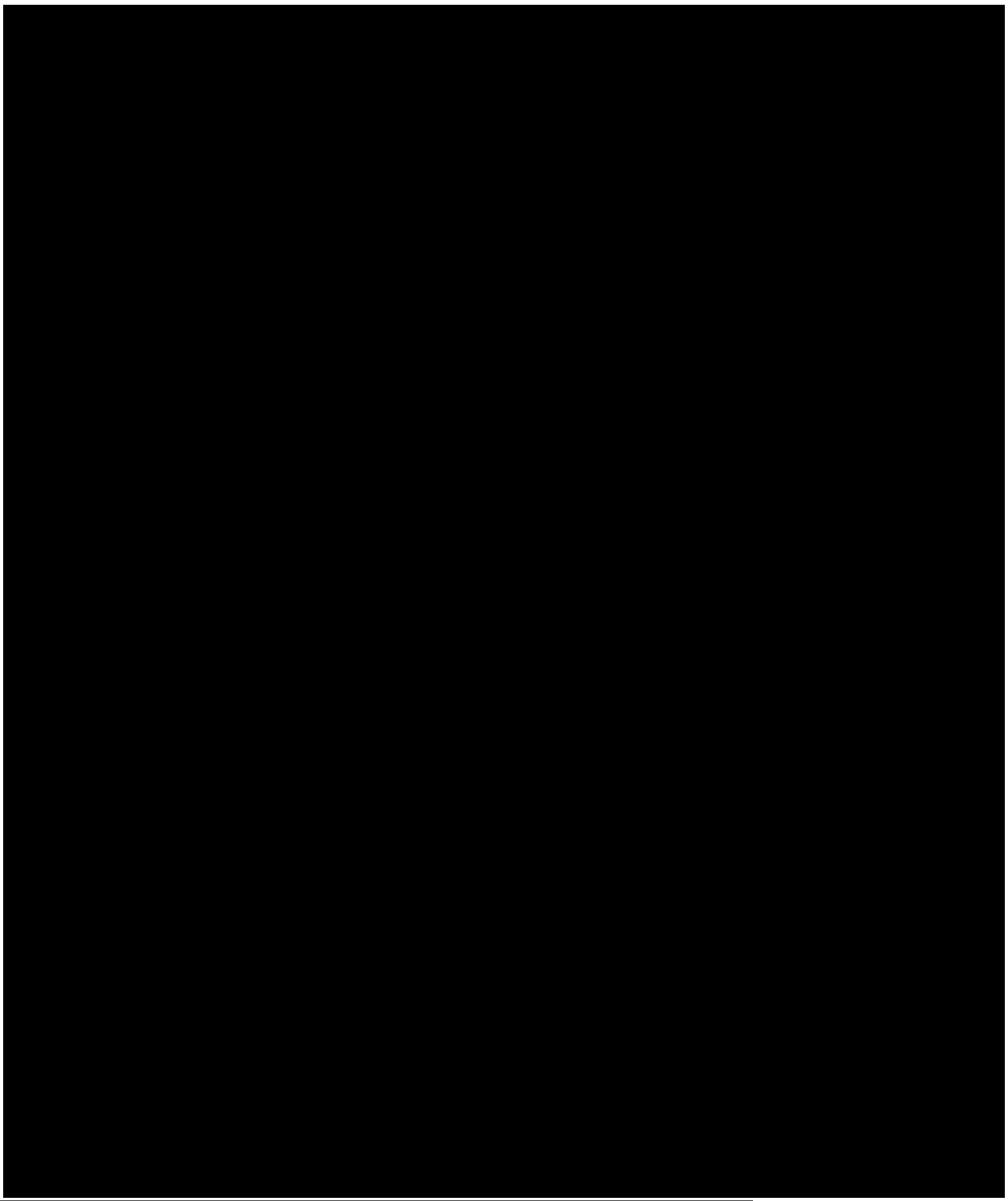


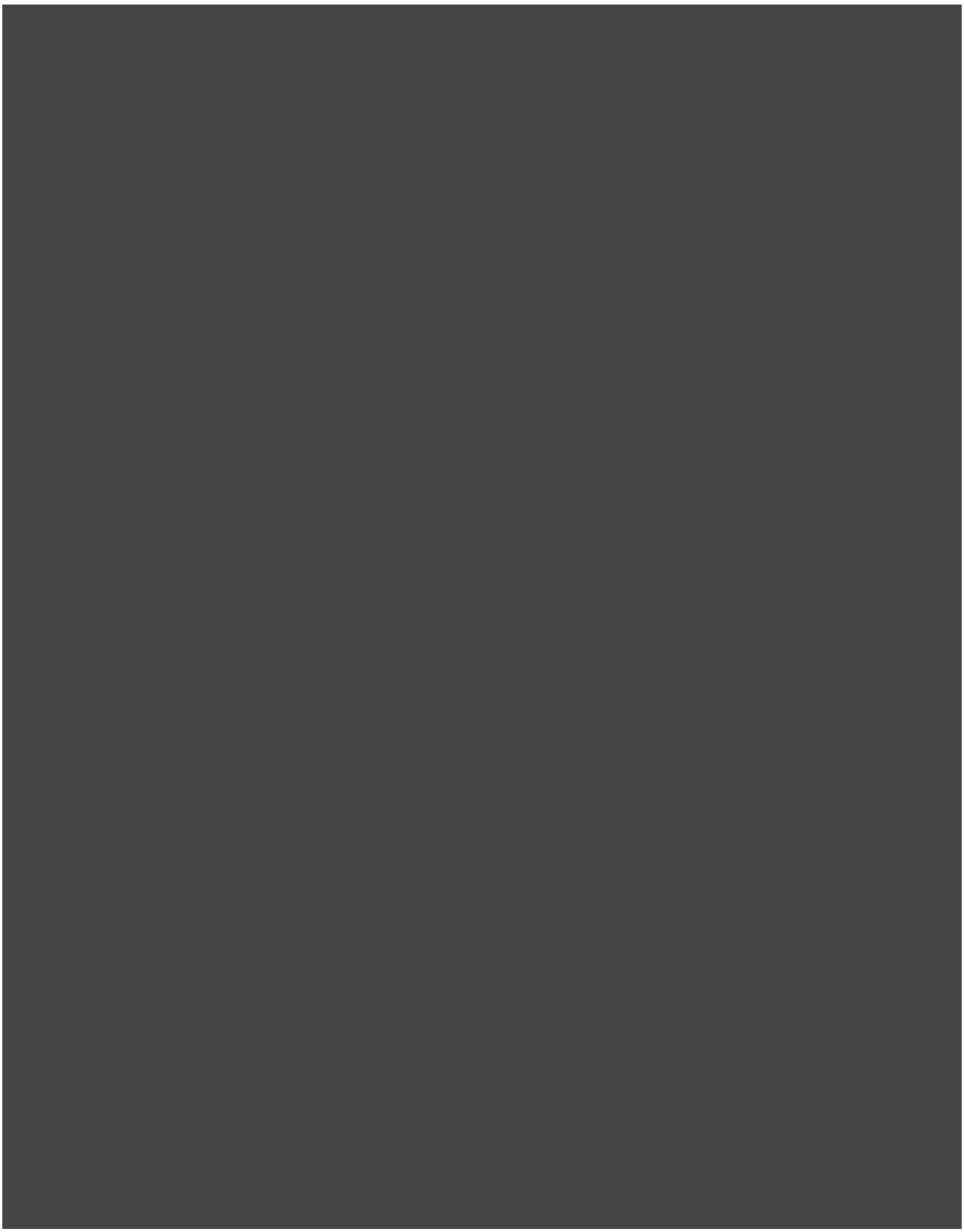
7.2.4 Biomarkers

7.2.4.1 Central determination of FLT3 ITD status

In this study, patients are permitted to enroll based on the locally known FLT3-ITD mutation status which was determined at diagnosis. In order to establish the concordance of the original FLT3 ITD mutation status with that which is determined centrally using a fully characterized

and analytical validated assay, FLT3-ITD mutation status will be re-assessed using remaining historical material, if available, from the original diagnostic specimen. All patients will be asked to provide a historical sample of tissue at the time from which they had confirmation of their diagnosis. The specimens which may be used for this purpose include stored frozen mononuclear cells or DNA if available.





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.

Patients whose FLT3-ITD status is known will sign the main study ICF.

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).

Except for screen failures, Adverse events that begin or worsen after informed consent should be recorded in the Adverse Events eCRF. Conditions that were already present at the time of informed consent should be recorded in the Relevant Medical History/Current Medical Conditions page of the patient's eCRF. Adverse event monitoring should be continued for at least 30 days (or 5 half-lives, whichever is longer) following the end of treatment as defined in Section 7.1.3. 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 according to the Common Terminology Criteria for Adverse Events (CTCAE) version 4.0.

If CTCAE grading does not exist for an adverse event, the severity of mild, moderate, severe, and life-threatening, corresponding to Grades 1 - 4, will be used. CTCAE Grade 5 (death) will not be used in this study; rather, information about deaths will be collected on the EOT/SEC/Survival Information eCRFs.

The occurrence of adverse events should be sought by non-directive questioning of the patient (subject) 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 (subject) 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 1-4)
2. Its duration (Start, End or Ongoing)
3. Its relationship to the study treatment (Reasonable possibility that AE is related: No, Yes, investigational treatment, Yes, the study treatment (non-investigational), Yes, both and/or indistinguishable)
4. Action taken with respect to study or investigational treatment (none, dose adjusted, temporarily interrupted, permanently discontinued, unknown, not applicable)

[redacted]

5. Whether medication or therapy was given (no concomitant medication/non-drug therapy, concomitant medication/non-drug therapy)
6. Outcome (not recovered/not resolved, recovered/resolved, recovering/resolving, recovered/resolved with sequalae, fatal, unknown)
7. Whether it is serious, where a serious adverse event (SAE) is defined as in Section 8.2.1.

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 eCRF.

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.

Progression of malignancy (including fatal outcomes), if documented by use of appropriate method should not be reported as a serious adverse event.

Adverse events separate from the progression of malignancy (example, deep vein thrombosis at the time of progression or hemoptysis concurrent with finding of disease progression) 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 Adverse event 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 Adverse Events eCRF. 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.

8.2 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

[redacted]

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

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

For patients with known FLT3-ITD status who sign the main study ICF, SAE collection starts at time of main study informed consent whether the patient is a screen failure or not.

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 SAEs experienced after this 30 days period (or 5 half-lives) whichever is longer) should only be reported to Novartis if the investigator suspects a causal relationship to the study treatment. Recurrent episodes, complications, or progression of the initial SAE 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.

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 send the completed, signed form by fax within 24 hours to the oncology Novartis Drug Safety and Epidemiology (DS&E) department.

The telephone and telefax number of the contact persons in the local department of Drug Safety and Epidemiology (DS&E), specific to the site, are listed in the investigator folder provided to each site. The original copy of the SAE Report Form and the fax confirmation sheet must be kept with the case report form documentation at the study site.

Follow-up information is sent to the same contact(s) to whom the original SAE Report Form was sent, using a new SAE Report Form stating that this is a follow-up to the previously reported SAE and giving the date of the original report. Each re-occurrence, complication, or

[redacted]

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 (new occurrence) and is thought to be related to the Novartis study treatment, an oncology Novartis Drug Safety and Epidemiology (DS&E) 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 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

Not applicable.

8.4 Pregnancy prevention requirements

Refer to Exclusion criteria Section 5.3.

8.5 Pregnancy reporting

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 Drug Safety and Epidemiology Department (DS&E). Pregnancy follow-up should be recorded on the same form and should include an assessment of the possible relationship to the study treatment any pregnancy outcome. Any SAE experienced during pregnancy must be reported on the SAE Report Form.

In addition, pregnancy outcomes must 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.

8.6 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.

[redacted]

8.7 Data Monitoring Committee

No Data Monitoring Committee (DMC) will be used in this trial since this is a double-arm, open label study. Safety data will be monitored by internal safety personnel in conjunction with the independent review committee (IRC).

8.8 Independent Review committee

The Independent review committee (IRC) will consist of 3 to 5 physicians that are transplant experts not participating in the trial.

The IRC will ensure transparent management of the study according to the protocol through recommending and approving modifications as circumstances require. The IRC will complete a safety review of the initital 10, 20, and 30 patients on SOC or SOC + midostaurin completing at least 3 cycles or discontinued. Additional patients may be reviewed up to complete trial enrollment at the IRC's discretion. The IRC will review safety information to include (but not limited to) adverse events, serious AEs, lab parameters, bone marrow results [redacted] in addition to protocol amendments as appropriate. Together with the clinical trial team, the IRC will also develop recommendations for publications of study results including authorship rules. The details of the role of the Independent Review Committee will be defined in a Independent Review Committee charter.

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 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.

[redacted]

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 eCRFs 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 eCRFs, the adherence to the protocol to Good Clinical Practice, the progress of enrollment, and to ensure that study drug 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 eCRFs 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 eCRFs are performed according to the study-specific monitoring plan.

9.3 Data collection

The designated investigator staff will enter the data required by the protocol into the Electronic Case Report Forms (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 Principal Investigator is responsible for assuring that the data entered into eCRF is complete, accurate, and that entry and updates are performed in a timely manner.

Results from FLT3 mutation analysis, [redacted], PK sampling [redacted] will be centrally analyzed and the data will be transferred to Novartis (or designated CRO) upon completion of analysis.

9.4 Database management and quality control

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 is 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

[redacted]

classification system. Medical history/current medical conditions and adverse events will be coded using the Medical dictionary for regulatory activities (MedDRA) terminology.

Biomarker and PK samples will be processed centrally and the results will be sent electronically to Novartis (or a designated CRO).

Diary data will be entered onto a paper diary by the patient. Planned and or changes in dosingwill be captured into the eCRF.

Screening, randomization and enrollment data changes will be tracked using an Interactive Web Response (IWRS). The system will be supplied by a vendor(s), who will also manage the database. The data will be sent electronically to Novartis personnel (or designated CRO).

At the conclusion of the study, 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. Authorization is required prior to making any database changes to locked data.

For EDC studies, after database lock, the investigator will receive a CD-ROM or paper copies of the patient data for archiving at the investigational site.

10 Statistical methods and data analysis

The primary analysis of RFS will be done when all patients have been followed up to 18 months post-HSCT.

The final safety and efficacy analyses will be conducted when all living patients have been followed up to 24 months post-HSCT.

All data will be analyzed by a designated CRO. Categorical data will be presented as frequencies and percentages. For continuous data, mean, standard deviation, median, 25^{th} and 75^{th} percentiles, minimum and maximum will be presented.

10.1 Analysis sets

10.1.1 Full Analysis Set

The Full Analysis Set (FAS) comprises all randomized patients. According to the intent to treat (ITT) principle, patients will be analyzed according to the treatment arm (SOC +/- midostaurin) they have been assigned to during the randomization procedure.

10.1.2 Safety Set

Patients are analyzed according to the treatment received. Patients who received at least one dose of midostaurin during the study will be allocated to the SOC + midostaurin treatment arm. Patients randomized to the SOC + midostaurin arm but who never received midostaurin will be allocated to the SOC treatment arm.

10.1.3 Per-Protocol Set

The Per Protocol Set (PPS) consists of all patients from the Full Analysis Set without any major protocol deviations. Protocol deviations leading to the exclusion of from the PPS will

[redacted]

be specified in the study Validation and Planning (VAP) and Report and Analysis Plan (RAP) documents prior to database lock.

10.1.4 Pharmacokinetic Analysis Set

The **Pharmacokinetic Set (PK Set)** comprises all patients that have been administered at least one dose of midostaurin and that have provided at least one evaluable PK sample.

10.2 Patient demographics/other baseline characteristics

Demographic and other baseline data (including disease characteristics) will be listed and summarized by treatment group using the FAS.

10.3 Treatments (study treatment, concomitant therapies, compliance)

Concomitant medications and significant non-drug therapies prior to and after the start of the study treatment will be summarized by treatment group for the safety set.

10.3.1 Study medication

The study drug (midostaurin) administration will be summarized. The number of treated patients, number of patients who had dose reduction/interruption and the duration of treatment will be presented.

The duration includes the periods of temporary interruption (of any component of the study treatment for any reason).

The safety population will be used for all above mentioned tables and listings.

10.3.2 Concomitant therapies

Concomitant medications and non-drug therapies taken concurrently with the study drugs will be listed and summarized by ATC class, preferred term and treatment arm by means of frequency counts and percentages. These summaries will include medications starting on or after the start of study treatment or medications starting prior to the start of study treatment and continuing after the start of study treatment.

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

The safety population will be used for all above mentioned concomitant medication tables and listings.

10.4 Primary objective

10.4.1 Relapse free survival

The primary endpoint is relapse free survival (RFS), defined as the time from transplant to relapse or death due to the disease 18 months post transplant. If a patient has more than one event (e.g. relapse then death) then the earliest date will be taken into account.

[redacted]

10.4.2 Statistical hypothesis, model, and method of analysis

Kaplan-Meier plots will be used to depict RFS over time in each treatment arm. Median survival will be obtained along with 95% CI calculated using the method of Brookmeyer & Crowley. Kaplan-Meier estimates with 95% CI will be summarized every 6 month using Greenwood's formula for the standard error of the Kaplan-Meier estimate. The primary objective is related to the Kaplan-Meier estimate at 18 months.

In addition to the Kaplan-Meier estimates, a Cox proportional hazards model will be used to provide an estimate of the Hazard Ratio ($HR_{SOC+Midaustorin/SOC}$) and associated Wald 95% Confidence Interval (CI).The primary analysis will be performed on the FAS.

10.4.3 Handling of missing values/censoring/discontinuations

Patients alive in remission at the time of the data cut-off point used for the analysis will have RFS censored at the time of last measurement prior to the data cut-off point. The number of patients having an event and number of patients censored will be summarized. A summary of reasons censoring will be provided by treatment arm.

Novartis AML guidance and the FDA guideline on endpoints (Clinical Trial Endpoints for the Approval of Cancer Drugs and Biologics, 2007) will not consider a relapse event if observed after two or more consecutive missing assessments and will censor the RFS and DFS at the last adequate assessment date.

10.4.4 Supportive analyses

The primary analysis will be repeated on the PP Set as a supportive analysis.

In addition to that, a sensitivity analysis will be performed on RFS using the time from randomization as reference time-point instead of the time from transplant.

The same statistical analyses as the previous one described Section 10.4.2 will be performed on this variable.

This sensitivity analysis will be performed on the FAS.

10.5 Secondary objectives

10.5.1 Key secondary efficacy evaluation

The secondary efficacy variables include:

- Disease Free Survival (DFS)
- Relapse Free Survival (RFS)
- Overall Survival (OS)

DFS is defined as the time from transplant to relapse or death from any cause. RFS is defined as the time from transplant to relapse or death due to the disease. OS is defined as the time from transplantation to the date of death from any cause. Follow up will continue until all patients have been followed for 24 months post HSCT unless all patients have died or have withdrawn from the study prior to that time.

[redacted]

Kaplan-Meier plots will be used to depict each secondary endpoint over time in each treatment arm. Median survival will be obtained along with 95% CI calculated using the method of Brookmeyer & Crowley. Kaplan-Meier estimates with 95% CI will be summarized every 6 month using Greenwood's formula for the standard error of the Kaplan-Meier estimate.

In addition to the Kaplan-Meier estimates, Cox proportional hazards models will be used to provide estimates of the Hazard Ratio ($HR_{SOC+Midaustorin/SOC}$) and associated Wald 95% Confidence Interval (CI) for each secondary endpoint.

These analyses will be performed on the FAS.

10.5.2 Safety objectives

10.5.2.1 Analysis set and grouping for the analyses

For all safety analyses, the Safety Set (SS) will be used. All listings and tables will be presented by treatment group.

The safety summary tables will include only "on-treatment" assessments. On treatment assessments will be considered as:

- SOC arm (whichever comes first):
  From randomization until discontinuation, relapse or completion of treatment phase (12cycles) + 30 days
- SOC + PKC arm:
  From first intake of study drug to last intake of study drug + 30 days

Safety will be assessed by the Common Toxicity Criteria for Adverse Events (CTCAE) version 4.0. Incidence of adverse events (AEs), serious adverse events (SAEs), changes from baseline in clinically notable changes in vital signs and CTC grading for laboratory results (hematology, blood chemistry, ECGs) will be reported.

10.5.2.2 Adverse events (AEs)

Summary tables for adverse events (AEs) have to include only AEs that started or worsened during the on-treatment period, the ***treatment-emergent*** AEs. However, all safety data (including those from the pre and post-treatment periods) will be listed and those collected during the pre-treatment and post-treatment period are to be flagged.

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), type of adverse event, relation to study treatment by treatment group.

Deaths reportable as SAEs and non-fatal serious adverse events will be listed by patient and tabulated by type of adverse event and treatment group.

10.5.2.3 Laboratory abnormalities

All laboratory values will be converted into SI units and the severity grade calculated using Common Toxicity Criteria for Adverse Events (CTCAE).

[redacted]

Shift tables using CTC grades to compare baseline to the worst post-baseline value will be produced for hematology and biochemistry laboratory parameters with CTC grades. In addition, shift tables using laboratory normal ranges to compare baseline to the worst post-baseline value will be produced for other parameters without CTC grades, if any (Ranges: Low, Normal, High).

All laboratory values will be listed by laboratory parameter and patient. Separate listings will display notable laboratory abnormalities (i.e. newly occurring CTCAE grade 3 or 4 laboratory toxicities).

10.5.2.4 Other safety data

Summary statistics for data from other tests will be provided, notable values will be flagged, and any other information collected will be listed as appropriate.

Descriptive summary statistics will be provided for data for:

ECG

- shift table baseline to worst on-treatment result for overall assessments
- listing of ECG evaluations for all patients with at least one abnormality.

Vital signs and weight

Summary statistics of raw data and change from baseline values (means, medians, standard deviations), newly occurring or worsening abnormalities of vital signs and weight.

Listings with flagged notable values and any other information collected will be provided as appropriate.

10.5.2.5 Tolerability

To determine whether midostaurin can be administered at a daily dose of 50mg twice daily at least 80% of the time to 50% or more of patients during the first 100 days after allogeneic HSCT

10.5.2.6 Non-relapse mortality

NRM is defined as the duration between the date of transplant and the date of patient death due to reasons other than relapse.

Kaplan-Meier plots will be used to depict non-relapse mortality over time in each treatment arm. Median survival will be obtained along with 95% CI calculated using the method of Brookmeyer & Crowley. Kaplan-Meier estimates with 95% CI will be summarized every 6 month using Greenwood's formula for the standard error of the Kaplan-Meier estimate.

In addition to the Kaplan-Meier estimates, Cox proportional hazards models will be used to provide estimates of the Hazard Ratio ($HR_{SOC+Midaustorin/SOC}$) and associated Wald 95% Confidence Interval (CI) for each secondary endpoint.

These analyses will be performed on the FAS.

[redacted]

10.5.3 Pharmacokinetics

Descriptive statistics will be presented for all concentration data of midostaurin and its metabolites obtained by Cycle, and/or Day and time-point. These include geometric and arithmetic means, standard deviation (SD), and coefficient of variance (CV).

10.5.3.1 FLT3 ITD mutation status

Descriptive statistics of FLT3 ITD mutation status centrally assessed will be provided.

10.5.3.2 Data handling principles

Missing concentration values will be reported as is in data listings. Concentration values below Lower Limit of Quantitation (LLOQ, BLLOQ) will be handled as zero in summary statistics, and reported as is in data listings. Any missing pharmacokinetic parameter data will not be imputed.

10.5.4 Biomarkers

The FLT3 results from the centralized assay using archived material will be compared to the local result, and differences will be described.

In addition, the clinical outcome of RFS and DFS based on the FLT3 ITD result from the centralized assay compared to the local FLT3 ITD status will also be described.

10.7 Interim analysis

Not applicable

10.8 Sample size calculation

This study is a Phase II exploratory trial and is not powered to detect a statistical difference between the two arms. The sample size for the trial was chosen; 30 patients per treatment arm to haveseparate estimates of the primary endpoint relapse free survival. Powering of the trial

is not feasible considering the rare nature of FLT3-ITD mutant AML receiving a HSCT. With a 22-25% FLT3-ITD mutation rate and approximately 25% rate of HSCT, estimated from the ongoing Phase III study (2301, CALGB 10603, Ratify), more than 1050 newly diagnosed AML patients would need to be evaluated to identify 60 patients undergoing HSCT in CR1. The control arm, Standard of Care (SOC), in this study provides the first prospective subjects treated at the same centers in the same timeframe which will allow an estimate of treatment effect which can be used to design a larger trial. There are no published sets of prospective, FLT3-ITD AML outcomes after transplantation

If the two arms were compared, the following gives the power that could be achieved under 2 scenarios of relapse rate with 30 patients per treatment arm.

Scenario 1: Assuming a 30% relapse rate in the SOC arm

Scenario 2: Assuming a 50% reduction with midostaurin (experimental arm)

i.e., 15% relapse rate in the experimental arm, a sample size of 30 patients in each arm will detect the reduction with 71% power. This calculation is based on one-sided type I error rate of 20%. The power would be 81% if we assume relapse rate to be even lower at 12% keeping everything else the same.

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 ICH Harmonized Tripartite Guidelines for Good Clinical Practice, 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.

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 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 or, if incapable of doing so, after such consent has been provided by a legally acceptable representative of the patient. In cases where the patient's representative gives consent, the patient should be informed about the study to the extent possible given his/her understanding. If the patient is

[redacted]

capable of doing so, he/she should indicate assent by personally signing and dating the written informed consent document or a separate assent form.

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 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. If there is any question that the patient will not reliably comply, they should not be entered in the study.

[redacted]

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 4.3.

11.5 Publication of study protocol and results

Novartis assures that the key design elements of this protocol will be posted in a publicly accessible database such as clinicaltrials.gov. In addition, upon study completion and finalization of the study report the results of this study will be either submitted for publication and/or posted in a publicly accessible database of clinical study results.

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

[redacted]

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.

Data collection is the responsibility of the clinical trial staff at the site under the supervision of the site Principal Investigator. The study electronic case report form (eCRF) 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 eCRFs and all other required reports. Data reported on the eCRF, that are derived from source documents, should be consistent with the source documents or the discrepancies should be explained. All data requested on the eCRF must be entered. Any missing data must be explained. For electronic eCRFs 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.

[redacted]

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 (e.g. UK requires the notification of urgent safety measures within 3 days) but not later than 10 working days.

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