NOVARTIS

Oncology Global Medical Affairs

PKC412 / MIDOSTAURIN

Oncology Clinical Trial Protocol CPKC412A2408 / NCT03379727

An open-label, multicenter, Phase IIIb study to assess the safety and efficacy of midostaurin (PKC412) in patients 18 years of age or older with newly-diagnosed FLT3-mutated Acute Myeloid Leukemia who are eligible for "7+3" or "5+2" chemotherapy

Document type	Amended Protocol Version
EUDRACT number	2016-004440-12
Version number	01 (Clean)
Development phase	IIIb
Document status	Final
Release date	26-Mar-2018

Template version 6-Apr-2017

[redacted]

Table of contents

[redacted]

[redacted]

[redacted]

[redacted]

List of figures

List of tables

List of abbreviations

AE	Adverse Event
Allo HSCT	Allogeneic Hematopoietic Stem Cell Transplantation
ALT/GPT	Alanine aminotransferase / glutamic pyruvic transaminase
AML	Acute Myeloid Leukemia
ARA-C	cytosine arabinoside
ASM	Aggressive systemic mastocytosis
AST/GOT	Aspartate aminotransferase / glutamic oxaloacetic transaminase
AUC	AUC area under the (concentration-time) curve
b.i.d.	bis in diem / twice a day
CALGB	Cancer and Leukemia Group B
C_{max}	Maximum plasma drug concentration
C_{min}	Minimal plasma drug concentration
CMO&PS	Chief Medical Office and Patient Safety
CNS	Central Nervous System
CR / CRi	Complete remission / Complete remission with incomplete recovery
CRF/eCRF	Case Report / Record Form; the term CRF can be applied to either EDC or Paper
CRO	Contract Research Organization
CSR	Clinical study report
CTCAE	Common Toxicity Criteria for Adverse Events
DFS	Disease-free Survival
DLT	Dose Limiting Toxicity
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
EDC	Electronic Data Capture
EFS	Event-free survival
[redacted]	[redacted]
FAS	Full Analysis Set
FLT3	Fms-like tyrosine kinase 3
HiDAC	High Dose Ara-Cytarabine
[redacted]	[redacted]
IC_{50}	Half maximal inhibitory concentration
ICF	Inform Consent Form
ICH	International Conference on Harmonization
IEC	Independent Ethics Committee
IRB	Institutional Review Board
IRT	Interactive Response Technology that includes Interactive Voice Response System and Interactive Web Response System
ITD	Internal tandem duplication
LPFV	Last Patient First Visit
LPLV	Last Patient Last Visit
LVEF	Left Ventricular Ejection Fraction
MCL	Mast cell leukemia
MDS	Myelodysplasia Syndrome
MUGA	Multiple gated acquisition
NE	Not estimable

[redacted]

NCCN	National Comprehensive Cancer Network
NOEL	No observable effect level
NPM1	Nucleophosmin (nucleolar phosphoprotein B23)
NYHA	New York Heart Association
ORR	Overall Response Rate
OS	Overall survival
[redacted]	[redacted]
P-gp	P glycoprotein
PHI	Protected Health Information
[redacted]	[redacted]
QTc	Corrected QT Interval
R Value	ALT / ALP in x ULN
REB	Research Ethics Board
RT	Radiation therapy
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SCT	Stem Cell Transplantation
TBIL	Total Bilirubin
TKD	Tyrosine kinase domain
WT	Wild-type

[redacted]

Glossary of terms

Assessment	A procedure used to generate data required by the study
Biologic Samples	A biological specimen including, for example, blood (plasma, serum), saliva, tissue, urine, stool, etc. taken from a study subject or study patient
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 (e.g.: q28 days)
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 treatment whose properties are being tested in the study; this definition is consistent with US CFR 21 Section 312.3 and is synonymous with "investigational new drug."
Investigational treatment	Drug whose properties are being tested in the study as well as their associated placebo and active treatment controls (when applicable). This also includes approved drugs used outside of their indication/approved dosage, or that are tested in a fixed combination. Investigational treatment generally does not include other study treatments administered as concomitant background therapy required or allowed by the protocol when used in within approved indication/dosage
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 (Patient No. NOVDD) Subject Number (Subject No. NCDS)	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.
Stage in cancer	The extent of a cancer in the body. Staging is usually based on the size of the tumor, whether lymph nodes contain cancer, and whether the cancer has spread from the original site to other parts of the body
Stop study participation	Point/time at which the patient came in for a final evaluation visit or when study treatment was discontinued whichever is later
Study treatment	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.
Study treatment discontinuation	Point/time when patient permanently stops taking study treatment for any reason
Treatment group	A treatment group defines the dose and regimen or the combination, and may consist of 1 or more cohorts. Cohorts are not expanded, new cohorts are enrolled.
Variable	Identifier used in the data analysis; derived directly or indirectly from data collected using specified assessments at specified time points
Withdrawal of consent	Withdrawal of consent occurs only when a patient does not want to participate in the study any longer, and does not want any further visits or assessments, and does not want any further study related contact

[redacted]

Amendment 1 (26-Mar-2018)

Amendment rationale

The primary purpose of this amendment is 3 folds.

The first is to allow the use of historical bone marrow aspiration (BMA) result performed for AML diagnosis if available within 15 days before C1D1 of the first chemotherapy, in order to limit the repetition on this invasive assessment.

The second is an adaptation of the recovery periods in induction phase and the first cycle of consolidation based on the RATIFY study results analysis (Figure 4-2).

The third is to align between Section 5.3 exclusion criteria #8 and Section 6.4.1.2 Contraceptives with midostaurin, the duration of the post study contraception to 4 months, as per approved midostaurin labeling information.

Other minor changes and corrections were made throughout the protocol for consistency and/or clarifications.

Changes to the protocol

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 underline for insertions.

- Section 2.2: Rationale for the study design. To explain the change of administration of Midostaurin in comparison with the label (Day 21 --> Day 28). This change is considered as non-substantial.
- Table 6-2: Dose and treatment schedule – Consolidation. Cytarabine dose, route and frequency has been updated with infusion over 3 hours every 12h on days 1, 3 and 5, up to 4 cycles based on age and per investigator discretion. This change is considered as non-substantial.
- Section 6.3.4.1: Cytarabine – dose modifications for neurotoxicity section number has been updated to 6.3.5. This change is considered as non-substantial.
- Section 6.3.4.2.: Dose modification for obese patients: section number has been updated to 6.3.6. This change is considered as non-substantial.
- Section 6.3.5: Anticipated risks and safety concerns of the study drug section has been updated to 6.3.7. This change is considered as non-substantial.
- Section 6.3.6: Follow-up for toxicities: section number has been updated to 6.3.8. This change is considered as non-substantial.
- Section 6.3.6.1: Follow up on potential drug-induced liver injury (DILI) cases: section number has been updated to 6.3.8.1. This change is considered as non-substantial.
- Section 6.4.1.2: Contraceptives with midostaurin. The duration of the post study contraception has been increased from 3 months to 4. This change is considered as substantial.
- Table 7-1: Visit evaluation schedule. A screening period has been defined within the screening/baseline visit between C1D1-C1D7. This change is considered as non-substantial.

[redacted]

- Section 7.1.2: Screening. To allow investigators to use the BMA result used for AML diagnosis if available within 15 days before C1D1 of the first chemotherapy. This change is considered as substantial.
- Section 7.2.1: Efficacy assessments. During the first induction therapy a period window of 7 days has been added for the bone marrow assessment. This change is considered as substantial.
- Section 7.2.1: Efficacy assessments. Within the second induction therapy paragraph the notion of "if applicable" has been added for a better understanding. This change is considered as non-substantial.
- Section 7.2.2.5.3: Pregnancy and assessments of fertility. Paragraph aligned with safety follow up requirement, pregnancy test requires day 1 of every cycles in maintenance phase. This change is considered as substantial.
- Section 11.3: Informed consent procedures. The last paragraph starting with; "Women of child bearing potential..." has been updated mentioning that: "the patients must adhere to the contraception requirement for the duration of the study, and after treatment stop." This change is considered as non-substantial.

IRBs/IECs

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

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

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

[redacted]

Protocol summary

Title	An open-label, multi-center, Phase IIIb study to assess the safety and efficacy of midostaurin (PKC412) in patients 18 years of age or older with newly-diagnosed FLT3-mutated Acute Myeloid Leukemia who are eligible for "7+3" or "5+2" chemotherapy
Brief title	Study to assess the safety and efficacy of midostaurin (PKC412) in combination with standard chemotherapy during induction and consolidation followed by 12 months of monotherapy in patients with newly-diagnosed FLT3-mutated Acute Myeloid Leukemia
Sponsor and Clinical Phase	Novartis Pharma AG Phase IIIb
Investigation type	Drug
Study type	Interventional
Purpose and rationale	The purpose of this study is to gather and evaluate additional safety and efficacy data on the combination of midostaurin and standard of care for adult patients with newly diagnosed Fms-like tyrosine kinase receptor (FLT3) mutated Acute Myeloid Leukemia (AML) who are eligible for standard induction and consolidation
Primary Objective(s) and Key Secondary Objective	To further assess the safety of midostaurin in induction, consolidation and maintenance therapy, including, the "7+3" regimen, daunorubicin (60-90mg/m^2/day), the substitution of daunorubicin by idarubicin (12mg/m^2/day) and cytarabine (100-200 mg/m^2/day) and allowing the "5+2" reduced dose regimen
Secondary Objectives	To assess the clinical efficacy of midostaurin in combination with chemotherapy regimens in induction and consolidation and the clinical efficacy of midostaurin in maintenance phase (measured by CR/CRi rate)
Study design	A global, open-label, single arm, multicenter, Phase IIIb study to assess the safety and efficacy of midostaurin (PKC412)
Population	Approximately 300 patients will be enrolled. This protocol is intended for patients (male and female) 18 years of age or older with newly-diagnosed FLT3-mutated AML who are eligible for "7+3" or "5+2" chemotherapy
Inclusion criteria	Patients eligible for inclusion in this study have to meet all of the following criteria: 1. Written informed consent must be obtained prior to any screening procedures 2. Patients must be 18 years of age or older at the time of signing informed consent 3. Patients must have a documented unequivocal diagnosis of AML according to WHO 2008 classification. A bone marrow or blood blast count of ≥20% is required, except for AML with t(15;17), t(8;21), inv(16) or t(16;16) where blast count may be <20%,and excluding M3 (acute promyelocytic leukemia) 4. Patients with secondary AML are eligible, e.g. patients with antecedent history of treatment for prior malignancy. AML patients with a history of antecedent treatment for myelodysplasia (MDS), e.g. azacitidine or decitabine, remain eligible for treatment on this study. These agents must have been discontinued for a period of at least 30 days or 5 half-lives of the drug (whichever is greater) before midostaurin can be administered 5. Patients must have started "7+3" or "5+2" first induction chemotherapy regimen 6. Patients must have a documented FLT3 mutation (ITD or TKD) 7. Patients must have an ECOG Performance Status of ≤ 2 8. Patients requiring intrathecal chemotherapy must have a minimum washout of 48 hours prior to the first dose of midostaurin 9. Patients must have Total Bilirubin ≤ 2.5 x ULN 10. Patients must have Serum Creatinine ≤ 2.5 x ULN 11. Patients must be able to communicate well with the investigator to understand and comply with the requirements of the study

	12. Women of child-bearing potential must have a negative pregnancy test before starting use of midostaurin.
Exclusion criteria	Patients eligible for this study must not meet any of the following criteria: 1. Prior therapy for AML with the following exceptions: a. emergency leukapheresis b. emergency treatment for hyperleukocytosis with hydroxyurea for ≤ 7 days c. cranial RT for CNS leukocytosis (one dose only) d. growth factor/cytokine support 2. Patients with Left Ventricular Ejection Fraction (LVEF) less than 45% (by echocardiogram or MUGA) or symptomatic congestive heart failure (Class III or IV) according to New York Heart Association (NYHA) classification 3. Patients with any pulmonary infiltrate including those suspected to be of infectious origin (unless resolved to < Grade 1 within screening timeframe) 4. Patients with any uncontrolled illness, including, but not limited to, acute or chronic pancreatitis or uncontrolled infection 5. QTc >470 msec on screening ECG 6. History of hypersensitivity to any drugs or metabolites of similar chemical classes as the study treatment 7. Participation in a prior investigational interventional (drug) study with administration of the investigational product within 30 days or 5 half-lives of the investigational product, whichever is longer 8. Pregnancy statements and contraception requirements: Women of child-bearing potential, defined as all women physiologically capable of becoming pregnant, unless they are using highly effective methods of contraception during dosing and for at least 4 months after stopping medication. Highly effective contraception methods include: • Total abstinence (when this is in line with the preferred and usual lifestyle of the subject). Periodic abstinence (e.g. calendar, ovulation, symptothermal, post-ovulation methods) and withdrawal are not acceptable methods of contraception • Female sterilization (have had surgical bilateral oophorectomy with or without hysterectomy), total hysterectomy, or tubal ligation at least six weeks before taking study treatment. In case of oophorectomy alone, only when the reproductive status of the woman has been confirmed by follow up hormone level assessment • Male sterilization (at least 6 months prior to screening). The vasectomized male partner should be the sole partner for that subject • Use of oral, injected or implanted hormonal methods of contraception or placement of an intrauterine device or intrauterine system, or other forms of hormonal contraception that have comparable efficacy (failure rate <1%), for example hormone vaginal ring or transdermal hormone contraception In case of use of oral contraception women should also add a barrier method of contraception, particularly as it is currently unknown whether midostaurin may reduce the effectiveness of hormonal contraceptives Sexually-active males unless they use a condom during intercourse with females of reproductive potential or pregnant women and for at least 4 months after stopping treatment to avoid conception or embryo-fetal harm 9. Patients enrolled in this study are not permitted to participate in additional parallel study drug or device studies
Investigational and reference therapy	Midostaurin (PKC412)
Efficacy assessments	Efficacy of midostaurin used with chemotherapy regimens in induction, consolidation and maintenance phases will be assessed by CR/CRi rate.

[redacted]

Safety assessments	Safety will be assessed by using the Common Toxicity Criteria for Adverse Events (CTCAE) Version 4.03. Incidence of adverse event (AEs), serious adverse events (SAEs), AEs leading to treatment discontinuation and death will be reported. Other safety assessments include physical examination, vital signs, ECOG performance status, ECG, cardiac imaging and laboratory tests.
Other assessments	[redacted] Additionally, an assessment of resource utilization will be performed in order to quantify the proportion of patients by reason for hospitalization, number of hospital days, discharge reason, and concomitant medications during hospital stay.
Data analysis	Data will be summarized with respect to demographic and baseline characteristics and safety observations and measurements. Categorical data will be presented as frequencies and percentages. For continuous data, mean, standard deviation, median, minimum, and maximum will be presented.
Key words	Midostaurin (PKC412), FMS-like tyrosine kinase receptor (FLT3), Acute Myeloid Leukemia (AML), “7+3” or “5+2” chemotherapy

[redacted]

1 Background

1.1 Overview of disease pathogenesis, epidemiology and current treatment

Acute Myeloid Leukemia (AML) is the most common type of acute leukemia in adults, with an estimated incidence in the United States of 4.1 per 100,000 (approximately 20,000 new cases per year) (SEER 2016). The incidence increases with age, with more than 50% of AML patients being over 60 years old. The majority of patients with AML die from the disease, with an estimated 10,000 AML-related deaths occurring annually in the United States, i.e. approximately 2% of cancer deaths. In the European Union, based on data from RARECARE.net, the number of cases collected in the RARECAREnet database from 2000-2007 was 54,789 and the crude incidence rate was 3.5 per 100,000 (RARECARE.net October 2015). Acute Myeloid Leukemia shows heterogeneous molecular characteristics with the presence of acquired mutations as well as cytogenetic and epigenetic alterations that influence disease prognosis.

Mutations in the FMS-like tyrosine kinase-3 (FLT3) gene are found in approximately one third of patients with newly diagnosed AML, and these comprise internal tandem duplications (ITD) in 20% of patients, point mutations in the tyrosine kinase domain (TKD) in 6-8% of patients, and very rarely point mutations in the juxtamembrane domain (Kayser and Levis 2014). The FLT3 gene encodes a protein in the class III tyrosine kinase receptor family, and it serves a key role in the proliferation and differentiation of normal hematopoietic precursor cells. FLT3-ITD and FLT3-TKD mutations constitutively activate its receptor tyrosine kinase activity and thereby activate downstream signaling pathways (Meshinchi and Appelbaum 2009). FLT3-ITD mutations, particularly when they are present at a high allelic ratio relative to wild-type FLT3, are associated with poor prognosis (Thiede et al 2002, Gale et al 2008, Schlenk et al 2014).

For the past three decades, the standard therapy for younger patients with newly diagnosed AML, regardless of their cytogenetic and molecular markers, has been the “7+3”remission-induction regimen with cytarabine and daunorubicin followed by high-dose cytarabine for remission-consolidation. Studies showed that modification of the induction chemotherapy regimen resulted in little additional benefit for patients with high-risk AML, including patients with FLT3-mutations. Patients with poor prognostic features, including those with FLT3-ITD mutations, are recommended to enroll into clinical studies and/or to undergo stem cell transplantation (SCT) following achievement of remission with standard induction chemotherapy. Significant improvements in overall survival (OS) and disease-free survival (DFS) for AML patients harboring FLT3-ITD mutations have been reported with allo-SCT compared to consolidation with chemotherapy or autologous SCT (Kayser et al 2009), especially for patients with FLT3-ITD mutations with a high allelic ratio (Schlenk et al 2014). Because of the adverse prognostic impact of FLT3 gene mutations and the lack of effective therapy, there is a significant unmet need in patients with FLT3-mutated AML.

[redacted]

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

1.2.1 Overview of midostaurin

Midostaurin, also known as PKC412 or CGP41251, is an orally administered inhibitor of multiple tyrosine kinases, including the wild-type (WT) and mutated fms-like tyrosine kinase-3 (FLT3) and others implicated in the pathogenesis of AML, including the KIT tyrosine kinase (KIT), and tyrosine kinase receptors such as the vascular endothelial growth factor receptor (VEGFR), and Platelet-derived growth factor receptor (PDGFR).

1.2.1.1 Non-clinical experience

1.2.1.1.1 Non-clinical pharmacokinetics

Midostaurin is an inhibitor of several protein kinase C (PKC) isoforms, of the tyrosine kinase VEGFR and most importantly of the class III tyrosine protein kinases FLT3 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 mitogenic signaling of the respective growth factors in cells and results in growth arrest. Midostaurin is equally active against ITD- and TKD-mutated FLT3, and has been shown to exert inhibitory activity over mutated protein kinases implicated in other types of diseases, such as the proto-oncogene encoding KIT in aggressive systemic mastocytosis (ASM).

The oral absorption of [^{14}C]midostaurin in all species was moderate to high and the bioavailability was low to moderate. Given midostaurin's low aqueous solubility (<0.001 mg/mL) and its high absorption in human (>90%), midostaurin is classified as a BCS II drug.

In rats, dogs and rabbits, the total systemic plasma clearance (0.24 - 0.98 L/h/kg) and the volume of distribution at steady state (1.20 - 3.77 L/kg) were moderate indicating that midostaurin was distributed to tissues. The half-life was relatively short in animals (3.2-7.3 h). In human the apparent terminal half-life was relatively long (~20 h) following a single oral dose.

Radioactivity derived from [^{14}C]midostaurin was extensively distributed into tissues in the rat.

The concentrations in most tissues were higher than that in blood, and the highest radioactivity was observed in the liver after an oral dose and in the brown fat, adrenal glands, and liver after an intravenous dose. Radioactivity was taken up by the pituitary gland and crossed the blood brain barrier. After multiple doses, the radioactivity in tissues was 2-10-fold higher than that after a single dose. No melanin binding was observed. [^{14}C]midostaurin showed a high protein binding in the rat, dog and human (>98-99%). The protein binding was independent of concentration in animals. In human, a concentration dependent increase in fraction unbound was observed over a concentration range of 100-20,000 ng/mL. The two major metabolites of midostaurin, [^{14}C]CGP52421 and [^{3}H]CGP62221, showed a similar plasma protein binding to midostaurin, indicating no potential protein binding replacement *in vivo* with its metabolites.

Midostaurin was extensively metabolized in the rat, dog, rabbit and human. The primary biotransformation pathways observed included hydroxylation, O-demethylation, N-demethylation and amide hydrolysis. The major circulating components were midostaurin and CGP52421 (two epimers) in all species. CGP62221 (the O-demethylation product) was also

[redacted]

a major human circulating metabolite and detectable in the dog and rabbit. The total recovery of radioactivity was high in the rat, rabbit, dog and human (81.5% - 99.4%). In all these species, radioactivity was mainly excreted via fecal excretion. Renal excretion was apparently very minor (<4%).

Based on recombinant enzymes and human liver microsomes, cytochrome P450 3A4 enzyme

(CYP3A4) is the major enzyme involved in midostaurin oxidative metabolism. Midostaurin appears to have little inhibitory effect on *in-vitro* activities associated with CYP enzymes, 1A2, 2C8, 2C9, 2C19, 2D6, and 2E1. However, inhibition of CYP3A4 (probe substrate: midazolam 1'-hydroxylation) is observed with a half maximal inhibitory concentration (IC_{50}) value of approximately 1.5 μ M. With estimated clinical plasma concentrations being above the present IC_{50} concentrations, it is possible that midostaurin and/or the main metabolites could inhibit the metabolic clearance of comedications metabolized by CYP3A4. Midostaurin is a P-glycoprotein (P-gp) inhibitor with IC_{50} value of 1.7 μ M thus its concomitant use with P-gp substrates could lead to clinical drug-drug interactions. Midostaurin drug transport inhibition experiments indicated that midostaurin is not likely to be a substrate of P-gp, (multidrug resistance associated protein 2), and is not actively taken up into the liver.

1.2.1.1.2 Toxicology

Midostaurin has been extensively evaluated in various *in vitro* systems and *in vivo* models.

Studies relevant to clinical dosing of midostaurin include repeat dose toxicology studies with durations of up to 52 weeks, genetic toxicology, reproductive and developmental toxicity, juvenile toxicity and safety pharmacology studies. Additional toxicology studies have been performed with the combination of midostaurin and daunorubicin/Ara-C (cytarabine). No carcinogenicity studies have been performed.

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

Developmental toxicity was seen at 10 mg/kg or higher. NOEL for fertility and general reproductive toxicity was defined at 30 mg/kg.

Treatment with midostaurin at doses ≥3 mg/kg in dogs and ≥10 mg/kg in rats at durations up to 12 months was associated with effects on proliferating tissues, especially the intestine (mucosal alteration), testes (degenerated spermatogonia), and bone marrow (hypocellularity).

The effect on the bone marrow was accompanied by hematological changes (decreased total white cells, lymphocytes and erythrocytic parameters).

In conclusion, preclinical safety data obtained from various toxicology studies performed with midostaurin support further clinical development of midostaurin.

[redacted]

1.2.1.2 Clinical experience

1.2.1.2.1 Pharmacokinetics and drug metabolism in humans

Midostaurin is rapidly absorbed after oral administration, with peak plasma concentrations observed at 1-3 hours post dose. The mean apparent volume of distribution of midostaurin (99L) is higher than that of total body water (42 L), indicating a high tissue distribution. Midostaurin is mainly eliminated by metabolism via fecal excretion. Midostaurin is predominantly metabolized by CYP3A4 into two major active circulating metabolites, CGP62221 (via O-demethylation) and CGP52421 (via hydroxylation).

The major circulating components in plasma are CGP52421, CGP62221 and midostaurin, accounting for 38, 28, and 22% of AUC0-168h, respectively with geometric mean terminal half-lives of midostaurin, CGP62221 and CGP52421 in plasma after a single dose, are 19.6, 32.2 and 482 h.

The compound related materials are mainly distributed to plasma, and minimally to red blood cells. The mean apparent plasma clearance of midostaurin is low (3.71 L/h). The recovery in excreta is 81.6% of the dose.

The *in-vivo* drug-drug interaction studies indicated that midostaurin and its metabolites are metabolized by CYP3A4.

1.2.1.2.2 Clinical studies

Overall 502 healthy volunteers and 1902 patients have been enrolled into the Novartis-sponsored midostaurin clinical program, of which 383 of healthy volunteers and 1462 patients (includes 294 patients who were enrolled and received midostaurin in the integrated Third Party study, [CPKC412ADE02T] - AMLSG 16-10) have received midostaurin as a single agent and in combination with standard antineoplastic chemotherapeutic regimens.

The clinical development of midostaurin is currently focused on two indications:

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

Study [CPKC412D2201], the largest clinical trial performed in ASM/MCL, enrolled 116 patients. In 89 patients who were eligible for response assessments, the ORR was 60%; most responses were major responses (40/53, 75%). With a median follow-up of 43 months (range 29-70m), the median duration of response and median OS were 31.4 and 26.8 months respectively. Median OS in responders was 33.9 months. Of 16 MCL patients, 8 responded, including 7 MRs (44%). Median OS was 9.4 months among all patients with MCL and not yet reached among responders.

Midostaurin demonstrated single agent activity in AML/MDS patients with FLT3 mutations (Study A2104).

In a phase Ib trial (Study [CPKC412A2106]), promising data for complete remissions (CRs) in AML patients, particularly those with FLT3-mutated AML, were observed with midostaurin.

[redacted]

The study investigated different doses and schedules of midostaurin in combination with daunorubicin and cytarabine induction and high-dose cytarabine consolidation therapy in younger (age 18-60) patients with newly-diagnosed AML. At the best tolerated dose of 50 mg b.i.d. on days 8-21, CRs occurred in 32/40 (80%) of all patients, 20/27 (74%) of FLT3-WT patients, and 12/13 (92%) of FLT3-mutant patients. One and 2 year overall survival for the patients with FLT3-mutant AML were 85% and 62%, respectively; these values were comparable to those of the FLT3-WT subgroup (81% and 59%, respectively), suggesting that the addition of midostaurin to chemotherapy may improve outcomes for newly diagnosed younger patients with FLT3-mutant AML (Stone et al 2012). Overall, the tolerability of the midostaurin 50 mg b.i.d dosing regimen was better than that of the 100 mg b.i.d dosing regimens in both treatment arms. In addition to a lower rate of discontinuation with the lower midostaurin dose, certain AEs were less severe with 50 mg b.i.d dose; there were no GI toxicity SAEs (nausea, vomiting, diarrhea) in the 50 mg b.i.d dose cohort in either arm, nor were there SAEs associated with increases in liver function test results (ALT, AST, bilirubin)

Furthermore, sequential administration of chemotherapy and midostaurin appeared to be better tolerated overall than concomitant administration. Based on these data, the sequential administration schedule with midostaurin 50 mg b.i.d is considered to be the recommended regimen for subsequent clinical investigation in patients with AML.

This data inspired the phase III RATIFY pivotal trial (CPKC412A2301) in this patient population.

RATIFY study (CPKC412A2301/CALGB 10603)

The efficacy and safety of midostaurin in combination with standard chemotherapy has been further investigated in newly diagnosed AML with FLT3 mutation patients in the pivotal phase III, randomized, placebo-controlled RATIFY trial (Stone et al 2015).

The primary end point of the study is overall survival (OS), not censored for stem cell transplantation (SCT). The key secondary endpoint is event-free survival (EFS). Other secondary endpoints include OS censored for SCT, complete remission (CR) rate, disease-free survival (DFS), DFS rate one year after completing the planned therapy, safety, and population pharmacokinetics.

719 patients were randomized in RATIFY Study. 717 patients were included in the analyses, 360 patients were randomized to the midostaurin arm, 357 to the placebo arm. The primary endpoint, OS non-censored at the time of SCT, showed a statistically significant difference (p=0.0078) at a one-sided alpha level of 0.0239 that favored midostaurin treatment. Midostaurin reduced the risk of death vs placebo by 23% (HR, 0.774 [95% CI, 0.629-0.953]). The estimated probability of being alive at 3 years (36 months) was higher in the midostaurin arm compared to the placebo arm (54% [95% CI: 0.49, 0.59] vs 47% [95% CI: 0.41, 0.52]). The protocol-defined CR rate within 60 days of initiation of protocol therapy was 58.9% in the midostaurin arm and 53.5% in the placebo arm (p=0.073, one-sided p-value). In the midostaurin arm, more patients had a CR after induction Cycle 1 (51.7%) than in the placebo arm (43.1%). In a sensitivity analysis that considered an expanded CR definition of all CRs occurring during the induction phase (including CRs that occurred outside of the 60-day window), the CR rate was 65.0% in the midostaurin arm and 58.0% in the placebo arm (p=0.027, one-sided p-value). The

[redacted]

primary DFS analysis was aligned with the key secondary EFS endpoint analysis and included patients who achieved a CR by Day 60 after study treatment initiation. DFS was measured from the date of first CR to the date of relapse or death from any cause, whichever occurred first. Median DFS was 26.7 months (19.35, NE) in the midostaurin arm and 15.5 months (11.33, 23.46) in the placebo arm (HR=0.71; 95% CI: 0.55, 0.92; p=0.0051 one-sided).

The sensitivity analysis considering all CRs during induction reflects more accurately the benefit of midostaurin. The median DFS was 28.1 months in the midostaurin arm and 14.1 months in the placebo arm (HR=0.66; 95% CI: 0.52, 0.85; p=0.0006 one-sided).

Remission duration was measured from the date of first CR to relapse or death due to AML (CR within 60 days of study treatment start, uncensored at the time of SCT), whichever occurred first. Patients who died from other causes without relapse were censored. The median duration of remission for midostaurin was 61.0 months (95% CI: 21.68, NE) and 22.2 months (95% CI: 14.13, NE) for the placebo arm. The risk of relapse or death due to AML for patients in the midostaurin arm who had achieved a CR was reduced by 26% (HR=0.74; 95% CI: 0.56, 0.99) compared to those who had achieved a CR in the placebo arm.

Censoring for SCT, the median remission duration was 20.27 months (16.43, NE) in the midostaurin arm versus 17.58 months (9.63, NE) in the placebo arm, a reduction of 20% (HR=0.80; 95% CI: 0.58, 1.11) in the risk of relapse or death due to AML.

Anti-fungal agents are commonly administered to AML patients receiving intensive induction and consolidation therapy; 61%, 46% and 11% of patients in this study received antifungal agents during the induction, consolidation and continuation phase, respectively.

Because midostaurin is metabolized by CYP3A4, potent CYP3A4 inhibitors (e.g., some antifungal medications) may represent a potential for drug-drug interactions. Upon co-administration with CYP3A4 inhibitors, an increase in concentration of 1.44-fold is observed for midostaurin exposure in RATIFY (CPKC412A2301).

This increase of exposure did not impact the benefit-risk balance of midostaurin in AML treatment, and therefore are deemed not clinically relevant. Based on these data, no change in dose is required when midostaurin is co-administered with CYP3A4 inhibitors.

Midostaurin was generally well tolerated. Most of the AEs, AEs suspected to be related to study drug, SAEs, and AEs leading to study discontinuation occurred due to the underlying disease at similar frequencies in both treatment groups. Adverse events not related to hematological toxicities were generally of grade 1 or 2 severity. Grade 3/4 exfoliative dermatitis and grade 3/4 device related infections occurred more frequently (>5%) in the midostaurin group than in the placebo group. Fewer patients in the midostaurin group than in the placebo group died on treatment due to causes other than disease progression (15 patients vs 21 patients, respectively). On treatment deaths suspected to be related to study drug were balanced between the treatment groups (2.6% and 2.1%), and included sepsis (2 patients), multi-organ failure, infectious colitis, acute respiratory failure, colitis, myocardial infarction, neutropenic sepsis, pulmonary hemorrhage and septic shock in the midostaurin treatment group (one patient each).

The results of this study indicate that the addition of midostaurin 50 mg b.i.d to standard chemotherapy followed by up to one year of single-agent continuation treatment significantly decreases mortality in patients aged 18 to <60 years with newly-diagnosed FLT3-mutated AML.

[redacted]

Although more than 50% of patients in both arms underwent SCT, survival analyses censored for SCT, as well as analyses of survival post-CR1 SCT demonstrated a significant benefit for these patients.

These outcomes support a positive benefit-risk profile for midostaurin 50 mg b.i.d, both, in combination with standard induction/consolidation chemotherapy and as a subsequent single-agent continuation therapy for up to 12 months for patients in remission.

Elderly study data

Study [CPKC412ADE02T] (AMLSG 16-10) conducted in Germany, a Phase-II third party study, evaluated midostaurin in induction, consolidation and maintenance therapy also after allogeneic blood stem cell transplantation in patients with newly diagnosed acute myeloid leukemia (AML) exhibiting FLT3 internal tandem duplication. The preliminary data from this study of 149 patients (patients ≥18 and ≤70 year, median age 54 years, 32% ≥ 60 years) demonstrated that the addition of midostaurin to intensive induction therapy and as maintenance after Allogeneic Hematopoietic Stem Cell Transplantation or High Dose Ara-Cytarabine (HiDAC) is feasible and seems to be effective without an impact of age in comparison to historical group. This study is the most relevant experience in elderly patients demonstrating a favorable benefit/risk profile (Schlenk et al 2016).

2 Rationale

2.1 Study rationale and purpose

AML is amongst the most challenging hematological malignancies to treat, and patients with activating FLT3 mutations have a particularly poor prognosis and often relapse or are refractory to current treatment options. There is a high unmet medical need in this patient population. Initial therapy for AML to induce remission has changed little in the past 25 years, and for patients with an adequate performance status, it comprises cytarabine and an anthracycline, followed by post-remission therapy with additional intensive chemotherapy or with SCT. AML patients carrying FLT3 mutations, particularly ITD mutations, have a poor prognosis with a high risk of relapse. Midostaurin is a novel tyrosine kinase inhibitor that has been studied in a large, randomized, double-blind study of midostaurin 50 mg b.i.d vs placebo in combination with standard induction/consolidation chemotherapy conducted in patients with newly diagnosed, FLT3-mutated (ITD or TKD) AML (Study [CPKC412A2301]/RATIFY). The primary endpoint of RAFITY study was overall survival (OS). With positive Phase III data supporting the efficacy of midostaurin in newly-diagnosed FLT3-mutated AML, the purpose of this new Phase IIIb is to further evaluate the safety and efficacy of midostaurin in induction, consolidation and maintenance therapy in patients 18 years of age or older with newly diagnosed FLT3 mutated AML.

The age limit for patients in the Phase III RATIFY trial (CPKC412A2301) was 60 years old. This protocol allows enrollment of patients beyond age 60, and the “5+2” regimen will permit per physician’s decision inclusion of patients above 70 years old.

[redacted]

2.2 Rationale for the study design

Considering the limited safety impact and the significant clinical benefit of the addition of midostaurin to the standard "7+3" regimen in the RATIFY study (CPKC412A2301), this Phase IIIb study is designed as a single arm study and allows the assessment of variation of the "7+3" regimen in an extended patient population compared to RATIFY (higher dose of daunorubicin (60-90 mg/m^2/day), the substitution of daunorubicin by idarubicin (12mg/m^2/day), and lower dose of cytarabine (100-200 mg/m^2/day) and the "5+2" reduced dose regimen). Safety is the primary endpoint. CR/CRi (see Section 7.2.1) in induction, consolidation and maintenance therapy is collected as secondary endpoint.

Patients who are newly diagnosed with AML, have a known FLT3 ITD or TKD, mutation and have recently started on "7+3" or "5+2" in induction and high dose of cytarabine in consolidation will be consented and screened for the clinical study.

While standard chemotherapy may be initiated at the investigator's discretion during screening, the patient must be enrolled prior to completion of induction chemotherapy (by day 8) and midostaurin added on day 8.

No age limitation:

Based on Walter (2015), Klepin (2013), Klepin (2014), and Ossenkoppele (2015), this protocol allows enrollment of patients beyond age 60 for both "7+3" and "5+2", as it is common real-world practice to offer standard induction therapy to elderly patients. As there is not a standard definition of fitness, the decision depends on the clinical judgement of the investigator according to the local guidelines.

Preliminary data from [CPKC412ADE02T - AMLSG 16-10] clinical study (patients ≥18 and ≤70 years, 34% ≥60 years) demonstrated that in patients with AML FLT3 ITD positive the combination of midostaurin to intensive induction therapy and as maintenance after Allo HSCT or HiDAC is feasible and more effective in comparison to AML historical group (Schlenk et al 2016).

Additionally, patients who can't tolerate the intensive chemotherapy due to age or toxicity can receive "5+2" regimen per the investigator's discretion.

2.3 Rationale for dose and regimen selection

The dosing regimen in this study is midostaurin 50 mg b.i.d, in combination with standard chemotherapy sequentially in induction and consolidation therapy and as a single-agent in maintenance therapy.

In a Phase 1, open-label, dose-escalation study [CPKC412A0002], midostaurin was evaluated in adult patients with non-hematologic malignancies.

The maximum tolerated dose could not be reached. However, based on the drop-outs at 225-300 mg daily dose due to gastrointestinal (GI) toxicity, and the maximum acceptable number of 12 capsules for the dosing of 300 mg/day, the maximum feasible dose for practical purposes in this population was regarded as 225-300mg/day even though no dose-limiting toxicity was observed.

[redacted]

In two single-agent clinical studies with midostaurin [CPKC412A2104] (75 mg, three times daily) and [CPKC412A2104E1] (50 mg b.i.d or 100 mg b.i.d), bone marrow or peripheral blood blast responses ≥50% were observed in 70% and 42% of patients with FLT3-mutant (N=55) and FLT3‑wild-type (N=60) AML, respectively.

Overall survival was similar for the 50 mg b.i.d and 100 mg b.i.d doses. Overall, there was a similar level of biological activity of midostaurin in the mutated FLT3 and wild-type FLT3 patients at either the 50 mg b.i.d or 100 mg b.i.d doses and in the FLT3-mutated patients treated at either 100 mg b.i.d (200 mg daily) or 75 mg three times daily (225 mg daily) doses.

Furthermore, the study [CPKC412A2104E2] indicated that there were no obvious improvements in clinical response in patients with AML receiving midostaurin doses higher than 50 mg b.i.d, suggesting that increasing midostaurin exposure beyond 50 mg b.i.d would not necessarily produce discernable evidence of increased efficacy.

In Study [CPKC412A2106], a total of 69 AML/MDS patients (n=34 in arm 1; n=35 in arm 2) were enrolled to explore the safety, tolerability, PK and preliminary clinical efficacy of the two arms/regimens below:

- Sequential administration of midostaurin with daunorubicin and cytarabine
- Concomitant administration of midostaurin with daunorubicin and cytarabine

The choice of the sequential regimen, rather than simultaneous regimen of midostaurin, was based on the following:

- Cell culture data showed that simultaneous administration of a FLT3 inhibitor with or after cytarabine enhanced cytotoxic effects, whereas exposure of cells to FLT3 inhibitors before cytarabine (i.e. midostaurin followed by cytarabine) had antagonistic effects on cytotoxicity (Levis et al 2003). Therefore, the simultaneous regimen would have the potential for an antagonistic interaction that the sequential regimen clearly avoids.
- Study PKC412A2106 investigated the administration of midostaurin 50 mg b.i.d or 100 mg b.i.d, sequentially or concomitantly with induction chemotherapy. The midostaurin 50 mg b.i.d sequential regimen was the preferred investigational regimen for AML in the current study based on the favorable safety and tolerability profile.

Based on the initial activity and the acceptable safety and tolerability profile, a dose of 50 mg b.i.d midostaurin in combination with standard chemotherapy was believed to provide a reasonable risk-benefit balance, and was selected for the Phase III Study [CPKC412A2301] (RATIFY).

In order to achieve IC_{50} values at steady state and allow the most tolerable dosing, the dose for patients receiving midostaurin on this current study will be 50mg b.i.d, i.e., the same dose used in the RATIFY trial (Stone et al 2015). For patients unable to tolerate the proposed dose, dose adjustments are outlined in Section 6.3.

Choice of chemotherapy – (“7+3” or “5+2”)

Standard chemotherapy 7+3 or 5+2 includes induction and consolidation therapies

[redacted]

"7+3"

RATIFY study demonstrated that the addition of midostaurin to standard chemotherapy "7+3" followed by 12 cycles of maintenance therapy with midostaurin alone significantly improved EFS and OS in both uncensored and censored for transplant analyses.

In this Phase IIIb study, newly diagnosed AML patients will receive "7+3" induction therapy with cytarabine (100-200mg/m^2) and daunorubicin (60-90mg/m^2) (or idarubicin 12 mg/m^2/day) as defined by NCCN treatment guidelines.

"5+2"

The "5+2" regimen consists of similar regimen as "7+3" with reduced duration to 5 and 2 days, respectively. "5+2" is used in advanced age to prevent toxicity and/or increase tolerability.

The "5+2" regimen will be allowed for patients who were not able to receive the 7+3, per physician's decision.

Midostaurin treatment between Day 8 to Day 28

Enrolled patients will subsequently receive oral midostaurin 50 mg (two 25 mg capsules) twice a day on days 8-28 of a 28 day cycle. Midostaurin treatment is extended to D28, the end of each cycle, compared with RATIFY dose regimen ending at D21.

In Study [CPKC412ADE02T] (AMLSG 16-10), patients received midostaurin 50 mg, orally twice daily in addition to standard induction and consolidation and as single agent in maintenance therapy also after allogeneic blood cell transplantation, midostaurin demonstrate acceptable toxicity and confirmed a similar safety profile and a high rate of complete remission. In this study the use of midostaurin was extended until 48 hours before the start of the next cycle, demonstrating that an increase in the exposure to midostaurin increases the potential response.

In [CPKC412A2408] study, the use of midostaurin was therefore extended to day 28 of each cycle in induction and consolidation phases (midostaurin administration from day 8 to day 28 of each cycle).

No new safety findings have been revealed in the study.

Maintenance therapy

Standard therapy of adults with AML does not routinely involve a maintenance phase after completion of consolidation. However, published data suggested that the detection of minimal residual disease in AML patients with FLT3 mutations predicted rapid relapse once chemotherapy was completed (Kottaridis et al 2001). Therefore, the continued administration of an oral, non-cytotoxic drug such as midostaurin post-chemotherapy could continue to inhibit growth or even kill residual FLT3-mutated blasts present at the end of a routine course of chemotherapy, thereby potentially prolonging OS and DFS. In RATIFY, when assessed from the start of maintenance therapy, a benefit of midostaurin treatment on OS was seen (HR 0.80). Similarly, DFS was assessed from the start of the maintenance phase. Prior to one year, the Kaplan-Meier curves remain superior in the midostaurin arm however after one year (when all patients would no longer be receiving midostaurin) the curves cross, and DFS events occur

more frequently on the midostaurin arm. Although the relapse rate was similar in the two arms during continuation therapy, the secondary endpoint of DFS one year after completion of maintenance therapy demonstrated that patients on the midostaurin arm relapsed quickly once maintenance therapy was stopped. This data may support maintenance of midostaurin until relapse (particularly given the good tolerability and safety).

Approval by the US Food and Drug Administration has been received in April 2017 for using midostaurin in newly diagnosed AML patients who are FLT3 mutation positive in combination with standard cytarabine and daunorubicin induction and cytarabine consolidation (Rashidi et al 2016).

2.4 Rationale for choice of combination drugs

For patients' ≤ 60 years of age with newly diagnosed AML, the standard chemotherapy induction regimen for the past two decades has been an anthracycline and cytarabine, followed by consolidation with high-dose cytarabine. More details on the cytarabine/anthracycline induction and cytarabine consolidation regimens can be found in the NCCN guidelines (Updated version 1.2017: NCCN Clinical Practice Guidelines in Oncology: Acute Myeloid Leukemia). The induction regimen of cytarabine and daunorubicin/idarubicin used in this Phase IIIb study is similar to that used in the clinical studies with midostaurin, the Phase 1b study [CPKC412A2106] (Stone et al 2012) and the Phase 3 study (RATIFY ([CPKC412A2301]) (Stone et al 2015)

A placebo will not be used in this study.

2.5 Rationale for choice of comparators drugs

Not Applicable

2.6 Risks and benefits

The risk to subjects in this trial may be minimized by compliance with the eligibility criteria and study procedures, and close clinical monitoring. There may be unforeseen risks with study treatment which could be serious.

The risk and benefit have been identified in the [PKC412A2106] and RATIFY' studies ([CPKC412A2301]).

The phase Ib study (A2106) investigated different doses and schedules of midostaurin in combination with daunorubicin and cytarabine induction and high-dose cytarabine consolidation therapy in 69 patients with newly-diagnosed AML. At the best tolerated dose of 50 mg b.i.d CRs occurred in 32/40 (80%) of all patients, 20/27 (74%) of FLT3-WT patients, and 12/13 (92%) of FLT3-mutant patients. One and 2-year overall survival (OS) for the patients with FLT3–mutant AML were 85% and 62%, respectively, and were comparable to those of the FLT3–WT subgroup (81% and 59%, respectively). These data were based on small numbers and were not stratified for type of FLT3 mutation (i.e. TKD vs ITD, ITD length, location, or allelic ratio) (Stone et al 2009, Stone et al 2012).

With the recommended sequential treatment schedule (where midostaurin is started on day 8 after the completion of chemotherapy), AEs reported in ≥ 50% of patients included

[redacted]

hematological AEs (thrombocytopenia, neutropenia, febrile neutropenia) and nausea, diarrhea, vomiting, pyrexia, hypokalemia, chills, and headache. The most frequent grade 3 and grade 4 AEs were hematological AEs (thrombocytopenia, neutropenia, febrile neutropenia, anemia, and leukopenia). Grade 3 non-hematological AEs reported in >10% of patients in either arm were those associated with GI toxicity (nausea, vomiting), increases in liver function test results (ALT, AST, bilirubin), electrolyte imbalance (hypocalcemia, hypokalemia, hypophosphatemia), and pyrexia, hypoxia, and device-related infection. One on-treatment death was reported in the study. The patient died due to fungal infection associated with multi-organ failure that was not considered to be related to study drug by the Investigator. AEs that led to discontinuation were reported for 8.8% of patients (5% with 50 mg b.i.d, and 14% with 100 mg b.i.d).

The data available for midostaurin in acute myeloid leukemia (AML), taken from early stage single agent and combination trials, indicates a favorable benefit- risk profile that was confirmed in the randomized phase III RATIFY trial ([CPKC412A2301]; CALGB 10603). RATIFY data confirm the significant improvement of the overall survival for the midostaurin arm and the safety profile identified in the A2106 study. (RATIFY data summary Section 1.2.1.2).

It should be recognized that the assessment of causality is challenging in AML patients given the combination with standard chemotherapy, the complexity of the clinical presentation of the disease, and the use of multiple concomitant medications.

In summary, the expected benefit (with an improvement of overall survival) support a positive benefit-risk profile for midostaurin 50 mg b.i.d, both, in sequential combination with standard induction/consolidation chemotherapy and as a subsequent single agent maintenance therapy for up to 12 months for patients in remission.

3 Objectives and endpoints

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

[redacted]

Table 3-1 Objectives and related endpoints

Objective	Endpoint	Analysis
Primary		Refer to Section 10.4.
To further assess the safety of midostaurin in induction, consolidation and maintenance therapy, including, the "7+3" regimen, daunorubicin (60-90mg/m^2/day), the substitution of daunorubicin by idarubicin (12mg/m2/day), cytarabine (100-200 mg/m^2/day) and also allowing the "5+2" reduced dose regimen.	Proportion of patients with AEs, Grade 3&4 AEs, SAEs, AEs leading to discontinuation, and deaths.	
Secondary		Refer to Section 10.5.
To assess the clinical efficacy of midostaurin in combination with chemotherapy regimens in induction and consolidation and the clinical efficacy of midostaurin maintenance phase (measured by CR/CRi rate).	Proportion of patients with CR/CRi as per local assessment	
Exploratory		Refer to Section 10.6.
[redacted]	[redacted]	
To assess resource utilization	Proportion of patients by reason for hospitalization, number of hospital days, discharge reason and concomitant medications taken during hospital stay	

4 Study design

4.1 Description of study

This is an open-label, multi-centre, phase IIIb study in patients 18 years of age or older with newly-diagnosed FLT3-mutated Acute Myeloid Leukemia (AML) who have started "7+3" or "5+2" chemotherapy regimen.

Investigators must obtain FLT3 testing results prior to ICF signature in order to allow patients to initiate midostaurin treatment per protocol.

NPM1 mutation status will also be collected if available.

The protocol treatment will allow the following treatment phases:

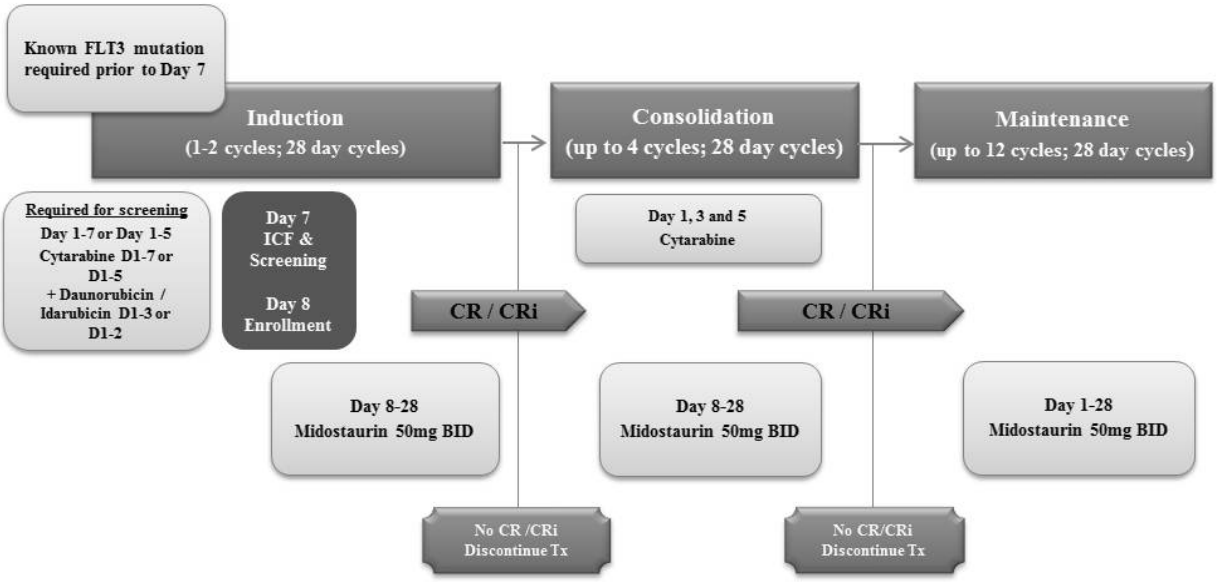
- Induction phase: 1 or 2 cycles of "7+3" or "5+2" regimens (switching between regimens is not allowed).
- Consolidation phase: up to 4 cycles of cytarabine consolidation, with midostaurin given sequentially during each cycle,
- Maintenance phase: up to 12 cycles of maintenance therapy with single-agent midostaurin or until relapse, unacceptable toxicity, or death, physician's decision, subject/guardian's decision, protocol deviation, study termination by sponsor, lost to follow-up, technical

[redacted]

problems, pregnancy, subject withdrew consent or until the end of study, whichever event occurs first.

The estimated study duration is about 3.5 years, including about 18 months for recruitment and around 18 to 25 months for completion of the induction, consolidation and maintenance therapy.

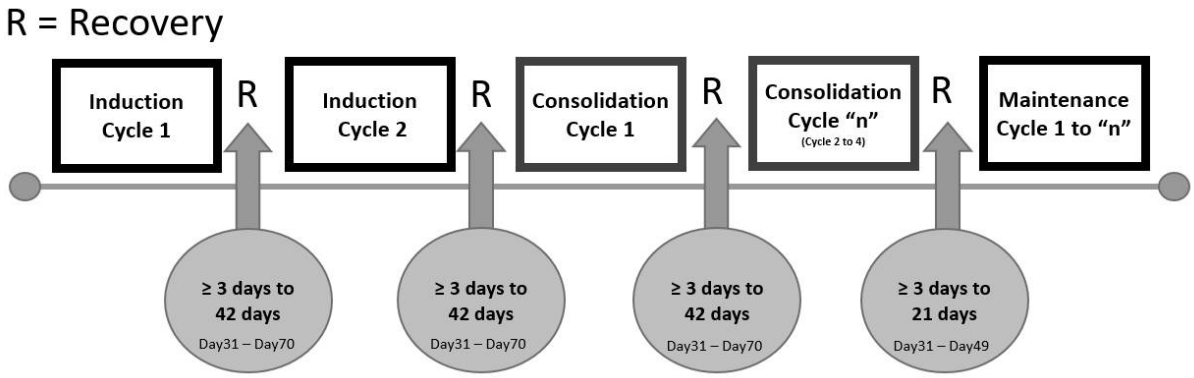
Figure 4-1 Study design



		Chemotherapy - First induction cycle			
Day -2	Day -1	Day 1 to Day 6	**Day 7**	**Day 8**	**Day 9 to Day 28**
			Study start		
			Screening / Baseline Day -1	**Enrollment Day 1**	
AML Diagnosis	AML Diagnosis	"7+3" or "5+2" chemotherapy	If FLT3 (ITD or TKD) positive and complete first induction "7+3" or "5+2" chemotherapy patient may sign **ICF** and start screening activities.	**Eligibility and Midostaurin administration**	Study treatment
FLT3 testing up to Day 6					

[redacted]

Figure 4-2 Recovery periods



4.2 Timing of interim analyses and design adaptations

Not Applicable

4.3 Definition of end of study

The study will end around 18 to 25 months after LPFV depending on number of cycles and recovery durations. Study treatment will be provided until disease progression, death, unacceptable toxicities, physician's decision, subject/guardian's decision, protocol deviation, study termination by sponsor, lost to follow-up, technical problems, pregnancy, patient withdrew consent or until the end of study, whichever event occurs first. Patients will be contacted for safety evaluations. All patients must have safety evaluations for 30 days, after the last dose of study treatment except if consent was withdrawn. Patients who present CR/CRi may be eligible for transplant. Patients who undergo SCT will have midostaurin discontinued prior to conditioning for transplantation, and will be removed from the study following completion of scheduled safety monitoring.

4.4 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 for a discontinued or 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. Patients who discontinue study treatment, including those who refuse to return for a final visit will be contacted for safety evaluations during 30 days following the end of treatment. All patients must have safety evaluations for 30 days, after the last dose of study treatment except if consent was withdrawn.

[redacted]

5 Population

5.1 Patient population

The patient population will consist of male or female individuals, aged 18 years or older with newly diagnosed AML and must have documented FLT3 mutations (ITD or TKD) and have started "7+3" or "5+2" first induction chemotherapy to be eligible for the study. 300 patients are expected to be enrolled into this trial.

5.2 Inclusion criteria

The Investigator or designee must ensure that only patients who meet all the following inclusion and none of the exclusion criteria are offered treatment in the study.

Inclusion Criteria:

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

1. Written informed consent must be obtained prior to any screening procedures.
2. Patients must be 18 years of age or older at the time of signing informed consent.
3. Patients must have a documented unequivocal diagnosis of AML according to WHO 2008 classification. A bone marrow or blood blast count of ≥ 20% is required, except for AML with t(15;17), t(8;21), inv(16) or t(16;16) where blast count may be <20%, and, excluding M3 (acute promyelocytic leukemia).
4. Patients with secondary AML are eligible, e.g., patients with antecedent history of treatment for prior malignancy. AML patients with a history of antecedent treatment for myelodysplasia (MDS), e.g., azacitidine or decitabine, remain eligible for treatment on this study. These agents must have been discontinued for a period of at least 30 days or 5 half-lives of the drug (whichever is greater) before midostaurin can be administered.
5. Patients must have started "7+3" or "5+2" first induction chemotherapy regimen.
6. Patients must have a documented FLT3 mutation (ITD or TKD).).
7. Patients must have an ECOG Performance Status of ≤ 2
8. Patients requiring intrathecal chemotherapy must have a minimum washout of 48 hours prior to the first dose of midostaurin
9. Patients must have Total Bilirubin ≤ 2.5 x ULN
10. Patients must have Serum Creatinine ≤ 2.5 x ULN
11. Patients must be able to communicate well with the investigator to understand and comply with the requirements of the study
12. Women of child-bearing potential must have a negative pregnancy test before starting use of midostaurin.

5.3 Exclusion criteria

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

1. Prior therapy for AML with the following exceptions:
   a. emergency leukapheresis
   b. emergency treatment for hyperleukocytosis with hydroxyurea for ≤ 7 days

[redacted]

c. cranial RT for CNS leukostasis (one dose only)
d. growth factor/cytokine support

2. Patients with LVEF less than 45% (by echocardiogram or MUGA) or symptomatic congestive heart failure (Class III or IV) according to New York Heart Association (NYHA) classification
3. Patients with any pulmonary infiltrate including those suspected to be of infectious origin (unless resolved to ≤ Grade 1 within screening timeframe)
4. Patients with any uncontrolled illness, including, but not limited to, acute or chronic pancreatitis or uncontrolled infection
5. QTc >470 msec on screening ECG (Fridericia's formula)
6. History of hypersensitivity to any drugs or metabolites of similar chemical classes as the study treatment.
7. Participation in a prior investigational interventional (drug) study with administration of the investigational product within 30 days or 5 half-lives of the investigational product, whichever is longer.
8. Pregnancy statements and contraception requirements:
   Women of child-bearing potential, defined as all women physiologically capable of becoming pregnant, **unless** they are using highly effective methods of contraception during dosing and for at least 4 months after stopping medication. Highly effective contraception methods include:
   - Total abstinence (when this is in line with the preferred and usual lifestyle of the subject). Periodic abstinence (e.g., calendar, ovulation, symptothermal, post-ovulation methods) and withdrawal are not acceptable methods of contraception
   - Female sterilization (have had surgical bilateral oophorectomy with or without hysterectomy), total hysterectomy, or tubal ligation at least six weeks before taking study treatment. In case of oophorectomy alone, only when the reproductive status of the woman has been confirmed by follow up hormone level assessment
   - Male sterilization (at least 6 months prior to screening). The vasectomized male partner should be the sole partner for that subject
   - Use of oral, injected or implanted hormonal methods of contraception or placement of an intrauterine device or intrauterine system, or other forms of hormonal contraception that have comparable efficacy (failure rate <1%), for example hormone vaginal ring or transdermal hormone contraception.

In case of use of oral contraception women should also add a barrier method of contraception, particularly as it is currently unknown whether midostaurin may reduce the effectiveness of hormonal contraceptives.

Sexually-active males unless they use a condom during intercourse with females of reproductive potential or pregnant women and for at least 4 months after stopping treatment to avoid conception or embryo-fetal harm.

9. Patients enrolled in this study are not permitted to participate in additional parallel study drug or device studies.

[redacted]

6 Treatment

6.1 Study treatment

Patients will have started first induction chemotherapy with cytarabine (Days 1-7) and daunorubicin (or idarubicin) (Days 1-3) or cytarabine (Day 1-5), daunorubicin (or idarubicin) (Days 1-2). Patients will start midostaurin on Day 8 up to Day 28, for 1-2 cycles, consolidation with cytarabine (Days 1, 3, 5) plus midostaurin (Days 8-28) for up to 4 cycles, and continuous dosing of midostaurin (Days 1-28) for up to 12 cycles (maintenance phase) or until relapse, unacceptable toxicity, death physician's decision, subject/guardian's decision, protocol deviation, study termination by sponsor, lost to follow-up, technical problems, pregnancy, subject withdrew consent or until the end of study, whichever event occurs first.

Patients treated with 7+3 or 5+2 per investigator's discretion may not be switched from 7+3 to 5+2 and vice versa.

Investigational drug refers to any Novartis study drug(s) whose properties are being tested in the study. For this study, the term "Investigational drug" refers to midostaurin (PKC412) supplied in 25 mg soft gelatin capsules which are packaged in blister packs.

Study treatment includes any drug or combination of drugs administered to the patient (subject) as part of the required study procedures.

6.1.1 Dosing regimen

Table 6-1 Dose and treatment schedule – Induction

Treatment	Dose, route and frequency (based on 28-day cycles)
Standard-dose cytarabine* with anthracycline* (idarubicin or daunorubicin) (7+3)	Ara-C:100-200 mg/m^2/day by CIVI days 1-7 (168 hours infusion) daunorubicin: 60-90 mg/m^2/day by IV push on days 1-3 Or idarubicin: 12 mg/m^2/day by IV push on days 1-3
Cytarabine* with anthracycline* (idarubicin or daunorubicin) (5+2)	Ara-C:100 mg/m^2/day by CIVI days 1-5 daunorubicin 60 mg/m^2/day by IV push on days 1-2 Or idarubicin: 12 mg/m^2/day by IV push on days 1-2
Midostaurin	50 mg (two 25 mg capsules) twice a day by mouth on days 8-28 Patients should take their doses at approximately the same time each day, and approximately 12 hours should elapse between doses. Each daily should be given with food and a glass of water (~240 mL). Patients should be instructed to swallow capsules whole and not chew capsules. If vomiting occurs, no re-dosing is allowed before the next scheduled dose.

Table 6-2 Dose and treatment schedule – Consolidation

Treatment	Dose, route and frequency (based on 28-day cycles)
Cytarabine*	1-3 g/m^2 infusion over 3 hours every 12 h on days 1, 3 and 5, up to 4 cycles based on age and per investigator discretion
Midostaurin	50 mg (two 25 mg capsules) twice a day by mouth on Days 8-28. Patients should take their doses at approximately the same time each day, and approximately 12 hours should elapse between doses. Each daily should be given with food and a glass of water (~240 mL). Patients should be instructed to swallow capsules whole and not chew capsules. If vomiting occurs, no re-dosing is allowed before the next scheduled dose.

[redacted]

Table 6-3 Dose and treatment schedule – Maintenance

Treatment	Dose, route and frequency (based on 28-day cycles)
Midostaurin	50 mg (two 25 mg capsules) twice a day by mouth on days 1-28, for 12 cycles or until relapse, unacceptable toxicity, or death. Patients should take their doses at approximately the same time each day, and approximately 12 hours should elapse between doses. Each dose should be given with food and a glass of water (~240 mL). Patients should be instructed to swallow capsules whole and not chew capsules. If vomiting occurs, no re-dosing is allowed prior to the next scheduled dose.

*Treatment formulation availabilities depend on countries marketing authorization as a local commercial supply is used.

6.1.2 Ancillary treatments

Patients should receive full supportive care, including transfusions of blood and blood products, antibiotics, antiemetics, allopurinol, etc., when appropriate. The use of aprepitant is not permitted.

Treatment with hormones or other chemotherapeutic agents may not be administered except for steroids given for adrenal failure; and hormones administered for non-disease-related conditions (e.g., insulin for diabetes). Steroids may be used to treat and/or prevent hypersensitivity reactions or transfusion reactions.

Brief use of corticosteroids as anti-emetics is permitted but not recommended in these immunocompromised patients. Their use must be reported in patient records.

Myeloid growth factors should not be used routinely or prophylactically, but are permitted as indicated by the ASCO guidelines for neutropenic patients with prognostic factors that are predictive of clinical deterioration such as pneumonia, hypotension, multi-organ dysfunction (sepsis syndrome) or fungal infection (Smith 2015). The use of CSF (filgrastim, PEG-filgrastim, or sargramostim) must be documented and reported in the patient's records. The use of epoetin or darbepoetin (EPO) in this protocol is permissible but not recommended.

6.1.3 Rescue medication

Not Applicable

6.1.4 Guidelines for continuation of treatment

Not Applicable

6.1.5 Treatment duration

The study treatment may last approximately 18 months; in addition there are recover periods, and up to 30 days follow-up for safety evaluation. The study may last up to 25 months after LPFV depending on number of cycles and recovery durations.

Patients may receive up to 3 phases of treatment:

- Induction: up to 2 cycles (28 days of treatment/cycle and recovery periods)
- Consolidation: up to 4 cycles (28 days of treatment/cycle and recovery periods)
- Maintenance: up to 12 cycles (28 days of treatment/cycle)

[redacted]

Patients may receive treatment as outlined in the study schema (Figure 4-1 and Figure 4-2).

6.2 Dose escalation guidelines

Not Applicable

6.2.1 Starting dose rationale

Not Applicable

6.2.2 Provisional dose levels

Not Applicable

6.2.3 Guidelines for dose escalation and determination of midostaurin

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. The following guidelines may be applied:

A patient must discontinue treatment with midostaurin (PKC412) if, after treatment is resumed at a lower dose, the toxicity recurs with the same or worse severity.

Patients who discontinue the study for a study related adverse event or an abnormal laboratory value must be followed as described in Section 7.1.5.

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

6.3.2 Dose modifications and management of toxicity during induction, consolidation therapy

6.3.2.1 Hematologic toxicity

There will be no dose modifications for hematologic toxicity due to midostaurin.

6.3.2.2 Pulmonary toxicity >/= grade 3

For ≥ grade 3 pulmonary infiltrate, interrupt midostaurin and resume with midostaurin 50 mg twice daily when infiltrates resolve to ≤ grade 1. Missed doses of midostaurin will not be made up.

6.3.2.3 Cardiac toxicity

For QTc interval >470 ms and ≤ 500 ms, check magnesium and potassium levels and correct any abnormalities. If possible, stop any medication, which may prolong the QTc interval. Decrease midostaurin to 50 mg once daily until QTc interval improves to ≤ 470 ms, and then resume midostaurin with 50 mg twice daily.

[redacted]

For QTc interval > 500 ms, immediately stop midostaurin, check magnesium and potassium levels and correct any abnormalities. If possible, stop any medication, which may prolong the QTc interval Re-start with midostaurin 50 mg once daily if QTc interval is between >470ms and ≤ 500 ms. Once QTc interval improves to ≤ 470 ms, resume midostaurin with 50mg twice daily. If QTc interval remains > 470 ms for more than three weeks, discontinue midostaurin until QTc improves to < 470 ms, then resume midostaurin with 50 mg twice daily.Missed doses of midostaurin will not be made up.

6.3.2.4 Other non-hematologic toxicities

If a patient experiences other grade 3/4 non-hematologic toxicity, which is considered to be at least possibly related to midostaurin, midostaurin must be interrupted until toxicity resolves to ≤ grade 1. Missed doses of midostaurin will not be made up.

6.3.3 Dose modifications and management of toxicity during maintenance therapy

6.3.3.1 Hematologic toxicity

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

6.3.3.2 Pulmonary toxicity >/= grade 3

For ≥ grade 3 pulmonary infiltrate, interrupt midostaurin and resume with midostaurin 50 mg twice daily when infiltrates resolve to ≤ grade 1. Missed doses of midostaurin will not be made up.

6.3.3.3 Cardiac toxicity

For QTc interval >470ms and ≤ 500 ms, check magnesium and potassium levels and correct any abnormalities. If possible, stop any medication, which may prolong the QTc interval. Decrease midostaurin to 50 mg once daily until QTc interval improves to ≤ 470 ms, and then resume midostaurin with 50 mg twice daily.

For QTc interval > 500 ms, immediately stop midostaurin, check magnesium and potassium levels and correct any abnormalities. If possible, stop any medication, which may prolong the

QTc interval Re-start with midostaurin 50 mg once daily if QTc interval is between >470ms and ≤ 500 ms. Once QTc interval improves to ≤ 470 ms, resume midostaurin with 50 mg twice daily. If QTc remains > 470 ms for more than three weeks, discontinue midostaurin until QTc improves to < 470 ms, then resume midostaurin with 50 mg twice daily. Missed doses of midostaurin will not be made up.

6.3.3.4 Other non-hematologic toxicities

If a patient experiences other grade 3/4 non-hematologic toxicity, which is considered to be at least possibly related to midostaurin, midostaurin must be interrupted until toxicity resolves to

[redacted]

≤ grade 2. If midostaurin is held for more than 28 days, then discontinue midostaurin. Missed doses of midostaurin will not be made up.

Persistent grade 1 or 2 toxicities during maintenance therapy that patients may deem unacceptable may prompt drug holidays of as long as 28 days. No drug holidays longer than 28 days are allowed. Missed doses of midostaurin will not be made up.

6.3.4 Daunorubicin- dose modifications for hepatotoxicity

Initial and subsequent doses of daunorubicin should be modified as follows for hepatotoxicity:

Table 6-4 Daunorubicin hepatoxicity dose modifications

Total bilirubin (mg/dl)	Daunorubicin Dose Modification
Grade < 2	None
Grade ≥ 2 and ≤ 3	25% dose reduction
Grade > 3	50% dose reduction

6.3.5 Cytarabine - dose modifications for neurotoxicity

For neurotoxicity ≥ grade 2 due to cytarabine during consolidation therapy, discontinue cytarabine for the remainder of the cycle. Cytarabine may be considered at the next consolidation therapy cycle with a dose modification from 3 g/m^2 to 2 mg/m^2 or from 2 g/m^2 to 1 g/m^2 if the toxicity has resolved to ≤ grade 1.For patient receiving 1 g/m^2, cytarabine may be discontinued at the discretion of the Investigator.

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

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

6.3.6 Dose modification for obese patients

There is no clearly documented adverse impact of treatment of obese patients when dosing is performed according to actual body weight. Therefore, all dosing is to be determined solely by the patient's BSA as calculated from actual weight. This will eliminate the risk of calculation error and the possible introduction of variability in dose administration. The calculation is by the DuBois and DuBois formula: = 0.20247 x height (m)$^{0.725}$ x weight (kg)$^{0.425}$

Failure to use actual body weight in the calculation of drug dosages will be considered a major protocol deviation. Investigators who are uncomfortable with administering chemotherapy dose based on actual body weight should not enroll obese patients on this study.

6.3.7 Anticipated risks and safety concerns of the study drug

Appropriate eligibility criteria and specific DLT definitions, as well as specific dose modification and stopping rules are included in this study. Recommended guidelines for prophylactic or supportive treatment for expected toxicities are provided in Section 6.3.2 Refer to preclinical toxicity and or clinical data found in the [Investigator's Brochure Section 4.3 and Section 5].

[redacted]

6.3.8 Follow-up for toxicities

Patients whose treatment is interrupted or permanently discontinued due to an adverse event or laboratory abnormality above must be followed at least once a week (or more frequently if required by institutional practices, or if clinically indicated) during drug-hold and for 4 weeks, and subsequently at 4-week intervals, until resolution or stabilization of the event, or until the adverse event is considered permanent per investigators discretion, whichever comes first.

For adverse events and serious adverse events, patients will continue to be followed for toxicity for 30 days following the end of study treatment period.

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

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

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

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

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

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

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

1. Laboratory tests should include ALT, AST, albumin, creatine kinase, total bilirubin, direct and indirect bilirubin, GGT, prothrombin time (PT)/INR and alkaline phosphatase.
2. A detailed history, including relevant information, such as review of ethanol, concomitant medications, herbal remedies, supplement consumption, history of any pre-existing liver conditions or risk factors, should be collected.
3. Further testing for acute hepatitis A, B, C or E infection and liver imaging (e.g. biliary tract) may be warranted.
4. Additional testing for other hepatotropic viral infection (CMV, EBV or HSV), autoimmune hepatitis or liver biopsy may be considered as clinically indicated or after consultation with specialist/hepatologist.

[redacted]

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

6.4 Concomitant medications

The patient must be told to notify the investigational site about any new medications he/she takes after the start of the study treatment. All medications taken within 28 days prior to enrollment and all concomitant medications/therapies must be recorded on the Prior and Concomitant Medications eCRF. Anticancer agents (e.g. chemotherapy, radiation therapy, or biologic response modifiers or FLT3 inhibitors) other than those agents specified in this protocol are not permitted.

6.4.1 Permitted concomitant therapy

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

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.

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 midostaurin 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-diarrheal 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

[redacted]

suggested. However, the kind and dose of anti-diarrheal should be chosen per investigator discretion.

6.4.1.1.3 Liver toxicity management with midostaurin

As midostaurin is extensively metabolized by the liver, patients with significantly impaired liver function or with hepatic failure should not receive midostaurin. Monitoring of LFTs (transaminases and bilirubin) is recommended particularly when used in combination with chemotherapeutic regimens that are known to be associated with increased hepatic risk. Labels for both daunorubicin and cytarabine contain hepatotoxicity warnings.

6.4.1.1.4 Ocular toxicity management during consolidation

For the management of ocular toxicity during consolidation administer 0.1% Dexamethasone or other corticosteroid ophthalmic solution 2 drops to each eye 4 times a day to begin 6-12 hours prior to the initiation of the cytarabine infusion and to continue for at least 24 hours after the last cytarabine dose.

6.4.1.2 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, refer to Section 5.3, 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 4 months post study because of the long half-life of the metabolite, CGP52421.

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. 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 (A2109) where midostaurin was co-administrated with the potent CYP450 3A4 inhibitor ketoconazole, at steady-state of ketoconazole, midostaurin C_{max} increased by 1.8-fold, AUC_{inf} by 10-fold.

Another study, [CPKC412A2104E2], evaluated two midostaurin dosing regimens with an intra-patient dose escalation of midostaurin up to 600 mg/day (300mg b.i.d, N=12) and concomitant administration of midostaurin 50 mg b.i.d with itraconazole as an inhibitor of CYP3A4 enzymatic activity in a subset of patients (N=12). The study could not establish a maximum tolerated dose, suggesting that exposure to a midostaurin dose of up to 600mg/day was deemed tolerable. Moreover, the itraconazole cohort of the study did not indicate overt increase in midostaurin steady-state concentration, as only three patients showed a 2-3 fold increase in their steady-state C_{min}.

[redacted]

Taken together, the data indicates that co-administration of strong CYP3A4 inhibitors with midostaurin has the potential to increase exposure of midostaurin.

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.

Please see Section 6.4.2.2 for the suggested antifungal regimens.

Here below is a list of strong CYP3A4 inhibitors:

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

A list of moderate CYP450 3A4 can be found on:

//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 (A2110) where midostaurin was co-administrated with the potent CYP450 3A4 inducer rifampicin, the C_{max} and AUC of midostaurin decreased by 73% and 94%, respectively. To avoid sub-therapeutic exposure to midostaurin, moderate or potent CYP450 3A4 inducers should not be co-administered.

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:

In study A2112, Midostaurin at a single dose of 100 mg was administered concomitantly with midazolam on Day 3 and, then 50 mg twice daily from Day 4 to Day 6. Overall, the PK of midazolam (sensitive CYP34A probe) or its metabolite 1'-hydroxymidazolam were not affected in a clinically meaningful manner following four dosing days of midostaurin in healthy subjects.

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 are described below:

Prophylaxis

- Fluconazole (moderate CYP3A4 inhibitor)

[redacted]

- Micafungin

If a patient requires active treatment for a fungal or mold infection and the only treatment options is an azole that is a strong CYP3A4 inhibitor, then 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, patients should be monitored closely for signs of increased toxicity.

6.4.3 Prohibited concomitant therapy

There is no prohibited concomitant therapy, however, as described in Section 6.4.2, it is highly recommended to avoid concomitant strong CYP3A4 inhibitors.

6.4.4 Use of bisphosphonates (or other concomitant agents)

Not Applicable

6.5 Patient numbering, treatment assignment or randomization

6.5.1 Patient numbering

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

Once assigned, the Patient No. must not be reused for any other patient and the Patient No. for that individual must not be changed, even if the patient is re-screened. If the patient fails to be dosed, the reason will be entered into the Screening Log page.

6.5.2 Treatment assignment

Patients who fulfill all entry criteria will receive midostaurin (investigational drug) on day 8 of the first induction cycle.

6.5.3 Treatment blinding

Not Applicable

6.6 Study drug preparation and dispensation

The Investigator or responsible site personnel must instruct the patient or caregiver to take the study treatment as per protocol. Study treatment will be dispensed to the patient by authorized

[redacted]

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 6-5 Preparation and dispensing

Study treatments	Dispensing	Preparation
Midostaurin (PKC412)	Soft Gelatin Capsules (SGC) 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.	Not applicable
Daunorubicin	Not applicable	Refer to local product information
Idarubicin	Not applicable	Refer to local product information
Cytarabine	Not applicable	Refer to local product information

6.6.1 Study treatment packaging and labeling

Midostaurin will be provided as global supply by Novartis Drug Supply Management. Midostaurin will be supplied via a blister pack, with a study specific label. Labeling of these supplies will be done at global level under the responsibility of Novartis DSM.

Medication labels will be in the local language and comply with the legal requirements of each country. They will include storage conditions for the drug and study number but no information about the patient.

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, midostaurin should be stored according to the instructions specified on the drug labels and in the [Investigator's Brochure].

Table 6-6 Supply and storage of study treatments

Study treatments	Supply	Storage
Midostaurin (PKC412)	Centrally supplied by Novartis	Per label requirements

6.6.3 Study drug compliance and accountability

6.6.3.1 Study drug compliance

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

6.6.3.2 Study drug accountability

The Treating Investigator or designee must maintain an accurate record of the shipment and dispensing of study treatment in a drug accountability log. Drug accountability will be noted by the field monitor during site visits and at the completion of the study. Patients will be asked to

return all unused study treatment and packaging on a regular basis, at the end of the study or at the time of study treatment discontinuation.

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

6.6.3.3 Handling of other study treatment

Not applicable.

6.6.4 Disposal and destruction

The study drug supply can be destroyed at the local Novartis facility, Drug Supply group or third party, as appropriate.

Please do not destroy any study drug until your monitor has had the opportunity to review your inventory and complete drug accountability reconciliation. If your site cannot destroy the drug locally, you can return it to a designated Novartis vendor for safe destruction. Please discuss this process with your monitor.

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.

Note: If treatment with midostaurin is withheld at any time, all study visits, and safety assessments should continue according to the appropriate study days from Day 1 of each cycle as per the schedule of assessments.

All data obtained from these assessments must be supported in the patient's source documentation. No eCRF will be used as a source document. The table indicates which assessments produce data to be entered into the database (D) or remain in the source documents (S).

The number of cycles in each phase (induction, consolidation and maintenance) is decided on at the discretion of the investigator, based on the patient's clinical status.

[redacted]

Table 7-1 Visit evaluation schedule

	Category	Protocol Section	Screening / Baseline	Induction Phase Up to 2 cycles (Pre-dose/cycle)			Consolidation Phase Up to 4 Cycles (pre-dose/cycle)								Maintenance Phase Up to 12 Cycles (pre-dose/cycle)	End of Study Treatment	30 Day Safety Follow up
Visit Name			**(C1D1 - C1D7)**	**C1D8 Enrollment**	**C2D1**	**C2D8**	**C1D1**	**C1D8**	**C2D1**	**C2D8**	**C3D1**	**C3D8**	**C4D1**	**C4D8**	**C1D1 up to C12D1**		
Study day(s)			**-1**	**1**													
Cycle Days			**7**	**8**	**1**	**8**	**1**	**8**	**1**	**8**	**1**	**8**	**1**	**8**	**1**	**Last**	
Obtain Informed Consent	D	11.7.	X														
Patient history	S	7.1.2.3.	X														
Interactive Response Technology		9.4.	X	X			X								X	X	
End of disposition	D	7.1.4.1. 7.1.4.2.					Done prior C1D1 of this phase								Done prior C1D1 of this phase	X	
Demography	D	7.1.2.3.	X														
Inclusion /exclusion criteria	D	5.2 and 5.3.	X														
Medical History	D	7.1.2.3.	X														
Prior Antineoplastic / Chemotherapy	D	7.1.2.3.	X														
Diagnosis and extent of cancer	D	7.1.2.3.	X														

[redacted]

	Category	Protocol Section	Screening / Baseline	Induction Phase Up to 2 cycles (Pre-dose/cycle)			Consolidation Phase Up to 4 Cycles (pre-dose/cycle)								Maintenance Phase Up to 12 Cycles (pre-dose/cycle)	End of Study Treatment	30 Day Safety Follow up
Visit Name			**(C1D1 - C1D7)**	**C1D8 Enrollment**	**C2D1**	**C2D8**	**C1D1**	**C1D8**	**C2D1**	**C2D8**	**C3D1**	**C3D8**	**C4D1**	**C4D8**	**C1D1 up to C12D1**		
Study day(s)			**-1**	**1**													
Cycle Days			**7**	**8**	**1**	**8**	**1**	**8**	**1**	**8**	**1**	**8**	**1**	**8**	**1**	**Last**	
FLT3 mutation status known (ITD/TKD)	D	7.1.2.	X														
NPM1 mutation	D	4.1.	NPM1 mutation status will be collected if available														
Prior and Concomitant Medications	D	7.1.2.3.	X	X			X								X	X	
Surgical and Medical Procedures	D	7.1.2.3.	X	X			X								X	X	
Physical examination	S	7.2.2.1.	X	X			X								X	X	
Height	D	7.2.2.3.	X													X	
Weight	D	7.2.2.3.	X	X			X								X	X	
Vital signs	D	7.2.2.2.	X	X			X								X	X	
ECOG Performance status	D	7.2.2.4.	X													X	
	Laboratory assessments (local lab)																
Hematology	D	7.2.2.5.1.	X	For CR/CRi assessments and when justified for the assessment of a treatment related AE or SAE and at physician's discretion													

[redacted]

	Category	Protocol Section	Screening / Baseline	Induction Phase Up to 2 cycles (Pre-dose/cycle)			Consolidation Phase Up to 4 Cycles (pre-dose/cycle)								Maintenance Phase Up to 12 Cycles (pre-dose/cycle)	End of Study Treatment	30 Day Safety Follow up
Visit Name			**(C1D1 - C1D7)**	**C1D8 Enrollment**	**C2D1**	**C2D8**	**C1D1**	**C1D8**	**C2D1**	**C2D8**	**C3D1**	**C3D8**	**C4D1**	**C4D8**	**C1D1 up to C12D1**		
Study day(s)			**-1**	**1**													
Cycle Days			**7**	**8**	**1**	**8**	**1**	**8**	**1**	**8**	**1**	**8**	**1**	**8**	**1**	**Last**	
Chemistry	D	7.2.2.5.	X	When justified for the assessment of a treatment related AE or SAE and at physician's discretion													
Urinalysis	D	7.2.2.5.	X														
Coagulation	D	7.2.2.5.	X														
Blood transfusion	D	6.4.1.		To be captured in the eCRF during the study													
Pregnancy test	D	7.2.2.5.3	Within 2 days prior to midostaurin dosing in induction and consolidation phase.												X	X	
Chest x-ray	D	7.2.2.6.	X														
ECG	D	7.2.2.7.1	X		X		X		X		X		X		X	X	
Cardiac Imaging (LVEF)	D	7.2.2.7.2	X	When justified for the assessment of a treatment related AE or SAE and at physician discretion												X	
	Safety																
Adverse events	D	8.1.	To be recorded continuously														
	Study treatment																
Study treatment administration	D	6.6.		X			X								X	X	
	Other assessments																
[redacted]																	

[redacted]

	Category	Protocol Section	Screening / Baseline	Induction Phase Up to 2 cycles (Pre-dose/cycle)			Consolidation Phase Up to 4 Cycles (pre-dose/cycle)								Maintenance Phase Up to 12 Cycles (pre-dose/cycle)	End of Study Treatment	30 Day Safety Follow up
Visit Name			**(C1D1 - C1D7)**	**C1D8 Enrollment**	**C2D1**	**C2D8**	**C1D1**	**C1D8**	**C2D1**	**C2D8**	**C3D1**	**C3D8**	**C4D1**	**C4D8**	**C1D1 up to C12D1**		
Study day(s)			**-1**	**1**													
Cycle Days			**7**	**8**	**1**	**8**	**1**	**8**	**1**	**8**	**1**	**8**	**1**	**8**	**1**	**Last**	
[redacted]																	
Resource utilization	D	7.2.5.													X	X	
Bone marrow aspiration	D		Please refers to Section 7.1.2	To be performed between Day 21 to Day 28 at each cycle			Prior to first consolidation cycle C1D1, and if necessary per investigator's decision during the consolidation phase								Prior to first maintenance cycle C1D1 and every 3 months	X	
CR/CRi	D	7.2.1.		Day 21-28 for each induction cycle.			CR/CRi in induction, consolidation and maintenance therapy is collected as secondary endpoint. Prior to first consolidation cycle and If necessary per investigator's decision during the consolidation phase								Prior to first maintenance cycle C1D1 and every 3 months	X	

[redacted]

7.1.1 Molecular pre-screening

Not Applicable

7.1.2 Screening

Patients who are newly diagnosed with AML, have a known FLT3 ITD or TKD mutation and who have already started a "7+3" or "5+2" chemotherapy regimen in first induction will be consented and screened during the screening/baseline period (between C1D1 (chemotherapy already started) to C1D7) at least all the activities should be completed at Day 7 of the first chemotherapy (at Day -1). Re-screening is not allowed in this study.

The historical BMA result used to diagnose AML to the patients can be considered a part of inclusion criteria in the study.

If an historical BMA is available within 15 days before C1D1 of the first chemotherapy there is no need to repeat this assessment during the screening/baseline period.

If in case an historical BMA is not available within the 15 days before C1D1 of the first chemotherapy, a BMA should be performed during the screening/baseline period of the study.

7.1.2.1 Eligibility screening

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

Screening assessments should be performed at the time of the screening except for pregnancy test if result is available and negative within 7 days prior to screening, or for cardiac imaging and chest x ray if results are within 14 days prior to screening.

7.1.2.2 Information to be collected on screening failures

Patient who signed an Informed Consent Form but failed to start on midostaurin for any reason will be considered as a screen failure. The reason for not being started on midostaurin will be entered on the Screening Phase Disposition eCRF. The demographic information, informed consent, and Inclusion/Exclusion pages must also be completed for Screen Failure patients. No other data will be entered into the clinical database for patients who are screen failures, unless the patient has a Serious Adverse Event during the Screening Phase (see Section 8.2 for SAE reporting details). The following eCRFs must be completed for screening failure patients:

- Screening Phase Disposition page
- Informed consent
- Demography
- Adverse Events (only if an SAE occurs. Refer to Section 8.2.)
- Inclusion/Exclusion Criteria

[redacted]

7.1.2.3 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 including, but not limited to, the following information:

- Demography (including: date of birth, age, patient initials, gender, childbearing potential, race and ethnicity, or as allowed by local regulations)
- Relevant medical history
- Date of diagnosis
- Physical Examination (Height, Weight, Vital Signs)
- Performance status
- FLT3 mutation status (ITD or TKD)
- Bone marrow aspiration
- Any additional mutation information, if known
- Prior and Concomitant Medications
- Surgical and Medical Procedures
- Chemotherapy information from induction cycle 1 day 1 to day 7

Additionally all other medications and significant non-drug therapies taken within 28 days prior to the first dose of midostaurin being 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 Investigator prescriptions and 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

7.1.3 Run-in period

Not Applicable

7.1.4 Treatment period

Patients will begin midostaurin after completing all screening procedures and fulfilling all of the eligibility criteria. The study design is outlined in Figure 4-1 and Figure 4-2 by treatment phase; induction; consolidation; maintenance. Patients achieving CR/CRi following 1 to 2 cycles of induction will continue to consolidation therapy for up to 4 cycles. Patients who maintain a CR/CRi following consolidation may continue to the maintenance phase up to 12 cycles. The duration of each phase may vary based on investigator discretion. Patients will be treated on protocol for about 18 months. Patients may be removed from treatment due to unacceptable toxicity, disease progression, at the discretion of the Investigator, withdrawal of consent, or as explained in Section 7.1.3, whichever comes first.

[redacted]

For details of assessments, refer to Table 7-1.

7.1.4.1 Induction phase

Newly diagnosed AML patients will receive "7+3" or "5+2" induction therapy with cytarabine and daunorubicin (or idarubicin) as defined by NCCN treatment guidelines (NCCN Guidelines v1.2017). Enrolled patients will subsequently receive oral midostaurin 50 mg (two 25 mg capsules) twice a day on days 8-28 (see Table 6-1). Patients should take their doses at approximately the same time each day, and approximately 12 hours should elapse between the morning and evening doses. Each daily dose should be given with food and a glass of water (~240 mL). Patients should be instructed to swallow capsules whole and not chew capsules. If vomiting occurs, no re-dosing is allowed prior to the next scheduled dose.

A switch between regimens is not allowed.

Refer to Table 6-1 for Induction treatment schedule.

Patients who achieved a CR/CRi after the first cycle may continue with the consolidation phase, all other patients may get a second induction cycle as per investigator's discretion.

Second induction cycle

For patients requiring a second induction cycle, treatment will begin at least 3 days and no later than 42 calendar days after completing midostaurin. The treatment regimen must also adhere to the guidelines specified above for the first induction. Please refer to Section 7.2.1.

Patients who have achieved a CR/CRi after the second cycle may continue with the consolidation phase; all other patients should be removed from protocol.

Patients may start consolidation treatment at least 3 days and no later than 42 calendar days after the last midostaurin dose of induction.

An end phase disposition will be completed prior the C1D1 of the consolidation phase.

7.1.4.2 Consolidation phase

Patients who achieved a CR/CRi after either one or two induction cycles will receive consolidation therapy with cytarabine as defined by NCCN treatment guidelines plus subsequent midostaurin during each cycle. Patients will receive up to four cycles of consolidation therapy. Fewer cycles are accepted as per investigator's discretion.

Each consolidation cycle is 28 days treatment. It is recommended that subsequent cycle start at least 3 days after the previous cycle is completed and no later than 70 calendar days from the start of the first cycle of consolidation. For the other consolidation cycles a recovery periods of 21 days maximum will be applied. Refer to Table 6-2 for consolidation treatment schedule.

An end phase disposition will be completed prior the C1D1 of the maintenance phase.

7.1.4.3 Maintenance phase

Patients who continue to achieve CR/CRi after (up to) four cycles of consolidation therapy will receive midostaurin maintenance therapy. Prior to initiation of midostaurin maintenance

[redacted]

therapy, all significant acute toxicity from consolidation therapy must have resolved to < grade 2.

For CR patients, midostaurin maintenance therapy will begin after hematologic recovery (ANC ≥ 1 000/µL, platelet count ≥ 100 000/µL) occurs and for CRi patients per investigator discretion and at least 3 days and no later than 28 calendar days after the last dose of consolidation midostaurin.

Each maintenance cycle is 28 days treatment. Subsequent cycles start on the day after the previous cycle is completed. In other words, subsequent cycles start 29 calendar days from the start of the previous cycle.

Patients who are unable to complete the cytarabine consolidation cycles because of toxicity or insufficient hematologic recovery may still be eligible for maintenance therapy. Discuss this situation in advance with the Novartis Study Team.

Refer to Table 6-3 for maintenance treatment schedule.

7.1.5 Discontinuation of study treatment

At the time patients discontinue study treatment; a visit should be scheduled as soon as possible, at which time all of the assessments listed for the End of Treatment visit will be performed. An End of Treatment eCRF page should be completed, giving the date and reason for stopping the study treatment.

Patients who discontinue study treatment should be considered withdrawn from the study after the final visit assessments are performed or when it is clear that the patient will not return for these assessments.

If a study withdrawal occurs, or if the patient fails to return for visits, the Investigator must determine the primary reason for a patient's premature withdrawal from the study and record this information in eCRF.

At minimum, patients who discontinue study treatment, including those who refuse to return for a final visit will be contacted for safety evaluations. All patients must have safety evaluations for 30 days, after the last dose of study treatment unless they have withdrawn consent.

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

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

Patients may be withdrawn from study treatment under the following circumstances:

- Adverse events
- Pregnancy
- Subject withdrew consent

[redacted]

- Lost to follow up
- Technical problems
- Death
- Progressive disease*
- Protocol deviation
- Study terminated by sponsor
- Investigator decision
- Subject/guardian decision

*The progressive disease refers to CR/CRi not achieved at the end of induction and/or consolidation therapy and relapse.

7.1.5.1 Replacement policy

Not Applicable

Escalation part:

Not Applicable

Expansion part:

Not Applicable

7.1.6 Withdrawal of consent

Patients may voluntarily withdraw consent to participate in the study for any reason at any time. Withdrawal of consent occurs only when a patient does not want to participate in the study any longer, and does not want any further visits or assessments, and does not want any further study related contact.

Novartis will continue to retain and use all research results that have already been collected for the study evaluation. All biological samples that have already been collected may be retained and analyzed at a later date (or as required by local regulations).

If a patient withdraws consent, the investigator should make a reasonable effort (e.g. telephone, e-mail, letter) to understand the primary reason for this decision and record this information.

Study treatment must be discontinued and no further assessments conducted.

Further attempts to contact the patient are not allowed unless safety findings require communication or follow up.

7.1.7 Follow up for safety evaluations

All patients must have safety evaluations for 30 days, after the last dose of study treatment except if a patient withdraws consent.

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

[redacted]

7.1.8 Lost to follow-up

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

7.2 Assessment types

7.2.1 Efficacy assessments

Induction therapy

FLT3 mutated patients will receive induction therapy (cytarabine with anthracycline (idarubicin or daunorubicin) (for details refer to Section 6.1.1) sequentially followed by midostaurin.

In the first Induction phase, a bone marrow aspiration will be performed in all patients on Day 21-28 (according to local standard of care) to determine the need for a second induction cycle. If the marrow aspirate is inadequate to make a determination, repeat the bone marrow assessment within one week.

If the Day 21-28 (according to local standard of care) bone marrow aspiration reveals <5% blasts in a cellular marrow (> 20%), then a bone marrow aspiration must be performed within one week after recovery of ANC ≥ 1 000/μL and platelets ≥ 100 000/μL to document complete remission. Patients in CR will proceed to consolidation therapy. Patients with CRi will proceed to consolidation therapy as per investigator discretion.

If the Day 21-28(according to local standard of care) bone marrow aspiration reveals ≥ 5% leukemic blasts in a cellular marrow (> 20%) a second induction will be given.

Second Induction therapy (if applicable)

For patients requiring a second induction, treatment will begin at least 3 days after completing midostaurin.

Bone marrow aspiration will be performed within one week after recovery of ANC ≥1000/μL and platelets ≥100,000/μL to assess for response.

Patients in CR will proceed to consolidation therapy. Patients who have residual AML at this time after a second remission induction should be removed from protocol therapy. Patients with CRi will proceed to consolidation therapy as per investigator's discretion.

Consolidation therapy (up to four cycles per investigator's discretion)

Based upon the superior results reported for AML patients less than 60 years old with normal karyotypes in prospective clinical trials (Farag et al 2005) and RATIFY, who achieve a CR/CRi after induction will receive further therapy with midostaurin. Patients will receive up to four cycles of consolidation therapy. Each consolidation cycle is four weeks in duration, and should begin within two weeks following hematologic recovery (ANC ≥1000/μL, platelet count ≥100,000/μL), but not sooner than 31 days from the beginning of the previous cycle. If a

[redacted]

remission consolidation cycle is delayed > 8 weeks (56 days) from the start of the previous course due to slow resolution of toxicity or slow recovery of complete blood counts (CBC), please contact Novartis. A bone marrow aspiration must be performed prior to the first consolidation cycle C1D1 and later can be performed if necessary per investigator's decision at any time during consolidation phase.

Maintenance therapy (for patients in CR/CRi after consolidation therapy)

Patients who continue in CR/CRi (by bone marrow aspiration and blood evaluation) after four cycles of remission consolidation therapy will receive midostaurin. Prior to maintenance therapy, all significant acute toxicity from consolidation therapy must have resolved to ≤ grade 2.

Patients with CRi will proceed to maintenance therapy as per investigator's discretion and for CR patients maintenance therapy will begin after hematologic recovery (ANC ≥ 1000/μL, platelet count ≥ 100,000/μL) from remission consolidation, and at least 3 days after the last dose of midostaurin during consolidation. Patients who are unable to complete four courses of HiDAC consolidation because of toxicity may still be eligible for maintenance therapy at the discretion of the principal investigator after the last dose of consolidation after recovery from hematologic and other significant acute toxicity. A bone marrow examination should be performed prior to the first maintenance and every 3 months during maintenance phase.

Based on the results of this bone marrow examination (during maintenance phase) the physician will decide if the patient pursues the study treatment.

- Complete remission (CR): Bone marrow blasts <5% with spicules; absence of blasts with Auer rods; absence of extramedullary disease; absolute neutrophil count (ANC) ≥ 1000/μL; platelet count ≥ 100,000/μL; independent of transfusions.
  Transfusion independence is defined as at least 7 days transfusion free prior to CR/CRi assessments.
- CR with incomplete recovery (CRi): All CR criteria except for residual neutropenia (<1000/μL) or thrombocytopenia (<100,000/μL) with transfusion independence but persistent cytopenia.
- Partial remission (PR) is designated by normalization of blood values but with a decrease from baseline of at least 50% in the percentage of blasts to 5% to 25% in the bone marrow aspirate. A value of ≤ 5% blasts may also be considered a PR if Auer rods are present.
- Treatment failure includes patients for whom treatment that failed to achieve a CR/CRi or equal or less than a PR.
- Relapse/recurrence following complete response is a reappearance of leukemic blasts in the peripheral blood or finding of ≥5% blasts in the bone marrow not attributable to another cause. The appearance of new dysplastic changes should also be considered relapse. The reappearance or development of cytologically proven extramedullary disease also indicates relapse. Molecular and/or genetic relapse is characterized by reappearance of a cytogenetic or molecular abnormality.

[redacted]

7.2.2 Safety and tolerability assessments

Safety will be monitored by assessing proportion of patients with AEs, Grade 3 and 4 AEs, SAEs, AEs leading to discontinuation, and deaths as well as collecting of the adverse events at every visit. For details on AE collection and reporting, refer to Section 8.

7.2.2.1 Physical examination

A physical examination must be performed as per Table 7-1 and on the day of discontinuation/End of Treatment.

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

7.2.2.2 Vital signs

Vital signs include blood pressure (supine position preferred), pulse measurement, and body temperature. Data on vital signs will be tabulated and listed, notable values will be flagged.

7.2.2.3 Height and weight

Height in centimeters 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 as per Table 7-1.

Body weight will be measured at screening and at subsequent time points as specified in Table 7-1.

7.2.2.4 Performance status

The ECOG Performance status scale will be used, as described in the Table 7-2.

Table 7-2 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 self-care but unable to carry out any work activities. Up and about more than 50% of waking hours
3	Capable of only limited self-care, confined to bed or chair more than 50% of waking hours
4	Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair
5	Dead

7.2.2.5 Laboratory evaluations

Laboratory evaluations must be performed according to the Table 7-1. 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.

All laboratory samples must be drawn **PRIOR** to the first dose of midostaurin.

[redacted]

All other laboratory evaluations should be performed when justified for the assessment of a treatment related AE or SAE and at physician discretion.

All efforts should be made to collect the labs prior to dosing. Fasting is not required.

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

The following laboratory assessment will be done by the local laboratory:

Table 7-3 Local clinical laboratory parameters collection plan

Test Category	Test Name
Hematology	Hemoglobin, Platelets, Red blood cells, White blood cells, Differential (Basophils, Eosinophils, Lymphocytes, Monocytes, Neutrophils, Bands)
Chemistry	Albumin, Alkaline phosphatase, ALT, AST, Lactate dehydrogenase (LDH), Calcium, Magnesium, Phosphorus, Sodium, Potassium, Creatinine, Creatine kinase, Direct Bilirubin, Total Bilirubin, Total Cholesterol, Blood Urea Nitrogen (BUN) or Urea, Uric Acid Amylase, Lipase, Glucose (fasting) or Glucose (non fasting)
Urinalysis	Macroscopic Panel (Dipstick) (Color, Bilirubin, Blood, Glucose, Ketones, Leukocytes esterase, Nitrite, pH, Protein, Specific Gravity, Urobilinogen)
Coagulation	International normalized ratio [INR]), Activated partial thromboplastin time or Activated thromboplastin time %
Pregnancy Test	When effective contraception is required pregnancy testing is mandated at screening and/or pre-dose and at the end of the trial. A serum pregnancy test should be performed; while at the end of trial urinary pregnancy tests are sufficient.
Note: All efforts should be made to collect the labs prior to dosing. Fasting is not required.	

7.2.2.5.1 Hematology

Hemoglobin, white blood cell count with differential, and platelet count will be measured.

7.2.2.5.2 Chemical chemistry

Blood urea, creatinine, total bilirubin, AST, ALT, alkaline phosphatase, sodium, potassium, calcium, phosphorous, albumin, and uric acid will be measured.

7.2.2.5.3 Pregnancy and assessments of fertility

For women of childbearing potential, pregnancy testing is mandatory at screening, and within 2 days prior to midostaurin dosing in induction and consolidation phases, day 1 of every cycle in maintenance and at the end of the study. At screening, a serum pregnancy test should be performed, while during and at the end of study urinary pregnancy tests are sufficient.

U-HCG or serum HCG: Women of childbearing potential must have a negative serum or urine pregnancy test within 2 days prior to administration of the first dose of midostaurin.

Women are 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).

When effective contraception is required pregnancy testing is recommended at screening and/or pre-dose and at the end of the study.

[redacted]

7.2.2.6 Radiological examination

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

7.2.2.7 Cardiac assessment

7.2.2.7.1 Electrocardiogram (ECG)

A standard 12 lead ECG will be performed as indicated in Table 7-1. All initial ECG assessment must be done **PRIOR** to the first dose of midostaurin.

Interpretation of the tracing must be made by a qualified physician and documented on the ECG CRF 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 CRF 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 CRF page.

For dose modifications for cardiac toxicity refer to Section 6.3.2.3 for induction and consolidation, and Section 6.3.3.3 for maintenance.

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

An echocardiogram or MUGA scan must be performed as indicated in the Table 7-1. 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 study.

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 including an additional mandatory test at the end of treatment to verify cardiac safety.

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

7.2.2.7.3 Cardiac enzymes

Not Applicable

7.2.2.8 Tolerability

Not Applicable

7.2.3 Pharmacokinetics

Not Applicable

[redacted]

7.2.3.1 Analytical method

Not Applicable

7.2.4 Biomarkers

Not Applicable

7.2.4.1 Additional biomarker assessments

Not Applicable

Other assessments

No additional tests will be performed on patients entered into this study.

7.2.5 Resource utilization

Collection of health care resource utilization data for this study will focus on hospitalization: the reason for the hospitalization, i.e. related to AML symptoms, adverse events (and type of adverse event) or other reason, number of hospital days by ward type (e.g. hospital unit, emergency room, intensive care unit), discharge reason, and the names of concomitant medications during hospital stay. These measures will be used to quantify the number of hospital day's impact of therapy during the maintenance phase and derive components of the economic impact of midostaurin during maintenance.

[redacted]

[redacted]

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.

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

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

Adverse events will be assessed and graded according to the CTCAE version 4.03.

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

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,

[redacted]

laboratory test, or other assessments. As far as possible, each adverse event should be evaluated to determine:

1. The severity grade (CTCAE Grade 1-5)
2. Its duration (Start and end dates)
3. Its relationship to the study treatment (Reasonable possibility that AE is related: No, Yes)
4. Action taken with respect to study or investigational treatment (none, dose adjusted, temporarily interrupted, permanently discontinued, unknown, not applicable)
5. Whether medication or therapy was given (no concomitant medication/non-drug therapy, concomitant medication/non-drug therapy)
6. Whether it is serious, where a serious adverse event (SAE) is defined as in Section 8.2.1 and which seriousness criteria have been met

If the event worsens the event should be reported a second time in the CRF noting the start date when the event worsens in toxicity. For grade 3 and 4 adverse events only, if improvement to a lower grade is determined a new entry for this event should be reported in the CRF noting the start date when the event improved from having been Grade 3 or Grade 4.

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

Once an adverse event is detected, it should be followed until its resolution or until it is judged to be permanent, and assessment should be made at each visit (or more frequently, if necessary) of any changes in severity, the suspected relationship to the study treatment, the interventions required to treat it, and the outcome.

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 CRF. Whenever possible, a diagnosis rather than a symptom should be provided (e.g. anemia instead of low hemoglobin). Laboratory abnormalities that meet the criteria for Adverse Events should be followed until they have returned to normal or an adequate explanation of the abnormality is found. When an abnormal laboratory or test result corresponds to a sign/symptom of an already reported adverse event, it is not necessary to separately record the lab/test result as an additional event.

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

[redacted]

8.1.3 Adverse events of special interest

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

Adverse events of special interest are defined on the basis of an ongoing review of the safety data. AESIs are discussed in detail in the [Investigator Brochure].

8.2 Serious adverse events

8.2.1 Definitions

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

- Is fatal or life-threatening
- Results in persistent or significant disability/incapacity
- Constitutes a congenital anomaly/birth defect
- Is medically significant, i.e., defined as an event that jeopardizes the patient or may require medical or surgical intervention to prevent one of the outcomes listed above
- 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 mutation 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 additional information for the SAE including complications, progression of the initial SAE, and recurrent episodes must be reported as follow-up to the original episode within 24 hours of the investigator receiving the follow-up information. An SAE occurring at a different time

[redacted]

interval or otherwise considered completely unrelated to a previously reported one should be reported separately as a new event.

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

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

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

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

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

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

[redacted]

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

8.5 Warnings and precautions

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

8.6 Data Monitoring Committee

Not Applicable

8.7 Steering Committee

Not Applicable

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.

Prior to entering key sensitive personally identifiable information (Subject Initials and exact Date of Birth), the system will prompt site to verify that this data is allowed to be collected. If the site indicates that country rules or ethics committee standards do not permit collection of these items, the system will not solicit Subject Initials. Year of birth will be solicited (in the

[redacted]

place of exact date of birth) to establish that the subject satisfies protocol age requirements and to enable appropriate age-related normal ranges to be used in assessing laboratory test results.

9.2 Site monitoring

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

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

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

9.3 Data collection

For studies using Electronic Data Capture (EDC), the designated investigator staff will enter the data required by the protocol into the 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.

9.4 Data management and quality control

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

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

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, by joint written agreement between the Global Head of Biostatistics and Data Management and the Global Head of Clinical Development.

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

Novartis or a designated Contract Research Organization will perform all analyses. Any data analysis carried out independently by the investigator should not be presented or published before the final analysis is completed. The data from all centers that participate will be combined in the analyses.

Final analyses will be performed when all patients have been followed for 30 days after they have either prematurely discontinued or been discontinued from the study after completing treatment as per protocol.

Data will be summarized with respect to demographic and baseline characteristics including FLT3 (ITD&TKD) and NPM1 mutation (when available), and safety and efficacy observations and measurements. Data may be summarized by different chemotherapy regimens (i.e. the "7+3" and the "5+2" induction regimens) and treatment phases (induction, consolidation and maintenance).

Categorical data will be presented as frequencies and percentages. For continuous data, mean, standard deviation, median, minimum, and maximum will be presented. For selected parameters, 25^{th} and 75^{th} percentiles will also be presented.

10.1 Analysis sets

The following analysis sets will be used for statistical analysis and data reporting.

The 'All enrolled patients' set comprises all screened patients who are not screening failures.

10.1.1 Full Analysis Set

The Full Analysis Set (FAS) comprises all patients who received at least one dose of midostaurin and have a documented FLT3 mutation (ITD or TKD).

10.1.2 Safety set

The Safety Set comprises all patients who received at least one dose of midostaurin.

10.1.3 Per-Protocol set

Not applicable

10.1.4 Dose-determining analysis set

Not applicable

[redacted]

10.1.5 Pharmacokinetic analysis set

Not Applicable

10.1.6 Other analysis sets

Not Applicable

10.1.6.1 Efficacy/evaluable set

Not Applicable

10.2 Patient demographics/other baseline characteristics

Demographic and other baseline data will be summarized descriptively for the safety set.

Relevant medical histories and current medical at baseline will be summarized by system organ class and preferred term for all patients.

10.3 Treatments (study treatment, concomitant therapies, compliance)

The safety set will be used for the analyses below. Categorical data will be summarized as frequencies and percentages. For continuous data, mean, standard deviation, median, 25th and 75th percentiles, minimum, and maximum will be presented.

Duration of midostaurin treatment exposure in days and cumulative dose and dose intensity will be summarized overall and by period and induction chemotherapy regimen by means of descriptive statistics using the safety set.

The number of patients with dose adjustments (reductions, interruption, or permanent discontinuation) and the reasons will be summarized for all patients and all dosing data will be listed.

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

10.4 Primary objective

The primary objective is to further assess the safety of midostaurin in induction, consolidation and maintenance therapy including the '7+3' regimen, daunorubicin (60-90mg/m^2/day), the substitution of daunorubicin by idarubicin (12 mg/m^2/day) and cytarabine (100-200 mg/m^2/day) and also allowing the "5+2" reduced dose regimen.

The safety set will be used for the analysis of clinical safety data.

10.4.1 Variable

The analysis of the primary objective is described in Section 10.5.3.

[redacted]

10.4.2 Statistical hypothesis, model, and method of analysis

No statistical hypotheses are being tested in this study.

10.4.3 Handling of missing values/censoring/discontinuations

No imputation will be applied for any missing data.

10.4.4 Supportive and sensitivity analyses

Not Applicable

10.5 Secondary objectives

The secondary objectives in this study are to assess the clinical efficacy of midostaurin in sequential combination with chemotherapy regimens in induction and consolidation and the clinical efficacy of midostaurin in maintenance phase (measured by CR/CRi rate).

Clinical efficacy rate is defined as the proportion of patients with complete remission (CR) or complete remission with incomplete hematologic recovery (CRi) as per local assessment, in induction, consolidation and maintenance. CR and CRi are defined according to the Revised Recommendations of the International Working Group for Diagnosis, Standardization of Response Criteria, Treatment Outcomes, and Reporting Standards for Therapeutic Trials in Acute Myeloid Leukemia, described in the ELN recommendations 2017 (Dohner et al 2016) (ENL).

Clinical efficacy rate will be calculated based on the FAS. Clinical efficacy rate and its 95% confidence interval will be presented by induction regimen and age category as described in Section 10.5.3.1.

10.5.1 Key secondary objective(s)

Not Applicable

10.5.2 Other secondary efficacy objectives

Not Applicable

10.5.3 Safety objectives

10.5.3.1 Analysis set and grouping for the analyses

For all safety analyses, the safety set will be used.

The overall observation period may be summarized into the following mutually exclusive periods:

1. **Pre-treatment period:** prior to first dose of midostaurin
2. **On-treatment period** (includes 3 mutually exclusive periods):
   a. Induction period: From day of first dose of midostaurin to the day before start of consolidation period (i.e. end of induction phase plus any rest/recovery days)

[redacted]

b. Consolidation period: From day of first dose of study treatment in consolidation phase to the day before start of maintenance (i.e. end of consolidation phase plus any rest/recovery days)
c. Maintenance period: From day of first dose of midostaurin in the maintenance phase to the date of last dose of midostaurin + 30 days

It is noted that if a patient permanently discontinues study treatment during any of these periods, on-treatment is considered until the date of last dose of study treatment + 30 days (unless patient died before then, then it is till the death date)

3. **Post-treatment period:** from last date of study treatment + 31 days to end of study

Each period will contain all patients who entered that period (including withdrawal, drop-outs etc.).

Data may also be summarized by different chemotherapy regimens (i.e. the "7+3" and the "5+2" induction regimens) and by age category (i.e. patients younger than 60 years old and patients 60 years old or older).

10.5.3.2 Adverse events (AEs)

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

The incidence of treatment-emergent adverse events (new or worsening from baseline) will be summarized by system organ class, preferred term, severity (based on CTCAE grades), type of AE, relation to study treatment, periods and regimens as specified above and overall. AEs with different starts dates in different periods will be counted within each period.

AEs leading to discontinuation, serious AEs (SAE) and non-SAEs during the on-treatment period will be tabulated by type of AE.

All deaths (on-treatment and post-treatment) reportable as SAEs and non-fatal SAEs will be listed by patient and tabulated by type of AE.

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

10.5.3.3 Laboratory abnormalities

Not Applicable

10.5.3.4 Other safety data

Other safety data (including vital signs and weight) will be summarized and listed, notable values will be flagged, and any other information collected will be listed as appropriate.

ECG

A standard 12-lead ECGs including PR, QRS, QT and QTcF intervals will be obtained for each subject during the study. ECG data will be read and interpreted locally.

Listing will be provided with notable values flagged.

[redacted]

Vital signs

Data on vital signs will be tabulated and listed, notable values will be flagged.

10.5.3.5 Supportive analyses for secondary objectives

Not Applicable

10.5.3.6 Tolerability

Tolerability will be studied in terms of dose reductions or dose interruption due to an AE. Number and percentage of patients who have a dose modification due to a treatment related adverse event will be summarized by type of dose modification (interruption, dose reduction, and permanent discontinuation).

10.5.4 Pharmacokinetics

Not Applicable

10.5.4.1 Data handling principles

Not Applicable

10.5.5 Biomarkers

Not Applicable

10.5.6 Resource utilization

See Section 10.6.

[redacted]

10.6 Exploratory objectives

[redacted]

[redacted]

10.6.2 Resource utilization

Similarly descriptive statistics will be applied to assess resource utilization, e.g. on the reason for hospitalization, number of hospital days by ward type, discharge reason, and the concomitant medications used during hospital stay.

10.7 Interim analysis

No formal interim analysis is planned for this study. Analyses may be performed periodically (e.g. annually), if needed, to fulfill regulatory requests, safety updates or for publication purposes.

10.7.1 Progression free survival (PFS)

Not Applicable

10.7.2 Key secondary endpoint: Overall survival (OS)

Not Applicable

10.8 Sample size calculation

Approximately 300 patients will be enrolled in this study. The planned sample size is based on the average expected accrual rate (17 patients per month) and the planned recruitment duration (18 months) of the trial. The actual sample size may differ from this planned number. A sample size of 300 patients provides a 95% probability of observing at least one patient with an adverse event (AE) assuming a true probability of occurrence of 1%.

Table 10-1 provides probabilities to detect at least one patient with an AE for different sample sizes and different true AE incidences.

Table 10-1 Probability to detect at least one patient with an AE for different sample sizes and different true AE incidences

Incidence of an adverse event	Sample size		
	N=200	N=250	N=300
0.4%	0.5514	0.6329	0.6995
0.5%	0.6330	0.7144	0.7777
0.6%	0.6999	0.7779	0.8356
0.8%	0.7994	0.8657	0.9102
1.0 %	0.8660	0.9189	0.9510
1.3%	0.9270	0.9620	0.9803

10.9 Power for analysis of key secondary variables

Not Applicable

[redacted]

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.

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

Additional consent/information forms

Additional consent forms include:

- Information for female partners of male study participants
- Pregnancy follow-up for pregnant participants
- Pregnancy follow-up for the pregnant partner of participants

[redacted]

Male participants will be requested to provide the Information for female partners of male study participants form to their partners.

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 7.1.5.

11.5 Publication of study protocol and results

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

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

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

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

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

11.6 Study documentation, record keeping and retention of documents

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

Source data are all information, original records of clinical findings, observations, or other activities in a clinical trial necessary for the reconstruction and evaluation of the trial. Examples of these original documents and data records include, but are not limited to, hospital records, clinical and office charts, laboratory notes, memoranda, subjects' diaries or evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, copies or

transcriptions certified after verification as being accurate and complete, microfiches, photographic negatives, microfilm or magnetic media, x-rays, and subject files and records kept at the pharmacy, at the laboratories, and medico-technical departments involved in the clinical trial.

Data collection is the responsibility of the clinical trial staff at the site under the supervision of the site Principal Investigator. The study case report form (CRF) is the primary data collection instrument for the study. The investigator should ensure the accuracy, completeness, legibility, and timeliness of the data reported in the CRFs and all other required reports. Data reported on the CRF, that are derived from source documents, should be consistent with the source documents or the discrepancies should be explained. All data requested on the CRF must be recorded. Any missing data must be explained. Any change or correction to a paper CRF should be dated, initialed, and explained (if necessary) and should not obscure the original entry. For electronic CRFs an audit trail will be maintained by the system. The investigator should retain records of the changes and corrections to paper CRFs.

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

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

11.7 Confidentiality of study documents and patient records

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

11.8 Audits and inspections

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

11.9 Financial disclosures

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

12 Protocol adherence

Investigators ascertain they will apply due diligence to avoid protocol deviations. Under no circumstances should the investigator contact Novartis or its agents, if any, monitoring the study to request approval of a protocol deviation, as no authorized deviations are permitted. If the investigator feels a protocol deviation would improve the conduct of the study this must be considered a protocol amendment, and unless such an amendment is agreed upon by Novartis

and approved by the IRB/IEC/REB it cannot be implemented. All significant protocol deviations will be recorded and reported in the CSR.

12.1 Amendments to the protocol

Any change or addition to the protocol can only be made in a written protocol amendment that must be approved by Novartis, Health Authorities where required, and the IRB/IEC/REB. Only amendments that are required for patient safety may be implemented prior to IRB/IEC/REB approval. Notwithstanding the need for approval of formal protocol amendments, the investigator is expected to take any immediate action required for the safety of any patient included in this study, even if this action represents a deviation from the protocol. In such cases, Novartis should be notified of this action and the IRB/IEC at the study site should be informed according to local regulations (e.g. UK requires the notification of urgent safety measures within 3 days) but not later than 10 working days.

13 References (available upon request)

American Cancer Society. Leukemia–acute myeloid (myelogenous). https://www.cancer.org/cancer/acute-myeloid-leukemia/about/key-statistics.html.

Döhner H, Estey E, Grimwade D, et al (2016). Diagnosis and management of AML in adults: 2017 ELN recommendations from an international expert panel. Blood, pp.blood-2016.

Farag SS, et al (2005). Outcome of Induction and Post remission Therapy in Younger Adults With Acute Myeloid Leukemia With Normal Karyotype: A Cancer and Leukemia Group B Study Journal of Clinical Oncology 23:3, 482-493.

Gale RE, Green C, Allen C, et al (2008). The impact of FLT3 internal tandem duplication mutant level, number, size, and interaction with NPM1 mutations in a large cohort of young adult patients with acute myeloid leukemia. Blood; 111:2776-2784.

Kayser S, Levis MJ (2014). FLT3 tyrosine kinase inhibitors in acute myeloid leukemia: clinical implications and limitations. Leukemia & Lymphoma, 55(2), 243–255. http://doi.org/10.3109/10428194.2013.800198.

Kayser S, Schlenk RF, Londono MC, et al (2009). Insertion of FLT3 internal tandem duplication in the tyrosine kinase domain-1 is associated with resistance to chemotherapy and inferior outcome. Blood; 114:2386-2392.

Klepin HD (2014). Geriatric perspective: how to assess fitness for chemotherapy in acute myeloid leukemia. Hematology Am Soc Hematol Educ Program. 2014; 2014(1):8-13.

Klepin HD, Geiger AM, Tooze JA, et al (2013). Geriatric assessment predicts survival for older adults receiving induction chemotherapy for acute myelogenous leukemia. Blood. Blood. 2013; 121(21): 4287-4294.

Kottaridis PD, Gale RE, Frew ME, et al (2001). The presence of a FLT3 internal tandem duplication in patients with acute myeloid leukemia (AML) adds important prognostic information to cytogenetic risk group and response to the first cycle of chemotherapy: analysis of 854 patients from the United Kingdom Medical Research Council AML 10 and 12 trials. Blood; 98:1752-1710.

Levis M, Pham R, Small D (2003). CEP-701, a selective FLT3 tyrosine kinase inhibitor that is cytotoxic to FLT3/ITD-expressing leukemia cells, is synergistic with chemotherapeutic agents in vitro when used in time-sequential fashion. Blood: 102.66a.

Meshinchi, Appelbaum (2009). Structural and functional Alterations of FLT3 in Acute Myeloid Leukemia. Clin Cancer Res. 15(13): 4263–4269

NCCN Clinical Practice Guidelines in Oncology: Acute Myeloid Leukemia. Version 1.2017, https://www.nccn.org/professionals/physician_gls/pdf/aml.pdf, last accessed on 27 March 2017.

Ossenkoppele G, Lowenberg B (2015). How I treat the older patient with acute myeloid leukemia. Blood. 2015; 125(5):767-774.

RARECAREnet, http://www.rarecarenet.eu/rarecarenet/index.php/cancerlist, last accessed 7 February 2017.

[redacted]

Rashidi A, et al (2016). The effect of FLT3-ITD and NPM1 mutation on survival in intensively treated elderly patients with cytogenetically normal acute myeloid leukemia. Aug; 57(8):1977-9.

Schlenk, et al (2014). Differential impact of allelic ratio and insertion site in FLT3-ITD positive AML with respect to allogeneic hematopoietic stem cell transplantation. Blood 2014 124:3441-3449.

Schlenk, et al (2016). Midostaurin in Combination with Intensive Induction and As Single Agent Maintenance Therapy after Consolidation Therapy with Allogeneic HematopoieticStem Cell Transplantation or High-Dose Cytarabine (NCT01477606) Blood; 128:449.

SEER (2016). https://seer.cancer.gov/statfacts/html/amyl.html.

Smith TJ, et al (2015). Recommendations for the Use of WBC Growth Factors: American Society of Clinical Oncology Clinical Practice Guideline Update. Journal of Clinical Oncology 33:28, 3199-3212.

Stone RM, DeAngelo DJ, Klimek V, et al (2005). Patients with acute myeloid leukemia and an activating mutation in FLT3 respond to a small-molecule FLT3 tyrosine kinase inhibitor, PKC412. Blood. 105:54–60.

Stone RM, et al (2012). Phase IB study of the FLT3 kinase inhibitor midostaurin with chemotherapy in younger newly diagnosed adult patients with acute myeloid leukemia. Leukemia 26(9): 2061–2068.

Stone RM, Fischer T, Paquette R, et al (2009). A phase 1b study of midostaurin (PKC412) in combination with daunorubicin and cytarabine induction and high-dose cytarabine consolidation in patients under age 61 with newly diagnosed de novo acute myeloid leukemia: Overall survival of patients whose blasts have FLT3 mutations is similar to those with wild-type FLT3. Blood 114:634.

Stone RM, Mandrekar S, Sanford BL, et al (2015). The multi-kinase inhibitor midostaurin (M) prolongs survival compared with placebo (P) in combination with daunorubicin (D)/cytarabine (C) induction (ind), high-dose C consolidation (consol), and as maintenance (maint) therapy in newly diagnosed acute myeloid leukemia (AML) patients (pts) age 18-60 with FLT3 mutations (muts): An international prospective randomized (rand) P-controlled double-blind trial (CALGB 10603/RATIFY [Alliance]). Blood 126:6.

Thiede C, Steudel C, Mohr B, et al (2002). Analysis of FLT3-activating mutations in 979 patients with acute myelogenous leukemia: association with FAB subtypes and identification of subgroups with poor prognosis. Blood; 99(12):4326-4335.

Walter RB, Estey EH (2015). Management of older or unfit patients with acute myeloid leukemia. Leukemia, 29(4), pp.770-775.

[redacted]

14 Appendices