NOVARTIS

Clinical Development

PKC412/Midostaurin/Rydapt®

CPKC412A2408 / NCT03379727

An open-labeled, 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

Statistical Analysis Plan (SAP) – Amendment 3

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Document History – Changes compared to previous final version of SAP

Date	Time point	Reason for update	Outcome for update	Section and title impacted (Current)
22-Aug-2017	Prior to FPFV	N/A – Initial version	N/A	N/A
14-Jan-2020	Prior to database lock	Rules to select one assessment among several assessments in the same visit	Selection of assessment to analyze among multiple values in the same visit	2.1.5
		Time windows for unplanned visits	Time windows to assign unplanned visits in scheduled ones	
		Added rules to assign patients to 7+3 and 5+2 groups	Patients who do not have exactly 7+3 or 5+2 are assigned	2.1.8
		Category/Value missing	Added treatment exposure category “>28”.Cardiac imaging changed “>” to “>-“ for 20	2.4.2 2.8.4.2
		Change in CSR template	Concomitant medications will be analyzed with FAS instead of SAF	2.4.3
		Clinical efficacy response derivation and subgroup analyses	Selection of best response among several assessment in the same period. Response analyzed by sex	2.6.1
		AEs by subgroup	AEs to be analyzed by age category	2.8.1
		Resource utilization updated to CRF	Updated with variables only included in CRF	2.13.3
		Additional details on imputation rules	Derivation rules updated	6.1
		BUN/Urea imputation rules	To impute BUN or Urea missing values	6.2
26-Jun-2020		Study treatment exposure	Rules od study treatment exposure clarified.	2.1.1
		Analysis set	All enrolled subjects added	2.2
		Subgroups analyses added : type of induction drugs	Efficacy and safety outputs provided by Idarubicin and Daunorubicin.	2.3
		Age subgroups	<= 60 vs. >60 instead of <60 vs. >=60	2.3 and 2.4.2

Date	Time point	Reason for update	Outcome for update	Section and title impacted (Current)
		Efficay	If patient discontinued prior to first efficacy assessment then 'unknown' is assigned as best response	2.7.1
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
15-Jun-2021	Prior to database lock	PD	The number (%) of protocol deviations with COVID-19 relationship will be presented by type of deviation for all enrolled subjects.	2.5.4
09-Nov-2021	Post to database lock	Subgroups analysis amended for a new agesubgroup/category.	Included the following age subgroup/category: <= 60 / >60 to <=70 / > 70 years old	2.3, 2.4.2, 2.5.2 and 2.7.1

FPFV: First patient first visit

Table of contents

List of abbreviations

AE	adverse event
AESI	adverse events of special interest
ALT	aspartate aminotransferase
AML	acute myeloid leukemia
Ara-C	cytarabine, also known as cytosine arabinoside
AST	alanine aminotransferase
ATC	anatomical therapeutic chemical classification
CIVI	continuous intravenous infusion
CR	complete remission
CRi	complete remission with incomplete recovery
CRS	case retrieval sheet
CSR	clinical study report
CTCAE	common terminology criteria for adverse events
DI	dose intensity
ECG	electrocardiogram
ECOG	eastern cooperative oncology group
eCRF	electronic case report form
[redacted]	[redacted]
FAS	full analysis set
FLT3	fms-like tyrosine kinase receptor
GPS	global programming & statistical environment
IV	intravenous
LPLV	last patient last visit
LVEF	left ventricular ejection fraction
MedDRA	medical dictionary for drug regulatory affairs
MUGA	multi gated acquisition scan
NCCN	national comprehensive cancer network
NCDS	Novartis clinical data standards
PD	pharmacodynamics
PDS	programming data specifications
[redacted]	[redacted]
PK	pharmacokinetics
[redacted]	[redacted]
PT	preferred term
QTc	corrected QT interval
SAE	serious adverse event
SAP	statistical analysis plan
SI	international system of units
SOC	system organ class
TFLs	tables, figures, listings
WHO	world health organization

1 Introduction

This statistical analysis plan (SAP) provides detailed statistical methodology for the analyses of data which will be used for preparation of the PKC412A2408 clinical study report (CSR) and is based on the study protocol Amendment 1, dated 26-Mar-2018. At the time of this amendment, enrollement was completed with 301 patients.

The shells for the in-text tables and figures as well as the post-text tables, figures and listings (TFLs) are in the TFL shells document. Programming specifications for datasets, including derivation of variables, are given in the programming data specifications (PDS) document.

All data will be analyzed by Novartis using Novartis clinical data standards (NCDS). Analysis data sets and statistical outputs will be produced using the SAS system Version 9.4 or higher (UNIX environment) in the global programming & statistical (GPS) environment.

1.1 Study design

This is an open-label, single arm, multicenter, Phase IIIb study of midostaurin (PKC412 or CGP41251) in adults with newly-diagnosed fms-like tyrosine kinase receptor (FLT3)-mutated acute myeloid leukemia (AML) who have started on “7+3” or “5+2” induction chemotherapy.

The purpose of this study is to gather and evaluate additional safety and efficacy data on the combination of midostaurin and standard of care.

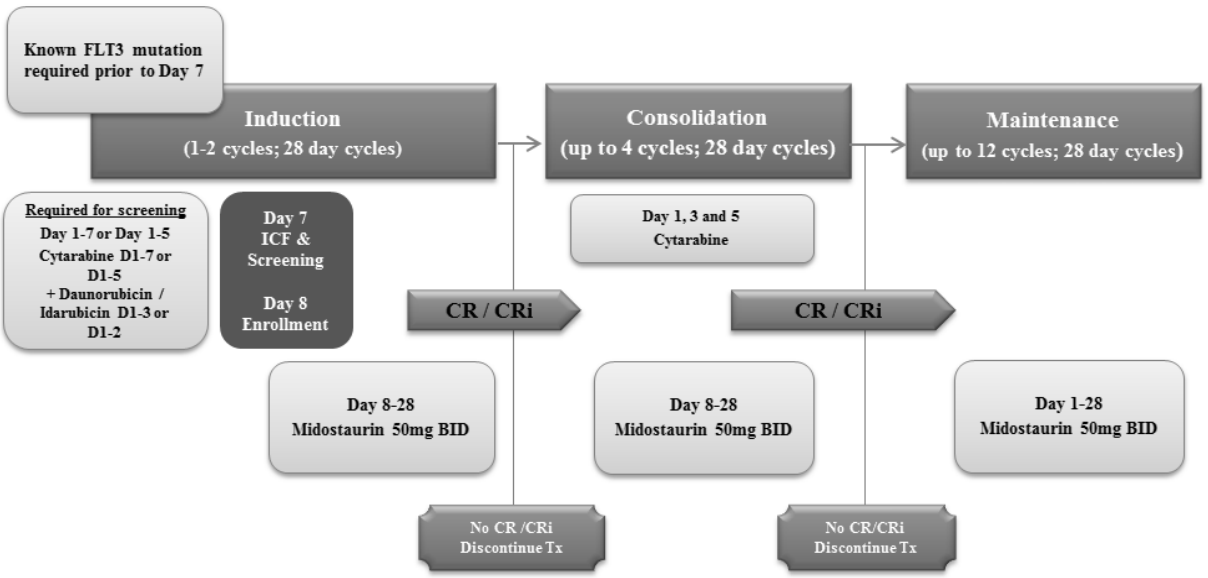
Midostaurin is used in combination with chemotherapy sequentially in **induction** and **consolidation** phase and as a single agent in **maintenance** phase as outlined in Figure 1-1.

Approximately 300 patients are planned to be enrolled.

No formal interim analyses are planned.

The final (primary) analysis will be performed after database lock when all patients have either completed the study as per protocol (including their safety evaluation 30 days after the last dose of study treatment) or they have prematurely discontinued.

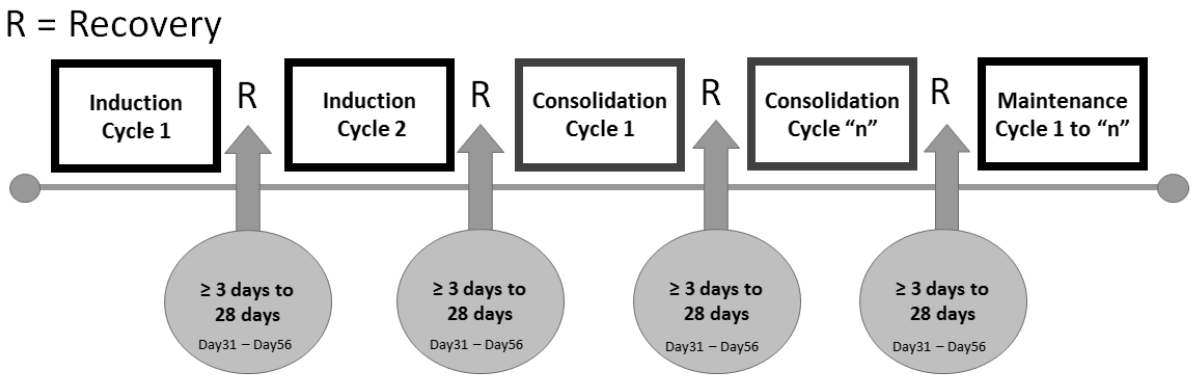
Figure 1-1 Study design



Complete remission (CR): Bone marrow blasts <5%; absence of blasts with Auer rods; absence of extramedullary disease; absolute neutrophil count (ANC) >1.0 x10^9/L; platelet count >100 x 10^9/L; independence of red cell transfusions

CR with incomplete recovery (CRi): All CR criteria except for residual neutropenia (<1.0 x10^9/L) or thrombocytopenia (<100 x 10^9/L)

Figure 1-2 Recovery periods



1.2 Study objectives and endpoints

Objective	Endpoint
Primary	
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	
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	
[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

AE: adverse event

[redacted]

2 Statistical methods

2.1 Data analysis general information

Categorical data will be presented as frequencies and percentages. For continuous data, n, mean, standard deviation, median, 25th and 75th percentiles, minimum, and maximum will be presented.

The data from all centers that participate will be combined in the analyses.

Final (primary) analysis will be performed after database lock has occurred (after last patient last visit (LPLV)).

2.1.1 General definitions

The overall observation period is divided into the following **mutually exclusive** periods:

1. **Pre-treatment**: from day of patient's informed consent to the day before first dose of midostaurin

2. **On-treatment**: from start date of midostaurin to last date of study treatment + 30 days. Further details provided in Section 2.1.3.

   On-treatment 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).

      Up to 2 cycles (28 days of treatment/cycle and a recovery period)

   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).

      Up to 4 cycles (28 days of treatment/cycle and a recovery period)

   c. **Maintenance** period: From day of first dose of midostaurin in the maintenance phase to the date of last dose of midostaurin + 30 days.

      Up to 12 cycles (28 days of treatment/cycle)

   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 withdraws study informed consent or dies before then, then it is till the withdrawal/death date)

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

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

Study drug and study treatment

Study drug refers to the individual drugs used in the study after signing of informed consent, i.e. the Novartis investigational drug midostaurin, or its partners, cytarabine and daunorubicin (or idarubicin).

Study treatment refers to any component of the study drugs, midostaurin, cytarabine and daunorubicin (or idarubicin).

Date of first administration of study drug

The date of first administration of study drug is derived as the first date when a nonzero dose of study drug is administered. The date of first administration of study drug is also referred to as ***start date of study drug***. Start date of study drug is defined for each drug which is part of study treatment, by period (induction, consolidation, maintenance, where applicable) and overall.

Date of last administration of study drug

The date of last administration of study drug is defined as the last date when a nonzero dose of study drug is administered. This date is also referred to as ***last date of study drug.*** Last date of study drug is defined for each drug which is part of study treatment, by period (induction, consolidation, maintenance, where applicable) and overall.

Date of first administration of study treatment

The date of first administration of study treatment (will be midostaurin for all patients) is derived as the first date when a nonzero dose of any component of study treatment is administered. It is derived by period (induction, consolidation, maintenance) and overall.

For example, if the 1st dose of midostaurin is taken on 08-Feb-2016, and 1st dose of a combination partner (e.g. cytarabine), is taken on 01-Feb-2016, then the date of first administration of study treatment is 01-Feb-2016. The date of first administration of study treatment is also referred to as ***start date of study treatment.***

Date of last administration of study treatment

The date of last administration of study treatment is derived as the last date when a nonzero dose of any component of study treatment is administered. It is derived by period (induction, consolidation, maintenance) and overall.

For example if the last dose of midostaurin is taken on 21-Mar-2016, and the last dose of a combination partner is taken on 03-Apr-2016, then the date of last administration of study treatment is on 03-Apr-2016. This date is also referred to as ***last date of study treatment***.

Duration of exposure

Daunorobucin, Idarubicin and Cytarabine

The duration of exposure for the **study drugs** will be calculated by cycle, period (induction, consolidation, maintenance, when applicable) and overall as:

- Duration of study drug exposure (days) in a **cycle** = [(date of last administration of study drug in that cycle) - (date of first administration of study drug in that cycle) + 1]
- Duration of study drug exposure (days) in a **period** = sum of durations of study drug exposure (days) in each cycle of that period
- **Overall** duration of study drug exposure (days) = sum of durations of study drug exposure (days) in each cycle

Study treament and Midostaurin

The duration of exposure for the **study treatment and Midostaurin** will be calculated by cycle, period (induction, consolidation, maintenance) and overall as:

- Duration of study treatment/Midostaurin exposure (days) in a **cycle** = [(date of last administration of study treatment/Midostaurin in that cycle) - (date of first administration of study treatment/Midostaurin in that cycle) + 1]
- Duration of study treatment exposure (days) in a **period** = sum of durations of study trt/Mido exposure (days) in each cycle of that period**.**
- **Overall** duration of study treatment exposure (days) = [(date of last administration of study treatment/Midostaurin) - (date of first administration of study treatment/Midostaurin) + 1]
- If the start or end date of a study drug is missing, the duration will be missing. The durations will include periods of temporary interruption (planned or actual) for any reason.

Dose interruption

For **midostaurin**: An interruption is defined as a zero dose on one or more days between two non-zero dosing records. Any rest period as part of the regimen/schedule is not considered as an interruption e.g. Days 1 to 7 at the start of a cycle in the induction and consolidation phases is not considered as an interruption.

For **daunorubicin (**or **idarubicin)** and **cytarabine**: An interruption is defined as a zero dose administered on one or more scheduled days of administration e.g. a zero dose on Days 1, 3 or 5 for cytarabine in the consolidation phase.

Note: The last zero dose of a study drug (followed by permanent discontinuation) is not considered as a dose interruption. Additionally, two consecutive zero doses will be counted as one interruption if the reasons for these two consecutive dose interruptions are the same.

For the purpose of summarizing interruptions and reasons, in case multiple entries for interruption are entered on consecutive days with different reasons these will be counted as separate interruptions. However, if the reason is the same in these multiple entries on consecutive days, then it will be counted as one interruption.

Dose reduction

A dose reduction is where the prescribed dose is lower than the previous prescribed dose or where the actual dose administered/total daily dose is lower than the prescribed dose. Any dose change to correct a dosing error will not be considered a dose reduction, e.g. if due to a dosing error, a patient receives higher than protocol planned starting dose and moves down to the planned starting dose then this is not counted as a reduction, however if they move directly from a higher than planned starting dose down to a lower than protocol planned starting dose, then this is counted as a reduction.

Note: It is assumed that if there is a dose reduction, then the 'Dose changed' box was ticked on the dose administration electronic case report form (eCRF) page.

If dose is recorded by regimen is missing or entered as 'none', it is assumed that the study drug was taken as per-protocol.

Actual cumulative dose

Cumulative doses will be derived for each of the study drugs: midostaurin, daunorubicin and idarubicin.

The actual cumulative dose refers to the total actual dose administered, over the duration for which the patient is on study drug as documented in the dose administration eCRF.

For patients who did not take any study drug, the actual cumulative dose is by definition equal to zero.

The actual cumulative dose is the sum of the non-zero doses recorded over the study drug dosing periods. Rest periods are not included.

Actual dose intensity (DI)

Dose intensity (DI) will be derived for each of the study drugs: midostaurin, daunorubicin and idarubicin.

DI for patients with non-zero duration of exposure is defined as follows:

DI (*dosing unit / unit of time*) = Actual cumulative dose (*dosing unit*) / Duration of exposure (*unit of time*).

For example, DI (mg/day) = Actual cumulative dose (mg) / Duration of exposure (day)
= 1300 mg / 14 days
= 92.9 mg/day

For patients who did not take any study drug the DI is by definition equal to zero.

Study day

The study day describes the relative day of the event related to the start date of midostaurin.

The reference start date is designated as **Study Day 1.** Study Day –1 is the day that precedes Day 1. Study Day 0 is not defined. Study day is not to be used in numerical computations, for example in calculating exposure.

The study day will be calculated as:

- The date of the event (visit date, onset date of an event, assessment date etc.) - reference start date + 1, if event is on or after the reference start date
- The date of the event (visit date, onset date of an event, assessment date etc.) - reference start date, if event precedes the reference start date

The reference start date for all assessments (adverse events (AEs), laboratory etc.) will be the start date of study treatment.

The study day will be displayed in the data listings. If an event starts before the reference start date, the study day displayed in the listing will be negative.

2.1.2 Baseline

Baseline is the result of an investigation describing the “true” uninfluenced state of the patient, defined as the period from the date of signing any informed consent document to the start date of midostaurin.

The last non-missing assessment, including unscheduled assessments on or before the first dose of midostaurin is defined as “baseline value” or “baseline assessment”. Assessments, specified to be collected post-dose on the first date of midostaurin are not considered for baseline.

Where electrocardiogram (ECG) replicates are provided, the average of the ECG parameters at that assessment will be used in the analyses.

If patients have no value as defined above, the baseline value will be missing.

2.1.3 On-treatment assessment/event

The definition of on-treatment is given below, depending on the context.

For safety summary tables (over the entire duration of the study) an on-treatment AE is defined as any AE reported in the following time interval (including the lower and upper limits):

- <date of first administration of midostaurin; date of last administration of study treatment + 30 days>

This corresponds to the definition of treatment-emergent AEs given in the protocol, i.e. AEs which are newly reported or worsening from baseline.

An on-treatment assessment is defined as any assessment performed after the date of first administration of midostaurin (except for assessments specified to be collected post-dose on that day), i.e. assessments performed in the following time interval (including the lower and upper limits):

- <date of first administration of midostaurin + 1; date of last administration of study treatment + 30 days>

For patients whose last date of study treatment is missing, on-treatment assessments/events include any assessment/event present in the database occurring after the start date of study treatment.

Listings will contain all data, flagging assessments/events outside of the on-treatment period where applicable.

2.1.4 Definition of months and years

A month will be calculated as (365.25 / 12) = 30.4375 days. If duration is to be reported in months, duration in days will be divided by 30.4375. If duration is to be reported in years, duration in days will be divided by 365.25.

2.1.5 Time windows

Time windows for assessments are based on protocol specified windows, see protocol Table 7-1.

If more than one assessment is done within the same time window, the assessment performed closest to the target date will be used. For two assessments within a time window are equidistant from the target date then the earlier of the two assessments will be used. If there are multiple assessments for the same date, then the worst case will be used.

For unplanned visits, will be classified as follows:

Assessment	Target day of assessment	Time Interval
Baseline	Date when visit = IND C1D8 (or Day1)	Last date <= date of IND C1D8
INDC1	Date when visit = INDC1D8	Date of IND C1D8 - 7 <= date < date of IND C2D1
INDC2	Date when visit = INDC2D8	Date of IND C2D1 <= date < date of CON C1D1
CONC1	Date when visit = CONC1D8	Date of CON C1D1 <= date < date of CON C2D1
CONC2	Date when visit = CONC2D8	Date of CON C2D1 <= date < date of CON C3D1
CONC3	Date when visit = CONC3D8	Date of CON C3D1 <= date < date of CON C4D1
CONC4	Date when visit = CONC4D8	Date of CON C4D1 <= date < date of MAIN C1D1
MAINC1	Date when visit = MAIN C1D1	Date of MAIN C1D1 <= date < date of MAIN C2D1

…	…	…
MAINC12	Date when visit = MAIN C12D1	Date of MAIN C12D1 <= date <= date of last non-zero dose +30
End Of Treatment	Date when visitnum =399	Date when visitnum in (399, 399.001,399.002,…)

2.1.6 Definition of end of study

The study will end around 18 to 25 months (mo) after LPFV depending on number of cycles and recovery durations (2mo induction + 2mo recovery + 4mo consolidation + 4mo recovery + 12mo maintenance + 1mo safety follow-up). Study treatment will be provided until disease progression, death, unacceptable toxicities, physician's decision, patient/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. All patients must have safety follow-up for 30 days, after the last dose of study treatment except if study consent was withdrawn.

2.1.7 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 for a discontinued or withdrawn patient.

2.1.8 Chemotherapy group assignment

Patients will be assigned to '7+3' or '5+2' chemotherapy groups considering the following rules of the first induction cycle:

- If cytarabine duration is ≥ 7 days, '7+3' group will be assigned, without considering the duration of daunorubicin/idarubicin.
- If cytarabine duration is < 7 days, '5+2' group will be assigned, without considering the duration of daunorubicin/idarubicin.

2.2 Analysis sets

2.2.1 All enrolled patients

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

2.2.2 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).

2.2.3 Safety set

The safety set comprises all patients who received at least one dose of midostaurin.

Screening failures

Patients who sign an informed consent form but fail to start on midostaurin for any reason.

2.3 Subgroup analysis

Safety and efficacy data will be repored for the following subgroups:

- Age [(i) <= 60 / > 60 years old and/or (ii) <= 60 / >60 to <=70 / > 70 years old]
- Gender (female / male)
- Chemotherapy groups ('7+3' / '5+2')
- Type of induction drugs (Daunorubicin (<60 mg/m^2), daunorubicin (>= 60 mg/m^2) and Idarubicin)

2.4 Patient disposition, demographics and other baseline characteristics

2.4.1 Patient disposition

Disposition data will be listed and summarized descriptively by screening and period (induction, consolidation and maintenance) for the FAS.

Summaries will also include the number of patients who did not receive any dose of study treatment, having received at least one dose of study treatment, treatment completed as per protocol criteria or treatment permanently discontinued with reason, as reported in the dose administration record eCRF pages.

Informed consent and inclusion/exclusion criteria data will be listed. Screening data for screen failure patients will be listed.

2.4.2 Patient demographics and other baseline characteristics

Demographic and other baseline data (e.g. medical history, diagnosis and extent of cancer, eastern cooperative oncology group (ECOG) performance status, FLT3 mutation status etc.) will be summarized descriptively or listed as appropriate for the FAS.

Age will also be categorized as:

- <=60, > 60 years and/or
- <= 60 / >60 to <=70 / > 70 years old.

Demographic data for screen failure patients will also be listed.

2.5 Treatments (study treatment, concomitant therapies, compliance)

2.5.1 Dosing regimen

All patients on study will receive standard chemotherapy plus midostaurin.

The protocol treatment allows 1-2 cycles of standard induction therapy with cytarabine and daunorubicin (or idarubicin) and up to 4 cycles of cytarabine consolidation, with midostaurin

given sequentially during each cycle, and up to 12 cycles of maintenance therapy with single-agent midostaurin as given in Figure 1-1.

Table 2-1 Dose and treatment schedule – Induction

Treatment	Dose, route and frequency (based on 28-day cycles)
Cytarabine (Ara-C) with anthracycline (Idarubicin or Daunorubicin) (7+3)	Ara-C:100-200 mg/m^2/day by CIVI days 1-7 (168 hour 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

Table 2-2 Dose and treatment schedule – Consolidation

Treatment	Dose, route and frequency (based on 28-day cycles)
Cytarabine	1-3 g/m^2 every 12 h on days 1, 3, 5 x 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

Table 2-3 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

2.5.2 Study treatment and tolerability

Study treatment

Duration of exposure (days), actual cumulative dose and actual dose intensity will be summarized by period and overall for each of the study drugs: midostaurin, daunorubicin and idarubicin for the safety set. Duration of exposure (days), actual cumulative dose and actual dose intensity will be summarized also by cycle. The number of patients with midostaurin dose changes, interruptions and permanent discontinuations will be presented by age category and overall, along with reasons for the dose change/interruption/permanent discontinuation.

Duration of midostaurin treatment exposure (days) will also be categorized and summarized by period and overall for the safety set using the following intervals:

- $\leq$ 20; >20; >40; >60; >120; >180; >240; >300; >360

Duration of study treatment exposure (days) will be summarized by period and overall for the safety set using the following intervals:

- $\leq$ 28; >28; >56; >84; >112; >196; >280; >364; >448; >532

Duration include the rest/recovery days between cycles and will be derived as the following:

Last intake of any study treatment component – first intake of any study treatment component +1

If there are more than 10 patients in each regimen exposure will be further summarized by regimen (“7+3” and “5+2”).

Data will be listed for all patients in the safety set.

Tolerability

Tolerability of midostaurin will be evaluated in terms of dose reductions or dose interruptions due to an AE.

2.5.3 Prior, concomitant and post therapies

Medications and significant non-drug therapies prior to and after the start of the study treatment will be coded according to the world health organization (WHO) Drug Reference List and summarized by anatomical therapeutic chemical (ATC) classification and preferred term.

A summary table and listing for prior antineoplastic therapies will be provided for the full analysis set.

Summary tables for concomitant medications and concomitant non-drug therapies by treatment period and overall for the full analysis set will be provided. Prior, concomitant and post study treatment medications and non-drug therapies will be listed for the safety set. Records outside of on-treatment period will be flagged.

2.5.4 Protocol deviations

Protocol deviations will be listed for all screened patients. In addition, the number (%) of protocol deviations with COVID-19 relationship will be presented by type of deviation for all enrolled subjects.

2.6 Analysis of the primary objective

2.6.1 Primary endpoint

The analysis of the primary endpoint is described in Section 2.8.

2.6.2 Statistical hypothesis, model, and method of analysis

Not applicable.

2.6.3 Handling of missing values/censoring/discontinuations

See Section 2.8.

2.6.4 Supportive analyses

Not applicable.

2.7 Analysis of the secondary objectives

2.7.1 Secondary endpoints

The secondary objectives in this study are 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.

Clinical efficacy rate will be presented for the FAS. All assessments before the last available on-treatment assessment will be included. Listings will include all data and will be based on the FAS. Records outside of on-treatment period will be flagged. For patients who discontinued prior to the first efficacy assessment, the response will be reported as 'unknown'.

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 review. The CR and CRi are defined by the national comprehensive cancer network (NCCN) guidelines version 1.2017 for AML.

Clinical efficacy rate and its 95% confidence interval will be presented by period (induction, consolidation and maintenance) and overall as described in Section 2.1.1. The best overall response will be analyzed in each period and overall. If there are more than 10 patients in each regimen and age category, the clinical efficacy rate will be further summarized by regimen ("7+3" and "5+2") and age category (e.g. <=60, >60 years and/or <= 60 / >60 to <=70 / > 70 years old) and by sex.

2.7.2 Statistical hypothesis, model, and method of analysis

Not applicable.

2.7.3 Handling of missing values/censoring/discontinuations

Not applicable.

2.8 Analysis of secondary efficacy objective(s)

Not applicable.

2.9 Safety analyses

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.

Except for baseline values, safety summary tables will only include on-treatment assessments (up to 30 days after study treatment discontinuation) and will be based on the safety set. Listings will include all data and will be based on the safety set.

2.9.1 Adverse events (AEs)

The AEs will be re-coded using the latest version of the medical dictionary for regulatory activities (MedDRA) at the time of the analysis.

AEs will be graded using the common toxicity criteria for adverse events (CTCAE) Version 4.03. AEs will be summarized by period and overall for the safety set. AEs tables will be provided by age category. AEs with different starts dates in different periods will be counted within each period. If a patient reported more than one AE with the same preferred term (PT), the AE with the greatest severity will be presented. If a patient reported more than one AE within the same primary system organ class (SOC), the patient will be counted only once with the greatest severity at the SOC level, where applicable. An AE with missing CTCAE grade will be included in the 'All grades' column of the summary tables.

In AE summaries, the primary SOC will be presented alphabetically and the PTs will be sorted within the primary SOC in descending frequency.

Summary tables will be provided for:

- Overview of AEs and age category
  - In-text table
- All AEs regardless of relationship to study treatment by primary system organ class (SOC), preferred term (PT) and maximum severity and age category
  - In-text table by SOC and maximum severity
  - In-text table by PT and maximum severity
- AEs suspected to be related to study treatment by SOC, PT and maximum severity and age category
  - In-text table by PT and maximum severity
- AEs leading to treatment discontinuation regardless of relationship to study treatment by SOC, PT and maximum severity and age category
  - In-text table by PT and maximum severity
- AEs leading to treatment reduction or interruption regardless of relationship to study treatment by SOC, PT and maximum severity and age category
  - In-text table by PT and maximum severity
- Serious AEs (SAEs) regardless of relationship to study treatment by SOC, PT and maximum severity and age category
  - In-text table by PT and maximum severity
- On-treatment deaths by SOC and PT and age category
  - In-text table by SOC and PT
- All deaths by SOC, PT and age category
- *Non-SAEs regardless of relationship to study treatment (threshold=5%) by SOC and PT
- *On treatment deaths and SAEs by SOC and PT

*(For the legal requirements of ClinicalTrials.gov and EudraCT, two required tables on <on-treatment/treatment emergent> AEs which are not SAEs with an incidence greater than 5% and on <on-treatment/treatment emergent> SAEs and SAE suspected to be related to study treatment will be provided by SOC and PT on the safety set.

If for a same patient, several consecutive AEs (irrespective of study treatment causality, seriousness and severity) occurred with the same SOC and PT:

- a single occurrence will be counted if there is ≤ 1 day gap between the end date of the preceding AE and the start date of the consecutive AE
- more than one occurrence will be counted if there is > 1 day gap between the end date of the preceding AE and the start date of the consecutive AE

For occurrence, the presence of at least one SAE/SAE suspected to be related to study treatment/non SAE has to be checked in a block e.g., among AEs in a ≤ 1 day gap block, if at least one SAE is occurring, then one occurrence is calculated for that SAE.

The number of deaths resulting from SAEs suspected to be related to study treatment and SAEs irrespective of study treatment relationship will be provided by SOC and PT.

Listings will be provided for all AEs, SAEs and AEs leading to discontinuations (including those from the pre and post-treatment periods). Records outside of on-treatment period will be flagged.

2.9.1.1 Adverse events of special interest / grouping of AEs

The adverse events of special interest (AESI) are maintained and updated on a regular basis in the project case retrieval sheet (CRS) and the latest version at the time of the analyses will be used. The CRS to produce AESI outputs will be stated in listing 14.3.2-8.

A summary table for AESIs will be provided by period and overall for the safety set.

2.9.2 Deaths

See Section 2.8.1. A listing will be provided of all deaths. Deaths outside of the on-treatment period will be flagged.

2.9.3 Laboratory data

Laboratory values are converted to the international system of units (SI). CTCAE Grade 0 will be assigned for all non-missing values not graded as 1 or higher. Grade 5 will not be used. For laboratory results where grades are not defined by CTCAE v4.03, results will be categorized as low/normal/high based on laboratory normal ranges.

The following summaries will be generated separately for key hematology and biochemistry by period and overall for the safety set:

- Shift tables by grade (or low/normal/high if grades not available) to compare baseline to the worst on-treatment value:
  - Hematology: Neutrophils (absolute) and platelets
  - Chemistry: Creatinine, total bilirubin, aspartate aminotransferase (AST), alanine aminotransferase (ALT) and alkaline phosphatase

Listing of all laboratory data (including urinalysis, coagulation, thyroid panel, pregnancy test etc.) will be provided with the corresponding CTCAE grades, if applicable, and the classifications relative to the laboratory normal ranges. Records outside of on-treatment period will be flagged.

2.9.4 Other safety data

2.9.4.1 Electrocardiogram (ECG)

Electrocardiogram (ECG) data will be listed. Listing will include date of assessment, position=supine, any new clinically significant abnormalities (yes/no), QTcF (Fridericia's correction), mean heart rate and mean PR, QT and QRS durations. Notable values and records outside of on-treatment period will be flagged.

Where ECG replicates are provided for an assessment, the average of the ECG parameters at that assessment will be used in the analyses.

Table 2-4 Notable criteria for ECG parameters[1]

Parameter	Notable low value	Notable high value
QTcF		New value of >450 and ≤ 480 ms New value of >480 and ≤ 500 ms New value of >500 ms Increase from baseline of >30 ms to ≤ 60 ms Increase from baseline of >60 ms
Heart rate	Decrease >25% from baseline and to a value <50 bpm	Increase >25% from baseline and to a value >100 bpm
PR	--	Increase >25% from baseline and to a value >200 ms New value of >200 ms
QRS	--	Increase >25% from baseline and to a value >120 ms New value of >120 ms

2.9.4.2 Cardiac imaging

The left ventricular ejection fraction (LVEF) data will be summarized for change from baseline to the worst on-treatment value by period and overall for the safety set. A listing will be provided showing the imaging method (multi gated acquisition scan (MUGA) or echocardiogram), date of assessment, LVEF percentage, the overall interpretation (normal, clinically insignificant abnormality or clinically significant abnormality) and the corresponding ejection fraction CTCAE v4.03 grades. Records outside of on-treatment period will be flagged.

Grades:

- Grade 0: Non missing value below Grade 2
- Grade 1: NA
- Grade 2: 50-40% or 10-19% drop from baseline i.e.
  - 40% ≤ LVEF ≤ 50% or -20% < absolute change from baseline ≤ -10%
- Grade 3: 39-20% or ≥20% drop from baseline i.e.
  - 20% ≤ LVEF <40% or absolute change from baseline ≤-20%
- Grade 4: <20% i.e.
  - LVEF < 20%

2.9.4.3 Chest X-ray

Chest x-ray data will be listed showing date of assessment and the overall interpretation (normal, clinically insignificant abnormality or clinically significant abnormality). Records outside of on-treatment period will be flagged.

2.9.4.4 Vital signs

Vital signs (height, weight, body surface area, temperature, position, pulse and systolic/diastolic blood pressure) will be summarized by period and overall for the safety set. Listings will be provided with notable values and records outside of on-treatment period flagged.

Table 2-5 Notable criteria for vital signs[1]

Vital sign (unit)	Notable low value	Notable high value
Weight (kg)	decrease ≥ 10% from baseline	increase ≥ 10% from baseline
Body temperature (°C)	--	≥ 39.1
Pulse rate (bpm)	≤ 50 and decrease from baseline of >25%	≥ 100 and increase from baseline of >25%
Systolic blood pressure (mmHg)	≤ 90 and decrease from baseline of ≥ 20	≥ 180 and increase from baseline of ≥ 20
Diastolic blood pressure (mmHg)	≤ 50 and decrease from baseline of ≥ 15	≥ 105 and increase from baseline of ≥ 15

2.9.4.5 ECOG performance status

ECOG performance status data will be listed. Records outside of on-treatment period will be flagged. Baseline summary will be provided as part of the demographics table.

Table 2-6 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

2.10 Pharmacokinetic endpoints

Not applicable.

2.11 PD and PK/PD analyses

Not applicable.

[redacted]

2.13 Biomarkers

Not applicable.

2.14 Other Exploratory analyses

[redacted] resource utilization will be used to evaluate the impact on symptom burden, overall quality of life and change in status of a patient's overall satisfaction with.

The safety set will be used for analyzing [redacted] resource utilization data unless otherwise specified.

[redacted]

[redacted]

2.14.3 Resource utilization

Descriptive statistics will be used to summarize resource utilization, e.g. the reason for hospitalization due to AE or not, if number of hospital days by facility/ward type and discharge status used during hospital stay(s). Listings will flag records outside of the on-treatment period.

2.15 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.

3 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 3-1 provides probabilities to detect at least one patient with an AE for different sample sizes and different true AE incidences.

Table 3-1 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

4 Change to protocol specified analyses

None.

5 References

1. Oncology guideline for safety analysis, v1.0, dated 09-Jun-2016
2. Oncology standard outputs TFL v3.1, dated 03-Aug-2017
3. 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
4. Cheson et al. (2003) 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. Journal of Clinical Oncology 21:24, 4642-4649

6 Appendix

6.1 Imputation rules

6.1.1 AE, CM date imputation

Table 6-1 Imputation of start dates (AE, CM)

Missing Element	Rule
day, month, and year	• No imputation will be done for completely missing dates
day, month	• If available year = year of study treatment start date then o If stop date contains a full date and stop date is earlier than study treatment start date then set start date = 01JanYYYY o Else set start date = study treatment start date. • If available year > year of study treatment start date then 01JanYYYY • If available year < year of study treatment start date then 01JulYYYY
day	• If available month and year = month and year of study treatment start date then o If stop date contains a full date and stop date is earlier than study treatment start date then set start date= 01MONYYYY. o Else set start date = study treatment start date. • If available month and year > month and year of study treatment start date then 01MONYYYY • If available month and year < month year of study treatment start date then 15MONYYYY

Table 6-2 Imputation of end dates (AE, CM)

Missing Element	Rule (*=last treatment date plus 30 days not > (death date, cut-off date, withdrawal of consent date))
day, month, and year	• Completely missing end dates (incl. ongoing events) will be imputed by the end date of the on-treatment period*
day, month	• If partial end date contains year only, set end date = earliest of 31DecYYYY or end date of the on-treatment period *
day	• If partial end date contains month and year, set end date = earliest of last day of the month or end date of the on-treatment period*

In the case of the imputed end date is before than start date, then the end date will be imputed equals to start date.

Any AEs and ConMeds with partial/missing dates will be displayed as such in the data listings.

Any AEs and ConMeds which are continuing as per data cut-off will be shown as ‘ongoing’ rather than an imputed end date provided.

6.1.2 Prior therapies date imputation

Missing day is defaulted to the 15th of the month and missing month and day is defaulted to 01-Jan for start and end dates in ZT domain.

6.2 Laboratory parameters derivations

CTC grading for blood differentials is based on absolute values. However, this data may not be reported as absolute counts but rather as percentage of WBC.

If laboratory values are provided as '<X' (i.e. below limit of detection) or '>X', prior to conversion of laboratory values to SI unit, these numeric values are set to X.

The following rules will be applied to derive the WBC differential counts when only percentages are available for a xxx differential

xxx count = (WBC count) * (xxx %value / 100)

Further derivation of laboratory parameters might be required for CTCAE grading. For instance, corrected calcium can be derived using the reported total calcium value and albumin at the same assessment using the following formula:

Corrected Calcium (mg/dL) = Calcium (mg/dL) – 0.8 [Albumin (g/dL)-4]

In order to apply the above formula, albumin values in g/L will be converted to g/dL by multiplying by 0.1, calcium values in mmol/L will be converted to mg/dL by dividing by 0.2495. For calculation of laboratory CTC grades 0 and 1, the normal range for derived corrected calcium is set to the same limits (in mg/dL) as for calcium.

For missing Blood Urea Nitrogen (BUN) or urea values the following formulae will be applied:

Urea (mg/dL) = BUN (mg/dL) / 0.357

BUN (mg/dL) = Urea (mg/dL) / 2.1428