Clinical Development

PKC412, MIDOSTAURIN

Protocol CPKC412AUS23 / NCT01883362

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

Statistical Analysis Plan (SAP)

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List of abbreviations

AE	Adverse event
ATC	Anatomical Therapeutic Classification
bid	bis in diem/twice a day
CSR	Clinical Study report
CTC	Common Toxicity Criteria
CTCAE	Common Terminology Criteria for Adverse Events
FAS	Full Analysis Set
HSTC	Hematopoietic Stem Cell Transplantation
eCRF	Electronic Case Report Form
IVRS	Interactive Voice Response Technology
IWRS	Interactive Web Response Technology
MedDRA	Medical Dictionary for Regulatory Activities
[redacted]	[redacted]
NCI	National Cancer Institute
o.d.	Once Daily
OS	Overall Survival
PK	Pharmacokinetics
PPS	Per-Protocol Set
qd	Qua'que di'e / once a day
QoL	Quality of Life
RECIST	Response Evaluation Criteria in Solid Tumors
RFS	Relapse-Free Survival
SAP	Statistical Analysis Plan
SOC	System Organ Class
TEAE	Treatment Emergent Adverse Event
TLFs	Tables, Listings, Figures
WHO	World Health Organization

1 Introduction

The purpose of this statistical analysis plan (SAP) is to describe the statistical methods for all safety and efficacy analyses planned to be included for the clinical study report (CSR) of study CPKC412AUS23 (A Phase II, randomized trial of standard of care, with or without midostaurin to prevent relapse following allogeneic hematopoietic stem cell transplantation (HSCT) in patients with FLT3-ITD mutated acute myeloid leukemia).

The content of this SAP is based on protocol CPKC412AUS23 Amendment Version 02. All decisions regarding final analysis, as defined in the SAP document, have been made prior to database lock of the study data.

The planned analysis identified in this SAP may be included in clinical study reports (CSRs), regulatory submissions, conference submissions or future manuscripts. Post-hoc [redacted] not identified in this SAP may be performed to further examine study data. Any post-hoc, unplanned, [redacted] performed will be clearly identified as such.

In addition to the study protocol, the following documents were reviewed in preparation of this SAP:

- Electronic case report form (eCRF) for Protocol CPKC412AUS23
- ICH Guidance on Statistical Principles for Clinical Trials (E9)

1.1 Study design

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

Subjects will be treated with the Standard of Care (SOC) treatment with or without (+/-) midostaurin in a 1:1 randomization. All subjects who have engrafted and recovered counts by day 42 after HSCT will be eligible for randomization no later than 60 days after transplant (may occur as early as day 28 post transplant), regardless of treatment assignment.

Midostaurin will be given at a dose of 50mg twice daily continuously in cycles of 4 weeks (28 days) each for up to 12 cycles or disease relapse or withdrawal due to any cause, whichever occurs earlier.

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

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

No formal interim efficacy analysis is planned in this study. Safety will be evaluated by an independent review committee after 10, 20, and 30 subjects, regardless of treatment arm, have completed at least 3 cycles or discontinued. An independent review committee of 3 to 5 study

investigators will review safety information to include (but not limited to) adverse events, serious AEs, lab parameters, bone marrow results [redacted].

1.1.1 Subject Population

Male and Female subjects, aged 18 to ≤ 70 years old, with acute myeloid leukemia (AML) must have documented FLT3-ITD mutation and have undergone allogeneic HSCT in first complete remission (CR1) to be eligible to enter the study. Sixty (60) subjects will be enrolled during the study

1.1.2 Randomization

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

The two arms will be: (1) Standard of Care and (2) Standard of Care plus midostaurin. The randomization numbers will be generated using the following procedure to ensure that treatment assignment is unbiased. A subject randomization list will be produced by the Interactive Web Response Technology (IWRS) provider using a validated system that automates the random assignment of subject numbers to randomization numbers. These randomization numbers are linked to the different treatment arms.

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

1.2 Interim and Final Analysis

No formal interim analysis will be performed for this study. However, there will be 2 snapshots of the data taken per year for the purpose of publication and IRC data review.

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

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

1.3 Study objectives and endpoints

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

2 Statistical methods

2.1 Data analysis general information

The final analysis will be performed [redacted]. No interim analysis will be performed for this study. SAS version 9.3 or later software will be used to perform all data analyses and to generated tables, figures, and listings.

Data included in the analysis

The analysis cut-off date for the primary analysis of study data will be established after all subjects have been followed up to 18 months post-HSCT or have discontinued study. All statistical analyses will be performed using all data collected in the database up to the data cutoff date. All data with an assessment date or event start date (e.g. vital sign assessment date or start date of an adverse event) prior to or on the cut-off date will be included in the analysis. Any data collected beyond the cut-off date will not be included in the analysis and will not be used for any derivations.

All events with start date before or on the cut-off date and end date after the cut-off date will be reported as 'ongoing. The same rule will be applied to events starting before or on the cut-off date and not having documented end date. This approach applies, in particular, to adverse event and concomitant medication reports. For these events, the end date will not be imputed and therefore will not appear in the listings.

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

All listings will be presented by actual treatment received.

General analysis conventions

Qualitative data (e.g., gender, race, etc.) will be summarized by means of contingency tables by treatment group; a missing category will be included as applicable. Percentages will be calculated using the number of subjects in the relevant population as the denominator.
Quantitative data (e.g., age, body weight, etc.) will be summarized by appropriate descriptive statistics (i.e. mean, standard deviation, median, minimum, and maximum) by treatment group.

2.1.1 General definitions

Investigational drug and study treatment

The term investigational treatment will refer to midostaurin. The term study treatment will refer to either standard of care (SOC) or SOC+Midostaurin.

Date of first administration of investigational drug

The date of first administration of investigational drug is defined as the first date when a non-zero dose of investigational drug is administered and recorded on the Dosage Administration Record (DAR) (e) CRF. The date of first administration of study drug will also be referred as start of investigational drug.

Date of last administration of investigational drug/study treatment

The date of last administration of investigational drug is defined as is the last date when a nonzero dose of investigational drug is administered and recorded on DAR eCRF. The date of last administration of investigational drug will also be referred as end of investigational drug.

Date of first administration of study treatment

The date of first administration of study treatment is derived as the first date when a nonzero dose of study treatment was administered as per the Dosage Administration CRF if the subject received midostaurin or date of randomization if the subject received Standard of Care. The date of first administration of study treatment will also be referred as ***start of study treatment***.

Date of last administration of study treatment

The date of last administration of study treatment is defined as the last date when a nonzero dose of study treatment was administered as per Dose Administration (e) CRF if the subject received midostaurin or date of end of treatment visit, end of cycle 12, date of first relapse or date of discontinuation whichever occurs first if the subject received Standard of Care.

Date of study completion

The date of study completion is defined as the date the study completion evaluation visit is complete.

Study day

The study day, describes the day of the event or assessment date, relative to the date of randomization

The study day is defined 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 randomization start date;
- The date of the event (visit date, onset date of an event, assessment date etc.) − reference start date if event precedes the randomization start date.

The reference start date for safety assessments (e.g. adverse event onset, laboratory abnormality occurrence, vital sign measurement, dose interruption, pk etc.) is the start of study treatment.

The reference start date for all other, non-safety assessments (i.e., survival time, disease relapse) is the date of randomization.

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

Time unit

A year length is defined as 365.25 days. A month length is 30.4375 days (365.25/12). If duration is reported in months, duration in days will be divided by 30.4375. If duration is reported in years, duration in days will be divided by 365.25.

Baseline

For efficacy evaluations, the last non-missing assessment, including unscheduled assessments on or before the date of randomization is taken as "baseline" value or "baseline" assessment. In the context of baseline definition, the efficacy evaluations also include PRO and performance status.

For safety evaluations, the last available assessment on or before the date of start of study treatment is taken or ''baseline" assessment.

In case time of assessment and time of treatment start is captured (e.g. pre-dose ECG), the last available assessment before the treatment start date/time is used for baseline.

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

On-treatment assessment/event and observation periods

For adverse event reporting the overall observation period will be divided into three mutually exclusive segments:

1. ***pre-treatment period***: from day of subject's informed consent to the day before first administration of study treatment
2. ***on-treatment period***:
    a. SOC arm (whichever comes first): From randomization until discontinuation, relapse or completion of treatment phase (12 cycles) + 30 days
    b. SOC + Midostaurin arm: From date of first study drug to date of last of study drug + 30 days
3. ***follow-up period***: starting at day 30+1 after last administration of study treatment.

If dates are incomplete in a way that clear assignment to pre-, on-, follow-up period cannot be made, then the respective data will be assigned to the on-treatment period.

Safety summaries (tables, figures) include only data from the on-treatment period with the exception of baseline data which will also be summarized where appropriate (e.g. change from baseline summaries). In addition, a separate summary for death including on treatment and post treatment deaths will be provided. In particular, summary tables for adverse events (AEs) will summarize only on-treatment events, with a start date during the on-treatment period (***treatment-emergent*** AEs).

However, all safety data (including those from the follow-up period) will be listed and those collected during the pre-treatment and follow-up period will be flagged.

Windows for multiple assessments

In order to summarize data collected over time (including unscheduled visits), the assessments will be time slotted. The following general rule will be applied in creating the assessment windows: If more than one assessment is done within the same time window, the assessment performed closest to the target date will be used. If 2 assessments within a time window are equidistant from the target date, then the earlier of the 2 assessments will be used. If multiple assessments on the same date then the average will be used. Data from all assessments (scheduled and unscheduled), including multiple assessments, will be listed.

Table 1 Time windows for assessments

Assessment	Target day of assessment	Time Window
Screening	-7	Day -14 to -1
Cycle 1 Day 1	1	Day 1 to 2
Cycle 1 Day 3	3	Day 3 to 7
Cycle 1 Day 15	15	Day 8 to day 21
Cycle 2 Day 1	29	Day 22 to day 42
Cycle 3 Day 1	57	Day 43 to day 70
Cycle 4 Day 1	85	Day 71 to day 98
Cycle 5 Day 1	113	Day 99 to day 126
Cycle k Day 1 (k≥5)	d=(k-1)*28+1	Day d-14 to day d+13
End of Treatment		Assessment taken at the end of treatment visit

Last contact date

The last contact date will be derived for subjects not known to have died at the analysis cut-off using the last complete date among the following:

Table 2 Last contact date data sources

Source data	Conditions
Date of Randomization	No Condition
Last contact date/last date subject was known to be alive from Survival Follow-up page or Study Completion Evaluation	- Subject status is reported to be alive, lost to follow-up or unknown.
Start/End* dates from drug administration record	Non-missing dose. Doses of 0 are allowed.
End of treatment date from end of treatment page	No condition.
Laboratory/PK collection dates	Sample collection marked as ‘done’.
Vital signs date	At least one non-missing parameter value
Performance Status date	Non-missing performance status

Source data	Conditions
GVHD Assessment date	Non-missing grade or type
Start/End dates of AE	Non-missing verbatim term

The last contact date is defined as the latest complete date from the above list on or before the data cut-off date. The cut-off date will not be used for last contact date, unless the subject was seen or contacted on that date. No date post cut-off date will be used. Completely imputed dates (e.g. the analysis cut-off date programmatically imputed to replace the missing end date of a dose administration record) will not be used to derive the last contact date. Partial date imputation is allowed for event (death)/censoring if coming from 'Survival information' eCRF.

The last contact date will be used for censoring of subjects in the analysis of overall survival.

2.2 Analysis sets

Full Analysis Set

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

Safety Set

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

Per-Protocol Set

The Per Protocol Set (PPS) consists of all subjects from the Full Analysis Set without any major protocol deviations.
Protocol deviations leading to the exclusion from the PPS will be specified in the Statistical Analysis Plan (SAP) prior to database lock.

Pharmacokinetic Analysis Set

The Pharmacokinetic Set (PK Set) comprises all subjects that have been administered at least one dose of midostaurin and that have provided at least one evaluable PK sample. A profile is considered evaluable if all of the following conditions are satisfied:

- Subject receives one of the planned treatments
- Subject provides at least one primary PK parameter

Withdrawal of Informed Consent

Any data collected in the clinical database after a subject withdraws informed consent from all further participation in the trial, will not be included in the analysis. The date on which a subject withdraws full consent is recorded in the eCRF.

2.3 Subject disposition, demographics and other baseline characteristics

The Full Analysis Set (FAS) will be used for all baseline and demographic summaries and listings unless otherwise specified. Summaries will be reported by treatment group and for all subjects and listings will be reported by treatment group to assess baseline comparability. No inferential statistics will be provided.

2.3.1 Basic demographic and background data

All demographic and baseline disease characteristics data will be summarized and listed by treatment group on the FAS. Categorical data (e.g. gender, race) will be summarized by frequency counts and percentages; the number and percentage of subjects with missing data will be provided. Continuous data (e.g. age, weight, height, body mass index) will be summarized by descriptive statistics (N, mean, median, standard deviation, minimum and maximum).

BMI (kg/m2) will be calculated as weight[kg] / (height[m]2) using weight at Baseline. Body Surface Area (BSA) will be calculated using Gehan and George formula: BSA[m2]=234.94*(height[cm]**0.422)*(weight[kg]**0.515)/10000 unless otherwise specified.

Additionally, the number of day since transplant to randomization, donor type and product type will be summarized by treatment group on the FAS.

These summaries will be repeated on the safety set.

2.3.2 History of AML Disease

Summary statistics will be tabulated for history of AML Disease at initial diagnosis and post-diagnosis. This analysis will include the following: AML Status. AML (2016 revision of the WHO) subclassification, months since initial diagnosis to randomization, WBC counts (x 10^9/L), bone marrow results (%),

Cytogenetics details (i.e. sample type, number of metaphases examined, abnormalities, method and % abnormal) will be summarized for initial post-diagnosis separately.

2.3.3 Pre-HSCT Treatment for AML

All pre-HSCT treatment for AML details will be listed. The purpose of therapy, number of cycles, type of therapy and duration (days), if applicable, will be summarized. The best response to the line of therapy across all therapies will be summarized using frequency counts.

2.3.4 Pre-HSCT Preparative Regimen, Disease Status

All Pre-HSCT preparative regimen details will be listed. Details regarding the disease status assessment prior to preparative regimen will also be listed.

2.3.5 FLT3-ITD Positive Mutational Analysis at Diagnosis

Subjects were permitted to enroll based on the locally known FLT3-ITD mutation status which was determined at diagnosis. Specimen type, length of ITD nucleotides, ITD Alleic ratio, whether the subject has TKD mutation and whether an archived sample retrieved for central lab confirmation of FLT3-ITD mutations was obtained will be summarized for the FAS.

All data will be listed.

2.3.6 Medical history

Medical history and ongoing conditions, including cancer-related conditions and symptoms entered on (e) CRF will be listed and summarized by treatment group and grade. Separate summaries will be presented for active and non-active medical conditions.

The summaries will be presented by primary system organ class (SOC), preferred term (PT) and treatment group. Medical history and current medical conditions will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) terminology. The MedDRA version used for reporting will be specified in the CSR and as a footnote in the applicable tables/listings.

2.3.7 Subject disposition

The following summaries will be provided (with % based on the total number of FAS subjects) and presented overall and by treatment group:

- Number (%) of subjects who were randomized
- Number (%) of subjects who were randomized but not treated
- Number (%) of subjects who completed and discontinued the study treatment period (based on the ‘End of Treatment’ page)
- Primary reason for study treatment period discontinuation (based on the ‘End of Treatment’ page)
- Number (%) of subjects who have entered the post-treatment follow-up (based on the ‘End of Treatment’ page);
- Number (%) of subjects who have completed and discontinued from the post-treatment follow-up (based on the Study Evaluation Completion page);
- Reasons for discontinuation from the post-treatment follow-up (based on Study Evaluation Completion page);

2.3.8 Protocol deviations

The number (%) of subjects in the FAS with any protocol deviation will be tabulated by deviation category, overall and by treatment group for the FAS. Major protocol deviations leading to exclusion from the Per Protocol Set will be tabulated separately overall and by treatment group. All protocol deviations identified from both edit check and monitoring will be listed.

2.3.9 Analysis sets

The number (%) of subjects in each analysis set (defined in Section 2.2) will be summarized by treatment group. Percentages will be based on the FAS

2.4 Treatments (study treatment, concomitant therapies, compliance)

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

2.4.1 Study treatment / compliance

Duration of investigational drug exposure, actual cumulative dose, dose intensity (DI) and relative dose intensity (RDI) will be summarized by treatment group.

Subject level listings of all doses administered on treatment along with dose change reasons will be produced.

The safety set will be used for all summaries and listings of study treatment.

Duration of exposure to investigational drug

Duration of exposure to investigational drug (months) = (last date of exposure to investigational drug) – (date of first administration of investigational drug) + 1 divided by 30.4375.

Duration of exposure will be summarized as continuous summaries (i.e. mean, standard deviation etc.) and categorized into time intervals (< 3 months, 3 to < 6 months, 6 to < 9 months, 9 months to 12 months greater than 12 months); frequency counts and percentages will be presented for the number (%) of subjects in each interval.

Cumulative dose

Cumulative dose of investigational drug is defined as the total dose given during the investigational drug exposure and will be summarized.

The **planned cumulative dose** for investigational drug refers to the total planned dose as per the protocol up to the last date of investigational drug administration. The planned dose is as follows: 50mg b.i.d for 28 consecutive days of each cycle for 12 cycles.

The planned cumulative dose will not summarized/listed. It will be used for relative dose intensity calculations.

The **actual cumulative dose** refers to the total actual dose administered, over the duration for which the subject is on the investigational drug as documented in the Dose Administration eCRF.

For patients randomized to receive investigational drug and did not take any investigational drug the cumulative dose is by definition equal to zero.

For continuous dosing, the actual cumulative dose is the sum of the non-zero doses recorded over the dosing period and the planned cumulative dose is the planned starting dose summed over the same dosing period.

For intermittent dosing, the actual cumulative dose should be defined based on the days when the subject is assumed to have taken a non-zero dose during dosing periods.

Dose intensity and relative dose intensity

Dose intensity (DI) for patients with non-zero duration of exposure is defined as follows:

DI (mg /days) = Actual Cumulative dose (mg) / Duration of exposure to study treatment (days).

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

Planned dose intensity (PDI) is defined as follows:

PDI (mg /days) = Planned Cumulative dose (mg) / Duration of exposure (days).

Relative dose intensity (RDI) is defined as follows:

RDI = DI (mg /days) / PDI (mg /days)

DI and RDI will be summarized safety subjects who received investigational drug.

Dose reductions, interruptions or permanent discontinuations

The number of subjects who have dose reductions, permanent discontinuations or interruptions along with the reasons will be summarized. Similarly, subjects who are re-challenged will also be summarized

'Dose interrupted', and 'Dose permanently discontinued' fields from the Dosage Administration CRF pages (DAR) will be used to determine the dose reductions, dose interruptions, and permanent discontinuations, respectively.

The corresponding fields 'Reason for dose change/dose interrupted' and 'Reason for permanent discontinuation' will be used to summarize the reasons.

A dose change is either 'change in prescribed dose level' or 'dosing error' where actual dose administered/total daily dose is different from the prescribed dose.

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

Reduction: A dose change where the prescribed dose level is lower than the previous prescribed dose level or where the actual dose administered/total daily dose is lower than the calculated dose amount based on the prescribed dose. Therefore any dose change to correct a dosing error will not be considered a dose reduction. Only dose change is collected in the CRF, number of reductions will be derived programmatically based on the change and the direction of the change.

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

2.4.2 Prior, concomitant and post therapies

2.4.2.1 Prior Antineoplastic Therapy - Surgery

The number and percentage of patients who received any prior anti-neoplastic surgery will be summarized. Prior anti-neoplastic surgeries will be summarized by lowest System Organ Class and preferred term as coded by MedDRA Version 16.0.

All prior antineoplastic therapy data will be listed for the FAS.

The above analyses will be performed using the safety set.

2.4.2.2 Prior and Concomitant Medications

Concomitant therapy is defined as all interventions (therapeutic treatments and procedures) other than the study treatment administered to a patient coinciding with the study treatment period.

Prior and concomitant medications will be coded using the World Health Organization (WHO) Drug Dictionary v13.3 and summarized by ATC class 4 and preferred term using frequency counts and percentages. Surgical and medical procedures will be coded using MedDRA and summarized by SOC and preferred term.

Medications will be classified as prior or concomitant based on the following rules:

- Prior medications are medications that started before the first dose of study treatment regardless of whether the medication ended before or after the first dose of study treatment
- Concomitant therapy include medications (other than study drugs) starting on or after the start date of study treatment or medications starting prior to the start date of study treatment and continuing after the start date of study treatment.
    - Medications starting on or after the start of study treatment but no later than 30 days after start of last dose of study treatment and
    - Medications starting prior to start of study treatment and continuing after the start of study treatment

All concomitant therapies will be listed. Any concomitant therapies starting and ending prior to the start of study treatment or starting more than 30 days after the last date of study treatment will be flagged in the listing. A separate summary of subjects who received strong

CYP3A4 inhibitors will be provided. In the listing of concomitant medications, these inhibitors will be flagged. The safety Analysis Set will be used for all prior and concomitant medication tables and listings.

2.5 Analysis of the primary objective

The primary objective of this study is to determine if the addition of midostaurin to standard of care (SOC) therapy compared to SOC reduces relapse after at least 18 months of follow-up following allogeneic HSCT in FLT3-ITD mutant AML patients in first complete remission (CR1).

2.5.1 Primary endpoint

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

2.5.2 Statistical hypothesis, model, and method of analysis

The primary efficacy variable, RFS will be analyzed based on the data observed in the FAS up-to the cut-off date, according to the treatment group assigned at randomization. The survival distribution of RFS will be estimated using the Kaplan-Meier method. Kaplan-Meier plots will be used to depict RFS over time in each treatment group. 25th percentile, Median, and 75th percentile survival will be obtained along with 95% CI calculated using the method of Brookmeyer & Crowley. Kaplan-Meier estimates with 95% CI will be summarized every 6 month using Greenwood's formula for the standard error of the Kaplan-Meier estimate.

2.5.3 Handling of missing values/censoring/discontinuations

The final analysis for RFS will be performed after all subjects have reached approximately 18 months post- transplant. An analysis cut-off date will be established after these subjects have reached this milestone.

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

If no post-baseline assessments are available (before an event or a censoring reason occurred) then the date of randomization/start date of treatment will be used.

Refer to Table 3 for censoring and event date options and outcomes for RFS.

Table 3 Outcome and event/censor dates for RFS analysis

Situation	Date	Outcome
No baseline assessment	Date of randomization	Censored

Situation	Date	Outcome
Relapse or death at or before next scheduled Assessment	Date of relapse (or death) whichever is earlier	Relapsed
Relapse or death after exactly one missing assessment	Date of relapse (or death) whichever is earlier	Relapsed
Relapse or death after two or more missing assessments	Date of last adequate assessment prior to missed assessment	Censored
No relapse (or death)	Date of last adequate assessment	Censored
Treatment/Study discontinuation due to 'Relapse'	Date of Relapse	Relapsed
Death before first assessment	Date of death	Relapsed

2.5.4 Supportive analyses

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

In addition, a sensitivity analysis will be performed on RFS using the time from randomization as reference time-point instead of the time from transplant. The same statistical analyses as the previous one described will be performed on this variable. This sensitivity analysis will be performed on both the FAS and PPS.

2.6 Analysis of the secondary objective

2.6.1 Secondary Objectives

The secondary objectives of this study are:

- To evaluate disease free survival (DFS)
- To evaluate relapse free survival (RFS) all along the study
- To evaluate non-relapse mortality (NRM)
- To evaluate overall survival (OS)
- To evaluate safety and tolerability of midostaurin in patients FLT3-ITD AML in the post-transplant setting
- To evaluate pharmacokinetics (PK) of midostaurin
- To assess FLT3-ITD mutation status centrally in archived material from diagnosis (if available) including the mutant:wild type ratio

2.6.2 Secondary endpoints

The secondary efficacy variables include:

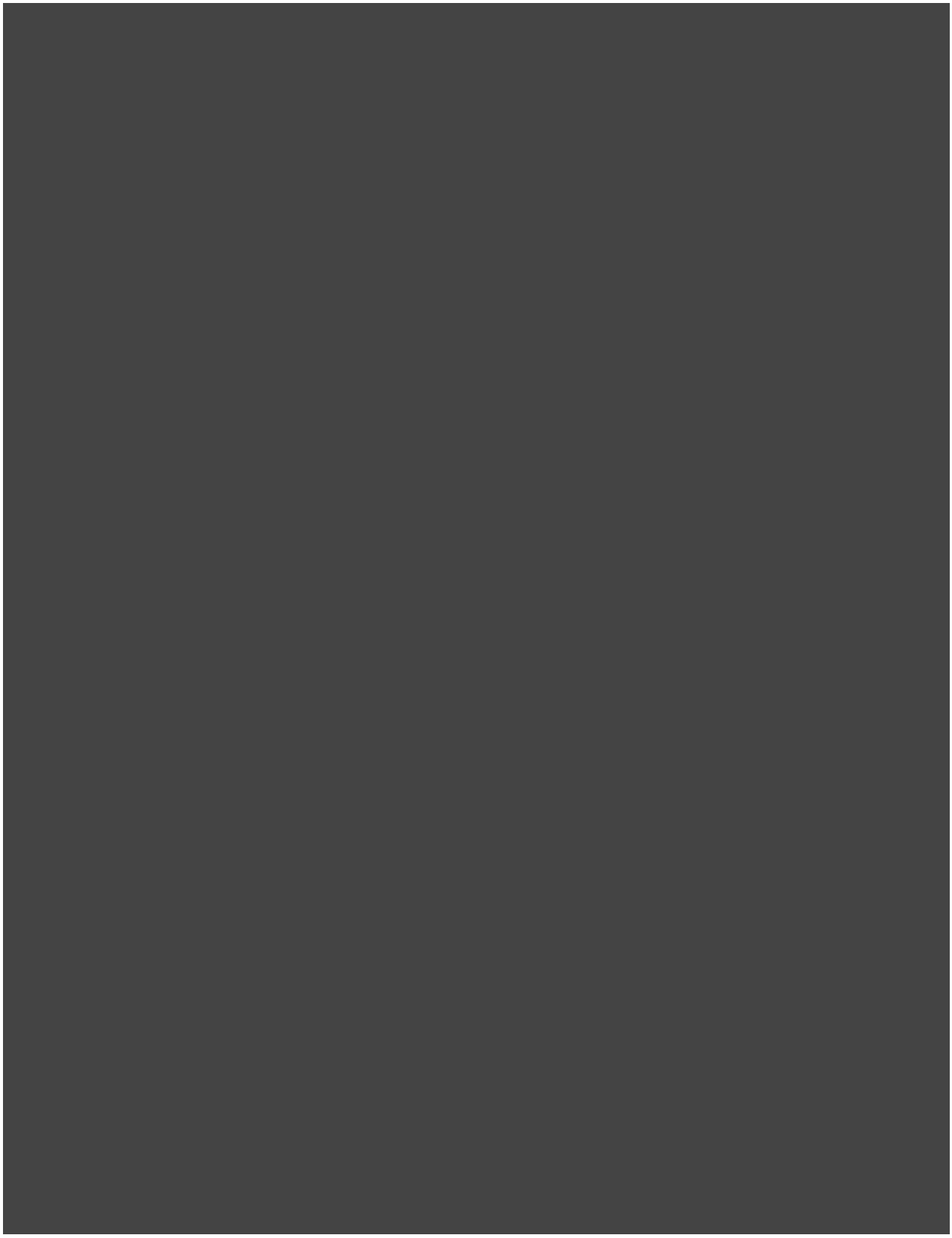
- Disease Free Survival (DFS): defined as the date from transplant to date of relapse or death from any cause.

- Relapse Free Survival (RFS): defined as the date from transplant to date of relapse or death due to the disease 24 months post HSCT.
- Overall Survival (OS): defined as the date from transplant to the date of death from any cause.
- NRM: defined as the date from transplant to date of patient death due to reasons other than relapse/progressive AML.
- PK concentration-steady state levels
- FLT3-ITD mutation status, including the mutant: wild type ratio.

Kaplan-Meier plots will be used to depict DFS, RFS, OS and NRM over time in each treatment group. Median survival will be obtained along with 95% CI calculated using the method of Brookmeyer & Crowley.

Kaplan-Meier estimates with 95% CI will be summarized every 6 month using Greenwood's formula for the standard error of the Kaplan-Meier estimate.

In addition to the Kaplan-Meier, Cox proportional hazard model will be used to provide estimate of the hazard ratio ($HR_{SOC+Midaustorin/SOC}$) and associated Wald 95% CI for each secondary endpoint. These analyses will be performed on the FAS.



2.10 Safety analyses

All safety analyses will be based on the safety set. Safety analyses will be presented overall, by treatment group (SOC or SOC + Midostaurin) and visit within treatment group if applicable. All safety listings will be presented on the FAS unless otherwise specified.

2.10.1 Treatment Emergent Adverse events (AEs)

Treatment emergent AEs (TEAEs) are defined as AEs that started or worsened during the on-treatment period. The start day used to define the TEAEs in the entire study is the first day of study treatment administration. AEs with a start day before or after on-treatment period will not be summarized, they will be listed.

TEAEs will be summarized by number and percentage of subjects having at least one AE, having at least one AE in each primary system organ class (SOC) and for each preferred term (PT) using MedDRA Version 16.0 coding. A subject with multiple occurrences of an AE will be counted only once in the respective TEAE category. A subject with multiple CTCAE grades for the same preferred term will be summarized under the maximum CTCAE grade recorded for the event. TEAE with missing CTCAE grade will be included in the 'All grades' column of the summary tables.

In TEAE summaries, the primary system organ class will be presented alphabetically and the preferred terms will be sorted within primary SOC in descending frequency. The sort order for the preferred term will be based on their frequency in the treatment group.

The following TEAE summaries will be produced by treatment group:

- Overview of TEAEs and deaths (number and % of subjects with any AE, any TEAE, died, any SAE, AE leading to treatment discontinuation, any dose adjustments/interruptions, TEAE suspected to be related to study treatment)
- TEAEs by SOC and PT
- Most common (>=5%) TEAEs

- TEAEs by maximum severity
- TEAEs suspected to be related to study treatment
- Serious Adverse Events
- TEAEs leading to treatment discontinuation,
- TEAEs leading to dose interruption/adjustment
- TEAEs leading to fatal outcome.

If partial dates occur, the convention for replacing missing dates for the purposes of calculating derived using the same method as described in Section 5.1.2. .

If an AE has a missing severity, it will be imputed as "Grade 4"; any missing relationship to study drug of an AE will be imputed as related. No other missing data will be imputed unless otherwise specified.

All AEs, SAEs, TEAEs leading to treatment discontinuation, TEAEs suspected to be related and TEAEs leading to fatal outcome will be presented in separate listings on the FAS.

2.10.2 Laboratory data

All laboratory values will be converted into SI units and the severity grade calculated using Common Toxicity Criteria for Adverse Events (CTCAE) version 4.03. For laboratory tests covered by CTCAE, a Grade 0 will be assigned for all non-missing values not graded as 1 or higher. Grade 5 will not be used. A table of CTCAE grades for the parameters of interest in the study is given below (U.S. HHS Dept., 2010).

Observed and change from baseline for Biochemistry and Hematology parameters will be summarized using descriptive statistics included 25^{th} and 75^{th} percentiles by treatment group and overall.

Table 5 Common Toxicity Criteria for Adverse Events (CTCAE) version 4.03

Parameter	Event	Grade 1	Grade 2	Grade 3	Grade 4
Hemoglobin (g/L)	Anemia	<LLN – 100	<100 – 80	<80	Life-threatening consequences; urgent intervention indicated
Hemoglobin (g/L)	Hemoglobin increased	Increase in >0 – 20 above ULN or above BL if BL is above ULN	Increase in >20 – 40 above ULN or above BL if BL is above ULN	Increase in >40 above ULN or above baseline if baseline is above ULN	N/A
White blood cells (10^9/L)	White blood cell decreased	<LLN – 3x10^9/L	<3 – 2x10^9/L	<2 – 1x10^9/L	<1x10^9/L
Lymphocytes (10^9/L)	Lymphocyte count decreased	<LLN – 0.8x10^9/L	<0.8 – 0.5x10^9/L	<0.5 – 0.2x10^9/L	<0.2x10^9/L
Lymphocytes (10^9/L)	Lymphocyte count increased	N/A	>4 - 20	>20	N/A
Neutrophils (10^9/L)	Neutrophil count decreased	<LLN – 1.5x10^9/L	<1.5 – 1.0x10^9/L	<1.0 – 0.5x10^9/L	<0.5x10^9/L
Platelets (10^9/L)	Platelet count decreased	<LLN – 75.0x10^9/L	<75.0 – 50.0x10^9/L	<50.0 – 25.0x10^9/L	<25.0x10^9/L
Albumin (g/L)	Hypoalbuminemia	<LLN – 30	<30 – 20	<20	Life-threatening consequences; urgent intervention indicated
Alkaline phosphatase (IU/L)	Alkaline phosphatase increased	>ULN – 2.5xULN	>2.5 – 5.0xULN	>5.0 – 20.0xULN	>20.0xULN
Alanine aminotransferase (IU/L)	Alanine aminotransferase increased	>ULN – 3.0xULN	>3.0 – 5.0xULN	>5.0 – 20.0xULN	>20.0xULN
Aspartate aminotransferase (IU/L)	Aspartate aminotransferase increased	>ULN – 3.0xULN	>3.0 – 5.0xULN	>5.0 – 20.0xULN	>20.0xULN
Bilirubin (umol/L)	Blood bilirubin increased	>ULN – 1.5xULN	>1.5 – 3.0xULN	>3.0 – 10.0xULN	>10.0ULN
Calcium (mmol/L)	Hypocalcemia	Corrected serum calcium <LLN – 2.0; Iodized calcium	Corrected serum calcium <2.0 - 1.75; Ionized calcium	Corrected serum calcium<1.75 - 1.5; Ionized	Corrected serum calcium <1.5; Ionized calcium <0.8;

Parameter	Event	Grade 1	Grade 2	Grade 3	Grade 4
		<LLN – 1.0	<1.0- 0.9	calcium <0.9-0.8; hospitalization indicated	life-threatening consequences
Calcium (mmol/L)	Hypercalcemia	Corrected serum calcium of >ULN -2.9; Ionized calcium >ULN - 1.5	Corrected serum calcium of >2.9 - 3.1; Ionized calcium >1.5- 1.6; symptomatic	Corrected serum calcium of >3.1 - 3.4; Ionized calcium >1.6-1.8; hospitalization indicated	Corrected serum calcium of >3.4; Ionized calcium >1.8; life-threatening consequences
Cholesterol (mmol/L)	Cholesterol high	>ULN – 7.75	>7.75 – 10.34	>10.34 – 12.92	>12.92
Creatinine	Creatinine increased	>1 - 1.5 x baseline; >ULN - 1.5 x ULN	>1.5 - 3.0 x baseline; >1.5 - 3.0 x ULN	>3.0 baseline; >3.0 - 6.0 xULN	>6.0 x ULN
Glucose (mmol/L)	Hypoglycemia	<LLN – 3.0	<3.0 – 2.2	<2.2 – 1.7	<1.7; life-threatening consequences; seizures
Glucose (mmol/L)	Hyperglycemia	>ULN – 8.9	>8.9 – 13.9	>13.9 – 27.8; hospitalization indicated	>27.8; life-threatening consequences
Lipase	Lipase increased	>ULN – 1.5xULN	>1.5 – 2.0xULN	>2.0 – 5.0xULN	>5.0xULN
Magnesium (mmol/L)	Hypomagnesemia	<LLN – 0.5	<0.5 – 0.4	<0.4 – 0.3	<0.3; life-threatening consequences
Magnesium (mmol/L)	Hypermagnesemia	>ULN – 1.23	N/A	>1.23 – 3.30	>3.30; life-threatening consequences
Phosphate (mmol/L)	Hypophosphatemia	<LLN – 0.8	<0.8 – 0.6	<0.6 – 0.3	<0.3; life-threatening consequences
Potassium (mmol/L)	Hypokalemia	<LLN – 3.0	<LLN – 3.0; symptomatic; intervention indicated	<3.0 – 2.5; hospitalization indicated	<2.5; life-threatening consequences
Potassium (mmol/L)	Hyperkalemia	>ULN – 5.5	>5.5 – 6.0	>6.0 – 7.0; hospitalization indicated	>7.0; life-threatening consequences
Sodium (mmol/L)	Hyponatremia	<LLN - 130	N/A	<130 - 120	<120; life-threatening consequences
Sodium (mmol/L)	Hypernatremia	>ULN - 150	>150 - 155	>155 – 160; hospitalization indicated	>160; life-threatening consequences
Triglycerides (mmol/L)	Hypertriglyceridemia	1.71 – 3.42	>3.42 – 5.7	>5.7 – 11.4	>11.4; life-threatening consequences

Shift tables using CTC grades to compare baseline to the worst post-baseline value will be produced for hematology and biochemistry laboratory parameters with CTC grades.

In addition, shift tables using laboratory normal ranges to compare baseline to the worst postbaseline value will be produced for all parameters, if any (Ranges:
Low, Normal, High).

All laboratory values will be listed by laboratory parameter and visit for each subject. Separate listings will display notable laboratory abnormalities which will include only newly occurring CTCAE grade 3 or 4 laboratory toxicities.

2.10.3 Pregnancy and assessments of fertility

All Pregnancy test data will be listed only.

2.10.4 Radiological examinations

A screening chest image; Chest x-ray (CXR) or CT scan will be performed to assess study eligibility. All data collected will be listed only.

2.10.5 Extramedullary Disease Assessment

The extramedullary disease assessment (EMD) will be performed at Screening, Cycle 1: Day 1 and at End of Treatment. If there is evidence of extra-medullary involvement, the location and method will be summarized by treatment group and visit.

2.10.6 ECG

A standard 12 lead ECG will be performed at Screening, Cycle 1: Day 1 (pre-dose), Cycle 1: Day 3, Cycles 2-12: Day 1 and End of Treatment (EOT) or Treatment Discontinuation.

Summary statistics (mean, median, SD, 25^{th} and 75^{th} percentile) for observed values and change from baseline of heart rate, PR interval, QRS duration, QT interval, QTcF, and frequencies and percentages of presence of clinically significant abnormalities will be presented by treatment group and visit.

In case the study requires ECG replicates at any assessment, the average of the ECG parameters at that assessment will be used in the analyses.

A change from baseline to worst on-treatment result for post-baseline assessments will be presented by treatment group.

The number and percentage of subjects with any post-baseline notable ECG value will be presented by treatment group.

- QT or QTcF
  - Value > 450 and ≤ 480 ms
  - Value > 480 and ≤ 500 ms
  - Value > 500 ms
  - Increase from Baseline > 30 ms to ≤ 60ms

  - Increase from Baseline > 60 ms
- HR
  - Increase from baseline >25% and to a value > 100 bpm
  - Decrease from baseline >25% and to a value < 50 bpm
- PR
  - Increase from baseline >25% and to a value > 200 ms
  - Value > 200 ms
- QRS
  - Increase from baseline >25% and to a value > 120 ms
  - Value > 120 ms

A listing of all ECG assessments will be produced by treatment group. A separate listing with notable results will be produced. A separate listing of ECG evaluations for all patients with at least one abnormality will be presented including only subjects with an abnormality and the visit the abnormality occurred in.

2.10.7 Vital signs

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

Summary statistics of actual value and change from baseline values (means, medians, standard deviations, 25th and 75th percentile) of vital signs and weight collected on treatment will be summarized.

For analysis of vital signs the clinically notable vital sign criteria are provided in Table 6 below.

Table 6 Clinically notable changes in vital signs

Vital sign (unit)	**Clinically notable criteria**	
	above normal value	**below normal value**
Weight (kg)	increase > 10% from Baseline	decrease > 10% from Baseline
Systolic blood pressure (mmHg)	>=180 with increase from baseline of >=20	<=90 with decrease from baseline of >=20
Diastolic blood pressure (mmHg)	>=105 with increase from baseline of >=15	<=50 with decrease from baseline of >=15
Pulse rate (bpm)	>=100 with increase from baseline of >25%	<=50 with decrease from baseline of > 25%
Body	>= 39.1	-

Vital sign (unit)	Clinically notable criteria	
	above normal value	below normal value
temperature		

The number and percentage of subjects with notable vital sign values (high/low) will be presented by treatment group.

All vital sign data will be listed. A separate listing with notable values will be provided.

2.10.8 ECOG Performance Status

The ECOG PS scale Table 7 will be used to assess physical health of patients, ranging from 0 (most active) to 5 (least active):

Table 7 ECOG Performance Scale

Score	Description
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

Frequency counts and percentages of patients in each score category will be provided by treatment group and visits based on the windows defined in Section 2.1.

2.10.9 Cardiac imaging - MUGA (multiple gated acquisition) scan or Echocardiogram

An echocardiogram or MUGA scan will be performed on screening prior to Day 1, at Cycle 3, 6 and at the EOT visit

The left ventricular ejection fraction (LVEF) will be summarized and the overall interpretation will be summarized using frequency and percentages by treatment group and visit.

2.11 Pharmacokinetic Concentrations

Plasma concentrations of midostaurin and its two major metabolites CGP52421 and CGP62221will be measured using a validated liquid chromatography/ mass spectrometry (LC-MS/MS) assay with a lower

Descriptive statistics (n, m (number of non-zero concentrations), mean, CV% mean, SD, median, geometric mean, CV% geo-mean, minimum and maximum) for Midostaurin concentration will be presented at each scheduled time point for the Pharmacokinetic analysis set.

All concentration values below the lower limit of quantitation (LLOQ) are set to zero by the Bioanalyst, and will be displayed in the listings as zero and flagged. LLOQ values will be treated as zero in any calculations of summary statistics, and treated as missing for the calculation of the geometric means and their CV%. The number of non-zero concentrations will also be reported in the summary statistics.

Missing values for any PK data will not be imputed and will be treated as missing.

The mean (+/- SD) and geometric mean trough concentration-time profiles for Midostaurin over time will be displayed graphically for Pharmacokinetic analysis set.

All individual plasma Midostaurin concentration data will be listed for the PK analysis set.

General Data Handling and preprocessing

The Cycle 1 Day 1 assessment (pre-dose) will be used as the baseline value.

When more than one biomarker data value are available for a subject at any time point, the mean of the replicate values will be used for all statistical analyses.

Derivation of Change and Percent Change Variables

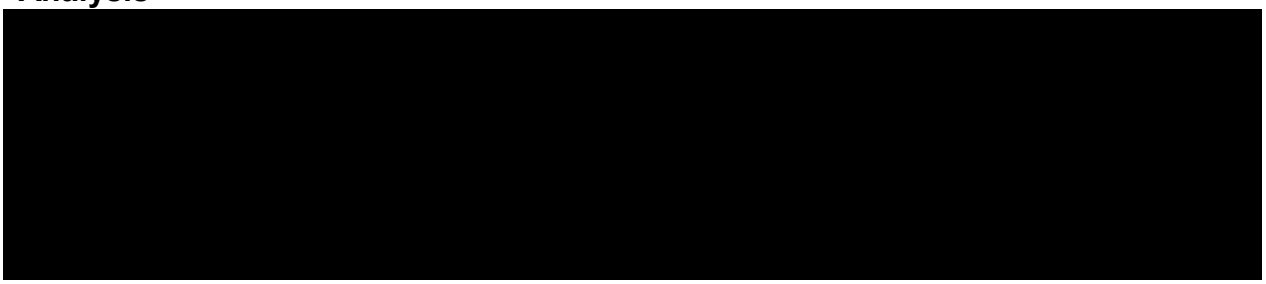
Absolute and relative change (percent change) and fold change from baseline will be calculated for each subject and/or treatment group.

Fold change is calculated as the ratio of biomarker value at ((visit i) / (Baseline biomarker value)), while percent change is computed as ((visit i – baseline) / baseline) * 100.

The average percent change from baseline is computed as the average expression level at each time point and then the percent change using the average values. Please note that the number of subjects for the average of percent change from baseline might vary due to potential missing values at respective time points.

If both the baseline and post baseline values are below LLOQ, absolute change, percent change and fold change from baseline will not be imputed and reported as missing.

Analysis



2.12 Interim analysis

No formal interim analysis is planned for this study. However, there will be two interim snapshots of the data taken per year.

3 Sample size calculation

This study is a Phase II exploratory trial and is not powered to detect a statistical difference between the two arms. The sample size for the trial was chosen; 30 patients per treatment arm to have separate estimates of the primary endpoint relapse free survival. Powering of the trial is not feasible considering the rare nature of FLT3-ITD mutant AML receiving a HSCT. With a 22-25% FLT3-ITD mutation rate and approximately 25% rate of HSCT, estimated from the ongoing Phase III study (2301, CALGB 10603, Ratify), more than 1050 newly diagnosed AML patients would need to be evaluated to identify 60 patients undergoing HSCT in CR1.

The control arm, Standard of Care (SOC), in this study provides the first prospective subjects treated at the same centers in the same timeframe which will allow an estimate of treatment effect which can be used to design a larger trial. There are no published sets of prospective, FLT3-ITD AML outcomes after transplantation

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

Scenario 1: Assuming a 30% relapse rate in the SOC arm
Scenario 2: Assuming a 50% reduction with midostaurin (experimental arm)

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

4 Change to protocol specified analyses

No change from protocol specified analysis was made.

5 Appendix

5.1.1 Study drug

The following rule should be used for the imputation of the dose end date for a given study treatment component:

Scenario 1: If the dose end date is completely missing and there is no EOT page and no death date, the patient is considered as on-going:

The patient should be treated as on-going and the cut-off date should be used as the dose end date.

Scenario 1 should not applicable for final analyses. All patients should have EOT page complete before the Database lock for Final CSR

Scenario 2: If the dose end date is completely or partially missing and the EOT page is available:

Case 1: The dose end date is completely missing, and the EOT completion date is complete, then this latter date should be used.

Case 2: Only Year (yyyy) of the dose end date is available and yyyy < the year of EOT date:

Use Dec31yyyy

Case 3: Only Year (yyyy) of the dose end date is available and yyyy = the year of EOT date:

Use EOT date

Case 4: Both Year (yyyy) and Month (mm) are available for dose end date, and yyyy = the year of EOT date and mm < the month of EOT date:

Use last day of the Month (mm)

All other cases should be considered as a data issue and the statistician should contact the data manager of the study.

After imputation, compare the imputed date with start date of treatment, if the imputed date is < start date of treatment:

Use the treatment start date

Patients with missing start dates are to be considered missing for all study treatment component related calculations and no imputation will be made. If start date is missing then end-date should not be imputed.

5.1.2 AE, ConMeds and safety assessment date imputation

Table 8 Imputation of start dates (AE, CM) and assessments (LB, EG, VS)

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
	  ○ If stop date contains a full date and stop date is earlier than study treatment start date then set start date = 01JanYYYY
	  ○ 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

Missing Element	Rule
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 9 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*

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 the end date provided.

The above imputations are only used for determination of on-treatment assessments/events (i.e. concomitant medication, treatment emergent adverse event).

5.1.2.1 Other imputations

Incomplete date of initial diagnosis of cancer and date of most recent recurrence

Missing day is defaulted to the 15th of the month and missing month and day is defaulted to 01-Jan.

5.2 Laboratory parameters derivations

Imputation Rules

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 an 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.

CTC grades for the derived absolute WBC differential counts (neutrophils, lymphocytes) and corrected calcium will be assigned as described above for grading

5.3 Statistical models

Analysis of time to events Data

The following endpoints will be analyzed in the same manner:

- Disease free survival (DFS)
- Relapse Free Survival (RFS)
- Non-relapse mortality (NRM)
- Overall survival (OS)

Kaplan-Meier estimates

An estimate of the survival function in each treatment group will be constructed using Kaplan-Meier (product-limit) method as implemented in PROC LIFETEST with METHOD=KM option. The PROC LIFETEST statement will use the option CONFTYPE=LOGLOG.

Median survival for each treatment group will be obtained along with 95% confidence intervals calculated from PROC LIFETEST output using the method of [Brookmeyer and Crowley 1982]. Kaplan-Meier estimates of the survival function with 95% confidence intervals at specific time points will be summarized. The standard error of the Kaplan-Meier estimate will be calculated using Greenwood's formula [Collett 1994].

Treatment of ties

The STRATA statement in LIFETEST procedure will be used to analyze time to event data with ties. The PHREG procedure in SAS with option TIES=EXACT will be used to fit the Cox proportional hazards model.

Checking proportionality of hazard assumption

Plots (SURVIVAL LOGSURV LOGLOGS) generated by LIFETEST procedure in SAS will be used to provide visual checks of the proportional hazard assumption.

- SURVIVAL plots estimated survivor functions. The shape of the curves should be basically the same if hazards are proportional.
- LOGSURV plots the cumulative hazard functions The larger cumulative hazard should be a multiple of smaller if hazards are proportional
- LOGLOGS plots log (cumulative hazard). The LOGLOG plot will show parallel curves if hazards are proportional.

6 Reference

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