NOVARTIS

Clinical Development

Midostaurin/PKC412

CPKC412A2220/NCT03280030

A phase II, randomized, double-blind, multi-center, placebo-controlled study to evaluate the efficacy and safety of twice daily oral midostaurin in combination with daunorubicin/cytarabine induction, high-dose cytarabine consolidation, and midostaurin single agent continuation therapy in newly diagnosed patients with FLT3-mutated acute myeloid leukemia (AML)

# Statistical Analysis Plan (SAP) for final analysis

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| Date | Time point | Reason for update | Outcome for update | Section and title impacted (Current) |
|---|---|---|---|---|
| 06-Dec-2022 | Before final DBL | | Original version for final analysis | |

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## List of abbreviations

| | |
|---|---|
| AE | Adverse Event |
| AESI | Adverse Event of Special Interest |
| ATC | Anatomical Therapeutic Classification |
| AUC | Area Under the Curve |
| CI | Confidence Interval |
| CIR | Cumulative Incidence of Relapse |
| CR | Complete Remission |
| CRp | Morphologic Complete Remission with incomplete platelet count recovery |
| CSR | Clinical Study report |
| CTC | Common Toxicity Criteria |
| CTCAE | Common Terminology Criteria for Adverse Events |
| CTP | Clinical Trial Protocol |
| CV | Coefficient of Variation |
| DAR | Dosage Administration Record |
| DI | Dose Intensity |
| EFS | Event-Free Survival |
| EOT | End of Treatment |
| FAS | Full Analysis Set |
| eCRF | Electronic Case Report Form |
| HR | Hazard Ratio |
| ISC | Independent Safety Committee |
| IRT | Interactive Response Technology |
| LLOQ | Lower Limit of Quantitation |
| LPLV | Last patient last visit |
| MedDRA | Medical Dictionary for Regulatory Activities |
| NCI | National Cancer Institute |
| OS | Overall Survival |
| PDI | Planned Dose Intensity |
| PK | Pharmacokinetics |
| PPS | Per-Protocol Set |
| PR | Partial Remission |
| PRO | Patient-reported Outcomes |
| PT | Preferred Term |
| RAP | Report and Analysis Process |
| RDI | Relative Dose Intensity |
| SAP | Statistical Analysis Plan |
| SCT | Stem Cell Transplantation |
| SD | Standard Deviation |
| SMQ | Standardized MedDRA Queries |
| SOC | System Organ Class |
| WBC | White Blood Cell |
| WHO | World Health Organization |

# 1 Introduction

This statistical analysis plan (SAP) describes all planned analyses for the clinical study report(s) (CSR) of study CPKC412A2220, a phase II, randomized, double-blind, multi-center, placebo-controlled study to evaluate the efficacy and safety of twice daily oral midostaurin in combination with daunorubicin/cytarabine induction therapy, high-dose cytarabine consolidation and midostaurin single agent continuation therapy in newly diagnosed patients with FLT3-mutated acute myeloid leukemia (AML).

The content of this SAP is based on protocol CPKC412A2220 version 03 (released on 10-Sep-2020). All decisions regarding final analysis, as defined in the SAP document, have been made prior to database lock.

## 1.1 Study design

This study is a phase II, multi-center trial consisting of 2 parts.

- Part 1: open label, safety evaluation part in Japan only (minimum of three evaluable patients)
- Part 2: double-blind, randomized, placebo-controlled part (60 patients)

Part 1 in Japan and Part 2 outside Japan will be conducted in parallel. At the completion of Part 1, and depending on the findings of the safety evaluation, the trial in Japan will advance to Part 2.

### 1.1.1 Part 1: Safety evaluation part

The part 1 will be conducted to evaluate the safety and tolerability of midostaurin in combination with daunorubicin/cytarabine induction and high-dose cytarabine consolidation in Japanese patients. Data from the part 1 will be reviewed by an Independent Safety Committee designated by the Sponsor (Figure 1-1).

Patients will be enrolled into the study irrespective of leukemia FLT3 genotype (i.e., patients with either FLT3-WT or FLT3-mutated AML will be eligible).

The safety evaluation period will begin on Day 1 of the first induction cycle (Cycle 1 Day 1) and will continue until Day 21 of the first consolidation cycle. The period will allow for an assessment of the safety of midostaurin with chemotherapy throughout induction and will provide also an assessment of Safety Events (for example, CNS neurotoxicity and ocular toxicity) specific to consolidation with high dose cytarabine. The first safety review by the Independent Safety Committee will take place when at least three evaluable patients have completed the safety evaluation period without a potential Safety Event or have experienced a potential Safety Event within this period. A Safety Event is defined as death or serious adverse event leading to treatment discontinuation during the safety evaluation period and that is determined by the Independent Safety Committee to be definitely or probably related to midostaurin. All potential deaths and treatment discontinuations due to serious adverse events will be adjudicated by the Independent Safety Committee; it will take into consideration the attribution of the event by the investigator, but in its decision-making for trial conduct the attribution of event by the Independent Safety Committee will prevail.

The Independent Safety Committee will review all available safety data in patients from Japan up to the time of the safety review data cut-off date. After determining whether each death or serious adverse event leading to treatment discontinuation during the safety evaluation period meets criteria for a Safety Event, it will consider this tabulation in combination with the entire safety experience in Japanese patients to determine the ongoing conduct of the trial.

The Independent Safety Committee will be provided through its charter with guidelines for determining the conduct of the trial:

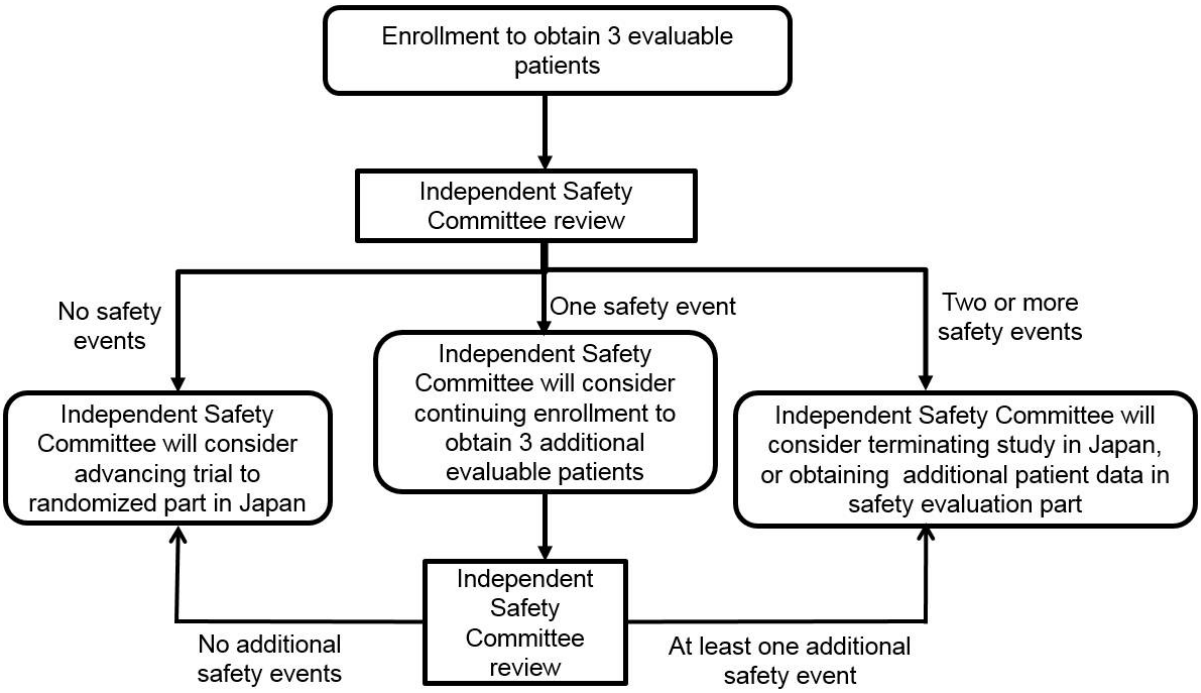
- If one Safety Event occurs among the first three patients enrolled during the safety evaluation period, then the Independent Safety Committee will determine whether an additional cohort of three patients should be enrolled into the part 1.
- If there is no Safety Event among the first three evaluable patients or no more than one Safety Event among the first six evaluable patients during the safety evaluation period, then the Independent Safety Committee will determine whether the trial may advance to the part 2 in Japan.
- If two or more Safety Events are observed in the first three or six evaluable patients, the Independent Safety Committee will determine whether conduct of the trial in Japan should be terminated without advancement to the part 2. The Independent Safety Committee may determine that additional information is needed through continued recruitment of patients into the part 1 before making a final determination regarding advancement to the part 2 or termination of the study in Japan.

Although the Independent Safety Committee will consider these guidelines in its determination of continuing study conduct in Japan, it will also take into consideration the individual circumstances of the Safety Events and will make use of the clinical judgement of the Independent Safety Committee members.

Patients in the part 1 in Japan may be treated with midostaurin in combination with the JALSG or RATIFY regimen. Although it is anticipated that most patients would be treated in Japan with the JALSG regimen, there is no required minimum number of patients to be treated with either chemotherapy regimen. Both regimens may contribute to the overall safety evaluation, or the Independent Safety Committee may consider during its deliberation potential differences in the two combination regimens.

Prior to the decision of the Independent Safety Committee to initiate the part 2 of the trial (if applicable), patients in the part 1 who remain in remission will continue to be treated according to the study protocol. If a decision is made by the Independent Safety Committee to defer initiation of the part 2 in Japan or to suspend treatment of patients in Japan, then the continued treatment with midostaurin of patients already enrolled in the part 1 will be determined by the Study Steering Committee, the individual investigators, and the Sponsor, and the decision will take into consideration the findings of the Independent Safety Committee (ISC).

**Figure 1-1 Independent Safety Committee review in Part 1 safety evaluation part (Japan only)**




### 1.1.2 Part 2: Randomized Part

For the part 2 of the study, the start of patient enrollment in countries outside Japan will be concurrent with the start of the part 1 in Japan. The part 2 in Japan will begin only after the Independent Safety Committee agrees that midostaurin in combination with chemotherapy is adequately tolerated in Japanese patients. Novartis will report the decision to the full Study Steering Committee ([study protocol Section 8.7]).

Patients meeting all eligibility criteria (except FLT3 mutation) may begin the study treatment with chemotherapy. The FLT3 mutation status will be evaluated in a Novartis designated laboratory.

Patients who are determined to have AML with a FLT3 mutation (ITD and/or TKD) will be randomized on Cycle 1 Day 8 (first cycle of induction therapy) and will be assigned to midostaurin or placebo by using a stratified randomization according to FLT3 mutation and treatment regimen (see [study protocol Section 2.2]).

- Patients who are determined to have AML without a FLT3 mutation or with an unknown FLT3 mutation status by Cycle 1 Day 8 will be discontinued from the treatment.

Outside Japan, only the RATIFY regimen will be used.

During Part 1 (implemented in Japan only), safety and tolerability of midostaurin with the JALSG or with the RATIFY regimen will be assessed. There is no requirement for a minimum number of patients treated with each regimen. It is therefore possible, for example, that Part 1 will be completed only with patients treated with JALSG or only with patients treated with

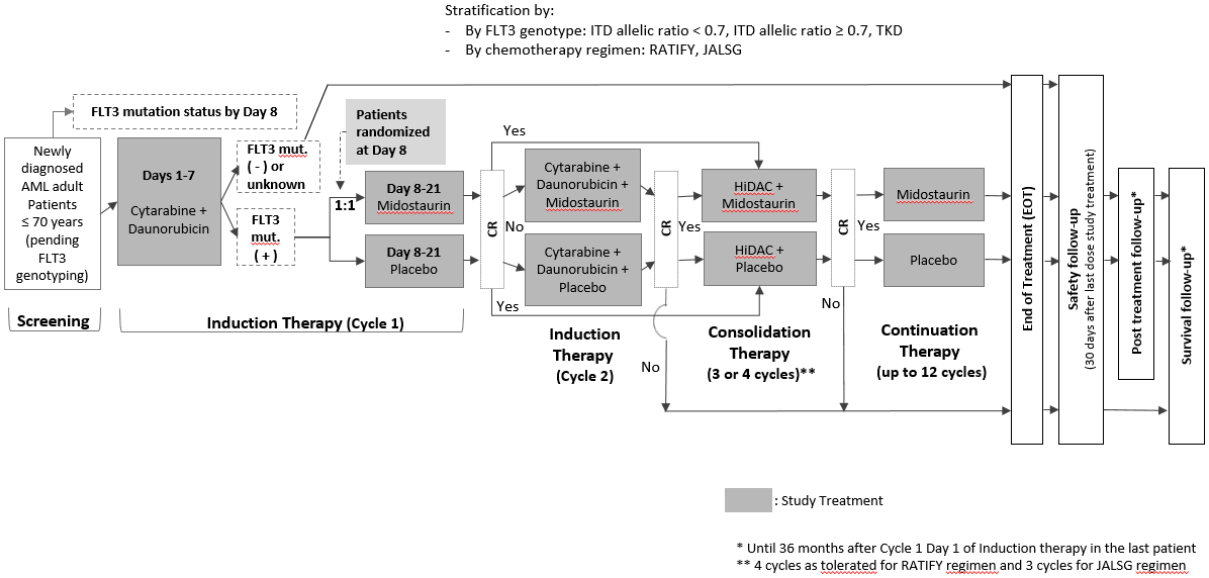
RATIFY. If the ISC endorses proceeding to Part 2, then investigators in Japan may choose either RATIFY or JALSG for future patients. Once patients are enrolled in the study, their regimen must not be switched during the course of the study.

The study will include:

- Screening phase (7 days);
- Treatment phase composed of up to 18 cycles of midostaurin/placebo treatment in combination with chemotherapy (daunorubicin and cytarabine) during induction and consolidation and alone during continuation and 30 days safety follow up from last dose of study treatment (daunorubicin or cytarabine or midostaurin/placebo);
- Follow up phase for continued remission and survival.

Refer to Figure 1-2 for study design.

**Figure 1-2 Overview of Randomized Part (Part 2)**




### 1.1.2.1 Screening phase

Patients who provided written informed consent will be screened for eligibility during the period up to 7 days immediately prior to starting chemotherapy (daunorubicin and cytarabine). The patient will be randomized at Day 8 and will receive either midostaurin or placebo only if FLT3 status is mutated.

During the screening phase the investigator must:

- Obtain signed informed consent from the patient prior to any study procedures
- Assess the inclusion and exclusion criteria as detailed in [protocol Section 5]
- Perform all screening procedures as detailed in [study protocol Table 7-1]

Results of all screening/baseline evaluations must be reviewed by the investigator or his/her designee prior to enrollment of each patient into the study to ensure that all inclusion and exclusion criteria are satisfied.

The diagnosis of AML by BMA may be confirmed before or during the screening period. In case of dry tap (failure to obtain bone marrow after BMA attempts), bone marrow biopsy can be used for confirming AML diagnosis; alternatively peripheral blood (showing ≥20% blasts) may be used at investigator's discretion if bone marrow biopsy may delay treatment initiation.

#### 1.1.2.2 Treatment phase

### Induction therapy

All screened patients will start induction therapy with chemotherapy (daunorubicin and cytarabine) from Day 1 to Day 7, while the FLT3 mutation is being determined.

An Interactive Response Technology (IRT) system will be used to randomize patients to the study treatment groups and the patient eligibility checklist will be embedded into the IRT randomization process.

Only randomized patients (with FLT3 mutation) will receive midostaurin/placebo, orally twice a day, on days 8 to 21.

Patients who achieve CR already with induction cycle 1 will go directly to consolidation therapy without a second cycle of induction therapy. Patients who do not achieve CR with one cycle of induction will receive a second induction cycle with same treatment than in cycle 1.

Patients not achieving CR after induction 2 will discontinue study treatment and will be followed in safety follow-up and survival follow-up.

### Consolidation therapy

Patients who achieved a CR after 1 or 2 cycles of induction will receive consolidation therapy with 3 cycles of high-dose cytarabine for JALSG regimen and 4 cycles of high-dose cytarabine as tolerated for RATIFY regimen.

Patients will receive midostaurin/placebo, orally twice a day, on days 8 to 21 of each cycle.

Each consolidation cycle will begin within two weeks following hematopoietic recovery (ANC $\geq 1.0 \times 10^9$/L, platelet count $\geq 100 \times 10^9$/L) but no sooner than four weeks from the beginning of the previous cycle.

For patients of age 60 years or older at the time of study entry, the dose of cytarabine may be reduced at the discretion of the investigator to 1500 mg/m$^2$/dose for JALSG regimen and to 1000-1500 mg/m$^2$/dose for RATIFY regimen.

### Continuation therapy

After hematopoietic recovery (ANC $\geq 1.0 \times 10^9$/L, platelet count $\geq 100 \times 10^9$/L) following the final cycle of consolidation but no sooner than 14 days after the last dose of midostaurin/placebo during the last consolidation cycle, patients who maintain a CR will receive up to 12 cycles (28 days/cycle) of continuous therapy with midostaurin or placebo twice a day.

Study treatment will continue until completion of 12 cycles of continuation therapy, persistent AML, relapse, intolerable toxicity, withdrawal of consent by the patient, lost to follow up, death, or the sponsor terminates the study, whichever is earlier.

Safety will be assessed in this treatment phase for each patient until 30 days after the end of treatment (EOT) and will include routine safety monitoring except in case of death, loss to follow up or withdrawal of consent.

#### 1.1.2.3 Follow up phases

The follow-up period will comprise the following:

**Post treatment follow-up**

During the post treatment follow-up, use of subsequent anti-neoplastic cancer therapies (i.e., surgery, SCT, radiotherapy, local and systemic anti-neoplastic medications) initiated after study treatment discontinuation will be recorded.

Following the end of study treatment for any reason other than persistent AML, relapse, withdrawal of consent, death, or loss to follow up, all patients will continue to be assessed for relapse i.e., every 2 months during years 1 and 2, every 3 months on year 3 and 4 and then yearly and at time of relapse until relapse, withdrawal of consent, death, loss to follow up, or end of study, whichever is earlier. For further details see [study protocol Section 7].

**Survival follow up**

Patients who discontinued study treatment due to persistent AML or relapse and the post treatment follow-up phase due to relapse will enter a follow-up period during which survival will be recorded every 3 months (see [protocol Section 4.3]). Survival information can be obtained by clinical visits or telephone calls or other means until death, withdrawal of consent, loss to follow-up or end of study, whichever is earlier.

During the survival follow-up, subsequent anti-neoplastic therapies initiated after discontinuation of study treatment will be reported until death, withdrawal of consent, loss to follow-up or end of study, whichever is earlier.

### 1.1.3 Timing of interim analyses and design adaptations

During the part 1, the Independent Safety Committee will evaluate all available safety data from patients treated in Japan to determine if the midostaurin combination with chemotherapy is safe and is adequately tolerated in Japanese patients. All patients enrolled in part 1 will be listed and reviewed irrespective of the combination treatment (JALSG or RATIFY regimen). For additional information, see [protocol Section 4.1] and [Section 10.7].

During the part 2, an interim analysis for efficacy will be conducted when 60 patients are randomized and at least 24 EFS events are documented (expected around 14 months from the date of first patient randomized assuming the recruitment period as 14 months). This interim analysis will be assessed by a DMC, however, even if interim success criteria are met, the study will be continuing blinded to patients, investigators and monitors until the primary analysis and thereafter unblinded. At the final analysis more mature data can be evaluated. In case that 36

EFS events are documented before randomization completion, the interim analysis can be skipped and Novartis will conduct primary analysis. For detailed information, please refer to [protocol Section 10.7].

### 1.1.4 Definition of end of study

The end of study will occur at the latest 36 months after the start of the study treatment for the last patient. All patients will remain in post-treatment or survival follow-up until the data cut-off date of the final analysis (i.e., last patient last visit (LPLV)), and all available data will be analyzed.

### 1.1.5 Early study termination

The study may be terminated at any time for any reason by Novartis. Should this be necessary, the patient should be seen as soon as possible for the End of Treatment (EOT) visit, and assessments for EOT as described in [study protocol Section 7] should be performed for a discontinued or withdrawn patient. The investigator may be informed of additional procedures to be followed in order to ensure that adequate consideration is given to the protection of the patient's interests. The investigator will be responsible for informing IRBs and/or ECs of the early termination of the trial.

## 1.2 Study objectives and endpoints

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

**Table 1-1 Objectives and related endpoints**

| Objective | Endpoint | Analysis |
|---|---|---|
| **Primary** | | |
| **Safety Evaluation part (Part 1, Japan only)** | | Section 2.5 |
| To Evaluate the safety and tolerability of midostaurin in combination with daunorubicin/cytarabine induction and high-dose cytarabine consolidation in Japanese patients with newly diagnosed AML. | Incidence and severity of Safety Events, defined as death or serious adverse event leading to treatment discontinuation that occurs on or before Day 21 of the first Consolidation cycle and that is determined by the Independent Safety Committee to be definitely or probably related to midostaurin. | |
| **Double-blind, randomized, placebo-controlled (Part 2)** | | |
| To Evaluate the efficacy based on event-free survival (EFS) of midostaurin versus placebo in combination with daunorubicin/cytarabine induction, with high-dose cytarabine consolidation, and with midostaurin single agent continuation therapy in newly diagnosed patients with FLT3-mutated AML. | Event-free survival (EFS) defined as the time from the date of randomization until an EFS event is observed. An EFS event is defined as a failure to obtain a CR within induction 2, relapse after CR, or death due to any cause, whichever occurs first. | |
| **Secondary** | | |

| Objective | Endpoint | Analysis |
|---|---|---|
| **Randomized part (Part 2)** | | |
| Determine overall survival (OS) in the two treatment groups | Overall survival (OS), defined as the time from the date of randomization to date of death due to any cause. | Section 2.7 |
| Determine rate of complete remission (CR) in the two treatment groups | CR rate, defined as the proportion of patients with a CR according to Cheson criteria, at various timepoints. | |
| Determine cumulative incidence of relapse (CIR) in the two treatment groups | CIR (only for patients who have achieved CR after study treatment initiation), as measured from the date of first CR to relapse or death due to AML, whichever occurs first. | |
| Evaluate safety of midostaurin compared to placebo in combination with chemotherapy and as single agent continuation therapy | Frequency/severity of AEs, ECG and laboratory abnormalities. | Section 2.8 |
| Evaluate the pharmacokinetics of midostaurin and its two major metabolites CGP52421 and CGP62221 | Pharmacokinetic parameters for midostaurin and two major metabolites CGP52421 and CGP62221. | Section 2.10 |
| Determine the effect of study treatment on quality of life | European Organization for Research and Treatment of Cancer (EORTC) QLQ-C30 total score and functional scales scores (scores and absolute change from baseline at each scheduled assessment).<br><br>PGIC score as frequencies and percentages by scheduled timepoint. | Section 2.11 |
| [redacted] | | |

# 2 Statistical methods

## 2.1 Data analysis general information

The final analyses will be performed by Novartis and/or a designated CRO. SAS version 9.4 or later will be used to perform all data analyses and to generate tables, figures and listings.

### Safety evaluation part (Part 1, Japan only)

The safety and tolerability of midostaurin in combination with chemotherapy in Japan will be assessed based on the incidence of Safety Events during the safety evaluation period. A Safety Event is defined as death or serious adverse event leading to treatment discontinuation that occurs on or before Day 21 of the first consolidation cycle and that is determined by the Independent Safety Committee to be definitely or probably related to midostaurin.

All Japanese patients who signed ICF by 25Sep2018, the date when Independent Safety Committee review was held, will be assessed as patients enrolled in part 1. All patients enrolled part 1 will be listed and reviewed irrespective of the combination treatment (JALSG or RATIFY regimen). Separate SAP for Indenpendent Safety Committee (ISC) was created.

### Randomized part (Part 2)

In the part 2, interim, primary analyses were conducted and final analyses will be conducted.

For screening failure, patients who signed the informed consent but never started the study treatment for any reason, and non-randomized patients, the eCRF data collected will not be included in analyses, but will be reported in CSR as separate listings as appropriate.

### Data included in the analysis

The interim analysis for efficacy were conducted when 60 patients were to be randomized (actual 62 patients) and at least 24 EFS events were documented. In case that 36 EFS events were documented before randomization completion, the interim analysis could be skipped and Novartis would plan to conduct primary analysis.

The primary analysis was performed using a pre-defined cut-off date of 30 November 2020 with the number of EFS events were documented as per amended protocol version 03 (released date 10-Sep-2020) by this date.

The end of study will occur at the latest 36 months after the start of the study treatment for the last patient. At this time, the final analysis will be performed.

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.

At final analysis the cut-off date means LPLV.

### General analysis conventions

**Pooling of centers:** Unless specified otherwise, data from all study centers will be pooled for the analysis. Due to expected small number of patients enrolled at centers, no center effect will be assessed.

**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 patients in the relevant population or subgroup 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

***Investigational drug*** will refer to the midostaurin. ***Control drug*** will refer to the placebo. The ***study drug*** will refer to investigational and control drugs. Whereas, ***study treatment*** will refer to treatment with daunorubicin, cytarabine, or midostaurin/placebo.

### 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) eCRF. The date of first administration of study drug will also be referred as start of investigational drug.

### Date of last administration of investigational drug

The date of last administration of investigational drug is defined asthe 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 any component of study treatment was administered as per the Dosage Administration Record (DAR) eCRF (Example: if 1$^{st}$ dose of midostaurin/placebo is administered on 05-Jan-2015, and 1$^{st}$ dose of a combination partner is administered on 03-Jan-2015, then the date of first administration of study treatment is on 03-Jan-2015). 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 derived as the last date when a nonzero dose of any component of study treatment was administered as per the DAR eCRF. (Example: if the last midostaurin/placebo is administered on 15-Apr-2014, and the last dose of a combination partner is administered on 17-Apr-2014, then the date of last administration of study treatment is on 17-Apr-2014).

### Study day

The study day describes the day of the event or assessment date, relative to the reference start date.

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 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 efficacy assessments, including PRO and performance status, is the date of randomization.The reference start date for all other assessments is the start of the 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 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 randomization date 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 non-missing assessment, including unscheduled assessments on or before the date of start of study treatment is taken as “baseline” value or “baseline” assessment.

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

### On-treatment assessment/event and observation periods

For all safety analyses, the overall observation period will be divided into three mutually exclusive segments:

1. **pre-treatment period:** from day of patient’s informed consent to the day before first dose of study treatment

2. **on-treatment period:** from day of first dose of study treatment to 30 days after last dose of study treatment
3. **post-treatment period:** starting at day 31 after last dose of study treatment.

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 post-treatment period) will be listed and those collected during the pre-treatment and post-treatment period will be flagged.

## Last contact date

The last contact date will be derived for patients not known to have died at the LPLV using the last complete date among the following:

**Table 2-1 Last contact date data sources**

| Source data | Conditions |
|---|---|
| Date of start of study treatment | No Condition |
| Date of Randomization | No Condition |
| Last contact date/last date patient was known to be alive from Survival Follow-up page | Patient status is reported to be alive, lost to follow-up or unknown |
| Start/End dates from further antineoplastic therapy | Non-missing medication/procedure term |
| 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 |
| Any specific efficacy assessment date | Evaluation is marked as ‘done’ |
| Laboratory [redacted] PK collection dates | Sample collection marked as ‘done’ |
| Vital signs, ECG date | At least one non-missing parameter value |
| Performance Status date | Non-missing performance status |
| 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 LPLV. The LPLV will not be used for last contact date, unless the patient was seen or contacted on that date. No date post LPLV 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 is coming from ‘Survival information’ eCRF.

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

### Hematological toxicities and recovery

Thrombocytopenia is defined as a platelet count below 20.0 x $10^9$/L as reported on the eCRF Local Lab Results - Hematology.

The duration of thrombocytopenia is defined as (first date of increase of platelets over 20.0 x $10^9$/L – first date of decrease of platelets below 20.0 x $10^9$/L for the considered period + 1). If the patient had a platelet transfusion during the period, the patient is considered as not assessable.

The time between chemotherapy start and non-transfused recovery from thrombocytopenia is defined as (first date of increase of platelets over 20.0 x $10^9$/L – date of first chemotherapy (cytarabine or daunorubicin in induction phase, or high dose cytarabine in conslidation phase) administration for the considered period + 1). If the patient had a platelet transfusion during the period, the patient is considered as not assessable.

Neutropenia is defined as an absolute neutrophil count below 0.5 x $10^9$/L as reported on the eCRF Local Lab Results - Hematology.

The duration of neutropenia is defined as (first date of increase of absolute neutrophil count over 0.5 x $10^9$/L – first date of decrease of absolute neutrophil count below 0.5 x $10^9$/L for the considered period + 1).

The time between chemotherapy start and recovery from neutropenia is defined as (first date of increase of absolute neutrophil count over 0.5 x $10^9$/L – date of first chemotherapy (cytarabine or daunorubicin in induction phase, or high dose cytarabine in consolidation phase) administration for the considered phase + 1).

Additional analyses might be performed, if need be, in order to better characterize the influence of concomedications and blood transfusions on the kinetics of hematologic recovery.

## 2.2 Analysis sets

### Full Analysis Set

The Full Analysis Set (FAS) comprises all patients to whom study drug (midostaurin/placebo) has been assigned by randomization. Therefore, all Japanese patients treated during the part 1 will not be eligible for the FAS. According to the intent to treat principle, patients will be analyzed according to the treatment and strata they have been assigned to during the randomization procedure.

### Per protocol set (PPS)

The Per-Protocol Set (PPS) consists of a subset of the patients in the FAS who are compliant with requirements of the study protocol.

Oncology standards for protocol deviations **potentially** leading to exclusion from the PPS are:

- type of indication different from those required by the CTP (e.g., incorrect histology/cytology, not refractory, not metastatic, different grade of cancer, etc.)
- if prior therapy does not match with CTP requirements in terms of number and types of previous therapy regimens

- missing or incomplete documentation of stage of disease (as required in the CTP)
- another anti-neoplastic therapy administered after start of study treatment and prior to first efficacy assessment
- study treatment received different from treatment assigned by randomization

### Safety set

The Safety Set includes all randomized patients who received at least one dose of study drug. Patients will be analyzed according to the part in which they are enrolled and the study treatment received, where treatment received is defined as the randomized treatment if the patient took at least one dose of that treatment or the first treatment received if the randomized treatment was never received.

### Other

### Pharmacokinetic analysis set for all (PAS-all)

The Pharmacokinetic analysis set for all (PAS-all) includes all patients who took at least one dose of midostaurin and provide at least one evaluable PK concentration.

For a concentration to be evaluable, patients are required to:

- Take the planned dose of midostaurin prior to sampling
- For pre-dose samples: do not vomit within 4 hours after the dosing of midostaurin prior to sampling, have the sample collected before the next dose administration
- For post-dose samples: do not vomit within 4 hours after the dosing of midostaurin

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

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

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

- Patient receives the planned dose of midostaurin on C1D8 of induction therapy
- Patient does not vomit within 4 hours of the dosing of midostaurin on C1D8 of induction therapy
- Patient provides at least one primary PK parameter

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

### Patient Classification:

Patients may be excluded from the analysis populations defined above based on the protocol deviations entered in the database and/or on specific subject classification rules defined in Table 2-2.

**Table 2-2 Subject classification based on protocol deviations and non-PD criteria**

| Analysis set | PD Identifer leading to exclusion (Edit Check Specifications V9.0) | Non protocol deviation leading to exclusion |
|---|---|---|
| FAS | INCL06 | Not applicable |
| Safety set | INCL06 | No dose of study drug |
| Per-protocol set | INCL01A, INCL01A01, INCL01A02, INCL01B, INCL04, INCL06, EXCL05, EXCL06, EXCL07, EXCL08, EXCL09, COMD01, TRT03, TRT07, TRT10, OTHER02, OTHER04, OTHER11, COMD03 | Patient randomized with confirming FLT3 is wild-type or undeterminate |
| PK Analysis Set | INCL06, EXCL07 | See definition of PK analysis set |
| Full PK Analysis Set | INCL06, EXCL07 | See definition of full PK analysis set |

### 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 patient withdraws full consent is recorded in the eCRF.

## 2.2.1 Subgroup of interest

### Efficacy

The EFS and OS will be summarized by the following subgroups to examine the homogeneity of treatment effect across demographic and baseline disease characteristics will be performed:

- FLT3 mutation status (stratification factor: ITD allelic ratio <0.7, ITD allelic ratio ≥ 0.7, TKD)
- chemotherapy regimen (stratification factor: RATIFY regimen, JALSG regimen)
- gender
- age category: < 60 years, ≥ 60 years
- [redacted]

For each of subgroups, the treatment effect will be assessed separately within each category. The HR and their 95% CIs will be presented by means of forest plots. Unstratified analysis will be performed for each of the subgroups.

The CR rate will also be summarized by the subgroup shown above. The difference of CR rate between treatments and their 95% CIs will be presented by means of forest plot.

### Safety

AEs, regardless of study treatment relationship, will be summarize by the following subgroups:

- age category: < 60 years, ≥ 60 years
- chemotherapy regimen (stratification factor: RATIFY regimen, JALSG regimen)

- strong CYP3A4 inhibitor intake (Yes/No), for patients who received/did not receive strong CYP3A4 inhibitor (listed in protocol appendix 2) concomitant treatments during the study.

For each subgroup, AEs regardless of study treatment relationship will be summarized by SOC, PT and maximum CTC grade, and by phase.

## 2.3 Patient disposition, demographics and other baseline characteristics

### 2.3.1 Safety evaluation part (Part 1, Japan only)

Patient disposition, demographics and other baseline characteristics will be listed for all patients enrolled in the safety evaluation part.

### 2.3.2 Randomized part (Part 2)

The FAS will be used for all baseline and demographic summaries and listings unless otherwise specified. Summaries will be reported by treatment arm and for all patients, and listings will be reported by treatment arm to assess baseline comparability. No inferential statistics will be provided.

#### 2.3.2.1 Basic demographic and background data

All demographic and baseline disease characteristics data will be summarized and listed by treatment arm. Categorical data (e.g. gender, age groups: <60, 60-<65 and ≥ 65 years, race, ethnicity, WHO performance status) will be summarized by frequency counts and percentages; the number and percentage of patients with missing data will be provided. Continuous data (e.g. age, weight, height, body surface area (BSA)) will be summarized by descriptive statistics (N, mean, median, standard deviation, minimum and maximum). BSA will be calculated using Gehan and George formula:

BSA[m2]= 234.94*(height[cm]**0.422)*(weight[kg]**0.515)/10000 using height and weight at baseline.

WBC at baseline will be categorized (<20, 20-<50, and ≥50 $10^9$/L) and summarized by frequency counts and percentages.

#### Baseline stratification factors

The number (%) of patients in each stratum (constructed by 3 FLT3 mutation status and 2 regimens) based on data obtained from the IRT system will be summarized overall and by treatment arm for the FAS. Discordances between the stratum recorded in IRT at the time of randomization and the actual stratum recorded in the clinical database through the data collected on eCRF will be cross-tabulated and listed.

#### Diagnosis and extent of cancer

Summary statistics will be tabulated for diagnosis and extent of cancer. This analysis will include the following: WHO 2016 classification of AML, and sub-classification of AML.

### Medical history

Medical history and ongoing conditions, including cancer-related conditions and symptoms entered on eCRF will be summarized and listed by treatment arm. Separate summaries will be presented for ongoing and historical medical conditions. The summaries will be presented by primary system organ class (SOC), preferred term (PT) and treatment arm. 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.

### Cytogenetics

Cytegenetic abnormality(ies) will be summarized.

### Extramedullary involvement

Location of extramedually involvement at screening will be summarized.

### Other

All data collected at baseline will be listed.

## 2.3.2.2 Patient disposition

Enrollment by country and center will be summarized for all screened patients and also by treatment group using the FAS. The number (%) of screened and the reason for screening failure will be displayed. Also, the number (%) of non-randomized patients and its reason will be displayed.

The following summaries will be provided overall and by treatment group using the FAS:

- Number (%) of patients who were randomized (based on data from IRT system)
- Number (%) of patients who were randomized but not treated study drug
- Primary reason for not being treated study drug
- Number (%) of patients who were treated study drug
- Number (%) of patients who are still on-treatment by therapy (induction, consolidation, continuation)
- Number (%) of patients who completed therapy (induction, consolidation, continuation)
- Number (%) of patients who discontinued the study treatment by therapy (induction, consolication, continuation)
- Primary reason for study treatment discontinuation by therapy (induction, consolidation, continuation)
- Number (%) of patients who are ongoing the post-treatment follow-up
- Number (%) of patients who have discontinued from the post-treatment follow-up
- Reasons for discontinuation from the post-treatment follow-up
- Number (%) of patients who are alive on the survival follow-up
- Number (%) of patients who dead on the survival follow-up

- Number (%) of patients who have entered the survival follow-up but whose status is unknown

#### 2.3.2.3 Protocol deviations

The number (%) of patients in the FAS with any protocol deviation will be tabulated by deviation category (as specified in the study PD Specification) overall and by treatment group for the FAS. Major protocol deviations leading to exclusion from analysis sets will be tabulated separately overall and by treatment group. All protocol deviations will be listed.

Protocol deviations related to COVID-19 pandemic will be tabulated separately by deviation category, overall and by treatment. PD relationship to COVID-19 pandemic will be displayed in the listing for all protocol deviations.

#### 2.3.2.4 Analysis sets

The number (%) of patients in each analysis set (defined in Section 2.2) will be summarized by treatment group and stratum.

## 2.4 Treatments (study treatment, rescue medication, concomitant therapies, compliance)

### 2.4.1 Safety evaluation part (Part 1, Japan only)

Study treatment, prior concomitant and post therapies will be listed for all patients enrolled in the safety evaluation part.

### 2.4.2 Randomized part (Part 2)

#### 2.4.2.1 Study treatment / compliance

Duration of exposure, actual cumulative dose, dose intensity (DI) and relative dose intensity (RDI) will be summarized by cycle for induction and consolidation, treatment phase (induction, consolidation and continuation), overall (for the study drug only) and treatment arm, separately for each component of study treatment (Investigational drug, control drug and combination partner). The duration of exposure to study treatment will also be presented.

The number (%) of subjects who have dose reductions or interruptions, and the reasons, will be summarized by cycle for induction and consolidation, treatment phase (induction, consolidation and continuation),and overall, separately for each component of study treatment.

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 unless otherwise specified.

### Duration of exposure to study treatment

Duration of exposure to study treatment is considered by taking into account the duration of exposure to the investigational drug or control, and any combination partners:

Duration of exposure to study treatment (months) = {(date of last administration of study treatment) – (date of first administration of study treatment) + 1}/30.4375.

Summary of duration of exposure of study treatment will include categorical summaries (<1 month ; ≥1 month ; ≥3 months ; ≥6 months ; ≥12 months ; ≥18 months , ≥24 months). based on clinically meaningful time intervals) and continuous summaries (i.e., mean, standard deviation etc.) using appropriate units of time.

### Duration of exposure to investigational drug, control drug and combination partner

The duration of exposure for the study drug (midostaurin/placebo), cytarabine, high dose cytarabine and daunorubicin (labeled as [medication] in the definitions below) will be calculated by cycle during induction and consolidation, by therapy (induction, consolidation and continuation, when applicable) and overall as below. Each durations will include the non-planned periods of temporary interruption of the medication for any reason:

- Duration of [medication] exposure (days) by cycle = number of days of administration during the cycle (including the days temporary interrupted).
- Duration of [medication] exposure (days) in induction/consolidation phase = sum of durations of [medication] exposure by cycle for all cycles during induction/consolidation phase.
- Duration of [medication] exposure (days) in continuation phase = [(date of last administration of [medication] during continuation phase) – (date of first administration of [medication] during continuation phase) + 1].
- Overall duration of [medication] exposure (days) = sum of durations of [medication] exposure by cycle for all cycles in induction, consolidation, and continuation phases.

In a given cycle and for a given medication, the duration of exposure is equal to zero for patients who entered the cycle but did not take the medication during this cycle. It is missing for patients who did not enter the cycle.

The duration of exposure will be summarized descriptively by cycle, treatment phase (induction, consolidation and continuation), overall and treatment group. In addition, the duration of exposure will be summarized descriptively by cycle, treatment, overall, regimen and treatment group.

### Cumulative dose

Cumulative dose of a study treatment is defined as the total dose given during the study treatment exposure and will be summarized for each of the study treatment components.

The **planned cumulative dose** for a study treatment component refers to the total planned dose as per the protocol up to the last date of investigational drug administration.

The **actual cumulative dose** refers to the total actual dose administered, over the duration for which the subject is on the study treatment as documented in the DAR eCRF.

For patients who did not take any 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-zerodose during dosing periods.

### Dose intensity and relative dose intensity of study treatment

The **Actual Dose Intensity (ADI)** for the study drug (midostaurin/placebo) is defined by cycle for induction and consolidation, by treatment phase (induction, consolidation and continuation) and overall as follows:

- ADI (mg / day) by cycle = (Cumulative dose during the cycle / duration of study drug exposure during the cycle).
- ADI (mg / day) by treatment phase = (Cumulative dose during the considered treatment phase / duration of study drug exposure during the considered treatment phase), for all patients who entered the considered treatment phase.
- Overall ADI (mg / day) = (Overall cumulative dose during the study / overall duration of exposure).

ADI for cytarabine, high dose cytarabine and daunorubicin (labeled as [medication] in the definitions below) is defined by cycle, and by treatment phase (induction and consolidation, when applicable) as follows (note: the Body Surface Area (BSA) reported at the beginning of each cycle should be taken into account in the calculations of the ADI for the considered cycle):

- ADI (mg/m²/cycle) by cycle = ((Cumulative dose during the cycle / BSA at the beginning of the cycle)).
- ADI (mg/m²/cycle) by treatment phase = (sum of (Cumulative dose during the cycle / BSA at the beginning of the cycle) for all cycles received during the considered treatment phase / number of cycle of which at least one [medication] is administered), for all patients who entered the considered treatment phase.

In a given cycle and for a given medication, the ADI is equal to zero for patients who entered the cycle but did not take the medication during this cycle. It is missing for patients who did not enter the cycle.

The **Planned dose intensity (PDI)** for the study drug (midostaurin/placebo) is defined, by cycle for induction and consolidation, by treatment phase (induction, consolidation and continuation), and overall as follows:

- PDI (mg/day) = 100 mg/day.

The PDI for cytarabine by cycle in the induction phase is defined as follows:

- PDI (mg/m² / cycle) during JALSG induction = 700 mg/m²/cycle during each cycle.
- PDI (mg/m² / cycle) during RATIFY induction = 1400 mg/m²/cycle during each cycle.

The PDI for high dose cytarabine by cycle in the consolidation phase is defined as follows:

- PDI (mg/m² / cycle) during JALSG consolidation = 20000 mg/m²/cycle on each cycle.
- PDI (mg/m² / cycle) during RATIFY consolidation = 18000 mg/m²/cycle on each cycle.

The PDI for daunorubicin by cycle in the induction phase is defined as follows:

- PDI (mg/m² / cycle) during JALSG induction = 250 mg/m²/cycle on each cycle.
- PDI (mg/m² / cycle) during RATIFY induction = 180 mg/m²/cycle on each cycle.

The PDI is not described but is used for the calculation of the Relative dose intensity (RDI).

The **Relative dose intensity** (RDI) is the percentage of planned dose that was actually received.

The RDI is defined for the study drug (midostaurin/placebo), cytarabine, high dose cytarabine and daunorubicin by cycle for induction and consolidation (when applicable), by treatment phase (induction, consolidation and continuation, when applicable) and overall as follows：

- RDI for the considered period (%) = ADI (mg or mg/m²/day or cycle) for the considered period / PDI (mg or mg/m²/day or cycle) for the considered period*100.

In a given cycle and for a given medication, the RDI is equal to zero for patients who entered th cycle but did not take the medication during this cycle. It is missing for patients who did not enter the cycle.

### Dose reductions, interruptions or permanent discontinuations

The number of subjects who have dose reductions, permanent discontinuations or interruptions, and the reasons, will be summarized by cycle for induction and consolidation, treatment (induction, consolidation and continuation), and overall (only for the study drug), separately for each component of study treatment.

‘Dose change’, ‘Dose interrupted’, and ‘Dose permanently discontinued’ fields from the DAR eCRF will be used to determine the dose reductions, dose interruptions, and permanent discontinuations, respectively. The corresponding fields ‘Reason’ 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 is different from the prescribed dose.

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

Dose reduction is defined as the dose change where the prescribed dose level is lower than the previous prescribed dose level or where the actual dose administered 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. Because only dose change is collected in the CRF, dose reductions will be clarified programmatically using the definition above.

#### 2.4.2.2 Prior, concomitant and post therapies

### Prior anti-cancer therapy

The number and percentage of patients who received any prior anti-neoplastic medications, will be summarized by ATC class, preferred term and treatment. Summaries will include total number of regimens, setting, and reason for discontinuation of therapy. Prior anti-neoplastic medications will be listed.

Anti-neoplastic medications will be coded using the WHO Drug Dictionary (WHO-DD). Details regarding WHO-DD version will be included in the footnote in the tables/listings.

The above analyses will be performed using the FAS.

### Post treatment anti-cancer therapy

Anti-neoplastic therapies since discontinuation of study treatment will be listed and summarized by ATC class, preferred term, and treatment group by means of frequency counts and percentages. The number of regimens of the new anti-neoplastic therapy initiated after discontinuation of study treatment regardleess of end of study treatment reason will be summarized. In addition, the regimen of the next line of therapy, defined as the first new anti-neoplastic therapy initiated after discontinuation of study treatment regardless of end of study treatment reason, and its setting, duration and best response will be summarized.

The above analyses will be performed using the FAS.

### 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. 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.

Concomitant medications will be coded using the WHO-DD and summarized by ATC class and preferred term using frequency counts and percentages. The same analyses will be performed for strong CYP3A4 inhibitors. Surgical and medical procedures will be coded using MedDRA and summarized by SOC and preferred term. These summaries will include:

1. 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
2. Medications starting prior to start of study treatment and continuing after the start of study treatment.

All prior and 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. The safety set will be used for all concomitant medication tables and listings.

### Hematopoietic Stem Cell Transplant (HSCT)

The number and percentage of patients who received SCT will be summarized by type of SCT (allogeneic related SCT, allogeneic unrelated SCT, autologous SCT, cord blood, and other) and treatment arm. According to Table 2-3, type of SCT will be categorized based on source, transpalent type, and allogeneic donor type collected in eCRF page. A summary table will be produced by:

- Overall
- Occurred in patients without Complete Remission
- Occurred during first CR
- Occurred after relapse

The difference in SCT rates with its 95% confidence interval will also be provided.

The time to SCT (defined as the time from randomization to the date of SCT) overall and that occurred during first CR will be summarized by treatment arm.

The above analyses will be performed using the FAS.

**Table 2-3 Type of SCT**

| Type | Source | Transplant type | Allogeneic donor type |
|---|---|---|---|
| Allogeneic related SCT | 1) Other than cord blood | Allogeneic-full conditioning | Sibiling fully matched |
| | | Allogeneic reduced conditioning | Sibiling any mismatch |
| | 2) Other than cord blood | Other than Autologous | Haploidentical |
| Allogeneic unrelated SCT | Other than cord blood | Allogeneic-full conditioning | Unrelated fully matched |
| | | Allogeneic reduced conditioning | Unrelated any mismatch |
| Autologous SCT | Other than cord blood | Autologous | Other than Haploidentical |
| Cord blood | Cord blood | Other than Autologous | Other than Haploidentical |
| Others | None of the above | | |

## 2.5 Analysis of the primary objective

### Safety evaluation part (Part 1, Japan only)

The primary objective for the part 1 is to evaluate the safety and tolerability of midostaurin in combination with chemotherapy in Japanese patients with newly diagnosed AML.

### Randomized part (Part 2)

The primary objective for the part 2 is to evaluate the efficacy based on event-free survival (EFS) of midostaurin versus placebo in combination with daunorubicin/cytarabine induction, with high-dose cytarabine consolidation, and with midostaurin single agent continuation therapy in newly diagnosed patients with FLT3-mutated AML.

### 2.5.1 Primary endpoint

#### Safety evaluation part (Part 1, Japan only)

The primary variable for the part 1 in Japan is the incidence of Safety Events, defined as death or serious adverse event leading to treatment discontinuation that occurs on or before Day 21 of the first consolidation cycle and that is determined by the Independent Safety Committee to be definitely or probably related to midostaurin, among evaluable patients.

#### Randomized part (Part 2)

The primary efficacy variable for the part 2 is event-free survival (EFS), defined as the time from the date of randomization until an EFS event is observed. An EFS event is defined as a failure to obtain a CR within induction 2, relapse after CR, or death due to any cause, whichever occurs first. Patients who do not complete first course of therapy without documented post-baseline CR should be considered a treatment failure. Clinical response (CR, CRp, PR and treatment failure, and relapse after CR) will be assessed via local review according to criteria defined in Section 2.7.1. Relevant assessment date collected in the eCRF International Working Group (IWG) Response page will be used for the date of clinical response. For patients with treatment failure, the EFS will be documented as event at day 1 (refer to Table 2-4).

The final analysis for the part 2 will be based on FAS and will include all data observed up to the LPLV. If a patient has not observed EFS event at the LPLV, EFS will be censored at the date of the last adequate clinical assessment before the LPLV.

### 2.5.2 Statistical hypothesis, model, and method of analysis

#### Safety evaluation part

As the final analysis for the part 1, all adverse events of all patients enrolled in the part 1 will be listed.

The Independent Safety Committee will review all available safety data in patients from Japan up to the time of the safety review data cut-off date. After determining whether each death or serious adverse event leading to treatment discontinuation during the safety evaluation period meets criteria for a Safety Event, it will consider this tabulation in combination with the entire safety experience in Japanese patients to determine the ongoing conduct of the trial.

#### Randomized part

The primary efficacy analysis for the part 2 will be the comparison of the distribution of EFS between the two treatment arms. The estimated hazard ratio (HR) of EFS not censored at SCT will be calculated using Cox regression model stratified according to the 2 stratification factors (FLT3 mutation status: ITD allelic ratio $< 0.7$, ITD allelic ratio $\geq 0.7$, TKD; and regimen: RATIFY regimen, JALSG regimen) as per IRT (or CRF as this is the same as IRT considering a subject with both ITD allelic ratio $< 0.7$ and TKD as that with ITD allelic ratio $< 0.7$). In addition, associated 95% Wald confidence interval (CI) will be calculated. The success of the study will be claimed when estimated HR is less than 1. (Note: The success criteria of the study was judged at interim and/or primary analysis and not at this final analysis.)

The survival distribution of EFS will be estimated using the Kaplan-Meier method. The results will be plotted graphically by treatment arm. The median of EFS along with 95% CIs will be presented by treatment arm.

### 2.5.3 Handling of missing values/censoring/discontinuations

In the final analysis for the part 2, EFS will be censored at the date of the last adequate clinical assessment if no EFS event is observed prior to the LPLV.

The date of last adequate clinical assessment will be the final timepoint for the evaluation of efficacy before an event or a censoring reason occurred. In this case the last clinical assessment date at that assessment will be used. If no post-baseline assessment is available and the patient is still on treatment at the time of the analysis, then the date of randomization will be used and EFS censored.

Refer to Table 2-4 for censoring and event date options and outcomes for EFS.

**Table 2-4 Outcome and event/censor dates for EFS analysis**

| Situation | Date | Outcome |
|---|---|---|
| No baseline assessment | Date of randomization | Censored |
| No post-baseline assessment | Date of randomization | Censored |
| Treatment failure | Date of randomization + 1 | EFS event |
| Relapse or death at or before next scheduled assessment | Date of relapse or death | EFS event |
| Relapse or death after exactly one missing assessment | Date of relapse or death | EFS event |
| 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 |
| Strong CYP3A4 inducer given prior to protocol defined progression | Date of last adequate assessment | Censored |
| New anticancer therapy given prior to protocol defined relapse | Ignore the new anticancer therapy and follow situations above | As per above situations |

### 2.5.4 Supportive analyses

#### Sensitivity analyses

The efficacy analysis for EFS will be repeated using the PPS if the number of patients in the FAS and PPS differ by more than 10 percent.

Further sensitivity analyses in the FAS will be performed for EFS per local review where:

- A sensitivity analysis by using EFS defined as the time from the start of the study treatment until an EFS event is observed.

- A sensitivity analysis considering SCT: patients are considered as censored at the time of the transplant if they received SCT.

In addition, the Bayesian posterior probability of (HR for EFS per local review < 1) will be calculated as a supportive analysis. Assuming a weakly informative prior distribution derived from Study [A2301] data, the distribution of the HR will be updated with all available data from the patients included in the FAS (for more detail, refer to [study protocol Section 14.1]).

If 36 EFS events are not documented at the time of final analysis, the Bayesian predictive probability of (HR for EFS when 36 EFS events are documented < 1) will be calculated. To calculate the predictive probability, assuming a weakly informative prior distribution derived from Study [A2301], data and the prior distribution will be updated using the available data from patients in the FAS at the time of analysis (for more details of weakly informative prior, refer to [study protocol Section 14.1]).

### Subgroup analyses

Subgroup analyses specified in Section 2.2.1 to assess the homogeneity of the treatment effect across demographic and baseline disease characteristics will be performed.

For each of the subgroups, the treatment effect will be assessed separately within each category. The HR and their 95% CIs will be presented by means of forest plots. Forest plot for EFS will be conducted by unstartified analysis for each subgroup because this study is small sample size study and it is difficult to conduct stratified analysis for each subgroup.

### Censoring pattern of EFS

Number of patients with a EFS event and number of patients censored for the EFS analysis will be summarized. In addition, a summary of reasons for EFS censoring will be provided by treatment arm based on the following reasons:

1. Ongoing without event
2. Lost to follow-up
3. Withdrew consent
4. Adequate assessment no longer available
5. Event after >= 2 missing efficacy assessments

The EFS censoring reasons are defined in the following way.

If the time interval between the last adequate date of the efficacy assessment and the earliest of the following dates is smaller or equal to interval of 2 missing efficacy assessments :

1. Analysis cut-off date (i.e., LPLV),
2. Date of consent withdrawal,
3. Visit date of study treatment discontinuation or end of post-treatment follow-up discontinuation due to lost to follow-up.

Then the EFS censoring reason will be:

1. ‘Ongoing’,
2. ‘Withdrew consent’,

3. 'Lost to follow-up'.

If the time interval is larger than the interval of 2 missing efficacy assessments with no event observed. then the EFS censoring reason will always default to 'Adequate assessment no longer available'. If the time interval between the last adequate efficacy assessment date and the EFS event date is larger than the interval of 2 missing efficacy assessments then the patient will be censored and the censoring reason will be 'Event documented after two or more missing efficacy assessments'.

[redacted]

## 2.6 Analysis of the key secondary objective

Not applicable.

## 2.7 Analysis of secondary efficacy objective(s)

The secondary objectives in this study are:

- To determine overall survival (OS) in the two treatment groups
- To determine the rate of complete remission (CR) in the two treatment groups
- To determine the cumulative incidence of relapse (CIR) in the two treatment groups
- To evaluate the safety of midostaurin compared to placebo in combination with chemotherapy and as single agent continuation therapy
- To evaluate the pharmacokinetics of midostaurin and its two major metabolites CGP52421 and CGP62221
- To determine the effect of the study treatment on quality of life

### 2.7.1 Secondary endpoints

#### Overall survival (OS)

OS is defined as the time from the date of randomization to date of death due to any cause. All deaths occurring on or before the LPLV in the FAS will be used in the OS analysis. If a patient is not known to have died at the time of LPLV, OS will be censored at the date of last contact.

#### Complete remission (CR) rate

CR rate is defined as the proportion of patients with a CR according to Cheson criteria (Cheson 2003) as per investigator assessment. CR rate will be calculated using the FAS.

#### Cumulative incidence of relapse (CIR)

Cumulative incidence of relapse (CIR) is defined for patients who have achieved CR only. CIR will be calculated from the date of first CR to relapse or death due to AML, whichever occurs first. If a patient is not known to have relapse at the time of LPLV, CIR will be censored at the

date of last adequate assessment. If a patient has died due to other reason than AML without relapse prior to death, CIR will be censored at the date of the death.

### 2.7.2 Statistical hypothesis, model, and method of analysis

#### Overall survival (OS)

The OS distribution not censored at SCT will be estimated using the Kaplan-Meier method, and the Kaplan-Meier curves, medians and 95% CIs of the medians will be presented for each treatment arm. The HR along with its 95% CI will be calculated, using a stratified Cox model using the randomization stratification factors.

As sensitivity analyses performed in the FAS, the hazard ratio and 95% CI for OS will be obtained from:

- A sensitivity analysis by using OS defined as the time from the start of the study treatment until an OS event is observed.
- A sensitivity analysis considering SCT: patients are considered as censored at the time of the transplant if they received SCT.

Regardless of OS results, subgroup analyses specified in Section 2.2.1 to assess the homogeneity of the treatment effect across demographic and baseline disease characteristics will be performed. Note: same analysis was conducted for primary CSR with changed from planned analysis at the time of primary analysis although original analysis plan was to conduct if overall OS HR was less than 1.

For each of the subgroups, the treatment effect will be assessed separately within each category. The HR and their 95% CIs will be presented by means of forest plots. Forest plot for OS will be conducted by unstartified analysis for each subgroup because this study is small sample size study and it is difficult to conduct stratified analysis for each subgroup.

#### Complete remission (CR) rate

CR rate will be summarized for end of induction cycle 1, end of induction cycle 2, end of consolidation, after treatment discontinuation and overall. The difference in CR rates along with two-sided 95% CIs.

#### Cumulative incidence of relapse (CIR)

The survival distribution of CIR distributions will be estimated using the Kaplan-Meier method, and Kaplan-Meier curves, medians and 95% CIs (Brookmeyer and Crowley 1982) of the medians will be presented for each treatment arm. The HR for CIR will be calculated, along with its 95% CI, using a stratified Cox model using the randomization stratification factors.

As a sensitivity analysis, the same analyses when patients are considered as censored at the time of the transplant if they received SCT will be performed.

## 2.8 Safety analyses

All safety analyses will be based on the safety set.

### 2.8.1 Adverse events (AEs)

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

Adverse events are coded using the Medical dictionary for regulatory activities (MedDRA) terminology.

AEs will be assessed according to the Common Terminology Criteria for Adverse Events (CTCAE) version 5.0. The CTCAE represents a comprehensive grading system for reporting the acute and late effects of cancer treatments. CTCAE grading is by definition a 5-point scale generally corresponding to mild, moderate, severe, life threatening, and death. This grading system inherently places a value on the importance of an event, although there is not necessarily proportionality among grades (a grade 2 is not necessarily twice as bad as a grade 1).

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

In AE 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 investigational arm

In AE summaries by phase, AEs newly recorded between the start date and the end date of the phase will be used, that is, AEs continued from the previous phases and not newly recorded will not be included in the summary. If a subject discontinued study treatment in a specific treatment phase, then all AEs observed within 30 days from the study treatment discontinuation in addition to those observed during this treatment phase will be considered.

The following AE summaries will be produced by phase and treatment group;

- overview of adverse events and deaths (number and % of subjects with any AE, any AE suspected to be related to study treatment, any SAE, any SAE suspected to be related to study treatment, any fatal SAE, any fatal SAE suspected to be related to study treatment, any AE leading to study drug discontinuation, any AE leading to study drug discontinuation suspected to be related to study treatment, any AE leading to dose reduction, any AE leading to dose interruption, AEs requiring additional therapy, AEs leading to fatal outcome)
- AEs, regardless of study treatment relationship, by SOC, PT and maximum CTC grade
- AEs, regardless of study treatment relationship, by PT and maximum CTC grade
- AEs, regardless of study treatment relationship, by SOC and maximum CTC grade
- AEs suspected to be related to study treatment, by SOC, PT and maximum CTC grade
- AEs suspected to be related to study treatment, by PT and maximum CTC grade
- SAEs, regardless of study treatment relationship, by SOC, PT and maximum CTC grade
- SAEs, regardless of study treatment relationship, by PT and maximum CTC grade

- SAEs suspected to be related to study treatment, by SOC, PT and maximum CTC grade
- Non-SAEs, regardless of study treatment relationship, by SOC, PT and maximum CTC grade
- Non-SAEs suspected to be related to study treatment, by SOC, PT and maximum CTC grade

The following AE summaries will be produced by treatment group;

- AEs leading to study treatment discontinuation, regardless of study drug relationship, by SOC, PT and maximum CTC grade
- AEs leading to study treatment discontinuation, regardless of study drug relationship, by PT and maximum CTC grade
- AEs leading to dose reduction of study treatment, regardless of study drug relationship, by SOC, PT and maximum CTC grade
- AEs leading to dose interruption of study treatment, regardless of study drug relationship, by SOC, PT and maximum CTC grade
- AEs requiring additional therapy, regardless of study drug relationship, by SOC, PT and maximum CTC grade
- AEs leading to fatal outcome, regardless of study drug relationship, by SOC and PT

In addition, a summary of non-SAEs with number of occurrences will be produced (an occurrence is defined as >1 day between start and prior end date of record of same preferred term) as per EudraCT requirements.

All AEs will be listed and those collected during the pre-treatment and post-treatment period will be flagged.

#### 2.8.1.1 Adverse events of special interest / grouping of AEs

**Data analysis of AESIs**

An adverse event of special interest is a grouping of adverse events that are of scientific and medical concern specific to compound midostaurin. These groupings are defined using MedDRA terms, SMQs (standardized MedDRA queries), HGLTs (high level group terms), HLT (high level terms) and PTs (preferred terms) in the Case Retrieval Sheet. Customized SMQs (Novartis MedDRA queries, NMQ) may also be used. A NMQ is a customized group of search terms which defines a medical concept for which there is no official SMQ available or the available SMQ does not completely fit the need. It may include a combination of single terms and/or an existing SMQ, narrow or broad. For each specified AESI, number and percentage of patients with at least one event of the AESI occurring during on treatment period will be summarized.

Summaries of these AESIs will be provided by treatment arm, (specifying grade, SAE, relationship, leading to treatment discontinuation, leading to dose adjustment/interruption, fatal outcome, etc.). If sufficient number of events occurred, analysis of time to first occurrence of AESI (CTCAE grade ≥3) will be applied. The time to first occurrence of AESI will be censored at the date of the last adequate safety assessment if no AESI event (CTCAE grade≥3) is observed prior to the LPLV. The date of last adequate safety assessment will be the final

timepoint for the safety before a censoring reason is occurred. If no post-baseline safety assessments are available then the date of the start of study treatment will be used.

### 2.8.2 Deaths

Separate summaries for on-treatment, post-treament and all (including both on-treatment and post-treatment) deaths will be produced by treatment arm, SOC and PT.

All deaths will be listed, post treatment deaths will be flagged. A separate listing of deaths prior to starting treatment will be provided for all screened subjects.

### 2.8.3 Laboratory data

#### CTC grading for Laboratory parameters

Grade categorization of lab values will be assigned programmatically as per NCI Common Terminology Criteria for Adverse Events (CTCAE) version 5.0. The calculation of laboratory CTC grades will be based on the observed laboratory values only, clinical assessments will not be taken into account. The criteria to assign CTC grades are given in Novartis internal criteria for CTC grading of laboratory parameters. The latest available version of the document based on the underlying CTCAE version 5.0 at the time of analysis will be used.

For laboratory tests where grades are not defined by CTCAE version 5.0, results will be graded by the low/normal/high (or other project-specific ranges, if more suitable) classifications based on laboratory normal ranges.

A severity grade of 0 will be assigned for all non-missing lab values not graded as 1 or higher. Grade 5 is not applicable. For laboratory tests that are graded for both low and high values, summaries will be done separately and labeled by direction, e.g., sodium will be summarized as hyponatremia and hypernatremia.

#### 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 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.

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

### Data analysis

On analyzing laboratory, data from all sources (central and local laboratories (as applicable)) will be combined. The summaries will include all assessments available for the lab parameter collected no later than 30 days after the last study treatment administration date (see Section 2.1.1).

All the outputs will be provided overall and by treatment phase (induction, consolidation and continuation).

The following summaries will be produced for hematology and biochemistry laboratory data (by laboratory parameter and treatment):

- For laboratory tests where grades are defined by CTCAE version 5.0, shift tables using CTC grades to compare baseline to the worst on-treatment value
- For laboratory tests where grades are not defined by CTCAE versoin 5.0, shift tables using the low/normal/high/(low and high) classification to compare baseline to the worst on-treatment value.

The following listings will be produced for the laboratory data:

- Listings of all laboratory data, with CTC grades and classification relative to the laboratory normal range. Lab data collected during the post-treatment period will be flagged.
- Listing of all CTC grade 3 or 4 laboratory toxicities

### Liver function parameters

Liver function parameters of interest are total bilirubin (TBL), ALT, AST and alkaline phosphatase (ALP).

The number (%) of patients with worst post-baseline values will be summarized:

- ALT or AST > 3xULN
- ALT or AST > 10xULN
- TBL > 2xULN
- TBL > 3xULN
- ALT or AST > 3xULN & TBL > 2xULN
- ALT or AST > 3xULN & TBL > 2xULN & ALP < 2xULN (potential Hy's law)

### Hematological toxicities and recovery

The following summary tables will be provided by cycle during induction and consolidation:

- Number and percentage of patients having at least one thrombocytopenia, and among them the duration of thrombocytopenia and the time between chemotherapy (cytarabine or daunorubicin) start and non-transfused recovery from thrombocytopenia (see definitions in

Section 2.1.1).

- Number and percentage of patients having at least one neutropenia, and among them the duration of neutropenia and the time between chemotherapy (cytarabine or daunorubicin) start and recovery from neutropenia (see definitions in Section 2.1.1).
- Number and percentage of patients requiring platelet transfusion.
- Number and percentage of patients requiring red blood cell transfusion.

All blood component transfusion data will be listed.

### 2.8.4 Other safety data

#### 2.8.4.1 ECG and cardiac imaging data

#### Data handling

The average of the ECG parameters at that assessment should be used in the analyses.

#### Data analysis

The number and percentage of subjects with notable ECG values collected during the on-treatment period will be presented by treatment arm.

- QT, 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 ≤ 60ms
  - Increase from Baseline of > 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
  - New value of > 200 ms
- QRS
  - Increase from baseline >25% and to a value > 120 ms
  - New values of QRS > 120 ms

A listing of all ECG assessments will be produced by treatment arm and notable values will be flagged. In the listing, the assessments collected during the post-treatment period will be flagged.

Summaries of grouped AEs ('QT prolongation') defined in eCRS will be provided by phase and treatment separately for all AEs, AEs suspectred to be related to study treatment and SAEs, and by treatment for AEs leading to study treatment discontinuation.

### 2.8.4.2 Vital signs

Vital sign assessments are performed in order to characterize basic body function. The following parameters were collected: height (cm), weight (kg), body temperature (°C), pulse rate (beats per minute), systolic and diastolic blood pressure (mmHg).

#### Data handling

Vital signs collected during on-treatment period will be summarized. Values measured outside of on treatment period will be flagged in the listings.

#### Data analysis

For analysis of vital signs the clinically notable vital sign criteria are provided in Table 2-5 below.

**Table 2-5 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 and increase from baseline of >=20 | <=90 and decrease from baseline of >=20 |
| Diastolic blood pressure (mmHg) | >=105 and increase from baseline of >=15 | <=50 and decrease from baseline of >=15 |
| Pulse rate (bpm) | >=100 and increase from baseline of >25% | <=50 and decrease from baseline of > 25% |
| Body temperature | >= 39.1 | - |

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

A listing of all vital sign assessments will be produced by treatment arm and notable values will be flagged. A separate listing of only the subjects with notable vital sign values will also be produced.

## 2.9 Pharmacokinetic endpoints

#### Exposure to the sum of active moieties

A further exposure variable will be derived to consider the contribution of the active metabolites to the total exposure of the compound.

The exposure to the sum of active moieties combines the concentration of the parent (PKC412) and the two active metabolites (CGP52421 and CGP62221) scaled based on their relative potencies, and parent to metabolite molecular weight ratio as shown below:

$$\text{PKC412+ CGP52421*}\ (0.06) * \frac{PKC412mwt}{CGP52421mwt} + \text{CGP62221*}\,(1.4) * \frac{PKC412mwt}{CGP62221mwt}$$

Where mwt is the molecular weight of each analyte is: PKC412=570.65, CGP52421=587.23, CGP62221=556.63.

The potencies of the active metabolites are different across indications.

### PK parameters

PK parameters for midostaurin and its two major metabolites CGP52421, CGP62221 will be determined using non-compartmental method(s) using Phoenix WinNonlin (Version 6.4 or later- Certara L.P.) for the patients who had full PK sampling on Cycle 1 Day 8 of the induction therapy. PK parameters listed in Table 2-6 will be estimated and reported, when feasible. AUClast, AUC0-t and Cmax are defined as primary parameters (contributing to PAS definition). All others are secondary and will be determined if feasible (including CL/F).

**Table 2-6 Non-compartmental PK parameters**

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

Descriptive statistics (n, arithmetic mean, CV% mean, standard deviation (SD), median, geometric mean, CV% geo-mean, minimum and maximum) will be presented by treatment for PAS-full for all PK parameters defined in Table 2-6 except Tmax, where only n, median, minimum and maximum will be presented.

All individual PK parameters will be listed using the PAS-all.

### Concentrations for full PK profile

Descriptive statistics (n, m (number of non-zero concentrations), arithmetic mean, CV% mean, SD, median, geometric mean, CV% geo-mean, minimum and maximum) for concentrations of midostaurin, its active metabolites (CGP52421, CGP62221), and the exposure to the sum of active moieties, will be presented at each scheduled time point on C1D8 for the PAS-full. PK parameters will also be summarized by analyte.Individual concentration-time profiles for midostaurin, its active metabolites, and the exposure to the sum of active moieties, concentrations on C1D8 with median will be displayed graphically for PAS-all on the semi-log view. In addition, the mean (+/- SD) and geometric mean concentration-time profiles for midostaurin, its active metabolites, and the exposure to the sum of active moieties, on C1D8 will be displayed graphically for PAS-full on the linear and semi-log view.

All individual plasma midostaurin, its active metabolites, and the exposure to the sum of active moieties concentration data will be listed for the PAS-all.

### Concentrations after multiple dosing

Descriptive statistics (n, m (number of non-zero concentrations), mean, CV% mean, SD, median, geometric mean, CV% geo-mean, minimum and maximum) for midostaurin. its active metabolites, and the exposure to the sum of active moieties, concentration will be presented at each scheduled time point (post-dose or pre-dose) by treatment part for the PAS-all.

The mean (+/- SD) and geometric mean trough concentration-time profiles for midostaurin, its active metabolites, and the exposure to the sum of active moieties, over time will be displayed graphically by treatment part for PAS-all on the linear view.

All individual plasma midostaurin, its active metabolites, and the exposure to the sum of active moieties, concentration data will be listed for the PAS-all.

### Handling of PK data below LLOQ or missing

All concentration values below the lower limit of quantitation (LLOQ) (<10.0 ng/mL) 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.

## 2.10 PD and PK/PD analyses

### Special population

The association of trough concentrations of midostaurin, its active metabolites, and the exposure to the sum of active moieties on C1D21 of Induction therapy, and FLT3 status will be investigated using a Wilcoxon test.

### Analysis of relationship between PKC412 exposure and efficacy/safety endpoints.

All exposure-response analyses will be conducted on parent midostaurin, its active metabolites, and the exposure to the sum of active moieties. PAS-all will be used however Part 1 patients will be excluded for efficacy related analyses.

EFS will be analysed using a Cox regression model with log-transformed concentration on C1D21 as covariate. Hazard ratios will be provided for a 2-fold decrease in exposure, along with 95% CI.

OS will be analysed using a Cox regression model with log-transformed concentration on C1D21 as covariate.

The occurrence of CR in cycle 1 or 2 of induction therapy will be modelled against log-transformed Cmin (continuous and categorical) of midostaurin and metabolites on C1D21 through a logistic regression model. Furthermore, the CR rate for the median observed Cmin C1D21 along with 95% CI, will be produced. Further the point estimate of the odds ratio of response for a 2-fold decrease in exposure, and corresponding 95% CI will also be produced.

AESIs suspected to be study drug related will be analysed with the last observed trough concentration collected prior to AE onset (log-transformed), with a logistic regression model. Probability of an AESI will be estimated along with 95% CI for the median concentration used in the analysis. Further point estimates of the difference in probability of response for a 2-fold increase in exposure, and corresponding 95% CI will also be produced. Time to onset of AESI will also be investigated with a Cox regression model, and HRs related to a 2-fold increase in exposure with corresponding 95% CIs will be produced.

AEs leading to discontinuation will also be analysed with log-transformed concentration (last observed trough concentration prior to AE onset) as for AESIs. PK/PD analyses related to AESI may not be performed if the number of AESI events are limited such as less than 10 events.

A linear mixed effects model will be used to fit the change from baseline in QTcF as a response variable, with time-matched concentration (of midostaurin and both metabolites), baseline parameter and relevant covariates (identified through backwards selection) fitted as fixed effects.

Time-matched QTcF assessments and concentrations are defined as both non-missing and non-zero concentrations. Assessments are taken within a 30 minute window of eachother. When there are multiple matching concentrations within a 30 minute window of the ECG assessment (or vice versa), the closest time match should be selected. When there is more than one closest match (before and after), then the PK sample should be after the ECG assessment.

Only observations where the ECG machine was synchronized will be considered. Subject ID will be fitted as a random effect. The change from baseline will be estimated (with 95% CI) for the median observed Peak Cmin at the therapeutic dose (50mg bid), the median of the observed values for each continuous covariate, and the level of the factor with higher observed frequency.

## 2.11 Patient-reported outcomes

The global health status/QoL score of the QLQ-C30 and PGIC score are identified as the primary PRO variables of interest. Physical functioning, emotional functioning and social functioning scale scores of the QLQ-C30 are identified as secondary PRO variables of interest. The FAS will be used for analyzing PRO data. Scoring of PRO data and methods for handling of missing items or missing assessments will be handled according to the scoring manual (see [study protocol Appendix 5]). No imputation procedures will be applied for missing items or missing assessments.

Descriptive statistics will be used to summarize the QLQ-C30 scores and absolute change from baseline scored scales by each scheduled timepoint and treament arm.

Between-treatment differences for the change in QLQ-C30 scores will be evaluated using a mixed effect repeated measures model. Treatment group, stratification factors (FLT3 mutation status and chemotherapy regimen), time of visit (in weeks counting from the time of randomization to the time of a particular post baseline measurement in time windows), treatment by time of visit interaction, and baseline score. An unstructured covariance structure will be assumed for the model. The differences in least square means between treatment and control group, and the corresponding 95% CI at selected timepoints will be presented.

The PGIC score will be presented as frequencies and percentages by scheduled timepoint and treatment arm.

## 2.12 Biomarkers

All [redacted] analyses other than baseline FLT3 mutational status and ELN 2017 AML risk classification will be reported in separate biomarker report with separate (stand-alone) analysis plan.

As a project standard, Novartis will analyze only biomarkers collected in the clinical database.

[redacted]

There may be circumstances whena decision is made to stop sample collection, or not perform or discontinue their analysis due to either practical or strategic reasons (e.g. issued related to the quality and/or quantity of the samples or issues related to the assay). Under such circumstances, the number of samples may be inadequate to perform a rigorous data analysis and the available data will only be listed and potentially summarized.

Additional analyses that may be performed after the completion of the end-of-study CSR will be documented in separate reports. These analyses may include but are not limited to the analysis of biomarkers generated from samples collected during the study but analyzed after the database lock and completion of the CSR. The data analysis will be described in an addendum of the SAP or in a stand-alone analysis plan document, as appropriate.

### 2.12.1 Biomarker analysis dataset

The FAS will be used for all biomarker analysis. Unless otherwise specified, all statistical analyses of biomarker data will be performed on patients with biomarker data.

The distribution of baseline clinical covariates in treatment arms, the demographic and disease characteristics of subjects with available biomarker data may be compared to those of the FAS.

[redacted]

### 2.12.3 List of biomarkers evaluated and the collection time points

The biomarkers evaluated in the study are listed in Table 2-7 below.

**Table 2-7 Sample biomarker summary table**

| Biomarker | Time point | Sample | Method |
|---|---|---|---|
| FLT3 mutation | Screening visit (eligibility) | Bone Marrow Aspirate<br>or<br>Peripheral Blood | PCR-CE |

[redacted]

### 2.12.4 General Data Handling and preprocessing

Data preprocessing and transformations are described in detail in the Programming Dataset Specification.

The screening assessment (pre-dose) will be used as the baseline value.

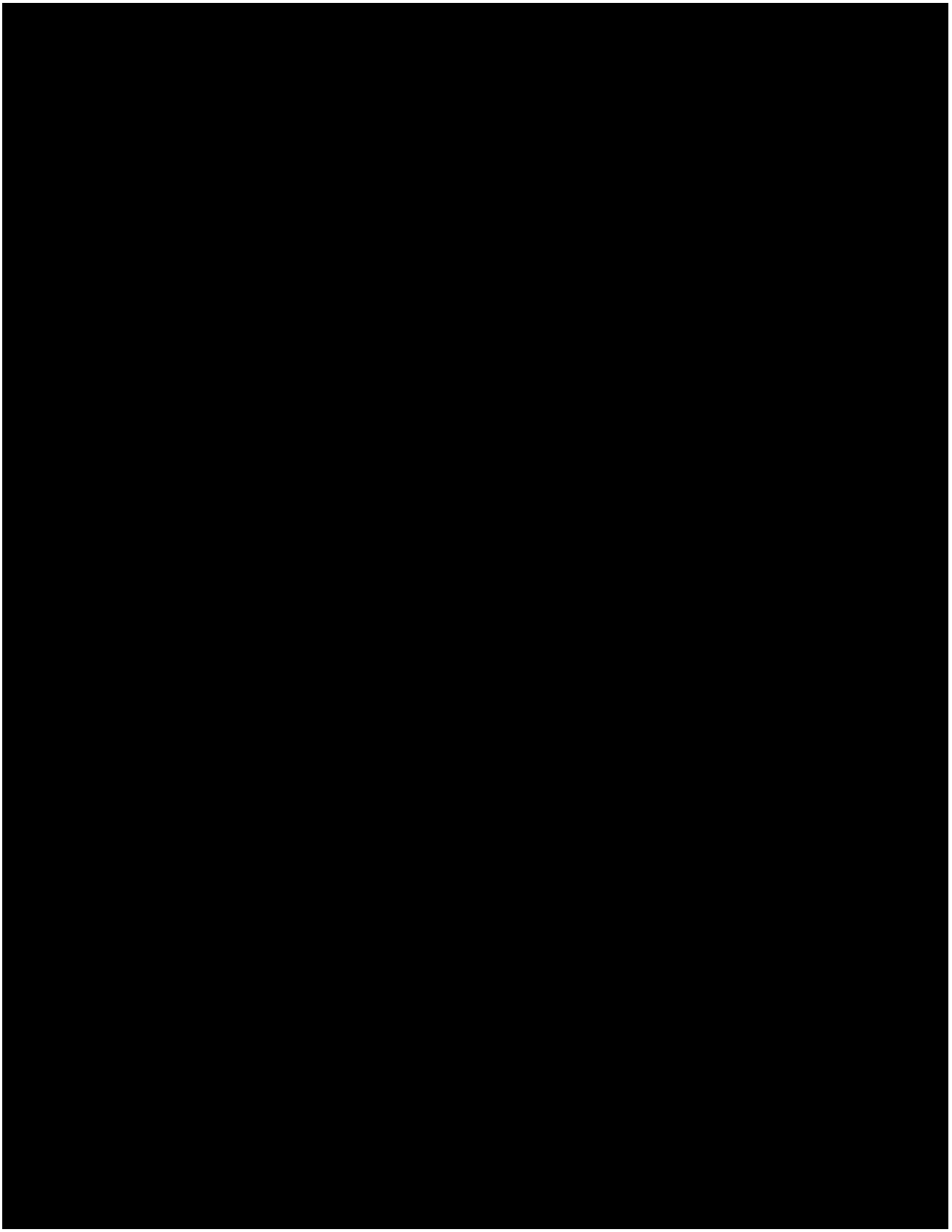
When more than one biomarker data value are available for a subject at any time point, the mean of the replicate values will be used for all statistical analyses.

Percent change is calculated as ((visit i – baseline) / baseline) * 100. To compute the average percent change from baseline is to compute the average expression level at each time point and then compute the percent change using the average values. Fold change is calculated as the ratio of biomarker value at ((visit i) / (Baseline biomarker value)). The number of subjects for the average of percent change from baseline might vary due to potential missing values at respective time points.

### 2.12.5 Data analysis

#### 2.12.5.1 FLT3 Mutation

FLT3 mutation will be identified by analysizing FLT3 gene for either an internal tandem duplication mutation (ITD) or a point mutation in the activating loop of the tyrosine kinase domain (TKD) at baseline. FLT3-ITD mutation will be stratified at ITD allelic ratio <0.7, ITD allelic ratio ≥ 0.7.



## 2.14 Interim analysis

For part 2, an interim analysis for efficacy will be conducted when 60 patients are randomized and at least 24 EFS events are documented (expected around 14 months from the date of first patient randomized in the study assuming the recruitment period as 14 months). In case that 36 EFS events are documented before randomization completion, the interim analysis can be skipped and Novartis will conduct primary analysis.

At the interim analysis, the study will be considered as a positive result when the following both success criteria are met:

- Criterion 1: estimated HR at interim analysis < 1.
- Criterion 2: the Bayesian predictive probability of (HR for EFS when 36 EFS events are documented < 1) given data up to the data cut off for interim analysis > 0.9. To calculate the predictive probability, assuming a weakly informative prior distribution derived from Study [A2301] data and the prior distribution will be updated using the available data from patients in the FAS at interim analysis (for more detail of weakly informative prior, refer to [study protocol Section 14.1]).

This interim analysis will be assessed by a DMC, however, even if interim success criteria are met, the study will be continuing blinded to patients, investigators and monitors until the primary analysis and thereafter unblinded. At the final analysis more mature data can be evaluated.

The interim analysis will be performed by an independent statistician and an independent programmer who provides the results to the DMC. The DMC will then be assessing the success criteria. Further details will be described in the DMC charter.

If Health Authorities require to submit the study results after interim analysis but before primary analysis, additional analysis may be performed.

The primary analysis will be performed using the pre-defined cut-off date of 30 November 2020 with the number of EFS events documented by this date. The end of study will occur at the latest 36 months after the start of the study treatment for the last patient. At this time, the final analysis will be performed.

For all of interim, primary and final analyses, the type I error alpha will not be considered because this study will pursue an estimation approach rather than formal hypothesis testing in which the criteria for success is based on the probability of HR< 1 in favor of midostaurin.

ISC will review all available safety data in the part 1 to evaluate whether the trial may advance to the part 2 in Japan. The analyses may be performed by a trial statistician internal to Novartis and their results will be provided to the Independent Safety Committee, when the available data is adequate to perform a data analysis. Details will be described in a separate SAP for the safety review.

# 3 Sample size calculation

## 3.1 Primary analysis

### Safety evaluation part (in Japan only)

A minimum of 3 (if no Safety Events) or 6 evaluable Japanese patients will be required to confirm the tolerability of midostaurin in combination with standard chemotherapy in the safety evaluation period. No formal statistical power calculations to determine sample size were performed for this study.

### Randomization part

This is a bridging study that will support the registration of midostaurin including in Japan. This study will pursue an estimation approach rather than formal hypothesis testing in which the criterion for success is based on the probability of HR< 1 in favor of midostaurin.

As per the initial protocol design (i.e. pre-Amendment 3), the required sample size for the part 2 of the study was determined based on the empirical probability to meet the success criterion. It was assumed that EFS for midostaurin and placebo in A2220 would follow the same survival distributions as observed in study A2301. Consequently all factors which might affect the EFS prolongation e.g., SCT rate in CR1 were also assumed to be the same as in Study A2301. It was also assumed that there was no difference between the two chemotherapy regimens (RATIFY regimen and JALSG regimen).

In order to calculate the probability to meet the success criterion, a simulation study was performed using actual EFS data from Study A2301. To simulate a study, 30 patient observations were randomly selected from each treatment arm of Study A2301 and 30000 studies were simulated. The, median EFS and HR for EFS were calculated for each study. The median EFS in the control arm averaged 5.4 months and in the midostaurin arm 10.3 months. The average hazard ratio was 0.77 (corresponding to a 23% reduction in the hazard rate for EFS), which was similar to estimated HR in Study A2301 of 0.728.

In addition to the above assumptions, assuming that enrollment will continue for approximately 15 months at a uniform rate of 4 patients a month and the primary analysis will occur when 36 EFS events are documented (expected 21 (95%CI: [14.4, 34.2]) months from date of first patient to be randomized), 60 patients will need to be randomized to the two treatment arms in 1:1 ratio to meet the success criterion with a probability of 84.1%.

In addition to the above simulation, another simulation was performed to calculate the probability of success at interim analysis. When the enrollment period will be 14 months considering the currently expected enrollment rate, the probability to meet success criteria at interim analysis (described in [study protocol Section 2.14]) is 78.1% and the time from first patient to be randomized to the interim analysis is expected to be 14.1 (2.5 - 97.5 percentile: [14.0 – 15.4]) months based on same survival distribution as in Study [A2301]. In addition, the conditional probability to meet the success criterion of primary analysis under showing positive result at interim analysis is 96.8%. For more details, please refer to [study protocol Section 14.1].

Based on the overall observed EFS events over time, the rate of discontinuations without EFS event and the predictions of future events, there is a risk that the targeted 36 EFS events will not be observed within a reasonable timeframe. Therefore the primary analysis will be performed using the pre-defined cut-off date of 30 November 2020 with the number of EFS events documented by this date.

As per the current number of patients who are still on follow-up for EFS and the survival distributions of EFS post-induction observed in study [A2301], additional 5 EFS events are expected to be observed until 30 November 2020. The study power would be approximately 82.7% when total 33 EFS events are observed under the original assumptions shown above (that is, EFS for midostaurin and placebo in A2220 would follow the same survival distributions as observed in study [A2301], consequently all factors which might affect the EFS prolongation e.g. SCT rate in CR1 were the same as in Study [A2301], and there was no difference between the two chemotherapy regimens).

## 3.2 Power for analysis of key secondary variables

Not applicable.

# 4 Change to protocol specified analyses

In section 2.11 (patient-reported outcomes), the primary PRO variables of interst of QLQ-C30 was changed from total score to the global health status/QoL score to revise to the correct variable.

[redacted]

# 5 Appendix

## 5.1 Imputation rules

### 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 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.AE, ConMeds and safety assessment date imputation

**Table 5-1 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<br>If stop date contains a full date and stop date is earlier than study treatment start date then set start date = 01JanYYYY<br>Else set start date = study treatment start date.<br>If available year > year of study treatment start date then 01JanYYYY<br>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<br>If stop date contains a full date and stop date is earlier than study treatment start date then set start date= 01MONYYYY.<br>Else set start date = study treatment start date.<br>If available month and year > month and year of study treatment start date then 01MONYYYY<br>If available month and year < month year of study treatment start date then 15MONYYYY |

**Table 5-2 Imputation of end dates (AE, CM)**

| Missing Element | Rule<br>(*=last treatment date plus 30 days not > (death date, cut-off date, withdrawl 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 * |

| Missing Element | Rule (*=last treatment date plus 30 days not > (death date, cut-off date, withdrawl of consent date)) |
|---|---|
| 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.

#### 5.1.1.1 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.

**Incomplete assessment dates for efficacy assessment**

If the date of assessment collected in the eCRF IWG Response page is incomplete but other relevant investigation dates (e.g., bone marrow aspirate, peripheral blood counts) are available, assessment date is calculated as the latest of all investigation dates (e.g., bone marrow aspirate, peripheral blood counts) if the overall response at that assessment is CR/CRp/PR (see [study protocol Section 7.2.1]). Otherwise – if overall response is treatment failure/relapse – the assessment date is calculated as the earliest date of all investigation dates at that evaluation. If all measurement dates have no day recorded, the 1st of the month is used. If the month is not completed, for any of the investigations, the respective assessment will be considered to be at the date which is exactly between previous and following assessment. If a previous and following assessment is not available, this assessment will not be used for any calculation.

**Applying the cut-off to efficacy assessment**

For efficacy related assessments, if an evaluation has some assessments done prior to cut-off date and others after the cut-off date, then the evaluation is considered post-cut-off date and will be excluded from analysis.

## 5.2 AEs coding/grading

Adverse events are coded using the Medical dictionary for regulatory activities (MedDRA) terminology.

AEs will be assessed according to the Common Terminology Criteria for Adverse Events (CTCAE) version 5.0.

The CTCAE represents a comprehensive grading system for reporting the acute and late effects of cancer treatments. CTCAE grading is by definition a 5-point scale generally corresponding to mild, moderate, severe, life threatening, and death. This grading system inherently places a value on the importance of an event, although there is not necessarily proportionality among grades (a grade 2 is not necessarily twice as bad as a grade 1).

## 5.3 Laboratory parameters derivations

Grade categorization of lab values will be assigned programmatically as per NCI Common Terminology Criteria for Adverse Events (CTCAE) version 5.0. The calculation of CTCAE grades will be based on the observed laboratory values only, clinical assessments will not be taken into account. The criteria to assign CTCAE grades are given in Novartis internal criteria for CTCAE grading of laboratory parameters. The latest available version of the document based on the underlying CTCAE version 5.0 at the time of analysis will be used. For laboratory tests where grades are not defined by CTCAE version 5.0, results will be graded by the low/normal/high (or other project-specific ranges, if more suitable) classifications based on laboratory normal ranges.

A severity grade of 0 will be assigned for all non-missing lab values not graded as 1 or higher. Grade 5 will not be used. For laboratory tests that are graded for both low and high values, summaries will be done separately and labelled by direction, e.g., sodium will be summarized as hyponatremia and hypernatremia.

### 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 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.

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

## 5.4 Statistical models

### 5.4.1 Analysis of time-to-event data

### Hazard ratio

Hazard ratio will be estimated by fitting the Cox proportional hazards model using SAS procedure PHREG (with TIES=EXACT option in the MODEL statement).

A stratified unadjusted Cox model will be, i.e. the MODEL statement will include the treatment group variable as the only covariate and the STRATA statement will include stratification variable(s).

Hazard ratio with two-sided 95% confidence interval will be based on Wald test.

### 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.

## 5.4.2 Analysis of Binary Data

### Confidence interval for response rate

Responses will be summarized in terms of percentage rates with $100(1-\alpha)\%$ confidence interval using exact binomial confidence interval (implemented using SAS procedure FREQ with EXACT statement for one-way table Clopper and Pearson 1934.

## 5.4.3 ELN 2017 risk stratification categories

Sub-classification of AML subjects will be categorized by using the ELN 2017 risk stratification categories Döhner 2017.

**Table 5-3 ELN 2017 risk stratification categories[a]**

| Risk Category[b] | Genetic Abnormality |
|---|---|
| Favorable | t(8;21)(q22;q22.1); *RUNX1-RUNX1T1* |
| | inv(16)(p13.1q22) or t(16;16)(p13.1;q22); *CBFB-MYH11* |
| | Mutated *NPM1* without *FLT3*-ITD or with *FLT3*-ITD$^{low(c)}$ |
| | Biallelic mutated *CEBPA* |
| Intermediate | Mutated *NPM1* and *FLT3*-ITD$^{high(c)}$ |
| | Wild type *NPM1* without *FLT3*-ITD or with *FLT3*-ITD$^{low(c)}$ (w/o adverse- risk genetic lesions) |
| | t(9;11)(p21.3;q23.3); *MLLT3-KMT2A*[d] |
| | Cytogenetic abnormalities not classified as favorable or adverse |
| Adverse | t(6;9)(p23;q34.1); *DEK-NUP214* |

| Risk Category[b] | Genetic Abnormality |
|---|---|
| | t(v;11q23.3); *KMT2A* rearranged |
| | t(9;22)(q34.1;q11.2); *BCR-ABL1* |
| | inv(3)(q21.3q26.2) or t(3;3)(q21.3;q26.2); *GATA2*,*MECOM(EVI1)* |
| | -5 or del(5q); -7; -17/abn(17p) |
| | Complex karyotype[e], monosomal karyotype[f] |
| | Wild type *NPM1* and *FLT3*-ITD$^{high(c)}$ |
| | Mutated *RUNX1*[g] |
| | Mutated *ASXL1*[g] |
| | Mutated *TP53*[h] |

a. Frequencies, response rates and outcome measures should be reported by risk category, and, if sufficient numbers are available, by specific genetic lesions indicated.

b. Prognostic impact of a marker is treatment-dependent and may change with new therapies.

c. Low, low allelic ratio (<0.5); high, high allelic ratio (≥0.5); semi-quantitative assessment of *FLT3*-ITD allelic ratio (using DNA fragment analysis) is determined as ratio of the area under the curve (AUC) "*FLT3*-ITD" divided by AUC "*FLT3*-wild type"; recent studies indicate that acute myeloid leukemia with *NPM1* mutation and *FLT3*-ITD low allelic ratio may also have a more favorable prognosis and patients should not routinely be assigned to allogeneic hematopoietic-cell transplantation.

d. The presence of t(9;11)(p21.3;q23.3) takes precedence over rare, concurrent adverse-risk gene mutations.

e. Three or more unrelated chromosome abnormalities in the absence of one of the World Health Organization-designated recurring translocations or inversions, i.e., t(8;21), inv(16) or t(16;16), t(9;11), t(v;11)(v;q23.3), t(6;9), inv(3) or t(3;3); AML with *BCR-ABL1*.

f. Defined by the presence of one single monosomy (excluding loss of X or Y) in association with at least one additional monosomy or structural chromosome abnormality (excluding core-binding factor AML).

g. These markers should not be used as an adverse prognostic marker if they co-occur with favorable-risk AML subtypes.

h. *TP53* mutations are significantly associated with AML with complex and monosomal karyotype.

# 6 Reference

1. Brookmeyer R and Crowley J (1982). A Confidence Interval for the Median Survival Time. Biometrics, 38, 29 - 41.
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4. Collett D (1994). Modelling survival data in medical research. London, Chapman & Hall.
5. Döhner H, Estey E, Grimwade D, et al (2017) Diagnosis and management of AML in adults: 2017 ELN recommendations from an international expert panel. Blood;129(4):424-447.