NOVARTIS

Clinical Development

Midostaurin/PKC412

Oncology Clinical Protocol 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)

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List of abbreviations

Advanced SM	Advanced systemic mastocytosis
AE	Adverse Event
AESI	Adverse event of special interest
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
AML	Acute myeloid leukemia
ANC	Absolute Neutrophil Count
APL	acute promyelocytic leukemia
ASM	Aggressive systemic mastocytosis
AST	Aspartate aminotransferase
ATC	Anatomical Therapeutic Chemical
AUC	Area under the curve
AUCinf	Area under the curve from time 0 to infinite
AUClast	Area under the curve from time zero to the last measurable concentration sampling time after the first dose (tlast)
AUC0-t	Area under the curve from time zero to a measurable concentration sampling time (t)
BCRP	breast cancer resistant protein
BCS	Biopharmaceutics classification system
bid	bis in diem/twice a day
BMA	bone marrow aspirate
BR	Blast reduction
BSA	Body Surface Area
CABG	Coronary artery bypass graft
CALGB	Cancer and Leukemia Group B
CIR	Cumulative incidence of relapse
CIVI	Continuous intravenous infusion
CL/F	mean apparent plasma clearance
Cmax	maximum plasma concentration
CMO&PS	Chief Medical Office and Patient Safety
CMV	Cytomegalovirus
CNS	Central Nervous System
CR	Complete remission
CRF	Case Report Form
CRO	Contract Research Organization
CRp	Morphologic complete remission with incomplete platelet count recovery
CSF	Cerebrospinal fluid
CSP	Clinical study protocol
CSR	Clinical study report
CTCAE	Common Terminology Criteria for Adverse Events
CYP	cytochrome P450
CYP3A4	Cytochrome P450 3A4 enzyme
DFS	Disease-free survival
DILI	Drug-induced liver injury
DMC	Data Monitoring Committee
EBV	Epstein-Barr Virus
ECG	Electrocardiogram

ECHO	Echocardiogram
ECOG PS	Eastern Cooperative Oncology Group Performance Status
eCRF	Electronic Case Report/Record Form; the term CRF can be applied to either EDC or Paper
EDD	Expected Delivery Date
EFS	Event-free survival
ELN	European LeukemiaNet
EORTC	European Organisation for the Research and Treatment of Cancer
EOT	End of Treatment
FAS	Full analysis set
FDA	Food and Drug Administration
FGFR	Fibroblast Growth Factor Receptor
FLT3	FMS-like tyrosine kinase receptor-3
GGT	Gamma-glutamyltransferase
GI	Gastrointestinal
HiDAC	High-dose cytarabine
HIV	Human Immunodeficiency Virus
HR	Hazard Ratio
HSV	Herpes simplex virus
I.V	Intravenous(ly)
IB	Investigator's Brochure
ICF	Informed Consent Form
ICH	International Conference on Harmonization
IEC	Independent Ethics Committee
ILD	Interstitial Lung disease
INR	International Normalized Ratio
IRB	Institutional Review Board
IRT	Interactive Response Technology that includes Interactive Voice Response System and Interactive Web Response System
ITD	Internal Tandem duplication
ITT	Intent-to-treat
JALSG	Japan Adult Leukemia Study Group
LFT	Liver function tests
LVEF	Left Ventricular Ejection Fraction
MCL	Mast cell leukemia
MDS	Myelodysplastic Syndrome
MI	Myocardial infarction
MR	Minor Response
[redacted]	[redacted]
MUGA	Multigated Acquisition Scan
NCA	Non-compartmental Analysis
NCCN	National Comprehensive Cancer Network
NGS	Next generation sequencing
NOEL	no observable effect level
OATP1B1	Organic Anion Transporting Polypeptide 1B1
OS	Overall Survival
p.o.	per os/by mouth/orally
PAS	Pharmacokinetic Analysis Set

[redacted]

PD	Pharmacodynamic
PGIC	Patient Global Impression of Change
P-gp	P-glycoprotein
PHI	Protected Health Information
[redacted]	[redacted]
PK	Pharmacokinetic(s)
popPK	Population pharmacokinetics
PPS	Per-Protocol Set
PR	Partial remission
PRO	Patient reported outcome
PT	Prothrombin time
QLQ	Quality of Life Questionnaire
QT/QTcF	QT interval/QT interval corrected with Fridericia's formula
RATIFY	Randomized AML Trial In FLT3+ patients <60 Years old
REB	Research Ethics Board
RoW	Rest of World
RT	Radiotherapy
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SCT	Hematopoietic Stem Cell Transplantation
SM	Systemic Mastocytosis
TBIL	Total bilirubin
TdP	Torsades de Pointes
TKD	Tyrosine Kinase Domain
ULN	Upper limit of normal
US	United States
VEGFR	Vascular endothelial growth factor receptor
WBC	white blood cell(s)
WHO	World Health Organization
WT	Wild Type

[redacted]

Glossary of terms

Assessment	A procedure used to generate data required by the study
Biologic Samples	A biological specimen including, for example, bone marrow, blood, plasma, serum, saliva, tissue, urine, stool, etc. taken from a study subject or study patient
Cycles	Number and timing or recommended repetitions of therapy are usually expressed as number of days (e.g.q28 days)
Enrollment	Point/time of patient entry into the study; the point at which informed consent must be obtained (i.e. prior to starting any of the procedures described in the protocol)
Investigational drug	The study treatment whose properties are being tested in the study; this definition is consistent with US CFR 21 Section 312.3 and is synonymous with “investigational new drug”
Investigational treatment	Drug whose properties are being tested in the study as well as their associated placebo and active treatment controls (when applicable). This also includes approved drugs used outside of their indication/approved dosage, or that are tested in a fixed combination. Investigational treatment generally does not include other study treatments administered as concomitant background therapy required or allowed by the protocol when used in within approved indication/dosage
Medication number	A unique identifier on the label of each study treatment package which is linked to one of the treatment arms of a study
Other study treatment	Any drug administered to the patient as part of the required study procedures that was not included in the investigational treatment
Personal data	Subject information collected by the Investigator that is transferred to Novartis for the purpose of the clinical trial. This data includes subject identifier information, study information and biological samples.
Phase	A subdivision of the study timeline; divides stages into smaller functional segments such as screening, treatment phase, follow up
Randomization number	A unique treatment identification code assigned to each randomized patient, corresponding to a specific treatment arm assignment
Subject Number	A unique identifying number assigned to each patient/subject/healthy volunteer who enrolls in the study
Stage related to study timeline	A major subdivision of the study timeline; begins and ends with major study milestones such as enrollment, randomization, completion of treatment, etc.
Stop study participation	Point/time at which the patient came in for a final evaluation visit or when study treatment was discontinued whichever is later
Study treatment	Includes any drug or combination of drugs in any study arm administered to the patient (subject) as part of the required study procedures, including placebo and active drug run-ins. In specific examples, it is important to judge investigational treatment component relationship relative to a study treatment combination; study treatment in this case refers to the investigational and non-investigational treatments in combination
Study treatment discontinuation	Point/time when patient permanently stops taking study treatment for any reason
Treatment group	A treatment group defines the dose and regimen or the combination
Variable	Identifier used in the data analysis; derived directly or indirectly from data collected using specified assessments at specified timepoints
Withdrawal of study consent	Withdrawal of consent occurs only when a patient does not want to participate in the study any longer, does not want any further visits or assessments, and does not allow any further collection of personal data

[redacted]

Amendment 3 (10-Sep-2020)

Amendment rationale

This is a global protocol amendment.

As of 21 November 2019, the study fully completed enrollment and 62 patients have been randomized in part 2 of the study. As of 9 September 2020, 28 EFS events have been documented, and 20 patients are still in follow-up for EFS.

The primary analysis of the study was planned to be conducted when at least 36 EFS events were observed which was assumed to take place 21 months after the first patient was randomized in November 2018. Considering the actual enrollment curve, the EFS accumulation curve until the time of this protocol amendment, and the rate of discontinuations without EFS event, a delayed occurrence of additional EFS events is expected and therefore a substantial longer follow-up than originally planned is needed to document at least 36 EFS events (expected cut-off is end of 2021 instead of August 2020 as originally anticipated).

Therefore, the present protocol amendment indicates now that 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. Based on current situation and assumption which has been used in protocol section 10.8, 33 EFS events in total are anticipated (5 additional EFS events expected) until 30 November 2020. Of note, we have observed only 2 EFS events (in 5 months) after 9 April 2020. The minimum follow-up period for all patients who are in follow-up for EFS will be at least 12 months (from last patient randomized from November 2019 to November 2020). The end of study will occur at the latest 36 months after the start of the study treatment for the last patient (anticipated as November 2022). At this time, the final analysis will be performed and the final CSR be written.

Changes to specific sections of the protocol are shown in the track changes version of the protocol using strike through red font for deletions and red underline for insertions.

Changes to protocol:

- Protocol summary, section 10, section 10.7 and section 10.8: revised the primary analysis to “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”.
- Section 4.3: removed the timing of the primary analysis.
- Section 4.3, section 10, and section 10.7: revised the timing of the end of study/final analysis to “The end of study will occur at the latest 36 months after the start of the study treatment for the last patient.”
- Protocol summary, section 4.2, section 10.4.2 and section 10.7: clarified that “the study will be continuing blinded to patients, investigators and monitors until the primary analysis and thereafter the study will be unblinded. At the final analysis more mature data can be evaluated”.
- Section 6.5.3: “at the time of the interim analysis (see Section 10.7)” and “at the time of the conclusion of the study” replaced by “at the time of the primary analysis (see Section 10.7)”. “prior to the study conclusion” removed.

[redacted]

- Section 10.8: removed “as well as Hong Kong, Korea, Russia and Taiwan”. “As per the initial protocol design (i.e. pre-Amendment 3)” added.
- Section 10.8: added the rationale to revise the timing of the primary analysis, expected additional EFS observed until the cut-off for the primary analysis and the study power under the original assumptions.

IRBs/IECs

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

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

[redacted]

Amendment 02 (25-Mar-2019)

Amendment rationale

Status of the study: At the time of this protocol amendment, part 1 conducted only in Japan is completed and 15 patients are randomized in part 2.

In order to detect earlier if the efficacy success criterion for EFS is met, an interim analysis is now introduced. Therefore additional text is added in the statistical section to indicate that an interim analysis for efficacy is to be conducted when 60 patients are randomized and at least 24 EFS events are documented. This interim analysis will be assessed by a DMC, however, even if interim success criteria are met, the study will be continuing until the final (primary) analysis at which more mature data can be evaluated and more precise estimates obtained. In case that 36 EFS events are documented before randomization completion, the interim analysis can be skipped and Novartis will conduct primary analysis as initially planned. Integrity of the study will not be compromised. Blinding of the study personnel, investigators and patients will be unequivocally maintained and a DMC is established for performing this interim analysis. At interim analysis, unblinding of study drug assignment will only occur when success criteria for interim analysis are met.

BMA is required to establish AML diagnosis in this protocol. However, in rare cases it is not possible to obtain bone marrow (dry tap). In case of failure to get bone marrow on attempted BMA, it is recommended to perform a bone marrow biopsy (Döhner 2017). Furthermore, the presence of ≥20% blasts in the bone marrow or peripheral blood is sufficient for confirming AML diagnosis (Arber et al 2016, Döhner 2017). These are the reason why the protocol is modified to indicate that in case of documented dry tap at study entry, a bone marrow biopsy has to be performed for confirming AML diagnosis. Moreover, as the results of a biopsy may take several days and may delay initiation of AML treatment, AML diagnosis based on peripheral blood showing ≥ 20% blasts will be accepted.

Exclusion criterion relating to chest X-ray at screening has been modified to specify that patients with a treated lung infection which is controlled by treatment are eligible. Lung infection is frequent in AML patients during the course of the disease; this intercurrent condition is usually controlled by adequate treatment and is compatible with AML treatment.

Concomitant therapy section has been updated to clarify management of permitted therapies requiring caution and/or action.

[redacted]

The management of patients who are confirmed as FLT3<0 or undeterminate before D8 of Induction Cycle 1 was clarified (End of Treatment (EoT) and Safety Follow-up visit).

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

Changes to the protocol

- Protocol summary: Exclusion criteria 7 and 11 updated. Data analysis updated for adding description of interim analysis

[redacted]

[redacted]

- Section 4.1.2: clarification for timepoint of 30 days safety follow-up visit: midostaurin/placebo replaced with study treatment; their regimen may not be switched during the course of the study: “may” replaced with “must”
- Figure 4-2 updated: clarification for patients not randomized due to FLT3<0 or unknown who should have EoT and Safety follow-up visit.
- Section 4.1.2.1: clarification added for patients who can’t have BMA (dry tap) for diagnosis.
- Section 4.1.2.2: Induction therapy: Patients not achieving CR after induction 2 will discontinue study treatment and will be followed in survival follow-up: addition of “and in safety follow up”.
- Section 4.2: ‘No interim efficacy analysis will be conducted’ removed and description of interim analysis added to comply with program
- Section 5.3: exclusion criteria #7 was updated to align with PKC412E2301 study
- Section 5.3: exclusion criteria #11 was modified; addition of “or a lung infection which is controlled by treatment”
- Section 6.1: management of patient not shown to have a qualifying FLT3 activating mutation clarified: discontinuation of study updated to discontinuation of treatment
- Section 6.1.1.1. JALSG Remission Induction. Addition of “More details are enclosed within the Investigator Brochure please refer to it”
- Table 6-2: updated for clarity
- Section 6.3.3: clarification for timepoint of 30 days safety follow-up visit: midostaurin/placebo replaced with study treatment
- Sections 6.4.2: addition of section related to “concomitant administration of drugs with a “known”, “possible” or “conditional” risk of Torsades de Pointes “
- Section 6.4.3: removal of section related to “concomitant administration of drugs with a “known”, “possible” or “conditional” risk of Torsades de Pointes “”
- Section 6.5.1: The IRT must be notified within 2 days that the patient was not randomized. Addition of “ by using appropriate form”.
- Section 6.5.3: description of independent statistician/programmer and unblinding condition added
- Table 7-1: addition of EOT assessments for FLT3<0 patients
- Table 7-1: Investigator assessment of Disease Response: “induction 1” removed for alignment with section 7.2.1
- Section 7.1.2: Addition of instructions for patients who have biopsy for diagnosis (if dry tap for BMA). Clarification added regarding repetition of laboratories assessments during screening period.
- Section 7.1.2.2: clarification added for patients who failed to be randomized. Addition of EOT and safety follow-up visits and information for patients who will move to PKC412E2301 study.

[redacted]

- Section 7.1.9: clarification on when should be done the safety follow-up visit: 30 days after the last dose of ... "midosaturin/placebo" replaced with "study treatment"
- Section 8.8: section related to DMC added
- Section 10: description of interim analysis added
- Section 10.4.1: clarified what analysis set used for all (interim, primary and final) efficacy analyses for part 2
- Section 10.4.2: description of interim analysis added
- Section 10.4.2: change wording 'sensitivity' to 'supportive'
- Section 10.7: 'No interim efficacy analysis is planned in this study.' removed and description of interim analysis added
- Section 10.8: description of interim analysis added and the simulation results with interim analysis added
- Section 14.1: description of operating characteristics for interim analysis added
- Section 14.2: updated to reflect changes in sections 6.4.2 and 6.4.3

IRBs/IECs

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

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

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

Amendment 01 (13-Aug-2018)

Amendment rationale

Status of the study: At the time of this protocol amendment, 6 patients are enrolled in the protocol, part 1 (1 screen failure, 1 discontinuation due to CR not achieved and 4 on treatment and 1 patient enrolled in part 2 (screen failure due to FLT3 negative).

Increase of age limit in inclusion criteria is implemented because international treatment guidelines for AML increasingly recommend that standard induction and consolidation chemotherapy be considered on the basis of patient tolerability as assessed by the treating physician and not chronological age. Additionally, clinical experience with midostaurin is increasingly established in older patients. Safety and tolerability is further assured on the basis of an interim clinical study report (CSR) for study ADE02T, an investigator initiated study in which FLT3-mutated patients ≤70 were treated with midostaurin combined with standard induction and consolidation chemotherapy followed by midostaurin monotherapy.Suitability to intensive chemotherapy is to be confirmed by the investigator, and a specific inclusion criterion has been added.

Addition of low-dose cytarabine as treatment allowed for cytoreduction prior to induction treatment is implemented to comply with Asian standard medical practice.

Procedures in relation to diagnosis confirmed by BMA, FLT3 testing, [redacted] during screening period is clarified and updated.

Timeframe for BMA is extended at the end of induction cycle (s) to comply with local standard medical practice and avoid additional BMA, which represents an invasive procedure for patients.

CR determination is an examination routinely done and there are a limited number of investigational sites in this Phase II study. This is why CR central review will not be performed for the study and all the related sections are modified accordingly. However, for CR documented, the sites are requested to store the relevant slides.

Changes in dose modifications guidelines are implemented for more clarity.

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

Changes to the protocol

Changes to specific sections of the protocol are shown in the track changes version of the protocol using strike through red font for deletions and red underline for insertions.

Minor typos and grammatical errors were updated throughout the protocol.

- Title and throughout the document: removed location specific information
- Throughout the document: updated wording related to data collection, Case Report Form (CRF) to align with evolving CRF standards, updated Common Terminology Criteria for Adverse Events (CTCAE) version (Version 4.03 replaced with Version 5.0)
- List of abbreviations: updated for completeness
- Glossary of terms: Updated ‘Personal data’ and ‘withdrawal of consent’ to coincide with new template.

[redacted]

- Section 1.2.1.1: Pharmacokinetics and drug metabolism: “in animals” removed in the title and section updated
- Section 1.2.1.1: pre-clinical toxicity: fertility section updated
- Section 1.2.1.2: Pharmacokinetics and drug metabolism in humans section updated
- Section 2.5: rationale for age of enrolled patients changed
- Section 4.1.2: Figure 4-2 updated to reflect clarification on diagnosis confirmed during screening period and age
- Section 4.1.2.1: screening phase updated for clarity
- Section 4.1.2.2: induction therapy: post-treatment follow up replaced with survival follow up to align with Figure 4-2
- Section 4.1.2.2: continuation therapy: guidance related to acute toxicity removed for clarity since all dose modifications are detailed in table 6-2
- Section 5.2: inclusion criterion #1 : addition of reference
- Section 5.2: inclusion criterion #3 modified
- Section 5.2: inclusion criterion #5 aligned with study E2301
- Section 5.2: inclusion criterion #7 added, suitability for intensive chemotherapy
- Section 5.3: exclusion criterion #8: low-dose cytarabine and other supportive therapy added to align with study E2301
- Section 5.3: exclusion criterion #17: barrier method of contraception language aligned with Investigator’s Brochure (IB)
- Section 6.1.1: dosing regimen: supply of chemotherapy updated
- Sections 6.1.1.1 and 6.1.1.2: Remission induction and second Remission induction: response assessment removed from those sections to avoid redundancy
- Section 6.1.1.3: continuation therapy: number of cycles requested during consolidation for RATIFY regimen clarified
- Section 6.3.1: table 6-2: dose modifications clarified when recommended or mandatory
- Section 6.4 and Appendix 2: permitted concomitant therapy, permitted requiring caution and prohibited concomitant therapy sections updated to align with program
- Section 6.5.3: treatment blinding: information related to central review removed
- Section 6.6.1: supply of chemotherapy updated
- Section 6.6.2 and Table 6-4: supply of chemotherapy updated
- Section 7.1: table 7-1: total bilirubin clarified, “D” removed and replaced with “S” for pregnancy test and for other hepatic tests, timeframe for BMA during induction changed (from D21 to D28), biopsy added for disease assessment, [redacted] cytogenetic data removed after screening and concomitant medication capture removed for patients in follow-up.

[redacted]

- Section 7.1.2.2: FLT3 data collection added for screen failures and addition of "until Day 8 of 1st cycle of induction" for information collected for patients who failed to be randomized
- [redacted]
- Section 7.1.6: withdrawal of consent updated to align with new template
- Section 7. 2.1: addition of biopsy requested if dry tap, information related to CR review changed (slides kept at site), addition of description of response assessment for induction cycles 1 and 2, [redacted]
- Section 7.2.2.1: Physical exam definition clarified
- Section 7.2.2.5, table 7-3: sediment analysis replaced with microscopic analysis for consistency with table 7-1
- Section 7.2.2.5.4 urinalysis: "specific gravity, blood, bilirubin, ketones and WBC" removed
- Section 7.2.2.5.5 Fertility information updated
- Section 7.2.3: PK analysis updated for clarity
- Table 7-5: window/period added for PK sample collection Day 8 and total volume added
- Table 7-6: clarification on the collection of BMA or (not and) blood for FLT3 and timepoint for BMA at Day21 extended until Day 28.
- Section 8.1.1: Updated AE outcome categories and relationship to study treatment updated to reflect CRF
- Section 10.5.3.5: subgroup analysis by country is removed and addition of "details of analysis described in the SAP if appropriate"
- Sections 10.4.4 and 10.5.2.3: analysis related to CR review removed
- Section 10.5.4 and Table 10-2: pharmacokinetics updated
- Section 13: references changed to reflect updates in rational sections
- Section 14.5 appendix 5: replacement of page 6

IRBs/IECs

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

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

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

[redacted]

Protocol summary

Title	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)
Brief title	A study of midostaurin efficacy and safety in newly diagnosed patients with FMS-like tyrosine kinase receptor-3 (FLT3)-mutated AML
Sponsor and Clinical Phase	Novartis, Phase II
Investigation type	Drug
Study type	Interventional
Purpose and rationale	● The purpose of this study is to obtain clinical data, comparable to those obtained in study [CPKC412A2301], from patients of variable ethnicity located in regions that did not participate in [CPKC412A2301]. This study will evaluate the efficacy and safety of 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). ● In Japan, an open-label safety evaluation part (Part 1) will be conducted in this population to evaluate the safety and tolerability of midostaurin in combination with standard chemotherapy in Japanese patients. This part will be conducted prior to participation of Japanese patients in the randomized part (below). ● A randomized part (Part 2) will be conducted to evaluate the efficacy and safety of midostaurin versus placebo in combination with standard chemotherapy in this patient population.
Primary Objective(s) and Key Secondary Objective	**Primary Objective:** ● Safety evaluation part (Part 1): 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. ● Randomized part (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. **Key Secondary Objective:** not applicable
Secondary Objectives	Randomized part (Part 2): Objective 1: Determine the overall survival (OS) in the two treatment groups Objective 2: Determine the rate of complete remission (CR) in the two treatment groups Objective 3: Determine the cumulative incidence of relapse (CIR) in the two treatment groups Objective 4: Evaluate the safety of midostaurin compared to placebo in combination with chemotherapy and as single agent continuation therapy Objective 5: Evaluate the pharmacokinetics (PK) of midostaurin and its two major metabolites CGP62221 and CGP52421 Objective 6: Determine the effect of study treatment on quality of life

[redacted]

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 begin 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. In Part 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). In part 2, patients will be enrolled only if they are confirmed in a Novartis-designated central laboratory to have FLT3-mutated AML. In Part 1, 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. This interval will allow for an assessment of the safety of midostaurin with chemotherapy throughout induction and will provide also an assessment of safety events after consolidation therapy with high-dose cytarabine. Part 2 will comprise three phases: ● Screening phase: written informed consent will be collected, and all eligibility criteria including diagnosis will be verified (up to 7 days) ● Treatment phase: patients will begin induction chemotherapy (daunorubicin and cytarabine) from Day 1 to Day 7. If the FLT3 mutation status is confirmed, then patients will be randomized on Day 8 to receive either midostaurin 50 mg bid or placebo 50 mg bid until Day 21. If a patient is shown to have achieved a CR after the first cycle of induction therapy, the patient will begin consolidation therapy; if the patient does not achieve a CR, a second cycle of induction therapy identical to that of the first cycle will be administered. Patients who do not achieve a CR after one or two cycles of induction therapy will be removed from study treatment. Patients who achieve a CR after induction therapy will proceed to consolidation therapy with high-dose cytarabine (3 or 4 cycles) with sequential midostaurin or placebo (Days 8 through 21 of each cycle) as assigned. Patients with a continued remission after consolidation therapy will receive midostaurin or placebo as a single agent continuation therapy for 12 cycles (D1 through D28 of each cycle). 60 patients will be randomized into Part 2. Randomization will be stratified according to FLT3 mutation status (FLT3- Internal Tandem duplication (ITD) low, FLT3-ITD high, FLT3-TKD) and according to the chemotherapy regimen (RATIFY or JALSG). Patients will continue study treatment until disease persistence or relapse (designated as Progressive Disease in the electronic Case Report Form (eCRF)) as assessed by Cheson criteria, intolerable toxicity, and withdrawal of consent, death, or discontinuation from the study treatment for any other reason, whichever is earlier. Regardless of the reason for treatment discontinuation (except death), all patients will be followed for safety for 30 days after the last dose of study treatment. ● Follow-up phase: following treatment discontinuation, patients who are alive will be followed for relapse (if not already demonstrated) and survival.
Population	Part 1: Safety evaluation part in Japan (minimum of three patients) ● Adult patients ≤ 70 years with newly diagnosed FLT3-mutated or FLT3-WT AML. Part 2: Double blind, randomized, placebo controlled (60 patients) ● Adult patients ≤ 70 years with newly diagnosed FLT3-mutated AML

[redacted]

Inclusion criteria	Patients eligible for inclusion in this study must meet **all** of the following eligibility criteria: 1. Diagnosis of AML (≥ 20% blasts in the bone marrow based on **WHO 2016 classification**). Patients with APL (acute promyelocytic leukemia) with PML-RARA are not eligible 2. Documented presence of an ITD and/or TKD activating mutation in the FLT3 gene, as determined by analysis in a Novartis designated laboratory An exception will be patients who are enrolled into the part 1 in Japan, who may be treated with midostaurin irrespective of AML FLT3 genotype 3. Age ≥ 18 years, ≤ 70 years of age 4. AML patients with a history of antecedent myelodysplasia (MDS) remain eligible for treatment on this trial but must not have received prior cytotoxic therapy (e.g., azacytidine or decitabine) 5. Patients must meet the following laboratory value criteria that indicate adequate organ function at the screening visit: • Estimated (by Cockcroft-Gault) creatinine clearance ≥ 30 ml/min • Total bilirubin ≤ 1.5 x ULN, except in the setting of isolated Gilbert syndrome • Aspartate transaminase (AST) ≤ 3.0 x ULN • Alanine transaminase (ALT) ≤ 3.0 x ULN 6. Written informed consent must be obtained prior to any screening procedures. For patients in Japan less than 20 years of age, written consent is required from the patient as well as from their legal representative. 7. Suitability for intensive chemotherapy in the judgment of the investigator
Exclusion criteria	Patients eligible for this study must not meet any of the following criteria: 1. Neurologic symptoms suggestive of CNS leukemia unless CNS leukemia has been excluded by a lumbar puncture. Patients with CSF fluid positive for AML blasts are not eligible 2. Developed therapy-related AML after prior radiotherapy (RT) or chemotherapy for another cancer or disorder 3. Isolated extramedullary leukemia (please refer to Section 7.2.2.1) 4. Known hypersensitivity to midostaurin, cytarabine or daunorubicin or to any of the excipients of midostaurin/placebo, cytarabine or daunorubicin 5. Any investigational agent within 30 days or 5 half-lives, whichever is greater, prior to Day 1. An investigational agent is defined as an agent with no approved medical use in adults or in pediatric patients 6. Prior treatment with a FLT3 inhibitor (e.g., midostaurin, quizartinib, sorafenib) 7. Patients who take strong CYP3A4/5 enzyme inducing drugs or strong CYP3A4/5 enzyme inducing herbal supplements (see Appendix 2) unless they can be discontinued or replaced prior to enrollment. 8. Prior chemotherapy for leukemia or myelodysplasia. However, the following prior therapies are allowed: a. Emergency leukapheresis b. Emergency treatment for hyperleukocytosis with hydroxyurea or low-dose cytarabine for ≤ 7 days c. Cranial radiotherapy (RT) for central nervous system (CNS) leukostasis (one dose only) d. Hematopoietic growth factor/cytokine support; other supportive therapy including antibiotics at the discretion of the investigator 9. Any surgical procedure, excluding central venous catheter placement or other minor procedures (e.g., skin or bone marrow biopsy) within 14 days prior to Day 1

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	10. Any other known disease or concurrent severe and/or uncontrolled medical condition (e.g., cardiovascular disease including congestive heart failure or active uncontrolled infection) that could compromise participation in the study 11. Abnormal chest X-ray unless the abnormality represents a non-active, or non-clinically significant finding, such as scarring or a lung infection which is controlled by treatment. 12. Known impairment of gastrointestinal (GI) function or GI disease that might alter significantly the absorption of midostaurin13. Known confirmed diagnosis of human immunodeficiency virus (HIV) 14. Evidence of active HBV or HCV viral infection (confirmed by peripheral blood viral load). Patients with positive serology results indicative of high risk for viral reactivation must have negative viral load results within 28 days prior to Day 1 15. Cardiac or cardiac repolarization abnormality, including any of the following: ● History of myocardial infarction (MI), angina pectoris, coronary artery bypass graft (CABG) within 6 months prior to Day 1 ● Clinically significant cardiac arrhythmias (e.g., ventricular tachycardia), complete left bundle branch block, high-grade AV block (e.g., bifascicular block, Mobitz type II and third degree AV block) ● Uncontrolled congestive heart failure ● Left ventricular ejection fraction of <50% ● Poorly controlled hypertension ● QT interval corrected with Fridericia's formula (QTcF) at screening > 470 ms ● Long QT syndrome, family history of idiopathic sudden death or congenital long QT syndrome, or any of the following: • Risk factors for torsades de pointe (TdP) including uncorrected hypokalemia or hypomagnesemia, history of cardiac failure, or history of clinically significant/symptomatic bradycardia • Concomitant medication(s) with a known risk of Torsades de Pointes that cannot be discontinued or replaced safely with an alternative medication • Inability to determine the QTcF interval 16. Pregnant or nursing (lactating) women 17. Women of child-bearing potential, unless they are using highly effective methods of contraception during dosing and for 4 months after stopping medication 18. Sexually active males unless they use a condom during intercourse while taking the drug during treatment and for 4 months after stopping treatment and should not father a child in this period
Investigational and reference therapy	**Part 1**: Midostaurin in sequential combination with daunorubicin and cytarabine induction, in sequential combination with high dose cytarabine consolidation, and as single agent continuation therapy **Part 2**: Midostaurin or placebo in sequential combination with daunorubicin and cytarabine induction, in sequential combination with high dose cytarabine consolidation, and as single agent continuation therapy
Efficacy assessments	Bone marrow aspirate (BMA) and peripheral blood specimens will be evaluated for remission versus persistent or relapsed disease (Progressive Disease) according to Cheson criteria. The following responses will be collected: ● Complete remission (CR) ● Morphologic complete remission with incomplete platelet count recovery (CRp) ● Partial Remission (PR) ● Treatment Failure ● Relapse after CR

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Safety assessments	● Physical examination ● ECOG PS (Eastern Cooperative Oncology Group Performance Status) ● Weight and vital signs ● 12-lead electrocardiogram (ECG) ● MUGA, ECHO ● Laboratory assessments including hematology, chemistry, coagulation and urinalysis ● Adverse events (AEs) with severity, relationship to study treatment and seriousness
Other assessments	● PK parameters Plasma concentrations of midostaurin and its active metabolites CGP62221 and CGP52421 will be measured using a validated liquid chromatography-tandem mass spectrometry (LC-MS/MS) assay with a lower limit of quantification (LLOQ) of approximately 10.0 ng/mL. [redacted] ● Patient reported outcomes assessment by the European Organization for Research and Treatment of Cancer quality of life (EORTC QLQ-C30) [redacted]
Data analysis	**Part 1:** Safety evaluation part in Japan The safety and tolerability of midostaurin in combination with chemotherapy in Japan will be assessed based on the incidence of Safety Events among evaluable patients. 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 (safety evaluation period) and that is determined by the Independent Safety Committee to be definitely or probably related to midostaurin. Evaluable patient is defined as patients who have completed the safety evaluation period without a potential Safety Event or have experienced a potential Safety Event within this period. All patients enrolled in part 1 will be listed and reviewed irrespective of the combination treatment (JALSG or RATIFY regimen). **Part 2:** Double Blind, randomized, placebo-controlled part The primary endpoint 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 complete remission (CR) in induction, relapse after CR, or death due to any cause, whichever occurs first. The interim and primary efficacy analyses will be the comparison of the distribution of EFS between the two treatment arms. The estimated hazard ratio (HR) of EFS not censored at stem cell transplantation (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 ≥ 0.7, TKD; and regimen: RATIFY regimen, JALSG regimen). 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. In addition, for interim analysis, 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 also need to be satisfied to declare the success of the study.

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	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% confidence intervals will be presented by treatment arm. The interim analysis will be performed when 60 patients are randomized and at least 24 EFS events are documented (expected around 14 months from the date of first patient to be randomized). This interim analysis will be assessed by a Data Monitoring Committee (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 the study will be 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.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 final analysis will be performed with a cut-off at 36 months after the start of the study treatment of the last patient. After treatment phase, all patients will be followed in the follow up phases (for continued remission and survival) until the cut-off at 36 months after the start of study treatment of the last patient. 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. Refer to Section 10.4.3 and Section 10.4.4 for details on censoring, as well as supportive and sensitivity analyses that will be performed for the primary endpoint.
Key words	PKC412, midostaurin, cytarabine, daunorubicin, acute myeloid leukemia, combination treatment, FLT3

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1 Background

1.1 Overview of disease pathogenesis, epidemiology and current treatment

AML, one of the most common types of acute leukemia in adults, is a heterogeneous group of neoplasms that is characterized by the presence of acquired mutations as well as cytogenetic and epigenetic alterations that mediate disease pathogenesis and determine prognosis. Risk stratification in AML is based principally on characterization of cytogenetic abnormalities and mutational profiling, and the latter is especially important in patients lacking karyotypic abnormalities (Döhner 2017, Arber et al 2016).

The FLT3 gene encodes a protein in the class III tyrosine kinase receptor family, and it serves a key role in the proliferation and differentiation of normal hematopoietic progenitor cells. Approximately 30% of patients with newly diagnosed AML have an activating mutation in the FLT3 gene, usually either an internal tandem duplication mutation (ITD, in approximately 20% of AML patients), or a point mutation in the activating loop of the tyrosine kinase domain (TKD, approximately 6-8% of AML patients); rarely, both occur in the same leukemia (Kayser and Levis 2014). In patients with newly diagnosed AML, the complete remission (CR) rates in patients with FLT3 mutations are generally similar, or only slightly lower, than in those without FLT3 mutations. FLT3-ITD mutations, particularly when they are present at a high allelic ratio relative to wild-type FLT3, are associated with poor prognosis; such leukemias are associated with an inferior disease-free survival (DFS) and overall survival (OS) and with a higher risk of relapse (Kottaridis et al 2001, Whitman et al 2001, Thiede et al 2002, Pratcorona et al 2013). The reported prognostic significance of the FLT3-TKD mutation has been inconsistent.

Initial therapy for AML in younger patients (generally less than 60 years of age) has a goal of inducing a durable complete remission and has changed little in the past three decades. For patients with an adequate performance status, initial therapy comprises the “7 + 3” remission induction regimen with daunorubicin and cytarabine, followed by high dose cytarabine for remission consolidation. The 5-year survival rate with this approach is 30 to 40% in patients under the age of 60 years, and the rate is less than 15% in older patients (Stone et al 2005). Patients with AML characterized by poor prognostic features are recommended to enroll into clinical trials and/or to undergo stem cell transplantation (SCT) following achievement of remission with standard induction chemotherapy (Schiller 2014). Significant improvements in OS and DFS for AML patients harboring FLT3-ITD mutations have been reported with allo-SCT compared to chemotherapy alone or autologous SCT (DeZern et al 2011, Brunet et al 2013), especially for patients with high FLT3-ITD allelic ratios (Schlenk et al 2014). However, these patients remain at high risk of relapse following SCT compared to patients without FLT3-ITD mutations, with a higher 2-year relapse incidence (30% vs 16%; p=0.006) and lower leukemia free survival (58% vs 71%; p=0.04) (Brunet et al 2012). Not all patients are eligible for transplantation, particularly those of advanced age. SCT is associated with a substantial risk of treatment-related complications and post-transplant relapses, particularly in leukemias with high risk features such as the FLT3-ITD mutation with a high allelic ratio. Thus, despite the availability of SCT therapy for some patients, there remains a high unmet medical need in FLT3-mutated AML.

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The ability to delay or prevent relapses in these patients would be a significant advance beyond current treatment. A prolonged duration of remission would provide potentially a major clinical benefit by allowing more eligible patients to undergo a SCT. This benefit would particularly apply to those patients who require an unrelated donor, because 3 to 6 months is generally required for the donor search alone. In addition, improving the response rate could also result in long-term clinical benefit. Currently there are no approved FLT3-targeted therapies. Because of the adverse prognostic impact of FLT3 gene mutations and the lack of effective therapy for many patients with this disease, an unmet medical need exists in patients with FLT3-mutated AML.

The CALGB10603 ([CPKC412A2301], RATIFY) trial, which enrolled patients principally in North America and Europe < 60 years of age with newly diagnosed FLT3-mutated acute myeloid leukemia (AML), showed that midostaurin combined with standard induction and consolidation therapy following by single agent midostaurin continuation treatment conferred a survival advantage compared to placebo plus chemotherapy.

The purpose of this present study is to extend these findings in additional patients from countries not involved in RATIFY trial and to obtain bridging clinical data in other regions.

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

1.2.1 Overview of Midostaurin

1.2.1.1 Non-clinical experience

Preclinical pharmacology

Midostaurin (PKC412, CGP41251) is an orally bioavailable staurosporine analog with potent activity against both the FLT3-ITD and FLT3 mutant kinases as well as against wild-type FLT3. In addition, it inhibits other molecular targets including several isoforms of protein kinase C, KIT, Vascular endothelial growth factor receptor (VEGFR)-2, fibroblast growth factor receptor (FGFR), and multi-drug resistance gene products, which are thought to be important for the pathogenesis of AML or its sensitivity to standard therapies.

The anti-proliferative effects of midostaurin were demonstrated in cell-based models with expression of the FLT3-ITD or FLT3-TKD mutant kinases (Weisberg et al 2002). Synergistic inhibitory activity of midostaurin in combination with daunorubicin or cytarabine was observed in AML patient cell lines. Moreover, a related FLT3 inhibitor provided enhanced, sequence-dependent cell cytotoxicity when administered simultaneously with or immediately following cytarabine, and the combinatorial activity of the FLT3 inhibitor with daunorubicin was also demonstrated (Levis et al 2004).

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Pharmacokinetics and drug metabolism

The oral absorption of [^{14}C]midostaurin in all species was shown to be moderate to high, and the bioavailability was low to moderate. Given midostaurin's low aqueous solubility (<0.001 mg/mL) and its high absorption in human (>90%), midostaurin is classified as a BCS II drug. In rats, dogs and rabbits, the total systemic plasma clearance (0.24 - 0.98 L/h/kg) and the volume of distribution at steady state (1.20 - 3.77 L/kg) were moderate. The half-life was relatively short in animals (3.2-7.3 h). In human subjects, the apparent terminal half-life was relatively long (~20 h) following a single oral dose.

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

Midostaurin was extensively metabolized in the rat, dog, rabbit and human. The primary biotransformation pathways observed included hydroxylation, O-demethylation, N-demethylation and amide hydrolysis. The major circulating components were midostaurin and CGP52421 (two epimers) in all species. CGP62221 (the O-demethylation product) was also a major human circulating metabolite and detectable in the dog and rabbit. The total recovery of radioactivity was high in the rat, rabbit, dog and human (81.5% - 99.4%). In all these species, radioactivity was mainly excreted via fecal excretion. Renal excretion was apparently very minor (<4%).

Midostaurin undergoes extensive hepatic metabolism through CYP3A4 enzymes which are either induced or inhibited by a number of concomitant drugs. Based on *in vitro* data, midostaurin and/or its metabolites have the potential to inhibit and to induce cytochrome P450 (CYP) enzymes. Therefore, midostaurin may be a victim or a perpetrator of drug-drug interactions *in vivo.*

Pre-clinical toxicology

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

In the repeat-dose studies, target organs for toxicity were the gastrointestinal (GI) tract (emesis in dogs and monkeys, diarrhoea and mucosal alteration), testes (decreased spermatogenesis), bone marrow (hypocellularity) and lymphoid organs (depletion/atrophy). The effect on the bone marrow and lymphoid organs was accompanied by hematological changes of decreased white blood cells, lymphocytes and erythrocytic parameters. An increase in liver enzymes (ALT and AST) was seen consistently, without histopathological correlates in rats, and in dogs and monkeys in long-term studies of ≥3 months duration. In dogs, a decrease in heart rate, prolongation of the P-Q interval, and sporadically occurring atrioventricular blocks was seen in

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individual animals. All findings were fully reversible or showed a trend towards reversibility. *In vitro* and *in vivo* mutagenicity tests revealed no genotoxicity. The no observable effect level (NOEL) in the 12-month toxicity studies was 3 mg/kg in rat and 1 mg/kg in dog. No carcinogenicity studies have been performed.

In animal studies, midostaurin caused embryo-fetal toxicities, including late embryo-fetal death and reduced fetal birth weight, with delays in fetal growth at doses lower that the recommended human dose. Effects on fertility and general reproductive toxicity were also found. In some, but not all, pre-clinical animal studies, midostaurin induced effects on testes that could potentially affect male fertility: degeneration of the seminiferous tubules to atrophy of the testes in rat and hypospermatogenesis with oligospermia/aspermia in dog. When recovery was evaluated, these effects were at least partially recoverable after 4 weeks out of treatment. This is to be expected since spermatogenesis in the dog requires about 40-60 days and full reversibility could not have occurred in the 1-month recovery period. In females from rat only, in two studies some adverse effects on the reproductive organs were observed: uterine atrophy and follicular effects (decrease number of corpora lutea or ovarian follicular distension). These effects could potentially affect female fertility. When evaluated, there was recovery in one out of the two studies. Of note these findings were observed at exposure multiples below one (i.e. compared with exposure in human at therapeutically efficacious dose, 50/100 mg bid).

In conclusion, non-clinical safety data obtained from various toxicology studies performed with midostaurin support its clinical development. For all study participants, the potential adverse effects on fertility as they have a likelihood of recovery will be managed via the Informed Consent Form (ICF).

Please refer to the Investigator's Brochure for additional information.

1.2.1.2 Clinical experience

Pharmacokinetics and drug metabolism in humans

Midostaurin is a compound with good absorption and poor solubility. Three of its metabolites demonstrated pharmacological activities (the constituent epimers of CGP52421 and CGP62221). Following multiple doses, the PK of midostaurin and CGP62221 was time-dependent with an initial increase observed the first week followed by a decline in concentration until reaching a steady-state on Day 28. CGP52421 concentrations do not appear to decline significantly such as observed for midostaurin and CGP62221. Midostaurin is rapidly absorbed after oral administration, with peak plasma concentrations observed at 1-3 hours post dose. The mean apparent volume of distribution of midostaurin (99 L) is higher than that of total body water (42 L), indicating a high tissue distribution. Midostaurin is predominantly metabolized by CYP3A4 into CGP62221 (via *O*-demethylation) and CGP52421 (via hydroxylation). The major circulating components in plasma are CGP52421, CGP62221 and midostaurin, accounting for 38, 28, and 22% of AUC0-168h, respectively. The compound related materials are mainly distributed to plasma and minimally to red blood cells. The median terminal half-lives of midostaurin, CGP62221 and CGP52421 in plasma are approximately 20.5, 32.3 and 471 hours, respectively. The mean apparent plasma clearance (CL/F) was 2.4-3.1 l/h in healthy patients. In AML and advanced systemic mastocytosis (advanced SM) patients, population

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pharmacokinetics (popPK) estimates for clearance of midostaurin- at steady-state were 5.9 l/h and 4.4 l/h, respectively.

The Human Mass Balance study results indicated that fecal excretion is the major route of excretion (78% of the dose), and mostly as metabolites (73% of the dose), while unchanged midostaurin accounts for 3% of the dose. Only approximately 4% of the dose is recovered in urine.

The exposure of midostaurin and its metabolites after single doses was generally similar among Caucasians, Asians and Black healthy subjects.

Although there was a slight decrease or increase of exposure in Blacks and Asians, respectively, compared to Caucasians, it is not deemed to be clinically relevant given the overall exposure-efficacy and exposure-safety profile of midostaurin. Similar conclusions were drawn from population PK analysis, where race (Caucasian vs non-Caucasian) showed no significant impact on PK of midostaurin and its active metabolites.

Additional information can be found in the midostaurin [Investigator's Brochure].

Summary of efficacy in clinical studies: midostaurin single agent therapy

Study [CPKC412A2104] was an open-label Phase II study conducted in 20 patients of 18 years and older with FLT3 mutated AML or high risk MDS, and it was designed to evaluate the preliminary anti-tumor activity of single agent midostaurin (75 mg tid). The primary endpoint of this study was best clinical response (CR and PR). No patient achieved a CR or PR based on the investigator assessment. However, the majority (15/20; 75%) of patients had a greater than 50% reduction in the peripheral blood blast count, and 6/15 (40%) achieved a greater than 50% reduction in bone marrow blast count.

Study [CPKC412A2104E1] was an open-label, randomized Phase II study conducted in 95 patients of 18 years and older with AML or high risk MDS (FLT3-mutated or FLT3-WT) to evaluate the clinical activity of single agent midostaurin. Patients were assigned to receive twice daily doses of either 50 or 100 mg until disease progression or the occurrence of unacceptable treatment-related toxicity. The primary endpoint of this study was best clinical response (CR/PR/MR/MR+BR/BR) (CR=complete response, PR=partial response, MR=minor response, BR=blast reduction). Ninety-five patients were enrolled and were included in the intent-to-treat (ITT) analyses: 35 in the FLT3-mutated group, and 60 in the FLT3-WT group. The overall clinical response rate (proportion of patients with CR, PR, MR+BR, MR or BR) was 71.4% in patients with FLT3-mutated AML and 56.1% in patients with FLT3-WT AML. Most of these patients had a best response of blast reduction +/- minor response. Overall, similar biological activity of midostaurin was observed in patients with mutated FLT3 and in those with wild-type FLT3 at either the 50 mg bid or 100 mg bid doses (Fischer et al 2010).

Study [CPKC412A2104E2] was an open-label Phase I/II study conducted in 29 patients of age 18 years and older with AML or high risk MDS (FLT3-mutated or FLT3-WT) to evaluate the clinical activity of intra-patient dose-escalation of midostaurin up to a maximum of 600 mg/day, or concomitant administration of midostaurin 50 mg bid with itraconazole 100 mg bid. Twenty-nine patients were enrolled and were included in the ITT analyses: 13 patients in the midostaurin+itraconazole arm, and 16 patients in the midostaurin dose escalation arm. All patients were diagnosed with AML. The primary efficacy endpoint of this study was best

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clinical response (CR/PR/MR/MR+BR/BR). In patients with FLT3-mutated AML, five (55.6%) patients achieved a clinical response (BR +/- MR) in the midostaurin dose escalation arm, and no patient obtained a clinical response in the midostaurin+itraconazole arm. In patients with FLT3-WT AML, two (28.6%) patients in the midostaurin dose escalation arm and four (66.7%) patients in the midostaurin+itraconazole arm obtained a clinical response; among these, one patient in the midostaurin+itraconazole arm obtained a CR. Based on these results, no additional benefit was observed by increasing the dosing of midostaurin beyond 100 mg bid or by combining midostaurin with itraconazole.

The collective findings from these studies supported further evaluation of midostaurin in combination with chemotherapy in patients with AML.

Summary of efficacy in clinical studies: midostaurin combination therapy

Study [CPKC412A2106] was a multi-center, open-label Phase Ib study conducted in 69 patients aged 18-60 years (19 with FLT3-mutated and 50 FLT3-WT) with newly diagnosed AML to evaluate the safety and PK of midostaurin administered in combination sequentially and concomitantly with standard induction and consolidation chemotherapy. A higher CR rate was reported in AML with a FLT3 mutation compared to FLT3-WT AML (15/19 patients, 78.9% vs 24/50 patients, 48.0%, respectively). Among 19 patients with FLT3-mutated AML, 4/6 (66.7%) in the 100 mg bid arm and 11/13 (84.6%) in the 50 mg bid arm obtained a CR. Single agent midostaurin (100 mg bid) was administered either sequentially or concomitantly with standard daunorubicin/cytarabine induction therapy followed by consolidation therapy with high dose cytarabine. During the study, a high proportion of patients experienced gastrointestinal AEs at a dose of 100 mg bid and discontinued the study. Subsequently, the midostaurin dose was reduced from 100 mg bid to 50 mg bid to optimize the tolerability of midostaurin through protocol amendment. The sequential regimen was also associated with improved tolerability. Based on the safety profile from this study, midostaurin 50 mg bid administered sequentially with standard induction/consolidation chemotherapy was established as the recommended regimen for subsequent studies in patients with AML (Stone et al 2012).

Study [CPKC412A2301], hereafter referred to as Study [A2301] and as the “RATIFY regimen”, is a randomized, double-blind, multi-center, placebo-controlled Phase III study conducted in 717 patients with newly diagnosed FLT3 mutation positive (ITD or TKD) AML. Patients were randomized in a 1:1 ratio (360 patients to the midostaurin arm and 357 to the placebo arm) with stratification by FLT3 mutation status (ITD allelic ratio <0.7, ITD allelic ratio ≥ 0.7, or TKD). The primary efficacy endpoint was OS non-censored at the time of SCT, and the key secondary endpoint was EFS non-censored at the time of SCT. The study met its primary objective: a significant improvement in OS was demonstrated with a hazard ratio (HR) of 0.77 (95% CI: 0.629, 0.953), corresponding to a 23% reduction in risk of death in favor of the midostaurin arm. The result was statistically significant with a p-value of 0.0078 at a one-sided alpha of 0.0239. The median EFS was 8.2 months for patients in the midostaurin arm compared to 3.0 months for patients in the placebo arm (HR=0.78; 95% CI 0.662, 0.930); this was statistically significant (p=0.0024) at a one-sided alpha level of 0.025. The efficacy results for midostaurin plus chemotherapy were consistently superior to that for placebo plus chemotherapy with respect to the CR rate, OS (censored for SCT), DFS, and cumulative incidence of relapse (CIR).

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Summary of safety in clinical studies

Midostaurin has been extensively studied in both oncologic and non-oncologic indications as well as in a large number of healthy volunteers over the past two decades.

The largest clinical safety experience for midostaurin has been in two indications:

- In combination with standard chemotherapy in patients with newly diagnosed FLT3-mutated AML
- As a single agent in patients with advanced systemic mastocytosis (Advanced SM) [formerly aggressive systemic mastocytosis (ASM) or mast cell leukemia (MCL) with or without an associated hematologic non-mast cell lineage disorder (AHNMD)]

In the pivotal phase III [A2301] trial of patients with AML, midostaurin or placebo was administered in combination with standard induction and consolidation therapy following by single agent continuation. The median duration of exposure to midostaurin and placebo was 42.0 days (range 2-576 days) and 34.0 days (range 1-465 days), respectively.

In this study, the safety profile for both the midostaurin and placebo groups was relatively consistent. Most AEs, AEs suspected to be related to study drug, SAEs and AEs leading to discontinuation occurred at similar frequencies in both midostaurin and placebo control groups. The most frequent adverse events reported in the combination setting were predominantly cytopenias (thrombocytopenia, anemia, neutropenia) and gastrointestinal events (nausea, vomiting) compared to those for patients receiving midostaurin monotherapy, as expected from the known toxicities of the RATIFY regimen.

As expected, the most frequent grade 3/4 AEs in both groups were related to myelosuppression (neutropenia, anemia, thrombocytopenia, febrile neutropenia) and occurred in nearly all patients during the induction/consolidation phases. Midostaurin did not increase the incidence or severity of cytopenias (leukopenia, neutropenia, thrombocytopenia) febrile neutropenia, infections or bleeding events and did not negatively impact time to recovery, suggesting that adding midostaurin to chemotherapy does not increase the risk for such events. Cytopenias are common findings in patients with AML who are treated with chemotherapy (Atallah et al 2007).

The most frequent non-hematologic grade 3/4 AEs in the midostaurin group were infections (device-related), diarrhea, and exfoliative dermatitis; for the placebo group, the most common were hypokalemia, diarrhea, and pneumonia. AEs were generally balanced between the two treatment arms, with the exception of exfoliative dermatitis and transaminase elevations, which occurred more frequently in midostaurin-treated patients.

Non-fatal cases of cardiac dysfunction, including congestive heart failure, occurred in a small proportion of patients (1.3% in both treatment groups). In the advanced SM population, 7.0% had cardiac dysfunction, and a few patients had notably decreased LVEF (<45%).

Pulmonary toxicity/ILD events (primarily pneumonitis) occurred in approximately 14% of patients in Study [A2301], with a similar frequency in the midostaurin (including one fatal case) and placebo groups. In the advanced SM population, ILD AEs were reported in 3.5% of patients, none of which had a fatal outcome.

Clinical data indicate that strong CYP3A4 inhibitors increase midostaurin steady-state exposure 2.7 fold, with limited impact on the two major metabolites. In Study [A2301], concomitant

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moderate or strong CYP3A4 inhibitors were administered to 45% of all patients, primarily in the induction and consolidation phases as part of routine antifungal prophylaxis, the midostaurin exposure was increased by 1.44 when co-administered with CYP3A4 inhibitors in this study. However, a review of the grade 3/4 AE in Study [A2301] showed no clinical difference in the incidence or pattern of grade 3-4 AEs between patients receiving CYP3A4 inhibitors and those who had not.

The impact of strong CYP3A4 inducers was investigated in healthy volunteers. The co-administration of rifampin (strong CYP3A4 inducer) with midostaurin led to a decrease of 94% of midostaurin exposure after a single dose. Prediction of exposures was made based on PBPK modeling suggesting a lesser impact at steady-state with a predicted decrease in exposure between 34% and 37%. However in absence of clinical evidence in patients at steady-state CYP3A4 inducers should be avoided.

Nonclinical studies demonstrated embryo-fetal toxicity of midostaurin in rats and rabbits, and the possibility that midostaurin can cause fetal harm when administered to a pregnant woman cannot be excluded. There are no adequate data of midostaurin in pregnant women. Midostaurin must not be taken during pregnancy or in women of childbearing potential not using contraception. Pregnant women must be advised of the potential risk to the foetus. Women of childbearing potential must be advised to use a highly effective method of contraception while receiving midostaurin and for four months post study for women because of the long half-life (T1/2) of the metabolite, CGP52421 (482 hours). Women using hormonal contraceptives should add a barrier method of contraception.

Sexually active males must use a condom during intercourse while taking drug and for 4 months after stopping midostaurin.

Animal studies showed adverse effects of midostaurin on fertility indices. Advise females and males of reproductive potential that midostaurin may impair fertility.

It is not known whether midostaurin is excreted in breast milk. Transfer of midostaurin and its active metabolites was observed in lactating rats. Women taking midostaurin should therefore not breast-feed, and such patients are ineligible for this trial.

Please refer to the [Investigator's Brochure] for additional information.

2 Rationale

2.1 Study rationale and purpose

Study [A2301] was conducted predominantly in Europe and North America and showed that midostaurin added to standard chemotherapy yielded a statistical improvement in overall survival compared to placebo plus chemotherapy (see Section 1 above). The present trial will provide additional information regarding midostaurin plus standard-of-care chemotherapy to supplement the limited data collected in Study [A2301] from patients in other regions.

In Japan, a dose-escalation, single-dose, phase I study (study [CPKC412A1101]; hereafter referred to as study [A1101]) was conducted to investigate the PK and tolerability of midostaurin administered alone in Japanese healthy adults. Overall the PK profiles of midostaurin and its metabolites (CGP62221 and CGP52421) in Japanese subjects were in

[redacted]

agreement with the results seen in non-Japanese subjects. No deaths or serious adverse events were observed in Study [A1101]; AEs that occurred in the study were similar to those in previous studies outside Japan, and many of them were mild. Therefore, there appear to be no major differences in the tolerability of midostaurin administered alone between Japanese and non-Japanese population.

The safety and efficacy of midostaurin combined with chemotherapy in newly diagnosed FLT3-mutated AML has not yet been studied in Japanese patients. In contrast to the regimen used in Study [A2301], a standard of care for adult patients up to age 64 years with newly diagnosed AML was independently established by the Japan Adult Leukemia Study Group (JALSG) in the AML201 study period. It was shown to produce CRs in 70-80% of newly diagnosed AML patients (Ohtake 2011, Miyawaki 2011). Approximately 40% of patients in remission survived for greater than 5 years without relapse. There is no large clinical experience of midostaurin with this chemotherapy regimen (hereafter termed the "JALSG regimen"), and this present study will provide needed information regarding this combination in Japanese patients.

The RATIFY and JALSG regimens both include daunorubicin and cytarabine chemotherapies. The doses and administration schedules for these chemotherapies are similar in the two regimens, but the JALSG regimen uses a lower dose of cytarabine during induction, a higher cumulative dose of daunorubicin during induction, and a higher cumulative dose of cytarabine during consolidation (see Table 6-1).

In summary, this trial will provide needed clinical information about midostaurin in combination with standard-of-care chemotherapy in newly diagnosed FLT3-mutated AML in populations that were underrepresented in Study [A2301], and it will provide additional information in particular within Japan where an alternative regimen is typically the treatment standard. Outside Japan, where the RATIFY regimen is one standard of care for adults with newly diagnosed AML, midostaurin will be combined with this chemotherapy standard.

2.2 Rationale for the study design

By assessing the safety and efficacy of midostaurin versus placebo in patients from countries not involved in study [A2301] with newly diagnosed FLT3 mutated AML (treated with intensive induction chemotherapy and consolidation therapy), this study will allow a side-by-side comparison to patients from Study [A2301]. The justification for randomization is that the primary endpoint, event free survival, can be affected by patient related factors in this previously underrepresented (in Study [A2301]) patient population, and will be best assessed through a randomized comparison to placebo.

Patients who have AML with a FLT3 mutation will be randomly assigned in a 1:1 ratio to one of two study treatments within six strata, which are defined by:

1. RATIFY or JALSG regimen, and
2. FLT3 genotype: FLT3-TKD, FLT3-ITD with a mutant signal ratio < 0.7, or FLT3-ITD with a mutant signal ratio ≥ 0.7.

Stratified randomization will be performed as follows: each patient will be classified into the corresponding stratum according to the FLT3 genotype and according to the treatment regimen that is selected, and then either midostaurin or placebo will be assigned to the patient randomly

[redacted]

using a block randomization scheme within each stratum, thereby ensuring balance of the treatment groups with respect to the FLT3 genotype and to the treatment regimen.

Patients will be treated with one or two cycles of remission induction with daunorubicin and cytarabine, followed by sequential midostaurin or placebo. Patients who demonstrate a CR during either induction cycle will receive three or four cycles as tolerated of high-dose cytarabine consolidation chemotherapy with sequential midostaurin/placebo as assigned (in Japan, only patients will receive 3 cycles of consolidation as per their standard of care). If a patient continues to be in remission, continuation therapy for up to twelve 28-day cycles will be administered with midostaurin/placebo as assigned. Patients who receive SCT therapy will be removed from study treatment but will be followed for continued remission and for survival.

In countries other than Japan, the study will begin with the randomized part. However, in Japan a safety evaluation part will precede advancement to the randomized part of the study. The purpose of this safety evaluation part will be to provide an assessment of the safety of midostaurin combined with chemotherapy in Japanese patients. Either the RATIFY regimen or the JALSG regimen may be used in Japan in combination with midostaurin. Given the prevailing practice pattern in Japan, it is anticipated that the majority of patients will receive midostaurin with the JALSG regimen. A committee of independent medical experts (hereafter termed the "Independent Safety Committee") will assess the safety experience of the midostaurin plus chemotherapy in Japanese patients before additional patients are enrolled into the randomized part in Japan. If the Independent Safety Committee determines that midostaurin plus chemotherapy is safe and adequately tolerated in Japanese patients, then in this country the trial will advance to the randomized part.

2.3 Rationale for dose and regimen selection

The recommended dose of midostaurin in combination with standard chemotherapy for newly diagnosed AML was established in the [CPKC412A2106] trial described in Section 1.2.1.2, which indicated that midostaurin 50 mg administered twice daily in sequential combination with chemotherapy was the best tolerated regimen. Study [A2301] confirmed the safety and efficacy of the midostaurin combination in patients with newly diagnosed FLT3 mutated AML. In addition, preliminary analyses suggest that midostaurin exposure is similar between Asian and Caucasian populations.

2.4 Rationale for choice of combination drugs

For all regions participating in this bridging study, midostaurin/placebo will be evaluated in combination with the chemotherapy used in Study [A2301], the "RATIFY regimen".

In addition, in Japan, physicians will have the option of treating patients using midostaurin (midostaurin or placebo in the randomized part) in combination with the JALSG regimen, which is the most common therapy used in Japan for adults with newly diagnosed AML (see Section 2.2). Physicians in Japan may also select the RATIFY regimen as the chemotherapy combination. Patients will be enrolled first in a safety evaluation part to evaluate the safety of midostaurin plus chemotherapy in Japanese patients.

In Japan, either the RATIFY or JALSG regimens will be used. In other countries, only the RATIFY regimen will be used.

[redacted]

2.5 Rationale for age range of enrolled patients

Study [A2301] enrolled patients from age 18 to less than 60 years and showed that midostaurin combined with chemotherapy was adequately tolerated (Stone 2015).

Since the time that Study [A2301] was developed, there has been an emerging awareness that older patients (age ≥ 60 years) with newly diagnosed AML can benefit from intensive remission induction chemotherapy (Juliusson et al 2009, Juliusson et al 2011). AML occurs mainly in patients aged 65 years or older, median age at diagnosis is between 65 and 72 years and this median age is increasing (Juliusson et al 2009).

The current standard of care is not to limit intensive induction chemotherapy to patients <60 years of age, taking into account other important clinical parameters including disease factors, comorbidities, fitness or performance status. The United States National Comprehensive Cancer Network (US NCCN) Guidelines (O'Donnell et al. 2017) recommends for older patients (age>60 years) with AML, using patient performance status, in addition to adverse features and comorbid conditions, to select treatment options rather than to rely on a patient's chronologic age alone. Similar treatment recommendations are offered by the European Leukemia Network (Döhner et al 2017). As the basis for the European LeukemiaNet (ELN) recommendations, a model is referenced (Sorror et al 2017) concluding that intensive therapy leads to better long term survival than does non-intensive therapy even in older patients with significant co-morbidities. Hence, age alone should not be the decisive and sole determinant to guide therapy (Döhner et al 2017). In Japan, a similar trend in terms of treatment approach is reported (Miyawaki 2017), suitability to chemotherapy is judged by the treating physician and intensive treatment including transplantation is now sometimes performed up to the age 70 years.

The presence of FLT3 mutations is associated with very poor survival in both younger and older patients. [ADE02T] study was conducted to investigate the efficacy and safety of midostaurin combined with chemotherapy in FLT3 mutated AML patients up to 70 years. The analysis of interim ADE02T results from the first 245 patients enrolled (median age: 53.6 years old, range 20 – 69) showed that overall the safety and tolerability of the treatment in ADE02T was very similar compared to [A2301] both in patients >60 and ≤60 years. A similar pattern of superior OS and EFS was observed both in patients >60 and ≤60 years of age in Study ADE02T. In order to better define efficacy of midostaurin for patients ≥60 years of age from the ADE02T trial, a propensity score has been prepared in order to compare ADE02T to a large cohort of historical controls with FLT3-ITD mutations. This analysis shows an OS and EFS midostaurin treatment benefit in patients regardless of age (≥60 or <60 years). In conclusion, the available evidence indicates that midostaurin, added to chemotherapy, is well tolerated both in younger and older patients with FLT3-mutated AML, and may provide additional benefit in patients who are eligible for intensive chemotherapy regardless of age.

The efficacy, safety and tolerability of intensive induction chemotherapy in patients ≥60 years is better understood and clinical experience with midostaurin is more established in the older patients; this the reason why this study will enroll patients up to ≤70 years.

2.6 Rationale for choice of comparator drugs

As discussed in Section 2.2 above, patients treated in the midostaurin plus chemotherapy group will be compared to those treated in the placebo plus chemotherapy group. This comparator will

[redacted]

provide the best means of determining the safety and incremental clinical activity of midostaurin in the setting of standard chemotherapy with the RATIFY or JALSG regimens.

[redacted]

2.8 Risks and benefits

The safety of midostaurin has been evaluated in an extensive clinical program including more than 1800 patients, including the large, placebo-controlled Study [A2301] of midostaurin in combination with chemotherapy, two Phase II studies in advanced SM, 9 other Phase I-II studies conducted in patients with AML and other indications, and clinical pharmacology trials.

The potential benefit of midostaurin combined with chemotherapy in this setting is suggested by Study [A2301], which showed that in comparison with placebo plus chemotherapy there was a statistically significant improvement in OS and EFS (see Section 1.2.1.2), and other endpoints were consistent in showing the treatment benefit of midostaurin.

All patients developed one or more grade 3-4 cytopenias during chemotherapy, which are common findings in patients with AML who are treated with chemotherapy (Atallah et al 2007). The main non-hematologic adverse effects of midostaurin were GI disturbances, primarily nausea, vomiting and diarrhea, and these were observed consistently in clinical trials with midostaurin. This is consistent with the toxicity profiles of the backbone chemotherapy drugs: reported in >50% of AML patients having intensive chemotherapy despite the use of anti-emetic therapy (Lopez-Jimenez et al 2006).

[redacted]

Midostaurin undergoes extensive hepatic metabolism through CYP3A4, and midostaurin and/or its metabolites have been shown to inhibit and to induce CYPP450 enzymes in vitro.

Nonclinical studies demonstrated embryo-fetal toxicity of midostaurin in rats and rabbits, and the possibility that midostaurin can cause fetal harm when administered to a pregnant woman cannot be excluded. There are no adequate data of midostaurin in pregnant women.

It is not known whether midostaurin is excreted in breast milk. Transfer of midostaurin and its active metabolites was observed in lactating rats. Women taking midostaurin should therefore not breast-feed, and such patients are ineligible for this trial.

3 Objectives and endpoints

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

[redacted]

Table 3-1 Objectives and related endpoints

Objective	Endpoint	Analysis
Primary		
Safety Evaluation part (Part 1, Japan only)		Section 10.4
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		
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 10.5.2
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 10.5.3
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 10.5.4

[redacted]

Objective	Endpoint	Analysis
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). PGIC score as frequencies and percentages by scheduled timepoint.	Section 10.5.5
[redacted]		

4 Study design

4.1 Description of 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.

4.1.1 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 4-1)

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:

[redacted]

- 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.

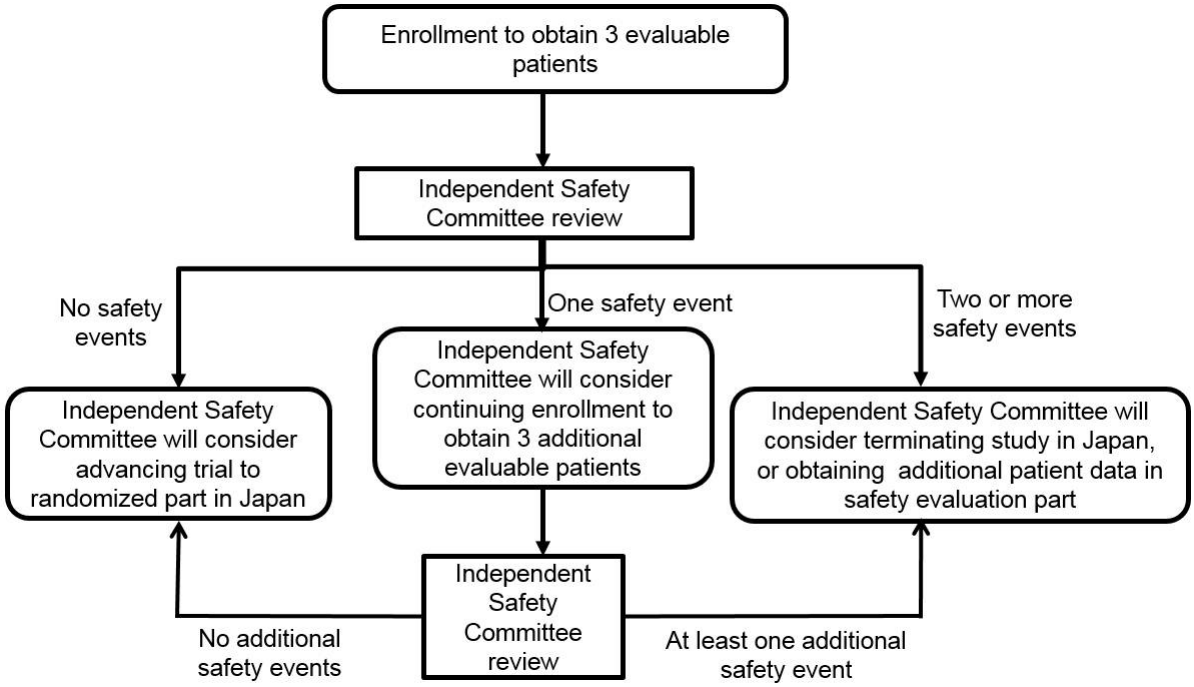
Although the Independent Safety Committee will consider these guidelines in its determination of continuing study conduct in Japan, it will also take into consideration the individual circumstances of the Safety Events and will make use of the clinical judgement of the Independent Safety Committee members.

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.

[redacted]

Figure 4-1 Independent Safety Committee review in Part 1 safety evaluation part (Japan only)



4.1.2 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 (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 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

[redacted]

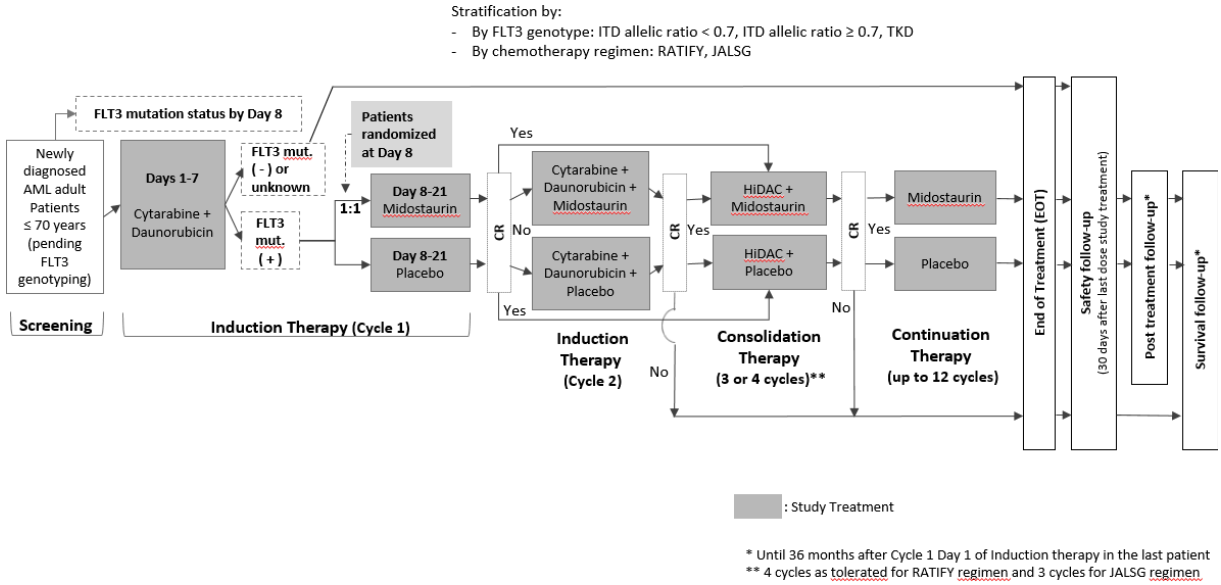
either RATIFY or JALSG for future patients. Once patients are enrolled in the study, their regimen must not be switched during the course of the study.

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 4-2 for study design.

Figure 4-2 Overview of Randomized Part (Part 2)



4.1.2.1 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 Section 5
- Perform all screening procedures as detailed in 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.

[redacted]

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.

4.1.2.2 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 status 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.

[redacted]

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.

4.1.2.3 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 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 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.

4.2 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 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 the study will be 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 Section 10.7.

[redacted]

4.3 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, and all available data will be analyzed.

4.4 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 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.

5 Population

5.1 Patient population

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

5.2 Inclusion criteria

Patients eligible for inclusion in this study must meet **all** of the following eligibility criteria:

1. Diagnosis of AML (≥ 20% blasts in the bone marrow based on **WHO 2016 classification** (Arber et al 2016). Patients with APL (acute promyelocytic leukemia) with PML-RARA are not eligible
2. Documented presence of an ITD and/or TKD activating mutation in the FLT3 gene, as determined by analysis in a Novartis designated laboratory

   An exception will be patients who are enrolled into the part 1 in Japan, who may be treated with midostaurin irrespective of AML FLT3 genotype
3. Age ≥ 18 years, ≤ 70 years of age
4. AML patients with a history of antecedent myelodysplasia (MDS) remain eligible for treatment on this trial but must not have received prior cytotoxic therapy (e.g., azacytidine or decitabine)
5. Patients must meet the following laboratory value criteria that indicate adequate organ function at the screening visit:
   - Estimated (by Cockcroft-Gault) creatinine clearance ≥ 30 ml/min
   - Total bilirubin ≤ 1.5 x ULN, except in the setting of isolated Gilbert syndrome
   - Aspartate transaminase (AST) ≤ 3.0 x ULN
   - Alanine transaminase (ALT) ≤ 3.0 x ULN
6. Written informed consent must be obtained prior to any screening procedures.

[redacted]

For patients in Japan less than 20 years of age, written consent is required from the patient as well as from their legal representative.

7. Suitability for intensive chemotherapy in the judgment of the investigator (Miyawaki 2017, O'Donnell et al 2017, Döhner et al 2017)

5.3 Exclusion criteria

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

1. Neurologic symptoms suggestive of CNS leukemia unless CNS leukemia has been excluded by a lumbar puncture. Patients with CSF fluid positive for AML blasts are not eligible.
2. Developed therapy-related AML after prior radiotherapy (RT) or chemotherapy for another cancer or disorder
3. Isolated extramedullary leukemia (please refer to Section 7.2.2.1)
4. Known hypersensitivity to midostaurin, cytarabine or daunorubicin or to any of the excipients of midostaurin/placebo, cytarabine or daunorubicin
5. Any investigational agent within 30 days or 5 half-lives, whichever is greater, prior to Day 1. An investigational agent is defined as an agent with no approved medical use in adults or in pediatric patients
6. Prior treatment with a FLT3 inhibitor (e.g., midostaurin, quizartinib, sorafenib)
7. Patients who take strong CYP3A4/5 enzyme inducing drugs or strong CYP3A4/5 enzyme inducing herbal supplements (see Appendix 2) unless they can be discontinued or replaced prior to enrollment
8. Chemotherapy for leukemia or myelodysplasia. However, the following prior therapies are allowed:
    a. Emergency leukapheresis
    b. Emergency treatment for hyperleukocytosis with hydroxyurea or low-dose cytarabine for ≤ 7 days
    c. Cranial radiotherapy (RT) for central nervous system (CNS) leukostasis (one dose only)
    d. Hematopoietic growth factor/cytokine support; other supportive therapy including antibiotics at the discretion of the investigator
9. Any surgical procedure, excluding central venous catheter placement or other minor procedures (e.g., skin or bone marrow biopsy) within 14 days prior to Day 1
10. Other known disease or concurrent severe and/or uncontrolled medical condition (e.g., cardiovascular disease including congestive heart failure or active uncontrolled infection) that could compromise participation in the study
11. Abnormal chest X-ray unless the abnormality represents a non-active, or non-clinically significant finding, such as scarring or a lung infection which is controlled by treatment
12. Known impairment of gastrointestinal (GI) function or GI disease that might alter significantly the absorption of midostaurin
13. Known confirmed diagnosis of human immunodeficiency virus (HIV)

[redacted]

14. Evidence of active HBV or HCV viral infection (confirmed by peripheral blood viral load). Patients with positive serology results indicative of high risk for viral reactivation must have negative viral load results within 28 days prior to Day 1.
15. Cardiac or cardiac repolarization abnormality, including any of the following:
    - History of myocardial infarction (MI), angina pectoris, coronary artery bypass graft (CABG) within 6 months prior to Day 1
    - Clinically significant cardiac arrhythmias (e.g., ventricular tachycardia), complete left bundle branch block, high-grade AV block (e.g., bifascicular block, Mobitz type II and third degree AV block)
    - Uncontrolled congestive heart failure
    - Left ventricular ejection fraction of <50%
    - Poorly controlled hypertension
    - QTcF at screening > 470 ms
    - Long QT syndrome, family history of idiopathic sudden death or congenital long QT syndrome, or any of the following:
        - Risk factors for torsades de pointe (TdP) including uncorrected hypokalemia or hypomagnesemia, history of cardiac failure, or history of clinically significant/symptomatic bradycardia
        - Concomitant medication(s) with a "Known risk of Torsades de Pointes" per wwwqtdrugs.org that cannot be discontinued or replaced safely with an alternative medication
        - Inability to determine the QTcF interval
16. Pregnant or nursing (lactating) women
17. Women of child-bearing potential, defined as all women physiologically capable of becoming pregnant, unless they are using highly effective methods of contraception during dosing and for 4 months after stopping medication. Highly effective contraception methods include:
    - Total abstinence (when this is in line with the preferred and usual lifestyle of the subject. Periodic abstinence (e.g., calendar, ovulation, symptothermal, post-ovulation methods) and withdrawal are not acceptable methods of contraception
    - Female sterilization (have had surgical bilateral oophorectomy with or without hysterectomy), total hysterectomy, or tubal ligation at least six weeks before taking study treatment. In case of oophorectomy alone, only when the reproductive status of the woman has been confirmed by follow up hormone level assessment
    - Male sterilization (at least 6 months prior to screening). The vasectomized male partner should be the sole partner for that subject
    - Use of oral, injected or implanted hormonal methods of contraception or placement of an intrauterine device (IUD) or intrauterine system (IUS), or other forms of hormonal contraception that have comparable efficacy (failure rate <1%), for example hormone vaginal ring or transdermal hormone contraception
    - In case of use of oral contraception women should have been stable on the same pill for a minimum of 3 months before taking study treatment

[redacted]

It is currently unknown whether midostaurin may reduce the effectiveness of hormonal contraceptives; therefore, females using systemically acting hormonal contraceptives should add a barrier method of contraception.

Women are considered post-menopausal and not of child-bearing potential if they have had 12 months of natural (spontaneous) amenorrhea with an appropriate clinical profile (i.e., age appropriate, history of vasomotor symptoms) or have had surgical bilateral oophorectomy (with or without hysterectomy), total hysterectomy, or tubal ligation at least six weeks ago. In the case of oophorectomy alone, only when the reproductive status of the woman has been confirmed by follow up hormone level assessment is she considered not of child bearing potential

18. Sexually active males unless they use a condom during intercourse while taking the drug during treatment and for 4 months after stopping treatment and should not father a child in this period. A condom is required to be used also by vasectomized men as well as during intercourse with a male partner in order to prevent delivery of the drug via semen
19. Patients/parents unwilling or unable to comply with the protocol

6 Treatment

6.1 Study treatment

In this study, the term “Study drug” indicates midostaurin or placebo.

The term “Study treatment” indicates treatment with daunorubicin, cytarabine, or midostaurin/placebo.

In the part 1, patients may be enrolled irrespective of their FLT3 mutation status.

In the part 2, induction therapy may begin while the FLT3 mutation status is being determined. A patient may not receive midostaurin or placebo unless eligibility has been confirmed based on the presence of a FLT3 mutation as determined by the Novartis designated laboratory. If the patient is not shown to have a qualifying FLT3 activating mutation, then the patient will be discontinued from treatment by Cycle 1 Day 8 of the first cycle of induction and will not receive study drug.

6.1.1 Dosing regimen

On Day 1 of study treatment, the first dose of induction chemotherapy will be administered, and each day is 24 hours in length.

Daunorubicin and cytarabine are approved drugs.

Daunorubicin and cytarabine will be supplied globally by Novartis or supplied locally as per local practice if agreed and approved by the global clinical team. Please refer to the Package Insert for complete guidelines for administration and for safety monitoring guidelines.

The dosage of daunorubicin and cytarabine will be adjusted based on body surface area (BSA) calculated before administration. To calculate BSA, the height at baseline and weight on the first day of the respective treatment cycle will be used, and sites will use a formula for BSA calculation according to the local standard.

[redacted]

Dose modification for obese patients: there is no clearly documented adverse impact of treatment of obese patients when dosing is performed according to actual body weight. Therefore, all dosing is to be determined solely by the patient's BSA as calculated from actual weight. This will eliminate the risk of calculation error and the possible introduction of variability in dose administration. Failure to use actual body weight in the calculation of drug dosages will be considered as a protocol deviation. Physicians who are uncomfortable with administering chemotherapy dose based on actual body weight should not enroll obese patients.

6.1.1.1 Induction and Consolidation therapies for JALSG Regimen (Japan only)

JALSG Remission Induction:

- **Cytarabine** 100 mg/m^2/day will be administered by continuous intravenous infusion (CIVI) on Days 1-7 (168 hour infusion).
- **Daunorubicin** 50 mg/m^2/day will be administered intravenously by IV push (IVP) or short (30 minutes) infusion on Days 1-5.
- **Study drug (midostaurin** 50 mg [two 25 mg capsules] or **placebo** [2 capsules]) will be administered twice per day by mouth on Days 8-21. Patients should take their doses at approximately the same time each day, and approximately 12 hours should elapse between the morning and evening doses. On days that PK samples are obtained, the patient should take midostaurin/placebo during the clinic visit after the pre-dose PK sample and prior to post-dose PK samples, when instructed by the study staff. Each dose should be given with food and a glass of water (~240 mL). Patients should be instructed to swallow capsules whole and not chew capsules. If vomiting occurs, no re-dosing is allowed prior to the next scheduled dose. The soft gelatin capsules should be removed from the blister pack only shortly prior to administration. The patient may notice a strong odor when he/she opens the blister card. No worry, this is normal. The odor is due to a chemical in the capsules interacting with a chemical in the blister card foil. The capsules are not affected by this and the odor will go away shortly after opening the blister card. More details are enclosed within the Investigator Brochure please refer to it.

Response assessment: see Section 7.2.1

JALSG Second Remission Induction:

For patients who do not achieve a CR in their first remission induction treatment, a second remission induction will begin no earlier than Day 24 and ≥ 3 days after completing midostaurin/placebo (whichever is latest).

- **Cytarabine** 100 mg/m^2/day will be administered by continuous intravenous infusion (CIVI) on Days 1-7 (168 hour infusion).
- **Daunorubicin** 50 mg/m^2/day will be administered intravenously by IV push (IVP) or short (30 minutes) infusion on Days 1-5.

[redacted]

- **Study drug (midostaurin** 50 mg [two 25 mg capsules] or **placebo** [2 capsules]) will be administered twice per day by mouth on Days 8-21 as described above for JALSG remission induction midostaurin/placebo.

- **Response assessment:** see Section 7.2.1

JALSG Remission Consolidation (3 Cycles):

Patients who achieve a CR after remission induction will receive consolidation therapy with midostaurin/placebo + chemotherapy according to their initial treatment assignment.

Patients will receive three cycles of consolidation therapy.

Each cycle of consolidation therapy will comprise:

- **High-dose cytarabine** (HiDAC) 2000 mg/m^2 will be administered by intravenous infusion over 3 hours every 12 hours on Days 1-5. Serial neurologic evaluations will be performed before and following the infusion of high-dose cytarabine. For patients of age 60 years or older at the time of study entry, the dose may be reduced as an option to 1500 mg/m^2/dose at the discretion of the investigator.
- Ocular or systemic administration of **corticosteroid** therapy for prophylaxis against corneal toxicity due to high-dose cytarabine is required. Dosing and administration should adhere to local standard of care.
- **Study drug (midostaurin** 50 mg [two 25 mg capsules] or **placebo** [2 capsules]) will be administered twice a day by mouth on Days 8-21 as described above for JALSG remission induction midostaurin/placebo.

Each consolidation cycle will begin within two weeks following hematopoietic recovery (ANC $\geq$ 1.0 x 10^9/L, platelet count $\geq$ 100 x 10^9/L) but no sooner than four weeks from the beginning of the previous cycle. At the end of the final consolidation cycle, a bone marrow examination will be performed to evaluate for continued remission.

6.1.1.2 Induction and Consolidation therapies for RATIFY regimen (for all countries):

RATIFY Remission Induction:

- **Cytarabine** 200 mg/m^2/day will be administered by continuous intravenous infusion (CIVI) on Days 1-7 (168 hour infusion).
- **Daunorubicin** 60 mg/m^2/day will be administered intravenously by IV push (IVP) or short (30 minutes) infusion on Days 1-3.

[redacted]

- **Study drug** (**midostaurin** 50 mg [two 25 mg capsules] or **placebo** [2 capsules]) will be administered twice per day by mouth on Days 8-21. Patients should take their doses at approximately the same time each day, and approximately 12 hours should elapse between the morning and evening doses. On days that PK samples are obtained, the patient should take midostaurin/placebo during the clinic visit after the pre-dose PK sample and prior to post-dose PK samples, when instructed by the study staff. Each dose should be given with food and a glass of water (~240 mL). Patients should be instructed to swallow capsules whole and not chew capsules. If vomiting occurs, no re-dosing is allowed prior to the next scheduled dose. The soft gelatin capsules should be removed from the blister pack only shortly prior to administration. The patient may notice a strong odor when he/she opens the blister card. No worry, this is normal. The odor is due to a chemical in the capsules interacting with a chemical in the blister card foil. The capsules are not affected by this and the odor will go away shortly after opening the blister card.

Response assessment: see Section 7.2.1.

RATIFY Second Remission Induction:

For patients who do not achieve a CR in their first remission induction treatment, a second remission induction will begin no earlier than Day 24 and ≥ 3 days after completing midostaurin/placebo (whichever is latest).

- **Cytarabine** 200 mg/m^2/day will be administered by continuous intravenous infusion (CIVI) on Days 1-7 (168 hour infusion).
- **Daunorubicin** 60 mg/m^2/day will be administered intravenously by IV push (IVP) or short (30 minutes) infusion on Days 1-3.
- **Study drug (midostaurin** 50 mg [two 25 mg capsules] or **placebo** [2 capsules]) will be administered twice per day by mouth on Days 8-21 as described above for RATIFY remission induction midostaurin/placebo.

Response assessment: see Section 7.2.1

RATIFY Remission Consolidation (4 Cycles as tolerated):

Patients who achieve a CR after remission induction will receive consolidation therapy with midostaurin/placebo + chemotherapy according to their initial treatment assignment.

Patients will receive four cycles as tolerated of consolidation therapy.Each cycle of consolidation therapy will comprise:

- **High-dose cytarabine** (HiDAC) 3000 mg/m^2 will be administered by intravenous infusion over 3 hours every 12 hours on Days 1, 3 and 5. Serial neurologic evaluations will be performed before and following the infusion of high-dose cytarabine. For patients of age 60 years or older at the time of study entry, the dose may be reduced to 1000-1500 mg/m^2/dose at the discretion of the investigator.
- Ocular or systemic administration of **corticosteroid** therapy for prophylaxis against corneal toxicity due to high-dose cytarabine is required. Dosing and administration should adhere to local standard of care.

[redacted]

- **Study drug (midostaurin** 50 mg [two 25 mg capsules] or **placebo** [2 capsules]) will be administered twice a day by mouth on Days 8-21 as described above for RATIFY remission induction midostaurin/placebo.

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. At the end of the final consolidation cycle, a bone marrow examination will be performed to evaluate for continued remission.

6.1.1.3 Continuation therapy (up to 12 cycles) for either JALSG or RATIFY regimen:

Patients treated either with the JALSG or RATIFY regimen and who maintain a CR (by bone marrow aspirate and peripheral blood evaluation) after completing 3 (JALSG) or 4 cycles as tolerated (RATIFY) of consolidation therapy will receive midostaurin/placebo continuation therapy according to the initial treatment assignment.

Prior to initiation of midostaurin/placebo Continuation therapy, all significant acute toxicity from consolidation therapy must have resolved to a severity of less than Grade 2. Midostaurin/placebo continuation therapy will begin 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 are unable to complete 4 cycles of HiDAC consolidation because of toxicity may still be eligible for continuation therapy after 3 cycles of consolidations.

Each cycle of continuation therapy will comprise:

- **Study drug (midostaurin** 50 mg [two 25 mg capsules] or **placebo** [2 capsules]) will be administered twice per day by mouth for 28 consecutive days. Patients should take their doses at approximately the same time each day, and approximately 12 hours should elapse between the morning and evening doses. On days that PK samples are obtained, the patient should take midostaurin/placebo during the clinic visit after the pre-dose PK samples and prior to post-dose PK samples, when instructed by the study staff.

  Each dose should be given with food and a glass of water (~240 mL). Patients should be instructed to swallow capsules whole and not chew capsules. If vomiting occurs, no re-dosing is allowed prior to the next scheduled dose. The soft gelatin capsules should be removed from the blister pack only shortly prior to administration. The patient may notice a strong odor when he/she opens the blister card. No worry, this is normal. The odor is due to a chemical in the capsules interacting with a chemical in the blister card foil. The capsules are not affected by this and the odor will go away shortly after opening the blister card.

[redacted]

Table 6-1 Dose and treatment schedule

Study phase	Regimen	Study treatment	Pharmaceutical form and route of administration	Dose	Frequency and/or Regimen
Induction phase	JALSG	Cytarabine	Continuous intravenous infusion (CIVI)	100 mg/m^2/day	Days 1-7 (168 hour infusion)
		Daunorubicin	Intravenously by IV push or short (30 minutes) infusion	50 mg/m^2/day	Days 1-5
		Midostaurin / Placebo	Capsules for oral use	50 mg/dose	Twice daily on Days 8-21
	RATIFY	Cytarabine	Continuous intravenous infusion (CIVI)	200 mg/m^2/day	Days 1-7 (168 hour infusion)
		Daunorubicin	Intravenously by IV push or short (30 minutes) infusion	60 mg/m^2/day	Days 1-3
		Midostaurin / Placebo	Capsules for oral use	50 mg/dose	Twice daily on Days 8-21
Consolidation phase	JALSG	High-dose cytarabine	Intravenous over 3 hours	2000 mg/m^2/dose*	12-hour intervals on Days 1-5
		Midostaurin / Placebo	Capsules for oral use	50mg/dose	Twice daily on Days 8-21
	RATIFY	High-dose Cytarabine	Intravenous over 3 hours	3000 mg/m^2/dose**	12-hour intervals on Days 1, 3 and 5
		Midostaurin/ Placebo	Capsules for oral use	50 mg/dose	Twice daily on Days 8-21
Continuation phase	JALSG or RATIFY	Midostaurin/ Placebo	Capsules for oral use	50 mg/dose	Twice daily for 28 consecutive days of each 28-day treatment cycle
For patients of age 60 years or older at the time of study entry, the dose may be reduced as an option to: * 1500 mg/m^2/dose at the discretion of the investigator ** 1000-1500 mg/m^2/dose at the discretion of the investigator					

6.1.1.4 Hematopoietic stem cell transplantation

A patient who is treated with hematopoietic stem cell transplantation (SCT) according to investigator judgement will discontinue study treatment prior to the start of the SCT conditioning regimen. The study treatment will not be resumed at any time thereafter. The patient will continue to be followed for remission in post treatment follow up.

6.1.2 Ancillary treatments

High dose cytarabine during Consolidation cycles: Ocular or systemic administration of corticosteroid therapy with high-dose cytarabine will be local standard of care.

6.1.3 Rescue medication

Not applicable

[redacted]

6.1.4 Guidelines for continuation of treatment

Patients who meet criteria for CR by the end of the second cycle of induction will proceed to consolidation therapy cycles. A patient who meets criteria for persistent disease will be removed from study treatment. Thereafter, a patient who continues to be in remission according to Cheson criteria (Cheson 2003) will continue each cycle of study treatment.

Criteria for dose interruption are described in Section 6.3. Study drug interruptions of greater than 28 consecutive days will require discontinuation from study treatment.

6.1.5 Treatment duration

The treatment phases, and the total maximum planned duration of treatment is 18 cycles. Planned durations of each therapy are:

- Induction therapy: 1 or 2 cycles (daunorubicin, cytarabine and midostaurin/placebo). One cycle is defined as the time from the start of study treatment to the time of hematopoietic recovery or determination of persistent disease, whichever is first.
- Consolidation therapy: 3 cycles for JALSG regimen and 4 cycles as tolerated for RATIFY regimen (high-dose cytarabine and midostaurin/placebo). One cycle is defined as the time from the start of study treatment to the time of hematopoietic recovery or determination of disease relapse, whichever is first.
- Continuation therapy: up to 12 cycles (midostaurin/placebo). Each cycle is 28 days in duration.

Patients may be discontinued from study treatment prior to treatment completion for reasons of unacceptable toxicity, disease persistence or relapse (designated as Progressive Disease in eCRF), withdrawal of consent by the patient, failure to adhere the protocol, or at the discretion of the investigator.

6.2 Dose Escalation Guidelines

Not applicable

6.3 Dose modifications

6.3.1 Dose modification and dose delay

For patients who do not tolerate the protocol-specified dosing schedule, dose interruptions and/or reductions are either recommended or mandated in order to maximize patient safety and to allow patients to continue the study treatment. The schedule of dose modifications applies both to patients in the part 1 and in the part 2.

Dose modifications are summarized in Table 6-2. Deviations to mandatory dose interruptions and/or reductions are not allowed. Permanent treatment discontinuation is mandatory for specific events indicated as such in Table 6-2 or listed in Section 7.1.5.

Dose changes will be recorded on the appropriate CRF.

[redacted]

Study drug (midostaurin/placebo)

Table 6-2 describes adverse events, laboratory values, or other assessments that require interruption or dose modification of study drug.

During induction and consolidation therapies, modifications should be done in case of non-hematologic toxicities (pulmonary, cardiac or other non-hematologic toxicities) related or unrelated to midostaurin/placebo.

During continuation therapy, modifications should be done in case of hematologic and non-hematologic toxicities (pulmonary, cardiac or other non-hematologic toxicities) related or unrelated to midostaurin/placebo.

If interruptions occur, missed doses of study drug will not be made up.

Study drug interruptions of greater than 28 consecutive days will require discontinuation from study treatment.

Cytarabine

Doses will be modified only during the consolidation phase with high-dose cytarabine and in case of neurotoxicity for RATIFY regimen and in case of hematology and non-hematology toxicity for JALSG regimen. Please follow Table 6-2 for each regimen.

Daunorubicin

Doses will be modified during induction phase in case of hepatotoxicity. Please follow Table 6-2 for each regimen (RATIFY or JALSG).

[redacted]

Table 6-2 Criteria for dose reduction / interruption and re-initiation of midostaurin/placebo, daunorubicin and cytarabine treatment for adverse events

Dose modifications for midostaurin/placebo	
Hematologic toxicities	
During induction and consolidation cycles During continuation cycles	No dose modifications are required for hematologic toxicity due to midostaurin/placebo during induction and consolidation therapy. In the presence of grade 4 neutropenia during continuation therapy, midostaurin/placebo must be held until ANC ≥ 1.0 x 10^9/L Once ANC ≥ 1.0 x 10^9/L, then resume midostaurin/placebo at the previous dose. If neutropenia persists for more than two weeks, midostaurin/placebo study treatment must be discontinued.
Non-Hematologic toxicities:	
● **Pulmonary toxicities**	
During induction, consolidation and continuation cycles	**For ≥ grade 3** pneumonitis or interstitial lung disease without an infectious etiology, midostaurin/placebo must be interrupted for the remainder of the cycle. Resume midostaurin/placebo at the same dose when infiltrate resolves to ≤ grade 1. **Missed doses of midostaurin/placebo will not be made up.** If the toxicity does not resolve to ≤ grade 1 within 28 days after midostaurin/placebo interruption, the patient must be discontinued from the study treatment.
● **Cardiac Toxicity**	
During induction, consolidation and continuation cycles	● **For QTcF interval > 470 ms and ≤ 500 ms**, check magnesium and potassium levels and correct any abnormalities. If possible, stop any medications that may prolong the QTcF interval. Midostaurin/placebo dose must be decreased to 50 mg once daily for the remainder of the cycle. Resume midostaurin/placebo at the initial dose in the next cycle provided that QTcF interval improves to ≤ 470 ms at the start of that cycle. Otherwise continue midostaurin/placebo 50 mg once daily. ● **For QTcF interval > 500 ms and/or QTcF prolongation >60 ms from baseline,** check magnesium and potassium levels and correct any abnormalities. Midostaurin/placebo must be held or interrupted for the remainder of the cycle, and, if possible, stop any medications that may prolong the QTcF interval. If QTcF improves to ≤ 470 ms just prior to the next cycle, resume midostaurin/placebo at the initial dose. If QTcF interval is not improved in time to start the next cycle, midostaurin/placebo may be held up to 28 days. If there is no improvement of QTcF to ≤ 470 ms within 28 days after midostaurin/placebo interruption, the patient must be discontinued from study treatment.
● **Other Non-Hematologic toxicity**	
During induction and consolidation cycles	● **Grade 1/2:** No dose modifications for any grade 1 or 2 non-hematologic toxicity. ● **Grade 3/4**: If a patient experiences **other grade 3/4 non-hematologic toxicities that are considered related to midostaurin/placebo,** midostaurin/placebo must be interrupted until toxicity resolves to ≤ grade 2. If the toxicity resolves prior to day 21, then restart at same dose to complete current cycle. Missed doses of midostaurin/placebo will not be made

[redacted]

	up. If the toxicity does not resolve to ≤ grade 2 within 28 days after midostaurin/placebo interruption, the patient must be discontinued from the study treatment.	
During continuation cycles	● Grade 1/2: **Persistent grade 1 or 2 toxicity during continuation therapy** that patients deem to be unacceptable may prompt a study drug interruption for as long as 28 days. If the study drug is interrupted for more than 28 days, the patient must be discontinued from the study treatment. ● Grade 3/4: For other **grade 3/4 non-hematologic toxicities that are considered to be related to midostaurin/placebo,** interrupt midostaurin/placebo. Resume midostaurin/placebo at the same dose when toxicity resolves to ≤ grade 2. If the toxicity does not resolve to ≤ grade 2 within 28 days after midostaurin/placebo interruption, the patient must be discontinued from the study treatment.	
Dose modifications for high-dose cytarabine (HiDAC) consolidation therapy		
	RATIFY regimen	**JALSG regimen**
During consolidation cycles	Contributions of concomitant medications to neurotoxicity should be assessed and other medications discontinued if possible. For neurotoxicity ≥ grade 2 due to high-dose cytarabine during consolidation therapy, discontinue high-dose cytarabine for the remainder of the cycle. High-dose cytarabine may be considered at the next consolidation therapy cycle with a dose modification from 3000 mg/m^2 to 2000 mg/m^2 if the toxicity has resolved to ≤ grade 1.	For any grade 2 or higher central nervous system AE (neurotoxicity) that is attributed by the investigator to HiDAC, this drug should not be used for further treatment. If there are any following AEs in a given cycle that are attributed by the investigator to be related to HiDAC, the number of days of administration of HiDAC should be decreased as described below. Once the dose is reduced, the dose may not be re-escalated at any time even if there are no additional AEs occuring after the dose reduction. Non-hematologic toxicity: ● Grade 3 (not including grade 3 anorexia, nausea, vomiting), decrease 1 day administration (4 days instead of 5 days) ● Grade 4, decrease 2 days administration (3 days instead of 5 days)
	For a second occurrence of neurotoxicity ≥ grade 2, high-dose cytarabine should be permanently discontinued.	Hematologic toxicity: ● Grade 4 febrile neutropenia with life threatening sepsis, decrease 1 day administration (4 days instead of 5 days) ● Delayed recovery of ANC and platelet (failure to reach ANC ≥ 1.0 x 10^9/L, platelet count ≥ 100 x 10^9/L by Day 35 of treatment cycle), then decrease 1 day administration (4 days instead of 5 days)

[redacted]

		• If ANC < 2.0 x 10^9/L or platelet count < 150 x 10^9/L just before administration, decrease cytarabine administration by 1 day (4 days instead of 5 days)

Dose modifications for daunorubicin due to hepatotoxicity (except in the setting of isolated Gilbert syndrome)			
		RATIFY regimen	**JALSG regimen**
During induction cycles	**Total Bilirubin (mg/dL)**	**% daunorubicin dose to administer**	**% daunorubicin dose to administer**
	≤ 2	100%	100%
	> 2 – ≤ 3.0	75% (25% dose reduction)	75% (25% dose reduction)
	> 3.0	50% (50% dose reduction)	50% (50% dose reduction)
All dose modifications should be based on the worst preceding toxicity. Common Toxicity Criteria for Adverse Events (CTCAE Version 5.0)			

[redacted]

6.3.2 Dose adjustments for QTcF prolongation

Guidelines on dose modification instructions are provided in Table 6-2 above. Dose reductions will be based on local assessment of the ECG and corrected if discrepancy occurred on the central review report.

6.3.3 Follow-up for toxicities

Patients whose treatment is interrupted or permanently discontinued due to an adverse event or clinically significant laboratory value will be followed at least weekly (or more frequently if required by institutional practices, or if clinically indicated) for 4 weeks, and subsequently at approximately 4-week intervals, until resolution or stabilization of the event, whichever comes first. Appropriate clinical experts should be consulted as deemed necessary. All patients must be followed up for adverse events and serious adverse events for 30 days following the last dose of study treatment (midostaurin/placebo or daunorubicin or cytarabine).

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

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

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

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

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

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

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

- Laboratory tests should include ALT, AST, albumin, creatinine kinase, TBIL, direct and indirect bilirubin, GGT, prothrombin time (PT) or INR and ALP.
- A detailed history, including relevant information, such as review of ethanol, concomitant medications, herbal remedies, supplement consumption, history of any pre-existing liver conditions or risk factors, should be collected.

[redacted]

- Further testing for acute hepatitis A, B, C or E infection and liver imaging (e.g. biliary tract) may be warranted.
- Obtain PK sample, as close as possible to last dose of study drug, if PK analysis is performed in the study.
- Additional testing for other hepatotropic viral infection (CMV, EBV or HSV), autoimmune hepatitis or liver biopsy may be considered as clinically indicated or after consultation with specialist/hepatologist.

All cases confirmed on repeat testing meeting the laboratory criteria defined above, with no other alternative cause for LFT abnormalities identified, should be considered as "medically significant"; such an event therefore will meet the definition of an SAE and is reported as an SAE using the term "potential drug-induced liver injury". All such events should be followed up with the outcome clearly documented.

6.4 Concomitant medications

Administration of certain concomitant medications may lead to the requirement for subject to be discontinued. Discussions regarding discontinuation of patients requiring concomitant medication should be discussed with Novartis on a case by case basis.

6.4.1 Permitted concomitant therapy

Supportive therapy including prophylactic antibiotic and antifungal treatments, transfusions, growth factors etc. will be administered at the discretion of the investigators according to standard of care. It is required that all patients receive maximal prophylaxis for the prevention of nausea and vomiting, using antiemetics according to local practice.

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

6.4.2 Permitted concomitant therapy requiring caution and/or action

Strong CYP3A4 inhibitors should be used with caution due to potential increase in midostaurin exposure. Alternative medicinal products that do not strongly inhibit CYP3A4 activity should be considered. In situations where satisfactory therapeutic alternatives do not exist, patients should be closely monitored for midostaurin-related toxicity.

Based on in vitro data, midostaurin and its active metabolites may have the potential to inhibit P-glycoprotein (P-gp), breast cancer resistant protein (BCRP), and Organic Anion Transporting Polypeptide 1B1 (OATP1B1).

Midostaurin, CGP62221 and CGP52421 can potentially induce the following CYPs: CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP3A4 and inhibit the following ones: CYP1A2, CYP2C8, CYP2C9, CYP2D6, CYP2E1, CYP3A4/5. In absence of clinical data medicinal products with a narrow therapeutic range that are substrates of these CYPs should be used with caution when administered concomitantly with midostaurin, and may need dose adjustment to maintain optimal exposure. Therefore medicinal products with a narrow therapeutic range that

[redacted]

are substrates of CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2E1, CYP3A4/5, P-gp, BCRP or OATP1B1 should be used with caution when administered concomitantly with midostaurin and may need dose adjustment to maintain optimal exposure.

A list of strong CYP3A4 inhibitors, substrates with narrow therapeutic index for CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2E1, CYP3A, P-gp and substrates of BCRP and OATP1B1 is available in Appendix 2 (Section 14.2.2).

As far as possible avoid co-administering drugs with a "Known", "Possible", or "Conditional" risk of Torsades de Pointes (TdP) during the course of the study.

- If concomitant administration of drugs with a "known risk of TdP" is required and cannot be avoided, then the study drug must be interrupted. If, based on the investigator assessment and clinical need, study drug is resumed, close ECG monitoring is advised. In such scenarios, the study drug should be resumed only after the discontinuation (preferably after five half-lifes after discontinuation) of the drugs with a known risk of TdP.
- If during the course of the study, concomitant administration of a drug with ¨Possible risk of TdP¨ or ¨Conditional risk of TdP¨ is required, based on the investigator assessment and clinical need, study treatment may be continued with close ECG monitoring to ensure patient safety.

A list of drugs associated with QT prolongation and/or TdP is available online at https://crediblemeds.org/and in Appendix 2.

6.4.3 Prohibited concomitant therapy

Strong CYP3A4 inducers: Concomitant use of midostaurin with strong inducers of CYP3A4 should be avoided. Strong CYP3A4 inducers decrease exposure of midostaurin and its active metabolites (CGP52421 and CGP62221). In a study in healthy subjects, co-administration of the strong CYP3A4 inducer rifampicin (rifampin; 600 mg daily) to steady state with a single dose of midostaurin decreased maximum plasma midostaurin concentration (Cmax) by 73% and area under the curve from time 0 to infinite (AUC_{inf}) by 96% in average, respectively. CGP62221 exhibited a similar pattern. The mean area under the curve from time zero to the last measurable concentration sampling time after the first dose (AUC_{last}) of CGP52421 decreased by 60%. In absence of clinical data, the impact of strong CYP3A4 inducers on midostaurin exposure at steady-state was investigated based on physiologically-based PK models. Exposure was predicted to be decreased by 60%.

A list of strong inducers of CYP3A4 is available in Appendix 2.

6.5 Patient numbering, treatment assignment or randomization

6.5.1 Patient numbering

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

[redacted]

the informed consent form, the patient is assigned to the next sequential Subject Number available to the investigator through the Clinical Data Management System interface.

The investigator or designated staff will contact the Interactive Response Technology (IRT) and provide the requested identifying information for the patient to register them into the IRT. Once assigned, the Subject Number must not be reused for any other patient and the Subject Number for that individual must not be changed. If the patient is not randomized or does not start study treatment, the reason will be entered into the Disposition CRF.

The IRT must be notified within 2 days that the patient was not randomized by using appropriate form.

6.5.2 Treatment assignment or randomization

In double blind part 2, patients will be assigned to one of the 2 treatment arms, midostaurin or placebo (Section 4.1 and Section 6.1) in a ratio of 1:1.

Randomization will be stratified by chemotherapy regimen (JALSG or RATIFY) and by AML FLT3 genotype: tyrosine kinase domain (TKD) mutation, FLT3 internal tandem duplication (ITD) mutation with allelic ratio < 0.7, or FLT3-ITD mutation with allelic ratio ≥ 0.7.

The randomization numbers will be generated using the following procedure to ensure that treatment assignment is unbiased and is concealed from patients and investigator staff. A patient randomization list will be produced by the IRT provider using a validated system that automates the random assignment of patient numbers to randomization numbers. These randomization numbers are linked to the different treatment arms, which in turn are linked to medication numbers. A separate medication randomization list will be produced by or under the responsibility of Novartis Drug Supply Management using a validated system that automates the random assignment of medication numbers to medication packs containing each of the study treatments.

On study Day 8, all patients who fulfill all inclusion/exclusion criteria, who have AML with a demonstrated FLT3 mutation through the Novartis-designated central laboratory, and who have begun induction chemotherapy will be randomized via IRT to one of the treatment arms. The investigator or delegate will call or log on to the IRT and confirm that the patient fulfills all the inclusion/exclusion criteria. The IRT will assign a randomization number to the patient, which will be used to link the patient to a treatment arm and will specify a unique medication number for the first package of study drug to be dispensed to the patient. The randomization number will not be communicated to the caller.

6.5.3 Treatment blinding

Patients, investigators, study team members, and anyone involved in the study conduct will remain blinded to the identity of the study drug from the time of randomization until database lock for the primary analysis.

Randomization data will be kept strictly confidential until the time of unblinding and will not be accessible to anyone involved in the conduct of the study except for an independent statistician and an independent programmer who will perform the interim analysis and the bioanalyst to avoid the unnecessary analysis of placebo samples. The identity of the study drug

[redacted]

will be concealed by the use of study drug (midostaurin or placebo) that is identical in packaging, labeling, schedule of administration, appearance, and odor. Confidentiality of randomization data is required to limit the occurrence of potential bias arising from the influence that the knowledge of treatment may have on the recruitment and allocation of patients.

Unblinding of study drug assignment will only occur in the case of patient emergencies (Section 8.3) and at the time of the primary analysis (see Section 10.7). Although not anticipated, for any health authority that requests such information, every effort will be made to have an independent team respond to the request while keeping the study team blinded. In rare cases when unblinding occurs because of emergency patient management, the actual treatment arm will not be communicated to any Novartis employee involved trial conduct in order to maintain their blinded status.

6.6 Study drug preparation and dispensation

The investigator or responsible site personnel must instruct the patient or caregiver to take the study drugs as per protocol. Study drug(s) will be dispensed to the patient by authorized site personnel only. All dosages prescribed to the patient and all dose changes during the study must be recorded on the appropriate CRF.

Study drug provided is midostaurin 25 mg and matching placebo control.

Study drug will be supplied by Novartis as soft gelatine capsules and will be packaged in child-resistant blisters. Each blister pack contains eight capsules, and each medication kit contains eight blisters for a total of sixty-four capsules per kit.

Table 6-3 Dispensing and preparation

Study treatment	Dispensing	Preparation
Midostaurin or placebo	Capsules including instructions for administration are dispensed by study personnel on an outpatient basis. Patients will be provided with adequate supply of study drug for self-administration at home until at least their next scheduled study visit.	Not applicable
Daunorubicin	Not applicable	Refer to product information
Cytarabine	Not applicable	Refer to product information

6.6.1 Study treatment packaging and labeling

Study drug: midostaurin/placebo:

In part 1 of the study, midostaurin will be provided as global clinical open label supply and will be packed and labeled under the responsibility of Novartis Drug Supply Management. In part 2, midostaurin/placebo, will be provided as global clinical blinded supply and will be packed and labeled under the responsibility of Novartis Drug Supply Management.

Labels will comply with the legal requirements of each country and will include storage conditions and a unique medication number (corresponding to study treatment and strength). Responsible site personnel will identify the study drug package(s) to be dispensed by the

[redacted]

medication number(s) assigned by IRT to the patient. Site personnel will add the patient number on the label. The label has 2-parts (base plus tear-off label); immediately before dispensing the package to the patient, site personnel will detach the outer part of the label from the package and affix it to the patient's source document.

Chemotherapy: daunorubicin and cytarabine:

Daunorubicin and cytarabine will be commercial open label and will be supplied globally by Novartis or supplied locally as per local practice if agreed and approved by the global clinical team.

When supplied globally, daunorubicin will be supplied as a vial of 20 mg powder for preparation of a solution for injection and cytarabine as vials of 100 mg and 1000 mg solution for injection.

For chemotherapy supplied globally, the labels will comply with the legal requirements of each country and will include storage conditions, a unique medication number (corresponding to study treatment and strength).The label has 2-parts; immediately before dispensing the package to the patient, site personnel will detach the outer part of the label from the package and affix it to the patient's source document.

6.6.2 Drug supply and storage

Study treatment must be received by designated personnel at the study site, handled and stored safely and properly, and kept in a secured location to which only the investigator and designated site personnel have access. Upon receipt, the study treatment should be stored according to the instructions specified on the drug labels and in the Investigator's Brochure for midostaurin/placebo or the package insert for daunorubicin and cytarabine.

These instructions should be made clear to the patient for storage and self-administration of midostaurin/placebo at home.

Site staff will be responsible for managing re-supplies for the chemotherapy (daunorubicin or idarubicin and cytarabine) and for midostaurin/placebo.

Midostaurin/placebo as well as chemotherapy supplied globallywill be managed by IRT system.

Site staff should enter dispensed drugs into the IRT system immediately so that the IRT can provide drug re-supplies in a timely manner.

Chemotherapy supplied locally according to local practice and regulation as agreed by the global clinical team will not be managed by IRT system.

Table 6-4 Supply and storage of study treatments

Study treatments	Supply	Storage
Midostaurin/placebo	Centrally supplied by Novartis	Refer to study drug label and product information
Daunorubicin Cytarabine	Supplied globally by Novartis or supplied locally as per local practice if agreed and approved by the global clinical team.	Refer to drug label and product information

[redacted]

6.6.3 Study drug compliance and accountability

6.6.3.1 Study drug compliance

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

6.6.3.2 Study drug accountability

The investigator or designee must maintain an accurate record of the shipment and dispensing of study treatment in a drug accountability log. Drug accountability will be noted by the field monitor during site visits and at the completion of the study. Patients will be asked to return all unused study treatment and packaging on a regular basis, at the end of the study or at the time of study treatment discontinuation.

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

6.6.3.3 Handling of other study treatment

Not applicable

6.6.4 Disposal and destruction

The study drug supply can be destroyed at the local Novartis facility, Drug Supply group or third party, as appropriate. Arrange for drug supply to be destroyed at the site only if permitted by local regulations and authorized by Novartis in a prior agreement.

Drug supplies will be destroyed only after the approval of monitor and after the completion of drug accountability reconciliation.

7 Visit schedule and assessments

7.1 Study flow and visit schedule

Table 7-1 lists all of the assessments and indicates with an “X”, the visits when they are performed. All data obtained from these assessments must be supported in the patient’s source documentation.

The table indicates which assessments produce data to be entered into the clinical database (D) or remain in source documents only (S) (“Category” column). No CRF will be used as a source document. Allowed visit windows are specified as follows:

- Screening assessments listed below, must occur within 7 days prior to Day 1 as per Table 7-1.

[redacted]

- During each induction and consolidation cycle, PK and ECG assessments must be performed on the specified day. Other assessments will be performed within a strict +/- three days window.
- Then during continuation cycles, all other assessments will be performed within a strict +/- three days window to take into account scheduling over public holidays if not explicitly specified otherwise.

Reasonable effort should be made to follow the schedule outlined in Table 7-1.

[redacted]

Table 7-1 Visit evaluation schedule

A: Screening until end of consolidation phase

	Category	Protocol Section	Screening	Induction Phase Cycle 1 -2													EOT (FLT3<0)	End of Induction Phase / EOT	Prior to each Consolidation cycle	Consolidation Phase Cycle 1-4								End of Consolidation Phase / EOT
Visit name	**D**		**Screening**	**IND C1-IND C2**																**CON C1-CON C4**								**CON DISPOSITION**
Day of cycle			**-7 to -1**	**1**	**2**	**3**	**4**	**5**	**7**	**8**	**11**	**15**	**18**	**21**	**24**	**28**				**1**	**3**	**5**	**8**	**11**	**15**	**21**	**28**	
Visit Number (For incremental cycle, follow the convention of +10 from previous visit)																											
Visit Number			**1**	**110**	**120**	**130**	**140**	**150**	**160**	**170**	**180**	**190**	**200**	**210**	**220**	**230**		**1979**	**370**	**380**	**390**	**400**	**410**	**420**	**430**	**440**	**450**	**1989**
Informed consent																											
Obtain study Informed Consent	D		x																								
IRT (not apply for part1)																											
Registration	D		x																								
Eligibility checklist	D		x	Induction 1: when FLT3 mutation status is confirmed																							
Randomization	D									x																	
Patient history																											
Diagnosis/ Disease history	D		x																								
Demography	D		x																								
Inclusion/ exclusion criteria	D	5.2 / 5.3	x																								

[redacted]

	Category	Protocol Section	Screening	Induction Phase Cycle 1 -2													EOT (FLT3<0)	End of Induction Phase / EOT	Prior to each Consolidation cycle	Consolidation Phase Cycle 1-4								End of Consolidation Phase / EOT
Visit name	**D**		**Screening**	**IND C1-IND C2**																**CON C1-CON C4**								**CON DISPOSITION**
Day of cycle			**-7 to -1**	**1**	**2**	**3**	**4**	**5**	**7**	**8**	**11**	**15**	**18**	**21**	**24**	**28**				**1**	**3**	**5**	**8**	**11**	**15**	**21**	**28**	
Visit Number (For incremental cycle, follow the convention of +10 from previous visit)																											
Visit Number			**1**	**110**	**120**	**130**	**140**	**150**	**160**	**170**	**180**	**190**	**200**	**210**	**220**	**230**	**1979**		**370**	**380**	**390**	**400**	**410**	**420**	**430**	**440**	**450**	**1989**
FLT3 mutation status on BMA (Table 7-6)	D		x																								
FLT3 mutation status on PB (see Table 7-6)	D		x																								
Cytogenetics	D		x																								
Medical History	D		x																								
Prior antineo plastic medications	D		x																								
Prior / concomitant medications and procedures	D		x	Continuous													X	X	Continuous								

[redacted]

	Category	Protocol Section	Screening	Induction Phase Cycle 1 -2													EOT (FLT3<0)	End of Induction Phase / EOT	Prior to each Consolidation cycle	Consolidation Phase Cycle 1-4								End of Consolidation Phase / EOT
Visit name	**D**		**Screening**	**IND C1-IND C2**																**CON C1-CON C4**								**CON DISPOSITION**
Day of cycle			**-7 to -1**	**1**	**2**	**3**	**4**	**5**	**7**	**8**	**11**	**15**	**18**	**21**	**24**	**28**				**1**	**3**	**5**	**8**	**11**	**15**	**21**	**28**	
Visit Number (For incremental cycle, follow the convention of +10 from previous visit)																											
Visit Number			**1**	**110**	**120**	**130**	**140**	**150**	**160**	**170**	**180**	**190**	**200**	**210**	**220**	**230**		**1979**	**370**	**380**	**390**	**400**	**410**	**420**	**430**	**440**	**450**	**1989**
Physical examination																											
Performance status	D	7.2.2.4	x	x														x (at EOT)	x	x			x		x	x	x	x (at EOT)
Height	D	7.2.2.3	x																								
Weight	D	7.2.2.3	x	x														x (at EOT)		x							x (at EOT)
Vital signs	D	7.2.2.2	x	x			x			x	x	x	x	x	x	x		x (at EOT)	x	x			x		x	x	x	x (at EOT)
Physical examination	S	7.2.2.1	x	x			x			x	x	x	x	x	x	x		x (at EOT)	x	x			x		x	x	x	x (at EOT)
Extamedullary involvement	D		x	x			x			x	x	x	x	x	x	x		x (at EOT)	x	x			x		x	x	x	x (at EOT)
Lab assessments (see Table 7-3)																											
Hematology	D	7.2.2.5.1	x	x			x			x	x	x	x	x	x	x		x (at EOT)	x	x			x		x	x	x	x (at EOT)
Chemistry (B: total bili only)	D	7.2.2.5.2	x	x	xB	xB	xB	xB		x		x		x				x (at EOT)	x	x			x		x	x		x (at EOT)
Coagulation	D	7.2.2.5.3	x	x						x		x		x		x												
Other hepatic tests for suspected DILI	S	6.3.3.1	If clinically indicated																								
Urinalysis dipstick and microscopic analysis	D	7.2.2.5.4	x	If clinically indicated																							

[redacted]

	Category	Protocol Section	Screening	Induction Phase Cycle 1 -2													EOT (FLT3<0)	End of Induction Phase / EOT	Prior to each Consolidation cycle	Consolidation Phase Cycle 1-4								End of Consolidation Phase / EOT
Visit name	**D**		**Screening**	**IND C1-IND C2**																**CON C1-CON C4**								**CON DISPOSITION**
Day of cycle			**-7 to -1**	**1**	**2**	**3**	**4**	**5**	**7**	**8**	**11**	**15**	**18**	**21**	**24**	**28**				**1**	**3**	**5**	**8**	**11**	**15**	**21**	**28**	
Visit Number (For incremental cycle, follow the convention of +10 from previous visit)																											
Visit Number			**1**	**110**	**120**	**130**	**140**	**150**	**160**	**170**	**180**	**190**	**200**	**210**	**220**	**230**		**1979**	**370**	**380**	**390**	**400**	**410**	**420**	**430**	**440**	**450**	**1989**
Serum (S) or Urine (U) Pregnancy test	S	7.2.2.5.5	X (S)							x (U)							x U	x (U at EOT)					x (U)					x (U at EOT)
Imaging/other assessments																												
Chest X-ray		7.2.2.6	x	If clinically indicated																								
ECG (Table 7-4)	D	7.2.2.7.1	x							x	x			x									x	x		x		
Cardiac MUGA/ECHO	D	7.2.2.7.2	x	If clinically indicated														x	If clinically indicated									x
Safety																												
Adverse events	D	8.1	x	Continuous													x	x	Continuous									
Pharmacokinetics																												
PK sampling (see Table 7-5)	D	7.2.3								X (I1 only)	X (I1 only)	X (I1 only)	X (I1 only)	X (I1 only)									X (C1 and C3)			X (C1 and C3)		
[redacted]																												

[redacted]

	Category	Protocol Section	Screening	Induction Phase Cycle 1 -2													EOT (FLT3<0)	End of Induction Phase / EOT	Prior to each Consolidation cycle	Consolidation Phase Cycle 1-4								End of Consolidation Phase / EOT
Visit name	**D**		**Screening**	**IND C1-IND C2**																**CON C1-CON C4**								**CON DISPOSITION**
Day of cycle			**-7 to -1**	**1**	**2**	**3**	**4**	**5**	**7**	**8**	**11**	**15**	**18**	**21**	**24**	**28**				**1**	**3**	**5**	**8**	**11**	**15**	**21**	**28**	
Visit Number (For incremental cycle, follow the convention of +10 from previous visit)																											
Visit Number			**1**	**110**	**120**	**130**	**140**	**150**	**160**	**170**	**180**	**190**	**200**	**210**	**220**	**230**		**1979**	**370**	**380**	**390**	**400**	**410**	**420**	**430**	**440**	**450**	**1989**

[redacted]

[redacted]

	Category	Protocol Section	Screening	Induction Phase Cycle 1 -2													EOT (FLT3<0)	End of Induction Phase / EOT	Prior to each Consolidation cycle	Consolidation Phase Cycle 1-4								End of Consolidation Phase / EOT
Visit name	**D**		**Screening**	**IND C1-IND C2**																**CON C1-CON C4**								**CON DISPOSITION**
Day of cycle			**-7 to -1**	**1**	**2**	**3**	**4**	**5**	**7**	**8**	**11**	**15**	**18**	**21**	**24**	**28**				**1**	**3**	**5**	**8**	**11**	**15**	**21**	**28**	
Visit Number (For incremental cycle, follow the convention of +10 from previous visit)																											
Visit Number			**1**	**110**	**120**	**130**	**140**	**150**	**160**	**170**	**180**	**190**	**200**	**210**	**220**	**230**		**1979**	**370**	**380**	**390**	**400**	**410**	**420**	**430**	**440**	**450**	**1989**
Assessment of disease																											
Investigator assessment of Disease Response (BMA or biopsy and PB)	D	7.2.1	x											x				X (if previous BMA not sufficient to confirm CR)		if clinically appropriate and at time of relapse								x
Patient reported outcomes																											
EORTC QLQ-C30	D	7.2.6.1	x											x				x (at EOT)							x		x (at EOT)
PGIC	D	7.2.6.2												x				x (at EOT)							x		x (at EOT)
[redacted]																											
Disposition	D		x														x	x									x
IRT																											
Dispensation Midostaurin/Placebo	D									x												x					
Treatment Discontinuation	D																X	x (at EOT)									x (at EOT)

[redacted]

	Category	Protocol Section	Screening	Induction Phase Cycle 1 -2													EOT (FLT3<0)	End of Induction Phase / EOT	Prior to each Consolidation cycle	Consolidation Phase Cycle 1-4								End of Consolidation Phase / EOT
Visit name	**D**		**Screening**	**IND C1-IND C2**																**CON C1-CON C4**								**CON DISPOSITION**
Day of cycle			**-7 to -1**	**1**	**2**	**3**	**4**	**5**	**7**	**8**	**11**	**15**	**18**	**21**	**24**	**28**				**1**	**3**	**5**	**8**	**11**	**15**	**21**	**28**	
Visit Number (For incremental cycle, follow the convention of +10 from previous visit)																											
Visit Number			**1**	**110**	**120**	**130**	**140**	**150**	**160**	**170**	**180**	**190**	**200**	**210**	**220**	**230**		**1979**	**370**	**380**	**390**	**400**	**410**	**420**	**430**	**440**	**450**	**1989**
Study treatment administration																											
Midostaurin / Placebo	D									Continuous twice daily													Continuous twice daily				
Daunorubicin JALSG (J) / RATIFY (R)	D			J/R	J/R	J/R	J	J																			
Cytarabine JALSG (J) / RATIFY (R)	D			continuous IVCI (J/R)																J: continuous Day 1 to 5 R: Days 1, 3 and 5								

[redacted]

B.: End of consolidation phase until end of study

	Category	Protocol Section	Prior to 1st cycle of Continuation phase	Continuation Phase Cycle 1-12		End of Continuation Phase /EoT	30 day safety follow up	Post treatment follow up (until 36 months after Day 1 of the last patient)	Survival follow up (until 36 months after Day 1 of the last the patient
Visit name	**D**			**CONT C1- CONT C12**					
Day of cycle				**1**	**15**				
Visit Number (For incremental cycle, follow the convention of +10 from previous visit)			**730**	**740**	**750**	**1999**			
Patient history									
Prior/concomitant medications and procedures	D		continuous						
Antineoplastic therapies after discontinuation of study treatment	D						x	Every 2 months for years 1 and 2 and every 3 months for years 3 and 4 and then yearly	x
Transplant after discontinuation of study treatment	D						x	Every 2 months for years 1 and 2 and every 3 months for years 3 and 4 and then yearly	x
Physical examination									
Performance status	D	7.2.2.4	X	x		x			
Weight	D	7.2.2.3	x	x		x			
Vital signs	D	7.2.2.2	x	x		x		Every 2 months for years 1 and 2 and every 3 months for years 3 and 4 and then yearly	
Physical examination	S	7.2.2.1	x	x		x			
Extramedullary involvement	D		x	x		x			
Lab assessments (see Table 7-3)									
Hematology	D	7.2.2.5.1	x	x	X (C1 and C2 continuation only if no grade 2 or higher	x		Every 2 months for years 1 and 2 and every 3 months for years 3 and 4 and then yearly	

[redacted]

	Category	Protocol Section	Prior to 1st cycle of Continuation phase	Continuation Phase Cycle 1-12		End of Continuation Phase /EoT	30 day safety follow up	Post treatment follow up (until 36 months after Day 1 of the last patient)	Survival follow up (until 36 months after Day 1 of the last the patient
Visit name	**D**			**CONT C1- CONT C12**					
Day of cycle				**1**	**15**				
Visit Number (For incremental cycle, follow the convention of +10 from previous visit)			**730**	**740**	**750**	**1999**			
					anemia, thrombocytopenia, or neutropenia				
Chemistry	D	7.2.2.5.2	x	x		x			
Other hepatic tests for suspected DILI	S	6.3.3.1	If clinically indicated						
Urinalysis dipstick and microscopic analysis	D	7.2.2.5.4	If clinically indicated						
Serum (S) or Urine (U) Pregnancy test	S	7.2.2.5.5		x (U)		x (U)	x (S)		
Imaging/other assessments									
Chest X-ray	D	7.2.2.6	If clinically indicated						
ECG (Table 7-4)	D	7.2.2.7.1	x	X (cycle 2 to cycle 12)		Completion of C12 or at EOT			
Cardiac MUGA/ECHO	D	7.2.2.7.2	If clinically indicated			x			
Safety									
Adverse events	D	8.1	Continuous						
Pharmacokinetics									

[redacted]

	Category	Protocol Section	Prior to 1st cycle of Continuation phase	Continuation Phase Cycle 1-12		End of Continuation Phase /EoT	30 day safety follow up	Post treatment follow up (until 36 months after Day 1 of the last patient)	Survival follow up (until 36 months after Day 1 of the last the patient
Visit name	**D**			**CONT C1- CONT C12**					
Day of cycle				**1**	**15**				
Visit Number (For incremental cycle, follow the convention of +10 from previous visit)			**730**	**740**	**750**	**1999**			
PK sampling (see Table 7-5)	D	7.2.3	x	C5, C9		Completion of C12			
[redacted]									
Assessment of disease									
Investigator assessment of Disease Response (BMA or biopsy and Peripheral blood)	D			C5, C9		Completion of C12/At relapse		Every 4 months after completion of continuation therapy up until 1 year. OR, If discontinuation of study treatment for any other reason than	

[redacted]

	Category	Protocol Section	Prior to 1st cycle of Continuation phase	Continuation Phase Cycle 1-12		End of Continuation Phase /EoT	30 day safety follow up	Post treatment follow up (until 36 months after Day 1 of the last patient)	Survival follow up (until 36 months after Day 1 of the last the patient
Visit name	**D**			**CONT C1- CONT C12**					
Day of cycle				**1**	**15**				
Visit Number (For incremental cycle, follow the convention of +10 from previous visit)			**730**	**740**	**750**	**1999**			
								relapse, every 4 months until relapse or until 30 months after the start of treatment, whichever comes first AND at time of relapse for all patients	
Patient reported outcomes									
EORTC QLQ-C30 / PGIC	D	7.2.6.1 / 7.2.6.2		x		x		Every 4 months during the first year	
[redacted]									
Disposition	D					x		X	
IRT									
Dispensation Midostaurin/Placebo	D			x					
Treatment Discontinuation	D					x			
Study treatment administration									
Midostaurin/Placebo	D			continuous twice daily (from D1 to D28)					
Follow-up									
Survival Follow-up	D								x every 3 months

[redacted]

7.1.1 Molecular pre-screening

Not applicable

7.1.2 Screening

Written informed consent must be obtained prior to any screening procedures. Screening assessments to confirm eligibility into the study should be performed as per visit evaluation schedule between Day-7 and Day-1. Serum pregnancy test must be conducted within 72 hours prior to start of study treatment and must be confirmed negative before the first dose of study treatment. ECG should be obtained within 3 days prior to start of study treatment.

Assessments done according to the timelines above as per local practice or under a local protocol, prior to signing the study specific informed consent form will not have to be repeated during the screening phase and results can be used for the study. At the discretion of the investigator, the final diagnosis of AML by BMA can be confirmed after the informed consent form has been signed for the study. In case of dry tap (failure to obtain bone marrow after BMA attempt): confirmation of AML diagnosis can be based on a bone marrow biopsy or on peripheral blood (documenting presence ≥ 20% blasts) at investigator's discretion if bone marrow biopsy may delay initiation of the treatment.

For patients with diagnosis already confirmed at a referral site, the relevant samples must be available and must be used by the investigational site to confirm the diagnosis and cytogenetics. [redacted]

If the relevant samples are not available, BMA or any relevant samples will be collected to confirm the diagnosis and cytogenetics at screening. [redacted]

As part of screening procedures, a BMA or a whole blood sample will be collected and shipped immediately to the Novartis designated central laboratory for FLT3 mutation assessment. In case both sample types are collected/available, FLT3 screening will be preferentially performed only on the bone marrow sample and the peripheral blood sample will be banked for future testing and diagnostic assay development.

Re-screening is not allowed, and a patient who does not meet all inclusion/exclusion criteria will be considered to be a screen failure. However, hematology and biochemistry laboratories assessments could be repeated during the screening period if needed.

7.1.2.1 Eligibility screening

Dosing with chemotherapy may begin while FLT3 mutation results are pending. FLT3 mutation results from the central laboratory must be received by Day 8 for the patient to be eligible for randomization and to receive midostaurin/placebo.

Following registering in the IRT for screening, patient eligibility will be checked once all screening procedures are completed (except FLT3 status). The eligibility check will be embedded in the IRT system.

[redacted]

FLT3 status will be entered in the IRT by the Novartis-designated central laboratory that analyzed the samples. An email with the results will be sent to the site by IRT.

Please refer and comply with detailed guidelines in the IRT manual.

7.1.2.2 Information to be collected on screening failures

A patient who signs an informed consent but fails to begin chemotherapy for any reason will be considered as a screen failure. The reason for not being started on chemotherapy will be entered on the Disposition CRF. The Demographics, Informed Consent, and Inclusion/Exclusion Criteria CRF must also be completed for Screen Failure patients. FLT3 data will be collected for all patients including screen failures. No other data will be entered into the clinical database for patients who are screen failures, unless the patient experienced a Serious Adverse Event during the Screening Phase (see Section 8 for SAE reporting details).

Information to be collected on patients who failed to be randomized

Patients who are determined to have negative or unknown FLT3 mutation at Day 8 of 1st cycle of induction will be not randomized at Day 8 and then will be discontinued from the treatment.

In addition to data collected at screening until Day 8 of 1st cycle of induction, the reason for end of treatment will be entered on the Disposition CRF, data from EOT (FLT3<0) and any AEs/SAEs if applicable, will be collected until safety follow up visit. However, if a patient with FLT3 mutation negative is enrolled in Novartis sponsored study (PKC412E2301) the AE/SAE collection will be performed in study PKC412E2301 as per protocol and the same information will not be collected again in study A2220.

No other data will be collected for those patients.

7.1.2.3 Patient demographics and other baseline characteristics

The data to be collected on subject characteristics at screening includes:

- Diagnosis and extent of cancer (WHO and FAB classification)
- Demography (age, gender, race and ethnicity, or as allowed by local regulations)
- Cytogenetics
- Medical history
- Prior antineoplastic medications
- Prior and concomitant medications

Assessments to be performed at screening/baseline include:

- Physical examination (i.e., performance status (ECOG), height, weight, vital signs)
- Extramedullary involvement
- Laboratory assessments (i.e., hematology, chemistry, coagulation, urinalysis, serum pregnancy test)
- Cardiovascular assessments (i.e., ECG; ECHO or MUGA)
- Chest x-ray
- Assessment of disease (in blood and bone marrow)

[redacted]

[redacted]

7.1.3 Run-in period

Not applicable

7.1.4 Treatment period

Patients will be assigned on Cycle 1 Day 8 of induction therapy to midostaurin or placebo using a stratified randomization according to FLT3 mutation and treatment regimen.

- Study treatment will begin on Day 1 of Cycle 1 with chemotherapy: daunorubicin from Day 1 to Day 3 or Day 5 and cytarabine from Day 1 to Day 7. Study treatment will continue on Day 8 with midostaurin/placebo until Day 21.
- Chemotherapy and midostaurin/placebo will be administered as indicated in Table 7-1 and until the subject experiences any of the following: persistent disease, relapse as determined by investigator, unacceptable toxicity that precludes further treatment, pregnancy, start of non-protocol anti-cancer therapy, discontinuation at the discretion of the Investigator or patient, loss to follow-up, death, or study termination by the Sponsor.

Visit frequency

- Induction phase cycle 1: assessments will be scheduled 2 times per week until hematology recovery. This cycle may be longer than 28 days (until hematology recovery occurs), and the assessments will be performed accordingly. If the patient has evidence of persistent leukemia on a bone marrow evaluation from Day 21 to Day 28 or at the end of the first induction cycle, then a second cycle of induction therapy will be administered.
- Induction phase cycle 2: assessments will be the same as for Cycle 1, except for the PK [redacted]. For details of assessments in induction Cycles 1 and 2, refer to Table 7-1.
- Patients who achieve a CR will continue with consolidation therapy for up to 4 cycles. In case of toxicities with RATIFY regimen, patients are allowed to have 3 cycles only at the discretion of the investigator. For JALSG regimen, patients will have 3 cycles during consolidation therapy.
- Patients who remain in remission after consolidation therapy will begin continuation therapy for up to 12 cycles of 28 days each. Continuation therapy will begin no sooner than 14 days after the last dose of midostaurin/placebo during the last cycle of consolidation therapy. Patients who remain in remission after 12 cycles of continuation therapy will continue in post-treatment follow-up.

Time windows for scheduling assessments

- Reasonable effort should be made to follow the schedule of assessments as described in the protocol and especially during the induction and consolidation cycles for PK and ECG assessments.
- All other assessments have a strict ± 3 days window, unless otherwise indicated.

[redacted]

- Patients who discontinue study treatment must have an End of Treatment (EOT) visit performed ≤ 7 days after stopping study treatment.

7.1.5 Discontinuation of study treatment

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

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

Study treatment must be discontinued under the following circumstances:

- Emergence of specific adverse events or laboratory abnormalities under some circumstances outlined in Section 6.3.
- Disease Progression (disease persistence or relapse after CR)
- Pregnancy (pregnancy will be followed for outcome)
- Any other protocol deviation that results in a significant risk to the patient's safety

The appropriate personnel from the site and Novartis will assess whether study treatment should be discontinued for any patient whose treatment code has been broken inadvertently for any reason.

Patients who discontinue study treatment should NOT be considered withdrawn from the study. They should return for the assessments indicated in Section 7.2.1. If they fail to return for these assessments for unknown reasons, every effort (e.g. telephone, email, and letter) should be made to contact them as specified in Section 7.1.9 and Section 7.1.10.

For patients who discontinue treatment for reasons other than documented disease persistence or relapse (designated as Progressive Disease in eCRF), death, loss to follow-up, or withdrawal of consent, a bone marrow aspirate must continue to be performed every 4 months until relapse or until 30 months after the start of treatment, whichever comes first.

The investigator (or designee) must also contact the IRT to register the patient's discontinuation from study treatment within 2 days.

7.1.5.1 Replacement policy

Part 1: Safety evaluation part in Japan

If a subject is considered to be non-evaluable for the safety evaluation, a new subject will be enrolled until the minimum number of 3 evaluable patients is obtained prior to the next schedule Independent Safety Committee evaluation.

Part 2: Randomized part

Patients will not be replaced during the part 2.

[redacted]

7.1.6 Withdrawal of consent

Patients may voluntarily withdraw consent to participate in the study for any reason at any time. Withdrawal of consent occurs only when a patient:

- Does not want to participate in the study anymore, and
- Does not allow further collection of personal data

In this situation, the investigator should make a reasonable effort (e.g. telephone, e-mail, letter) to understand the primary reason for the subject's decision to withdraw his/her consent and record this information.

Study treatment must be discontinued and no further assessments conducted, and the data that would have been collected at subsequent visits will be considered missing.

Further attempts to contact the subject are not allowed unless safety findings require communicating or follow-up.

All efforts should be made to complete the assessments prior to study withdrawal. A final evaluation at the time of the subject's study withdrawal should be made as detailed in the assessment table.

Novartis will continue to keep and use collected study information (including any data resulting from the analysis of a subject's samples until their time of withdrawal) according to applicable law.

For Japan: All biological samples not yet analyzed at the time of withdrawal may still be used for further testing/analysis in accordance with the terms of this protocol and of the informed consent form.

For Rest of Word (RoW): All biological samples not yet analyzed at the time of withdrawal will no longer be used, unless permitted by applicable law. They will be stored according to applicable legal requirements.

7.1.7 Follow up for safety evaluations

All patients must have safety evaluations for 30 days, after the last dose of study treatment (including cytarabine, daunorubicin or midostaurin/placebo).

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

7.1.8 Follow up for efficacy evaluations

Patients who discontinue study treatment for reasons other than death, disease persistence or relapse (designated as Progressive Disease in the eCRF) should continue to have bone marrow assessments as scheduled in the protocol until relapse, as outlined in Section 7.1.

After the Safety Follow-up visit, patients will enter the post-treatment follow-up phase.

During this phase, the following data will be collected:

- Antineoplastic therapy/transplantation after discontinuation of treatment: every 2 months during first 2 years then every 3 months for years 3 and 4, and then yearly.

[redacted]

The following assessments will be performed:

- Vital signs, blood samples for hematology [redacted] every 2 months for years 1 and 2, every 3 months for years 3 and 4 and then yearly

[redacted]

- Questionnaires (EORTC QLQ-C30 / PGIC): Every 4 months during the first year.

Patients will be followed in post-treatment follow up until relapse or end of study, whichever occurs first.

7.1.9 Survival follow up

Patients will enter the survival follow-up phase once they complete the safety follow up period (30 days after the last dose of study treatment) or have relapse during post-treatment follow-up (see Figure 4-2). Patients will then be contacted by telephone every 3 months +/- 2 weeks or have a visit to follow up on their survival status. Any new antineoplastic medications that have been started since the last contact date will also be collected during these phone calls or visits.

7.1.10 Lost to follow-up

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

7.2 Assessment types

7.2.1 Efficacy assessments

Disease assessments will be performed locally through evaluation of bone marrow specimens, peripheral blood samples, and other relevant data that will be collected as described in Table 7-1. The response assessment will be according to Cheson criteria (Cheson 2003). Response assessments will require a bone marrow aspirate to be performed. In the event of a dry tap or an aspiration that is inadequate for interpretation, a bone marrow biopsy is required for response assessment.

Complete remission (CR): Complete remission is defined as all of the following:

- Peripheral Blood Counts
  - Absolute neutrophil count $\geq 1.0 \times 10^9$/L.
  - Platelet count $\geq 100 \times 10^9$/L.
  - No leukemic blasts in the peripheral blood.

[redacted]

- Adequate erythroid recovery so that RBC transfusions are not necessary.
- No Auer rods.

- Bone Marrow
  - Adequate cellularity.
  - No Auer rods.
  - < 5% blast cells.
  - No extramedullary leukemia (such as CNS or soft tissue involvement).

Morphologic complete remission with incomplete platelet count recovery (CRp)

- CRp satisfies all CR criteria except platelets < 100 x 10^9/L, but platelet transfusions are not necessary.

Partial Remission (PR)

- Must meet all criteria of a CR except that the bone marrow may contain 5%-24% blasts.

Treatment Failure

- Resistance disease:
  - Patient survives ≥ 7 days post chemotherapy; persistent AML in blood and bone marrow.
- Aplasia:
  - Patient survives ≥ 7 days post chemotherapy; death while cytopenic, with aplastic bone marrow
- Indeterminate cause:
  - Patient who die < 7 days post therapy
  - Patient who die > 7 days post therapy with no peripheral blood blasts, but no bone marrow examination
  - Patient who do not complete the first course of therapy

Relapse

Any of the following, occurring after CR:

- The reappearance of circulating blast cells not attributable to "overshoot" following recovery from myelosuppressive therapy.
- >5% blasts in the marrow, not attributable to another cause (e.g., CSF, bone marrow regeneration).
- Development of extramedullary leukemia.

Remission Induction cycle 1

For the first induction cycle, a bone marrow aspirate will be obtained from Day 21 to Day 28 to determine the presence of residual leukemia (≥ 5% blasts) according to Cheson criteria (Cheson 2003) and the need for a second induction cycle or CR.

If the bone marrow aspirate is insufficient to make a determination of remission, then the bone marrow assessment should be repeated after about one week.

[redacted]

- If the Day 21 or subsequent bone marrow aspirations show ≥5% leukemic blasts in a cellular marrow (>20%) or otherwise meet criteria for persistent leukemia, then the patient will receive a second cycle of induction therapy.
- Patients for whom a CR is documented on Day 21-Day 28 BMA, will advance to consolidation therapy.
- In absence of "hematology recovery" (defined as ANC ≥ 1.0 x 10^9/L and platelets ≥ 100 x 10^9/L) at the time of the Day 21-Day 28 bone marrow aspiration showing <5% leukemic blasts in a cellular marrow (>20%), the patient will be observed until hematology recovery and another bone marrow aspiration will be performed within about one week after recovery of ANC and platelets to document continued presence of CR. Physicians should consider earlier bone marrow exams in patients, as clinically indicated.

If a CR (as described in Section 10.5.2.2) is documented, then the relevant slides must be kept at the site.

Remission Induction cycle 2

For the second induction cycle, a bone marrow aspirate will be obtained from Day 21 to Day 28 to determine the presence of residual leukemia (≥ 5% blasts) or CR according to Cheson criteria (Cheson 2003).

If the bone marrow aspirate is insufficient to make a determination of remission, then the bone marrow assessment should be repeated after about one week.

- Patients for whom a CR is documented, will advance to consolidation therapy.
- In absence of "hematology recovery" (defined as ANC ≥ 1.0 x 10^9/L and platelets ≥ 100 x 10^9/L) at the time of the Day 21-Day 28 bone marrow aspiration showing <5% leukemic blasts, the patient will be observed until hemotology recovery and another bone marrow aspiration will be performed within about one week after recovery of ANC and platelets to document continued presence of CR. Physicians should consider earlier bone marrow exams in patients, as clinically indicated.
- Patients failing to achieve CR will be discontinued from study treatment but will continue to be followed for survival.

If a CR (as described in Section 10.5.2.2) is documented, then the relevant slides must be kept at the site.

Consolidation therapy:

A bone marrow examination will be performed to evaluate for continued remission at the end of the final cycle of consolidation and within one week of hematopoietic recovery (ANC ≥ 1.0 x 10^9/L and platelets ≥ 100 x 10^9/L).

Continuation therapy:

A bone marrow examination will be performed to evaluate for continued remission at the start of Cycle 5, at the start of Cycle 9, and at the end of Cycle 12 of continuation therapy or at any time at relapse.

[redacted]

Post-treatment follow-up:

A bone marrow examination will be performed to evaluate for continued remission every four months after completion of continuation therapy, up until 1 year. For patients who discontinue study treatment for other reasons than relapse prior to completion of continuation therapy, every 4 months until relapse or until 30 months after the start of treatment, whichever comes first. A bone marrow examination will also be performed at any time of relapse.

7.2.2 Safety and tolerability assessments

Safety will be monitored by assessing physical examination, performance status, laboratory examinations, ECGs, MUGA as well as collecting of the adverse events at every visit. For details on AEs collection and reporting, refer to Section 8.

More frequent examinations may be performed at the investigator's discretion, if clinically indicated.

7.2.2.1 Physical examination

A physical examination will be performed as described in Table 7-1 and will include the examination of general appearance, skin, neck (including Thyroid), eyes, ears, nose, throat, lungs, heart, abdomen, back, lymph nodes, extremities, vascular and neurological assessments.

Information about the physical examination must be present in source documents at the study site. Significant findings that were present prior to the signing of informed consent must be included in the Medical History CRF. Significant new findings that begin or worsen after informed consent must be recorded on the Adverse Events CRF.

Extramedullary involvement will be assessed at the time of physical examination.

7.2.2.2 Vital signs

Vital signs include blood pressure (supine position preferred when ECG is collected), pulse measurement, and body temperature and will be measured at screening and at subsequent time points as specified in Table 7-1.

7.2.2.3 Height and weight

Height will be measured at screening.

Body weight (in indoor clothing, but without shoes) will be measured at screening and at subsequent time points as specified in Table 7-1.

7.2.2.4 Performance status

ECOG Performance status scale will be used as described in the Table 7-1. More frequent examinations may be performed at the investigator's discretion, if medically indicated. ECOG performance status scale will be used as described in the Table 7-2.

[redacted]

Table 7-2 ECOG performance status scale

Score	Performance Status
0	Fully active, able to carry on all pre disease performance without restriction
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature ,light housework, office work
2	Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about more than 50% of waking hours
3	Capable of only limited self-care, confined to bed or chair more than 50% of waking hours
4	Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair
5	Dead

7.2.2.5 Laboratory evaluations

Table 7-3 Clinical laboratory parameters collection plan

Test Category	Test Name
Hematology (Local)	Hgb, WBC with differential (including basophils, eosinophils, lymphocytes, monocytes, neutrophils, bands, blasts), platelets
Biochemistry (Local)	Albumin, alkaline phosphatase, ALT, AST, LDH, calcium, magnesium, phosphorous, sodium, potassium, creatinine, creatine kinase, total bilirubin, direct bilirubin, total cholesterol, BUN/urea, uric acid, amylase, lipase, fasting glucose
Coagulation (Local)	International normalized ratio (INR), activated partial thromboplastin time (aPTT)
Urinalysis (Local)	Dipstick examination includes protein, glucose, pH; microscopic analysis
Other hepatic tests in case of suspected DILI (Local)	GGT, creatinine kinase, alkaline phosphatase, other tests for diagnosis of acute hepatitis A,B, C or E infection or testing for hepatotropic viral infection or autoimmune hepatitis
Pregnancy Test (Local)	Pregnancy test of serum/urine

Clinical laboratory analyses are to be performed by the local laboratory (in the investigational' site) according to the schedule of assessments and collection plan outlined respectively in Table 7-1 and Table 7-3. Novartis must be provided with a copy of the local laboratory's certification and a tabulation of the normal ranges and units of each parameters collected in the eCRF. Any changes regarding normal ranges and units for laboratory values assessed during the study must be reported via an updated tabulation indicating the date of revalidation. Additionally, if at any time a patient has laboratory parameters obtained from a different laboratory, Novartis must be provided with a copy of the certification and a tabulation of the normal ranges and units for this laboratory as well. The investigator is responsible for reviewing all laboratory reports for patients in the study and evaluating any abnormalities for clinical significance.

At any time during the study, abnormal laboratory parameters which are clinically significant and require an action to be taken with study treatment (e.g; require dose modification and/or interruption of study treatment, lead to clinical symptoms or signs, or require therapeutic intervention), whether specifically requested in the protocol or not will be recorded on the Adverse Events eCRF. Laboratory data will be summarized using the Common Terminology Criteria for Adverse events (CTCAE) version 5.0. Additional laboratory evaluations are left to the discretion of the investigator.

[redacted]

7.2.2.5.1 Hematology

Hematology tests are to be performed by the local laboratory according to the schedule of assessments and collection plan outlined respectively in Table 7-1 and Table 7-3.

More frequent hematology testing may also be performed as medically necessary. Additional results from unscheduled hematology lab evaluations should be recorded on the appropriate unscheduled visit eCRF.

7.2.2.5.2 Clinical chemistry

Clinical chemistry tests are to be performed by the local laboratory according to the schedule of assessments and collection plan outlined respectively in Table 7-1 and Table 7-3.

More frequent clinical chemistry testing may also be performed as medically necessary. Additional results from unscheduled chemistry lab evaluations should be recorded on the appropriate unscheduled visit eCRF.

It should be noted in the patient's eCRF if the patient was fasting as the time of blood sampling.

7.2.2.5.3 Coagulation

Coagulation analyses (International normalized ratio (INR) and activated partial thromboplastin time (aPTT)) are to be performed by the local laboratory according to the schedule of assessments and collection plan outlined respectively in Table 7-1 and Table 7-3.

7.2.2.5.4 Urinalysis

Dipstick analysis (including pH, glucose and protein) is to be performed by the local laboratory at screening and during treatment phase if clinically indicated.

Abnormal findings will be followed up with a microscopic analysis and/or additional assessments as clinically indicated.

7.2.2.5.5 Pregnancy and assessments of fertility

Women of child-bearing potential will have serum pregnancy tests at screening and at 30-day Safety follow up visit. During the treatment phases, the absence of pregnancy will be confirmed by urine pregnancy test prior to the first dose of study treatment (at day 8 during induction and consolidation cycles and Day 1 during continuation cycles).

Urine pregnancy tests will be required to be performed as well as at the End of Treatment visit. Every effort must be made for the women of child bearing potential to return to the site for the final pregnancy test. However if the patient is unable to return then the patient will administer the urine pregnancy test at home using the kit provided. For all pregnancy test performed at home, the site personnel will follow up with the patient via telephone call to collect the date and the test results and document the information in the patient's source documents.

Women of child-bearing potential will be instructed to contact the site immediately at any time during the study (on treatment or during follow-up) should they have a positive pregnancy test.

[redacted]

Male patients treated with daunorubicin or cytarabine should receive appropriate advice on the risk of infertility and the option of sperm conservation. Midostaurin may impair both male and female fertility and this should be communicated to patients.

7.2.2.6 Radiological examinations

Radiological examinations should be performed as clinically indicated.

7.2.2.7 Cardiac assessments

7.2.2.7.1 Electrocardiogram (ECG)

A standard triplicate 12 lead ECG will be performed according to the relevant Visit Evaluation Schedule (Table 7-1 and Table 7-4).

Table 7-4 Central ECG assessment monitoring schedule

Cycle	Day	Time	ECG Type
Screening	-3 to -1	Pre-dose (baseline ECG)	12 Lead, triplicate
Induction Phase, cycles 1 and 2	Day 8, Day 11, Day 21	Pre-dose (before PK) Post-dose at 3 hours ± 0.5 hour (before pK)	12 Lead, triplicate
Consolidation Phase, each cycle	Day 8, Day 11, Day 21	Pre-dose (before PK) Post-dose at 3 hours ± 0.5 hour (before pK)	12 Lead, triplicate
Prior to 1st cycle of Continuation		Pre-dose (before PK)	12 Lead, triplicate
Continuation, cycle 2 to cycle 12	Day 1	Pre-dose (before PK)	12 Lead, triplicate
Continuation, cycle 12	D28	Pre-dose (before PK)	12 Lead, triplicate
Continuation	Treatment discontinuation		12 Lead, triplicate
Unscheduled sample		Anytime	12 Lead, triplicate

Interpretation of the tracing must be made by a qualified physician. Each ECG tracing should be labeled with the study number, patient initials (where regulations permit), patient number, date, and kept in the source documents at the study site. Clinically significant abnormalities present at screening should be reported on the Medical History CRF.

Standard triplicate 12 lead ECG recording will be performed after the patient has been resting for approximately 10 min prior to each ECG collection time point indicated in Table 7-1 and prior to PK samples.

The individual ECGs should be recorded approximately 2 minutes apart. The mean QTcF value for each visit will be calculated from the triplicate ECGs for each patient.

Dose adjustments in case of QT prolongation should be performed per Section 6.3.

Additional, unscheduled, safety ECGs may be repeated at the discretion of the investigator at any time during the study as clinically indicated. Unscheduled ECGs with clinically significant findings should be collected in triplicate. Local cardiologist ECG assessment may also be performed at any time during the study at the discretion of the investigator.

[redacted]

All ECGs, including unscheduled triplicate safety ECGs with clinically relevant findings, collected during the study should be transmitted to the central core ECG laboratory for review.

The results of the centrally assessed ECGs are automatically transferred into the clinical database.

Clinically significant ECG abnormalities present at screening should be reported on the Medical History CRF. New or worsened clinically significant findings occurring after informed consent must be recorded on the Adverse Events CRF.

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

Cardiac Imaging will be performed at screening, EOT and whenever clinically indicated.

7.2.2.7.3 Cardiac enzymes

Not applicable

7.2.2.8 Tolerability

Not applicable

7.2.3 Pharmacokinetics

Serial blood samples will be collected from all patients to assess single dose and steady-state plasma PK midostaurin and its two active metabolites. Non-compartmental Analysis (NCA) PK parameters will be estimated from each individual plasma concentration-time profile using appropriate methods and software. Refer to Section 10.5.4 for a table of PK parameters that will be estimated.

7.2.3.1 Pharmacokinetic blood collection and handling

Blood samples will be taken by either direct venipuncture or an indwelling cannula inserted in a forearm vein. At specified time points described in Table 7-5, 3 mL blood draws will be collected into tubes containing sodium heparin and gently inverted several times to thoroughly mix the anticoagulant. Tubes will be centrifuged to separate plasma and plasma will immediately be transferred into labeled 1.8 mL polypropylene screw-cap tubes. Plasma samples will be placed in a freezer in an upright position until shipment to the bioanalytical laboratory for analysis.

The exact collection date and time of all samples must be documented on the PK blood collection CRF. The date and exact time of dosing, as well as the date and actual time of blood sampling must be recorded on the CRF.

Refer to the [CPKC412A2220 Laboratory Manual] for detailed instructions for the collection, handling, and shipment of PK samples.

[redacted]

Table 7-5 Pharmacokinetic blood collection log for midostaurin, CGP52421 and CGP62221

Dose Reference ID (2)	PK Sample number	Cycle (Period number)	Study day for each cycle	Time(1)	Blood volume (mL)
1	101	Induction 1 Cycle 1*	8	Pre-dose	3
1	102	Induction 1 Cycle 1*	8	1h (+/- 5min)	3
1	103	Induction 1 Cycle 1*	8	3h (+/- 15min)	3
1	104	Induction 1 Cycle 1*	8	6h (+/- 30min)	3
1	105	Induction 1 Cycle 1*	8	12h (+/- 30min)	3
2/201	106	Induction 1 Cycle 1	11	Pre-dose	3
2	107	Induction 1 Cycle 1	11	Post-dose 3hrs +/- 0.5 hrs	3
3/301	108	Induction 1 Cycle 1	15	Pre-dose	3
4/401	109	Induction 1 Cycle 1	18	Pre-dose	3
5/501	110	Induction 1 Cycle 1	21	Pre-dose	3
5	111	Induction 1 Cycle 1	21	Post-dose 3hrs +/- 0.5 hrs	3
6/601	112	Consolidation, cycle 1	8	Pre-dose	3
6	113	Consolidation Cycle 1	8	Post-dose 3hrs +/- 0.5 hrs	3
7/701	114	Consolidation, cycle 1	21	Pre-dose	3
7	115	Consolidation, cycle 1	21	Post-dose 3hrs +/- 0.5 hrs	3
8/801	116	Consolidation, cycle 3	8	Pre-dose	3
8	117	Consolidation, cycle 3	8	Post-dose 3hrs +/- 0.5 hrs	3
9/901	118	Consolidation, cycle 3	21	Pre-dose	3
9	119	Consolidation, cycle 3	21	Post-dose 3hrs +/- 0.5 hrs	3
[redacted]					
11/1101	121	Continuation , cycle 5	1	Pre-dose	3
12/1201	122	Continuation, cycle 9	1	Pre-dose	3
13/1301	123	Completion of C12	28	Pre-dose	3
Total volume					69
Unscheduled samples					
NA	100x	NA	NA	Unscheduled	

*: When medically feasible full blood sample to be collected
(1): When PK is collected at the same time point as ECG, ECG should be done first.
(2): Dose reference ID: The first number refers to the administration at the day, the second number refer to the administration the day before (The information has to be collected)
Unscheduled blood samples will be uniquely, sequentially numbered 1001, 1002, …

[redacted]

7.2.3.2 Analytical method

Plasma concentrations of midostaurin and its active metabolites CGP62221 and CGP52421 will be measured using a validated liquid chromatography-tandem mass spectrometry (LC-MS/MS) assay with a lower limit of quantification (LLOQ) of approximately 10.0 ng/mL. Concentrations below the LLOQ will be reported as 0.00 ng/mL and missing samples will be labeled accordingly.

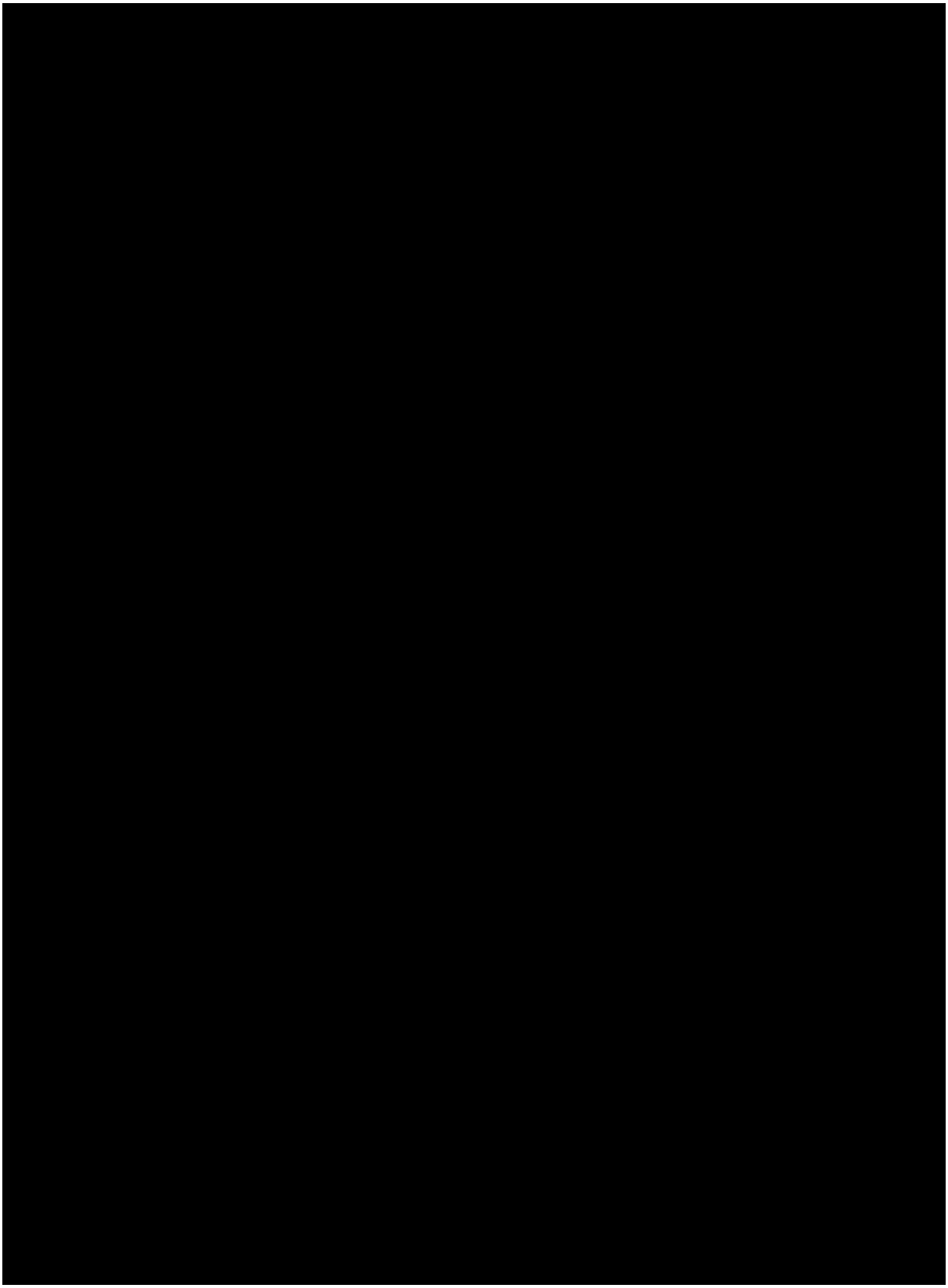
7.2.4 Biomarkers

In addition to establishing FLT3 mutation status in order to determine patient eligibility for the study, [redacted]

Table 7-6 Biomarker sample collection plan

Sample Type	Blood volume/visit	Visit	Time Point
Samples for Molecular Screening			
Bone Marrow Aspirate for FLT3 mutational testing	2 mL	Screening (eligibility confirmation)	Anytime, as early as possible after patient signed ICF
Peripheral Blood for FLT3 mutational testing	6 mL	Screening (eligibility confirmation)	Anytime, as early as possible after patient signed ICF
A bone marrow aspirate or a whole blood sample will be collected. In case both sample types are collected/available, FLT3 screening will be preferentially performed only on the bone marrow sample; and the peripheral blood sample will be banked for future testing			

[redacted]



[redacted]

7.2.4.2 Additional biomarker assessments

Not applicable

[redacted]

Other assessments

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

[redacted]

7.2.6 Patient reported outcomes

The European Organization for Research and Treatment of Cancer's core quality of life questionnaire (EORTC-QLQ-C30, version 3.0) will be used to evaluate patient-reported outcome measures of health-related quality-of-life, functioning, disease symptoms, treatment-related side effects, and global health status. The EORTC QLQ-C30 is recognized as reliable and valid measures (Aaronson 1993, Rabin 2001, Cormier 2008) frequently used in clinical trials of patients with newly diagnosed acute myeloid leukemia. In addition, the patient global impression of change (PGIC) will also be administered at the same time. This one item questionnaire will be used to anchor the results of the EORTC QLQ-C30.

All patient-reported outcome (PRO) measures will be administered at screening, at Day21 of each cycle until the end of consolidation phase, then Day1 of each cycle during the continuation phase, at End of study treatment and during the post treatment follow-up every 4 months during the first year, according to the Visit Evaluation in Table 7-1. However, the PGIC will not be administered at screening.

PRO data will be collected using an electronic tablet device and should be administered in the patient's local language at the beginning of the study visit prior to any interaction with the study investigator including any tests, treatments or receipt of results from any tests to avoid biasing the patient's perspective. Patients should be given sufficient space and time to complete all study questionnaires and all administered questionnaires should be reviewed for completeness. If missing responses are noted, patients should be encouraged to complete them. Attempts should be made to collect responses to the questionnaire for all patients, including from those who discontinue prior to the study evaluation completion visit, however, if patients refuse to complete questionnaire, this should be documented in study source records. Patient's refusal to complete study questionnaire is not protocol deviation.

Completed questionnaires, including both responses to the questions and any unsolicited comments written by the patient, must be reviewed and assessed by the investigator before the clinical examination for responses which may indicate potential AEs or SAEs. This review should be documented in study source records.

If an AE or SAE is confirmed then the physician should record the event as instructed in Section 8 of this protocol. Investigators should not encourage the patients to change responses reported in questionnaires.

7.2.6.1 EORTC QLQ-C30

The EORTC QLQ-C30 contains 30 items and is composed of both multi-item scales and single-item measures. These include five functional scales (physical, role, emotional, cognitive and social functioning), three symptom scales (fatigue, nausea/vomiting, and pain), six single items (dyspnea, insomnia, appetite loss, constipation, diarrhea and financial impact) and a global health status/QoL scale (Aaronson 1993). All of the scales and single-item measures range in score from 0 to 100. A high scale score represents a higher response level. Thus, a high score for a functional scale represents a high / healthy level of functioning; a high score for the global health status / QoL represents a high QoL, but a high score for a symptom scale / item represents a high level of symptomatology / problems. All scoring will follow the scoring procedures defined by the EORTC Scoring Manual (Fayers 2001).

7.2.6.2 Patient Global Impression of Change (PGI-C)

The PGI-C is a single self-reported item that asks about change in status of a patient's overall satisfaction with medication since starting the standalone study. The specific wording of the PGI-C is "Directions: Circle the one number that best describes how your overall satisfaction with your medication has changed since starting the study": "Very much improved" =1; "Much improved" =2; "Minimally improved" =3; "No change" =4; "Minimally worse" =5; "Much worse" =6; "Very much worse" =7. PGI-C questions have been widely used to assess the patient perspective of improvement in clinical trials and have shown clinical validity in a variety of indications, including depression (Mallinckrodt et al 2005), urinary incontinence (Kinchen et al 2005) and adult asthma (Guy 1976, Hahn 1995).

8 Safety monitoring and reporting

8.1 Adverse events

8.1.1 Definitions and reporting

An adverse event is defined as the appearance of (or worsening of any pre-existing) undesirable sign(s), symptom(s), or medical condition(s) that occur after patient's signed informed consent has been obtained.

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

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

[redacted]

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

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

The occurrence of adverse events should be sought by non-directive questioning of the patient (subject) during the screening process after signing informed consent and at each visit during the study. Adverse events also may be detected when they are volunteered by the patient (subject) during the screening process or between visits, or through physical examination, laboratory test, or other assessments. As far as possible, each adverse event should be evaluated to determine:

1. The severity grade (CTCAE Grade 1-5)
2. Its duration (Start and end dates)
3. Its relationship to the study treatment (Reasonable possibility that AE is related: No, Yes)
4. Action taken with respect to study or investigational treatment (none, dose adjusted, temporarily interrupted, permanently discontinued, unknown, not applicable)
5. Whether medication or therapy was given (no concomitant medication/non-drug therapy, concomitant medication/non-drug therapy)
6. Whether it is serious, where a serious adverse event (SAE) is defined as in Section 8.2.1 and which seriousness criteria have been met
7. Outcome (not recovered/not resolved, recovered/resolved, recovered/resolved with sequalae, fatal, unknown)
8. If the event worsens, the event should be reported a second time in the CRF noting the start date when the event worsens in toxicity. For grade 3 and 4 adverse events only, if improvement to a lower grade is determined a new entry for this event should be reported in the CRF noting the start date when the event improved from having been Grade 3 or Grade 4.

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

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

Progression of malignancy (including fatal outcomes), if documented by use of appropriate method (for example, as per Cheson's guidelines for hematological malignancies), should not be reported as a serious adverse event.

Adverse events separate from the progression of malignancy (example, deep vein thrombosis at the time of progression or hemoptysis concurrent with finding of progressive disease) will be reported as per usual guidelines used for such events with proper attribution regarding relatedness to the drug.

[redacted]

8.1.2 Laboratory test abnormalities

8.1.2.1 Definitions and reporting

Laboratory abnormalities that constitute an Adverse event in their own right (are considered clinically significant, induce clinical signs or symptoms, require concomitant therapy or require changes in study treatment), should be recorded on the Adverse Events CRF. Whenever possible, a diagnosis, rather than a symptom should be provided (e.g. anemia instead of low hemoglobin). Laboratory abnormalities that meet the criteria for Adverse Events should be followed until they have returned to normal or an adequate explanation of the abnormality is found. When an abnormal laboratory or test result corresponds to a sign/symptom of an already reported adverse event, it is not necessary to separately record the lab/test result as an additional event.

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

8.1.3 Adverse events of special interest

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

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

8.2 Serious adverse events

8.2.1 Definitions

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

- Is fatal or life-threatening
- Results in persistent or significant disability/incapacity
- Constitutes a congenital anomaly/birth defect
- Is medically significant, i.e., defined as an event that jeopardizes the patient or may require medical or surgical intervention to prevent one of the outcomes listed above
- Requires inpatient hospitalization or prolongation of existing hospitalization,
- Note that hospitalizations for the following reasons should not be reported as serious adverse events:

[redacted]

- Routine treatment or monitoring of the studied indication, not associated with any deterioration in condition
- Elective or pre-planned treatment for a pre-existing condition that is unrelated to the indication under study and has not worsened since signing the informed consent
- Social reasons and respite care in the absence of any deterioration in the patient's general condition

- Note that treatment on an emergency outpatient basis that does not result in hospital admission and involves an event not fulfilling any of the definitions of a SAE given above is not a serious adverse event.

8.2.2 Reporting

To ensure patient safety, every SAE, regardless of suspected causality, occurring after the patient has provided informed consent and until at least 30 days after the patient has stopped study treatment must be reported to Novartis within 24 hours of learning of its occurrence.

Any additional information for the SAE including complications, progression of the initial SAE, and recurrent episodes must be reported as follow-up to the original episode within 24 hours of the investigator receiving the follow-up information. An SAE occurring at a different time interval or otherwise considered completely unrelated to a previously reported one should be reported separately as a new event.

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

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

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

If the SAE is not previously documented in the Investigator's Brochure or Package Insert (new occurrence) and is thought to be related to the Novartis study treatment, an oncology Novartis Chief Medical Office and Patient Safety (CMO&PS) department associate may urgently require further information from the investigator for Health Authority reporting. Novartis may need to issue an Investigator Notification (IN), to inform all investigators involved in any study with the same drug that this SAE has been reported. Suspected Unexpected Serious Adverse Reactions (SUSARs) will be collected and reported to the competent authorities and relevant ethics committees in accordance with Directive 2001/20/EC or as per national regulatory requirements in participating countries.

[redacted]

8.3 Emergency unblinding of treatment assignment

Emergency unblinding should only be undertaken when it is essential for effective treatment of the patient. Most often, study treatment discontinuation and knowledge of the possible treatment assignments are sufficient to treat a study patient who presents with an emergency condition. Emergency code breaks are performed using the IRT. When the investigator contacts the IRT to unblind a patient, he/she must provide the requested patient identifying information and confirm the necessity to unblind the patient. The investigator will then receive details of the drug treatment for the specified patient and a fax confirming this information. The system will automatically inform the Novartis monitor for the site and the Study Lead that the code has been broken.

It is the investigator's responsibility to ensure that there is a procedure in place to allow access to the IRT in case of emergency. The investigator will inform the patient how to contact his/her backup in cases of emergency when he/she is unavailable. The protocol number, study treatment name if available, patient number, and instructions for contacting the local Novartis CPO (or any entity to which it has delegated responsibility for emergency code breaks) will be provided to the patient in case emergency unblinding is required at a time when the investigator and backup are unavailable. However, if a mechanism is already in place to ensure that the investigator and/or back-up can always be reached in case of emergency then the procedure above is not required.

Study treatment must be discontinued once emergency unblinding has occurred.

8.4 Pregnancies

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

Pregnancy should be recorded on a Clinical Trial Pregnancy Form and reported by the investigator to the oncology Novartis Chief Medical Office and Patient Safety (CMO&PS). Pregnancy follow-up should be recorded on the same form and should include an assessment of the possible relationship to the study treatment for any pregnancy outcome. Any SAE experienced during pregnancy must be reported on the SAE Report Form.

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

If pregnancy occurs in a patient in the study, the **study treatment must be discontinued**, though the patient may stay in the study and follow the assessments, if she wishes to do so. All assessments that are considered as a risk during pregnancy must not be performed. The patient may continue all other protocol assessments.

Follow up of the pregnancy (female patient or female partner of patient) should be according to the following schedule:

[redacted]

- Tracking of pregnancy cases occurs until after Expected Delivery Date (EDD) for all prospective pregnancy cases received from clinical studies (including pregnancies where the patient was exposed to placebo or comparator and pregnancies due to the conduct of the study).
- EDD +1 month (mandatory for all cases). Requesting the pregnancy outcome and other clinically relevant pregnancy data or changes in data.
- EDD+2 month (mandatory if no answer is obtained after request at EDD+1 month). A reminder letter for the outcome.
- The follow up at EDD+3 months is mandatory for all cases of live birth. Information on the status of the baby 3 months after delivery and information on any development issue or abnormality that would not be seen at birth must be collected.
- The follow up at EDD+12 months is mandatory for all cases of live birth. Information on the status of the baby 12 months after delivery and information on any development issue or abnormality that would not be seen at birth must be collected.

If the pregnancy case is lost to follow-up (e.g. no response after 3 attempts) this information must be transferred to the Safety Desk of the CPO.

8.5 Warnings and precautions

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

8.6 Independent Safety Committee

The data from the part 1 in Japan will be evaluated by the Independent Safety Committee, which will comprise three external Japanese medical experts who will comprehensively determine the safety and tolerability of midostaurin in combination with the JALSG or RATIFY regimen in Japanese patients. The Independent Safety Committee will evaluate data from the part 1 only.

The Independent Safety Committee will take into consideration all available safety data up to the time of the safety review data cut-off date, which comprises data during induction therapy through to the end of the safety evaluation period (Day 21 of first consolidation cycle).

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. However, the Independent Safety Committee may review the safety of patients before this time if deemed necessary based on the ongoing safety experience.

[redacted]

8.7 Study Steering Committee

The Study Steering Committee will be established comprising investigators participating in the trial.

The Study Steering Committee will ensure transparent management of the study according to the protocol through recommending and approving modifications as circumstances require. The Study Steering Committee will review protocol amendments as appropriate. Together with the clinical trial team, the Study Steering Committee will also develop recommendations for publications of study results including authorship rules. The details of the role of the Study Steering Committee will be defined in a Steering Committee charter.

The Study Steering Committee will not have access to un-blinded trial data prior to the primary analyses.

8.8 Data Monitoring Committee

This study will include a data monitoring committee (DMC) that will be used only for the interim analysis, which will function independently of all other individuals associated with the conduct of this clinical trial, including the site investigators participating in the study. The DMC will review efficacy and safety data, and inform the sponsor whether the success criteria will be met at the interim analysis (for more detailed information for the interim analysis, see Section 10.7).

Specific details regarding composition, responsibilities, data monitoring and meeting frequency, documentation of DMC reports, minutes, and recommendations will be described in a separate charter that is established between the sponsor and the DMC.

9 Data collection and management

9.1 Data confidentiality

Information about study patients will be kept confidential and managed under the applicable laws and regulations. Those regulations require a signed subject authorization informing the subject of the following:

- What protected health information (PHI) will be collected from patients in this study
- Who will have access to that information and why
- Who will use or disclose that information
- The rights of a research subject to revoke their authorization for use of their PHI.

In the event that a subject revokes authorization to collect or use PHI, the investigator, by regulation, retains the ability to use all information collected prior to the revocation of subject authorization. For subjects that have revoked authorization to collect or use PHI, attempts should be made to obtain permission to collect follow-up safety information (e.g. has the subject experienced any new or worsened AEs) at the end of their scheduled study period.

The data collection system for this study uses built-in security features to encrypt all data for transmission in both directions, preventing unauthorized access to confidential participant information. Access to the system will be controlled by a sequence of individually assigned

[redacted]

user identification codes and passwords, made available only to authorized personnel who have completed prerequisite training.

9.2 Site monitoring

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

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

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

9.3 Data collection

For studies using Electronic Data Capture (EDC), the designated investigator staff will enter the data required by the protocol into the Electronic Case Report Forms (eCRF). The eCRFs have been built using fully validated secure web-enabled software that conforms to 21 CFR Part 11 requirements, Investigator site staff will not be given access to the EDC system until they have been trained. Automatic validation programs check for data discrepancies in the eCRFs and, allow modification or verification of the entered data by the investigator staff.

The Investigator must certify that the data entered into the electronic Case Report Forms are complete and accurate and that entry and updates are performed in a timely manner. Data collected by site by analyzed centrally such as [redacted] PK, ECG will be sent electronically to Novartis.

9.4 Database management and quality control

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

Concomitant treatments and prior medications entered into the database will be coded using the WHO Drug Reference List, which employs the Anatomical Therapeutic Chemical classification

[redacted]

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

Samples and/or data will be processed centrally, and the results will be sent electronically to Novartis (or a designated CRO) or entered into the eCRFs by the designated laboratory staff.

Randomization codes and data about all study treatments dispensed to the patient and all IRT assigned dosage changes will be tracked using an Interactive Response Technology. The system will be supplied by a vendor(s), who will also manage the database. The data will be sent electronically to Novartis personnel (or designated CRO).

At the conclusion of the study, the occurrence of any emergency code breaks will be determined after return of all code break reports and unused drug supplies to Novartis personnel (or designated CRO). The occurrence of any protocol violations will be determined. After these actions have been completed and the data has been verified to be complete and accurate, the database will be declared locked and the treatment codes will be unblinded and made available for data analysis. Authorization is required prior to making any database changes to locked data, by joint written agreement between the Global Head of Biostatistics, Global Head of Data Management and the Global Head of Clinical Development.

After database lock, the investigator will receive copies of the patient data for archiving at the investigational site.

10 Statistical methods and data analysis

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 patients enrolled part 1 will be listed and reviewed irrespective of the combination treatment (JALSG or RATIFY regimen).

The analyses for the safety review will be performed when the available data is adequate to perform a data analysis. Details will be described in a separate SAP for the safety review (see Section 10.7).

Randomized part (Part 2)

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

The interim analysis will be performed when 60 patients are randomized and at least 24 EFS events are documented. The interim analysis will be performed by an independent statistician and an independent programmer. Please refer to Section 10.7 for more details.

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.

[redacted]

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 patients will remain in post-treatment or survival follow-up until the cut-off date of the final analysis and all available data from all patients up to this cut-off date will be analyzed.

For screen 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.

10.1 Analysis sets

10.1.1 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.

10.1.2 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.

10.1.3 Per-Protocol set

The Per-Protocol Set (PPS) consists of a subset of the patients in the FAS who are compliant with the 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 CSP (e.g., incorrect histology/cytology, not refractory, not metastatic, different grade of cancer, etc.)
- if prior therapy does not match with CSP requirements in terms of number and types of previous therapy regimens
- missing or incomplete documentation of classification of disease (as required in the CSP)
- another anti-neoplastic therapy administered after start of study treatment and prior to first efficacyassessment
- study treatment received different from treatment assigned by randomization

10.1.4 Dose-determining analysis set

Not applicable.

[redacted]

10.1.5 Pharmacokinetic analysis set

10.1.5.1 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.

10.1.5.2 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 did 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.

10.1.6 Other analysis sets

Not applicable.

10.2 Patient demographics/other baseline characteristics

Demographic and other baseline data including disease characteristics will be listed and summarized descriptively by treatment arm for the FAS and the Safety Set.

Categorical data will be presented as frequencies and percentages. For continuous data, mean, standard deviation, median, minimum, and maximum will be presented.

Relevant medical histories and current medical at baseline will be summarized by system organ class and preferred term, by treatment arm.

10.3 Treatments (study treatment, concomitant therapies, compliance)

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

[redacted]

The duration of exposure in day to study drug (midostaurin/placebo), daunorubicin and cytarabine as well as the dose intensity (computed as the ratio of actual cumulative dose received and actual duration of exposure) and the relative dose intensity (computed as the ratio of dose intensity and planned dose intensity) will be summarized by means of descriptive statistics using the safety set.

The duration of exposure for the study treatment will also be presented by chemotherapy regimen and treatment arm.

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

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

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 for the FAS. 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 duration and best response will be summarized for the FAS.

10.4 Primary objective

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.

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.

10.4.1 Variable

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.

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. Clinical response (CR, CRp, PR and treatment failure after CR) will be assessed via local review according to criteria defined in Section 10.5.2.2. For patients with treatment failure, the EFS will be replaced to 1.

All efficacy analyses for the part 2 will be based on FAS and will include all data observed up-to the cut-off date. If a patient has not observed EFS event at the analysis cut-off date, EFS will be censored at the date of the last adequate clinical assessment before the cut-off date.

[redacted]

10.4.2 Statistical hypothesis, model, and method of analysis

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

The interim and primary efficacy analyses 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 ≥ 0.7, TKD; and regimen: RATIFY regimen, JALSG regimen). 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. In addition, for the interim analysis, 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 also need to be satisfied to declare the success of the study (described in Section 10.7). 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 the study will be unblinded. At the final analysis more mature data can be evaluated .

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% confidence intervals will be presented by treatment arm.

10.4.3 Handling of missing values/censoring/discontinuations

In the primary 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 analysis cut-off date.

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 assessments are available (before an event or a censoring reason occurred) then the date of randomization will be used.

Refer to Table 10-1 for censoring and event date options and outcomes for EFS.

Table 10-1 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

[redacted]

Situation	Date	Outcome
New anticancer therapy given prior to protocol defined progression	Ignore the new anticancer therapy and follow situations above	As per above situations

10.4.4 Supportive and Sensitivity analyses

In part 2, 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 Section 14.1).

If the primary analysis shows successful, subgroup analyses to assess the homogeneity of the treatment effect across demographic and baseline disease characteristics will be performed. The subgroups are as follows:

- 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

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.

10.5 Secondary objectives

10.5.1 Key secondary objective(s)

Not applicable.

10.5.2 Other secondary efficacy objectives

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

[redacted]

10.5.2.1 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 cut-off date in the FAS will be used in the OS analysis. If a patient is not known to have died at the time of analysis cut-off, OS will be censored at the date of last contact.

The OS distribution 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.

If the estimated HR by a stratified Cox model using the randomization stratification factors is less than 1, subgroup analyses to assess the homogeneity of the treatment effect across demographic and baseline disease characteristics will be performed. The subgroups are as follows:

- 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

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.

10.5.2.2 Complete remission (CR) rate

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

CR rate will be summarized for end of induction cycle 1, end of induction cycle 2, end of consolidation and after treatment discontinuation. The difference in CR rates along with two-sided exact 95% CIs (Clopper and Pearson 1934).

10.5.2.3 Cumulative incidence of relapse

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 analysis cut-off, 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.

[redacted]

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.

10.5.3 Safety objectives

10.5.3.1 Analysis set and grouping for the analyses

For all safety analyses, the safety set will be used. All listings and tables will be presented by treatment arm.

The overall observation period will be divided into three mutually exclusive segments:

- pre-treatment period: from day of patient's informed consent to the day before first dose of study treatment
- on-treatment period: from day of first dose of study treatment to 30 days after last dose of study treatment
- post-treatment period: starting on day 31 after last dose of study treatment.

10.5.3.2 Adverse events (AEs)

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

The incidence of treatment-emergent AEs (new or worsening from baseline) will be summarized by system organ class and or preferred term, severity (based on CTCAE grades), type of adverse event, relation to study treatment.

Serious AEs, non-serious AEs and AEs of special interest (AESI) during the on-treatment period will be tabulated.

All deaths (on-treatment and post-treatment) will be summarized.

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

10.5.3.3 Laboratory abnormalities

Grading of laboratory 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.

CTCAE Grade 0 will be assigned for all non-missing values not graded as 1 or higher. Grade 5 will not be used.

For laboratory tests where grades are not defined by CTCAE version 5.0, results will be categorized as low/normal/high based on laboratory normal ranges.

[redacted]

The following listings/summaries will be generated separately for hematology, and biochemistry tests:

- Listing of all laboratory data with values flagged to show the corresponding CTCAE version 5.0 grades if applicable and the classifications relative to the laboratory normal ranges
- For laboratory tests where grades are defined by CTCAE version 5.0, shift tables using CTCAE version 5.0 grades to compare baseline to the worst on-treatment value
- For laboratory tests where grades are not defined by CTCAE version 5.0, shift tables using the low/normal/high/ (low and high) classification to compare baseline to the worst on-treatment value.

10.5.3.4 Other safety data

ECG

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

Categorical Analysis of QT/QTcF interval data based on the number of patients meeting or exceeding predefined limits in terms of absolute QT/QTcF intervals or changes from baseline will be presented. In addition, a listing of these patients will be produced by treatment arm.

Vital signs

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

Other assessments

Cardiac MUGA/ECHO will be collected at baseline, EOT visit and during the study if clinically needed.

Chest X ray will be collected at baseline and during the study if clinically needed.

10.5.3.5 Supportive analyses for secondary objectives

To assess the homogeneity of the treatment safety profile of study drug across demographic and baseline disease characteristics, subgroup analyses may be performed. Details of such analyses will be described in the SAP if appropriate.

10.5.3.6 Tolerability

Tolerability of study drug will be assessed by summarizing the number of dose interruptions and dose reductions. Reasons for dose interruption and dose reductions will be listed by patient and summarized.

10.5.4 Pharmacokinetics

PK parameters for midostaurin and its two major metabolites CGP52421 and 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

[redacted]

therapy. PK parameters listed in Table 10-2 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).

PK parameters and all concentrations will be summarized and reported. Summary statistics will include n (number of values to be reported), arithmetic and geometric mean, median, SD, CV, geometric CV, minimum and maximum.

Trough concentrations will be summarized by treatment part and time point. Summary statistics will include n (number of values to be reported), arithmetic and geometric mean, median, SD, CV, and geometric CV, minimum and maximum. Concentrations below the LLOQ will be treated as zero in summary statistics except for geometric mean. Zero concentrations will not be included in the geometric mean calculation. For Tmax, the median and range will be provided.

More details on the PK analysis will be given in the SAP.

Exposure-response analyses for relevant efficacy and safety endpoints will be further discussed as appropriate in the SAP.

Table 10-2 Noncompartmental pharmacokinetic 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}). 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)

10.5.5 Patient-reported outcomes

The total 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 Appendix 5). No imputation procedures will be applied for missing items or missing assessments.

The QLQ-C30 scores will be analyzed using a repeated measures model for longitudinal data to assess the treatment effect over time including terms for treatment, stratification factors, 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. The differences in least square means between treatment and control group, and the corresponding 95% CI at selected timepoints will be presented. All available data until the end of treatment will be used in the repeated measures models for longitudinal data which assume

[redacted]

that the missing scores at any time point are missing-at-random. Additional sensitivity analysis may be performed to assess the possible violation of missing-at-random assumption for the missing data mechanism if deemed appropriate. Details will be specified in the SAP.

Descriptive statistics will be used to summarize the QLQ-C30 scores and absolute change from baseline scored scales at each scheduled assessment.

Also, the PGIC score will be presented as frequencies and percentages by scheduled timepoint and treatment arm.

Patient reported Outcomes will be administered electronically (ePROs), questionnaires will be loaded on a tablet. The site will need to register the patient's arrival prior to handing the site based tablet. The site coordinator has to make sure that the tablets are charged and the site sets up their log in information (user ID and passwords) prior to handing the device to patients. Note that if one site has multiple ePRO devices, and if they plan to have the same patient use different devices to fill out their PRO data at different points of time, they must ask the patients to create their log in ID's in each of the devices. Please ask site staff to train patients, provide them with helpdesk information and reference guides for ePROs. In exceptional cases only, e.g., in the event of technical problems with the ePRO device(s), the patient should be asked to complet a paper version of the questionnaire(s).

[redacted]

10.7 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.

[redacted]

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 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 the study will be 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.

10.8 Sample size calculation

Safety evaluation part (in Japan only)

A minimum of 3 (if no Safety Events) or 6 eligible 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.

[redacted]

Randomized part

This is a bridging study that will support the registration 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 Section 10.7) 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 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

[redacted]

e.g. SCT rate in CR1 were the same as in Study [A2301], and there was no difference between the two chemotherapy regimens).

10.9 Power for analysis of key secondary variables

Not applicable.

11 Ethical considerations and administrative procedures

11.1 Regulatory and ethical compliance

This clinical study was designed, shall be implemented and reported in accordance with the ICH Harmonized Tripartite Guidelines for Good Clinical Practice, with applicable local regulations (including European Directive 2001/20/EC and US Code of Federal Regulations Title 21), and with the ethical principles laid down in the Declaration of Helsinki.

11.2 Responsibilities of the investigator and IRB/IEC/REB

The protocol and the proposed informed consent form must be reviewed and approved by a properly constituted Institutional Review Board/Independent Ethics Committee/Research Ethics Board (IRB/IEC/REB) before study start. Prior to study start, the investigator is required to sign a protocol signature page confirming his/her agreement to conduct the study in accordance with these documents and all of the instructions and procedures found in this protocol and to give access to all relevant data and records to Novartis monitors, auditors, Novartis Clinical Quality Assurance representatives, designated agents of Novartis, IRBs/IECs/REBs and regulatory authorities as required.

11.3 Informed consent procedures

Eligible patients may only be included in the study after providing written (witnessed, where required by law or regulation), IRB/IEC/REB-approved informed consent.

Informed consent must be obtained before conducting any study-specific procedures (i.e. all of the procedures described in the protocol). The process of obtaining informed consent should be documented in the patient source documents. The date when a subject's Informed Consent was actually obtained will be captured in their CRFs.

Novartis will provide to investigators, in a separate document, a proposed informed consent form (ICF) that is considered appropriate for this study and complies with the ICH GCP guideline and regulatory requirements. Any changes to this ICF suggested by the investigator must be agreed to by Novartis before submission to the IRB/IEC/REB, and a copy of the approved version must be provided to the Novartis monitor after IRB/IEC/REB approval.

Women of child bearing potential should be informed that taking the study medication may involve unknown risks to the fetus if pregnancy were to occur during the study and agree that in order to participate in the study they must adhere to the contraception requirement for the duration of the study. If there is any question that the patient will not reliably comply, they should not be entered in the study.

11.4 Additional consent form

Not applicable

11.5 Discontinuation of the study

Novartis reserves the right to discontinue this study under the conditions specified in the clinical study agreement. Specific conditions for terminating the study are outlined in Section 4.4.

11.6 Publication of study protocol and results

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

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

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

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

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

11.7 Study documentation, record keeping and retention of documents

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

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

[redacted]

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

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

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

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

11.8 Confidentiality of study documents and patient records

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

11.9 Audits and inspections

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

11.10 Financial disclosures

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

12 Protocol adherence

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

[redacted]

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

12.1 Amendments to the protocol

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

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14 Appendices

14.1 Appendix 1 - The Bayesian model, prior, and operating characteristics

14.1.1 Introduction

In this study, the Bayesian predictive probability of (HR for EFS when 36 EFS events are documented < 1) will be calculated at the interim analysis and the Bayesian posterior probability of (HR for EFS per local review < 1) will be calculated as a supportive analysis at the primary analysis. This section provides details of the statistical model, the derivation of prior distributions for the model parameters, and the operating characteristics of the study design.

14.1.2 Motivation

Because this is the bridging study and its target population is very rare, the sample size of this study is very small. Therefore, the available information should be very limited. At the interim analysis, the available information should be more limited.

In such a case, borrowing available information from the original study is very useful to strengthen the result of this study. Bayesian approach is one of effective way to borrow the available information from the original study.

14.1.3 Statistical model

Let Y denote the natural logarithm of the observed hazard ratio (HR). We assume that the asymptotic normality of the log-rank statistic for Y holds [see D. Schoenfeld, Biometrika, Vol. 68, No. 1 (Apr., 1981), pp. 316-319] such that under a 1:1 randomization we have that:

$Y|\theta \sim N(\theta, \sqrt{4/k_0}^2)$, where θ is the unknown true log(HR) and k_0 is the number of events.

The prior for the true log(HR) parameter θ is defined as a mixture between an informative and a non-informative prior. For the informative part of the prior we use the meta-analytic-predictive (MAP) approach which facilitates the Study [A2301] data and accounts for between-study heterogeneity. Its derivation is detailed below. The non-informative mixture component is used in order to account for the possibility that the data in the new study is strongly deviating from the previously observed Study [A2301] result. We place equal weight of 50% on each prior component. The definition of the non-informative prior and the overall operating characteristics are detailed below.

14.1.4 Prior specifications

Description of the meta-analytic-predictive (MAP) approach

The aim of the MAP approach is to derive an informative prior for the log(HR) parameter in the new study which we denote with θ^*. The MAP approach accounts for possible between-trial heterogeneity using an exchangeability model for the study specific mean of the log(HR) values of the historical studies (i.e., Study [A2301]).

[redacted]

Let Y_h and k_h be the log(HR) and the total number of events in the historical study h (h= 1, … , H). Under the normal approximation of the log(HR) the MAP prior is defined by:

$$Y_h \mid \theta_h \sim N\left(\theta_h, \sqrt{4/k_h}^2\right)$$

$$\theta_h \mid \mu, \tau \sim \mathrm{N}(\mu, \tau^2), \qquad \mathrm{h} = 1, \ldots, \mathrm{H}$$

$$\theta^* \mid \mu, \tau \sim \mathrm{N}(\mu, \tau^2),$$

$$\mu \sim P_\mu$$

$$\tau \sim P_\tau$$

$$\theta^* \mid (y_h, k_h : h = 1, \ldots, H)$$

The model is a standard hierarchical normal-normal model with the population mean parameter μ and the between-trial heterogeneity parameter τ . The priors P_μ and P_τ for the population parameters will be defined below. The MAP prior for the model parameter θ^* is the predictive distribution.

Since the predictive distribution is not available analytically, MCMC is used to simulate values from this distribution. This is implemented using Stan version 2.7.0. The sample from this distribution, which is obtained as numerical MCMC sample, is then approximated by a mixture of normal distributions. Normal mixtures with increasing numbers of mixture components are fitted to the sample using the expectation-maximization (EM) algorithm (Dempster 1977). The optimal number of components of the mixture is then identified using the Akaike information criterion (AIC) (Akaike 1974).

Weakly informative prior derived by MAP approach

Available log(HR) from the Study [A2301] study are used to derive the MAP prior for the model parameter θ. The MAP prior for the model parameter is derived as follows:

- H = 1.
- We set the prior P_μ for μ to be non-informative by assigning it a normal distribution with mean 0 and standard deviation of 2. This corresponds to a single observation of no effect such that $\mu \sim \mathrm{N}(0, 2^2)$.
- In order to incorporate the moderate heterogeneity between the Study [A2301] data and the current data, the prior P_τ for the between-trial standard deviation τ is assumed to follow a half-normal distribution with the standard deviation set to 1/2. This represents the assumption of heterogeneous trails as the sampling standard deviation is 2, see [DOI: 10.1002/bimj.201500236].
- From the historical data of Study [A2301] (Table 14-1), Y_1=log(0.728) = -0.317 and k_1= 521.

[redacted]

Table 14-1 Data from CPKC412A2301 study

Event Free Survival	MIDOSTAURIN N=360	PLACEBO N=357	HR [95% CI] MIDOSTAURIN / PLACEBO (1)
Number of events (%)	244 (67.8)	277 (77.6)	0.728 (0.613, 0.866)
Treatment failure	125 (34.7)	150 (42.0)	
Relapse	98 (27.2)	102 (28.6)	
Death	21 (5.8)	25 (7.0)	

(1) Hazard ratio (HR) estimated using Cox regression model stratified according to the randomization FLT3 mutation factor. CI: Wald Confidence Interval.
An EFS event is defined as a failure to obtain a CR in Induction, relapse from CR, or death due to any cause, whichever occurs first.

Prior mixture

In order to account for the possibility that the data of the new study A2220 is potentially very different (non-exchangeable), the mixture for the MAP prior is complemented with a non-informative prior corresponding to a single event of no effect.

To obtain the mixture prior, 50% weight will be assigned to the MAP prior θ^* and 50% weight will be assigned to the non-informative component. These weights are a priori fixed and will be updated by the trail data for the observed log(HR).

14.1.5 Operating characteristics for interim analysis

In order to show how the Bayesian interim study design performs, a simulation study is used. Several example scenarios were investigated (Section 14.1.5.1), and in each case 15,000 trials were simulated, with results summarized in Section 14.1.5.3.

14.1.5.1 Scenarios

In order to show how the design performs, 4 hypothetical scenarios shown in Table 14-2 were investigated. Scenarios 1 to 3 follows our expected assumption that both survival distributions are as observed in Study [A2301] with different enrollment periods (14 months as assumed, shorter period of 10 months and longer period of 18 months). Scenario 4 considers that there is no difference of survival distributions for EFS in midostaurin and placebo.

Table 14-2 Hypothetical scenarios

Scenario	Survival distribution for EFS in midostaurin in A2220	Survival distribution for EFS in placebo in A2220	Enrollment period
1	Same distribution as observed in midostaurin in study A2301	Same distribution as observed in placebo in study A2301	14 months
2			10 months
3			18 months
4	Same distribution as observed in placebo in study A2301	Same distribution as observed in placebo in study A2301	14 months

14.1.5.2 Simulation details

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

[redacted]

observations in each arm were randomly selected from Study [A2301] according to scenarios shown in Table 14-2.

In this simulation, the interim analysis occurs when 60 patients are randomized and 24 EFS events are documented. When both the Bayesian predictive probability of (HR when 36 EFS events are documented < 1) exceeds 90% and the estimated HR at interim analysis < 1, then the study is assessed as positive at the interim analysis.

The primary analysis occurs when 36 EFS events are documented. When estimated HR < 1, then the study is assessed as positive at the primary analysis.

Metrics

Operating characteristics were reviewed for the simulations to compare the relative performance under each scenario. The metrics reviewed were:

1. Probability to show study is positive at the interim analysis (I)

2. Probability to show study is negative at the interim analysis but positive at the primary analysis (II)

3. Conditional probability to show study is negative at primary analysis after showing it to be positive at interim analysis (risk to declare study positive at interim analysis) (III)

4. Mean number of EFS events documented at interim analysis (IV)

5. Estimated study duration at interim analysis from date of first patient randomized (V)

6. Estimated study duration at primary analysis from date of first patient randomized (VI)

14.1.5.3 Simulation results

Table 14-3 below summarizes the simulated operating characteristics of the model for the 4 different scenarios studied.

Table 14-3 Simulation results

Scenario	Metric							
	I (%)	II (%)	I+II (%)	III (%)	IV	V (Months) Mean [2.5% quantile, 97.5% quantile]	VI (months) Mean [2.5% quantile, 97.5 quantile]	Probability to show study is positive when only primary analysis is conducted (%)
1	78.1	8.8	86.9	3.2	28.3	14.1 [14.0, 15.4]	20.7 [13.9, 33.7]	84.3
2	74.3	12.7	87.0	3.0	26.2	10.4 [10.0, 13.0]	18.3 [11.1, 31.1]	84.7
3	80.5	6.5	87.0	3.2	30.0	18.0 [18.0, 18.0]	23.2 [17.0, 36.6]	83.8
4	48.7	6.7	55.4	11.6	30.6	14.0 [14.0, 14.0]	16.9 [13.0, 24.6]	49.9

[redacted]

Simulation results suggested the following:

1. The probability to show positive study (metric I+II) is almost 87% irrespective of enrollment speed under our expected assumption that both survival distributions are as observed in [A2301]

2. The risk to show positive but there is no effect on midostaurin is increased by about 5% (i.e. 55.4 – 49.9) compared to the study design without interim analysis

3. The time to declare positive study might be shortened by about 6 months by conducting an interim analysis

14.1.6 Operating characteristics for supportive analysis

In order to show how the Bayesian model performs, different scenarios were investigated. Table 14-4 shows the probability for a successful trial result of a median HR < 1 (median log(HR) < 0) under some hypothetically assumed true HR values and number of EFS events.

Table 14-4 Posterior probability to show median HR < 1 under several hypothetical true scenarios

#EFS events/assumed true HR	0.37	0.60	0.76	1.00	1.20	1.35
30	0.999	0.974	0.904	0.709	0.520	0.393
35	1.000	0.980	0.911	0.704	0.499	0.363
39	1.000	0.983	0.917	0.700	0.482	0.340
45	1.000	0.987	0.924	0.695	0.460	0.310

[redacted]

14.2 Appendix 2 – Concomitant medications

The following lists are not comprehensive and are only meant to be used as a guide. The lists are based on the Novartis PK Sciences' guidance, Drug-Drug Interaction and Co-Medication Considerations (v07, release date: Jan 2018), which was compiled from the Indiana University School of Medicine's P450 Drug Interaction Table (http//medicine.iupui.edu/clinpharm/ddis/main-table) and supplemented with the Food and Drug Administration (FDA) Draft Guidance for Industry, Drug Interaction Studies – Study Design, Data Analysis, and Implications for Dosing and Labeling (February 2012) (http//.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm292362.pdf), and the University of Washington's (UW) Drug Interaction Database (http//wwwdruginteractioninfo.org/).

14.2.1 List of prohibited medications

Strong inducers of CYP3A4	carbamazepine, enzalutamide, lumacaftor, phenobarbital, phenytoin, rifabutin, rifampicin (rifampin), mitotane, St. John's wort (Hypericum perforatum)[1]

[1] Herbal product

14.2.2 Permitted medications to be used with caution

Strong inhibitors of CYP3A	ombitasvir/paritaprevir/dasabuvir/ritonavir (Viekira Pak)[1], indinavir/ritonavir[1], tipranavir/ritonavir[1], ritonavir, cobicistat, indinavir, ketoconazole, troleandomycin, telaprevir, danoprevir/ritonavir[1], elvitegravir/ritonavir[1], saquinavir/ritonavir[1], lopinavir/ritonavir[1], itraconazole, voriconazole, mibefradil, posaconazole, telithromycin, grapefruit juice[2], conivaptan, nefazodone, nelfinavir, idelalisib, boceprevir, atazanavir/ritonavir[1], darunavir/ritonavir[1]
Substrates with narrow therapeutic index (NTI)	
CYP1A2	theophylline, tizanidine (also sensitive)
CYP2B6	No substrate with narrow therapeutic index known.
CYP2C8	paclitaxel
CYP2C9	(S)-warfarin
CYP2C19	(S)-mephenytoin (also sensitive)
CYP2E1	No substrate with narrow therapeutic index known.
CYP3A	alfentanil, cyclosporine, dihydroergotamine, ergotamine, fentanyl, sirolimus, tacrolimus
Transporter substrates	
NTI substrates of P-gp[3]	cyclosporine, digoxin, fentanyl, paclitaxel, sirolimus, tacrolimus
BCRP substrates	atorvastatin daunorubicin, doxorubicin, hematoporphyrin, imatinib, methotrexate, mitoxantrone, pitavastatin, rosuvastatin, SN-38 (irinotecan), ethinyl estradiol, simvastatin, sulfasalazine, sofosbuvir, topotecan, sulfasalazine, tenofovir, topotecan.
OATP1B1 substrates (including OATP1B3, and OATP2B1 substrates)	aliskiren, ambrisentan, anacetrapib, atenolol, asunaprevir, atrasentan, atorvastatin, bosentan, bromociptine, caspofungin, cerivastatin, celiprolol, danoprevir, digoxin, docetaxel, eliglustat, epangliflozin, ezetimibe, fimasartan, fexofenadine, fluvastatin, glyburide, maraviroc, methotrexate, sn-38, rosuvastatin, saquinavir, simvastatin acid, paritaprevir, pitavastatin, pravastatin, repaglinide, rosuvastatin, simvastatin, valsartan, olmesartan, telmisartan, montelukast, ticlopidine, thyroxine

[redacted]

Medications with a known risk for QT prolongation	
Medications with a known risk for QT prolongation[4]	amidarone, anagrelide, arsenic trioxide, astemizole, azithromycin, chloroquine, chlorpromazine, cilostazol, cisapride, citalopram, clarithromycin, disopyramide, dofetilide, domperidone, donepezil, dronedarone, droperidol, erythromycin, escitalopram, flecainide, fluconazole, gatifloxacin, halofantrine, haloperidol, ibutilide, levofloxacin, levomepromazine, levosulpiride, methadone, moxifloxacin, ondansetron, oxaliplatin, papaverine HCl (intra-coronary), pentamidine, pimozide, procainamide, propofol, quinidine, roxithromycin, sevoflurane, sotalol, sulpiride, sultopride, terlipressin, terodiline, thioridazine, vandetanib

[1] Combination ritonavir-boosted regimens are listed here in the Drug-Drug Interaction (DDI) memo as strong CYP3A inhibitors (to avoid potential confusion), even though some are considered moderate CYP3A inhibitors in the UW DDI Database.

[2] The effect of grapefruit juice varies widely among brands and is concentration-, dose-, and preparation-dependent. Studies have shown that it can be classified as a “strong CYP3A inhibitor” when a certain preparation was used (e.g., high dose, double strength) or as a “moderate CYP3A inhibitor” when another preparation was used (e.g., low dose, single strength).

[3] These drugs have both a narrow therapeutic index and an *in vivo* DDI outcome partly ascribed to P-gp inhibition or induction that exceeds 20% change in AUC.

[4] For current lists of medications that may cause QT prolongation and/or Torsades de Pointes (TdP), refer to the CredibleMeds® website (https://crediblemeds.org). Please contact the medical monitor with any questions.

14.3 Appendix 3 – PGIC questionnaire

Patient Global Impression of Change (PGIC) - AML

Instructions: Circle the answer that is most appropriate.

Since the start of the treatment you've received in this study, your AML symptoms are:

1. Very much improved
2. Much improved
3. Minimally improved
4. No change
5. Minimally Worse
6. Much worse
7. Very much worse

[redacted]

14.4 Appendix 4 – EORTC QLQ-C30 (version 3)

ENGLISH

EORTC QLQ-C30 (version 3)

We are interested in some things about you and your health. Please answer all of the questions yourself by circling the number that best applies to you. There are no "right" or "wrong" answers. The information that you provide will remain strictly confidential.

Please fill in your initials: ⌊_⌋⌊_⌋⌊_⌋⌊_⌋
Your birthdate (Day, Month, Year): ⌊_⌋⌊_⌋⌊_⌋⌊_⌋⌊_⌋⌊_⌋⌊_⌋⌊_⌋
Today's date (Day, Month, Year): 31 ⌊_⌋⌊_⌋⌊_⌋⌊_⌋⌊_⌋⌊_⌋⌊_⌋⌊_⌋

	Not at All	A Little	Quite a Bit	Very Much
1. Do you have any trouble doing strenuous activities, like carrying a heavy shopping bag or a suitcase?	1	2	3	4
2. Do you have any trouble taking a long walk?	1	2	3	4
3. Do you have any trouble taking a short walk outside of the house?	1	2	3	4
4. Do you need to stay in bed or a chair during the day?	1	2	3	4
5. Do you need help with eating, dressing, washing yourself or using the toilet?	1	2	3	4

During the past week:	Not at All	A Little	Quite a Bit	Very Much
6. Were you limited in doing either your work or other daily activities?	1	2	3	4
7. Were you limited in pursuing your hobbies or other leisure time activities?	1	2	3	4
8. Were you short of breath?	1	2	3	4
9. Have you had pain?	1	2	3	4
10. Did you need to rest?	1	2	3	4
11. Have you had trouble sleeping?	1	2	3	4
12. Have you felt weak?	1	2	3	4
13. Have you lacked appetite?	1	2	3	4
14. Have you felt nauseated?	1	2	3	4
15. Have you vomited?	1	2	3	4
16. Have you been constipated?	1	2	3	4

Please go on to the next page

[redacted]

ENGLISH

During the past week:	Not at All	A Little	Quite a Bit	Very Much
17. Have you had diarrhea?	1	2	3	4
18. Were you tired?	1	2	3	4
19. Did pain interfere with your daily activities?	1	2	3	4
20. Have you had difficulty in concentrating on things, like reading a newspaper or watching television?	1	2	3	4
21. Did you feel tense?	1	2	3	4
22. Did you worry?	1	2	3	4
23. Did you feel irritable?	1	2	3	4
24. Did you feel depressed?	1	2	3	4
25. Have you had difficulty remembering things?	1	2	3	4
26. Has your physical condition or medical treatment interfered with your family life?	1	2	3	4
27. Has your physical condition or medical treatment interfered with your social activities?	1	2	3	4
28. Has your physical condition or medical treatment caused you financial difficulties?	1	2	3	4

For the following questions please circle the number between 1 and 7 that best applies to you

29. How would you rate your overall health during the past week?

1	2	3	4	5	6	7
Very poor						Excellent

30. How would you rate your overall quality of life during the past week?

1	2	3	4	5	6	7
Very poor						Excellent

[redacted]

14.5 Appendix 5 - EORTC QLQ-C30 Scoring Manual

EORTC QLQ-C30 Scoring Manual

The EORTC QLQ-C30

Introduction

The EORTC quality of life questionnaire (QLQ) is an integrated system for assessing the health-related quality of life (QoL) of cancer patients participating in international clinical trials. The core questionnaire, the QLQ-C30, is the product of more than a decade of collaborative research. Following its general release in 1993, the QLQ-C30 has been used in a wide range of cancer clinical trials, by a large number of research groups; it has additionally been used in various other, non-trial studies.

This manual contains scoring procedures for the QLQ-C30 versions 1.0, (+3), 2.0 and 3.0; it also contains summary information about supplementary modules.

All publications relating to the QLQ should use the scoring procedures described in this manual.

This manual will be updated at regular intervals, to reflect future changes to the QLQ and to incorporate new supplementary modules.

[redacted]

Background

The EORTC

The European Organisation for Research and Treatment of Cancer (EORTC) was founded in 1962, as an international non-profit organisation. The aims of the EORTC are to conduct, develop, co-ordinate and stimulate cancer research in Europe by multidisciplinary groups of oncologists and basic scientists. Research is accomplished mainly through the execution of large, prospective, randomised, multicentre, cancer clinical trials.

The EORTC Central Office Data Center, created in 1974, is concerned with all aspects of phase II and phase III cancer clinical trials, from their design to the publication of the final results. Since its inception, over 80,000 patients have been entered in trials handled by the EORTC Data Center.

In 1980, the EORTC created the Quality of Life Group, which in 1986 initiated a research programme to develop an integrated, modular approach for evaluating the QoL of patients participating in cancer clinical trials. This led to the development of the EORTC QLQ-C30, a quality of life instrument for cancer patients. To date, more than 2200 studies using the QLQ-C30 have been registered.

EORTC QLQ-C36

A first generation core questionnaire, the EORTC QLQ-C36, was developed in 1987. This 36-item questionnaire was designed to be (1) cancer specific, (2) multidimensional in structure, (3) appropriate for self-administration (i.e. brief and easy to complete), and (4) applicable across a range of cultural settings. Detailed results of the international field-testing of the EORTC QLQ-C36 have been reported (Aaronson *et al.*, 1991). While the overall psychometric results were promising, they also pointed to some areas in which the questionnaire could benefit from further development. Most of the revision involved only minor changes in the wording of items. A few items were found to be non-informative, and were discarded. The only scale requiring substantial revision, because of inadequate reliability, was the eight-item emotional functioning scale. In the next generation of the instrument, this scale was substituted by a four-item emotional functioning scale that had been used previously in EORTC clinical trials.

EORTC QLQ-C30 version 1.0

A second generation core questionnaire, the first version of the 30-item EORTC QLQ-C30 (Appendix 1a), was subsequently developed. The content areas covered by the questionnaire reflect the multi-dimensionality of the QoL construct. This questionnaire was field tested in a cross-cultural sample of lung cancer patients in 13 countries to confirm the hypothesised scale structure, to establish reliability and to evaluate validity (Aaronson *et al.*, 1993).

The QLQ-C30 version 1.0 (QLQ-C30(v1)) incorporates five functional scales (physical, role, cognitive, emotional, and social), three symptom scales (fatigue, pain, and nausea and vomiting), a global health status / QoL scale, and a number of single items assessing additional symptoms commonly reported by cancer patients (dyspnoea, loss of appetite, insomnia, constipation and diarrhoea) and perceived financial impact of the disease.

[redacted]

EORTC QLQ-C30 (+3)

The third generation core questionnaire, the 33-item EORTC QLQ-C30(+3) (Appendix 1b), arose following international testing of the QLQ-C30(V1), when refinement of the questionnaire by adding three new test items was recommended. Two of these test items (QLQ-C30(+3)/Q_{26}, and QLQ-C30(+3)/Q_{27}) were introduced as possible alternatives to the two-item role functioning scale (QLQ-C30(V1)/Q_6, QLQ-C30(V1)/Q_7), which was found to have sub-optimal internal consistency in previous studies. The third new test item, overall health (QLQ-C30(+3)/Q_{32}), was evaluated as a possible replacement for the overall physical condition item (QLQ-C30(V1)/Q_{29}) in the global health status / QoL scale, and employed the same 7-point response scale as the other two questions in that scale.

EORTC QLQ-C30 version 2.0

The QLQ-C30(+3) was an interim version, which retained all the original questions of the QLQ-C30 version 1.0 while evaluating the additional three items. There was a marked improvement in the internal consistency of the new role functioning scale. The new overall health item places less emphasis upon physical functioning, and did not alter the internal consistency. Having formally validated these new items, the older questions were replaced by the new ones (Osoba *et al.*, 1997). The result was the 30-item version 2.0 of the QLQ, the QLQ-C30(V2) (Appendix 1c).

EORTC QLQ-C30 version 3.0

Version 3.0 of the QLQ-C30 differs from version 2.0 in that it has four-point scales for the first five items (QLQ-C30(V3), Appendix 1d). These are coded with the same response categories as items 6 to 28, namely "Not at all", "A little", "Quite a bit" and "Very much." To allow for these categories, question 4 has been re-worded as "Do you have to stay in a bed or a chair during the day?" Version 3.0 has been tested in EORTC field studies (Bjordal *et al.*, 2000).

Version 3.0 is currently the standard version of the QLQ-C30, and should be used for all new studies unless investigators wish to maintain compatibility with previous studies, which used an earlier version of the QLQ-C30.

Latest information about development of the QLQ-C30 and its modules may be found on the EORTC Quality of Life web pages, at:
http://www.eortc.be/home/qol/

[redacted]

Citation and Availability

Citation in published reports
Any publications which describe the use of the EORTC QLQ-C30 or its modules, or which describe analyses of data arising from application of these questionnaires, should explicitly cite the following reference:

> Aaronson NK, Ahmedzai S, Bergman B, Bullinger M, Cull A, Duez NJ, Filiberti A, Flechtner H, Fleishman SB, de Haes JCJM, Kaasa S, Klee MC, Osoba D, Razavi D, Rofe PB, Schraub S, Sneeuw KCA, Sullivan M, Takeda F.
> The European Organisation for Research and Treatment of Cancer QLQ-C30: A quality-of-life instrument for use in international clinical trials in oncology.
> *Journal of the National Cancer Institute* 1993; **85:** 365-376.

For details of the scoring procedure, a suggested format of citation for this manual is:

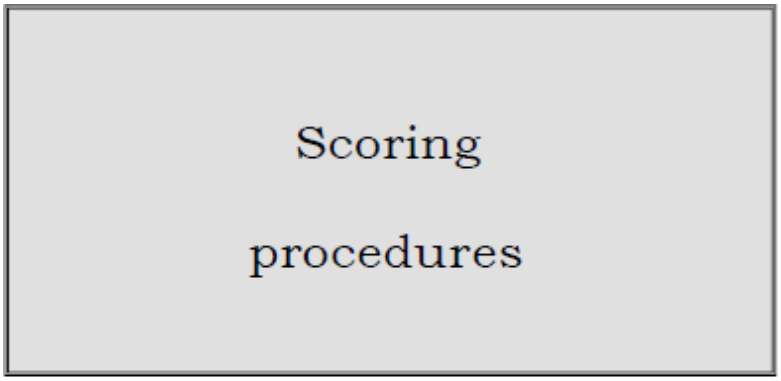
> Fayers PM, Aaronson NK, Bjordal K, Groenvold M, Curran D, Bottomley A, on behalf of the EORTC Quality of Life Group.
> *The EORTC QLQ-C30 Scoring Manual (3rd Edition).*
> Published by: European Organisation for Research and Treatment of Cancer, Brussels 2001.

Contact address
For information about terms and conditions for using the questionnaire, please contact the Quality of Life Unit, EORTC Data Center.

QL Coordinator,
Quality of Life Unit,
EORTC Data Center,
Avenue E Mounier 83 - B11,
1200 Brussels,
BELGIUM

Tel: +32 2 774 1611
Fax: +32 2 779 4568
Email: abo@eortc.be

[redacted]



[redacted]

General principles of scoring

The QLQ-C30 is composed of both multi-item scales and single-item measures. These include five functional scales, three symptom scales, a global health status / QoL scale, and six single items. Each of the multi-item scales includes a different set of items - no item occurs in more than one scale.

All of the scales and single-item measures range in score from 0 to 100. A high scale score represents a higher response level.
Thus a **high score for a functional scale** represents a *high / healthy level of functioning*,
a **high score for the global health status / QoL** represents a *high QoL*,
but a **high score for a symptom scale / item** represents a *high level of symptomatology / problems*.

The principle for scoring these scales is the same in all cases:

1. Estimate the average of the items that contribute to the scale; this is the *raw score*.

2. Use a linear transformation to standardise the raw score, so that scores range from 0 to 100; a higher score represents a higher ("better") level of functioning, or a higher ("worse") level of symptoms.

Coding of the scoring procedure is presented in Appendix 3 for three major statistical packages.

Technical Summary

In practical terms, if items $I_1, I_2, \ldots I_n$ are included in a scale, the procedure is as follows:

Raw score
Calculate the raw score
$RawScore = RS = (I_1 + I_2 + \ldots + I_n)/n$

Linear transformation
Apply the linear transformation to 0-100 to obtain the score S,

Functional scales: $$S = \left\{1 - \frac{(RS-1)}{range}\right\} \times 100$$

Symptom scales / items: $S = \{(RS-1)/range\} \times 100$

Global health status / QoL: $S = \{(RS-1)/range\} \times 100$

Range is the difference between the maximum possible value of *RS* and the minimum possible value. The QLQ-C30 has been designed so that all items in any scale take the same range of values. Therefore, the range of *RS* equals the range of the item values. Most items are scored 1 to 4, giving *range* = 3. The exceptions are the items contributing to the global health status / QoL, which are 7-point questions with *range* = 6, and the initial yes/no items on the earlier versions of the QLQ-C30 which have *range* = 1.

[redacted]

Scoring the EORTC QLQ-C30 version 3.0

Table 1: Scoring the QLQ-C30 version 3.0

	Scale	Number of items	Item range*	Version 3.0 Item numbers	Function scales
Global health status / QoL					
Global health status/QoL (revised)†	QL2	2	6	29, 30	
Functional scales					
Physical functioning (revised)†	PF2	5	3	1 to 5	F
Role functioning (revised)†	RF2	2	3	6, 7	F
Emotional functioning	EF	4	3	21 to 24	F
Cognitive functioning	CF	2	3	20, 25	F
Social functioning	SF	2	3	26, 27	F
Symptom scales / items					
Fatigue	FA	3	3	10, 12, 18	
Nausea and vomiting	NV	2	3	14, 15	
Pain	PA	2	3	9, 19	
Dyspnoea	DY	1	3	8	
Insomnia	SL	1	3	11	
Appetite loss	AP	1	3	13	
Constipation	CO	1	3	16	
Diarrhoea	DI	1	3	17	
Financial difficulties	FI	1	3	28	

* *Item range* is the difference between the possible maximum and the minimum response to individual items; most items take values from 1 to 4, giving *range* = 3.

† (revised) scales are those that have been changed since version 1.0, and their short names are indicated in this manual by a suffix "2" – for example, PF2.

For all scales, the *RawScore*, *RS*, is the mean of the component items:

$$RawScore = RS = (I_1 + I_2 + ... + I_n)/n$$

Then for **Functional scales**:

$$Score = \left[1 - \frac{(RS-1)}{range}\right] \times 100$$

and for **Symptom scales / items** and **Global health status / QoL:**

$$Score = \{(RS-1)/range\} \times 100$$

Examples:

Emotional functioning	$RawScore = (Q_{21} + Q_{22} + Q_{23} + Q_{24})/4$ $\text{EF } Score = \{1 - (RawScore - 1)\beta\} \times 100$
Fatigue	$RawScore = (Q_{10} + Q_{12} + Q_{18})/3$ $\text{FA } Score = \{(RawScore - 1)\beta\} \times 100$

[redacted]

Scoring earlier versions of the EORTC QLQ-C30

Table 2: Scoring the QLQ-C30 version 2.0
For the QLQ-C30(V2), the only difference is that Q_1 to Q_5 are coded yes/no, with *range* = 1.
The following should be added to Table 1, and the revised scale for PF2 deleted.

	Scale	Number of items	Item range*	**Version 2.0** Item numbers	Function scales
Physical functioning (original scale)	PF	5	1	1 to 5	F
Delete PF2					

* *Item range* is the difference between the possible maximum and the minimum response to individual items; most items take values from 1 to 4, giving *range* = 3.

Table 3: Scoring the QLQ-C30 (+3)
The QLQ-C30(+3) used the earlier scale for PF, and included both the original and revised versions of QL and RF. The items for SF and FI were placed after the new items 26 and 27, and are hence numbered 28 to 30. The following changes should be made to Table 1, and the revised scale for PF2 deleted.

	Scale	Number of items	Item range*	**Version (+3)** Item numbers	Function scales
Global health status/QoL	QL	2	6	31, 33	
Global health status/QoL (revised)	QL2	2	6	32, 33	
Physical functioning	PF	5	1	1 to 5	F
Role functioning	RF	2	1	6, 7	F
Role functioning (revised)	RF2	2	3	26, 27	F
Social functioning	SF	2	3	28, 29	F
Financial difficulties	FI	1	3	30	
Delete PF2					

* *Item range* is the difference between the possible maximum and the minimum response to individual items; most items take values from 1 to 4, giving *range* = 3.

Table 4: Scoring the QLQ-C30 version 1.0
The QLQ-C30(V1) used the original scales for QL, PF and RF, and so QL2, RF2 and PF2 should be deleted and the following changes made to Table 1.

	Scale	Number of items	Item range*	**Version 1.0** Item numbers	Function scales
Global health status/QoL	QL	2	6	29, 30	
Physical functioning	PF	5	1	1 to 5	F
Role functioning	RF	2	1	6, 7	F
Delete QL2, RF2 and PF2					

* *Item range* is the difference between the possible maximum and the minimum response to individual items; most items take values from 1 to 4, giving *range* = 3.

[redacted]

Missing data

Missing data may be classified as either missing items (one or more missing answers to questions within a questionnaire), or missing forms (the whole questionnaire is missing for a patient). Fayers and Machin (2000) describe methods of analysis for use when data are missing, including imputation techniques.

Missing items

Sometimes a patient will fail to answer a few questions on the QLQ-C30. Our experience to date suggests that less than 2% of patient data will be missing for the QLQ core questionnaire. However, supplementary modules addressing, for example, sexuality issues may have more serious problems with patient compliance. In theory it is important to distinguish between items, which are accidentally missing (commonly described as "missing completely at random"), and items, which are missing for a particular reason. For example, if patients feel very poorly with respect to one item they might wish to avoid answering that question. In practice, however, there is likely to be no way of deciding whether there was a specific reason for the missing values and, in general, it would seem likely that most missing items occur completely at random. In such cases the investigator may wish to calculate the scores based upon those items that were completed, possibly by "imputing" or estimating the missing item.

Various statistical methods exist for imputing values. One might, for example, use multivariate techniques that attempt to estimate the most likely value given information about (a) that patient's previous responses to the same item, (b) other patients' responses at a similar stage in their disease progression and therapy, or (c) the inter-relations and covariance structure with other items.

A simple method for imputing items from multi-item scales, which has been used by many QoL instruments, is the following: if at least half of the items from the scale have been answered, assume that the missing items have values equal to the average of those items which *are* present for that respondent. However, this rule is not always appropriate, and caution should be exercised. Application of this method of imputation is simpler than it perhaps seems; it can be shown that this is algebraically equivalent to using all items, which were completed, and applying the equations already given under "Scoring procedures" for calculating the scale scores; the missing items are simply ignored when making the calculations. Hence the above equations for multi-item scales can be used whenever at least half the items are completed.

Example:

Emotional functioning if Q_{23} is missing (3 items not missing)

$$RawScore = (Q_{21} + Q_{22} + Q_{24})/3$$
$$\text{EF } Score = \{1 - (RawScore - 1)/3\} \times 100$$

For example, role functioning (RF) and cognitive functioning (CF) each contain 2 items, and so these scales can be estimated whenever one of their constituent items is present; physical functioning contains 5 items, and so at least 3 need to have been completed. Using this method, none of the single-item measures can be imputed.

[redacted]

Summary – Missing items

- Have at least half of the items from the scale been answered?
- If *Yes*, use all the items that were completed, and apply the standard equations given on the previous pages for calculating the scale scores; ignore any items with missing values when making the calculations.
- If *No*, set scale score to missing.
- For single-item measures, set score to missing.

Missing forms

As experience with QoL research has increased among the cancer treatment community, so has the need for innovative strategies to prevent, identify and deal with the problem of missing data. In addition to the potential for incomplete data that can occur when introducing researchers to a relatively new type of patient outcome, QoL assessments are likely to be missed because of negative events that are experienced by patients, such as treatment toxicities, and patients dropping out due to disease progression or even death. Successful integration of QoL endpoints into clinical trials, therefore, involves a comprehensive approach encompassing issues of research design, study implementation, and statistical analysis methods.

When initiating a clinical trial it is essential that an adequate infrastructure be in place to ensure that the study is managed properly and efficiently. The EORTC Quality of Life Group has developed a manual "*Guidelines for Assessing Quality of Life in EORTC Clinical Trials*" which details the issues which need to be addressed in the design of a clinical trial to ensure that QoL is adequately addressed in the study (Young *et al*., 1999). Education and training of clinical staff regarding the importance of QoL endpoints, combined with centralised quality assurance strategies, are crucial to the successful integration of these endpoints into clinical trials. Even with such efforts, however, there will be incomplete observations. Although the problem of missing forms is not unique to QoL research, it presents an unusual challenge in that the information is provided by patient self-report at a particular point in time, and thus cannot be retrieved at a later date from medical charts, as is often possible with other types of clinical data.

It is useful to document and report the extent of and reasons for missing data. By identifying the reasons for missing questionnaires it may be possible to learn more about the problems of collecting QoL questionnaires, e.g. institution-related factors, and circumvent these problems in future research. The reasons why questionnaires have not been completed may also provide useful information to take into account at the time of analysis. For example, if the main reasons for observing missing questionnaires is administrative failure, then provided the extent of missingness is not too large, the missing forms may not pose too much of a problem. However, if the main reason for missingness is due to patients feeling too ill to fill out the questionnaire, care has to be taken, as there may be a bias in terms of reporting of results. Fayers and Machin (2000) discuss the issue of bias and suggest ways in which it may be possible to reduce the bias by taking covariates into account. Logistic regression models can also be used to evaluate the association between compliance and selected factors.

[redacted]

Troxel *et al.* (1998) described some statistical techniques for assessing and analysing QoL data in the presence of incomplete observations.

Various approaches have been suggested for imputing values, such as mean imputation, regression imputation and last observation carried forward. A major advantage of imputation is that, once the values have been filled in, standard complete data methods of analysis can be used. Some problems do exist using single imputation, e.g. an imputed value is treated as if it were an observed value. This can cause problems, as summary statistics such as percentiles, variances and confidence intervals may have incorrect estimates and hence any inferences that are drawn may be misleading.

Summary – Missing forms

Sufficient care and attention should be taken at the design stage of a study to ensure that an adequate infrastructure, including appropriate personnel and material, is available to carry out the study. No matter how well the analysis is thought out and how accurate the assumptions are about the missing data process, inferences based on incomplete data are not as convincing as inferences based on a complete dataset.

[redacted]

Theory of scaling

The scaling technique described above is based upon the widely applied Likert method of summated scales, in which the constituent items within each scale are simply summed. This makes several assumptions about the nature of the items, the most important of which are (a) that it is appropriate to give equal weight to each item, and (b) that each item is graded on a linear or equal-interval scale. Both these assumptions are questionable, and it might be thought that more sophisticated scaling and scoring procedures would be preferable. Fortunately, however, it has been shown that simple linear scoring systems are surprisingly robust (Dawes, 1979). This has led Cox *et al.* (1992) to propose that "simple integer scoring is likely to be enough for many purposes."

Linearity of items

Methods for assessing the adequacy of linear scores have been reviewed by Cox and Wermuth (1994). At present we have no grounds to believe that the EORTC QLQ items are sufficiently non-linear to warrant any correction before using them in summated scales.

Weighting of items

The use of weights is a far more complex question. Alternative methods for assigning weights include:

- Analysis techniques such as factor analysis or other data-orientated weights (e.g. Gorsuch, 1983; Olschewski and Schumacher, 1990). However, many authors have noted the inherent instability of factor scores, and recommend that the use of factor analysis should be confined to exploring factor structures and testing hypotheses.
- Techniques which attempt to elicit patients' personal utilities or preferences. Drummond *et al.* (1997) describe some of the principal methods that are based upon either the "standard gamble" or the "time trade-off" method. Cox *et al.* (1992) offer a critique of the use of utility methods, and in particular time trade-off, in the context of clinical trials.
- Assignment of arbitrary weights according to opinions of the patients, the investigators, or similar groups (e.g. Simes, 1986).

Cox *et al.* (1992), Olschewski and Schumacher (1990) discuss alternative scaling systems and the problems of choosing, applying and evaluating scaling methods. The inherent difficulties, together with the relative robustness of simple methods, have led many QoL instruments to employ the Likert summated score method.

The EORTC Quality of Life Group is currently exploring alternative scoring procedures, including the use of Rasch models and item response theory (IRT). Structural equation modelling is also being used to investigate higher order factors. At the present time we recommend using scales based upon unweighted summed scores. Also, it should be noted that we caution strongly against the use of a total, global score based upon the sum of all items. The Global health status / QoL scale (based upon Q_{29} and Q_{30} in the QLQ-C30(v3)) should be used as the overall summary measure.

Summary

We currently advocate (unweighted) summated scales. However, work is in progress to explore alternative techniques for evaluating QLQ-C30 scores.

[redacted]

Interpretation of scores

As described in this manual, the raw QLQ-C30 scores can be transformed to scores ranging from 0 to 100. The use of these transformed scores has several advantages, but transformed scores may be difficult to interpret. For example, what does an emotional function score of 60 or a difference of 15 mean? Also, there are no grounds for regarding, say, an emotional function score of 60 as being equally good or bad as scores of 60 on the other functioning scales. However, there are a number of ways to ease the interpretation of QLQ-C30 results.

- One can *report the raw scores* in addition to the transformed scores. For example, it may be clinically relevant to know the proportion of patients that are 'Quite a bit' or 'Very much' constipated. This also applies to results from multi-item scales when the responses to the individual items are of interest. In some cases it may be useful to dichotomise scores, for example by grouping scores into 'Not at all' vs. 'Any extent'.

- The scores can be *compared against published data*, e.g. by using the data for comparable groups of patients published in the *EORTC QLQ-C30 Reference Values* manual (Fayers *et al.*, 1998). In the *Reference Values* manual, data are shown for the main cancer sites, divided by stage of disease. General population data based on large random samples from the general population in Norway and Sweden, and females in Denmark are also published (Hjermstad *et al.*, 1998; Klee *et al.*, 1997; Michelson *et al.*, 2000).

Changes in scores over time and *differences between groups* may be more difficult to interpret than absolute scores. The fact that a change is statistically significant does not necessarily imply that it also has clinical significance. Lydick and Epstein (1993) reviewed the different approaches used to define the 'Minimal Clinically Important Difference' and grouped these into *anchor-based* and *distribution-based interpretations*.

Anchor-based interpretations compare the changes seen in QoL scores ('anchored') against other clinical changes or results. Examples of such approaches used with the QLQ-C30 include:

- Osoba *et al.* developed the *Subjective Significance Questionnaire* (SSQ) (Osoba *et al.*, 1998). The SSQ asks patients about *perceived changes* in physical, emotional, and social functioning and in global QL, using a 7-point scale ranging from 'much worse' over 'no change' to 'much better'. Patients filled in the QLQ-C30 at two occasions. At the second completion they also filled in the SSQ. Patients who reported 'a little' change for better or worse on a particular scale (function or symptom) had QLQ-C30 changes about 5 to 10. Those reporting 'moderate' change had changed about 10 to 20, and 'very much' change corresponded to a change greater than 20.

- King (1996) used data from 14 published studies employing the QLQ-C30 or the QLQ-C36, grouping patients according to performance status, weight loss, toxicity, and extent or severity of disease. For each QLQ-C30 scale, the article shows differences in mean scores found between groups differing with respect to the clinical criteria.

Distribution-based interpretations are based on the statistical distributions of results. The most commonly used statistics are Cohen's *effect size* (ES), which relates the observed change to the baseline standard deviation (Fayers and Machin, 2000), or the *standardised response mean* (SRM), which uses the standard deviation of the change. In both Osoba's and King's articles, effect sizes were found to increase in concordance with increasing changes in QLQ-C30 scores and SSQ ratings.

[redacted]