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Sponsor

Novartis Pharmaceuticals

Generic Drug Name

midostaurin

Trial Indication(s)

Newly diagnosed subjects with *FLT3* mutation negative acute myeloid leukemia (AML)

Protocol Number

CPKC412E2301

Protocol Title

A phase III, randomized, double-blind study of chemotherapy with daunorubicin or idarubicin and cytarabine for induction and intermediate dose cytarabine for consolidation plus midostaurin (PKC412) or chemotherapy plus placebo in newly diagnosed patients with FLT-3 mutation negative acute myeloid leukemia (AML)

Clinical Trial Phase

Phase 3

Phase of Drug Development

Phase IV

Study Start/End Dates

Study Start Date: July 20, 2018 (Actual)
Primary Completion Date: February 12, 2021 (Actual)
Study Completion Date: February 12, 2021 (Actual)

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Reason for Termination (If applicable)

The study was analyzed to be futile hence was stopped after Futility Analysis.

Study Design/Methodology

This was a multi-center, multinational, randomized, double-blind Phase III study using a group sequential design. Subjects were stratified according to age (<60 vs. ≥ 60 years). Subjects within each stratum were randomized in a 1:1 ratio into one of two treatment arms: Midostaurin + chemotherapy 'or' Placebo + chemotherapy.

The study consisted of the following phases:

Screening/randomization phase: Subjects had to sign informed consent form before screening for enrollment. Subjects started chemotherapy at day 1 and were randomized at day 8.
Induction phase: All subjects received at least one cycle (28 days) of induction therapy with continuous infusion cytarabine (D1 – D7) and daunorubicin or idarubicin (D1 – D3) (induction 1). Subjects who did not achieve CR or CRi with adequate blood count recovery after Induction 1 received a second cycle with intermediate-dose cytarabine (D1 – D3) and daunorubicin or idarubicin (D1 – D3) (induction 2). Subjects who did not achieve CR or CRi with adequate blood recovery after induction 2 discontinued study treatment and were followed for survival.

Consolidation phase: Subjects who achieved CR or CRi with adequate blood count recovery after induction with one or two cycles of induction proceeded to consolidation therapy with either 3 or 4 cycles respectively of intermediate-dose cytarabine (D1 – D3), or to Hematopoietic Stem Cells Transplantation (HSCT) with or without preceding consolidation cycles.

Post-consolidation phase: Subjects who maintained CR or CRi with adequate blood count recovery at the end of the consolidation phase received 12 cycles (28 days/cycle) of continuous therapy with midostaurin or placebo twice daily at 50 mg. Subjects who underwent HSCT after achieving CR or Cri with adequate blood count recovery received midostaurin or placebo twice daily 50 mg post-transplant therapy, continuously, for up to 12 cycles (28 days/cycle). Post HSCT post-consolidation therapy began >30 days but not later than 100 days following HSCT.

Follow-up phase: All enrolled subjects were followed through the treatment period and until relapse/treatment failure, thereafter for start of new line of therapy and survival.

Centers

134 centers in 20 countries: Belgium(3), Germany(39), Israel(3), Australia(4), Spain(11), Czech Republic(2), Austria(3), Switzerland(2), Japan(20), Norway(2), Italy(18), France(9), Brazil(3), Portugal(2), United States(3), Turkey(3), Taiwan(4), Argentina(1), Poland(1), Bulgaria(1)

Objectives:

Primary Objective:

- To determine if the addition of midostaurin to standard induction and consolidation therapy, followed by single agent post-consolidation therapy improves event free survival (EFS) in subjects with newly diagnosed FLT3-MN (signal ratio (SR) <0.05) AML

Key Secondary Objective:

- To determine if the addition of midostaurin to standard induction and consolidation therapy, followed by single agent post-consolidation therapy improves OS in subjects with newly diagnosed *FLT3*-MN (SR<0.05) AML

Secondary Objectives:

- To compare CR+CRi with adequate blood count recovery rate in the two treatment groups
- To compare the percentage of subjects who reached MRD negative status in the two treatment groups
- To compare the percentage of subjects with MRD negative status in the post-consolidation phase in the two treatment groups
- To compare the time to MRD negative bone marrow between the two treatment arms in the two treatment groups
- To compare DFS, as well as the Cumulative Incidence of Relapse (CIR) and Cumulative Incidence of Death (CID) in the two treatment groups
- To compare the time to CR or CRi with adequate blood count recovery in the two treatment groups
- To compare the time to neutrophil recovery in the two treatment groups
- To compare the time to platelet recovery in the two treatment groups
- To assess the safety and tolerability of midostaurin in combination with chemotherapy and as monotherapy during post-consolidation.
- To further characterize the pharmacokinetics of midostaurin, CGP52421 and GP62221

Test Product (s), Dose(s), and Mode(s) of Administration

Novartis provided the study drug (midostaurin/placebo) as 25 mg capsules and supplied as double-blind in blister packs.

Statistical Methods

The statistical analysis of this study was performed by Novartis. SAS® version 9.4 or later (SAS Institute Inc., Cary, NC, USA) was used for all analyses. The study was stopped at first interim analysis for futility.
This first interim analysis of EFS was performed by an independent external statistician and an independent external programmer (CRO not involved with the conduct of the study). An updated EFS analysis performed by the Novartis study team using follow-up data from all subjects is provided in this report.

Analysis sets

Full analysis set comprised all subjects to whom study drug was assigned by randomization. According to the intent to treat principle, subjects were analyzed according to the treatment and stratum they were assigned to during the randomization procedure.
Safety set included all subjects who received at least one dose of study treatment starting at Day 1 and randomized with at least one dose of midostaurin or placebo. Subjects were analyzed according to the study treatment received.
Pharmacokinetic analysis set-all (PAS-all) included all subjects in the safety set who provided at least one evaluable PK concentration. It was the primary population used for all PK analyses using trough concentration data.
Pharmacokinetic analysis set for full PK profiles (PAS-full) included all subjects in the PAS-all who provided an evaluable PK profile.

Efficacy endpoints and analyses

Analysis of primary endpoint

The primary endpoint was EFS based on response assessment as per the modified IWG for AML criteria according to the investigator assessment. EFS was defined as the time from the date of randomization to failure to obtain a CR or CRi with adequate blood count recovery in induction (i.e. induction failure) within 93 days of start of treatment, relapse from CR or

CRi with adequate blood count recovery, or death due to any cause, whichever occurred first. The primary analysis was based on the FAS.
For EFS, the hazard ratio for treatment effect was estimated and its two-sided 95% confidence intervals were reported. The estimation was based on a cox proportional hazards model with treatment and the stratification factor in it.

Analysis of key secondary endpoint
OS was defined as the time from date of randomization to date of death due to any cause. If a subject was not known to have died, survival was censored at the date of last contact.
OS was estimated using the Kaplan-Meier method. The median OS along with 95% confidence intervals were presented by treatment arm. The stratified Cox regression was used to estimate the HR of OS, along with 95% confidence interval. All OS analyses were based on the FAS. OS analysis was also summarized by age subgroups (< 60 years/ ≥ 60 years).

Analysis of other secondary endpoints
The secondary efficacy variables included CR or CRi with adequate blood count recovery rate, DFS, CIR, CID and MRD by MFC. In addition, time to MRD negative, duration of MRD negative, a landmark analysis of OS at 3 months, time to neutrophil/platelet recovery, transfusions and HSCTs were analysed.
The definitions for these endpoints are available in the objectives and endpoints.

The rate of CR/CRi with adequate blood count recovery were analyzed based on the FAS. However, DFS, CIR and CID were analyzed based on data from responders (CR or CRi with adequate blood count recovery within 93 days after start of treatment) in the FAS. Assessment of relapse from CR or CRi with adequate blood count recovery or death occurrence were considered regardless of HSCT.

MRD status was reported for all subjects as best response of MRD assessment outcome. Thus, subjects who reached MRD negative status at least once their MRD status was recorded as MRD negative. If all MRD assessment were positive or undetermined then MRD status was reported as such.
The assessment of these endpoints, except MRD, were based on the modified IWG criteria for AML as per investigator assessment. All these endpoints were descriptively summarized with 95% CIs but without any p-values.

In addition, overall best response of CR, CRi with adequate blood count recovery and MRD at the same timepoint were reported.

A landmark analysis of OS at specific timepoints (e.g. at 3 months) was performed to assess any potential impact of MRD status on OS by treatment group and overall. Subjects who completed induction therapy were classified as per their MRD status at end of induction: MRD positive, MRD negative, MRD undetermined, MRD missing.

DFS, CIR, and CID were estimated using the Kaplan-Meier method. The median DFS, CIR and CID were presented by treatment group along with 95% CIs. The stratified Cox regression was used to estimate the HR of DFS, CIR and CID along with 95% CI.

Subjects with platelet values ≥100 x 109/L and neutrophils ≥ 1.0 x 109/L prior to start of treatment were excluded from 'time to neutrophil/platelet recovery' analysis. Subjects not meeting the recovery criteria were censored at last laboratory assessment. In case of no laboratory assessment, subject was censored at start of midostaurin. Subjects who died, failed induction were censored at maximum followup (i.e. LPLV). If subjects reached recovery after HSCT, this was taken into account and not censored at time of HSCT.

Time to platelet and to neutrophil recovery were plotted by treatment group along with their corresponding number of events, HR and 95% CIs.

The number of transfusion per subject were summarized by treatment phase and for each cycle using FAS.

Patient moving to HSCT were reported by treatment phase. HSCT in CR or CRi with adequate blood count recovery and relapse/induction failure were distinguished in the analysis. HSCT analyses were based on the FAS.

Safety analyses: All safety analyses were based on the safety set. Safety summaries included data from the on-treatment period.

AEs were summarized via treatment group, preferred terms were coded using MedDRA version 23.1 and grading was based on CTCAE version 5.0. AE summaries included all treatment-emergent AEs starting on or after Study Day 1 (i.e. on or after the day of the first intake of study treatment) and starting no later than 30 days after study treatment discontinuation.

Death summaries for on-treatment and all (including both on-treatment and post-treatment) fatal cases were produced by treatment arm, SOC and PT.

On analyzing laboratory assessments, data from all sources (central and local laboratories) were combined. The summaries included on-treatment laboratory assessments. Subjects with clinically notable vital sign abnormalities were summarized. Liver function parameters of interest were total bilirubin, ALT and AST. Analyses of QT prolongation were based on QTcF and QTcB measurement.
Notable abnormalities were summarized.

Pharmacokinetics
The exposure variable was derived for all PK exposure endpoints with the exception of Tmax to consider the contribution of the active metabolites to the total exposure of the compound. The exposure to the sum of active moieties combined the concentration of the parent- (midostaurin) and the two active metabolites (CGP52421 and CGP62221) scaled based on their relative potencies, and parent to metabolite molecular weight ratio for AML indication.

Pharmacokinetic parameters
PK parameters for midostaurin and the active metabolites (CGP52421, CGP62221) and sum of active moieties (midostaurin+CGP52421+CGP62221) were determined using non-compartmental method(s) using Phoenix WinNonlin (Version 8.0) for the subjects who had full PK sampling on Cycle 1 Day 8 of the induction therapy. AUC0-t (AUC0-12h at C1D8) and Cmax were defined as primary parameters
(contributing to PAS-full definition).

Patient reported outcomes
The Functional Assessment of Cancer Therapy – Leukemia (FACT-Leu) and the 5-level EQ-5D version (EQ-5D-5L) were collected and assessed. Frequency tables for compliance to complete all subject-reported questionnaires were provided by treatment group and time point for FACT-G total, FACT-Leu, trial outcome index (TOI) total scores and EQ-5D-5L.

Study Population: Key Inclusion/Exclusion Criteria

Inclusion Criteria:
1. Diagnosis of AML (≥20% blasts in the bone marrow based on WHO 2016 classification). Patients with APL with PML-RARA are

not eligible.
2. Suitability for intensive induction chemotherapy in the judgment of the investigator
3. Documented absence of an ITD and TKD activating mutation at codons D835 and I836 in the FLT3 gene, as determined by analysis in a Novartis designated laboratory using a validated clinical trial assay with clinical cutoff of 0.05 mutant to wild type signal ratio
4. Age ≥18 years
5. Laboratory values that indicate adequate organ function assessed locally at the screening visit

Exclusion Criteria:
1. Central nervous system (CNS) leukemia
2. Therapy-related secondary AML
3. Isolated extramedullary leukemia
4. Prior therapy for leukemia or myelodysplasia
5. AML after antecedent myelodysplasia (MDS) with prior cytotoxic treatment (e.g., azacytidine or decitabine)
6. Prior treatment with a FLT3 inhibitor (e.g., midostaurin, quizartinib, sorafenib)

Participant Flow Table

Overall Study

	Midostaurin + chemotherapy	Placebo + chemotherapy	Total
Arm/Group Description	Participants received Midostaurin in Induction 50mg twice daily on Day 8 until 48 hrs before start of next cycle. During Induction 2 and consolidation 50mg twice daily on Day 4 until 48 hrs before start of next cycle. During post-consolidation 50mg twice daily for 28 consecutive days of each 28-day treatment cycle up to 12 cycles. For participants who could not tolerate the protocol-specified dosing schedule, dose interruptions and/or reductions were either recommended or	Participants received matching placebo to midostaurin with same dose, plus chemotherapy. Chemotherapy consisted of daunorubicin or idarubicin and cytarabine for induction and intermediate dose cytarabine for consolidation.	

	mandated allowing participants to continue the study treatment. Chemotherapy consisted of daunorubicin or idarubicin and cytarabine for induction and intermediate dose cytarabine for consolidation.		
Started	250	251	501
Treated with Midostaurin/Placebo	245	249	494
Entered Induction phase	250	251	501
Entered Consolidation phase	120	129	249
Entered post-Consolidation phase	45	27	72
Completed	2	1	3
Not Completed	248	250	498
Guardian decision	1	1	2
Lack of Efficacy	19	11	30
New Therapy for Study Indication	16	16	32
Physician Decision	60	60	120
Protocol Violation	0	2	2
Terminated by Sponsored	46	50	96
Subject Decision	15	12	27
Withdrawal of informed consent	20	14	34
Adverse Event	30	34	64
Death	14	9	23
Failure to meet Continuation Criteria	24	28	52
Missing	3	13	16

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Baseline Characteristics

	Midostaurin + chemotherapy	Placebo + chemotherapy	Total
Arm/Group Description	Participants received Midostaurin in Induction 50mg twice daily on Day 8 until 48 hrs before start of next cycle. During Induction 2 and consolidation 50mg twice daily on Day 4 until 48 hrs before start of next cycle. During post-consolidation 50mg twice daily for 28 consecutive days of each 28-day treatment cycle up to 12 cycles. For participants who could not tolerate the protocol-specified dosing schedule, dose interruptions and/or reductions were either recommended or mandated allowing participants to continue the study treatment. Chemotherapy consisted of daunorubicin or idarubicin and cytarabine for induction and intermediate dose cytarabine for consolidation.	Participants received matching placebo to midostaurin with same dose, plus chemotherapy. Chemotherapy consisted of daunorubicin or idarubicin and cytarabine for induction and intermediate dose cytarabine for consolidation.	
Number of Participants [units: participants]	250	251	501
Baseline Analysis Population Description	Full analysis set (FAS) comprised all participants to whom study drug was assigned by randomization.		
Age Continuous (units: Years)			

Analysis Population Type: Participants
Median (Full Range)

	58.0 (19.0 to 78.0)	58.0 (18.0 to 79.0)	58.0 (18.0 to 79.0)
Sex: Female, Male (units: Participants) Analysis Population Type: Participants Count of Participants (Not Applicable)			
Female	122	106	228
Male	128	145	273
Race/Ethnicity, Customized (units: Participants) Analysis Population Type: Participants Count of Participants (Not Applicable)			
White	213	208	421
Black or African American	1	2	3
Asian	22	22	44
Multiple	1	1	2
Missing	13	18	31
Study Specific Characteristic **ECOG performance status** (units: Participants) Description: ECOG performance status determines the ability of a patient to tolerate therapies in serious illness, specifically for chemotherapy. Analysis Population Type: Participants Count of Participants (Not Applicable)			
0 (Asymptomatic)	119	119	238
1 (Symptomatic, fully ambulatory)	107	115	222
2 (Symptomatic, in bed <50% of the day)	18	13	31
3 (Symptomatic, in bed >50% of the day)	2	0	2
Missing	4	4	8

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Summary of Efficacy

Primary Outcome Result(s)

Event Free Survival (EFS)

Description	EFS was defined as the time from randomization to failure to obtain a complete remission (CR) or Complete remission with incomplete hematologic recovery (CRi) with adequate blood count recovery in induction, relapse after CR or CRi with adequate blood count recovery or death due to any cause, whichever occurred first as assessed by the investigator.
Time Frame	From date of Randomization up to approx. 30 months
Analysis Population Description	Full analysis set comprised all participants to whom study drug was assigned by randomization.

	Midostaurin + chemotherapy	**Placebo + chemotherapy**
Arm/Group Description	Participants received Midostaurin in Induction 50mg twice daily on Day 8 until 48 hrs before start of next cycle. During Induction 2 and consolidation 50mg twice daily on Day 4 until 48 hrs before start of next cycle. During post-consolidation 50mg twice daily for 28 consecutive days of each 28-day treatment cycle up to 12 cycles. For participants who could not tolerate the protocol-specified dosing schedule, dose interruptions and/or reductions were either recommended or mandated allowing participants to continue the study treatment. Chemotherapy consisted of daunorubicin or idarubicin and cytarabine for induction and intermediate dose cytarabine for consolidation.	Participants received matching placebo to midostaurin with same dose, plus chemotherapy. Chemotherapy consisted of daunorubicin or idarubicin and cytarabine for induction and intermediate dose cytarabine for consolidation.
Number of Participants Analyzed [units: participants]	250	251
Event Free Survival (EFS) (units: Months)	**Median (95% Confidence Interval)**	**Median (95% Confidence Interval)**

	5.98 (2.33 to 8.97)	5.88 (3.65 to 7.52)

Statistical Analysis

Groups	Midostaurin + chemotherapy, Placebo + chemotherapy
Type of Statistical Test	Superiority
Hazard Ratio (HR)	1.0239
95 % Confidence Interval 2-Sided	0.8 to 1.31

Secondary Outcome Result(s)

Overall survival (OS) (Key Secondary)

Description	OS was defined as the time from randomization to date of death due to any cause. Patients entered the survival follow-up phase once they completed the safety follow up period (30 days after the last dose of midostaurin/placebo) in case of induction failure or if they had relapsed during post-treatment follow-up. Patients were then contacted by telephone every 3 months +/- 2 weeks or had a visit to follow up on their survival status, per Kaplan-Meier estimates.
Time Frame	Between randomization to date of death up to approx. 30 months
Analysis Population Description	Full analysis set comprised all participants to whom study drug was assigned by randomization.

	Midostaurin + chemotherapy	Placebo + chemotherapy
Arm/Group Description	Participants received Midostaurin in Induction 50mg twice daily on Day 8 until	Participants received matching placebo to midostaurin with same dose, plus

	48 hrs before start of next cycle. During Induction 2 and consolidation 50mg twice daily on Day 4 until 48 hrs before start of next cycle. During post-consolidation 50mg twice daily for 28 consecutive days of each 28-day treatment cycle up to 12 cycles. For participants who could not tolerate the protocol-specified dosing schedule, dose interruptions and/or reductions were either recommended or mandated allowing participants to continue the study treatment. Chemotherapy consisted of daunorubicin or idarubicin and cytarabine for induction and intermediate dose cytarabine for consolidation.	chemotherapy. Chemotherapy consisted of daunorubicin or idarubicin and cytarabine for induction and intermediate dose cytarabine for consolidation.
Number of Participants Analyzed [units: participants]	250	251
Overall survival (OS) (Key Secondary) (units: Months)	**Median** **(95% Confidence Interval)**	**Median** **(95% Confidence Interval)**
	N/A (15.54 to N/A)[1]	19.22 (13.8 to N/A)[2]

[1] N/A: Very low number of OS events did not allow to estimate median of OS nor the boundaries of CI. Study was stopped at first interim analysis and thus the survival follow-up was stopped also.
[2] N/A: Very low number of OS events did not allow to estimate the boundaries of CI. Study was stopped at first interim analysis and thus the survival follow-up was stopped also.

Statistical Analysis

Groups	Midostaurin + chemotherapy, Placebo + chemotherapy
Type of Statistical Test	Superiority
Hazard Ratio (HR)	0.8728
95 % Confidence Interval 2-Sided	0.59 to 1.29

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Percentage of participants with complete remission (CR) and complete remission with incomplete hematological recovery (CRi) but with adequate blood count recovery rate.

Description	Assessment was based on the International Working Group (IWG) criteria for AML as per investigator assessment. CR: Bone marrow: < 5% blasts no blasts with Auer rods; Peripheral blood: neutrophils ≥ 1.0 x 109/L platelets ≥ 100 x 109/L, no blasts; No evidence of extramedullary disease (such as central nervous system (CNS) or soft tissue involvement); Transfusion independent. CRi with adequate blood count recovery is defined as the following: Bone marrow < 5% blasts no blasts with Auer rods Peripheral blood Neutrophils >= 1.0 x 109/L and 50 x 109/L <=platelets < 100 x 109/L no blasts No evidence of extramedullary disease (such as CNS or soft tissue involvement).
Time Frame	At maximum 93 days from induction therapy start
Analysis Population Description	Full analysis set comprised all participants to whom study drug was assigned by randomization.

	Midostaurin + chemotherapy	Placebo + chemotherapy
Arm/Group Description	Participants received Midostaurin in Induction 50mg twice daily on Day 8 until 48 hrs before start of next cycle. During Induction 2 and consolidation 50mg twice daily on Day 4 until 48 hrs before start of next cycle. During post-consolidation 50mg twice daily for 28 consecutive days of each 28-day treatment cycle up to 12 cycles. For participants who could not tolerate the protocol-specified dosing schedule, dose interruptions and/or reductions were either recommended or mandated allowing participants to continue the study treatment. Chemotherapy consisted of daunorubicin or idarubicin and cytarabine for induction and intermediate dose cytarabine for consolidation.	Participants received matching placebo to midostaurin with same dose, plus chemotherapy. Chemotherapy consisted of daunorubicin or idarubicin and cytarabine for induction and intermediate dose cytarabine for consolidation.
Number of Participants Analyzed [units: participants]	250	251
Percentage of participants with complete remission (CR) and complete remission with incomplete hematological recovery	**Number (95% Confidence Interval)**	**Number (95% Confidence Interval)**

(CRi) but with adequate blood count recovery rate.
(units: Percentage of participants)

	59.2 (52.8 to 65.4)	61.0 (54.6 to 67.0)

Percentage of participants with Minimal Residual Disease (MRD) negative status

Description	MRD- rate was defined as the rate of participants reaching MRD at any timepoint. Participants with leukemic blasts below 0.1% were considered as MRD-negative based on leukemia-associated immunophenotype (LAIP). MRD was derived from bone marrow and blood data using cellular and molecular technologies and MRD status was measured using the flow cytometry assessments for LAIP irrespective of the investigator's overall clinical response assessment.
Time Frame	from start of treatment up to end of post-consolidation (approximately 17 months)
Analysis Population Description	Full analysis set comprised all participants to whom study drug was assigned by randomization.

	Midostaurin + chemotherapy	Placebo + chemotherapy
Arm/Group Description	Participants received Midostaurin in Induction 50mg twice daily on Day 8 until 48 hrs before start of next cycle. During Induction 2 and consolidation 50mg twice daily on Day 4 until 48 hrs before start of next cycle. During post-consolidation 50mg twice daily for 28 consecutive days of each 28-day treatment cycle up to 12 cycles. For participants who could not tolerate the protocol-specified dosing schedule, dose interruptions and/or reductions were either recommended or mandated allowing participants to continue the study treatment. Chemotherapy consisted of daunorubicin or idarubicin and cytarabine for induction and intermediate dose cytarabine for consolidation.	Participants received matching placebo to midostaurin with same dose, plus chemotherapy. Chemotherapy consisted of daunorubicin or idarubicin and cytarabine for induction and intermediate dose cytarabine for consolidation.

Number of Participants Analyzed [units: participants]	250	251
Percentage of participants with Minimal Residual Disease (MRD) negative status (units: Percentage of participants)		
	40.8	41.0

Percentage of participants with Minimal Residual Disease (MRD) negative status during Post-consolidation Phase

Description	MRD- rate was defined as the rate of participants reaching MRD at any timepoint during Post-consolidation phase. Participants with leukemic blasts below 0.1% were considered as MRD-negative based on leukemia-associated immunophenotype (LAIP). MRD was derived from bone marrow and blood data using cellular and molecular technologies and MRD status was measured using the flow cytometry assessments for LAIP irrespective of the investigator's overall clinical response assessment.
Time Frame	from start of post-consolidation to end of post-consolidation phase (up to 12 months)
Analysis Population Description	Full analysis in post-consolidation phase comprised of participants who entered post-consolidation phase

	Midostaurin + chemotherapy	**Placebo + chemotherapy**
Arm/Group Description	Participants received Midostaurin in Induction 50mg twice daily on Day 8 until 48 hrs before start of next cycle. During Induction 2 and consolidation 50mg twice daily on Day 4 until 48 hrs before start of next cycle. During post-consolidation 50mg twice daily for 28 consecutive days of each 28-day treatment cycle up to 12 cycles. For participants who could not tolerate the protocol-specified dosing schedule, dose interruptions and/or reductions were either recommended or mandated allowing participants to continue the study treatment. Chemotherapy consisted of daunorubicin or idarubicin and cytarabine for induction	Participants received matching placebo to midostaurin with same dose, plus chemotherapy. Chemotherapy consisted of daunorubicin or idarubicin and cytarabine for induction and intermediate dose cytarabine for consolidation.

	and intermediate dose cytarabine for consolidation.	
Number of Participants Analyzed [units: participants]	45	27
Percentage of participants with Minimal Residual Disease (MRD) negative status during Post-consolidation Phase (units: Percentage of participants)		
	33.3	33.3

Time to Measurable Residual Disease (MRD) negativity by flow cytometry

Description	Time to MRD- is defined as time from randomization to first occurrence of MRD-. Participants with leukemic blasts below 0.1% were considered as MRD-negative based on leukemia-associated immunophenotype (LAIP). MRD was derived from bone marrow and blood data using cellular and molecular technologies and MRD status was measured using the flow cytometry assessments for LAIP irrespective of the investigator's overall clinical response assessment.
Time Frame	From date of Randomization up to approx. 17 months
Analysis Population Description	Analysis set comprised all participants to whom study drug was assigned by randomization.

	Midostaurin + chemotherapy	**Placebo + chemotherapy**
Arm/Group Description	Participants received Midostaurin in Induction 50mg twice daily on Day 8 until 48 hrs before start of next cycle. During Induction 2 and consolidation 50mg twice daily on Day 4 until 48 hrs before start of next cycle. During post-consolidation 50mg twice daily for 28 consecutive days of each 28-day treatment cycle up to 12 cycles. For participants who could not tolerate the protocol-specified dosing schedule, dose interruptions and/or reductions were either recommended or mandated allowing participants to continue the study treatment. Chemotherapy consisted of daunorubicin	Participants received matching placebo to midostaurin with same dose, plus chemotherapy. Chemotherapy consisted of daunorubicin or idarubicin and cytarabine for induction and intermediate dose cytarabine for consolidation.

	or idarubicin and cytarabine for induction and intermediate dose cytarabine for consolidation.	
Number of Participants Analyzed [units: participants]	250	251
Time to Measurable Residual Disease (MRD) negativity by flow cytometry (units: Days)	**Median (95% Confidence Interval)**	**Median (95% Confidence Interval)**
	2.27 (1.61 to 5.68)	2.07 (1.68 to 6.80)

Disease-free survival (DFS)

Description	DFS as measured from the date of first CR or CRi with adequate blood count recovery to relapse or death due to any cause, whichever occurred first. Participants who did not relapse nor die were censored at the last adequate response assessment. Assessment was based on the IWG criteria for AML as per investigator assessment
Time Frame	From date of CR or CRi with adequate blood count recovery up to approx. 30 months
Analysis Population Description	Full analysis set comprised all participants to whom study drug was assigned by randomization. DFW was derived only for participants who reached CR or CRi with adequate blood count recovery in induction (during first 93 days).

	Midostaurin + chemotherapy	**Placebo + chemotherapy**
Arm/Group Description	Participants received Midostaurin in Induction 50mg twice daily on Day 8 until 48 hrs before start of next cycle. During Induction 2 and consolidation 50mg twice daily on Day 4 until 48 hrs before start of next cycle. During post-consolidation 50mg twice daily for 28 consecutive days of each 28-day treatment cycle up to 12 cycles. For participants who could not tolerate the protocol-specified dosing schedule, dose interruptions and/or reductions were either recommended or mandated allowing participants to continue the study treatment.	Participants received matching placebo to midostaurin with same dose, plus chemotherapy. Chemotherapy consisted of daunorubicin or idarubicin and cytarabine for induction and intermediate dose cytarabine for consolidation.

	Chemotherapy consisted of daunorubicin or idarubicin and cytarabine for induction and intermediate dose cytarabine for consolidation.	
Number of Participants Analyzed [units: participants]	148	153
Disease-free survival (DFS) (units: Months)	**Median (95% Confidence Interval)**	**Median (95% Confidence Interval)**
	10.5 (7.59 to N/A)[1]	9.1 (6.87 to 12.02)

[1] N/A: Upper limit of CI could not be reached because of low number of events due to premature study discontinuation

Statistical Analysis

Groups	Midostaurin + chemotherapy, Placebo + chemotherapy
Type of Statistical Test	Superiority
Hazard Ratio (HR)	0.98
95 % Confidence Interval 2-Sided	0.60 to 1.63

Cumulative incidence of relapse (CIR)

Description	Cumulative Incidence of Relapse (CIR) was defined for participants with CR or CRi with adequate blood count recovery and was the time from achieving the CR or CRi with adequate blood count recovery until the onset of relapse from CR or CRi with adequate blood recovery. Participants without relapse were censored at the last adequate response assessment. Participants who died without relapse were counted as a competing cause of failure.
Time Frame	From date of CR or CRi with adequate blood count recovery up to approx. 30 months
Analysis Population Description	Full analysis set comprised all participants to whom study drug was assigned by randomization. CIR was only for participants who achieved CR or CRi with adequate blood count recovery.

	Midostaurin + chemotherapy	Placebo + chemotherapy
Arm/Group Description	Participants received Midostaurin in Induction 50mg twice daily on Day 8 until 48 hrs before start of next cycle. During Induction 2 and consolidation 50mg twice daily on Day 4 until 48 hrs before start of next cycle. During post-consolidation 50mg twice daily for 28 consecutive days of each 28-day treatment cycle up to 12 cycles. For participants who could not tolerate the protocol-specified dosing schedule, dose interruptions and/or reductions were either recommended or mandated allowing participants to continue the study treatment. Chemotherapy consisted of daunorubicin or idarubicin and cytarabine for induction and intermediate dose cytarabine for consolidation.	Participants received matching placebo to midostaurin with same dose, plus chemotherapy. Chemotherapy consisted of daunorubicin or idarubicin and cytarabine for induction and intermediate dose cytarabine for consolidation.
Number of Participants Analyzed [units: participants]	148	153
Cumulative incidence of relapse (CIR) (units: Months)	**Median (95% Confidence Interval)**	**Median (95% Confidence Interval)**
	5.1 (2.83 to 7.56)	6.6 (4.99 to 8.77)

Statistical Analysis

Groups	Midostaurin + chemotherapy, Placebo + chemotherapy
Type of Statistical Test	Superiority
Hazard Ratio (HR)	1.5866

95 % Confidence Interval 2-Sided	0.88 to 2.87

Cumulative incidence of death (CID)

Description	Cumulative Incidence of Death (CID) was defined for all participants achieving CR or CRi with adequate blood count recovery measured from the date of achievement of CR or CRi until the date of death due to any reason. Participants not known to have died were censored on the last contact date. Participants who experienced relapse were counted as a competing cause of failure.
Time Frame	From date of CR or CRi with adequate blood count recovery up to approx. 30 months
Analysis Population Description	Full analysis set comprised all participants to whom study drug was assigned by randomization. CID was only for participants who achieved CR or CRi with adequate blood count recovery.

	Midostaurin + chemotherapy	**Placebo + chemotherapy**
Arm/Group Description	Participants received Midostaurin in Induction 50mg twice daily on Day 8 until 48 hrs before start of next cycle. During Induction 2 and consolidation 50mg twice daily on Day 4 until 48 hrs before start of next cycle. During post-consolidation 50mg twice daily for 28 consecutive days of each 28-day treatment cycle up to 12 cycles. For participants who could not tolerate the protocol-specified dosing schedule, dose interruptions and/or reductions were either recommended or mandated allowing participants to continue the study treatment. Chemotherapy consisted of daunorubicin or idarubicin and cytarabine for induction and intermediate dose cytarabine for consolidation.	Participants received matching placebo to midostaurin with same dose, plus chemotherapy. Chemotherapy consisted of daunorubicin or idarubicin and cytarabine for induction and intermediate dose cytarabine for consolidation.
Number of Participants Analyzed [units: participants]	148	153
Cumulative incidence of death (CID) (units: Months)	**Median (95% Confidence Interval)**	**Median (95% Confidence Interval)**

	N/A (18.00 to N/A)[1]	N/A (14.42 to N/A)[2]

[1] N/A: Very low number of events did not allow to estimate median of CID nor the boundaries of CI.
[2] N/A: Very low number of events did not allow to estimate median of CID nor the boundaries of CI

Statistical Analysis

Groups	Midostaurin + chemotherapy, Placebo + chemotherapy
Type of Statistical Test	Superiority
Hazard Ratio (HR)	0.7937
95 % Confidence Interval 2-Sided	0.41 to 1.54

Time to CR or CRi with adequate blood count recovery

Description	Time to CR or CRi with adequate blood count recovery was defined as the time from randomization to CR or CRi with adequate blood count recovery whichever occurred first
Time Frame	At maximum 93 days from induction therapy start
Analysis Population Description	Full analysis set comprised all participants to whom study drug was assigned by randomization.

	Midostaurin + chemotherapy	Placebo + chemotherapy
Arm/Group Description	Participants received Midostaurin in Induction 50mg twice daily on Day 8 until 48 hrs before start of next cycle. During Induction 2 and consolidation 50mg twice daily on Day 4 until 48 hrs before start of next cycle. During post-consolidation 50mg twice daily for 28 consecutive days of each 28-day treatment cycle up to 12	Participants received matching placebo to midostaurin with same dose, plus chemotherapy. Chemotherapy consisted of daunorubicin or idarubicin and cytarabine for induction and intermediate dose cytarabine for consolidation.

	cycles. For participants who could not tolerate the protocol-specified dosing schedule, dose interruptions and/or reductions were either recommended or mandated allowing participants to continue the study treatment. Chemotherapy consisted of daunorubicin or idarubicin and cytarabine for induction and intermediate dose cytarabine for consolidation.	
Number of Participants Analyzed [units: participants]	250	251
Time to CR or CRi with adequate blood count recovery (units: Days)	**Median (95% Confidence Interval)**	**Median (95% Confidence Interval)**
	1.12 (1.02 to 1.41)	1.15 (1.05 to 1.54)

Time to partial and full neutrophil recovery

Description	The time to neutrophil recovery was assessed for the following criteria: Partial neutrophil recovery: Number of days from start of treatment to the first day neutrophils ≥0.5 x 10^9/L. Full neutrophil recovery: Number of days from start of treatment to the first day neutrophils ≥1.0 x 10^9/L
Time Frame	At maximum 93 days from induction therapy start
Analysis Population Description	Full analysis set comprised all participants to whom study drug was assigned by randomization.

	Midostaurin + chemotherapy	**Placebo + chemotherapy**
Arm/Group Description	Participants received Midostaurin in Induction 50mg twice daily on Day 8 until 48 hrs before start of next cycle. During Induction 2 and consolidation 50mg twice daily on Day 4 until 48 hrs before start of next cycle. During post-consolidation 50mg twice daily for 28 consecutive days of each 28-day treatment cycle up to 12	Participants received matching placebo to midostaurin with same dose, plus chemotherapy. Chemotherapy consisted of daunorubicin or idarubicin and cytarabine for induction and intermediate dose cytarabine for consolidation.

	cycles. For participants who could not tolerate the protocol-specified dosing schedule, dose interruptions and/or reductions were either recommended or mandated allowing participants to continue the study treatment. Chemotherapy consisted of daunorubicin or idarubicin and cytarabine for induction and intermediate dose cytarabine for consolidation.	
Number of Participants Analyzed [units: participants]	250	251
Time to partial and full neutrophil recovery (units: Months)	**Median (95% Confidence Interval)**	**Median (95% Confidence Interval)**
Partial neutrophil recovery	1.1 (0.82 to 1.15)	0.9 (0.79 to 1.12)
Full neutrophil recovery	1.2 (1.05 to 1.48)	1.1 (0.95 to 1.35)

Statistical Analysis

Groups	Midostaurin + chemotherapy, Placebo + chemotherapy	partial neutrophil recovery
Type of Statistical Test	Superiority	
Hazard Ratio (HR)	0.93	
95 % Confidence Interval 2-Sided	0.75 to 1.16	

Statistical Analysis

Groups	Midostaurin + chemotherapy, Placebo + chemotherapy	full neutrophil recovery
Type of Statistical Test	Superiority	

Hazard Ratio (HR)	0.91
95 % Confidence Interval 2-Sided	0.72 to 1.14

Time to partial and full platelet recovery

Description	Time to platelet recovery was assessed for the following criteria: Partial platelet recovery: Number of days from start of treatment to the first day platelets ≥50 x 10^9/L. Full platelet recovery: Number of days from start of treatment to the first day platelets ≥100 x 10^9/L.
Time Frame	At maximum 93 days from induction therapy start
Analysis Population Description	Full analysis set comprised all participants to whom study drug was assigned by randomization.

	Midostaurin + chemotherapy	Placebo + chemotherapy
Arm/Group Description	Participants received Midostaurin in Induction 50mg twice daily on Day 8 until 48 hrs before start of next cycle. During Induction 2 and consolidation 50mg twice daily on Day 4 until 48 hrs before start of next cycle. During post-consolidation 50mg twice daily for 28 consecutive days of each 28-day treatment cycle up to 12 cycles. For participants who could not tolerate the protocol-specified dosing schedule, dose interruptions and/or reductions were either recommended or mandated allowing participants to continue the study treatment. Chemotherapy consisted of daunorubicin or idarubicin and cytarabine for induction and intermediate dose cytarabine for consolidation.	Participants received matching placebo to midostaurin with same dose, plus chemotherapy. Chemotherapy consisted of daunorubicin or idarubicin and cytarabine for induction and intermediate dose cytarabine for consolidation.
Number of Participants Analyzed [units: participants]	250	251

Time to partial and full platelet recovery (units: Months)	**Median** **(95% Confidence Interval)**	**Median** **(95% Confidence Interval)**
Partial platelet recovery	N/A (1.45 to N/A)[1]	N/A (3.5 to N/A)[1]
Full platelet recovery	0.953 (0.89 to 1.12)	0.887 (0.85 to 0.92)

[1] N/A: Very low number of events did not allow to estimate median nor the boundaries of CI.

Statistical Analysis

Groups	Midostaurin + chemotherapy, Placebo + chemotherapy	partial platelet recovery
Type of Statistical Test	Superiority	
Hazard Ratio (HR)	1.15	
95 % Confidence Interval 2-Sided	0.87 to 1.52	

Statistical Analysis

Groups	Midostaurin + chemotherapy, Placebo + chemotherapy	full platelet recovery
Type of Statistical Test	Superiority	
Hazard Ratio (HR)	0.82	
95 % Confidence Interval 2-Sided	0.67 to 1.00	

NOVARTIS

Plasma concentrations for midostaurin and its metabolites: CGP52421 and CGP62221 for Non-poor metabolizers

Description	Serial pharmacokinetics (PK) samples were collected in Non-poor metabolizer participants to assess the plasma concentrations of midostaurin, CGP52421 and CGP62221.
Time Frame	from Induction (IND) phase 0hr (predose) to Post-consolidation phase (POSTCONS) 12hr
Analysis Population Description	Pharmacokinetic analysis set-all (PAS-all) included all participants in the safety set who provided at least one evaluable PK concentration for Non-poor metabolizers. PK samples were not collected in all timepoints of all patients and reported for Non-poor metabolizers only.

	Midostaurin + chemotherapy	CGP52421	CGP62221
Arm/Group Description	Participants received Midostaurin in Induction 50mg twice daily on Day 8 until 48 hrs before start of next cycle. During Induction 2 and consolidation 50mg twice daily on Day 4 until 48 hrs before start of next cycle. During post-consolidation 50mg twice daily for 28 consecutive days of each 28-day treatment cycle up to 12 cycles. For participants who could not tolerate the protocol-specified dosing schedule, dose interruptions and/or reductions were either recommended or mandated allowing participants to continue the study treatment. Chemotherapy consisted of daunorubicin or idarubicin and cytarabine for induction and intermediate dose cytarabine for consolidation.	Active Midostaurin metabolite	Active Midostaurin metabolite
Number of Participants Analyzed [units: participants]	145	145	145

NOVARTIS

Plasma concentrations for midostaurin and its metabolites: CGP52421 and CGP62221 for Non-poor metabolizers (units: hour (hr))	**Mean ± Standard Deviation**	**Mean ± Standard Deviation**	**Mean ± Standard Deviation**
IND C1D8 0hr (Predose) (n = 34, 34, 34)	0 ± 0	0 ± 0	0 ± 0
IND C1D8 1hr (n= 6, 6, 6)	1110 ± 791	30.0 ± 35.4	37.6 ± 45.3
IND C1D8 3hr (n = 108, 104, 108)	2000 ± 897	80.6 ± 48.8	198 ± 178
IND C1D8 6hr (n= 7, 7, 7)	1370 ± 448	92.1 ± 47.1	285 ± 222
IND C1D8 12hr (n= 7, 7, 7)	1090 ± 365	79.3 ± 31.4	280 ± 196
IND C1D11 0hr (Predose) (n = 33, 33, 33)	5340 ± 3190	417 ± 162	1470 ± 812
IND C1D11 3hr (n = 92, 92, 92)	6840 ± 3480	451 ± 157	1520 ± 777
IND C1D11 12hr (n = 57, 57, 57)	4800 ± 2860	430 ± 167	1590 ± 732
IND C1D15 0hr (Predose) (n = 25, 25, 25)	8330 ± 5300	776 ± 261	3030 ± 1460
IND C1D15 12hr (n = 63, 63, 63)	7010 ± 4260	828 ± 229	3170 ± 1310
IND C1D18 0hr (Predose) (n = 19, 19, 19)	6520 ± 5230	1090 ± 304	4070 ± 1400
IND C1D18 12hr (n = 50, 50, 50)	5960 ± 4040	1050 ± 332	3990 ± 1580
IND C1D21 0hr (Predose) (n = 26, 26, 26)	6190 ± 4880	1310 ± 467	4540 ± 1950
IND C1D21 3hr (n = 89, 89, 89)	6740 ± 4390	1240 ± 380	4100 ± 1680
IND C1D21 12hr (n = 61, 61, 61)	5990 ± 4460	1220 ± 336	4320 ± 1660
CONS C1D4 0hr (predose) (n = 16, 15, 16)	72.0 ± 128	922 ± 246	269 ± 390
CONS C1D4 3hr (n = 49, 44, 49)	1110 ± 660	1090 ± 409	615 ± 601
CONS C1D4 12hr (n = 2, 2, 2)	187 ± 264	1060 ± 49.5	376 ± 531
CONS C1D17 0hr (predose) (n = 14, 14, 14)	1630 ± 780	1860 ± 387	1890 ± 608
CONS C1D17 3hr (n = 48, 47, 48)	2580 ± 1430	1620 ± 505	2030 ± 677
CONS C1D17 12hr (n = 29, 29, 29)	1950 ± 1630	1710 ± 500	1990 ± 746
CONS C3D4 0hr (predose) (n = 9, 9, 9)	94.3 ± 126	968 ± 469	274 ± 289
CONS C3D4 3hr (n = 25, 24, 25)	1030 ± 522	983 ± 465	437 ± 250

CONS C3D4 12hr (n = 2, 2, 2)	10.6 ± 14.9	996 ± 105	44.1 ± 41.6
CONS C3D17 0hr (predose) (n = 9, 9, 9)	1810 ± 1470	1460 ± 522	1750 ± 995
CONS C3D17 3hr (n = 24, 24, 24)	2620 ± 1230	1720 ± 640	2140 ± 1120
CONS C3D17 12hr (n = 17, 17, 17)	2430 ± 2450	1570 ± 644	1960 ± 1030
POSTCONS C1PRE 0hr (predose) (n = 2, 2, 2)	472 ± 407	1470 ± 148	786 ± 487
POSTCONS C1PRE 12hr (n = 1, 1, 1)	309 ± 0	1010 ± 0	887 ± 0
POSTCONS C4D1 0hr (predose) (n= 4, 4, 4)	496 ± 288	1070 ± 396	951 ± 650
POSTCONS C4D1 3hr (n = 4, 3, 4)	748 ± 136	1180 ± 458	857 ± 119
POSTCONS C4D1 12hr (n = 2, 2, 2)	419 ± 4.95	803 ± 30.4	784 ± 142
POSTCONS C7D1 0hr (predose) (n = 1, 1, 1)	311 ± 0	1120 ± 0	896 ± 0
POSTCONS C7D1 12hr (n = 3, 3, 3)	639 ± 174	960 ± 180	962 ± 344
POSTCONS C10D1 0hr (predose) (n = 1, 1, 1)	408 ± 0	1020 ± 0	1050 ± 0

AUC0-t: Pharmacokinetic (PK) parameter for midostaurin and its metabolites: CGP52421 and CGP62221 at Cycle 1, Day 8

Description	The AUC from time zero to a measurable concentration sampling time (t) (mass x time x volume-1). Note: as the last sampling time was at 12 h, AUC0-12h was determined after the first dose, reported at Cycle 1, Day 8
Time Frame	0 - 12 hrs
Analysis Population Description	Pharmacokinetic analysis set-all (PAS-all) included all participants in the safety set who provided at least one evaluable PK concentration.

	Midostaurin + chemotherapy	**CGP52421**	**CGP62221**
Arm/Group Description	Participants received Midostaurin in Induction 50mg twice daily on Day 8 until 48 hrs before start of next cycle. During Induction 2 and consolidation	Active Midostaurin metabolite	Active Midostaurin metabolite

	50mg twice daily on Day 4 until 48 hrs before start of next cycle. During post-consolidation 50mg twice daily for 28 consecutive days of each 28-day treatment cycle up to 12 cycles. For participants who could not tolerate the protocol-specified dosing schedule, dose interruptions and/or reductions were either recommended or mandated allowing participants to continue the study treatment. Chemotherapy consisted of daunorubicin or idarubicin and cytarabine for induction and intermediate dose cytarabine for consolidation.		
Number of Participants Analyzed [units: participants]	20	27	27
AUC0-t: Pharmacokinetic (PK) parameter for midostaurin and its metabolites: CGP52421 and CGP62221 at Cycle 1, Day 8 (units: hr*ng/mL)	**Geometric Mean (Geometric Coefficient of Variation)**	**Geometric Mean (Geometric Coefficient of Variation)**	**Geometric Mean (Geometric Coefficient of Variation)**
n = 20, 20, 20	14800 (37.5%)	712 (78.4%)	1830 (135%)

AUClast: Pharmacokinetic (PK) parameter for midostaurin and its metabolites: CGP52421 and CGP62221 at Cycle 1, Day 8

Description	The AUC from time zero to the last measurable concentration sampling time after the first dose reported at Cycle 1, Day 8
Time Frame	0 - 12 hrs
Analysis Population Description	Pharmacokinetic analysis set-all (PAS-all) included all participants in the safety set who provided at least one evaluable PK concentration.

	Midostaurin + chemotherapy	CGP52421	CGP62221
Arm/Group Description	Participants received Midostaurin in Induction 50mg twice daily on Day 8 until 48 hrs before start of next cycle. During Induction 2 and consolidation 50mg twice daily on Day 4 until 48 hrs before start of next cycle. During post-consolidation 50mg twice daily for 28 consecutive days of each 28-day treatment cycle up to 12 cycles. For participants who could not tolerate the protocol-specified dosing schedule, dose interruptions and/or reductions were either recommended or mandated allowing participants to continue the study treatment. Chemotherapy consisted of daunorubicin or idarubicin and cytarabine for induction and intermediate dose cytarabine for consolidation.	Active Midostaurin metabolite	Active Midostaurin metabolite
Number of Participants Analyzed [units: participants]	27	27	27
AUClast: Pharmacokinetic (PK) parameter for midostaurin and its metabolites: CGP52421 and CGP62221 at Cycle 1, Day 8 (units: hr*ng/mL)	**Geometric Mean (Geometric Coefficient of Variation)**	**Geometric Mean (Geometric Coefficient of Variation)**	**Geometric Mean (Geometric Coefficient of Variation)**
	12200 (59.6%)	493 (139%)	1130 (249%)

Cmax: Pharmacokinetic (PK) parameter for midostaurin and its metabolites: CGP52421 and CGP62221 at Cycle 1, Day 8

Description The maximum (peak) observed plasma drug concentration after the first dose administration reported at Cycle 1, Day 8

Time Frame	0 - 12 hrs
Analysis Population Description	Pharmacokinetic analysis set-all (PAS-all) included all participants in the safety set who provided at least one evaluable PK concentration.

	Midostaurin + chemotherapy	CGP52421	GCP62221
Arm/Group Description	Participants received Midostaurin in Induction 50mg twice daily on Day 8 until 48 hrs before start of next cycle. During Induction 2 and consolidation 50mg twice daily on Day 4 until 48 hrs before start of next cycle. During post-consolidation 50mg twice daily for 28 consecutive days of each 28-day treatment cycle up to 12 cycles. For participants who could not tolerate the protocol-specified dosing schedule, dose interruptions and/or reductions were either recommended or mandated allowing participants to continue the study treatment. Chemotherapy consisted of daunorubicin or idarubicin and cytarabine for induction and intermediate dose cytarabine for consolidation.	Active Midostaurin metabolite	Active Midostaurin metabolite
Number of Participants Analyzed [units: participants]	27	27	27
Cmax: Pharmacokinetic (PK) parameter for midostaurin and its metabolites: CGP52421 and CGP62221 at Cycle 1, Day 8 (units: ng/mL)	**Geometric Mean (Geometric Coefficient of Variation)**	**Geometric Mean (Geometric Coefficient of Variation)**	**Geometric Mean (Geometric Coefficient of Variation)**

	1910 (37.8%)	74.7 (72.3%)	183 (128%)

Tmax: Pharmacokinetic (PK) parameter for midostaurin and its metabolites: CGP52421 and CGP62221 at Cycle 1, Day 8

Description	The time to reach maximum (peak) plasma, blood, serum, or other body fluid drug concentration after single dose administration reported at Cycle 1, Day 8
Time Frame	0 - 12 hrs
Analysis Population Description	Pharmacokinetic analysis set-all (PAS-all) included all participants in the safety set who provided at least one evaluable PK concentration.

	Midostaurin + chemotherapy	GCP52421	CGP62221
Arm/Group Description	Participants received Midostaurin in Induction 50mg twice daily on Day 8 until 48 hrs before start of next cycle. During Induction 2 and consolidation 50mg twice daily on Day 4 until 48 hrs before start of next cycle. During post-consolidation 50mg twice daily for 28 consecutive days of each 28-day treatment cycle up to 12 cycles. For participants who could not tolerate the protocol-specified dosing schedule, dose interruptions and/or reductions were either recommended or mandated allowing participants to continue the study treatment. Chemotherapy consisted of daunorubicin or idarubicin and cytarabine for induction and	Active Midostaurin metabolite	Active Midostaurin metabolite

	intermediate dose cytarabine for consolidation.		
Number of Participants Analyzed [units: participants]	27	27	27
Tmax: Pharmacokinetic (PK) parameter for midostaurin and its metabolites: CGP52421 and CGP62221 at Cycle 1, Day 8 (units: hour (hr))	**Geometric Mean (Geometric Coefficient of Variation)**	**Geometric Mean (Geometric Coefficient of Variation)**	**Geometric Mean (Geometric Coefficient of Variation)**
	3.28 (101%)	5.38 (89.9%)	7.17 (57.8%)

Total score for each time point for the Functional Assessment of Cancer Therapy-Leukemia (FACT-Leu)

Description	The total FACT-Leu score consists of 44 items with total scores ranging from 0 to 176. Higher scores indicate better health-related quality of life (HRQoL). Negative changes from baseline indicate a worsening of HRQoL while positive changes indicate an improvement in HRQoL.
Time Frame	From date of Randomization up to approx. 18 months
Analysis Population Description	Full analysis set comprised all participants to whom study drug was assigned by randomization.

	Midostaurin + chemotherapy	**Placebo + chemotherapy**
Arm/Group Description	Participants received Midostaurin in Induction 50mg twice daily on Day 8 until 48 hrs before start of next cycle. During Induction 2 and consolidation 50mg twice daily on Day 4 until 48 hrs before start of next cycle. During post-consolidation 50mg twice daily for 28 consecutive days of each 28-day treatment cycle up to 12 cycles. For participants who could not tolerate the protocol-specified dosing schedule, dose interruptions and/or reductions were either recommended or mandated allowing participants to continue the study treatment.	Participants received matching placebo to midostaurin with same dose, plus chemotherapy. Chemotherapy consisted of daunorubicin or idarubicin and cytarabine for induction and intermediate dose cytarabine for consolidation.

	Chemotherapy consisted of daunorubicin or idarubicin and cytarabine for induction and intermediate dose cytarabine for consolidation.	
Number of Participants Analyzed [units: participants]	250	251
Total score for each time point for the Functional Assessment of Cancer Therapy-Leukemia (FACT-Leu) (units: Scores on a scale)	**Mean ± Standard Deviation**	**Mean ± Standard Deviation**
Baseline (n = 225, 223)	122.8 ± 22.64	123.1 ± 21.21
Induction Phase (n = 137, 147)	123.9 ± 21.50	122.1 ± 19.51
Induction I (n = 105, 90)	124.8 ± 20.34	123.5 ± 20.28
Induction II (n = 32, 57)	121.0 ± 25.09	119.8 ± 18.15
Consolidation (prior) (n = 210, 196)	135.9 ± 17.67	136.9 ± 21.03
Post- consolidation (n = 169, 114)	143.7 ± 21.45	140.1 ± 21.60
Follow-up (n = 74, 111)	136.4 ± 22.87	139.2 ± 25.00

Scores for each time point for the EQ5D-5L (a visual analogue scale (VAS))

Description	The EQ5D-5L questionnaire assesses 5 dimensions: mobility, self-care, usual activities, pain/discomfort and anxiety/depression. Each dimension has 5 response options (no problems, slight problems, moderate problems, severe problems and extreme problems) that reflect increasing levels of difficulty. The patient is asked to indicate his/her current health state by selecting the most appropriate level in each of the 5 dimensions. The questionnaire also included a Visual Analogue Scale (VAS), where the patient is asked to rate current health status on a scale of 0 to 100, with 0 being the worst imaginable health state.
Time Frame	From date of Randomization up to approx. 18 months
Analysis Population Description	Full analysis set comprised all participants to whom study drug was assigned by randomization.

	Midostaurin + chemotherapy	**Placebo + chemotherapy**
Arm/Group Description	Participants received Midostaurin in Induction 50mg twice daily on Day 8 until	Participants received matching placebo to midostaurin with same dose, plus

	48 hrs before start of next cycle. During Induction 2 and consolidation 50mg twice daily on Day 4 until 48 hrs before start of next cycle. During post-consolidation 50mg twice daily for 28 consecutive days of each 28-day treatment cycle up to 12 cycles. For participants who could not tolerate the protocol-specified dosing schedule, dose interruptions and/or reductions were either recommended or mandated allowing participants to continue the study treatment. Chemotherapy consisted of daunorubicin or idarubicin and cytarabine for induction and intermediate dose cytarabine for consolidation.	chemotherapy. Chemotherapy consisted of daunorubicin or idarubicin and cytarabine for induction and intermediate dose cytarabine for consolidation.
Number of Participants Analyzed [units: participants]	250	251
Scores for each time point for the EQ5D-5L (a visual analogue scale (VAS)) (units: Scores on a scale)	**Mean ± Standard Deviation**	**Mean ± Standard Deviation**
Baseline (n= 225, 220)	62.7 ± 22.98	64.3 ± 22.15
Induction Phase (n = 135, 146)	67.9 ± 20.95	64.4 ± 21.29
Induction I (n = 104, 89)	68.1 ± 21.02	64.0 ± 21.92
Induction II (n = 31, 57)	66.9 ± 21.03	65.2 ± 20.44
Consolidation (prior) (n = 207, 197)	79.1 ± 15.42	76.2 ± 16.37
Post-consolidation (n = 167, 113)	83.9 ± 15.00	77.3 ± 14.92
Follow-up (n- 74, 112)	74.3 ± 20.08	73.4 ± 1972

Other Pre-Specified Outcome Result(s)

No data identified.

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Post-Hoc Outcome Result(s)

All Collected Deaths

Description	On-treatment deaths were collected from start of treatment (FPFT) up to 30 days after study drug discontinuation, for a maximum duration of approx. 18 months. Randomized but not treated deaths were collected after randomization but before treatment with study drug. Post-treatment survival follow-up deaths were collected after the on-treatment period up to approx. 18 months. Participants who did not die during the on-treatment period and had not stopped study participation at the time of data cut-off (when study was terminated) were censored.
Time Frame	Start of study treatment up to 30 days post-treatment for approx. 1 year, prior to study treatment up to LPLV, approx. 18 months
Analysis Population Description	Clinical Database Population: all enrolled participants

	Midostaurin + chemotherapy	**Placebo + chemotherapy**
Arm/Group Description	Participants received Midostaurin in Induction 50mg twice daily on Day 8 until 48 hrs before start of next cycle. During Induction 2 and consolidation 50mg twice daily on Day 4 until 48 hrs before start of next cycle. During post-consolidation 50mg twice daily for 28 consecutive days of each 28-day treatment cycle up to 12 cycles. For participants who could not tolerate the protocol-specified dosing schedule, dose interruptions and/or reductions were either recommended or mandated allowing participants to continue the study treatment. Chemotherapy consisted of daunorubicin or idarubicin and cytarabine for induction and intermediate dose cytarabine for consolidation.	Participants received matching placebo to midostaurin with same dose, plus chemotherapy. Chemotherapy consisted of daunorubicin or idarubicin and cytarabine for induction and intermediate dose cytarabine for consolidation.
Number of Participants Analyzed [units: participants]	250	251
All Collected Deaths (units: Participants)	**Count of Participants (Not Applicable)**	**Count of Participants (Not Applicable)**

Total Deaths	48 (19.2%)	54 (21.51%)
Randomized but not treated deaths	2 (.8%)	1 (.4%)
Deaths on-treatment (n = 245, 249)	25 (10.2%)	21 (8.43%)
Post-treatment survival follow-up deaths	21 (9.55%)	32 (14.04%)

Summary of Safety

Safety Results

Time Frame	AEs were reported from 1st dose of study treatment until end of treatment plus 30 days, up to a maximum (max.) duration of 573 days (543 days max. exposure plus 30 days post-treatment) for midostaurin and up to a max. duration of 416 days (386 days max. exp. plus 30 days post-treatment) for placebo. Deaths - collected in the post-treatment survival follow-up period from 31 days after last dose of study medication until the end of the study, up to approx. 18 months. These are not considered AEs.
Additional Description	Any sign or symptom that occurs during the conduct of the trial and safety follow-up. Deaths in the post-treatment survival follow-up are not considered Adverse Events. The total number at risk in the post-treatment survival includes patients that entered the post-treatment survival follow-up period.
Source Vocabulary for Table Default	MedDRA (23.1)
Collection Approach for Table Default	Systematic Assessment

NOVARTIS

All-Cause Mortality

	Midostaurin + chemotherapy (On-treatment) N = 245	Placebo + chemotherapy (On-treatment) N = 249	Midostaurin + chemotherapy (Post-treatment survival follow-up) N = 220	Placebo + chemotherapy (Post-treatment survival follow-up) N = 228
Arm/Group Description	AEs during on-treatment period (up to 30 days post-treatment)	AEs during on-treatment period (up to 30 days post-treatment)	Deaths collected in the post- treatment survival follow-up phase (starting from day 31 post-treatment). No AEs were collected during this period	Deaths collected in the post- treatment survival follow-up phase (starting from day 31 post-treatment). No AEs were collected during this period
Total Number Affected	25	21	21	32
Total Number At Risk	245	249	220	228

Serious Adverse Events

	Midostaurin + chemotherapy (On-treatment) N = 245	Placebo + chemotherapy (On-treatment) N = 249	Midostaurin + chemotherapy (Post-treatment survival follow-up) N = 0	Placebo + chemotherapy (Post-treatment survival follow-up) N = 0
Arm/Group Description	AEs during on-treatment period (up to 30 days post-treatment)	AEs during on-treatment period (up to 30 days post-treatment)	Deaths collected in the post- treatment survival follow-up phase (starting from day 31 post-treatment). No AEs were collected during this period	Deaths collected in the post- treatment survival follow-up phase (starting from day 31 post-treatment). No AEs were collected during this period
Total # Affected by any Serious Adverse Event	95	114	0	0
Total # at Risk by any Serious Adverse Event	245	249	0	0

Blood and lymphatic system disorders		
Anaemia	0 (0.00%)	1 (0.40%)
Aplastic anaemia	1 (0.41%)	1 (0.40%)
Disseminated intravascular coagulation	0 (0.00%)	1 (0.40%)
Febrile bone marrow aplasia	1 (0.41%)	1 (0.40%)
Febrile neutropenia	16 (6.53%)	23 (9.24%)
Leukopenia	0 (0.00%)	1 (0.40%)
Lymphadenopathy	0 (0.00%)	1 (0.40%)
Neutropenia	1 (0.41%)	1 (0.40%)
Pancytopenia	3 (1.22%)	2 (0.80%)
Thrombocytopenia	1 (0.41%)	1 (0.40%)
Cardiac disorders		
Acute myocardial infarction	1 (0.41%)	0 (0.00%)
Atrial fibrillation	1 (0.41%)	3 (1.20%)
Bradycardia	0 (0.00%)	1 (0.40%)
Cardiac arrest	1 (0.41%)	1 (0.40%)
Cardiac failure congestive	0 (0.00%)	1 (0.40%)
Left ventricular dysfunction	1 (0.41%)	0 (0.00%)
Myocardial infarction	0 (0.00%)	1 (0.40%)
Myocarditis	1 (0.41%)	0 (0.00%)
Right ventricular dysfunction	1 (0.41%)	0 (0.00%)
Ventricular tachycardia	0 (0.00%)	1 (0.40%)

Congenital, familial and genetic disorders		
Aplasia	1 (0.41%)	1 (0.40%)
Endocrine disorders		
Thyrotoxic crisis	1 (0.41%)	0 (0.00%)
Gastrointestinal disorders		
Anal fistula	0 (0.00%)	1 (0.40%)
Colitis	0 (0.00%)	1 (0.40%)
Diarrhoea	1 (0.41%)	1 (0.40%)
Diverticular perforation	0 (0.00%)	1 (0.40%)
Gastrointestinal disorder	0 (0.00%)	1 (0.40%)
Intestinal ischaemia	1 (0.41%)	0 (0.00%)
Intestinal perforation	1 (0.41%)	0 (0.00%)
Jejunal stenosis	1 (0.41%)	0 (0.00%)
Mechanical ileus	0 (0.00%)	1 (0.40%)
Nausea	0 (0.00%)	2 (0.80%)
Neutropenic colitis	1 (0.41%)	3 (1.20%)
Oral dysaesthesia	0 (0.00%)	1 (0.40%)
Proctalgia	1 (0.41%)	0 (0.00%)
Small intestinal obstruction	0 (0.00%)	1 (0.40%)
Tongue haematoma	1 (0.41%)	0 (0.00%)
Ulcerative duodenitis	1 (0.41%)	0 (0.00%)
Vomiting	1 (0.41%)	2 (0.80%)

General disorders and administration site conditions		
Disease progression	2 (0.82%)	0 (0.00%)
General physical health deterioration	0 (0.00%)	1 (0.40%)
Mucosal inflammation	1 (0.41%)	1 (0.40%)
Multiple organ dysfunction syndrome	2 (0.82%)	4 (1.61%)
Pyrexia	4 (1.63%)	4 (1.61%)
Hepatobiliary disorders		
Biliary fistula	1 (0.41%)	0 (0.00%)
Cholecystitis	2 (0.82%)	3 (1.20%)
Drug-induced liver injury	1 (0.41%)	1 (0.40%)
Liver disorder	0 (0.00%)	1 (0.40%)
Immune system disorders		
Acute graft versus host disease	1 (0.41%)	0 (0.00%)
Anaphylactic reaction	0 (0.00%)	1 (0.40%)
Graft versus host disease in gastrointestinal tract	0 (0.00%)	1 (0.40%)
Haemophagocytic lymphohistiocytosis	1 (0.41%)	0 (0.00%)
Infections and infestations		
Abdominal infection	1 (0.41%)	0 (0.00%)
Abscess neck	1 (0.41%)	0 (0.00%)
Acinetobacter infection	0 (0.00%)	1 (0.40%)
Anal abscess	1 (0.41%)	1 (0.40%)

Appendicitis	0 (0.00%)	2 (0.80%)
Aspergillus infection	2 (0.82%)	0 (0.00%)
Bacteraemia	1 (0.41%)	1 (0.40%)
Biliary tract infection	1 (0.41%)	0 (0.00%)
Bronchopulmonary aspergillosis	1 (0.41%)	0 (0.00%)
Candida infection	0 (0.00%)	1 (0.40%)
Cellulitis	0 (0.00%)	2 (0.80%)
Cerebral fungal infection	1 (0.41%)	0 (0.00%)
Clostridial sepsis	1 (0.41%)	0 (0.00%)
Clostridium difficile colitis	1 (0.41%)	0 (0.00%)
Clostridium difficile infection	0 (0.00%)	1 (0.40%)
Coronavirus infection	1 (0.41%)	0 (0.00%)
Cytomegalovirus colitis	1 (0.41%)	0 (0.00%)
Device related infection	1 (0.41%)	2 (0.80%)
Diverticulitis	0 (0.00%)	1 (0.40%)
Enterococcal sepsis	1 (0.41%)	1 (0.40%)
Gastroenteritis	0 (0.00%)	1 (0.40%)
Gastroenteritis clostridial	1 (0.41%)	0 (0.00%)
H1N1 influenza	1 (0.41%)	0 (0.00%)
Hepatosplenic candidiasis	2 (0.82%)	0 (0.00%)
Infection	0 (0.00%)	2 (0.80%)
Kidney infection	1 (0.41%)	0 (0.00%)
Klebsiella bacteraemia	1 (0.41%)	0 (0.00%)

Klebsiella sepsis	1 (0.41%)	0 (0.00%)
Neutropenic sepsis	3 (1.22%)	1 (0.40%)
Pelvic abscess	1 (0.41%)	0 (0.00%)
Pharyngeal abscess	0 (0.00%)	1 (0.40%)
Pneumonia	9 (3.67%)	12 (4.82%)
Pneumonia fungal	2 (0.82%)	1 (0.40%)
Pneumonia viral	0 (0.00%)	1 (0.40%)
Pseudomonal sepsis	1 (0.41%)	0 (0.00%)
Pulmonary sepsis	0 (0.00%)	2 (0.80%)
Respiratory syncytial virus infection	1 (0.41%)	0 (0.00%)
Respiratory tract infection	1 (0.41%)	0 (0.00%)
Sepsis	11 (4.49%)	13 (5.22%)
Septic shock	8 (3.27%)	9 (3.61%)
Staphylococcal sepsis	1 (0.41%)	0 (0.00%)
Streptococcal infection	1 (0.41%)	0 (0.00%)
Streptococcal sepsis	3 (1.22%)	0 (0.00%)
Systemic candida	0 (0.00%)	2 (0.80%)
Systemic mycosis	0 (0.00%)	1 (0.40%)
Upper respiratory tract infection	0 (0.00%)	1 (0.40%)
Viral myocarditis	0 (0.00%)	1 (0.40%)
Injury, poisoning and procedural complications		
Expired product administered	0 (0.00%)	1 (0.40%)

Head injury	0 (0.00%)	1 (0.40%)
Lumbar vertebral fracture	0 (0.00%)	1 (0.40%)
Subdural haemorrhage	0 (0.00%)	1 (0.40%)
Thoracic vertebral fracture	0 (0.00%)	1 (0.40%)
Investigations		
Alanine aminotransferase increased	1 (0.41%)	1 (0.40%)
Aspartate aminotransferase increased	0 (0.00%)	1 (0.40%)
Body temperature increased	0 (0.00%)	1 (0.40%)
C-reactive protein increased	1 (0.41%)	0 (0.00%)
Eastern Cooperative Oncology Group performance status worsened	0 (0.00%)	1 (0.40%)
Electrocardiogram QT prolonged	0 (0.00%)	2 (0.80%)
Gamma-glutamyltransferase increased	0 (0.00%)	1 (0.40%)
Hepatic enzyme increased	0 (0.00%)	1 (0.40%)
Lymphocyte count increased	0 (0.00%)	1 (0.40%)
Neutrophil count decreased	0 (0.00%)	1 (0.40%)
Platelet count decreased	0 (0.00%)	3 (1.20%)
Pulmonary function test decreased	1 (0.41%)	0 (0.00%)
White blood cell count decreased	0 (0.00%)	1 (0.40%)
Metabolism and nutrition disorders		
Decreased appetite	0 (0.00%)	1 (0.40%)
Hypokalaemia	0 (0.00%)	1 (0.40%)
Hyponatraemia	1 (0.41%)	0 (0.00%)

Hypophosphataemia	0 (0.00%)	1 (0.40%)
Tumour lysis syndrome	0 (0.00%)	2 (0.80%)
Musculoskeletal and connective tissue disorders		
Chondrocalcinosis pyrophosphate	0 (0.00%)	1 (0.40%)
Cytarabine syndrome	0 (0.00%)	1 (0.40%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)		
Chloroma	0 (0.00%)	1 (0.40%)
Transitional cell carcinoma recurrent	0 (0.00%)	1 (0.40%)
Nervous system disorders		
Carotid artery stenosis	0 (0.00%)	1 (0.40%)
Cerebral haemorrhage	1 (0.41%)	0 (0.00%)
Cerebral infarction	1 (0.41%)	0 (0.00%)
Cerebrovascular accident	1 (0.41%)	1 (0.40%)
Dizziness	0 (0.00%)	1 (0.40%)
Facial paresis	0 (0.00%)	1 (0.40%)
Facial spasm	1 (0.41%)	0 (0.00%)
Myelopathy	0 (0.00%)	1 (0.40%)
Somnolence	1 (0.41%)	0 (0.00%)
Subarachnoid haemorrhage	1 (0.41%)	0 (0.00%)
Syncope	2 (0.82%)	1 (0.40%)
Transient ischaemic attack	0 (0.00%)	1 (0.40%)

Psychiatric disorders		
Depression	0 (0.00%)	1 (0.40%)
Renal and urinary disorders		
Acute kidney injury	0 (0.00%)	2 (0.80%)
Renal failure	0 (0.00%)	1 (0.40%)
Respiratory, thoracic and mediastinal disorders		
Acute pulmonary oedema	1 (0.41%)	0 (0.00%)
Cough	1 (0.41%)	0 (0.00%)
Dyspnoea	1 (0.41%)	0 (0.00%)
Hypoxia	1 (0.41%)	0 (0.00%)
Interstitial lung disease	1 (0.41%)	0 (0.00%)
Lung infiltration	1 (0.41%)	0 (0.00%)
Pulmonary haemorrhage	1 (0.41%)	0 (0.00%)
Pulmonary toxicity	0 (0.00%)	2 (0.80%)
Respiratory disorder	0 (0.00%)	1 (0.40%)
Respiratory failure	4 (1.63%)	6 (2.41%)
Skin and subcutaneous tissue disorders		
Drug eruption	0 (0.00%)	1 (0.40%)
Hypersensitivity vasculitis	1 (0.41%)	0 (0.00%)
Vascular disorders		
Embolism	1 (0.41%)	0 (0.00%)

Hypotension	1 (0.41%)	0 (0.00%)

Other (Not Including Serious) Adverse Events

Frequent Event Reporting Threshold 5%

	Midostaurin + chemotherapy (On-treatment) N = 245	**Placebo + chemotherapy (On-treatment) N = 249**	**Midostaurin + chemotherapy (Post-treatment survival follow-up) N = 0**	**Placebo + chemotherapy (Post-treatment survival follow-up) N = 0**
Arm/Group Description	AEs during on-treatment period (up to 30 days post-treatment)	AEs during on-treatment period (up to 30 days post-treatment)	Deaths collected in the post- treatment survival follow-up phase (starting from day 31 post-treatment). No AEs were collected during this period	Deaths collected in the post- treatment survival follow-up phase (starting from day 31 post-treatment). No AEs were collected during this period
Total # Affected by any Other Adverse Event	242	245	0	0
Total # at Risk by any Other Adverse Event	245	249	0	0
Blood and lymphatic system disorders				
Anaemia	77 (31.43%)	96 (38.55%)	0	0
Febrile neutropenia	102 (41.63%)	116 (46.59%)		
Leukopenia	20 (8.16%)	31 (12.45%)		
Neutropenia	34 (13.88%)	53 (21.29%)		
Pancytopenia	6 (2.45%)	13 (5.22%)		

Thrombocytopenia	62 (25.31%)	69 (27.71%)
Cardiac disorders		
Tachycardia	14 (5.71%)	16 (6.43%)
Gastrointestinal disorders		
Abdominal pain	41 (16.73%)	46 (18.47%)
Abdominal pain upper	24 (9.80%)	34 (13.65%)
Constipation	77 (31.43%)	84 (33.73%)
Diarrhoea	121 (49.39%)	142 (57.03%)
Dyspepsia	16 (6.53%)	16 (6.43%)
Haemorrhoids	27 (11.02%)	18 (7.23%)
Nausea	141 (57.55%)	137 (55.02%)
Neutropenic colitis	13 (5.31%)	5 (2.01%)
Proctalgia	13 (5.31%)	5 (2.01%)
Stomatitis	39 (15.92%)	36 (14.46%)
Vomiting	101 (41.22%)	63 (25.30%)
General disorders and administration site conditions		
Asthenia	17 (6.94%)	15 (6.02%)
Chills	16 (6.53%)	11 (4.42%)
Fatigue	36 (14.69%)	26 (10.44%)
Mucosal inflammation	47 (19.18%)	50 (20.08%)
Oedema	27 (11.02%)	21 (8.43%)
Oedema peripheral	44 (17.96%)	38 (15.26%)

Pain	15 (6.12%)	8 (3.21%)
Pyrexia	146 (59.59%)	138 (55.42%)
Infections and infestations		
Device related infection	9 (3.67%)	16 (6.43%)
Folliculitis	16 (6.53%)	4 (1.61%)
Pneumonia	32 (13.06%)	29 (11.65%)
Sepsis	13 (5.31%)	13 (5.22%)
Injury, poisoning and procedural complications		
Transfusion reaction	13 (5.31%)	11 (4.42%)
Investigations		
Alanine aminotransferase increased	29 (11.84%)	29 (11.65%)
Aspartate aminotransferase increased	24 (9.80%)	18 (7.23%)
Blood alkaline phosphatase increased	9 (3.67%)	13 (5.22%)
Blood bilirubin increased	19 (7.76%)	7 (2.81%)
C-reactive protein increased	15 (6.12%)	13 (5.22%)
Electrocardiogram QT prolonged	26 (10.61%)	13 (5.22%)
Gamma-glutamyltransferase increased	17 (6.94%)	26 (10.44%)
Neutrophil count decreased	20 (8.16%)	20 (8.03%)
Platelet count decreased	34 (13.88%)	50 (20.08%)
Weight increased	17 (6.94%)	24 (9.64%)
White blood cell count decreased	25 (10.20%)	35 (14.06%)

Metabolism and nutrition disorders		
Decreased appetite	31 (12.65%)	40 (16.06%)
Hyperglycaemia	11 (4.49%)	14 (5.62%)
Hypoalbuminaemia	18 (7.35%)	16 (6.43%)
Hypocalcaemia	15 (6.12%)	24 (9.64%)
Hypokalaemia	95 (38.78%)	102 (40.96%)
Hypomagnesaemia	16 (6.53%)	20 (8.03%)
Hypophosphataemia	16 (6.53%)	18 (7.23%)
Musculoskeletal and connective tissue disorders		
Arthralgia	22 (8.98%)	14 (5.62%)
Back pain	26 (10.61%)	32 (12.85%)
Bone pain	7 (2.86%)	13 (5.22%)
Pain in extremity	23 (9.39%)	15 (6.02%)
Nervous system disorders		
Dizziness	14 (5.71%)	23 (9.24%)
Headache	70 (28.57%)	64 (25.70%)
Psychiatric disorders		
Anxiety	9 (3.67%)	15 (6.02%)
Insomnia	16 (6.53%)	25 (10.04%)
Respiratory, thoracic and mediastinal disorders		
Cough	33 (13.47%)	37 (14.86%)

Dyspnoea	28 (11.43%)	27 (10.84%)
Epistaxis	44 (17.96%)	43 (17.27%)
Oropharyngeal pain	17 (6.94%)	22 (8.84%)
Skin and subcutaneous tissue disorders		
Alopecia	11 (4.49%)	14 (5.62%)
Dry skin	14 (5.71%)	8 (3.21%)
Erythema	20 (8.16%)	20 (8.03%)
Petechiae	20 (8.16%)	21 (8.43%)
Pruritus	28 (11.43%)	32 (12.85%)
Rash	80 (32.65%)	87 (34.94%)
Rash maculo-papular	17 (6.94%)	21 (8.43%)
Vascular disorders		
Hypertension	20 (8.16%)	27 (10.84%)
Hypotension	17 (6.94%)	25 (10.04%)

Other Relevant Findings

None

Conclusion:

- The study met the futility (lack of efficacy) criteria in a protocol-predefined interim analysis and was discontinued prematurely. As the study was prematurely stopped, the follow-up of the subjects until the relapse and or death was not performed. Hence, the efficacy results should be interpreted with caution considering the premature stop of subject's follow-up (i.e. follow-up up to relapse and/or death).
- Midostaurin combined with chemotherapy did not show favorable EFS results. The OS results showed a slightly favorable trend in the midostaurin arm. Overall, the efficacy results should be interpreted with caution due to premature termination of the study.
- The safety profile of midostaurin in this study is line with the current safety knowledge of midostaurin safety in *FLT3*-mutation-positive AML subjects.
- No new safety signal has been identified in the range of safety analyses performed, including those by chemotherapy received during the induction phase (daunorubicin vs. idarubicin).
- The safety analysis by age subgroup did not reveal any major findings

Date of Clinical Trial Report

Published CSR: 29 November 2021

Date of Initial Inclusion on Clinical Trial Results website

12 February 2022

Date of Latest Update

Not applicable

Reason for Update

Not applicable