# CLINICAL STUDY REPORT SYNOPSIS

## SYNOPSIS

**Study Title:** A Randomized (1:1), Double-Blind, Multi-Center, Placebo Controlled Study Evaluating Intensive Chemotherapy With or Without Glasdegib (PF-04449913) or Azacitidine (AZA) With or Without Glasdegib in Patients With Previously Untreated Acute Myeloid Leukemia

**Study Number:** B1371019

**Regulatory Agency or Public Disclosure Identifier Number:**

EudraCT Number: 2017-002822-19

ClinicalTrials.gov ID: NCT03416179

**Study Phase:** Phase 3

**Name of Study Intervention:** Glasdegib (PF-04449913)

**Trade Name:** DAURISMO™

**Name of Sponsor/Company:** Pfizer Inc.

**CSR Version and Report Date:** version 1.0; 23 June 2022

**Number of Study Center(s) and Investigator(s):**

A total of 325 participants were randomized for participation at 83 centers in 21 countries/regions.

A list of study centers and investigators involved in this study is provided in Appendix 16.1.4.1.

**Publications:** Not Applicable

**Study Period:**

Study Initiation Date (First Participant First Visit [FPFV]) – Non-intensive Cohort: 18 June 2018

Primary Completion Date (PCD) – Non-intensive Cohort: 05 June 2020

Data Cutoff Date – Non-intensive Cohort: The analyses presented in this report are based on a database lock date of 17 January 2022.

The non-intensive cohort was terminated due to the futility at an interim analysis by external data monitoring committee (E-DMC). The participants of the non-intensive cohort (in the

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investigator's clinical judgement) can continue to derive clinical benefit to access study medication(s) and can enroll in the continuation study.

### Rationale:

The non-intensive B1371019 study was designed to investigate if glasdegib in combination with azacitidine is superior to placebo in combination with azacitidine in prolonging overall survival (OS) in patients with untreated acute myelogenous leukemia (AML).

### Objectives, Endpoints, and Statistical Methods:

The objectives and endpoints of the study are listed in Table S1.

**Table S1. Study Objectives and Endpoints – Non-Intensive Study**

| Type | Objectives | Endpoints | Presentation of Results |
|---|---|---|---|
| **Primary** | | | |
| Efficacy | To demonstrate that glasdegib was superior to placebo in combination with azacitidine in prolonging OS in participants with untreated AML. | • OS. | Final presentation of OS |
| **Secondary** | | | |
| Efficacy | To compare fatigue score post-baseline as measured by MDASI-AML/MDS in both treatment arms. | • Fatigue score measured by the MDASI-AML/MDS questionnaire. | Analyzed |
| | To compare glasdegib versus placebo in combination with azacitidine in improving other clinical efficacy measures. | • Rate of CR (including $CR_{MRD-}$ as assessed by multiparametric flow cytometry), CRi as defined by the ELN recommendations (2017), MLFS, PR, and CRh. | Analyzed |
| | To estimate the DoR in both treatment arms. | • DoR (defined as CRi or better or CRh or better if applicable).[a] | Not Analyzed |
| | To estimate the TTR in both treatment arms. | • TTR (CRi or better or CRh or better).[a] | Analyzed |
| | To compare EFS in both treatment arms. | • EFS. | Not Analyzed |
| PRO | To compare PRO measurements in both treatment arms. | • PROs as measured by the MDASI-AML/MDS, EQ-5D-5L, PGI-S and PGI-C. | Not Analyzed |

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## Table S1. Study Objectives and Endpoints – Non-Intensive Study

| | | | |
|---|---|---|---|
| Safety | To evaluate the overall safety profile in both treatment arms. | • AEs as characterized by type, frequency, severity (as graded by NCI CTCAE version 4.03), timing, seriousness, and relationship to study therapy. | Analyzed |
| | To evaluate laboratory abnormalities in both treatment arms. | • Laboratory abnormalities as characterized by type, frequency, severity (as graded by NCI CTCAE version 4.03) and timing. | Analyzed |
| | To characterize treatment effects on the QTc interval. | • QTc interval | Analyzed |
| PK | To characterize the PK of glasdegib. | • PK of glasdegib. | Analyzed |
| **Exploratory** | | | |
| Biomarker and Other | Bone marrow and blood biomarkers of response and/or resistance to glasdegib in combination with azacitidine. | • Molecular, cellular, and soluble markers in peripheral blood and/or bone marrow which might include, but were not limited to: Hh pathway and/or AML gene and protein expression, epigenetic status and changes, and gene mutation profiling.<br>• Transfusion independence. | Not Analyzed |
| PRO | PROs for symptomatic AEs. | • As measured by a questionnaire containing 2 items from the PRO-CTCAE item library version 1.0 and an add-on item on muscle spasm. | Not Analyzed |

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### Table S1. Study Objectives and Endpoints – Non-Intensive Study

Abbreviations: AE = adverse event; CR = complete remission; CRh = complete remission with partial hematologic recovery; CRi = complete remission with incomplete hematologic recovery; $CR_{MRD-}$ = complete remission with negative minimal residual disease; CTCAE = common terminology criteria for adverse events; DoR = duration of response; EFS = event-free survival; ELN = European Leukemia Net; EQ-5D-5L = EuroQol 5-Dimension questionnaire 5-Level version; MDASI-AML/MDS = M.D. Anderson Symptom Inventory AML/MDS Module; MDS = myelodysplastic syndrome; MLFS = morphologic leukemia-free state; MRD = minimal residual disease; NCI = National Cancer Institute; OS = overall survival; PGI-C = Patient Global Impression of Change; PGI-S = Patient Global Impression of Symptoms; PK = pharmacokinetic; PR = partial remission; PRO = patient reported outcomes; QTc = QT interval corrected for rate; TTR = time to response;

a. CRi or better included CR (including $CR_{MRD-}$), CRh, or CRi for non-intensive chemotherapy participants. CRh or better was only defined for non-intensive chemotherapy participants as CR (including $CR_{MRD-}$) or CRh.

The non-intensive cohort achieved PCD on 05 June 2020 but was terminated thereafter (May 2020) for futility. The data as of the cutoff date (17 January 2022) was determined to be final data for the non-intensive study. This abbreviated CSR presents the final results for the non-intensive AML population.

There are participants who continue this study as of the data cutoff date (17 January 2022) and can have access to the study medication(s) and receive the benefit of treatment. For these participants, only safety and dosing data are to be collected after the data cutoff.

Some participants discontinued from the study after the E-DMC's conclusion that the study would not meet its primary objective. Due to this, some secondary and exploratory endpoints could not be analyzed as originally planned (see Table S1 for the endpoints that were not analyzed).

OS: the primary efficacy analysis compared OS between the experimental arm and the control arm, and was performed using a 1-sided stratified log-rank test. OS was defined as the time from randomization to the date of death due to any cause. OS time associated with each treatment arm was summarized using the Kaplan-Meier method (product-limit estimates). The OS rate at 6, 12, and 18 months was estimated with corresponding 2-sided 95% confidence intervals (CIs) for the non-intensive chemotherapy participants.

Fatigue: the "Fatigue" single-item from the MDASI-AML/MDS questionnaire was the key secondary endpoint. A repeated measures model was used to determine Clinically Important Responder (CIR). The change in Fatigue from baseline was used as the outcome and Subject Global Impression of Change using PGIS (SGIC-S) score was used as the anchor.

Responses: The proportion of participants achieving $CR_{MRD-}$, CR (including $CR_{MRD-}$), CRi, CRh, MLFS, and PR as their best overall response was estimated with 2-sided 95% CI (using normal approximation). The proportion and 2-sided 95% CI (using exact method) of participants achieving each response category for each stratum were also to be provided. The proportion of participants with $CR_{MRD-}$, CR (including $CR_{MRD-}$), CRi or better and CRh or

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better respectively was compared between the 2 treatment arms using a 1-sided Cochran Mantel Haenszel (CMH) stratified test and an unstratified chi-square test.

TTR: Time to Response (TTRi or TTRh) was defined, for participants achieved CRi or better or CRh or better, as the time from the date of randomization to the first documentation of response (CRi or better or CRh or better).

PK: the plasma trough concentration ($C_{trough}$) was reported. Descriptive statistics were provided for these PK parameters in tabular form by cycle and day. For drug concentrations, individual values and descriptive statistics were presented by cycle, day of assessment, and nominal time in tabular form.

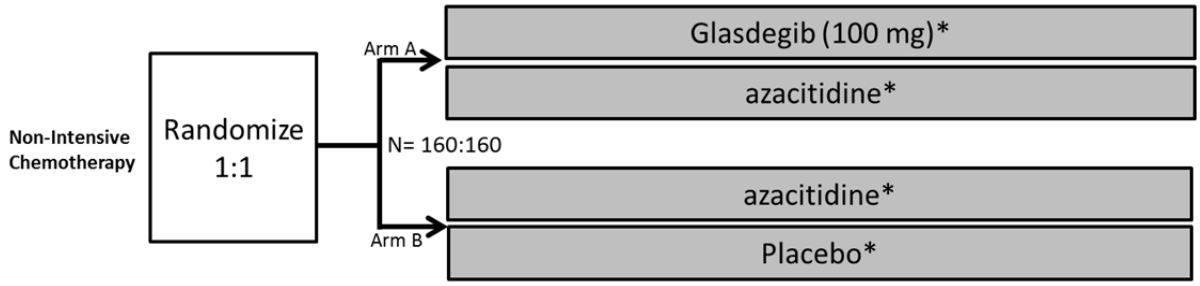
**Methodology:**

The B1371019 non-intensive study was a randomized (1:1), double-blind, multicenter, placebo-controlled study of azacitidine chemotherapy in combination with glasdegib versus (vs) azacitidine chemotherapy in combination with placebo in adult participants with previously untreated AML who were not candidates for intensive induction chemotherapy (Figure S1).

Study assignment was made by the investigator based on the 2017 ELN recommendations.

Participants were stratified at randomization by genetic risk (favorable vs intermediate vs adverse by ELN genetic risk categories) and age (<75 years vs ≥75 years).

**Figure S1. Schematic of Non-Intensive Study Design**




Throughout this report the glasdegib + azacitidine arm will be referred to as the glasdegib arm, and the placebo + azacitidine arm will be referred to as the placebo arm.

**Number of Participants (planned and analyzed):**

A total of 320 participants who were not candidates to receive intensive chemotherapy were planned to receive the treatment of non-intensive chemotherapy.

A total of 325 participants were randomized for participation at 83 centers in 21 countries/regions; 163 participants were randomized to the glasdegib arm and 162 participants to the placebo arm. A total of 322 (99.1%) participants were treated.

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As of the data cutoff date (17 January 2022) for this abbreviated CSR, 306 (95.0%) participants discontinued from the study treatment.

- The most common reason for glasdegib/placebo treatment discontinuations was progressive disease; 38 (23.5%) and 41 (25.6%) participants in the glasdegib and placebo arms, respectively, had progressive disease. This was followed by death (36 [22.2%] and 29 [18.1%] participants in glasdegib and placebo arms, respectively).

- The most common reason for azacitidine treatment discontinuations was progressive disease; 44 (27.2%) and 48 (30.0%) participants in the glasdegib and placebo arms, respectively, had progressive disease. This was followed by death (37 [22.8%] and 35 [21.9%] participants in glasdegib and placebo arms, respectively).

Participants who discontinued study treatment could go into either the follow-up phase, or the long-term follow-up phase (if a subsequent anti-cancer therapy was initiated at end of treatment or at the participant's request). In the follow-up phase, 11 (6.7%) participants in glasdegib arm and 6 (3.7%) participants in placebo arm were ongoing as of the cutoff date. In the long-term follow-up phase, 12 (7.4%) participants in glasdegib arm and 6 (3.7%) participants in placebo arm were ongoing as of the cutoff date.

Death was the primary reason for discontinuation from follow-up (98 [60.1%] participants in the glasdegib arm and 98 [60.5%] participants in the placebo arm), as well as from long-term follow-up (117 [71.8%] participants in the glasdegib arm and 113 [69.8%] participants in the placebo arm).

No participants in this non-intensive study discontinued study intervention or were discontinued from study due to coronavirus disease 2019 (COVID-19).

**Diagnosis and Main Criteria for Inclusion and Exclusion:**

Enrolled in this non-intensive study were adult participants with previously untreated AML who were not candidates for intensive induction chemotherapy. Participants with Acute Promyelocytic Leukemia (APL) and APL with promyelocytic leukemia – retinoic acid receptor alpha (PML-RARA), or AML with known breakpoint cluster region-Abelson 1 (BCR-ABL1) mutation or known t(9;22)(q34;q11.2) as a sole abnormality were excluded from this study.

**Study Interventions, Dose, Mode of Administration, and Batch Number(s):**

Glasdegib 100 mg QD or matching placebo was administered by mouth (PO) daily beginning on Day 1 of chemotherapy with azacitidine administered by subcutaneous (SC) injection or intravenous (IV) infusion daily for 7 days in 28-day cycles until disease progression, unacceptable toxicity, consent withdrawal, or death.

The manufacturing lot numbers for the study intervention(s) that were dispensed in this study are provided in Table S2.

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### Table S2. Manufacturing Lot Numbers for Study Drugs Administered

| Investigational Product Description | Vendor Lot Number | Pfizer Lot Number | Strength/Potency | Dosage Form |
|---|---|---|---|---|
| Glasdegib 100 mg Round Pale Orange Film Coated Tablet (Drug Count [DC]) | Not Applicable (N/A) | 18-000163 | 100 mg | Tablet |
| Glasdegib 100 mg Round Pale Orange Film Coated Tablet (DC) | 19-DP-00032 | 19-001635 | 100 mg | Tablet |
| Glasdegib 25 mg Round Yellow Film Coated Tablet (DC) | 19-DP-00031 | 19-001634 | 25 mg | Tablet |
| Glasdegib 100 mg Round Pale Orange Film Coated Tablet (DC) | 19-DP-00033 | 19-001636 | 100 mg | Tablet |
| Glasdegib 100 mg Round Pale Orange Film Coated Tablet (DC) | 17-001948 | 17-003503 | 100 mg | Tablet |
| Glasdegib 100 mg Round Pale Orange Film Coated Tablet (DC) | N/A | 17-000224 | 100 mg | Tablet |
| Glasdegib 25 mg Round Yellow Film Coated Tablet (DC) | N/A | 17-000222 | 25 mg | Tablet |
| Glasdegib 25 mg Round Yellow Film Coated Tablet (DC) | N/A | 18-000162 | 25 mg | Tablet |
| Glasdegib 25 mg Round Yellow Film Coated Tablet (DC) | N/A | 17-001947 | 25 mg | Tablet |
| Azacitidine 100 mg powder for 25 mg/mL suspension for injection vial | 9A146A | 19-004070 | 100 mg 25 mg/mL | Commercial Product |
| Azacitidine 100 mg powder for 25 mg/mL suspension for injection vial | 9A146A | 19-004071 | 100 mg 25 mg/mL | Commercial Product |
| Azacitidine 100 mg powder for 25 mg/mL suspension for injection vial | 9E200A | 19-004474 | 100 mg 25 mg/mL | Commercial Product |
| Azacitidine 100 mg powder for 25 mg/mL suspension for injection vial in 1×1 pack | 7A961A | 17-004252 | 100 mg 25 mg/mL | Commercial Product |
| Azacitidine 100 mg powder for 25 mg/mL suspension for injection vial in 1×1 pack | 6I920A | 17-003002 | 100 mg 25 mg/mL | Commercial Product |
| Azacitidine 100 mg powder for 25 mg/mL suspension for injection vial in 1×1 pack | 8H100A | 19-002518 | 100 mg 25 mg/mL | Commercial Product |
| Azacitidine 100 mg powder for 25 mg/mL suspension for injection vial in 1×1 pack | 8H100A | 19-000728 | 100 mg 25 mg/mL | Commercial Product |
| Azacitidine 100 mg powder for 25 mg/mL suspension for injection vial | 8I114A | 19-001767 | 100 mg 25 mg/mL | Commercial Product |
| Azacitidine 100 mg powder for 25 mg/mL suspension for injection vial in 1×1 pack | 6H912A | 17-001253 | 100 mg 25 mg/mL | Commercial Product |
| Placebo for Glasdegib 25 mg Round Yellow Film Coated Tablet | N/A | 17-000217 | 0 mg | Tablet |
| Placebo for Glasdegib 100 mg Round Pale Orange Film Coated Tablet | N/A | 17-000218 | 0 mg | Tablet |
| Placebo for Glasdegib 25 mg Round Yellow Film Coated Tablet | 19-DP-00029 | 19-001454 | 0 mg | Tablet |

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**Table S2. Manufacturing Lot Numbers for Study Drugs Administered**

| Investigational Product Description | Vendor Lot Number | Pfizer Lot Number | Strength/Potency | Dosage Form |
|---|---|---|---|---|
| Placebo for Glasdegib 100 mg Round Pale Orange Film Coated Tablet | 19-DP-00030 | 19-001633 | 0 mg | Tablet |

### Duration of Study Intervention:

Daily glasdegib (100 mg) PO or placebo PO could continue up to 2 years following randomization unless AML was confirmed MRD negative post hematopoietic stem cell transplant (HSCT) at 2 consecutive time points per central laboratory analysis. These 2 consecutive time points were approximately 3 months apart as part of the already scheduled marrow assessments.

The median duration of treatment was similar between the 2 treatment arms: 22.2 weeks (range: 0.4, 156.6) in the glasdegib arm and 24.2 weeks (range: 0.4, 127.3) in the placebo arm.

### Summary of Results:

### Demographic and Other Baseline Characteristics:

Of the 325 randomized participants, 186 (57.2%) were male and 139 (42.8%) were female; the majority of participants were White (60.3%); mean (standard deviation [SD]) age was 73.17 (6.99) years.

The distribution of disease characteristics (white blood cell [WBC], platelets, hemoglobin, peripheral blasts, bone marrow [BM] blasts, Eastern Cooperative Oncology Group [ECOG] performance status, age group, ELN risk group) was similar between the 2 treatment arms.

- The majority of participants had BM blasts ≥30%: 108 (66.3%) and 106 (65.4%) participants in the glasdegib and placebo arms, respectively.

- For the classification from Interactive Voice Response System (IVRS), the majority of participants had intermediate ELN risk, specifically 123 participants in the glasdegib arm and 124 participants in the placebo arm.

- As derived from case report form (CRF), the majority of participants had intermediate or adverse ELN risk, specifically 134 participants in the glasdegib arm and 140 participants in the placebo arm.

- Advanced age was the most common reason for enrollment of participants in the non-intensive chemotherapy in both the glasdegib arm (136 [83.4%] participants) and in the placebo arm (125 [77.2%] participants).

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**Exposure:**

Exposure to Glasdegib/Placebo

Both the median and mean study treatment exposures to glasdegib/placebo were similar between the 2 treatment arms.

- The median treatment exposure time was 21.8 weeks for the glasdegib arm and 24.1 weeks for the placebo arm.
- The median relative dose intensity was 95.0% for the glasdegib arm and 96.9% for the placebo arm.

Exposure to Azacitidine

Both the median and mean study treatment exposures to azacitidine were similar between the 2 treatment arms.

- The median treatment exposure time was 21.0 weeks for the glasdegib arm and 21.5 weeks for the placebo arm.
- The median relative dose intensity for azacitidine was 100% in both treatment arms.

**Efficacy Results:**

**Primary Endpoint - Overall Survival**

The non-intensive study did not meet its primary objective of demonstrating that glasdegib + azacitidine was superior to placebo + azacitidine in prolonging OS in all randomized participants with untreated AML.

- A total of 117 (71.8%) and 113 (69.8%) participants died in the glasdegib and placebo arms, respectively.
- Glasdegib did not extend OS with hazard ratio = 1.02 (95% CI: 0.787, 1.326) and 1-sided p-value = 0.5622.
- The estimated median OS for the glasdegib arm was 10.3 (95% CI: 7.6, 12.2) months while for the placebo arm was 10.9 (95% CI: 7.9, 12.9) months.
- The OS at 6, 12 and 18 months were comparable between the 2 treatment arms.
- An analysis of OS by baseline characteristics showed that the glasdegib arm performed better than the placebo arm in subgroups of Favorable and Intermediate ELN risk categories, females, ECOG performance status ≥2, de novo hematological disease history, and participants with baseline WBC $\geq 10 \times 10^9$/L, but the OS benefit was not statistically significant. In contrast, the placebo arm performed better in subgroups of

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adverse ELN risk category, males, Asian population, EGOG performance status 0 and 1, and Secondary hematological disease history, but the OS benefit was not statistically different. All these subgroup analyses are considered exploratory.

- The estimated median duration of follow-up for OS by reversed Kaplan-Meier method for the glasdegib arm was 22.0 (95% CI: 18.2, 23.7) months and for the placebo arm was 19.4 (95% CI: 16.4, 21.2) months.

**Key Secondary Endpoint - Fatigue by MDASI-AML/MDS**

At Week 12, the percentage of participants with improvement in fatigue was numerically lower in the glasdegib arm compared to that in the placebo arm with the CMH unstratified 1-sided p-value of 0.8397 and CMH stratified 1-sided p-value of 0.8359.

The estimated mean change in fatigue score anchored on PGI-S among clinically important responders was -1.35 (95% CI: -1.61, -1.09).

**Other Secondary Endpoints**

**Rate of CR, CRi, MLFS, PR and CRh**

The percentages of participants achieving CR (including $CR_{MRD-}$), CRi and MLFS were numerically greater in the glasdegib arm as compared to the placebo arm.

- A total of 32 (19.6%) participants in the glasdegib arm and 21 (13.0%) participants in the placebo arm had CR.

- A total of 4 (2.5%) participants in the glasdegib arm and 1 (0.6%) participant in the placebo arm had CRi.

- A total of 5 (3.1%) participants in the glasdegib arm and 1 (0.6%) participant in the placebo arm had MLFS.

The percentage of participants achieving PR was numerically lower in the glasdegib arm (4 [2.5%] participants) as compared to the placebo arm (8 [4.9%] participants). The number of participants achieving CRh was same between the 2 treatment arms (5 [3.1%] participants each).

The odds ratio (95% CI) of glasdegib arm vs placebo arm in objective response was 1.624 (0.941, 2.804) for $CR_{MRD-}$+CR+CRh and 1.767 (1.037, 3.013) for $CR_{MRD-}$+CR+CRh+CRi.

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### Time to Response

For participants who responded, the time to response was comparable between the 2 treatment arms (median TTRi of 3.76 months in both treatment arms; median TTRh of 3.88 months in the glasdegib arm, and 3.75 months in the placebo arm).

### Safety Results:

**AEs**

The incidence of treatment-emergent adverse events (TEAEs) was comparable between the 2 treatment arms.

- 161 (99.4%) participants and 158 (98.8%) participants in the glasdegib arm and placebo arm, respectively, experienced 1923 and 1836 all-causality TEAEs. A total of 133 (82.1%) participants and 123 (76.9%) participants in the 2 arms, respectively, had 748 and 562 treatment-related TEAEs.

All-causality TEAEs occurring in ≥10% participants were reported in 161 (99.4%) participants in the glasdegib arm and 158 (98.8%) participants in the placebo arm. Treatment-related TEAEs occurring in ≥10% participants were reported in 121 (74.7%) participants in the glasdegib arm and 107 (66.9%) participants in the placebo arm.

- The most frequently reported all-causality TEAEs (in the glasdegib arm and placebo arm) were anaemia (75 [46.3%] and 73 [45.6%] participants), constipation (59 [36.4%] and 52 [32.5%] participants), nausea (58 [35.8%] and 44 [27.5%] participants), pneumonia (43 [26.5%] and 48 [30.0%] participants), and pyrexia (48 [29.6%] and 42 [26.3%] participants).

- The most frequently reported treatment-related TEAEs (in the glasdegib arm and placebo arm) were anaemia (45 [27.8%] and 48 [30.0%] participants) and nausea (44 [27.2%] and 37 [23.1%] participants).

There were more participants with all-causality TEAEs of dysgeusia (38 [23.5%] participants vs 8 [5.0%] participants) and muscle spasms (31 [19.1%] participants vs 4 [2.5%] participants) in the glasdegib arm vs placebo arm. Consistently, there were more participants with treatment-related TEAEs of dysgeusia (34 [21.0%] participants vs 7 [4.4%] participants) and muscle spasms (30 [18.5%] participants vs 2 [1.3%] participants) in the glasdegib arm vs placebo arm. These TEAEs were expected as part of the glasdegib-specific AEs.

### Deaths

The incidence of TEAEs leading to death was comparable between the glasdegib arm (50 [30.9%] participants) and placebo arm (52 [32.5%] participants).

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- The most frequently reported TEAEs leading to death were disease progression (14 [8.6%] participants in the glasdegib arm and 22 [13.8%] participants in the placebo arm) and pneumonia (11 [6.8%] participants in the glasdegib arm and 7 [4.4%] participants in the placebo arm).

A total of 117 (71.8%) and 113 (69.8%) participants in the glasdegib and placebo arms, respectively, died in this non-intensive study. The most common cause of death was disease progression, which was reported in 69 (42.3%) and 68 (42.0%) participants in the glasdegib and placebo arms, respectively.

A total of 108 (33.2%) participants died within 28 days after last dose of study treatment, with the most common reasons of disease progression (50 [15.4%] participants) and AEs not related to study treatment (47 [14.5%] participants).

Two deaths were considered as associated with COVID-19 in this non-intensive study.

**Serious TEAEs**

The incidence of serious TEAEs was comparable between the 2 treatment arms (117 [72.2%] participants in the glasdegib arm and 124 [77.5%] participants in the placebo arm).

- The most frequently reported all-causality serious TEAEs in the glasdegib and placebo arms were pneumonia (29 [17.9%] and 36 [22.5%] participants, respectively) and febrile neutropenia (24 [14.8%] and 20 [12.5%] participants, respectively).

- The most frequently reported treatment-related serious TEAEs in the glasdegib and placebo arms were febrile neutropenia (12 [7.4%] and 6 [3.8%] participants, respectively) and pneumonia (9 [5.6%] and 8 [5.0%] participants, respectively).

**Discontinuations From Study Intervention or Dose Modifications Due to AEs**

The percentage of participants discontinued any study drug due to AEs was comparable between the glasdegib arm (67 [41.4%] participants) and placebo arm (63 [39.4%] participants).

The incidence of TEAEs leading to glasdegib/placebo permanent withdrawal was slightly higher in the glasdegib arm (64 [39.5%] participants) compared to the placebo arm (58 [36.3%] participants).

The incidence of TEAEs leading to any dose interruptions was comparable between the 2 treatment arms: 104 (64.2%) and 102 (63.8%) participants in the glasdegib and placebo arms, respectively.

The incidence of TEAEs leading to any dose reductions was higher in the glasdegib arm (25 [15.4%] participants) compared to the placebo arm (13 [8.1%] participants).

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### Adverse Events of Special Interest (AEoSI)

The incidence of treatment-emergent AEoSI was comparable between the glasdegib arm (133 [82.1%] participants) and the placebo arm (134 [83.8%] participants).

- Most AEoSI in the glasdegib and placebo arms were at CTCAE Grades 3-4 (74 [45.7%] participants and 81 [50.6%] participants, respectively) or Grades 3-5 (101 [62.3%] participants and 103 [64.4%] participants, respectively). The highest frequency of AEoSI in the glasdegib and placebo arms was observed in the cluster of cytopenic events (122 [75.3%] participants and 124 [77.5%] participants, respectively).

A total of 4 (2.5%) participants in the glasdegib arm and 7 (4.4%) participants in the placebo arm experienced treatment-emergent COVID-19-related AEoSI, and the maximum CTCAE Grades of these events were at Grades 3-5.

### Clinical Laboratory and Other Safety Evaluations

There were no clinically meaningful findings in the laboratory safety assessments. The assessments and observations were comparable between the 2 treatment arms.

Categorized absolute value and change from baseline in vital sign data were comparable between the 2 treatment arms. Based on TEAEs reported, there was no evidence of a clinically significant effect of glasdegib on vital signs.

The change from baseline in QTcF was similar between the 2 treatment arms. Percentages of participants with QTcF changes meeting pre-specified criteria in the 2 treatment arms, respectively, are summarized below:

- QTcF change from baseline <30 msec (glasdegib: 53.1%, placebo: 70.0%);
- QTcF change from baseline ≥30 msec to <60 msec (glasdegib: 35.2%, placebo: 23.1%);
- QTcF change from baseline ≥60 msec (glasdegib: 11.7%, placebo: 6.9%).

The shift results in QTcF category were similar between the 2 treatment arms. Percentages of participants with QTcF ≤450 msec at baseline and had QTcF abnormality category shifts in the 2 treatment arms, respectively, are summarized below:

- Shift from ≤450 msec at baseline to >450 - ≤480 msec post baseline (glasdegib: 25.2%, placebo: 23.2%);
- Shift from ≤450 msec at baseline to >480 - ≤500 msec post baseline (glasdegib: 4.5%, placebo: 0);

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- Shift from ≤450 msec at baseline to >500 msec post baseline (glasdegib: 0.6%, placebo: 0.6%).

There were no clinically significant differences between the 2 treatment arms in TEAEs of electrocardiogram QT prolonged, which was reported in 21 (13.0%) participants in the glasdegib arm and 20 (12.5%) participants in the placebo arm.

**Pharmacokinetic Results:**

For glasdegib plasma PK in this blinded study, only samples from the glasdegib treatment arm were analyzed and results reported. The samples collected from the placebo arm were not analyzed.

For the dose compliant participants, the geometric mean (geometric % coefficient of variation [CV]) value for glasdegib plasma $C_{trough}$ on Cycle 1 Day 15 and Cycle 2 Day 1 was 565.4 ng/mL (126%) and 472.4 ng/mL (122%), respectively.

**Conclusions:**

**Efficacy:**

- The non-intensive study did not meet its primary objective of demonstrating that glasdegib + azacitidine was superior to placebo + azacitidine in prolonging OS in all randomized participants with previously untreated AML.

- The non-intensive study did not demonstrate that glasdegib was superior to placebo in combination with azacitidine in percentage of participants with improvement in fatigue.

- The rates of CR, CRi and MLFS were numerically greater in the glasdegib arm as compared to the placebo arm. The percentage of participants achieving PR was numerically lower in the glasdegib arm as compared to the placebo arm. The number of participants achieving CRh was same between the 2 treatment arms.

**PK:**

- The plasma $C_{trough}$ exposures in participants on the non-intensive study were consistent with previously reported plasma exposures for glasdegib.

**Safety:**

- The evaluation of the safety of glasdegib plus azacitidine demonstrated a manageable safety profile in adult participants with previously untreated AML who were not candidates for intensive induction chemotherapy, and the overall safety profile was consistent with the known safety profiles of glasdegib as single agent.

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- There were no unexpected AEs with glasdegib + azacitidine non-intensive chemotherapy. The rates of TEAEs, CTCAE Grade 3 or 4 AEs, and serious TEAEs were similar between the glasdegib arm and the placebo arm.

- There were more participants with TEAEs of dysgeusia and muscle spasms in the glasdegib arm compared to the placebo arm. These TEAEs were expected as part of the glasdegib-specific AEs.

- Treatment with glasdegib was tolerable and AEs were manageable by temporary discontinuation, dose reduction, and/or standard medical therapy.

- There was no increase in treatment-related deaths in participants randomized to glasdegib compared to participants randomized to placebo.

- No new safety signals were identified in the combination of glasdegib and azacitidine, compared to glasdegib alone.

# CLINICAL STUDY REPORT SYNOPSIS

## SYNOPSIS

**Study Title:** A Randomized (1:1), Double-Blind, Multi-Center, Placebo Controlled Study Evaluating Intensive Chemotherapy With or Without Glasdegib (PF-04449913) or Azacitidine (AZA) With or Without Glasdegib in Patients With Previously Untreated Acute Myeloid Leukemia

**Study Number:** B1371019

**Regulatory Agency or Public Disclosure Identifier Number:**

EudraCT Number: 2017-002822-19

ClinicalTrials.gov ID: NCT03416179

**Study Phase:** Phase 3

**Name of Study Intervention:** Glasdegib (PF-04449913)

**Trade Name:** DAURISMO™

**Name of Sponsor/Company:** Pfizer Inc.

**CSR Version and Report Date:** Final CSR Version 1.0, 03 June 2022

**Number of Study Center(s) and Investigator(s):**

A total of 404 participants were randomized at 94 centers in 20 countries. No sites were terminated from the study.

A list of study centers and investigators involved in this study is provided in Appendix 16.1.4.1.

**Publications:** None

**Study Period:**

Study Initiation Date (First Participant First Visit [FPFV]): 20 April 2018

Primary Completion Date (PCD): 05 June 2020

Study Completion Date (Last Participant Last Visit [LPLV]) - Intensive Cohort: 01 February 2021

This study was neither discontinued nor interrupted.

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### Rationale:

The intensive B1371019 study was designed to investigate if glasdegib in combination with cytarabine and daunorubicin chemotherapy is superior to placebo in combination with cytarabine and daunorubicin chemotherapy in prolonging overall survival (OS) in participants with untreated acute myeloid leukemia (AML).

### Objectives, Endpoints, and Statistical Methods:

**Table S1. Study Objectives and Endpoints – Intensive Chemotherapy Study**

| Type | Objectives | Endpoints | Analyzed/Not Analyzed |
|---|---|---|---|
| **Primary** | | | |
| Efficacy | To demonstrate that glasdegib was superior to placebo in combination with cytarabine and daunorubicin in prolonging OS in participants with untreated AML. | OS | Analyzed |
| **Secondary** | | | |
| Efficacy | To compare fatigue score post-baseline as measured by MDASI-AML/MDS | Fatigue score measured by the MDASI-AML/MDS questionnaire | Analyzed |
| | To compare glasdegib versus placebo in combination with cytarabine and daunorubicin in improving other clinical efficacy measures. | Rate of CR (including $CR_{MRD-}$ as assessed by multiparametric flow cytometry), CRi as defined by the ELN recommendations (2017), MLFS, PR, and CR with CRh[a] | Analyzed |
| | To estimate the DoR[b] | DoR (defined as CRi or better or CRh or better if applicable) | Not Analyzed |
| | To estimate the TTR[b] | TTR (CRi or better or CRh or better) | Not Analyzed |
| | To compare EFS[b] | EFS | Not Analyzed |
| PRO | To compare PRO measurements[b] | PROs as measured by the MDASI-AML/MDS, EQ-5D-5L, PGI-S and PGI-C | Not Analyzed |
| Safety | To evaluate the overall safety profile | AEs as characterized by type, frequency, severity (as graded by NCI CTCAE version 4.03), timing, seriousness, and relationship to study therapy | Analyzed |
| | To evaluate laboratory abnormalities | Laboratory abnormalities as characterized by type, frequency, severity (as graded by NCI CTCAE v.4.03) and timing | Analyzed |
| | To characterize treatment effects on the QTc interval | QTc interval | Analyzed |
| Pharmacokinetics | To characterize the PK of glasdegib | PK of glasdegib | Analyzed |

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**Table S1. Study Objectives and Endpoints – Intensive Chemotherapy Study**

| Type | Objectives | Endpoints | Analyzed/Not Analyzed |
|---|---|---|---|
| **Exploratory** | | | |
| Biomarker | Bone marrow and blood biomarkers of response and/or resistance to glasdegib in combination with cytarabine and daunorubicin[b] | Molecular, cellular, and soluble markers in peripheral blood and/or bone marrow which might include, but were not limited to: Hh pathway and/or AML gene and protein expression, epigenetic status and changes, and gene mutation profiling | Not Analyzed |
| PRO | PROs for symptomatic AEs[b] | As measured by a questionnaire containing 2 items from the PRO-CTCAE item library version 1.0 and an add-on item on muscle spasm | Not Analyzed |

a: CRi or better included CR (including $CR_{MRD-}$), CRh, or CRi for non-intensive chemotherapy participants. CRh or better was only defined for non-intensive chemotherapy participants as CR (including $CR_{MRD-}$) or CRh.
b: Not analyzed as the intensive cohort ended in futility. Participants ended study intervention early and were not followed for the remainder of the study.

Abbreviations: AE = adverse event; CR = complete remission; CRh = complete remission with partial hematologic recovery; CRi = complete remission with incomplete hematologic recovery; $CR_{MRD-}$ = complete remission with negative minimal residual disease; CTCAE = Common Terminology Criteria for Adverse Events; DoR = duration of response; EFS = event-free survival; ELN = European Leukemia Net; EQ-5D-5L = EuroQoL 5-dimension questionnaire 5-level version; Hh = Hedgehog; MDASI-AML/MDS = M.D. Anderson Symptom Inventory AML/MDS Module; MLFS = morphological leukemia free state; NCI = National Cancer Institute; PGI-C = patient global impression of change; PGI-S = patient global impression of symptoms; PK = pharmacokinetics; PRO = patient reported outcome; QTc = QT interval corrected for heart rate; TTR = time to response.

Because the intensive cohort was terminated for futility, data for several endpoints were not collected as per the protocol, so analysis was not done for these endpoints.

### Methodology:

**Study Design:** The B1371019 study was a randomized (1:1) double-blind, multicenter, placebo-controlled study of ‘7+3’ intensive chemotherapy (cytarabine and daunorubicin) in combination with glasdegib versus ‘7+3’ chemotherapy in combination with placebo in adult participants with previously untreated AML (Figure S1).

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**Figure S1. Intensive Cohort Study Design**


The intensive cohort was stopped by the sponsor for futility.

**Number of Participants (planned and analyzed):**

- A total of 400 participants eligible to receive intensive chemotherapy per investigator assessment were planned to receive the treatment.
- 404 participants were randomized; 399 received treatment (198 in the glasdegib + intensive chemotherapy arm [glasdegib + '7+3'] and 201 in the placebo + intensive chemotherapy [placebo + '7+3'] arm).
- All randomized participants (404 participants) were included in the efficacy analysis (full analysis set), 399 were included in the safety analysis (safety analysis set), 196 in the PK concentration analysis, and 123 in the PK parameter analysis.

**Diagnosis and Main Criteria for Inclusion and Exclusion:**

Adult participants with previously untreated AML who were candidates for intensive induction chemotherapy.

**Study Interventions, Dose, Mode of Administration, and Batch Number(s):**

Glasdegib 100 mg by mouth (PO) or matching placebo PO began on Day 1 and was given once daily (QD) continuously in combination with Induction and Consolidation chemotherapy.

Study intervention information is provided in Table S2.

**Table S2. Manufacturing Lot Numbers for Study Intervention(s) Administered**

| Investigational Product Description | Vendor Lot No. | Pfizer Lot No. | Strength/ Potency | Dosage Form |
|---|---|---|---|---|
| Cytarabine 100 mg/ml solution for injection or infusion single dose 20 ml vial | CT31704A | 18-000111 | 2 g 100 mg/mL | Commercial Product |
| Cytarabine 100 mg/ml solution for injection or infusion single dose 20 ml vial | CT31804A | 18-002585 | 2 g 100 mg/mL | Commercial Product |
| Cytarabine 100 mg/ml solution for injection or infusion single dose 20 ml vial | CT31801B | 18-001352 | 2 g 100 mg/mL | Commercial Product |

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### Table S2. Manufacturing Lot Numbers for Study Intervention(s) Administered

| Investigational Product Description | Vendor Lot No. | Pfizer Lot No. | Strength/ Potency | Dosage Form |
|---|---|---|---|---|
| Cytarabine 100 mg/ml solution for injection or infusion single dose 20 ml vial | CT31901B | 19-000810 | 2 g 100 mg/mL | Commercial Product |
| Cytarabine 100 mg/ml solution for injection or infusion single dose 20 ml vial | CT31901C | 19-002314 | 2 g 100 mg/mL | Commercial Product |
| Cytarabine 100 mg/ml solution for injection or infusion single dose 20 ml vial | CT31905A | 19-004424 | 2 g 100 mg/mL | Commercial Product |
| Cytarabine 100mg (20mg/ml) solution for injection or infusion single dose vial | 7L366C8 | 18-000055 | 100 mg 20 mg/ml | Commercial Product |
| Cytarabine 100mg (20mg/ml) solution for injection or infusion single dose vial | 8D377H8 | 18-001986 | 100 mg 20 mg/ml | Commercial Product |
| Cytarabine 100mg (20mg/ml) solution for injection or infusion single dose vial | 8M391F9 | 19-000989 | 100 mg 20 mg/ml | Commercial Product |
| Daunorubicin 20mg Powder for I.V. Injection vial | 28233 | 17-003001 | 20 mg | Commercial Product |
| Daunorubicin 20mg Powder for I.V. Injection vial | 28474 | 18-001693 | 20 mg | Commercial Product |
| Daunorubicin 20mg Powder for I.V. Injection vial | 28584 | 19-000449 | 20 mg | Commercial Product |
| Daunorubicin 20mg Powder for I.V. Injection vial | 28643 | 19-001749 | 20 mg | Commercial Product |
| Glasdegib 100 mg Round Pale Orange Film Coated Tablet (DC) | N/A | 18-000163 | 100 mg | Tablet |
| Glasdegib 100 mg Round Pale Orange Film Coated Tablet (DC) | 19-DP-00032 | 19-001635 | 100 mg | Tablet |
| Glasdegib 100 mg Round Pale Orange Film Coated Tablet (DC) | 17-001948 | 17-003503 | 100 mg | Tablet |
| Glasdegib 100 mg Round Pale Orange Film Coated Tablet (DC) | N/A | 17-000224 | 100 mg | Tablet |
| Glasdegib 100 mg Round Pale Orange Film Coated Tablet (DC) | 19-DP-00033 | 19-001636 | 100 mg | Tablet |
| Glasdegib 25 mg Round Yellow Film Coated Tablet (DC) | N/A | 18-000162 | 25 mg | Tablet |
| Glasdegib 25 mg Round Yellow Film Coated Tablet (DC) | 19-DP-00031 | 19-001634 | 25 mg | Tablet |
| Glasdegib 25 mg Round Yellow Film Coated Tablet (DC) | N/A | 17-001947 | 25 mg | Tablet |
| Glasdegib 25 mg Round Yellow Film Coated Tablet (DC) | N/A | 17-000222 | 25 mg | Tablet |
| Placebo for Glasdegib 100 mg Round Pale Orange Film Coated Tablet | N/A | 17-000218 | 0 mg | Tablet |
| Placebo for Glasdegib 100 mg Round Pale Orange Film Coated Tablet | 19-DP-00030 | 19-001633 | 0 mg | Tablet |
| Placebo for Glasdegib 25 mg Round Yellow Film Coated Tablet | N/A | 17-000217 | 0 mg | Tablet |
| Placebo for Glasdegib 25 mg Round Yellow Film Coated Tablet | 19-DP-00029 | 19-001454 | 0 mg | Tablet |

Abbreviations: DC = Drug Count; N/A = not applicable.

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**Duration of Study Intervention:**

Glasdegib or placebo was to be continued for a maximum of 2 years (starting from randomization until 2 years) or until participant discontinued, or until confirmed $CR_{MRD-}$ with 2 consecutive central laboratory results post consolidation. Glasdegib or placebo therapy continued throughout Induction(s) and Consolidation Therapy regardless of any delays/modifications in the chemotherapy treatment.

**Summary of Results:**

**Demographic and Other Baseline Characteristics:**

- 58.4% of the participants were male, and 41.6% were female.
- The majority of the participants were White (57.7%) and non-Hispanic or Latino (83.4%); 30.4% were Asian.
- The mean (range) age was 56.55 (19-78) and 55.38 (19-86) years in the glasdegib + '7+3' and placebo + '7+3' arms, respectively.
- Median (range) of bone marrow blasts (%) was 51.5% (0-100.0%) and 50.0% (4.0%-98.0%) in the 2 arms, respectively.

**Exposure:**

***Exposure to Glasdegib/Placebo***

Both the median and mean study treatment exposure to glasdegib/placebo were similar between the treatment arms.

- The median treatment exposure time to glasdegib/placebo was 10.4 weeks in the glasdegib + '7+3' arm and 9.9 weeks in the placebo + '7+3' arm.
- The median relative dose intensity of glasdegib/placebo was 94.3% and 99.7%, respectively in the 2 arms.

***Exposure to Cytarabine (Induction)***

Both the median and mean study treatment exposure to cytarabine as part of the induction therapy (induction overall) were similar between the treatment arms.

- The median treatment exposure time of cytarabine (induction overall) was 1.1 weeks each in the glasdegib + '7+3' and placebo + '7+3' arms.
- The median dose intensity of cytarabine (induction overall) was 100.0 $mg/m^2$/day in each arm.

***Exposure to Cytarabine (Consolidation)***

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The median and mean study treatment exposure to cytarabine as part of the consolidation therapy (consolidation overall) were higher in the glasdegib + '7+3' arm than the placebo + '7+3' arm.

- The median treatment exposure time of cytarabine (consolidation overall) was 9.4 and 5.6 weeks, respectively, in the 2 arms.
- The median dose intensity of cytarabine (consolidation overall) was 3.0 $g/m^2$/day in each arm.

***Exposure to Daunorubicin (Induction)***

Both the median and mean study treatment exposure to daunorubicin as part of the induction therapy (induction overall) were similar between the treatment arms.

- The median treatment exposure time of daunorubicin (induction overall) was 0.4 week each in the glasdegib + '7+3' and placebo + '7+3' arms.
- The median dose intensity of daunorubicin (induction overall) was 60.0 $mg/m^2$/day in each arm.

**Efficacy Results:**

***Primary Endpoint Analysis: Overall Survival***

The intensive study did not meet its primary objective of demonstrating that glasdegib + '7+3' is superior to placebo + '7+3' in prolonging OS in all randomized participants with untreated AML.

- A total of 90 (44.8%) and 88 (43.3%) events were observed in the 2 arms, respectively.
- The median OS estimated by Kaplan-Meier method was 17.2 (95% confidence interval [CI]: 15.3, 18.5) and 20.0 (95% CI: 14.0, Not Estimable) months in the 2 arms, respectively.
- The observed stratified hazard ratio comparing the 2 arms was 0.97 (95% CI: 0.725, 1.309) with 1-sided p-value of 0.4321.
- The median time of follow-up for OS was 12.65 and 12.19 months in the 2 arms, respectively.
- The median duration of follow-up estimated by reversed Kaplan-Meier method was 15.2 and 15.8 months in the 2 arms, respectively.
- An analysis of OS by baseline characteristics showed the control arm (placebo + '7+3') had an OS survival advantage in participants with intermediate ELN risk, and in the

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Asian population. The experimental arm (glasdegib + '7+3') performed better than the control arm in the Favorable ELN risk category, and in the White population. All these subgroup analyses are considered exploratory.

***Key Secondary Endpoint Analysis: Fatigue MDASI-AML/MDS***

- A total of 17.41% and 17.24% of participants in the 2 arms, respectively, had improvement in fatigue.

***Other Secondary Endpoints: Overall Response***

- The proportion of participants achieving $CR_{MRD-}$, CR, PR, MLFS was similar between the 2 arms.

- The proportion of CRi responders was 3 (1.5%) and 11 (5.4%) in the 2 arms, respectively.

**Safety Results:**

***All-Causality Treatment-Emergent AEs (TEAE) and Serious AEs (SAEs):***

- 99.0% and 98.5% of participants in the glasdegib + '7+3' and placebo + '7+3' arms, respectively, experienced all-causality TEAEs, and 43.4% and 45.8% of participants, respectively, experienced all-causality SAEs.

- The most frequently reported all-causality TEAEs (≥30% of participants in any treatment arm) in the 2 arms, respectively, were: nausea (55.6%, 53.7%), febrile neutropenia (53.5%, 53.2%), anaemia (53.5%, 50.2%), diarrhoea (49.5%, 43.8%), pyrexia (41.9%, 43.3%), hypokalaemia (38.4%, 41.8%), platelet count decreased (40.4%, 37.8%), constipation (35.9%, 30.3%), and white blood cell count decreased (32.8%, 26.9%).

- The most frequently reported all-causality SAEs (≥5% of participants in any treatment arm) in the 2 arms, respectively, were febrile neutropenia (9.1%, 8.5%), sepsis (7.6%, 6.5%), pneumonia (7.6%, 5.5%), and electrocardiogram (ECG) QT prolonged (6.6%, 4.0%).

***Treatment-related AEs and SAEs:***

- 91.4% and 93.5% of participants in the glasdegib + '7+3' and placebo + '7+3' arms, respectively, experienced treatment-related TEAEs, and 24.2% and 29.9% of participants, respectively, experienced treatment-related SAEs.

- The most frequently reported treatment-related TEAEs (≥30% of participants in any treatment arm) in the 2 arms, respectively, were anaemia (46.5%, 43.8%), febrile neutropenia (35.4%, 37.8%), nausea (46.0%, 45.3%), diarrhoea (31.8%, 26.4%), platelet count decreased (38.4%, 32.3%), and white blood cell count decreased (32.3%, 25.9%).

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- The most frequently reported treatment-related SAEs (≥3% of participants in any treatment arm) in the 2 arms, respectively, were: febrile neutropenia (6.6%, 8.0%), sepsis (4.5%, 4.5%), and ECG QT prolonged (4.5%, 4.0%).

***Deaths:***

- A total of 44.8% and 43.3% of participants in the glasdegib + '7+3' and placebo + '7+3' arms, respectively, in the intensive cohort died. The primary reason for death was disease progression, with 25.9% and 24.1% of participants in the 2 arms, respectively.

***AEs of Special Interest***

- The most frequently reported AEs of Special Interest for glasdegib + '7+3'and placebo + '7+3' arms, respectively, were: cytopenic events: 75.8% and 81.1%; QT interval prolongation: 21.2% and 17.9%; and renal toxicity: 13.6% and 12.4%.

***Study Discontinuation:***

- A total of 10.6% and 10.0% of participants in the glasdegib + '7+3' and placebo + '7+3' arms, respectively, discontinued from study due to all-causality TEAEs. A total of 6.6% and 4.5% of participants in the 2 arms, respectively, discontinued from study due to treatment-related AEs.

***Treatment Discontinuation, Dose Modification or Reduction:***

- A total of 13.1% and 14.4% of participants in the glasdegib + '7+3' and placebo + '7+3' arms, respectively, discontinued any study intervention due to all-causality TEAEs.

- A total of 31.3% and 27.9% of participants in the 2 arms, respectively, had TEAEs leading to any study intervention dose interruptions.

- A total of 14.6% and 11.9% of participants in the 2 arms, respectively, had TEAEs leading to any study intervention dose reductions.

***Clinical Laboratory and Other Safety Evaluation***

- No clinically meaningful findings in the laboratory, vital signs measurements, ECGs, physical examination assessments, or other observations related to safety were observed in this study.

**Pharmacokinetic Results:**

For the dose compliant participants, the geometric mean (geometric percent coefficient of variation [%CV]) value for glasdegib plasma trough concentration ($C_{trough}$) on Day 10 of the induction cycle was 413.5 ng/mL (125%). Overall, the range of $C_{trough}$ observed across

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Induction and Consolidation 1 and 2 ranged from 245.5-413.5 ng/mL for geometric mean and 80-125% for geometric %CV.

**CONCLUSIONS:**

***Efficacy***

- The intensive study did not meet its primary objective of demonstrating that glasdegib + '7+3' is superior to placebo + '7+3' in prolonging OS in all randomized participants with untreated AML.
- At Week 8, the proportion of MDASI-AML/MDS responders was similar between the 2 arms.
- The proportion of participants achieving CR was similar between the 2 arms.

***Safety***

- The safety profile of glasdegib + '7+3' was consistent with the known safety profiles of glasdegib and of the combination of daunorubicin and cytarabine.
- There were no unexpected AEs with glasdegib + '7+3' intensive chemotherapy. The frequency of all-causality TEAEs and treatment-related AEs was generally similar between the treatment arms.
- There were more participants with TEAEs of dysgeusia (19.7% and 10.0%, respectively, in the 2 arms) and muscle spasms (12.6%, 1.5%) in the glasdegib + '7+3' arm. These TEAEs were expected as part of the glasdegib-specific AEs. There were more participants with TEAEs of hypertension (5.1%, and 12.4%, respectively in the 2 arms) reported in the placebo + '7+3' arm.

***PK***

- The plasma $C_{trough}$ exposures in participants on study were consistent with previously reported plasma exposures for glasdegib.