CLINICAL STUDY REPORT SYNOPSIS

Sponsor: Pfizer, Inc

Investigational Product: Glasdegib (PF-04449913)

Clinical Study Report Synopsis: Protocol B1371005

Protocol Title: A Phase 1 Study to Evaluate the Safety, Tolerability, Efficacy, Pharmacokinetics, and Pharmacodynamics of PF-04449913 (Glasdegib), an Oral Hedgehog Inhibitor, Administered as a Single Agent in Japanese Patients With Select Hematologic Malignancies and in Combination With Intensive Chemotherapy, Low-Dose Ara-C, or Azacitidine in Patients With Acute Myeloid Leukemia or High-Risk Myelodysplastic Syndrome

Investigators: Refer to Appendix 16.1.4.1 for a list of investigators involved in this study.

Study Centers: This study was conducted at 9 centers in Japan. Refer to Appendix 16.1.4.1 for a list of sites involved in this study.

Publications Based on the Study:

Minami Y, Minami H, Miyamoto T, et al. Phase 1 study of glasdegib (PF-04449913), an oral smoothened inhibitor, in Japanese patients with select hematologic malignancies. Cancer Sci. Aug 2017;108(8):1628-1633.

Study Initiation Date: 25 March 2014

Primary Completion Date: 12 February 2021

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Report Date: 26 November 2021

Previous Report Date(s): Not applicable

Phase of Development: Phase 1

Primary and Secondary Study Objectives and Endpoints: The primary and secondary study objectives and endpoints are summarized in Table S1.

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Table S1. Primary and Secondary Study Objectives and Endpoints

Type	Objective	Endpoint
Monotherapy Cohort		
Primary		
Safety	• To determine the safety and tolerability of glasdegib administered as monotherapy in Japanese patients with select advanced hematologic malignancies	• First-cycle DLTs; type, incidence, severity (graded by the NCI-CTCAE, Version 4.0), timing, seriousness, and relatedness of AEs; vital signs and laboratory test abnormalities
Secondary		
PK	• To evaluate the PK of glasdegib as monotherapy in Japanese patients with select advanced hematologic malignancies	• PK parameters of glasdegib
PD	• To evaluate the PD of glasdegib as monotherapy in Japanese patients with select advanced hematologic malignancies	• Potential biomarkers of target modulation, response or resistance to glasdegib in Japanese patients with advanced hematologic malignancies
Efficacy	• To assess preliminary evidence of clinical efficacy of glasdegib administered as monotherapy in Japanese patients with select advanced hematologic malignancies	• Objective disease response as assessed using the response criteria for the hematologic disease under study
Combination Cohorts 1 and 2 (Unfit and Fit Patients)		
Primary		
Safety	• To determine the safety and tolerability of glasdegib administered in combination with LDAC (Combination Cohort 1, unfit patients), or cytarabine/daunorubicin (7:3) (Combination Cohort 2, fit patients) to Japanese patients with previously untreated AML, or high-risk MDS	• First-cycle DLTs; type, incidence, severity (graded by NCI-CTCAE, Version 4.0), timing, seriousness, and relatedness of AEs; vital signs and laboratory test abnormalities
Secondary		
PK	• To evaluate the PK of glasdegib and potential DDI between glasdegib and LDAC (Combination Cohort 1, unfit patients) or cytarabine/daunorubicin (7:3) (Combination Cohort 2, fit patients) administered to Japanese patients with previously untreated AML or high-risk MDS	• PK parameters of glasdegib with: (i) LDAC, and (ii) cytarabine/daunorubicin (7:3) combinations
PD	• To evaluate the PD of glasdegib administered in combination with LDAC (Combination Cohort 1, unfit patients) or cytarabine/daunorubicin (7:3) (Combination Cohort 2, fit patients) to Japanese patients with previously untreated AML or high-risk MDS	• Potential biomarkers of target modulation, response or resistance to glasdegib in combination with chemotherapy in Japanese patients with previously untreated AML or high-risk MDS

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Table S1. Primary and Secondary Study Objectives and Endpoints

Type	Objective	Endpoint
Efficacy	• To assess preliminary evidence of clinical efficacy (including disease-specific measures) of glasdegib administered in combination with LDAC (combination Cohort 1, unfit patients) or cytarabine/daunorubicin (7:3) (combination Cohort 2, fit patients) to Japanese patients with previously untreated AML or high-risk MDS	• Objective disease response, as assessed using the appropriate response criteria for AML or MDS • Survival status (only combination Cohort 1)
Expansion Cohort of LDAC Combination for Efficacy (Unfit Patients)		
Primary		
Efficacy	• To evaluate the efficacy (DMR rate) of glasdegib administered in combination with LDAC to Japanese patients with previously untreated AML or high-risk MDS	• DMR rate
Secondary		
Safety	• To evaluate the safety of glasdegib administered in combination with LDAC to Japanese patients with previously untreated AML or high-risk MDS	• Type, incidence, severity (graded by NCI-CTCAE, Version 4.0), timing, seriousness, and relatedness of AEs; vital signs and laboratory test abnormalities
Efficacy	• To evaluate the efficacy (including OS) of glasdegib administered in combination with LDAC to Japanese patients with previously untreated AML or high-risk MDS	• OS • Objective disease response, as assessed using the appropriate response criteria for AML or MDS; CR rate; duration of response; time to response
PK and PD	• To evaluate the PK and PD of glasdegib administered in combination with LDAC to Japanese patients with previously untreated AML or high-risk MDS	• PK and potential biomarkers of target modulation, response or resistance to glasdegib in combination with LDAC in Japanese patients with previously untreated AML or high-risk MDS
Combination Cohort 3 (Azacitidine Combination)		
Primary		
Safety	• To determine the safety and tolerability of glasdegib administered in combination with azacitidine in Japanese patients with previously untreated AML who were eligible for non-intensive chemotherapy	• First-cycle DLTs; type, incidence, severity (graded by NCI-CTCAE, Version 4.0), timing, seriousness, and relatedness of AEs; vital signs and laboratory test abnormalities
Secondary		
PK	• To evaluate the PK of glasdegib and azacitidine when administered to Japanese patients with previously untreated AML who were eligible for non-intensive chemotherapy	• PK parameters of glasdegib and azacitidine

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Table S1. Primary and Secondary Study Objectives and Endpoints

Type	Objective	Endpoint
PD	• To evaluate the PD of glasdegib administered in combination with azacitidine to Japanese patients with previously untreated AML who were eligible for non-intensive chemotherapy	• Potential biomarkers of target modulation, response or resistance to glasdegib in combination with azacitidine in Japanese patients with previously untreated AML who were eligible for non-intensive chemotherapy
Efficacy	• To assess any preliminary evidence of clinical efficacy including OS of glasdegib administered in combination with azacitidine to Japanese patients with previously untreated AML who were eligible for non-intensive chemotherapy	• OS • Objective disease response, as assessed using the appropriate response criteria for AML; duration of response; time to response
Continuation Cohort (Monotherapy Cohort)		
Safety	• To assess the safety of glasdegib administered as monotherapy in the Japanese MF patient who had been treated with glasdegib in Study B1371013 and without documented objective progression of disease and with continuous clinical benefit at the time the patient discontinued from Study B1371013	• Type, severity (graded by NCI-CTCAE, Version 4.0), timing, seriousness, and relatedness of AEs; laboratory test abnormalities

Abbreviations: AEs=adverse events; AML=acute myeloid leukemia; CR=complete remission; DDI=drug-drug interactions; DLT=dose limiting toxicity; DMR=disease modifying response; LDAC=low-dose Ara-C; MDS=myelodysplastic syndrome; MF=myelofibrosis; NCI-CTCAE=National Cancer Institute - Common Terminology Criteria for Adverse Events; OS=overall survival; PD=pharmacodynamics; PK=pharmacokinetics.

METHODS

Study Design: This was an open-label, multicenter, Phase 1 study of glasdegib in Japanese patients. Glasdegib was administered orally as a single agent in up to 15 patients with select advanced hematologic malignancies (monotherapy cohort), or in combination with low-dose Ara-C (LDAC) (combination Cohort 1, unfit patients), or cytarabine and daunorubicin (7:3) (combination Cohort 2, fit patients) in up to 12 previously untreated patients with acute myeloid leukemia (AML) or high-risk myelodysplastic syndrome (MDS). Glasdegib was also administered in combination with azacitidine in a total of 6 patients with previously untreated AML, who were eligible for non-intensive chemotherapy (combination Cohort 3, azacitidine combination). Glasdegib was administered in combination with LDAC in a total of 15 patients with previously untreated AML or high-risk MDS (expansion cohort of LDAC combination for efficacy, unfit patients). Glasdegib was administered as a single agent in 1 Japanese myelofibrosis (MF) patient, who had been treated in Study B1371013 (a Phase 2, double-blind, randomized safety and efficacy study of glasdegib [PF-04449913] versus placebo in patients with MF previously treated with ruxolitinib [NCT02226172]) and was on

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study treatment at the time of the study discontinuation (continuation cohort [monotherapy cohort]).

Monotherapy Cohort

The monotherapy cohort evaluated the safety and tolerability of glasdegib administered as a single agent once daily (QD) continuously. Cycle 1 was preceded by a single lead-in dose of glasdegib administered on Day -5 (lead-in period) in order to characterize the single-dose pharmacokinetics (PK) of glasdegib prior to initiation of continuous dosing in the first cycle of treatment. From Cycle 1/Day 1 onwards, glasdegib was administered QD continuously, in 28-days cycles. In total, 13 patients were treated with 3, 4, and 6 patients in glasdegib 25 mg, 50 mg, and 100 mg treatment groups, respectively.

Combination Cohort 1 (Unfit Patients)

In this cohort, the patients who were "unfit for intensive chemotherapy" based on predefined criteria received glasdegib QD continuously at the starting dose of 100 mg in combination with LDAC over 28 days cycles. A total of 6 patients were treated in this cohort and followed up for dose limiting toxicity (DLT) evaluation.

Combination Cohort 2 (Fit Patients)

In this cohort, the patients who were "fit for intensive chemotherapy" based on predefined criteria received glasdegib QD continuously in combination with daunorubicin and cytarabine during induction and consolidation. For the first induction cycle only, glasdegib was commenced on Day -3 and was then given QD continuously at the starting dose of 100 mg for the duration of treatment. Following completion of induction and consolidation, single agent glasdegib could have been given to eligible patients as maintenance therapy for a maximum of 6 cycles. A total of 6 patients were treated in this cohort and followed up for DLT evaluation.

Combination Cohort 3 (Azacitidine Combination)

In this cohort, the patients who had previously untreated AML and were eligible for non-intensive chemotherapy received glasdegib QD continuously at the starting dose of 100 mg in combination with azacitidine over 28 days cycles. A total of 6 patients were treated in this cohort and followed up for DLT evaluation.

Expansion Cohort of LDAC Combination for Efficacy (Unfit Patients)

In this cohort, the patients who were "unfit for intensive chemotherapy" based on predefined criteria received glasdegib QD continuously at the starting dose of 100 mg in combination with LDAC over 28-day cycles. A total of 15 patients were treated in this cohort and disease modifying response (DMR) rate was evaluated.

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Continuation Cohort (Monotherapy Cohort)

One Japanese MF patient, who had been treated in Study B1371013 and without documented objective progression of disease and with continuous clinical benefit at the time the patient discontinued from Study B1371013, continued to receive glasdegib in this cohort at the same dose as the patient was previously taking in Study B1371013, administered orally QD continuously as a single agent over 28-day cycles. In this cohort, the patient receiving glasdegib continued to receive study treatment until the time of disease progression, unacceptable toxicity, death, withdrawal of consent or termination of the study by sponsor, whichever was first.

The terms subjects and patients were used interchangeably throughout this report.

Diagnosis and Main Criteria for Inclusion:

Patients with selected advanced hematologic malignancies who were refractory, resistant or intolerant to prior therapies for monotherapy cohort; patients with AML or refractory anemia with excess blasts (RAEB-2) High-Risk MDS who were newly diagnosed according to the World Health Organization (WHO) 2008 Classification and previously untreated for combination Cohorts 1 and 2 and expansion cohort of LDAC; patients with AML who were newly diagnosed according to the WHO 2008 Classification and previously untreated for combination Cohort 3 (azacitidine combination); patients who had adequate organ function and Eastern Cooperative Oncology Group (ECOG) performance status of 0, 1, or 2.

Patients were excluded from the study if patients: had active central nervous system involvement of the leukemia; had active malignancy with the exception of basal cell carcinoma, non-melanoma skin cancer, or carcinoma-in-situ cervical; or had an active, life threatening or clinically significant uncontrolled systemic infection.

Study Treatment:

Glasdegib was formulated in tablets containing 10 mg, 25 mg, and 100 mg of study drug. Commercially available daunorubicin and cytarabine were used in the study. Upon site activation, the sponsor provided a supply of azacitidine for clinical use.

In the monotherapy cohort, glasdegib administered as a single agent was evaluated. In the combination cohort, 3 different glasdegib combinations (with LDAC for the unfit patient population, with cytarabine/daunorubicin for the fit patient population, and with azacitidine for the azacitidine patient population) were evaluated. In the continuation cohort, glasdegib continuously administered as a single agent was evaluated for safety. Patients were instructed to take their medication at approximately the same time each day and not to take more than the prescribed dose at any time.

In all study cohorts, study drugs were administered in cycles. Only in Cycle 1, glasdegib was administered with plenty of water on an empty stomach ie, patients were refrained from food

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and beverages (except for water) where possible for at least 2 hours before and 2 hours after dosing throughout treatment administration. From Cycle 2 onwards, glasdegib could be administered with or without food. In the expansion cohort of LDAC combination for efficacy and continuation cohort, glasdegib could be administered with or without food in Cycle 1 and thereafter. Investigational product description is summarized in Table S2.

Table S2. Investigational Product Description

Investigational Product Description	Vendor Lot Number	Pfizer Lot Number	Strength/Potency	Dosage Form
Azacitidine 100 mg lyophilized powder for injection single-use vial	109001BX	17-003395	100 mg	Commercial product
Glasdegib 100 mg round pale orange film coated tablet (DC)	N/A	17-000225	100 mg	Tablet
Glasdegib 25 mg round yellow film coated tablet (DC)	N/A	17-000222	25 mg	Tablet
PF-04449913-01 100 mg oval tablet	CM-01612	12-000450	100 mg	Tablet
PF-04449913-01 100 mg oval tablet	N/A	15-000268	100 mg	Tablet
PF-04449913-01 25 mg tablet	CM-01512	12-000451	25 mg	Tablet
PF-04449913-01 25 mg tablet	N/A	15-000267	25 mg	Tablet

Abbreviations: DC=direct compression; N/A=not applicable.

Efficacy Evaluations:

Response Criteria:

For monotherapy cohort, the assessment of response was made using response criteria for selected hematologic diseases, each having specific clinical response criteria. For combination cohorts, the assessment of response was made using response criteria for MDS and AML derived and defined by the disease specific International Working Groups and WHO guidelines.

Bone Marrow:

The efficacy analyses also involved the collection of bone marrow aspirate and/or biopsy for clinical staging and for pharmacodynamics (PD) biomarker assessments. Blood samples for PD biomarkers were collected: a) on Cycle 1/Day 1 at predose; b) on Cycle 1/Day 21 at predose; c) at end of treatment.

Immunophenotyping, Cytogenetics and Mutation Analysis:

For all patients, quantitative immunophenotyping and cytogenetics on blood and/or bone marrow were collected at the same time as any scheduled or unscheduled bone marrow aspirate and/or biopsy, at end of treatment and at investigators discretion. For all chronic myeloid leukemia (CML) patients quantitative polymerase chain reaction for BCR-ABL were conducted on blood and/or bone marrow at the same time as any scheduled or

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unscheduled bone marrow aspirate and/or biopsy and at investigators discretion, mutation analyses were performed at screening only. If a bone marrow assessment was not performed a blood sample was used for the clinical assessments (immunophenotyping, cytogenetics, mutation analyses).

Pharmacokinetic and Pharmacodynamic Evaluations:

Pharmacokinetic Evaluations:

Blood samples for glasdegib concentrations were collected at approximately the same time as the PD samples and electrocardiograms (ECGs) whenever possible (even accounting for scheduling changes). Blood samples for glasdegib PK were collected: a) during the lead-in period on Day -5, at predose and at 0.5, 1, 2, 4, 8, 24, 48, 72, and 120 hours (±1 day) postdose (ie, predose on Cycle 1/Day 1); b) On Cycle 1 on Day 1, Day 8 and Day 15, at predose and 1 hour postdose (matched with the ECG); c) On Cycle 1/ Day 21 at predose and at 0.5, 1, 2, 4, 8, and 24 hours postdose; d) For Cycles 2, 3, and 4 on Day 1 at predose and 1 hour postdose (matched with the ECGs).

PK samples were obtained within 10% of the nominal time (eg, ±6 minutes of a 60-minute sample) and the exact time of the sample collection was noted. Further, the predose PK sample was collected within 15 minutes prior to administration of the study drug.

Pharmacodynamic Biomarker Evaluations:

The PD biomarker assessments were performed on all patients enrolled in this study. These assessments could include: evaluation of Hedgehog (Hh) pathway genes and proteins; circulating protein levels, and; molecular analysis of somatic mutations and translocations with a known frequency of occurrence in the AML and MDS populations. Additional PD biomarkers could also be included, based on emerging data on Hh pathway biology. Samples were collected for pharmacogenomics/biomarker analyses in this study.

Safety Evaluations:

Safety assessments consisted of the collection of adverse events (AEs), serious adverse events (SAEs), vital signs, physical examination, triplicate 12-lead ECGs, cardiac testing by multi-gated acquisition/ECHO, laboratory assessments, including pregnancy tests, and verification of concomitant medications use. Safety was monitored at regular intervals throughout the study.

Statistical Methods:

Analysis Sets:

The following analysis sets were used for the analyses although the patients enrolled in the expansion cohort of LDAC combination for efficacy were excluded from DLT-evaluable

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analysis set and the patient enrolled in the continuation cohort was excluded from all of these analysis sets except the safety analysis set:

- Full Analysis Set (FAS): The FAS included all enrolled patients who received at least 1 dose of study drug on or after Cycle 1/Day 1
- DLT-Evaluable Analysis Set ('Per Protocol' Analysis Set): The per protocol analysis set included all enrolled patients who received at least 1 dose of study drug and who did not have major treatment deviations during first cycle (DLT observation period)
- Safety Analysis Set: The safety analysis set included all enrolled patients who received at least 1 dose of study drug
- PK Analysis Set: The PK analysis set was defined as all treated patients who had at least 1 concentration of any of the study drugs. The PK parameter analysis population was defined as all treated patients who had at least 1 of the PK parameters of interest of any of the study drugs
- PD Analysis Set: The PD analysis set was defined as all enrolled patients who received at least 1 dose of glasdegib and had at least 1 PD parameter in active treatment period
- Corrected QT interval (QTc)-Evaluable Analysis Set: The QTc-evaluable analysis set was defined as all patients who had baseline and at least 1 triplicate ECG assessment after having at least 1 glasdegib dose on study

Efficacy

All efficacy analyses were secondary excluding the primary endpoint of disease modifying response (DMR) rate for expansion cohort of LDAC combination for efficacy (unfit patients). DMR and its rate included complete remission (CR), CR with incomplete blood count recovery (CRi), morphologic leukemia-free state, marrow CR and partial remission (PR).

The number and percentage of patients who had ever achieved DMR were summarized for patients in the FAS. For the expansion cohort of LDAC combination for efficacy, an exact test for a single proportion (1-sided significance level: 0.05) was used. The null hypothesis was that DMR rate=6.8%, and the alternative hypothesis was that DMR rate=34.1%. The 2-sided 90% and 95% confidence intervals (CIs) were also presented.

Pharmacokinetics

The PK analysis was done for all cohorts in the study excluding the continuation cohort. Standard plasma PK parameters including the maximum plasma drug concentration (C_{max}), time to reach C_{max} (T_{max}), and area under the plasma concentration-time curve (AUC) for each drug (and metabolite if relevant), were estimated using noncompartmental analysis. If data permitted or if considered appropriate, minimum plasma drug concentration, average

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plasma drug concentration, elimination half-life ($t_{½}$), apparent total clearance of the drug from plasma after oral administration (CL/F), apparent total body clearance of the drug from plasma, apparent volume of distribution after non-intravenous administration, apparent volume of distribution, and accumulation ratio (R_{ac}) were estimated. Descriptive statistics were provided for these PK parameters in tabular form (n, mean, standard deviation [SD], coefficient of variance [CV], median, minimum, maximum, geometric mean and its associated CV) by analyte, dose, administration route, cycle, and day.

Pharmacodynamic Biomarkers

The PD analysis was done for all cohorts in the study excluding the continuation cohort. The PD biomarkers were assessed separately for blood, serum, normal skin biopsies, bone marrow aspirate, and bone marrow biopsies. In each case, summaries of baseline levels, changes from baseline (where appropriate), and mutation status were reported. Summary statistics included the mean, SD, median, percent coefficient of variance (%CV), and minimum/maximum levels of biomarker measures or frequency statistics, as appropriate. Data from biomarker assays were analyzed using graphical methods.

Safety

AE summaries were presented based on the treatment-emergent adverse events (TEAEs) with initial onset or increasing in severity after the first dose of study drug. The number and percentage of patients who experienced any AE, SAE, treatment-related AE, and treatment-related SAE were summarized according to worst toxicity grades.

The number and percentage of patients who experienced laboratory test abnormalities were summarized according to worst toxicity grade observed for each laboratory assay. The summary and shift summary of baseline grade by maximum post-baseline Common Terminology Criteria for AEs (CTCAE) grade were presented.

ECG measurements (an average of the triplicate measurements) were used for the statistical analysis. Interval measurements from repeated ECGs were included in the outlier analysis as individual values obtained at unscheduled time points. The average of triplicate or duplicate measurements was rounded off and handled as integer in the analyses of ECG.

RESULTS

Subject Disposition and Demography:

The data cut-off date for this study was set as 12 February 2021.

Monotherapy Cohort

A total of 14 patients were screened (screened patients were registered in the database and randomized) and assigned to treatment. Of which, 13 patients were treated as follows: 3, 4, and 6 patients were assigned to glasdegib 25 mg, 50 mg, and 100 mg treatment groups,

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respectively. All patients discontinued the study treatments (end of treatment). The reasons for discontinuations from the study treatments were AEs (1 patient in glasdegib 50 mg and 2 patients in glasdegib 100 mg treatment groups), death (2 patients in glasdegib 50 mg treatment group), withdrawal by patient (1 patient each in glasdegib 25 mg, 50 mg, and 100 mg treatment groups), and objective progression or relapse (2 patients in glasdegib 25 mg and 3 patients in glasdegib 100 mg treatment groups, respectively). Overall, 6 patients (2, 1, and 3 patients in glasdegib 25 mg, 50 mg, and 100 mg treatment groups, respectively) completed the study (end of study). Seven patients (1, 3, and 3 patients in glasdegib 25 mg, 50 mg, and 100 mg treatment groups, respectively) discontinued from the study and the reasons for discontinuation from the study included: death (2 patients) and other (5 patients for starting chemotherapy.

A total of 8 (61.5%) male and 5 (38.5%) female patients were treated with the study drug in this cohort. The median age was 63.0, 66.5, and 71.5 years in patients receiving glasdegib 25 mg, 50 mg, and 100 mg treatment groups, respectively. Nine (69.2%) patients were enrolled in this cohort were ≥65 years of age.

Median weight was 68.9, 65.0, and 61.4 kg in patients receiving glasdegib 25 mg, 50 mg, and 100 mg treatment groups, respectively. All patients had ECOG score of 0 to 1 (except for 1 [16.7%] patient in glasdegib 100 mg treatment group [ECOG = 2]). One patient receiving glasdegib 50 mg was diagnosed with CML and had de novo hematological disease.

Seven patients were diagnosed with AML: 1, 2, and 4 patients in glasdegib 25 mg, 50 mg, and 100 mg treatment groups, respectively. Four AML patients had de novo hematological disease history, with 1 and 3 patients in glasdegib 50 mg and 100 mg treatment groups, respectively. Three AML patients had secondary AML/MDS hematological disease history, with 1 patient each in all 3 treatment groups. One patient receiving glasdegib 100 mg was diagnosed with MF and had de novo hematological disease history.

Combination Cohort 1

Six patients were screened (screened patients were registered in the database and randomized) and assigned to glasdegib + LDAC treatment. All patients discontinued the study treatment (end of treatment). The reasons for discontinuations from the study treatments were as follows: global deterioration of health status (1 patient), objective progression or relapse (3 patients), and other (2 patients: 1 patient each for starting chemotherapy and due to starting stem-cell transplant).

Overall, 2 patients completed the study (end of study). Four patients discontinued from the study and the reasons for discontinuation from the study included: death (1 patient), lost to follow-up (1 patient), and other (2 patients: 1 patient each for starting chemotherapy and the patient started next treatment).

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A total of 5 (83.3%) male and 1 (16.7%) female patients were enrolled in this cohort. The median age was 71.5 years. Five (83.3%) patients enrolled in this cohort were ≥65 years of age. Median weight was 60.6 kg. Three (50%) patients had ECOG score of 2.

Four patients receiving glasdegib + LDAC treatment were diagnosed with AML, out of which 1 patient had de novo hematological disease history. Three AML patients had secondary AML/MDS from prior hematologic disease. Two patients were diagnosed with MDS and had de novo hematological disease history.

Combination Cohort 2

Six patients were screened (screened patients were registered in the database and randomized) and assigned to glasdegib + cytarabine/daunorubicin treatment. Of which, 5 patients discontinued the study treatment (end of treatment) and 1 patient completed the study treatment. The reasons for discontinuations from the study treatment were AEs (3 patients) and objective progression or relapse (2 patients).

Overall, 3 patients completed the study (end of study). Three patients discontinued from the study and the reason for discontinuation from the study included: death (2 patients) and other (1 patient - the patient started the chemotherapy except the clinical study for bone marrow transplantation).

A total of 4 (66.7%) male and 2 (33.3%) female patients were enrolled in this cohort. The median age was 69.5 years. Five (83.3%) patients enrolled in this cohort were ≥65 years of age. Median weight was 55.8 kg. Four (66.7%) patients had ECOG score of 1.

All patients receiving glasdegib + cytarabine/daunorubicin treatment were diagnosed with AML, out of which 5 patients had de novo hematological disease history. One AML patient had secondary AML/MDS from prior hematologic disease.

Combination Cohort 3

Six patients were screened (screened patients were registered in the database and randomized) and assigned to glasdegib + azacitidine treatment. All patients discontinued the study treatment (end of treatment). The reasons for discontinuations from the study treatment were as follows: AEs (1 patient), objective progression or relapse (4 patients), and other (1 patient - the patient chose other treatment option).

Overall, 4 patients discontinued from the study (end of study) and the reason for discontinuation from the study included: death (4 patients). In addition, 2 patients were reported as ongoing at the time of data cut-off (12 February 2021).

A total of 4 (66.7%) male and 2 (33.3%) female patients were enrolled in this cohort. The median age was 73.5 years. All patients enrolled in this cohort were ≥65 years of age. Median weight was 56.6 kg. Three (50.0%) patients had ECOG score of 1.

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All patients receiving glasdegib + azacitidine treatment were diagnosed with AML, out of which 5 patients had de novo hematological disease history. One AML patient had secondary AML/MDS from prior hematologic disease.

Expansion Cohort

Fifteen patients were screened (screened patients were registered in the database and randomized) and assigned to glasdegib + LDAC for efficacy treatment. Thirteen patients discontinued the study treatment (end of treatment). The reasons for discontinuations from the study treatment were as follows: AEs (2 patients), global deterioration of health status (1 patient), objective progression or relapse (8 patients), and other (2 patients - request of the patient and the patient chose to stay with his family for the rest of his life. Two patients were reported as ongoing at the time of data cut-off (12 February 2021).

Overall, 10 patients discontinued from the study (end of study) and reason for discontinuation from the study included death (10 patients). In addition, 5 patients were reported as ongoing at the time of data cut-off (12 February 2021).

A total of 8 (53.3%) male and 7 (46.7%) female patients were enrolled in this cohort. The median age was 76.0 years. All patients enrolled in this cohort were ≥65 years of age. Median weight was 53.4 kg. Four (26.7%) patients had ECOG score of 2.

All patients receiving glasdegib + LDAC treatment for efficacy were diagnosed with AML, out of which 6 patients had de novo hematological disease history. Nine patients had secondary AML/MDS from prior hematologic disease.

Fifteen patients had AML, out of which 12 (80.0%) patients had intermediate-II AML risk, 3 (20.0%) patients had adverse AML risk, 11 (73.3%) patients had intermediate ELN risk, and 4 (26.7%) patients had adverse ELN risk.

Continuation Cohort

One patient in continuation cohort was reported as ongoing with the study treatment at the time of data cut-off (12 February 2021). One patient in continuation cohort was diagnosed with MF and had de novo hematological disease history.

Efficacy Results:

Primary Endpoint Result

Expansion Cohort

Of 15 patients, 7 (46.7% [90% CI: 24.4%, 70.0%] [95% CI: 21.3%, 73.4%]) patients achieved DMR with 1-sided p-value of <0.0001 (statistically significant) for H0: DMR=6.8%. All patients with DMR responses achieved CR/CRi.

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Secondary Endpoints Results

Combination Cohort 1 (Unfit Patients)

Best Overall Response: One (25.0%) AML patient each had morphologic CR and stable disease and 2 (50.0%) AML patients had treatment failure during the study. Best overall response (BOR) of all MDS (2 [100.0%]) patients had stable disease.

CR/CRi Rate and DMR Rate**:** One (25.0% [95% CI: 0.6%, 80.6%]) AML patient, none of the MDS patients, and 1 (16.7% [95% CI: 0.4%, 64.1%]) irrespective of AML and MDS patient achieved CR/CRi and DMR.

Duration of Response: The AML responder who achieved CR/CRi or DMR had reached progressed. Duration of CR/CRi and DMR was 13.9 months and 15.3 months, respectively.

Time to Response: The time to response of CR/CRi and DMR was 2.1 months and 0.8 months, respectively.

Overall Survival: Three (75.0%) of 4 AML patients, 1 (50.0%) of 2 MDS patients, and 4 (66.7%) of 6 irrespective of AML and MDS patients had events during the study. The probability of being event-free at 12 months was 0.500 (95% CI: 0.058, 0.845) in AML patients, not estimable (NE) in MDS patients, and 0.400 (95% CI: 0.052, 0.753) in irrespective of AML and MDS patients. The median OS was 18.0 (95% CI: 1.9, NE) months, 7.1 (95% CI: NE, NE) months, and 11.8 (95% CI: 1.9, NE) months in AML, MDS, and irrespective of AML and MDS patients, respectively.

Combination Cohort 3 (Azacitidine Combination)

Best Overall Response: Three (50.0%) patients had morphologic CR, 1 patient (16.7%) had partial remission with incomplete blood count recovery (PRi), and 2 (33.3%) patients had treatment failure during the study.
CR/CRi Rate and DMR Rate: Three (50.0% [95% CI: 11.8%, 88.2%]) patients achieved CR/CRi and DMR rates.

Duration of Response: Median duration of CR/CRi was 6.6 (95% CI: 5.6, 11.1) months. Median duration of DMR was 6.6 (95% CI: 5.6, 19.8) months.

Time to Response: Of 3 responders of CR/CRi and DMR, the median time to response was 5.9 (95% CI: 5.8, 11.5) months and 5.8 (95% CI: 2.8, 5.9) months, respectively.

Overall Survival: The probability of being event-free at 12 months was 0.833 (95% CI: 0.273, 0.975). The median OS was 30.3 (95% CI: 6.1, 36.9) months.

Transfusion History and Transfusion Status: Five (83.3%) patients on study were transfusion dependent irrespective of the transfusion histories.

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Expansion Cohort (LDAC Combination - Unfit Patients)

Best Overall Response: Six (40.0%) patients had morphologic CR, 2 (13.3%) patients had minor response, stable disease, and treatment failure during the study, 1 (6.7%) patient each had morphologic CRi, PRi, not evaluable response.

Duration of Response: Of 7 responders who achieved CR/CRi and DMR, 4 (57.1%) patients had progressed. Median duration of CR/CRi and DMR was 9.5 (95% CI: 3.9, NE) months and 10.1 (95% CI: 3.9, NE) months, respectively. The probability of being event-free at 12 months was 0.381 (95% CI: 0.061, 0.716) and 0.429 (95% CI: 0.098, 0.734) for duration of CR/CRi and DMR, respectively.

Time to Response: Of 7 responders of CR/CRi and DMR, the median time to response was 5.0 (95% CI: 0.9, 5.9) months and 2.3 (95% CI: 0.9, 5.0) months, respectively.

Overall Survival: Ten (66.7%) patients had events during the study. The probability of being event-free at 12 months was 0.533 (95% CI: 0.263, 0.744). The median OS was 13.9 (95% CI: 3.8, 18.8) months. Three (42.9%) of 7 DMR responders and 7 (87.5%) of 8 non-responders had events during the study. The probability of being event-free at 12 months was 1.000 (95% CI: 1.000, 1.000) for DMR responder AML patients and NE for non-responder AML patients. The median OS was 18.8 (95% CI: 13.9, NE) months and 4.9 (95% CI: 1.4, 11.0) months for DMR responder and non-responder AML patients, respectively.

Transfusion History and Transfusion Status: Fifteen (100.0%) patients on study including 7 DMR responder AML patients and 8 non-responder AML patients were transfusion dependent irrespective of the transfusion histories.

Pharmacokinetic and Pharmacodynamics Results:

Pharmacokinetics:

Plasma Glasdegib Pharmacokinetics in Monotherapy Cohort

Single Dose

Following single oral doses of 25, 50, and 100 mg, C_{max} was achieved with median T_{max} values of 1.97, 3.96, and 1.95 hours, respectively. Increases in exposure (area under the concentration-time profile from time 0 to time tau [τ], the dosing interval, where tau=24 hours [AUC_{tau}] and C_{max}) of glasdegib between the 25 mg, 50 mg, and 100 mg treatment groups were approximately dose proportional. Mean terminal $t_{½}$ values were 17.8, 30.7, and 18.7 hours at 25, 50, and 100 mg doses, respectively. The geometric mean values of CL/F were 7.42, 5.21, and 7.6 L/hr, and the geometric mean values of apparent volume of distribution (V_z/F) were 190, 228, and 202 L, at 25, 50, and 100 mg doses, respectively.

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Patient variability in glasdegib exposure based on geometric %CV for AUC_{inf} and C_{max} were 68% and 96% (25 mg treatment group), 65% and 57% (50 mg treatment group), and 20% and 25% (100 mg treatment group), respectively.

Multiple Dose

Following multiple daily oral doses of 25, 50, and 100 mg, T_{max} was achieved at 4 hours for the 25 and 50 mg treatment groups, and 2 hours for the 100 mg treatment group. Increases in exposure (AUC_{tau} and C_{max}) were approximately dose proportional. Geometric mean accumulation ratios were 1.9, 2.0, and 1.8, based on AUC_{tau} (R_{ac}) for the 25 mg, 50 mg, and 100 mg treatment groups, respectively.

Patient variability in glasdegib exposure based on geometric %CV for AUC_{tau} and C_{max} were 99% and 90% (25 mg treatment group), 14% and 10% (50 mg treatment group), and 26% and 12% (100 mg treatment group), respectively.

Plasma Glasdegib and LDAC Pharmacokinetics in Combination Cohort 1 (Unfit Patients)

Glasdegib

When glasdegib was co-administered with LDAC, median plasma glasdegib concentrations were slightly lower than those following administration of glasdegib alone. The median T_{max} of glasdegib was 1.9 hours when glasdegib was administered alone and 4.0 hours when co-administered with LDAC.

The adjusted geometric mean for AUC_{tau} and C_{max} decreased by approximately 3% and 11%, respectively, following co-administration LDAC as compared to administration of glasdegib alone. The ratio of the adjusted geometric means of glasdegib AUC_{tau} and C_{max} (90% CI) were 96.83% (48.15%, 194.74%) and 89.00% (50.14%, 157.96%), respectively following administration of glasdegib with LDAC, relative to administration of glasdegib alone.

Inter-patient variability for AUC_{tau} and C_{max} was higher when glasdegib was administered alone then when co-administered with LDAC. The geometric %CV for AUC_{tau} and C_{max} was 113% and 86% when was administered alone and 58% and 38% when co-administered with LDAC, respectively.

LDAC

When LDAC was co-administered with glasdegib, median plasma cytarabine concentrations were slightly higher than those following administration of LDAC alone. The median T_{max} of cytarabine was 0.25 hours when LDAC was administered alone and when co-administered with glasdegib.

The adjusted geometric mean for AUC_{inf}, AUC_{tau}, and C_{max} increased by approximately 38%, 39%, and 29%, respectively, following co-administration with glasdegib as compared to administration of LDAC alone. The ratio of the adjusted geometric means of cytarabine

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AUC_{inf}, AUC_{tau}, and C_{max} (90% CI) were 138.07% (73.62%, 258.93%), 139.25% (73.35%, 264.35%), and 128% (72.47, 228.63), respectively following administration of LDAC with glasdegib, relative to administration of LDAC alone.

Inter-patient variability for AUC_{inf}, AUC_{tau}, and C_{max} was higher when LDAC was administered alone then when co-administered with glasdegib. The geometric %CV for AUC_{inf}, AUC_{tau}, and C_{max} was 80%, 82%, and 105% when LDAC was administered alone and 18%, 18%, and 29% when co-administered with glasdegib, respectively.

Ara-U (Cytarabine Metabolite)

When LDAC was co-administered with glasdegib, median plasma Ara-U concentrations were slightly higher than those following administration of LDAC alone. The median T_{max} of Ara-U was 1.5 hours when LDAC was administered alone and 2.0 hours when co-administered with glasdegib. The geometric mean area under the concentration-time profile from time 0 to 6 hours (AUC_6) and C_{max} values for Ara-U were 2001 ng•hr/mL and 371.6 ng/mL, respectively, following administration of LDAC alone and 2428 ng•hr/mL and 454.3 ng/mL, respectively, when co-administered with glasdegib.

Inter-patient variability for AUC_6 and C_{max} were similar when LDAC was administered alone and when co-administered with glasdegib. The geometric %CV for AUC_6 and C_{max} were 38% and 37% when LDAC was administered alone and 35% and 33% when co-administered with glasdegib, respectively.

<u>Plasma Glasdegib and Cytarabine/Daunorubicin Pharmacokinetics in Combination Cohort 2 (Fit Patients)</u>

Glasdegib

When glasdegib was co-administered with cytarabine/daunorubicin, median plasma glasdegib concentrations were slightly lower than those following administration of glasdegib alone. The median T_{max} of glasdegib was 5.1 hours when glasdegib was administered alone and 6.0 hours when co-administered with cytarabine/daunorubicin.

The adjusted geometric mean for AUC_{tau} and C_{max} decreased by approximately 14% and 11%, respectively, following co-administration cytarabine/daunorubicin as compared to administration of glasdegib alone. The ratio of the adjusted geometric means of glasdegib AUC_{tau} and C_{max} (90% CI) were 86.28% (64.61%, 115.22%) and 88.68% (63.43%, 123.98%), respectively following administration of glasdegib with cytarabine/daunorubicin, relative to administration of glasdegib alone.

Inter-patient variability for AUC_{tau} and C_{max} were similar when glasdegib was administered alone then when co-administered with cytarabine/daunorubicin. The geometric %CV for AUC_{tau} and C_{max} was 58% and 54% when glasdegib was administered alone and 46% and 40% when co-administered with cytarabine/daunorubicin, respectively.

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Daunorubicin

When daunorubicin was co-administered with glasdegib and cytarabine, the daunorubicin geometric mean AUC_{tau} and C_{max} were 741.6 ng•hr/mL and 942.8 ng/mL, respectively. The median T_{max} of daunorubicin was 0.36 hours. The geometric %CV for daunorubicin AUC_{tau} and C_{max} was 27% and 35%, respectively.

Daunorubicinol (Daunorubicin Metabolite)

When daunorubicin was co-administered with glasdegib and cytarabine, the daunorubicinol geometric mean AUC_{tau} and C_{max} were 2800 ng•hr/mL and 244.4 ng/mL, respectively. The median T_{max} of daunorubicin was 0.36 hours. The geometric %CV for daunorubicinol AUC_{tau} and C_{max} was 13% and 37%, respectively.

Plasma Glasdegib and Azacitidine Pharmacokinetics in Combination Cohort 3

Glasdegib

When glasdegib was co-administered with azacitidine, median plasma glasdegib concentrations were slightly higher than those following administration of glasdegib alone. The median T_{max} of glasdegib was 2.5 hours when glasdegib was administered alone and 4.0 hours when co-administered with azacitidine.

The adjusted geometric mean for AUC_{tau} and C_{max} increased by approximately 29% and 31%, respectively, following co-administration azacitidine as compared to administration of glasdegib alone. The ratio of the adjusted geometric means of glasdegib AUC_{tau} and C_{max} (90% CI) were 129.46% (100.03%, 167.56%) and 130.81% (100.97%, 169.47%), respectively following administration of glasdegib with azacitidine, relative to administration of glasdegib alone.

Inter-patient variability for AUC_{tau} and C_{max} was higher when glasdegib was administered alone then when co-administered with azacitidine. The geometric %CV for AUC_{tau} and C_{max} was 44% and 51% when glasdegib was administered alone and 22% and 22% when co-administered with azacitidine, respectively.

Azacitidine

When azacitidine was co-administered with glasdegib, median plasma azacitidine concentrations were similar to those following administration of azacitidine alone. The median T_{max} of azacitidine was 0.25 hours when azacitidine was administered alone and when co-administered with glasdegib.

The adjusted geometric mean for AUC_{tau} and C_{max} were similar following co-administration with glasdegib as compared to administration of azacitidine alone. The ratio of the adjusted geometric means of azacitidine AUC_{tau} and C_{max} (90% CI) were 103.41% (94.71%,

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112.90%) and 95.21% (70.67%, 128.28%), respectively, following administration of azacitidine with glasdegib, relative to administration of azacitidine alone.

Inter-patient variability for AUC_{tau} and C_{max} was similar when azacitidine was administered alone and when co-administered with glasdegib. The geometric %CV for AUC_{tau} and C_{max} was 28% and 60% when azacitidine was administered alone and 30% and 49% when co-administered with glasdegib, respectively.

Pharmacodynamics:

Levels of Circulating Proteins

Levels of circulating proteins at baseline and ratio to baseline for monotherapy cohort, combination Cohort 1, combination Cohort 2, combination Cohort 3, and expansion cohort were analyzed.

Levels of Gene Expression

In monotherapy cohort, the median (min, max) of glioma-associated oncogene homologue 1 (GLI1) ratio (Cycle 1 Day 21: baseline) of delta CT for GLI1 mRNA (blood/skin biopsy) were 1.170 (0.97, 1.37), 1.568 (1.42, 1.77), 1.683 (1.56, 1.86) for glasdegib 25 mg (n=2), 50 mg (n=3), and 100 mg (n=5), respectively. Based on these results, dose-dependent decrease of GLI1 expression was suggested.

In a study, previously it was reported that a marked (>80%) downregulation of GLI1 expression from skin biopsies of glasdegib-treated patients was observed at steady state in the 50 mg and 100 mg groups. However, marked downregulation of GLI1 expression was not observed at steady state in the 25 mg group.

Gene Mutation Analysis

Gene mutation analysis results (bone marrow aspirate) by patient for monotherapy cohort, combination Cohort 1, combination Cohort 2, and combination Cohort 3 were reported.

Safety Results:

DLTs:

There was no DLT in all cohorts except for combination Cohort 2. A total of 6 patients were enrolled in combination Cohort 2 and evaluated for DLTs. One patient had a DLT of Grade 3 erythroderma (Cycle 1 Day 21). This patient was discontinued from the study treatment and study due to this event. The AE was considered related to the study drug (glasdegib, cytarabine and daunorubicin), and was resolved. Since there were ≤1/6 DLTs in this cohort, it was considered that this combination therapy is tolerable. There was no DLT in any other cohorts, indicating that the study treatment was tolerable in these cohorts.

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All-Causality TEAEs

Overall, 139, 77, 124, 89, 230 TEAEs were reported in monotherapy cohort, combination Cohort 1, combination Cohort 2, combination Cohort 3, and expansion cohort, respectively.

Monotherapy Cohort: The most frequently reported TEAEs of all grades (≥40%) were: pyrexia and pneumonia (2 [66.7%] patients each) in glasdegib 25 mg; dysgeusia, pyrexia, constipation, decreased appetite, muscle spasms (3 [75.0%] patients each), alopecia, diarrhea, fatigue, hypokalemia, thrombocytopenia, weight decreased, and eczema (2 [50.0%] patients each) in glasdegib 50 mg treatment group; decreased appetite and constipation (3 [50.0%] patients each), dysgeusia (5 [83.3%] patients) in glasdegib 100 mg treatment group.

Combination Cohort 1: The most frequently reported TEAEs of all grades (≥40%) were: dysgeusia (4 [66.7%]), anemia, febrile neutropenia (3 [50.0%] patients each).
Five (83.3%) patients had at least 1 ≥Grade 3 AE reported, with the most frequently reported events (≥40%) being anemia, febrile neutropenia (3 [50.0%] patients each).

Combination Cohort 2: The most frequently reported TEAEs of all grades (≥40%) were leukopenia, thromobocytopenia (6 [100%] patients each), dysgeusia, neutropenia (5 [83.3%] patients each), anemia, decreased appetite, febrile neutropenia, nausea (4 [66.7%] patients each), alopecia, hypokalemia, hypophosphatemia, pyrexia, rash, vomiting, and weight decreased (3 [50.0%] patients each).

Combination Cohort 3: The most frequently reported TEAEs of all grades (≥40%) were nausea (5 [83.3%] patients), dysgeusia, leukopenia, thrombocytopenia (3 [50.0%] patients each).

Expansion Cohort: The most frequently reported TEAEs of all grades (≥40%) were anemia, nausea (10 [66.7%] patients each), decreased appetite, fall, febrile neutropenia, pyrexia, platelet count decreased (7 [46.7%] patients each), constipation, and dysgeusia (6 [40.0%] patients each).

Treatment-related TEAEs

Monotherapy Cohort: The most frequently reported treatment-related TEAEs of all grades (≥40%) were dysgeusia (3 [75.0] patients), muscle spasms, alopecia, decreased appetite, constipation, diarrhea, fatigue, and weight decreased (2 [50.0%] patients each) in glasdegib 50 mg treatment group; dysgeusia (5 [83.3%] patients) in glasdegib 100 mg treatment group. None of the patients reported ≥Grade 3 TEAEs in glasdegib 25 mg and 50 mg treatment groups except 1 (16.7%) patient in glasdegib 100 mg treatment group.

Combination Cohort 1: The most frequently reported treatment-related TEAEs of all grades (≥40%) were dysgeusia (4 [66.7%] patients), anemia, and febrile neutropenia (3 [50.0%] patients each). Five (83.3%) patients had at least 1 ≥Grade 3 treatment-related

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TEAEs reported, with the most frequently reported related events (≥40%) being anemia and febrile neutropenia (3 [50.0%] patients each).

Combination Cohort 2: The most frequently reported treatment-related TEAEs of all grades (≥40%) were leukopenia and thromobocytopenia (6 [100.0%] patients each); dysgeusia and neutropenia (5 [83.3%] patients each); anemia, febrile neutropenia, and decreased appetite (4 [66.7%] patients each); alopecia, vomiting, and weight decreased (3 [50.0%]) patients each). Six (100.0%) patients had at least 1 ≥Grade 3 treatment-related TEAEs reported, with the most frequently reported related events (≥40%) being leukopenia and thromobocytopenia (6 [100.0%] patients each), neutropenia (5 [83.3%] patients), anemia and febrile neutropenia (4 [66.7%] patients each).

Combination Cohort 3: The most frequently reported treatment-related TEAEs of all grades (≥40%) were nausea (5 [83.3%] patients) and dysgeusia (3 [50.0%] patients). Five (83.3%) patients had at least 1 ≥Grade 3 treatment-related TEAEs reported and none of the events had frequency ≥40%.

Expansion Cohort: The most frequently reported treatment-related TEAEs of all grades (≥40%) were anemia and nausea (9 [60.0%] patients each) decreased appetite and febrile neutropenia (7 [46.7%] patients each), dysgeusia, platelet count decreased, and pyrexia (6 [40%] patients each). Thirteen (86.7%) patients had at least 1 ≥Grade 3 treatment-related TEAEs reported, with the most frequently reported events (≥40%) being anemia (8 [53.3%] patients), febrile neutropenia (7 [46.7%] patients), and platelet count decreased (6 [40%] patients).

Serious Adverse Events

Monotherapy Cohort: Overall, 5 patients were reported to have 8 SAEs in monotherapy cohort. Of which, 1 patient was reported to have an unrelated SAE of enteritis infectious in glasdegib 25 mg treatment group; 2 patients were reported to have unrelated SAEs of cerebral hemorrhage, disease progression and 1 patient was reported to have a related SAE of acute kidney injury in glasdegib 50 mg treatment group; and 1 patient was reported to have related SAEs of pyrexia (2 episodes of pyrexia) and colitis in glasdegib 100 mg treatment group.

Combination Cohort 1: One patient was reported to have an unrelated SAE of neoplasm progression in this cohort.

Combination Cohort 2: Four patients were reported to have 8 SAEs in this cohort. Of which, 1 patient was reported to have an unrelated SAE of acute lung injury; 1 patient was reported to have a related SAE of gingival bleeding; 2 patients were reported to have an unrelated SAEs of disseminated intravascular coagulation, pneumonia bacterial, pneumothorax, and related SAEs of interstitial lung disease, pneumonia cytomegaloviral, dermatitis exfoliative generalized, and erythroderma.

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Combination Cohort 3: One patient reported to have unrelated SAEs of femur fracture and pneumonia in this cohort.

Continuation Cohort: No SAEs were reported in this cohort.

Expansion Cohort: Nine patients had 13 SAEs in this cohort. The patients were reported to have unrelated SAEs of sepsis, compression fracture, pneumonia, febrile neutropenia, neoplasm progression, lung adenocarcinoma recurrent, secondary primary malignancy, bacteremia, clostridium difficile colitis and 1 patient had a related SAE of cellulitis.

Permanent or Temporary Discontinuations Due to Adverse Events

Study drug was withdrawn due to non-serious TEAEs were follows:

- Dysgeusia, vertigo, decreased appetite, nausea, diarrhea, dehydration, dissiminated intravascular coagulation, fatigue, weight decreased in monotherapy cohort
- Thromobocytopenia, gingival bleeding, interstitial lung disease, pneumonia cytomegaloviral, dermatitis exfoliative generalized in combination Cohort 2
- Delirium in combination Cohort 3

Study drug was permanently withdrawn due to SAEs of cerebral hemorrhage, disease progression, acute kidney injury (glasdegib 50 mg treatment group) in monotherapy cohort; SAEs of disseminated intravascular coagulation, pneumonia cytomegaloviral, pneumothorax, pneumonia bacterial, interstitial lung disease, dermatitis exfoliative generalized, and gingival bleeding in combination Cohort 2; SAEs of pneumonia, lung adenocarcinoma recurrent, second primary malignancy, and clostridium difficile colitis in expansion cohort.

Study drug was temporarily withdrawn due to: SAEs of pyrexia (glasdegib 100 mg treatment group) in monotherapy cohort; SAEs of dermatitis exfoliative generalized in combination Cohort 2; SAEs of femur fracture and pneumonia in combination Cohort 3; and SAEs of cellulitis, bacteremia, clostridium difficile colitis in expansion cohort.

Deaths

Monotherapy Cohort: Overall, 2 (15.4%) patients died during the study. Two (50.0%) patients in glasdegib 50 mg treatment group died during the on-treatment period and cause of the death being disease under study.

Combination Cohort 1: One (16.7%) patient died during the on-treatment period due to disease under study and 4 (66.7%) patients died during the follow-up period. The cause of

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the death being disease under study and other reasons (2 [33.3%] patients each). Other reasons included infections and suspicion of EBV-HLH.

Combination Cohort 2: One (16.7%) patient died during the on-treatment period and 1 (16.7%) patient died during the follow-up period. The cause of the death being disease under study and study treatment toxicity, respectively (1 [16.7%] patient each).

Combination Cohort 3: Four (66.7%) patients died during the follow-up period. The cause of the death being disease under study and unknown (2 [33.3%] patients each).

Expansion Cohort: Three (20.0%) patients died during the on-treatment period due to disease under study, and 7 (46.7%) patients died during the follow-up period. The cause of the death being disease under study (7 [46.7%] patients), and other – pneumonia cytomegaloviral (1 [16.7%] patient).

Vital Signs, Physical Examinations, and Clinical Laboratory Results

No clinically significant changes in vital signs and physical examinations were observed in all cohorts. The Grade 4 hematology laboratory test abnormalities were reported to be high in monotherapy cohort compared to other cohorts.

Conclusions:

PK:

- Monotherapy Cohort: Increases in exposure (AUC_{tau} and C_{max}) of glasdegib between the 25 mg, 50 mg, and 100 mg treatment groups were approximately dose proportional. Accumulation ratios were 1.9, 2.0, and 1.8, based on AUC_{tau} (R_{ac}) for the 25 mg, 50 mg, and 100 mg dose group, respectively

- Combination Cohort 1: When glasdegib was co-administered with LDAC, median plasma glasdegib concentrations were slightly lower than those following administration of glasdegib alone. The adjusted geometric mean for AUC_{tau} and C_{max} decreased by approximately 3% and 11%, respectively, following co-administration LDAC as compared to administration of glasdegib alone. When LDAC was co-administered with glasdegib, median plasma cytarabine concentrations were slightly higher than those following administration of LDAC alone. The adjusted geometric mean for AUC_{inf}, AUC_{tau}, and C_{max} increased by approximately 38%, 39%, and 29%, respectively, following co-administration with glasdegib as compared to administration of LDAC alone. Overall, PK was similar between glasdegib dose groups and co-administration (LDAC) treatments

- Combination Cohort 2: When glasdegib was co-administered with cytarabine/daunorubicin, median plasma glasdegib concentrations were slightly lower than those following administration of glasdegib alone. The adjusted geometric mean for

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AUC_{tau} and C_{max} decreased by approximately 14% and 11%, respectively, following co-administration cytarabine/daunorubicin as compared to administration of glasdegib alone. Overall, PK was similar between glasdegib dose groups and co-administration (LDAC) treatments

- Combination Cohort 3: When glasdegib was co-administered with azacitidine, median plasma glasdegib concentrations were slightly higher than those following administration of glasdegib alone. The adjusted geometric mean for AUC_{tau} and C_{max} increased by approximately 29% and 31%, respectively, following co-administration azacitidine as compared to administration of glasdegib alone. When azacitidine was co-administered with glasdegib, median plasma azacitidine concentrations were similar to those following administration of azacitidine alone. Overall, PK was similar between glasdegib dose groups and co-administration (LDAC) treatments

PD:

The median levels of mRNA at baseline (Cycle 1 Day 21) were 1.170 (0.97, 1.37), 1.568 (1.42, 1.77), 1.683 (1.56, 1.86) for glasdegib 25 mg (n=2), 50 mg (n=3), and 100 mg (n=5), respectively

Efficacy:

- In the expansion cohort, the primary objective of DMR was met. Addition of glasdegib to LDAC was statistically significant and clinically meaningful DMR achievement in expansion cohort and DMR rate was 46.7% (90% CI: 24.4%, 70.0%, 95% CI: 21.3%, 73.4%, the 1-sided p-value <0.0001 for H0: DMR=6.8%). Six (40.0%) patients had morphologic CR during the study. The median OS was 13.9 (95% CI: 3.8, 18.8) months, 18.8 (95% CI: 13.9, NE) months, and 4.9 (95% CI: 1.4, 11.0) months for all patients, DMR responder, and non-responder AML patients, respectively. These results suggest that glasdegib in combination with LDAC may represent a novel treatment strategy for patients with AML or high-risk MDS that are not suitable for intensive chemotherapy

- Preliminary evidence of efficacy was observed in the treatment with glasdegib and in combination with chemotherapy

Safety:

- First-cycle DLTs: Maximum tolerated dose was not reached for monotherapy cohort and for combination Cohort 1/2/3. One patient had a DLT of Grade 3 erythroderma in glasdegib 100 mg treatment group with cytarabine/daunorubicin (combination Cohort 2), although the frequency of 1/6 DLT suggested that this combination therapy is tolerable

- The safety profile of glasdegib 100 mg monotherapy and combined with chemotherapy backbones, was tolerable and manageable