AN OPEN-LABEL PHASE 1B STUDY OF PF-04449913 (GLASDEGIB) IN COMBINATION WITH AZACITIDINE IN PATIENTS WITH PREVIOUSLY UNTREATED HIGHER-RISK MYELODYSPLASTIC SYNDROME, ACUTE MYELOID LEUKEMIA, OR CHRONIC MYELOMONOCYTIC LEUKEMIA

Compound:	PF-04449913
Compound Name:	Glasdegib
United States (US) Investigational New Drug (IND) Number:	105,453
European Clinical Trials Database (EudraCT) Number:	2014-001345-24
Protocol Number:	B1371012
Phase:	1b

Document History

Document	Version Date	Summary of Changes
Original protocol	15-July-2014	N/A
Amendment 1	21 October 2014	Figures 1 and 3: Study Schematic updated to include the 2 additional safety analyses during the Randomized Phase 2 component. Added in all appropriate sections that patients with >30% BM blasts OR a rapidly progressive increase in the proportion of BM blasts at any point during the trial, must discontinue the study drug combination and enter follow-up. Added in all appropriate sections that two safety analyses will be performed following commencement of the randomized Phase 2 component of the study in order to carry out an early assessment of the safety profile of the study treatment combination in addition to the one performed at the end of the lead-in phase. One analysis will be carried out after 12 patients have completed 2 cycles of treatment, and one after 24 patients have completed 2 cycles of treatment. The EDMC will review the results of both analyses. Deleted all references to allowing the continuation of single agent PF-04449913/placebo in the event that azacitidine is permanently discontinued for reasons other than objective disease progression, patient refusal, or consent withdrawal. Updated in all appropriate sections that the Patient Dosing Diary for PF-04449913/placebo will now be required for all treatment cycles. Previously the Patient Dosing Diary was optional after Cycle 6. End of Treatment Visit added to Table 4.

Document	Version Date	Summary of Changes
		The following Exclusion Criteria was added: *"Patients with AML who are candidates for standard induction chemotherapy".* The following clarification of the definition of a missed dose was added to Section 5.5.1 General Guidelines in reference to PF-04449913*: "If a patient forgets to take their dose at the regularly scheduled time, and if less than 10 hours have passed since the scheduled dosing time, that dose should be taken as soon as possible. If more than 10 hours have passed since the scheduled dosing time, the dose should be skipped and the patient should continue on their normal dosing schedule."* For clarification the following sentence was added to Section 5.5.2.3.2: PF-04449913 or Placebo: *"PF-04449913/placebo treatment should be interrupted for ANC <100/mm^3 and /or platelets < 10,000/mm^3 regardless of when it occurs."* In Section 5.5.2.3.2. PF-04449913 or Placebo: Investigator judgment allowing re-commencement of PF-04449913/placebo treatment for non-hematological toxicities if returned to baseline or ≤ Grade 2 (if not considered a safety risk) was removed. Re-commencement can only occur when the non-hematological toxicity has returned to baseline or ≤ Grade 1. In Section 5.5.2.4. Dose Reduction for Azacitidine and PF-04449913 or Placebo the following sentence was deleted*: "No specific dose adjustments are recommended for Grade 1/2 treatment-related toxicity. Investigators should, however, manage their patients according to their medical judgment based on the clinical circumstances."*

Document	Version Date	Summary of Changes
		Table 7 was updated to include additional and new PF-04449913/placebo dose modification instructions. Table 7 Footnote was updated to include both definitions of recovery as well as clarification on PF-04449913/placebo interruption criteria. Table 8: Section referring to PF-04449913/placebo related Other Non-Hematologic Toxicities was updated to also exclude muscle spasms and myalgia. Table 9. Recommended Dose Modifications for PF-04449913/placebo related QTcF prolongation was updated. Table 10. Recommended Dose Modifications for PF-04449913/placebo in case of drug class related AEs was added. Section 7.6. Triplicate (12 Lead) ECGs was updated to agree with the updated Table 9. Minor administrative corrections adding clarifications and correction of typos.
Amendment 2	15 December 2014	In Section 3.3.2 Breaking the Blind and Section 5.2 Breaking the Blind the following sentence was removed: *"Whenever possible, the Investigator or sub investigator consults with the Sponsor prior to breaking the blind."* In Sections 3.3.2 Breaking the Blind and 5.2 Breaking the Blind the following sentence was added: *"Immediate unblinding for patient safety can occur via the IRT system."* In the Protocol Summary; Study Treatments, Section 3.3.1 Study Treatments, Section 5.5.1.3 Treatment Duration and Section 6.4 Follow-Up the following sentence was added: *"In cases of unacceptable toxicity or pregnancy, the patient must be withdrawn from study drug combination and entered into the follow-up phase of the study."*

Document	Version Date	Summary of Changes
		Throughout the document when referring to study endpoints and objectives the terms Objective Response Rate (ORR) and Objective Response (OR) were changed to Response Rate (RR) and Response respectively. Under Protocol Summary and under Section 2.2: Endpoints for the Phase 1b (Safety Lead-In Cohort [LIC]) Secondary Endpoints: Clarified the definition of Response Rate by adding the following in bold: *"Response Rate* ***(percentage of patients achieving*** *Complete Remission (CR) + Partial Remission (PR)) as defined by modified International Working Group (IWG) criteria (2006) Appendix 2:"* Under Protocol Summary and under Section 2.4: Endpoints for the Randomized Phase 2 Primary Endpoint: Clarified the definition of Response Rate by adding the following in bold*: "Response Rate* ***(percentage of patients achieving*** *CR + PR) as defined by modified IWG criteria (2006) Appendix 2."* Section 4.2 Exclusion Criteria 1 (updated in bold) to:*" Patients with AML who are candidates for standard induction chemotherapy* ***as first line treatment."*** Minor administrative corrections adding clarifications and correction of typos.
Amendment 3	17 February 2015	Section 5.5.2.4 Table 9 and Section 7.6: Will be updated with the following sentence: "*If Grade 3 QTcF prolongation (>500 msec) occurs, continuous ECG monitoring and cardiology specialist evaluation and guidance are recommended*." Minor administrative corrections adding clarifications and correction of typos.

Document	Version Date	Summary of Changes
		Updates to safety and communication of results by Pfizer text to incorporate latest template changes.
Amendment 4	04 January 2016	Study Title updated to include the drug International Nonproprietary Name (INN), Glasdegib. Abbreviations list updated. Table 1- Schedule of Activities for the Phase 1b Safety LIC: • Footnotes 14 and 25 updated to clarify that study treatment refers to PF-04449913 + Azacitidine • Footnote 25, corrected to remove mention of PRO assessment collection in the Long-Term Follow Up period of the Phase 1b Safety LIC. Table 2 "Pharmacokinetics and ECG Schedule for the Safety LIC" updated to expand ECG collection to Day 1 of every cycle and clarify that PK collection ends after Cycle 6. Table 4 "Pharmacokinetics & ECG Schedule for the Randomized Phase 2" updated to expand ECG collection to Day 1 of every cycle. Section 1.2.12 Summary of Benefit-Risk Assessment updated with information concerning QTc interval prolongation. Section 4.0 Patient Selection. The following statement was added to clarify that eligibility criteria must be met both at Screening and on Cycle 1 Day 1: *"These criteria must also be met prior to dosing on Cycle 1 Day 1."* Section 4.2 Exclusion Criterion 19 revised to include exclusion of all bundle branch blocks.

Document	Version Date	Summary of Changes
		Section 5.5.2 Dose Modifications updated: 1. The section heading and titles for Table 7- Dose Modifications for Hematologic Toxicities and Table 8-Dose Modifications for Non-Hematologic Toxicities amended to remove the term "Recommended". The term "Recommended" was also removed from all dose modification references throughout the protocol. 2. The following statement was added *"If there is a need to deviate from any of the dose modifications this first must be discussed with the Sponsor Medical Monitor."* 3. Table 9- Recommended Dose Modifications for PF-04449913/placebo related QTcF prolongation replaced with a new table entitled PF-04449913/placebo Dose Modifications for mean QTcF (mQTcF) Prolongation. 4. Table 10-Recommended Dose Modifications for PF-04449913/placebo in Case of Drug Class Related AEs updated to remove the term "Recommended" from the title and replaced with a new table. 5. Sub-Section 5.5.2.3.2 PF-04449913 or Placebo, added sub heading entitled "<u>QTcF Interval Monitoring and Management</u>" language concerning the monitoring of potential cardiovascular symptoms and guidance on the use of moderate/strong CYP3A4/5 inhibitors or drugs with a known risk of Torsade de pointes are added as concomitant therapy with PF-04449913/placebo.

Document	Version Date	Summary of Changes
		Section 5.8.1 Restricted or Prohibited Concomitant Medications: Added reference to new safety monitoring guidance provided in Section 7.6 and Table 9. Section 7.6 Triplicate (12-Lead) ECGs: New safety monitoring guidance provided when moderate/strong CYP3A4/5 inhibitors or drugs with a known risk of Torsade de pointes are added as concomitant therapy with PF-04449913/placebo. Section 8.12 Withdrawal due to Adverse Events updated to include the following statement: "*Please also refer to section 6.5 Patient Withdrawal."* Section 8.6.1 Protocol-Specified Serious Adverse Events updated to include the following sentence *"All cases of > Grade 2 mQTcF prolongation regardless of causality and treatment arm must be reported as an SAE for up to 28 calendar days after the last dose of study drug administered."* Appendix 4-Strong CYP3A4/5 Inducers source reference updated. Appendix 5- List of Drugs with Known Risk of Torsades de Pointes, Appendix 6-Strong CYP3A4/5 Inhibitors, and Appendix 7 -Moderate CYP3A4/5 Inhibitors replaced with new tables and updated source references.
Amendment 5	22 August 2017	Study Title updated to remove the Phase 2 part and reflect the hematologic malignancies enrolled in the entire Phase 1 study. Abbreviations list updated. Protocol Summary updated to reflect new study design: Phase 2 part removed and Phase 1 Expansion Component added.

Document	Version Date	Summary of Changes
		Table 2 title updated to remove number of LIC patients. Table 3 New "Schedule of Activities for the Expansion" added. Table 4 New "Pharmacokinetics & ECG Schedule for Expansion" added. References to "placebo" removed from the body of the document. Table of Content updated. Section 1.1. Indication for Expansion Component added. Section 1.2.1. Disease Overview updated to reflect new MDS and AML classification. Section 1.2.3. Rationale for PF-04449913/Azacitidine Combination Therapy in Patients with AML updated. Section 1.2.5. PF-04449913 Preclinical Toxicity Data updated. Section 1.2.10. Heading updated to "Clinical Relevance of Organ Toxicities Observed in Nonclinical studies" from "Impact of Preclinical Safety Findings on Patient Management", and data within section updated. Section 1.2.6. Bone Effects in Preclinical Studies updated. Section 1.2.13. Clinical Experience in Patients with Selected Myeloid Malignancies updated. Section 1.2.16.1.Azacitidine Dosing Schedule for Expansion Component updated. Section 1.2.18. Rationale for the Starting Dose of PF-04449913 updated.

Document	Version Date	Summary of Changes
		Section 1.2.20. Summary of Benefit-Risk Assessment updated. Section 2.3. and 2.4. Objectives and endpoints for the Expansion Component added. Section 3. Expansion Component added to the Study Design and Phase 2 study removed. Section 4. Inclusion/Exclusion Criteria for the Expansion Component added. Section 4.3. Contraception guidance updated to align with European regulations Section 5.4. Azacitadine administration revised for the Expansion Component. Section 5.4.4. Traetement duration in Expansion Component added. Section 6. Study Procedures updated to incorporate Expansion Component and clarified long term follow up duration. Section 7.7. Efficacy assessments updated to incorporate Expansion Component. CCI [redacted] CCI [redacted] Section 9. Data Analysis/ Statistical Methods updated for Expansion Component. Removed Appendices: EORTC QLQ C30; EQ 5D 5L. Added Apendices: IPSS-R Classification System for Myelodysplastic Syndromes; 2017 ELN Response Criteria for Acute Myeloid Leukemia (AML); 2016 WHO Classification of Myelodysplastic Syndromes (MDS); CCI [redacted]

Document	Version Date	Summary of Changes
Amendment 6	27 November 2017	Changes made per FDA comments where indicated. Other minor changes were added for clarity. Addition of safety criteria to evaluate stopping enrollment per FDA request (Sections 3.3 and 9.7.2). Objectives & Endpoints added per FDA (Sections 2.3, 2.4, 7.7.1): • Secondary: Complete Remission with partial hematologic recovery (CRh). • CCI [redacted] Schedule of Activities: • Immunophenotyping was removed as it is not required for any study analysis. Immunophenotyping was also removed from Section 7.7.2 for consistency. • Removed "X"s from long-term follow up in table for all lab studies and BM collections for consistency with footnotes. • Combined collection of BM biopsy and BM aspirate into a single line as a biopsy is required only if aspirate is not sufficient for disease assessment. • Aligned adverse event assessment periods to be consistent with protocol. • CCI [redacted] • CCI [redacted]

Document	Version Date	Summary of Changes
		• CCI [redacted] • Added detail to explanation of long term follow up (also modified section 6.4 for alignment). • Added acceptable windows for PK collections and ECGs. Section 5.3.3: Removed requirement that azacitidine be prepared and dispensed by study staff. Azacitidine can be prepared/dispensed by any qualified personnel. Section 5.4.6: Increased gap between intracycle azacitidine doses from 2 to 3 days in agreement with Schedule of Activities. Section 7.7.2: Included reference to appendices with list of genetic abnormalities required to be assessed. CCI [redacted] Section 8.2: Extended the reporting period for AEs to begin at time of informed consent through and including 28 days after administration of last dose of study drug to be consistent with the reporting period for SAEs. Section 9.3.6 & 9.3.9: Added analyses for new CRh CCI [redacted] Appendix 11: Added CRh to AML response criteria, clarified relationship of endpoints to one another, and simplified table for easier comprehension.

Document	Version Date	Summary of Changes
		CCI [redacted] CCI [redacted] Appendix 16: Added AML Risk Stratification by Genetics for reference as all abnormalities listed are required to be evaluated locally. Appendix 17: Added complete 2016 WHO Classification of myeloid neoplasms and acute leukemia for reference as only MDS classification was previously included. General spelling, grammar, and consistency issues corrected throughout the protocol.
Amendment 7	14 June 2018	Section 9.8: Addition of External Data Monitoring Committee per request of French National Agency for Medicines and Health Products Safety Schedule of Activities: • Defined elements of a physical exam; • For AML patients, added whole blood collection at C1D1 for MRD assessment & molecular profiling (also Section 7.8); • Increased period of time for contraception post-last dose of azacitidine or glasdegib to 180 days from 90 days for males and females (also sections 4.1.2 and 4.3); • Clarified disease assessment is to be done whenever complete response is suspected;

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		• Removed requirement that disease assessments be done >3 weeks from dosing of G-CSF or GM-CSF (also sections 5.7.4, 7.7.3, and 9.3.6). Section 1.2.20: Summary of glasdegib TQT study added. Sections 1.2.3 and 4.1.2: Added eligibility of CMML patients and MDS/MPN, unclassifiable patients, for the MDS cohort. Section 1.2.16: Updated toxicities reported for azacitidine. Sections 1.2.16.2, 5.4.5 and 5.7.4: Replaced all azacitidine dose modification criteria with reference to local label, Investigational Product Manual, or SPC. Throughout sections applicable to expansion cohorts: Clarified azacitidine dosing is to be done per local label, Investigational Product Manual, or SPC. Section 4.1.2: Revised definition of adequate organ function (inclusion criterion #4). Section 4.2.2.: Removed exclusion criterion for patients with HBV, HCV, HIV or AIDS related illness. Section 4.2.2: Revised cardiac exclusion criteria. Section 5.2: Restricted requirement for azacitidine dosage Preparation Record to cases where Pfizer is providing azacitidine. Section 5.4.5: Revised glasdegib dose modification. Sections 5.7.1 and 7.6: Removed requirement for additional ECGs when moderate/strrong CYP3A4/5 inhibitor or drug with TdP risk is initiated.

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		Section 5.7: Revised allowed and restricted concomitant medications. Section 8.6.2: Added definition of confirmed Hy's law case. Section 13: Defined end of trial as last patient last visit for all countries. Appendices 3, 10, 16: Corrected literature references. Appendix 4: Added list of moderate CYP3A4/5 inducers. Appendix 8: Edited description of urinalysis. Appendix 11: Added descriptions of additional AML response categories. Appendix 18: Added France-specific appendix. Replaced PF-04449913 with glasdegib throughout. Abbreviation list updated. Table of Contents updated. General spelling, grammar, and consistency issues corrected throughout the protocol.

This amendment incorporates all revisions to date, including amendments made at the request of country health authorities, institutional review boards/ethics committees (IRBs/ECs), etc.

Abbreviations

Abbreviation	Term
7 + 3	Induction Chemotherapy with Cytarabine (7 days) plus Daunorubicin (3 days)
AE	Adverse Event
AHD	Antecedent hematologic disease
AIDS	Acquired Immunodeficiency Syndrome
ALL	Acute lymphocytic leukemia
ALT	Alanine Aminotransferase
AML	Acute Myeloid Leukemia
ANC	Absolute Neutrophil Count
APL	Acute promyelocytic leukemia
ARA-C	Cytarabine
AST	Aspartate Aminotransferase
AUC	Area Under the Plasma Concentration Curve
AZA	Azacitidine
BM	Bone marrow
BSC	Best Supportive Care
BST	Best Supportive Therapy
C1D1	Cycle 1 Day 1
CBC	Complete blood count
CCR	Conventional Care Regimens
CHF	Congestive heart failure
CI	Confidence Interval
CID	clinically important difference
CL/F	Apparent oral clearance
Cmax	Maximum Plasma Concentration
CMH	Cochran-Mantel-Haenszel
CML	Chronic Myeloid Leukemia
CMML	Chronic Myelomonocytic Leukemia
CNS	Central Nervous System
CR	Complete Remission
CR MRD-	Complete Remission without Minimal Residual Disease
CRh	Complete remission with partial hematologic recovery
CRi	Complete Remission with Incomplete Blood Count Recovery
CRF	Case Report Form
CSA	Clinical Study Agreement
CTCAE	Common Terminology Criteria for Adverse Events
Ctrough	Lowest concentration before next dose administration
CV	Coefficient of variance
DAI	Dosage and Administration Instructions
DDI	Drug/Drug Interaction
Dhh	Dessert hedgehog
DLT	Dose Limiting Toxicity
DoR	Duration of Response
DNA	Deoxyribonucleic Acid
CCI	CCI [redacted]
DU	Dispensable unit
EC	Ethics Committee
ECG or EKG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group Performance Status
EDMC	External Data Monitoring Committee

Abbreviation	Term
EDP	Exposure During Pregnancy
EDTA	Ethylenediaminetetraacetic Acid
EORTC QLQ-C30	European Organization for Research and Treatment of Cancer
EOT	End of Treatment
ELN	European LeukemiaNet
EMD	Extramedullary Disease
EQ-5D-5L	EuroQol-Health Utilities Index
EU	European Union
EudraCT	European Clinical Trials Database
FAB	French American British
FAS	Final analysis set
FDA	Food and Drug Administration (United States)
FSH	Follicle stimulating hormone
GCP	Good Clinical Practice
G-CSF	Granulocyte Colony-Stimulating Factor
GI	Gastrointestinal
GliA	Gli activator
GliR	Gli repressor
GLP	Good Laboratory Practices
GM-CSF	Granulocyte Macrophage Colony-Stimulating Factor
HBV	Hepatitis B
HCG	Human Chorionic Gonadotropin
HDPE	High-density polyethylene
HCV	Hepatitis C
hERG	Human ether-à-go-go-related gene
Hh	Hedgehog
HHIP	Human hedgehog-interacting protein
HI	Hematologic Improvement
HIV	Human Immunodeficiency Virus
HMA	Hypomethylating Agent
HR	Hazard Ratio
HRQOL	Health-Related Quality of Life
HSCT	Hematopoietic Stem Cell Transplant
IB	Investigator's Brochure
IC50	Half maximal inhibitory concentration
ICH	International Conference on Harmonization
ID	Identification
Ihh	Indian hedgehog
IIR	Investigator Initiated Research
IND	Investigational New Drug Application
INN	International Nonproprietary Name
INR	International Normalized Ratio
IPSS	International Prognostic Scoring System
IPSS-R	International Prognostic Scoring System Revised Classification
IRB	Institutional Review Board
IRT	Interactive Response Technology
IUD	Intrauterine Device
IUS	Intrauterine hormone releasing system
IV	Intravenous
IWG	International Working Group
IWR	Interactive Web Response

Abbreviation	Term
IVR	Interactive Voice Response
LDAC	Low Dose Cytarabine
LIC	Lead-in Cohort
LFT	Liver Function Test
LSC	Leukemia Stem Cell
LPLV	Last Patient Last Visit
mCR	Marrow CR
MDASI	MD Anderson Symptom Inventory
MDS	Myelodysplastic Syndrome
MDR-1	Multi-Drug Resistance 1
MF	Myelofibrosis
MFC	Multiparameter Flow Cytometry
MLFS	Morphologic leukemia-free state
mOS	Median overall survival
MPN	Myeloproliferative Neoplasms
mQTcF	Mean Corrected QT interval using Fridericia Formula
MR	Minor response
MRD	Minimal Residual Disease
mRNA	Messenger ribonucleic acid
mOS	Median overall survival
MTD	Maximum Tolerated Dose
N/A	Not Applicable
NASH	Non-Alcoholic Steatohepatitis
NCI CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
NNRTI	Non-nucleoside Reverse Transcriptase Inhibitors
NOAEL	No Observed Adverse Effect Level
NRS	Numeric rating scale
OS	Overall Survival
PB	Peripheral blood
PCD	Primary Completion Date
PCR	Polymerase Chain Reaction
PD	Pharmacodynamics
PE	Physical examination
PFS	Progression-free survival
CCI	CCI
CCI	CCI
P-gP	P-glycoprotein
PK	Pharmacokinetics
PML-RARA	Promyelocytic leukemia/retinoic acid receptor alpha
PO	Orally (per os)
PR	Partial Remission
PRI	Partial Remission with Incomplete Blood Count Recovery
CCI	CCI
PT	Prothrombin Time
PTCH	Patched
QD	Once a Day
Qday	Once Daily
QTc	QT interval corrected for rate
QTcF	Corrected QT interval using Fridericia Formula
RNA	Ribonucleic Acid
RP2D	Recommended Phase 2 Dose

Abbreviation	Term
RR	Response Rate
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SC	Subcutaneous
SD	Stable Disease
SEER	Surveillance, Epidemiology, and End Results
Shh	Sonic hedgehog
SMO	Smoothened (G protein-coupled receptor)
SMOi	Smoothened Inhibitor
SOA	Schedule of Activities
SOP	Standard Operating Procedure
SPC	Summary of Product Characteristics
SRSD	Single Reference Safety Document
TdP	Torsade de pointes
TEAE	Treatment-emergent adverse event
TKI	Tyrosine kinase inhibitor
Tmax	Time to First Occurrence of Maximum Plasma Concentration
TQT	Thorough QT
TTR	Time to response
U/A	Urinalysis
ULN	Upper Limit of Normal
US	United States
USA	United States of America
USPI	United States Package Insert
UVA	Ultraviolet A
UVB	Ultraviolet B
Vs	Versus
Vz/F	Volume of distribution
WHO	World Health Organization

PROTOCOL SUMMARY

INTRODUCTION

Glasdegib (PF-04449913) is a novel small molecule inhibitor of the Sonic Hedgehog (Hh) pathway which is currently under development for the treatment of hematologic malignancies.

This multi-center open-label Phase 1b study is designed to evaluate the safety, efficacy, pharmacokinetics (PK), and pharmacodynamics (PD) of glasdegib when combined with azacitidine in patients with previously untreated Higher-Risk Myelodysplastic Syndrome (MDS), Acute Myeloid Leukemia (AML), and Chronic Myelomonocytic Leukemia (CMML). This clinical study includes two components: (a) a safety lead-in cohort (LIC) and (b) an expansion phase with two cohorts.

Indication

Safety Lead-In Cohort (LIC)

Previously untreated adult patients with Intermediate-2 or High-Risk MDS according to the International Prognostic Scoring System (IPSS), AML with 20%-30% blasts and multi-lineage dysplasia according to World Health Organization (WHO) 2008 classification, and CMML.

Expansion

(a) Previously untreated adult patients with Intermediate, High, or Very High risk MDS according to the International Prognostic Scoring System-Revised (IPSS-R) and (b) AML patients who are not candidates for intensive chemotherapy (according to WHO 2016 classification).

Background and Rationale

Disease Overview

MDS is a heterogeneous group of myeloid disorders defined by a common set of features, of which the most prominent is morphologic bone marrow and peripheral blood dysplasia associated with inefficient hematopoiesis, the development of peripheral cytopenias and an increased risk of transformation to AML. The incidence of MDS is around 4–5 per 100,000 individuals annually worldwide, with the prevalence increasing with age.

The French-American-British (FAB) classification system established in 1982 was the first approach allowing for a reliable diagnosis of a disease group that had previously been termed pre-leukemia. In 2001 the WHO classification of hematopoietic neoplasms was introduced, subsequently updated in 2008, and most recently in 2016. The principal modifications with respect to the FAB classification were to consider patients with 20% or more bone marrow or peripheral blood blasts as having AML, and to remove the CMML subtype and place it in a newly created category termed Myelodysplastic/ Myeloproliferative Neoplasms (MDS/MPN).

The standard of care treatment of higher risk (Intermediate-2 and High-Risk) MDS and AML with 20-30% bone marrow (BM) blasts and multi-lineage dysplasia, has previously been focused on intensive chemotherapy using anthracycline and cytarabine (Ara-C) combinations but this approach has led to lower complete response rates and a shorter response duration as compared to treatment outcomes in patients with de-novo AML ≥30% BM blasts. In response to this unmet medical need, several multi-center randomized studies comparing hypomethylating agent (HMA) treatment to supportive care have been conducted and demonstrated delayed progression to AML, with prolongation of median progression-free survival (PFS) of between 3 to 8 months as compared with best supportive therapy.

Azacitidine was approved in the US by the Food and Drug Administration (FDA) in 2004 for the treatment of all MDS subtypes according to the FAB classification. This approval was based on the overall response rate defined as Complete Response (CR) + Partial Response (PR) observed in the randomized CALGB-9221 study. The overall response rate (CR + PR) was 15.7% in the azacitidine treatment group, and there were no responders in the control group.

In 2009, results from the international AZA-001 trial, phase 3 randomized trial comparing azacitidine to conventional care regimens (CCR) in patients with Intermediate-2 or High Risk MDS, showed that the median overall survival (OS) was significantly prolonged in the azacitidine arm as compared with the CCR arm (24.5 months for azacitidine vs. 15.0 months for CCR; hazard ratio [HR] 0.58; 95% confidence interval [CI] 0.43–0.77) despite a low CR rate (17% in the azacitidine arm vs 8% in the CCR arm). Based on this observed survival benefit, azacitidine was approved in the European Union (EU) for the treatment of adults who are not eligible for hematopoietic stem cell transplantation and have Intermediate-2 or High-Risk MDS, CMML with 10-29% marrow blasts and lacking a myeloproliferative component, and AML with 20-30% blasts and multi-lineage dysplasia according to WHO 2008.

AML is a genetically heterogeneous hematologic malignancy characterized by multiple mutations and epigenetic dysregulation at the time of diagnosis that evolves with treatment, resulting in treatment resistance, disease relapse, and reduced survival. It is estimated that there will be 21,380 new cases and 10,500 deaths from AML in the United States in 2017.

Existing standards of care such as cytarabine + anthracycline (7+3), or hypomethylating agents like decitabine and azacitidine, can induce CR in 5-70% of patients; however, remissions are not durable and disease relapse occurs in up to 60% of patients. For AML patients unable to receive intensive chemotherapy, existing standard treatments like Low Dose Cytarabine (LDAC) are associated with response rates <20% and median OS times of 5-6.5 months. Hypomethylating agents, azacitidine and decitabine, although not approved in the US specifically for AML, have shown improved OS vs LDAC in AML patients who were not candidates for intensive chemotherapy. Reducing the incidence of disease progression to prolong survival remains the highest unmet medical need in the treatment of AML patients. In 2015, results from the international randomized phase 3 AZA-AML trial comparing azacitidine to CCRs in patients aged ≥65 years with newly diagnosed or secondary AML with >30% bone marrow blasts demonstrated a clinically meaningful improvement in median

overall survival (mOS) in the azacitidine arm of 10.4 months (95% CI, 8.0-12.7) versus (vs) 6.5 months (95% CI, 5.0-8.6) in the CCR arm (HR=0.85; 95% CI, 0.69-1.03; stratified log-rank p=0.1009), although the primary endpoint was not met. The CR rate in the azacitidine arm was lower than the CCR arm (19.5% vs 21.9%). The 1-year survival rate with azacitidine was 46.5% compared with 34.2% with conventional therapy (95% CI, 3.5%-21.0%). Based on the observed survival benefit, the EU expanded the approval of azacitidine in AML to adult patients aged 65 years or older who are not eligible for hematopoietic stem cell transplantation (HSCT) with >30% myeloblasts according to the WHO classification; previously, the indication covered AML patients with <30% blasts. Despite the modest increase in mOS and low CR rate, azacitidine is currently the standard of care for AML patients who are not candidates for intensive chemotherapy. New treatments are needed to improve outcomes in this older AML population.

Rationale for Glasdegib/Azacitidine Combination Therapy

Glasdegib was initially evaluated as a single-agent therapy in patients with select myeloid malignancies, and had a manageable safety profile at the recommended phase 2 dose (RP2D) of 100 mg once a day (QD) per os with early signs of efficacy observed in AML, MDS, chronic myeloid leukemia (CML), and Myelofibrosis (MF).

In the safety LIC of the current study, 12 patients with previously untreated high risk MDS (n=7), AML with 20-30% blasts and multi-lineage dysplasia (n=3), erythroleukemia (n=1), and CMML (n=1) were treated at the glasdegib, 100 mg QD per os, in combination with azacitidine 75 mg/m^2 daily for 7 days subcutaneously (SC) every 28 days. An internal safety review team reviewed the data from this component of the study and determined that the safety profile of the combination treatment appeared to be consistent with what was expected for glasdegib or azacitidine alone, with no unexpected toxicities identified, and deemed acceptable to proceed to the next phase of development. Preliminary efficacy data from the LIC showed 5 patients responded: 3 patients with CR, 2 patients with marrow complete remission (mCR): of note, after the data cutoff date, the complete blood count of 1 of the patients with mCR had normalized, consistent with CR. Of the 5 patients who responded, 4 responses occurred on or before Day 100. Of the 4 patients with CR (including the mCR patient who achieved a CR after the data cutoff date), 3 patients had AML (75% CR rate vs the historical control for azacitidine alone, 19.5%) and 1 patient had MDS (14% CR rate vs the historical control for azacitidine alone, 17%). A further 4 patients had stable disease (SD). No evidence of drug-drug interaction (DDI) was noted. As of September 2016, mOS had not been reached.

In the Phase 1b part of Study B1371003, 52 patients with AML or higher risk MDS were treated with glasdegib 100 mg or 200 mg by mouth daily (PO Qday) in combination with low dose cytarabine (LDAC) (n=23), decitabine (n=7), or 7 + 3 (n=22). Median OS in the combined AML and MDS patients were 4.4 months (80% CI: 2.5, 6.6), 11.5 months (80% CI: 4.5, 17.4) (vs historical mOS of 7.7 months with decitabine alone), and 34.7 months (80% CI: 14.5, not reached), respectively, in the 3 treatment arms. Of the AML patients treated in combination with decitabine, 2/5 (40%) responded (1 CR and 1 complete response with incomplete blood count recovery (CRi)). Of the high-risk MDS patients treated in combination with decitabine, 2/2 responded (2 mCR). The safety profile of glasdegib in

combination with chemotherapy was consistent with what was seen in an earlier monotherapy study in patients with selected myeloid malignancies. A similar population of newly diagnosed elderly AML patients was enrolled into a Phase 3 study of decitabine vs supportive care vs low dose cytarabine where the CR+ CRi rate was 25.6% in the decitabine only arm.

In the Phase 2 portion of Study B1371003, a prospective, randomized (2:1), open-label clinical trial in 132 previously untreated AML patients who were not candidates for intensive chemotherapy based on age or other risk factors and higher risk MDS, the addition of glasdegib 100 mg orally PO Qday to LDAC vs LDAC alone resulted in a significant improvement in OS (mOS 8.8 months (80% CI: 6.9, 9.9) vs 4.9 months (80% CI: 3.5, 6.0); hazard ratio [HR] 0.513 [80 % CI: 0.394-0.666]; 1-sided p-value=0.0004). The CR/CRi rate for AML patients in the glasdegib + LDAC arm was 25% (80% CI: 19.1, 30.9) vs 4.5% (80% CI: 0.5, 8.6) in the LDAC alone arm. The safety/tolerability profile was consistent with that in elderly AML patients receiving chemotherapy.

Glasdegib, which targets the Hh pathway component Smoothened (SMO), is an oral inhibitor of the Hh pathway currently in clinical development for patients with myeloid malignancies. The Hedgehog (Hh) signaling pathway regulates cell differentiation and self-renewal in the developing embryo, and is typically silenced in adult tissues. Aberrant Hh signaling in the post-embryonic stage may result from mutations in key pathway genes, non-mutational mechanisms related to the secretion of Hh ligands, or signals from cells in the tumor microenvironment. Aberrant Hh signaling has been identified in a variety of human myeloid malignancies, and specifically in leukemia stem cells (LSCs).

In a preclinical MDS model, blocking the Hh pathway with SMO inhibitors in combination with the hypomethylating agent (HMA) azacitidine generated synergy in vitro with growth inhibition in primary malignant myeloid cells ex vivo. Upregulation of Hh pathway components has been observed in chemoresistant AML cell lines in vitro, and pharmacological inhibition of the Hh pathway resulted in decreased multi-drug resistance 1(MDR-1) or P-glycoprotein (P-gp) expression in these cells. In nonclinical models SMO, acting via its effector GLI2, has been implicated in the maintenance of LSC dormancy and associated resistance to chemotherapy and targeted therapy, while inhibition of SMO via glasdegib can cause LSCs to re-enter the cell cycle. Recrudescence of LSCs is prevented in preclinical hosts pre-treated with Hh pathway inhibitors, including glasdegib. Consistent with these effects, glasdegib sensitized AML cells to cytosine arabinoside, and abrogated resistance to cytosine arabinoside in AML cells co-cultured with stromal cells.

The clinical safety database of glasdegib contains over 300 patients with hematologic malignancies who received the recommended dose of at least 100 mg daily. The safety profile observed so far appears consistent with what has been reported for other marketed smoothened (SMO) inhibitors and the underlying chemotherapy backbones when administered in combination. Glasdegib has shown clinical activity in patients with higher risk MDS and AML patients who were not candidates for intensive chemotherapy when combined with other treatments, such as azacitidine and decitabine and demonstrated a statistically significant and clinically meaningful improvement in OS when combined with LDAC vs LDAC alone.

Adding glasdegib to other existing standards of care such as HMA represents a rational approach in an attempt to improve treatment outcomes in patients for whom treatment with azacitidine is already indicated (namely those with higher-risk MDS, AML, and CMML).

STUDY OBJECTIVES AND ENDPOINTS

Objectives for the Safety Lead-In Cohort

Primary Objective

- To assess the safety and tolerability of glasdegib when administered in combination with azacitidine in patients with previously untreated Intermediate-2 or High-Risk MDS, AML with 20%-30% blasts and multi-lineage dysplasia, and CMML.

Secondary Objectives

- To assess the response rate (RR);
- To assess other clinical efficacy measures;
- To characterize the PK of glasdegib and azacitidine alone and in combination;
- To characterize any effects of glasdegib alone and in combination with azacitidine on QTc interval.

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- [redacted]
- [redacted]
- [redacted]

Endpoints for the Safety Lead-In Cohort

Primary Endpoint

- Adverse events as characterized by type, frequency, severity (as graded by National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE v.4.03), timing, seriousness and relationship to study therapy and laboratory abnormalities as characterized by type, frequency, severity (as graded by NCI CTCAE v.4.03) and timing.

Secondary Endpoints

- Response Rate (percentage of patients achieving Complete Remission (CR) + Partial Remission (PR)) as defined by modified International Working Group (IWG) criteria (2006) Appendix 2;
- Other efficacy measures of HI, marrow CR (mCR), Cytogenetic Response, and Stable Disease (SD) as defined by modified IWG criteria (2006) Appendix 2;
- PK parameters of glasdegib-and azacitidine, including, but not limited to maximum plasma concentration (C_{max}), time to maximum plasma concentration (T_{max}) and area under the plasma concentration versus time curve (AUC);
- QTc interval.

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- [redacted]
- [redacted]

Objectives for the Expansion

Primary Objective

- To determine the CR (Complete Remission) rate of glasdegib when administered in combination with azacitidine in patients with previously untreated Intermediate, High, or Very High risk MDS and AML patients who are not suitable candidates for intensive chemotherapy.

Secondary Objectives

- To assess Overall Survival (OS);
- To assess other clinical efficacy measures;
- To assess duration of CR;
- To assess time to CR;
- To evaluate the overall safety profile of glasdegib when administered in combination with azacitidine;
- To evaluate the pharmacokinetic parameters of glasdegib;

- To characterize any effects of glasdegib in combination with azacitidine on QT interval corrected for rate (QTc interval).

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- [redacted]
- [redacted]
- [redacted]

Endpoints for the Expansion

Primary Endpoint

- CR rate for MDS patients (Appendix 2) and AML patients (Appendix 11).

Secondary Endpoints

- OS;
- For MDS cohort: disease-specific efficacy measures, such as Marrow Complete Remission (mCR), Partial Remission (PR), Stable Disease (SD), Partial or Complete Cytogenetic Response, and Hematologic Improvement (HI) Appendix 2;
- For AML cohort: disease-specific efficacy measures, such as Complete Remission with Incomplete Hematologic Recovery (CRi), Complete Remission with partial hematologic recovery (CRh), Morphologic Leukemia-Free State (MLFS), Partial Remission (PR) and stable disease (SD) (Appendix 11);
- Duration of CR;
- Time to CR;
- Adverse events and laboratory abnormalities as graded by NCI CTCAE v.4.03;
- Pharmacokinetics parameters of glasdegib;

- QTc interval.

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STUDY DESIGN

This multi-center, open-label Phase 1b study is designed to evaluate the safety, efficacy, PK, and PD of glasdegib when combined with azacitidine in patients with previously untreated Higher-Risk MDS, AML, and CMML. The study includes two components: (a) a safety LIC, and (b) an expansion population with two cohorts.

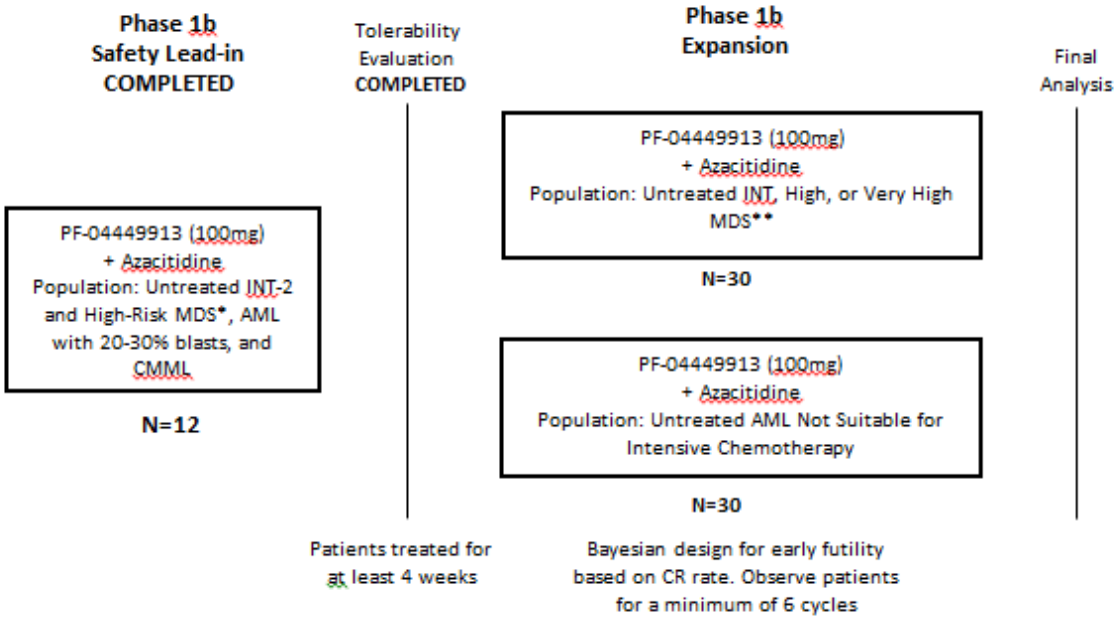
Safety Lead-In Cohort

As of 23 September 2015, a LIC of 12 patients with previously untreated Intermediate-2 or High-Risk MDS per IPSS (n=7), AML with 20-30% blasts and multi-lineage dysplasia (n=3), erythroleukemia (n=1), and CMML (n=1) were enrolled, and received open-label treatment with glasdegib at a starting dose of 100 mg QD given orally in combination with azacitidine at a starting dose of 75 mg/m^2 /day given subcutaneously (SC) for 7 consecutive days every 28 days. The purpose of this component of the study was to determine whether the combination had an acceptable safety and tolerability profile. Based on data collected in the safety LIC, an internal safety review team determined that the safety profile of gladegib in combination with azacitidine in the defined population appeared to be consistent with what was expected for glasdegib or azacitidine alone, with no unexpected toxicities identified, and deemed it acceptable to proceed to the next phase of development. An evaluation of the drug-drug interactions (DDI) potential between glasdegib and azacitidine in this component of the study revealed no evidence of DDI potential and early signs of clinical activity were reported.

Expansion

An open-label expansion consisting of approximately 60 patients with previously untreated Intermediate, High, or Very High risk MDS per IPSS-R (n=30) and AML patients who are not candidates for intensive chemotherapy (n=30). Patients will receive glasdegib at a starting dose of 100 mg QD given orally in combination with azacitidine per local label or per the Investigational Product Manual (or Summary of Product Characteristics [SPC]). Azacitidine may be administered by SC injection or intravenous (IV) infusion at the starting dose of 75 mg/m^2/day for 7 days every 28 days. Alternate dosing schedules to administer the 7 azacitidine doses to accommodate subject and treatment center availability are allowed. The primary objective of the expansion component of the study is to demonstrate that the CR rate of the combination treatment in each patient population is reasonably better than the historical CR rate for azacitidine alone using a Bayesian decision criterion allowing early stopping for futility. Analysis of specific safety criteria will also be performed to evaluate stopping enrollment for a specifc cohort when the rate of pre-defined safety events of interest surpasses a pre-defined threshold.

Figure 1. Schematic of Study Design



*MDS patients enrolled in the safety lead-in component must have Intermediate-2 or High-Risk disease according to IPSS. MDS patients enrolled in the expansion component must have Intermediate, High, or Very High risk disease according to IPSS-R.

Study Assessments

Patients will be followed for efficacy throughout the study by means of bone marrow aspirates. Following study entry, bone marrow biopsies will only be required if adequate bone marrow aspirates are not obtained. A CR or PR needs to be confirmed at least 4 weeks after the bone marrow (BM) evaluation by assessing the stability of improved counts on peripheral blood (PB) according to the 2006 IWG criteria; an additional marrow confirmatory specimen is not required (applies to all patients in the safety LIC and only MDS patients in the expansion component).

Blood counts will be monitored for signs of hematologic improvement (HI) (applies to all patients in the safety LIC and only MDS patients in the expansion component).

Transfusional support (packed red blood cells and platelets) will also be recorded. Timely and complete disease assessments (BM evaluation and peripheral blood (PB) counts) at screening and during the study, whenever clinically indicated, are essential. Failure to perform any of the required disease assessments will result in the inability to determine disease status for that time point and may weaken the study conclusions.

Safety assessments (laboratory, instrumental and clinical) and PK assessments will be performed regularly during the active treatment period in both components of the study.

DDI assessments were performed in the safety LIC component of the study.

PROs of Health-Related Quality of Life (HRQOL) will be assessed in the expansion component of the study.

Please refer to the Schedule of Activities for the Safety Lead-in and the Schedule of Activities for the Expansion: MDS and AML Patients for a complete list of assessments to be performed on patients in the study.

STUDY TREATMENTS

Treatment will be administered in 28-day cycles. Glasdegib will be administered at the starting dose of 100 mg QD given orally and continuously in combination with azacitidine.

Safety Lead-in Cohort

The safety lead-in cohort has been completed.

- All patients will be administered glasdegib-100 mg QD orally and continuously.
- Azacitidine will be administered SC at the starting dose of 75 mg/m^2/day on a continuous schedule from Day 1 to Day 7 of each cycle.

Expansion

- All patients will be administered glasdegib, 100 mg QD orally and continuously.
- Azacitidine will be administered per local label or per the Investigational Product Manual (or SPC). Azacitidine may be administered by SC injection or IV infusion at the starting dose of 75 mg/m^2/day for 7 days every 28 days. Alternate dosing schedules to administer the 7 doses to accommodate patient and treatment center availability are allowed.

Since responses to azacitidine may require 4-6 cycles of administration to emerge, treatment with the study drug combination should be continued for at least 6 cycles, or until unacceptable toxicity, patient refusal, or death, whichever occurs first. If documentation of disease progression occurs within the first 6 cycles of study treatment, the patient **SHOULD NOT** be withdrawn from study treatment if, in the Investigator's judgment, the patient is still likely to receive clinical benefit.

Treatment with the study drug combination should be continued beyond 6 cycles of treatment until objective disease progression or relapse, unacceptable toxicity, patient refusal, or death, whichever occurs first. Treatment should also be continued beyond 6 cycles if patients demonstrate reasonable evidence of clinical benefit, defined as HI or better in patients enrolled into the safety LIC. During the expansion component, clinical benefit will be defined as SD + HI or better in MDS patients, and not meeting the criteria for disease progression for AML patients.

If glasdegib is permanently discontinued for reasons other than objective disease progression, patient refusal, or consent withdrawal, single-agent treatment with azacitidine may be continued if, in the Investigator's judgment, a clinical benefit has been observed and following discussion between the Investigator and Sponsor.

In cases of unacceptable toxicity or pregnancy, the patient must be withdrawn from study drug combination and entered into the follow-up phase of the study.

When study treatment with both drugs (azacitidine and glasdegib) is permanently discontinued, all patients will enter into the follow-up phase.

STATISTICAL METHODS

Approximately 10 patients will be included in the LIC. This sample size provides at least 80% probability to observe at least one adverse event (AE) if the true incidence of the AE in the population is at least 15%.

In the expansion phase of the study, two cohorts of patients (MDS and AML respectively) approximately 30 patients each will be enrolled. Based on Bayesian decision rule, we will need 10 to 30 patients for each cohort. For the MDS cohort, with 30 patients the maximum width of the exact 2-sided 95% confidence interval for CR will be ≤0.374. For the AML cohort, with a maximum of 30 patients the maximum width of the exact 2-sided 95% CI for CR will be ≤0.374. An External Data Monitoring Committee (EDMC) will be established.

Pfizer procedures for periodic safety review will also be applied by an internal safety review team with medical and statistical capabilities to review individual and summary data collected in the safety and clinical databases.

For all efficacy analyses, the safety LIC will be analyzed separately from the expansion component. The two expansion cohorts will be analyzed separately as well. For safety reporting, the data from patients treated with glasdegib + azacitidine in the LIC and expansion components will be reported both separately and together.

Standard plasma PK parameters including the maximum plasma concentration (C_{max}), time to maximum plasma concentration (T_{max}), and area under the plasma concentration versus time curve (AUC) for glasdegib and azacitidine will be estimated using non-compartmental analysis. Population PK analyses may also be performed.

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Data from biomarker assays will be summarized and analyzed separately for the LIC and expansion components using appropriate methods such as Wilcoxon signed rank test. Correlations of biomarker results with PK parameters and measures of anti-cancer efficacy may be examined using Fisher's exact test, logistic regression, Kaplan-Meier analysis, or linear regression. Graphic displays will be presented as appropriate. Biomarker results from the safety LIC and expansion components may also be combined for similar statistical analyses as warranted.

SCHEDULE OF ACTIVITIES

The schedule of activities table provides an overview of the protocol visits and procedures. Refer to the Study Procedures and Assessments sections of the protocol for detailed information on each procedure and assessment required for compliance with the protocol.

The investigator may schedule visits (unplanned visits) in addition to those listed on the schedule of activities, in order to conduct evaluations or assessments required to protect the well-being of the patient.

NOTE: Tables 1 and 2 are applicable ONLY to patients in the lead-in cohort which has been completed.

Table 1. Schedule of Activities for the Safety Lead-in Cohort (LIC)

	Screening	Cycle 1 (28 –day cycle)				Cycle 2 (28–day cycle)		Cycles ≥3 (28 –day cycles)	End of Treatment Visit[27]	Long-term Follow up[29]
Protocol Activity	**(≤28 days from study entry)**	**Day 1**	**Day 2**	**Day 7**	**Day 15**	**Day 1 (±3 days)**	**Day 15 (±3 days)**	**Day 1 (±3 days)**		
Informed Consent[1]	X									
Medical History[2]	X									
ECOG Performance Status[3]	X	X				X		X	X	
Physical Examination[4]	X	X				X		X	X	
Laboratory Studies										
Hematology[5]	X	X		X	X	X	X	X	X	X
Blood Chemistry[6]	X	X		X	X	X	X	X	X	
Urinalysis[7]	X	X				X		X	X	
Coagulation[8]	X	X			X	X	X	X	X	
Pregnancy test[9]	X	X				X		X	X	
Triplicate 12 – lead ECG[10]	X	X	X	X	X	X		X	X	
Registration and Treatment[28]										
Glasdegib[11]			Oral Daily Continuous Dosing							
Azacitidine[12]		SC injection Days 1-7 (Schedule 1) ONLY								
Drug Compliance[13]						X		X	X	

Table 1. Schedule of Activities for the Safety Lead-in Cohort (LIC)

	Screening	Cycle 1 (28 –day cycle)				Cycle 2 (28–day cycle)		Cycles ≥3 (28 –day cycles)	End of Treatment Visit[27]	Long-term Follow up[29]
Protocol Activity	**(≤28 days from study entry)**	**Day 1**	**Day 2**	**Day 7**	**Day 15**	**Day 1 (±3 days)**	**Day 15 (±3 days)**	**Day 1 (±3 days)**		
Disease Assessments										
Bone Marrow biopsy[14]	X									
Bone Marrow Aspirate[14]	X							X	X	X
Bone marrow immunophenotyping and Cytogenetics[19]	X							X	X	
Other Clinical Assessments										
Adverse Event Monitoring[20]		X							X	
Review Prior/Concomitant Treatments[21]	X	X							X	
Recording of red blood cell and platelet transfusions[22]	X	X							X	
PK Sampling										
Blood Samples for PK evaluation[23]		X	X	X	X	X		X		
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Footnote for Schedule of Activities

1. **Informed Consent**: Must be obtained prior to undergoing any study procedure and may occur within 60 days prior to study entry.
2. **Medical History**: Includes cancer history, and prior and concomitant illnesses.
3. **ECOG**: See Appendix 9.
4. **Physical Examination**: Examination of major body systems, body weight, height, and vital signs (blood pressure and heart rate to be recorded in sitting position). Weight must be recorded at Screening and Day 1 of each cycle. Height need not be recorded after the first measurement at screening.
5. **Hematology**: Platelet count, absolute neutrophil count, hemoglobin, and blast count should be obtained twice during the 28-day screening period at least 1 week apart. No need to repeat on C1D1 if one of the 2 screening assessments is performed within **3 days** prior to that date. The list of required laboratory tests is provided in Appendix 8. Patients permanently discontinuing treatment with both study drugs with bone marrow blasts ≤30%, should have CBCs repeated every 3 months until blasts are >30% or until initiation of another anti-cancer therapy.
6. **Blood Chemistry**: No need to repeat on C1D1 if screening assessment performed within **3 days** prior to that date. The list of required laboratory tests is provided in Appendix 8.
7. **Urinalysis**: No need to repeat on C1D1 if screening assessment performed within **3 days** prior to that date. The list of required laboratory tests is provided in Appendix 8.
8. **Coagulation**: No need to repeat on C1D1 if screening assessment performed within **3 days** prior to that date. The list of required laboratory tests is provided in Appendix 8.
9. **Pregnancy Tests**: Pregnancy tests (serum/urine) for patients of child-bearing potential only must be performed on two occasions prior to starting study therapy (once at the start of screening and once at the baseline visit, immediately prior to initiation of treatment (first dose)), every cycle during the active treatment period and at the End of Treatment. Following a negative pregnancy result at screening, appropriate contraception (defined in Section on Lifestyle Guidelines) must be commenced and a further negative pregnancy result will then be required at the baseline visit before the patient may receive the investigational product. It may also be repeated as per request of IRB/ECs (or if required by local regulations), if one menstrual cycle is missed or when potential pregnancy is otherwise suspected during the active treatment period or as clinically indicated.
10. **ECG**: See Table 2 for detailed ECG Schedule.
11. **Glasdegib:** Treatment will be administered in 28-day cycles (cycle duration may be extended to allow for toxicity resolution). Glasdegib will be administered once daily continuously, in the morning at approximately the same time each day. **For Cycle 1 only glasdegib dosing will start on Day 2 to accommodate PK samples collection for DDI assessment**. In all subsequent cycles glasdegib administration will start on Day 1.
12. **Azacitidine Dosing**: Azacitidine will be administered subcutaneously on Days 1-7 of each 28-day cycle in the Safety LIC. The next cycle start can be delayed to allow for toxicity resolution.
13. **Drug Compliance**: All glasdegib bottles including any unused tablets and patient dosing diaries will be returned to the clinic for compliance assessment and drug accountability.

14. Bone Marrow Assessments for Disease Evaluation.
    - Type of Bone Marrow Sample: **For all patients:** a bone marrow aspirate and a biopsy sample are required at screening and will be used for clinical staging. Samples taken prior to consent but within the 28-day window can be used and need not be repeated. Thereafter only bone marrow aspirates are performed for disease evaluation and biopsies are optional unless required for clinical staging (eg, dry tap).
    - Timepoints for Bone Marrow Sampling.
15. MDS/CMML Patients: Bone marrow assessment must be completed at screening (within 28 days of first dose), and on C4D1 (±7 days), and every 3 cycles afterwards (C7D1, C10D1, C13D1 and so on ±7 days), at the EOT, and as clinically indicated.
16. AML Patients: Bone marrow assessment must be completed at screening (within 28 days of first dose). However, if progression is suspected during the screening period an additional BM aspirate should be collected prior first dose of study drug to confirm eligibility. Subsequent aspirates to be collected on C4D1 (±7 days), and every 3 cycles afterwards (C7D1, C10D1, C13D1 and so on ±7 days), at the EOT, and as clinically indicated.
17. If an on-treatment BM assessment is scheduled within 3 weeks from the last dose of G-CSF or GM-CSF growth factor, it should be considered "Not Evaluable" for response assessment and a BM evaluation should be repeated at least 3 weeks from the last dose of growth factor.
18. Patients discontinuing study treatment (Glasdegib and Azacitidine) with bone marrow blasts ≤30 %, should have BM assessments repeated every 3 months until blasts are >30% or until initiation of another anti-cancer therapy.
19. **Bone Marrow Immunophenotyping and Cytogenetics**: Quantitative immunophenotyping and cytogenetics will be conducted on all patients using any scheduled or unscheduled bone marrow samples collected during study participation. Please see Footnote 14 for details on bone marrow samples collection schedule. **Baseline cytogenetics classification must be completed within 28 days of first dose.**
20. **Adverse Event (AE) Assessments**: Adverse events should be documented and recorded at each visit using the NCI CTC AE version 4.03. Patients must be followed for AEs for 28 days after the last treatment administration or until all drug-related toxicities have resolved, whichever is later; or earlier than 28 days should the patient commence another anticancer therapy in the meantime. For serious adverse events (SAEs), the active reporting period to Pfizer or its designated representative begins from the time that the patient provides informed consent, which is obtained prior to the patient's participation in the study, (ie, prior to undergoing any study related procedure and/or receiving investigational product), through and including 28 calendar days after the last administration of the investigational product. Serious adverse events occurring to a patient after the active reporting period has ended should be reported to the sponsor if the investigator becomes aware of them; at a minimum, all serious adverse events that the investigator believes have at least a reasonable possibility of being related to study drug are to be reported to the sponsor.
21. **Concomitant Medications and Treatments**: All concomitant medications and treatments should be recorded in the CRF.
22. **Red Blood Cells and Platelets Transfusion Recording**: Transfusion history up to 24 weeks prior to screening should be recorded. All red blood cell and platelet transfusions, including date of **each** transfusion and number of red blood cell and platelet units transfused will be recorded while on treatment. Note that number of units, not number of bags, must be recorded.
23. **Blood samples for PK Evaluation:** See detailed information in Table 2 for PK timepoints.

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27. **End of Treatment**: Obtain these assessments if not completed in the last week (last 3 months for BM assessments, unless the patient is coming off study treatment for disease progression).

28. **Patient Registration**: Patient registration and assignment of treatment will be obtained from the centralized Interactive Response Technology (IRT).

29. **Long-term Follow-Up**: At least 28 days, and no more than 35 days after discontinuation of treatment patients will return to undergo review of concomitant medications and assessment for resolution of any treatment related toxicity. Patients continuing to experience toxicity at this point following discontinuation of treatment will continue to be followed at least every 4 weeks until resolution or determination, in the clinical judgment of the Investigator, that no further improvement is expected. Patients will be contacted every 3 months to confirm survival status and collect information on any new anti-cancer therapy initiated. Telephone calls are acceptable and patients will be followed up to death or withdrawal of consent. Patients who have discontinued study treatment (Glasdegib and Azacitidine) and are starting the study long-term follow-up phase with ≤30% BM blasts should have also disease assessments (BM aspirate and PB sampling) repeated every 3 months until blasts are >30% or until initiation of another anti-cancer therapy.

NOTE: Tables 1 and 2 are applicable ONLY to patients in the lead-in cohort which has been completed.

Table 2. Pharmacokinetics and ECG Schedule for the Safety Lead-in Cohort (LIC)

Dose Day	**Screening**	**Cycle 1, Day 1**							**Cycle 1 Day 2**		**Cycle 1, Day 7&15 (azacitidine samples taken only on C1D7)**								**Cycles ≥2 Day 1**			**EOT**
HOUR(s) post-dose		**0[1]**	**0.25**	**0.5**	**1**	**2**	**4**	**6**	**1**	**4**	**0[1]**	**0.25**	**0.5**	**1**	**2**	**4**	**6**	**24**	**0[1]**	**1**	**4**	**0**
Glasdegib PK Samples									X	X	X	X		X		X	X	X	X	X	X	
Azacitidine PK Samples			X	X	X	X		X			X	X	X	X	X		X					
Triplicate 12-lead ECG[2]	X	X							X	X				X		X			X	X	X	X

1. **PK sample collection:** In all instances, "0 hour" represents a pre-dose collection. The PK sample should be collected within 30 minutes prior to dose administration. Patients should be reminded not to take their study drug prior to arriving at the clinic on protocol scheduled visits. The PK time points for each compound (Azacitidine and Glasdegib) are in reference to their respective dosing times. PK samples should only be collected up until Cycle 6.

2. **Triplicate 12 lead ECGs:** At each time point, 3 consecutive supine 12 lead ECGs will be performed approximately 2 minutes apart to determine mean QTc interval. ECGs will be collected: prior to blood sample collection, such that the blood sample is collected at the appropriate time. All ECG timepoints are in reference to dosing of glasdegib.

Table 3. Schedule of Activities for the Expansion: MDS and AML Patients

	Screening	Treatment				Post Treatment	
		Cycle 1 (28 –day cycle) (±3 day time window)			Cycles ≥2 (28 –day cycles) (-3/+14 day time window)	End of Treatment Visit[29]	Long-Term Follow-Up Activity Log[30]
Protocol Activity	**(≤28 days prior to C1D1)**	**Day 1**	**Day 7 (±3 days)**	**Day 15 (±3 days)**	**Day 1 (-3/+14 days)**	**(Within 14 days after last dose)**	
Informed Consent[1]	X						
Medical History[2]	X						
ECOG Performance Status[3]	X	X			X	X	
Disease Classification[4]	X						
Physical Examination[5]	X	X			X	X	
Laboratory Studies							
Hematology[6]	X	X	X	X	X	X	
Blood Chemistry[7]	X	X	X	X	X	X	
Urinalysis[8]	X						
Coagulation[9]	X						
Pregnancy Test/Contraception Reminders[10]	X	X			X	X	
Triplicate 12 – Lead ECG[11]	X	X		X	X	X	
Registration and Treatment[12]							
Glasdegib[13]		Oral Once Daily Continuous Dosing					
Azacitidine[14]		SC injection or IV infusion Days 1-7 (±3 day time window applicable to each dose) per local label or per the Investigational Product Manual (or SPC)[14]					
Drug Compliance[15]					X	X	
Disease Assessments							
Bone Marrow Aspirate/Biopsy[16]	X				X-See Footnote 16	X	
Bone Marrow Genetics[16,17]	X				X-See Footnote 16	X	
Other Clinical Assessments							
Adverse Event/Serious Adverse Event Monitoring[18]	X	X				X	
Review Prior/Concomitant Treatments[19]	X	X				X	

	Screening	Treatment				Post Treatment	
		Cycle 1 (28 –day cycle) (±3 day time window)			Cycles ≥2 (28 –day cycles) (-3/+14 day time window)	End of Treatment Visit[29]	Long-Term Follow-Up Activity Log[30]
Protocol Activity	**(≤28 days prior to study entry)**	**Day 1**	**Day 7 (±3 days)**	**Day 15 (±3 days)**	**Day 1 (-3/+14 days)**	**(Within 14 days after last dose)**	
Recording of Red Blood Cell and Platelet Transfusions[20]	X	X				X	
CCI							
PGIS[21,30]		X	X	X	X	X	X
PGIC[21,30]			X	X	X	X	
Pharmacokinetic Sampling							
Blood samples for glasdegib PK[22]	Refer to Table 4 Pharmacokinetics & ECG Schedule for the Expansion: MDS and AML Patients Only						
CCI							
CCI							

	Screening	Treatment				Post Treatment	
		Cycle 1 (28 –day cycle) (±3 day time window)			Cycles ≥2 (28 –day cycles) (-3/+14 day time window)	End of Treatment Visit[29]	Long-Term Follow-Up Activity Log[30]
Protocol Activity	**(≤28 days prior to study entry)**	**Day 1**	**Day 7 (±3 days)**	**Day 15 (±3 days)**	**Day 1 (-3/+14 days)**	**(Within 14 days after last dose)**	
Follow Up Assessments							
Disease progression post treatment[30]							X
New anti-cancer therapies since discontinuation of study treatment[30]							X
Survival Follow-Up Telephone contact[30]							X

1. **Informed Consent:** Must be obtained prior to undergoing any study procedure. Informed consent document may be signed up to 60 days prior to study entry.
2. **Medical History**: Includes cancer history, and prior and concomitant illnesses.
3. **ECOG Performance Status:** See Appendix 9.
4. **Disease Classification**: MDS or AML by WHO 2016 classification (Appendix 17). For MDS patients only: Intermediate, High, or Very High Risk per the International Prognostic Scoring System Revised (IPSS-R) (Appendix 10). For AML patients only: Prognostic system using 2017 European Leukemia Net (ELN) criteria (Appendix 16).
5. **Physical Examination:** Examination of major body systems (includes general appearance, head, neck, lungs, heart, abdomen, musculoskeletal, extremities, skin, lymph nodes, neurological), body weight, height, and vital signs (blood pressure and heart rate to be recorded in sitting position). Weight must be recorded at Screening, Day 1 of each cycle, and End of Treatment. Height need not be recorded after the first measurement at screening.
6. **Hematology:** No need to repeat on C1D1 if screening assessment performed within 3 days prior to that date. The list of required laboratory tests is in Appendix 8.
7. **Blood Chemistry:** No need to repeat on C1D1 if screening assessment performed within 3 days prior to that date. The list of required laboratory tests is in Appendix 8.
8. **Urinalysis:** Should be performed after Screening if clinically indicated. The list of required laboratory tests is in Appendix 8.
9. **Coagulation:** Should be performed after Screening if clinically indicated. The list of required laboratory tests is in Appendix 8.
10. **Pregnancy Tests/Contraception Reminders**: Pregnancy tests (serum/urine) for patients of child-bearing potential only must be performed on two occasions prior to starting study therapy (once at the start of screening and once at the baseline visit, immediately prior to initiation of treatment (first dose), every cycle during the active treatment period and at the End of Treatment. Following a negative pregnancy result at screening, appropriate contraception for males and females (Refer to Section 4.3) must be commenced and a further negative pregnancy result will then be required at the baseline visit before the patient may receive the investigational product. It may also be repeated as per request of IRB/ECs (or if required by local regulations), if one menstrual cycle is missed or when potential pregnancy is otherwise suspected during the active treatment period or as clinically indicated.
11. **ECGs**: See Table 4 for detailed ECG Schedule.

12. **Patient Registration:** Patient registration and assignment of treatment will be obtained from the centralized Interactive Response Technology (IRT).
13. **Glasdegib Dosing**: Treatment will be administered in 28-day cycles (cycle duration may be extended to allow for toxicity resolution). Glasdegib will be administered once daily, continuously, in the morning at approximately the same time each day.
14. **Azacitidine Dosing:** Azacitidine will be administered per local label or per the Investigational Product Manual (or SPC). Treatment can be administered as a SC injection or IV infusion on Days 1-7 (±3 days). Visit time window added to accommodate varying azacitidine dosing schedules to accommodate patient and treatment center availability. The start of subsequent cycles can be delayed to allow for toxicity resolution.
15. **Drug Compliance:** All glasdegib bottles including any unused tablets and patient dosing diaries will be returned to the clinic for compliance assessment and drug accountability.
16. **Bone Marrow Assessments for Disease Evaluation.**
    - **Type of Bone Marrow Sample:** For all patients, a bone marrow aspirate sample is required at every disease evaluation, and will be used for both local clinical staging and centralized biomarker assessments. Bone marrow biopsies are optional unless required for clinical staging (eg, dry tap). Samples taken prior to consent but within the 28-day window may be used for disease evaluation and need not be repeated. Bone marrow samples required for other study assessments (eg, MRD assessment) must be collected after consent is signed. We recommend, but do not require, patients sign an informed consent prior to a diagnostic bone marrow aspiration to avoid an additional procedure to collect bone marrow aspirate for the biomarker assessments required during screening
    - **Timepoints for Bone Marrow Sampling:** Bone marrow assessment must be completed at screening (within 28 days prior to first dose), C7D1 (-3/+14 days) (unless done earlier due to suspected CR), C13D1 and every 12 cycles thereafter (C25D1, C37D1, C49D1, etc), and at any time as per investigators discretion if CR is suspected. No bone marrow assessment is necessary if non-response or progressive disease can be diagnosed from peripheral blood evaluation or radiological/clinical assessment.
17. **Bone Marrow Genetics**: Genetics analysis (local), including karyotyping, will be conducted on all patients using any scheduled or unscheduled bone marrow samples collected during study participation. Genetics to be analyzed are specified in Appendix 3 for MDS patients and Appendix 16 for AML patients. Baseline genetics classification must be completed on a sample collected within 28 days prior to first dose.
18. **Adverse Event (AE)/Serious Adverse Event (SAE) Monitoring**: Adverse events should be documented and recorded at each visit using the NCI CTCAE version 4.03. Recording of AEs/SAEs on the CRF commences with informed consent. Patients must be followed for AEs for 28 days after the last treatment administration or until all drug related toxicities have resolved, whichever is later; or earlier than 28 days should the patient commence another anticancer therapy in the meantime. For serious adverse events (SAEs), the active reporting period to Pfizer or its designated representative begins from the time that the patient provides informed consent, which is obtained prior to the patient's participation in the study, (ie, prior to undergoing any study related procedure and/or receiving investigational product), through and including 28 calendar days after the last administration of the investigational product, even if another anticancer therapy has been started. Serious adverse events occurring to a patient after the active reporting period has ended should be reported to the sponsor if the investigator becomes aware of them; at a minimum, all serious adverse events that the investigator believes have at least a reasonable possibility of being related to study drug are to be reported to the sponsor.
19. **Concomitant Medications and Treatments**: All concomitant medications and treatments should be recorded in the CRF.
20. **Red Blood Cells and Platelets Transfusion Recording:** Transfusion history up to 8 weeks prior to screening should be recorded. All red blood cell and platelet transfusions, including date of each transfusion and number of red blood cell and platelet units transfused will be recorded while on treatment. Note that number of units not number of bags must be recorded.

CCI [redacted]

22. **Blood samples for glasdegib PK:** See detailed information in (Table 4) for specific time points.

CCI [redacted]

CCI [redacted]

CCI [redacted]

CCI [redacted]

CCI [redacted]

CCI [redacted]

29. **End of Treatment:** Obtain these assessments if not completed in the last week (last 3 months for BM assessments, unless the patient is coming off study treatment for disease progression). Patients continuing to experience toxicity following discontinuation of treatment will be followed by the Investigator at least every 4 weeks until resolution or determination, in the clinical judgment of the investigator, that no further improvement is expected.

30. **Follow Up Activity Log: Survival Follow-Up Telephone contact, New Anti-cancer therapies since discontinuation of study treatment, and Disease progression:** A follow-up contact (can be by phone) per Section 6.4 should occur at least 28 calendar days, and up to 35 calendar days after the last administration of the investigational product to capture any potential adverse events (Section 6.4). Appropriate contraception useage for at least 180 days after the last dose of investigational product is to be confirmed. Patients will be contacted by telephone every 3 months starting from the last dose of study medication to confirm survival status, collect information on any new anti-cancer therapies initiated and record date of post-treatment disease progression. CCI [redacted] Patients receiving at least one dose of study treatment will be followed for survival for up to 2 years from the first visit of the last patient enrolled in the expansion component, or until death, lost to follow up, or consent withdrawal.

CCI [redacted]

Table 4. Pharmacokinetics & ECG Schedule for the Expansion: MDS and AML Patients

Assessment	Screening	Cycle 1, Day 1			Cycle 1, Day 15			Cycle 2-3, Day 1[3]			Cycles ≥4, Day 1	End of treatment
HOUR post-dose[1]		**0[1]**	**1**	**4**	**0[1]**	**1**	**4**	**0[1]**	**1**	**4**	**1**	
Gladegib PK Plasma Samples			X	X	X	X	X	X	X	X		
Triplicate 12-lead ECG[2]	X	X	X	X	X	X	X	X	X	X	X	X

1. **Glasdegib PK Sample Collection:** In all instances, "0 hour" represents a pre-dose collection. The PK sample should be collected within 30 minutes prior to dose administration. All post-dose samples are to be collected within 10% of the nominal time (eg, within 6 minutes of a 60 minute sample). Patients should be reminded not to take their study drug prior to arriving at the clinic on protocol scheduled visits. All PK timepoints are in reference to dosing of glasdegib.
2. **Triplicate 12-Lead ECGs:** At each time point, 3 consecutive supine 12-lead ECGs will be performed approximately 2 minutes apart to determine mean QTc interval. ECGs will be collected: prior to blood sample collection, such that the blood sample is collected at the appropriate time. All ECG timepoints are in reference to dosing of glasdegib). A 15 min window for each ECG collection is allowed around the nominal ECG time point.
3. PK samples to be collected only on Cycle 2 Day 1.

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

APPENDICES

1. INTRODUCTION

Glasdegib (PF-04449913) is a novel small molecule inhibitor of the Sonic Hedgehog (Hh) pathway which is currently under development for the treatment of hematologic malignancies.

This multi-center open-label Phase 1b study is designed to evaluate the safety, efficacy, pharmacokinetics (PK), and pharmacodynamics (PD) of glasdegib when combined with azacitidine in patients with previously untreated Higher-Risk Myelodysplastic Syndrome (MDS), Acute Myeloid Leukemia (AML), and Chronic Myelomonocytic Leukemia (CMML). This Phase 1b study includes two components: (a) a safety lead-in cohort (LIC) and (b) an expansion phase with two cohorts.

1.1. Indication

Safety Lead-In Cohort

Previously untreated adult patients with Intermediate-2 or High-Risk MDS according to the International Prognostic Scoring System (IPSS), AML with 20%-30% blasts and multi-lineage dysplasia, (according to World Health Organization (WHO) 2008 classification), and CMML.

Expansion

- Previously untreated adult patients with Intermediate, High, or Very High risk MDS according to the International Prognostic Scoring System-Revised (IPSS-R), and
- AML patients who are not candidates for intensive chemotherapy (according to WHO 2016 classification).

1.2. Background and Rationale

1.2.1. Disease Overview

MDS is comprised of a heterogeneous group of myeloid disorders defined by a set of common features, of which the most prominent is morphologic bone marrow and peripheral blood dysplasia associated with inefficient hematopoiesis, peripheral cytopenias, and increased risk of transformation to AML.

The incidence of MDS was previously estimated to be around 4–5 per 100,000 annually worldwide, with the prevalence increasing with age.[1] An older publication based on the Surveillance, Epidemiology, and End Results (SEER)–Medicare database, indicated that in the US the incidence of MDS in individuals aged ≥65 years might be as high as 75 per 100,000.[2] A recent analysis published in 2015 estimates the true incidence of MDS to be between 5.3 and 13.1 per 100,000 using newer case capture methods. Medicare claims data in the US shows the incidence of MDS in patients aged ≥65 years to now be as high as 162 per 100,000. MDS prevalence is estimated to be 60,000 and –170,000 in the United States of America (USA) and projected to increase (Cogle et al, 2015).[50]

Genetic and functional studies have demonstrated that MDS results from the acquisition of genetic and epigenetic alterations leading to abnormal differentiation and dysregulated self-renewal. Recent data indicate that cytogenetic patterns are not stable in MDS, and that as the disease progresses a significant fraction of patients acquire additional cytogenetic changes. This phenomenon is associated with an increased risk of transformation to AML and a worse overall survival.[3]

The French-American-British (FAB) 1982 classification system provided the first approach allowing a reliable diagnosis of the MDS group of diseases, previously termed pre-leukemia.[4]

In 2001[5] and subsequently in an updated version in 2008,[6] a group of clinicians, pathologists and cytogeneticists formulated the WHO classification of hematopoietic neoplasms. The principal modifications with respect to the FAB classification were to consider patients with 20% or more bone marrow or peripheral blood blasts as having AML, and to remove the CMML subtype and place it into a newly created category termed Myelodysplastic/ Myeloproliferative Neoplasms (MDS/MPN). The WHO 2008 version was used to classify patients in the safety LIC component of the current study. The WHO classification was recently updated again in 2016, providing more evidence on the impact of genetic markers on diagnosis and disease management and will be used to classify the MDS patients in the expansion component of the current study (Arber et al, 2016).[51]

Independent of the classification system applied, MDS prognosis is established by assessing key features that include: morphology, percentage blasts, cytopenias and cytogenetic characteristics. According to the 4 category International Prognostic Scoring System (IPSS), the higher-risk MDS group (Intermediate-2 and High-Risk) is characterized by a median overall survival of less than 12 months and by a high risk of transformation to AML.[8] The IPSS has been updated to the International Prognostic Scoring System-Revised (IPSS-R) via incorporation of additional elements of cytogenetics and further prognostication into 5 categories (Greenberg et al, 2012).[43] Patients enrolled into the safety LIC of the study were assessed using IPSS and patients enrolled into the expansion component of the study will be assessed using the more contemporary IPSS-R (Appendix 10). The inclusion of the IPSS-R risk of intermediate, high, or very high, has a concordance greater than 80% with the old IPSS scoring system.[43]

AML is a genetically heterogeneous hematologic malignancy characterized by increased blast counts, pancytopenias causing infections and bleeding, multiple mutations and epigenetic dysregulation at the time of diagnosis that evolves with treatment, resulting in treatment resistance, disease relapse, and reduced survival. Elderly AML patients ineligible for intensive chemotherapy present with many more comorbidities, a greater number of chromosomal abnormalities, and higher incidence of prior hematologic diseases as compared to AML patients able to receive intensive chemotherapy resulting in fewer treatment options, lower remission rates and poor survival outcomes. It is estimated that there will be 21,380 new cases and 10,500 deaths from AML in the United States in 2017.[44]

There are two staging systems commonly used for AML. The original FAB 1976 system provided the first approach at the morphologic classification of acute leukemias to define specific immunotypes, which has since been revised several times. The newer WHO 2008 classification system looked at chromosome translocations and evidence of dysplasia. In 2016, the WHO classification system was revised, providing more evidence on the impact of genetic markers on diagnosis and disease management and will be used to classify the AML patients in the expansion component of the current study (Arber et al, 2016).[51]

AML is a disease with large differences in prognosis, age and cytogenetic abnormalities constituting the strongest prognostic factors for OS (Röllig et al, 2011).[52] In 2011, the European LeukemiaNet (ELN) proposed a risk reporting system that integrated molecular and cytogenetic factors, dividing AML patients into 4 risk categories (favourable, intermediate-1, intermediate-2, adverse), demonstrating that these groups varied in terms of median survival times. Historical median OS for patients ≤60 years who did not receive an allogeneic stem-cell transplant by risk group are as follows: favorable (63.6 months), intermediate-1 (13.6 months), intermediate-2 (18.7 months), and adverse (6.0 months) (Röllig et al, 2011).[52] Historical mOS for patients >60 years by risk group are as follows: favorable (14.6 months), intermediate-1 (9.5 months), intermediate-2 (9.2 months), and adverse (4.8 months) (Röllig et al, 2011).[52] The ELN system was recently updated in 2017 to include new clinical, prognostic, morphologic, immunophenotypic, and genetic data that emerged over the last 6 years. In the revised system, the intermediate-1 and intermediate-2 risk groups are collapsed into one since they were prognostically indistinguishable in elderly patients, resulting in 3 risk categories (favourable, intermediate, adverse) (Döhner H et al, 2017).[42] In addition, the ELN group proposed new response categories (Appendix 11) for AML patients reflective of new data meant to integrate definitions across trials. The AML population proposed in the expansion component of the current study will be categorized by the 2017 ELN system and assessed by the updated response categories.

1.2.2. Hedgehog (Hh) Pathway Signaling in MDS

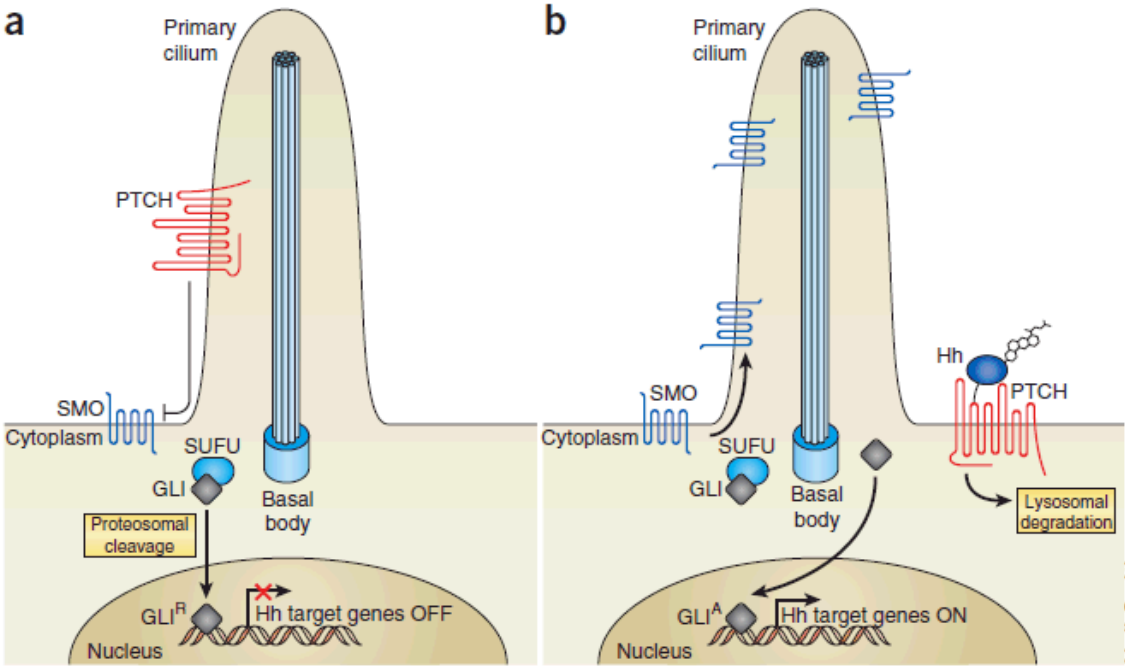
A milestone in perceiving cancer as a disorder of differentiation and development was the identification of cancer stem cells that self-renew, initiate, and re-initiate tumor development and give rise to the bulk of the tumor. The persistence of such tumor-initiating cells may contribute to tumor resistance and impact overall survival. Standard chemotherapy, radiotherapy and targeted therapies reduce tumor bulk, but are less effective at targeting tumor-initiating cells. The key challenge has been to identify the molecular mechanisms maintaining and sustaining tumor-initiating cell activity, self-renewal and survival.

Hh signaling is critical in animal patterning and terminal cell differentiation during embryogenesis, and may play a key role in human malignancies when aberrantly activated. Following birth, the Hh pathway is repressed in most cells, but activated during tissue repair and in self-renewing populations. Hh signaling is initiated when the Hh ligands: Indian Hh (Ihh), Sonic Hh (Shh), and/or Desert Hh (Dhh) bind to the Patched (PTCH) transmembrane protein and inactivate its function, which in the absence of Hh is to tonically inhibit SMO signal transduction. Following deactivation of PTCH in response to the binding of Hh

ligands, the seven-transmembrane protein Smoothened (SMO), which is normally held in an inactive state by PTCH, is released and activates a signaling cascade that regulates the Gli family of transcription factors (Figure 2). The Gli family of genes encode proteins that function either as transcriptional repressors (in the absence of Hh), or as transcriptional activators (in the presence of Hh) of genes controlled by the Hh pathway. Several proteins modulate the ratio of Gli activator (GliA) to Gli repressor (GliR) activity and in so doing determine the level of active cellular Hh ligand (Figure 2).[9]

Since its initial description, the Hh pathway has received increasing attention as a pleiotropic oncogenic pathway, and its aberrant activity has been implicated in both hematopoietic and solid tumor malignancies through a range of different mechanisms, including a direct cell cycle and anti-angiogenic effect.[10,11] Given that these cell types and mechanisms are unrelated in developmental origin, site, and function, a common dependence of tumor-initiating cells on Hh-Gli signaling for survival and self-renewal, paralleling its roles in normal development and homeostasis, may underlie its involvement in human cancers.[12] An important caveat, is that the Hh signaling pathway is dispensable for adult hematopoietic stem cell function.[13]

Figure 2. Hh Signaling Pathway



The expression of Hh-related genes has been assessed in primary human $CD34^+$ cells, $CD34^+$ blastic cells (from MDS and AML patients) and BM stromal cells. Both Ihh and its signal transducer SMO, were expressed in $CD34^+$ AML and MDS-derived cells. Moreover the expression of the intrinsic Hh-signaling inhibitor, human Hh-interacting protein (HHIP) was markedly lower in AML/MDS-derived stromal cells as compared with healthy donor-derived stromal cells. Furthermore, in vitro treatment with azacitidine rescued the HHIP expression

via demethylation of HHIP gene and reduced the leukemic cell-supporting activity of AML/MDS-derived stromal cells.[14] These data demonstrate the relevance of Hh signaling in primary $CD34^+$ blasts derived from AML and MDS and confirm its involvement in shaping the BM microenvironment during the development of myeloid malignancies.

Furthermore, over-expression of the Hh signaling target gene BMI1 was detected in MDS patients, and inversely correlated with the apoptosis of $CD34^+$ cells. In addition, over-expression of BMI1 was correlated with an elevated IPSS score and a shorter overall survival in MDS patients, facilitated proliferation, and inhibited apoptosis of MDS cells in vitro. This suggests that over-expression of BMI1, a target of the Hh signaling pathway, induces resistance to apoptosis and confers an adverse prognosis in MDS.[15]

Finally, the role of the Hh signaling pathway was investigated in total BM and in $CD34^+$ cells from MDS patients and healthy donors. PTCH and SMO showed decreased expression in MDS $CD34^+$ cells, whereas GLI1 overexpression was observed, indicating pathway activation in MDS progenitors.[16]

In nonclinical AML models, SMO, acting via its effector GLI2, has been implicated in the maintenance of LSC dormancy and associated resistance to chemotherapy and targeted therapy, while inhibition of SMO via glasdegib can cause LSCs to re-enter the cell cycle (Sadarangani, 2015; Tauchi, 2015; Fukushima, 2016).[54,55,53] Recrudescence of LSCs is prevented in preclinical hosts pre-treated with Hh pathway inhibitors, including glasdegib (Fukushima et al, 2016). Consistent with these effects, glasdegib sensitized AML cells to cytosine arabinoside, and abrogated resistance to cytosine arabinoside in AML cells co-cultured with stromal cells (Fukushima, 2016).[53]

In a preclinical MDS model, blocking the Hh pathway with SMO inhibitors in combination with the hypomethylating agent (HMA) azacitidine (Aza) generated synergy in vitro with growth inhibition in primary malignant myeloid cells ex vivo (Tibes, 2015).[56] Hh inhibition in combination with HMAs represents a mechanistically attractive approach for the elimination of the LSC population, while at the same time targets the deregulated gene expression in patients with higher-risk MDS. Taken together these results suggest that the Hh signaling pathway is frequently aberrantly activated in MDS patients and its inhibition represents an attractive therapeutic approach to improve disease control.

1.2.3. Rationale for Glasdegib/Azacitidine Combination Therapy in Patients with Higher-Risk MDS, AML, and CMML

Treatment of higher risk (Intermediate-2 and High-Risk) MDS and AML with 20-30% blasts and multi-lineage dysplasia, has typically been based on intensive chemotherapy using anthracycline and cytarabine (Ara-C) combinations. This has resulted in lower CR rates and shorter CR duration with respect to that observed in primary AML.[2,17]

In response to this unmet medical need, several multicenter randomized studies have compared treatment with a HMA treatment to supportive care in MDS patients, including the D-0007 (decitabine), AZA-001 (azacitidine), CALGB-9221 (azacitidine), and EORTC-06011 (decitabine) trials. These trials have demonstrated delayed progression to AML following HMA therapy, with an improvement in median PFS over supportive care ranging from 3 to 8 months.[18-21]

Indeed, MDS is characterized by frequent epigenetic abnormalities, including the hypermethylation of genes that control proliferation, adhesion, and other characteristic features of this pre- leukemic status. Aberrant deoxyribonucleic acid (DNA) hypermethylation is associated with a poor prognosis in MDS that can be accounted for by a more rapid progression to AML.[39]

Azacitidine was approved in the US by the Food and Drug Administration (FDA) in 2004 for the treatment of all MDS subtypes according to the FAB classification. Effectiveness was demonstrated in a randomized trial comparing azacitidine with best supportive care (BSC) and in two single-arm studies. The overall response rate (complete response + partial response) observed in the randomized study CALGB-9221 was 15.7% in the azacitidine treatment arm and there were no responders in the control arm (P <0.0001). The median duration of overall survival did not significantly differ between patients receiving azacitidine and those receiving supportive care, although the results were confounded by 49 best supportive care patients (53%) that crossed over to azacitidine during the course of the trial. In a landmark analysis designed to eliminate this confounding effect, the median duration of overall survival was significantly longer in patients initially randomized to azacitidine as compared with those initially randomized to supportive care who did not cross over to azacitidine or who crossed over after 6 months had elapsed (18 versus 11 months; p = 0.03).[21]

Results published in 2009 from the international AZA-001 phase 3 randomized trial comparing azacitidine to conventional care regimens (CCR), including BSC, low dose cytarabine (LDAC) and intensive chemotherapy, in 358 intermediate-2 and high-risk MDS patients presented additional data to suggest an overall survival benefit. Despite a low CR rate (17%), azacitidine treatment significantly prolonged OS with respect to CCR. Median OS was 24.5 months (9.9–not reached) for the azacitidine arm versus 15.0 months (5.6–24.1) for the CCR arm (hazard ratio 0.58; 95% CI 0.43–0.77). A significantly lower risk of progression to AML (HR=0.50, 95% CI 0.35–0.70; p<0.0001) was also observed with azacitidine as compared with CCR, and transfusion independence was achieved more frequently in the azacitidine arm.[18] Based on the results of this trial, azacitidine was approved in European Union for the treatment of adults who are not eligible for HSCT and have Intermediate-2 or High-Risk MDS, CMML with 10-29% marrow blasts without myeloproliferative component, and AML with 20-30% blasts and multi-lineage dysplasia, (according to the WHO 2008).

An important observation from the AZA-001 study was that the achievement of CR is not a prerequisite for increased OS. Indeed, the results of this trial demonstrated that patients who achieved hematologic improvement (HI) (based on the International Working Group (IWG) 2000 criteria for MDS) but never attained complete or partial response still obtained a survival benefit.[18]

Azacitidine has become the standard of care in front line higher risk MDS and AML patients with 20-30% blasts and multi-lineage dysplasia, although it is not curative. Continued treatment with azacitidine is necessary in order to maintain clinical responses and following failure of the azacitidine treatment, life expectancy among MDS patients is short with a median survival of less than 6 months.[22] As a result of these limitations, combination treatments of investigational agents with an HMA as a backbone are currently under investigation.[23]

AML is a genetically heterogeneous hematologic malignancy characterized by multiple mutations and epigenetic dysregulation at the time of diagnosis that evolves with treatment, resulting in treatment resistance, disease relapse, and reduced survival.

In 2015, results from the international randomized phase 3 AZA-AML trial comparing azacitidine to CCRs in patients aged ≥ 65 years with newly diagnosed or secondary AML with >30% bone marrow blasts demonstrated a clinically meaningful improvement in mOS in the azacitidine arm of 10.4 months (95% CI, 8.0-12.7) vs 6.5 months (95% CI, 5.0-8.6) in the CCR arm (HR=0.85; 95% CI, 0.69-1.03; stratified log-rank p=0.1009), although the primary endpoint was not met. The CR rate in the azacitidine arm was lower than the CCR arm (19.5% vs 21.9%). The 1-year survival rate with azacitidine was 46.5% compared with 34.2% with conventional therapy (95% CI, 3.5%-21.0%; Dombret et al, 2015).[57] Based on the observed survival benefit, the EU expanded the approval of azacitidine in AML to adult patients aged 65 years or older who are not eligible for HSCT with >30% myeloblasts according to the WHO classification; previously, the indication covered AML patients with <30% blasts. Despite the modest increase in mOS and low CR rate, azacitidine is the currently the standard of care for AML patients not suitable for intensive chemotherapy. New treatments are needed to improve outcomes in this older AML population.

Preliminary efficacy data from the safety LIC of the current study which enrolled patients with high risk MDS per IPSS, AML with 20-30% blasts and multi-lineage dysplasia, and CMML, treated with glasdegib 100 mg PO Qday in combination with azacitidine, showed 5 patients responded: 3 patients with CR, 2 patients with marrow mCR. Of note, after the data cutoff date, the complete blood count of 1 of the patients with mCR had normalized, consistent with CR. Of the 5 patients who responded, 4 responses occurred on or before Day 100. Of the 4 patients with CR (including the mCR patient who achieved a CR after the data cutoff date), 3 patients had AML (75% CR rate vs the historical control for azacitidine alone, 19.5%) and 1 patient had MDS (14% CR rate vs the historical control for azacitidine alone, 17%). A further 4 patients had SD. No evidence of drug-drug interaction (DDI) was noted. As of September 2016, mOS had not been reached. In the Phase 1b part of Study B1371003, 52 patients with previously untreated AML or higher risk MDS were treated with glasdegib 100 mg or 200 mg PO Qday in combination with low dose cytarabine (LDAC) (n=23),

decitabine (n=7), or 7 + 3 (n=22). Of the AML patients treated in combination with decitabine, 2/5 (40%) responded (1 CR and 1 complete response with incomplete blood count recovery [CRi]). Of the high-risk MDS patients treated in combination with decitabine, 2/2 responded (2 mCR). Median OS in the combined AML and MDS patients were 4.4 months, 11.5 months (vs historical mOS of 7.7 months with decitabine alone), and 34.7 months respectively in the 3 treatment arms. A similar population of newly diagnosed elderly AML patients was enrolled into a Phase 3 study of decitabine vs supportive care vs LDAC where the CR+ CRi rate was 25.6% in the decitabine only arm.

In the Phase 2 portion of Study B1371003, a prospective, randomized (2:1), open-label clinical trial in 132 previously untreated AML patients not suitable for intensive chemotherapy based on age or other risk factors and higher risk MDS, the addition of glasdegib 100 mg orally PO Qday to LDAC vs LDAC alone resulted in a significant improvement in OS (mOS 8.8 months (80% CI: 6.9, 9.9) vs 4.9 months (80% CI: 3.5, 6.0); hazard ratio [HR] 0.513 [80 % CI: 0.394-0.666]; 1-sided p-value=0.0004). In addition, the CR/CRi rate for AML patients in the glasdegib + LDAC arm was higher than the LDAC alone arm (25% [80% CI: 19.1, 30.9] vs 4.5% [80% CI: 0.5, 8.6]). When glasdegib was combined with treatments commonly used in patients with higher risk MDS and AML not suitable for intensive chemotherapy (azacitidine, decitabine, and LDAC), improvements in response rates and OS in the context of historical controls were observed.

The target population in the safety LIC for this study was aligned with the AZA 001 trial, which addressed changes in the FAB and WHO 2008 MDS classifications systems. The population included Intermediate-2 and High-Risk MDS according to IPSS, AML 20-30% BM blasts and with multi-lineage dysplasia, (WHO 2008) considered smoldering leukemias that may remain stable for weeks or months, somewhat MDS-like, and therefore not necessarily benefiting from the intensive treatments used for classic AML patients, and lastly CMML patients without a myeloproliferative component (MDS type), defined as white blood cells (WBC) $\leq 13 \times 10^9$/L according to the FAB classification. All three hematological malignancies described above have been shown to benefit from azacitidine treatment.

In the expansion component of this study, patients with Intermediate, High, or Very High risk MDS according to IPSS-R and AML patients who are not candidates for intensive chemotherapy (WHO 2016) will be enrolled. CMML patients and patients with unclassifiable MDS/MPN are eligible for enrollment into the MDS cohort. Based on the results of the AZA-AML trial, the azacitidine label was expanded in 2009, making azacitidine a standard of care treatment in elderly AML patients unable to tolerate intensive therapies. This historical data, coupled with the preliminary efficacy data from the safety LIC of the current study warrants further investigation of azacitidine's benefit in a larger AML population. Since several prognostic and classification systems were recently updated, the following will be implemented in the expansion component of the study to make it more contemporary: IPSS-R and the WHO 2016 classification system will be applied to the MDS patients and the updated 2017 ELN risk stratification and updated response categories and the revised WHO 2016 classification system will be applied to the AML patients.

Given the central role that Hh signaling plays in cellular differentiation through modulating both the leukemia stem cells (LSC) population and the surrounding stromal environment, Hh inhibition in combination with HMAs represents a mechanistically attractive approach for the elimination of the LSC population while targeting the gene expression deregulation involved in the pathway development in patients with Higher-Risk MDS, AML, and CMML.

1.2.4. Summary of Glasdegib Product Profile

Glasdegib is a potent and selective inhibitor of the Hh signaling pathway through binding to its target SMO. It is currently being developed for the treatment of hematologic malignancies. Complete information for glasdegib may be found in the single reference study document (SRSD), which for this study is the Investigator Brochure (IB).[26]

Glasdegib inhibited the binding of a known comparator inhibitor of SMO (PF-03451358) with an half maximal inhibitory concentration (IC_{50}) of 4 nM. In addition, in a Shh-induced Gli-Luciferase reporter assay, glasdegib inhibited the Hh pathway activity with an IC_{50} of 3 nM. Using human aortic adventitial fibroblasts, Shh stimulation for 48 hours induced a 300% increase in endogenous Gli1 levels, assessed using quantitative polymerase chain reaction (PCR); glasdegib at 100 nM inhibited 75% of the ligand-induced Gli1 levels. Glasdegib was also evaluated in mouse 3T3-L1 preadipocytes, a cell line that forms triglycerides through a mechanism activated by insulin and antagonized by Shh. In this model, glasdegib (50 nM) reproducibly antagonized Shh, restoring 60% of lipid production relative to control cultures induced with insulin alone.[26]

In the PTCH/P53 medulloblastoma mouse model of Hh pathway-driven tumors, glasdegib inhibited pathway activation (Gli1 expression) and produced rapid and complete tumor regression. Preclinical PK/PD modeling using this model suggests a target human dose of 15 mg/day is projected to yield at least 50% of tumor Gli1 messenger ribonucleic acid (mRNA) inhibition from baseline levels and approximately 20% of skin Gli1 mRNA suppression.[26]

A series of preclinical studies show that glasdegib has significant activity in imatinib resistant chronic myeloid leukemia (CML) blast crisis disease (Abrahamsson-Schairer A. et al).[38] Patient derived CD34+ imatinib resistant blast crisis CML cells xenotransplanted into immunocompromised mice treated with glasdegib alone or in combination with dasatinib reduced primary leukemic tumor burden. In addition, glasdegib treatment reduced leukemic tumor formation in secondary recipients, suggesting that glasdegib is able to inhibit the LSC population necessary for tumor propagation. Importantly, this was verified in CML T315I mutants, which have escaped tyrosine kinase inhibitor (TKI) inhibition.

1.2.5. Glasdegib Preclinical Toxicity Data

Glasdegib has been extensively characterized in nonclinical safety studies in rats, dogs and rabbits. Glasdegib was evaluated in safety pharmacology studies (cardiovascular, neurofunctional, respiratory), definitive toxicology assessments of up to 6- and 9-months duration, in vitro and in vivo genetic toxicity studies, local irritation study and embryo-fetal developmental toxicity studies. The primary target organs in rat included kidney, bone, and

tooth. Additional findings were observed in rat testis and peripheral nerve, and clinical observations included alopecia and muscle tremor/twitching. The no observed adverse effect level (NOAEL) determined from the 6 month Good Laboratory Practices (GLP) rat study was 10 mg/kg/day, corresponding to free plasma concentrations of 116 ng/mL (C_{max}) and 36 ng/mL (C_{avgss}). The primary target organs in the dog included kidney and liver. Additional observations of alopecia and skin irritation/inflammation, and QTc prolongation were identified in the dog. A NOAEL from the 9-month GLP dog study was not established. At the lowest dose tested in this study, 1 mg/kg/day, the free plasma concentrations were 16 ng/mL (C_{max}) and 2 ng/mL (C_{avgss}). Glasdegib was teratogenic at all doses tested in rats and rabbits.

1.2.5.1. Kidney Effects in Preclinical Studies

The kidney was identified as a target organ in both rat and dog toxicity studies. Adverse kidney damage (tubular degeneration/necrosis, cytomegaly, inflammation, regeneration) was observed in rats at ≥50 mg/kg/day and dogs at ≥1 mg/kg/day and was ascribed as the primary cause of unscheduled euthanasia in both species. Kidney damage partially reversed in rats and fully reversed in dogs during the recovery phase in both the GLP 6-month rat and 9-month dog studies.

1.2.6. Bone Effects in Preclinical Studies

Bone (epiphysis) and tooth (incisor) effects were observed in rat GLP studies with glasdegib. Bone changes in the femur and sternum were characterized by decreased/disorganized chondrocytes and partial to complete closure of epiphysis. The odontopathy were characterized by incisor tooth necrosis and/or complete loss of the tooth and in some animals was coincident with oral mucosal ulceration and inflammation. The effects on bone and teeth persisted during recovery phases and did not reverse. The changes in the epiphyseal growth plate are consistent with inhibiting the hedgehog (Hh) pathway in growing bone (Kimura et al, 2008)[24] and chondrogenesis (Amano et al, 2008)[25] and the generation of ameloblast progenitors from stem cells in the continuously growing rodent incisor (Seidel et al, 2010; Dassule et al, 2000)[61,62] is dependent on Hh pathway activity.

1.2.7. Cardiovascular Effects in Preclinical Studies

The potential for QT prolongation was identified from the in vitro human ether-à-go-go-related gene (hERG) assay and in vivo cardiovascular dog study. Glasdegib produced dose related changes in the QTc interval. At 5 mg/kg, a small (5 msec) but statistically significant increase in QTc interval occurred at free plasma exposures of 420 ng/mL (C_{max}). At 30 mg/kg, a statistically significant increase in QTc interval (24 msec) occurred at free plasma exposures of 1848 ng/mL (C_{max}). The QTc prolongation observed in the dog is consistent with the hERG IC_{50} for glasdegib (3.1 uM).

1.2.8. Embryo-fetal Effects in Nonclinical Studies

Teratogenicity was identified in rat and rabbit embryo fetal developmental toxicity studies. Glasdegib treatment was associated with increased spontaneous abortions, lower embryo-fetal survival, higher incidence of skeletal anomalies, lower fetal body weights, and higher incidences of external, visceral and skeletal malformations and variations. A

developmental NOAEL could not be established in rat or rabbit due to adverse teratogenic effects at all doses. Inhibition of Hh signaling has been shown to induce teratogenicity in animals as SMO is involved in embryonic development. Accordingly, inhibition of Hh signaling by small molecules can lead to teratogenic effects (Chen et al, 2002, Cooper et al, 1998).[63,64]

1.2.9. Other Findings in Preclinical Studies

Additional glasdegib-related findings in rats were observed in testis and peripheral nerve, and clinical observations included alopecia and muscle tremor/twitching. Microscopic changes in the nerve and clinical observations of alopecia and muscle tremors fully recovered. Testicular degeneration did not recover; however this finding was only seen in young growing rats and not in adult dogs and is consistent with inhibition of Hh signaling which plays a role in postnatal testis spermatogenesis (Mäkelä et al, 2011).[65] In dog toxicity studies with glasdegib, mild liver inflammation with increased liver enzymes was observed in some dogs. However, this finding was only evidenced in dogs with adverse renal damage and is likely secondary to kidney findings. The liver findings partially recovered.

Glasdegib was not genotoxic in any in vitro or in vivo assessment, did not cause local irritation when administered intravenously or perivascularly to rabbits and did not cause photo-irritancy in the eye or skin.

1.2.10. Clinical Relevance of Organ Toxicities Observed in Nonclinical studies

In general, many findings in the rat and dog predict drug reactions reported in the clinic with glasdegib; these include muscle spasms, alopecia and QTc prolongation. However; not all of the organ toxicities observed in animals have been observed in humans when treated with glasdegib. Although mild axonal degeneration was observed in rat mesenteric peripheral nerve, there have been no reported clinical effects related to worsening or new onset of peripheral nerve deficits. The kidney is a target organ in rat and dog. In the clinical program, at glasdegib, 100 mg dose, acute kidney injury has been reported, primarily Grade 1-2. These events were often associated with prerenal confounders or consequent to or exacerbated by other glasdegib effects (eg, diarrhea, vomiting, and/or decreased oral intake). An imbalance in creatinine elevations was not seen in the AML unfit LDAC + glasdegib arm versus the LDAC arm alone.

There have not been any liver events or significant increases in liver transaminases reported in the clinic. Findings in bone, teeth and testis are considered only a potential concern for pediatric patients as Hh signaling is important in growth and development of these tissues as cited above, thus, these effects have not manifest in adult patients and are not a risk for adults being treated with glasdegib.

1.2.11. Clinical Pharmacokinetic Summary

Data following single and multiple doses of glasdegib from Study B1371001 in patients with selected hematologic malignancies are summarized for all cohorts tested (5, 10, 20, 40, 80, 120, 180, 270, 400, and 600 mg QD).

The exposure [C_{max}, AUC_{inf} (single dose) and AUC_{tau} (multiple dose)] increased in a generally dose-proportional manner over the dose range of 5 to 600 mg following glasdegib administration on the lead-in day and Cycle 1 Day 21.

Following repeated daily dosing, steady-state was achieved by Day 8 based on comparison of C_{trough} values across PK days in Cycle 1. Median T_{max} of glasdegib ranged from 1-2 hours following a single dose and 1-4 hours following multiple dosing. The mean glasdegib volume of distribution (V_z/F) ranged from 185-455 L. The geometric % coefficient of variance (CV) for AUC_{inf} across all dose levels ranged from 19% to 109% following a single dose (safety LIC) and from 10% to 61% for AUC_{tau} after multiple dosing (Day 21). Similarly, the geometric % CV for C_{max} ranged from 3.0% to 79% after a single dose and 7.0% to 83% following multiple dosing.

The geometric mean $t_{½}$ for glasdegib ranged from 17.4 to 34.3 hours across the various dose levels; however, at most dose levels, the half-life was ~24 hours. The geometric mean apparent oral clearance (CL/F) ranged from 5.63 to 12.7 L/hour following a single dose and 5.33 to 13.3 L/hour following multiple dosing. Glasdegib accumulated following repeated dosing with a median R_{ac} ranging from 1.2 to 2.5. This was consistent with the observed $t_{½}$, as the predicted R_{ac} is in agreement with the estimated R_{ac}. The median linearity ratio (R_{ss}) ranged from 0.76 to 2.1, with the ratio being close to unity for most of the tested dose levels.

The geometric mean for the percentage of administered dose excreted unchanged in the urine over the dosing interval of 24 hours ranged from 5.89% to 16.8%. The geometric mean for renal clearance ranged from 0.385 L/hr to 1.36 L/hr.

1.2.12. Clinical Pharmacodynamic Summary

Analysis of Hh pathway gene expression changes in surrogate tissue (skin) in samples collected from both the B1371001 (n=3) and B1371002 (n=15) studies indicated >75% down regulation of the expression of the Hh pathway gene GLI1 at doses of 80 mg or higher in all patients with evaluable samples. Evaluation of circulating cytokine modulation demonstrated a post-treatment decrease in IL-8 and IL-10 in one MF patient who responded to treatment in B1371001, although limited conclusions can be drawn due to the small number of samples available for analysis.

1.2.13. Clinical Experience in Patients with Selected Myeloid Malignancies

Currently there are five clinical studies with glasdegib in patients with hematological malignancies (B1371001, B1371003, B1371005, B1371013, and Investigator Initiated Research (IIR) Studies (WS2233096 and WI171861). Study B1371001 was a multi-center, open-label, non-randomized, escalating dose Phase 1 study in patients with select advanced hematologic malignancies. Study B1371003 (ongoing) is a Phase 1b/2, open-label, multicenter safety and efficacy study of glasdegib in combination with low-dose cytarabine (Ara-C), decitabine, or intensive chemotherapy, in patients with AML or high risk MDS. Study B1371005 (ongoing) is a Phase 1 dose-finding study of single-agent glasdegib in Japanese patients with select advanced hematologic malignancies, or glasdegib in combination with intensive chemotherapy (cytarabine and daunorubicin) or LDAC in

patients with previously untreated AML or high-risk MDS. Study B1371013 (ongoing) is a Phase 2 study of single-agent glasdegib versus placebo in patients with primary or secondary myelofibrosis who have been previously treated with a Janus kinase inhibitor. An ongoing Phase 2 IIR study at the University of Colorado (WS2233096) is evaluating the effects of glasdegib monotherapy on relapse free survival, remission and OS in patients with AML, MDS, or acute lymphocytic leukemia (ALL) at high risk for relapse post-allogeneic HSCT. Additionally, an ongoing Phase 2 IIR study at the Lee Moffitt Cancer Center (WI171861) is evaluating the glasdegib in patients with MDS. Refer to the glasdegib IB for further details.[26]

1.2.13.1. Study B1371001: Patients with Select Myeloid Malignancies

A total of 47 patients were screened and assigned to treatment in this Phase 1 dose escalation study aimed to identify the Maximum Tolerated Dose (MTD) and RP2D of glasdegib in patients with select myeloid malignancies. The dose levels tested in this study were: 5, 10, 20, 40, 80, 120, 180, 270, 400 and 600 mg QD on a continuous regimen. The majority (28/47 patients, 59.6%) of patients were male. The median age was 69 years (range 25-89 years). The diagnoses of enrolled patients included: AML (28 patients, 59.6%), CML (5 patients, 10.6%), CMML (1 patient, 2.1%), MDS (6 patients, 12.8%), and MF (7 patients, 14.9%). The median duration of treatment with glasdegib was 64.5 days (range: 5-261 days) in AML patients, 36.0 days (range: 1-280 days) in CML patients, 54.0 days (range: 54-54 days) in CMML patients, 153.0 days (range: 36-537 days) in MDS patients, and 182.0 days (range: 44-371 days) in MF patients.

Out of the 41 dose limiting toxicity (DLT) evaluable patients, 2 patients experienced DLTs during Cycle 1. One patient in the 80 mg QD cohort experienced non hematologic DLTs of Grade 3 hypoxia and pleural effusion for which glasdegib dosing was interrupted temporarily, and the dose reduced. Additionally one patient in the 600 mg QD cohort experienced a non-hematologic DLT of Grade 3 peripheral edema for which glasdegib was stopped temporarily.

The majority of treatment related AEs reported were Grades 1 to 3 in severity. The most frequently reported treatment related AEs were dysgeusia (27.7%), decreased appetite (19.1%) and alopecia (14.9%). A summary of treatment related AEs occurring in >5% of all patients is provided in Table 5 below.

Grade 3 laboratory test results independent of causality included: lymphocytes decreased (n=16), platelets decreased (n=8), WBC decreased (n=8), hemoglobin decreased (n=10), neutrophils decreased (n=3), alanine aminotransferase (ALT) increased (n=1), alkaline phosphatase increased (n=2), total bilirubin increased, hypokalemia, hyponatremia (n=4 each), hyperglycemia (n=3), hypoalbuminemia, hypocalcemia and hypophosphatemia (n=1 each). Grade 4 laboratory test results independent of causality included: platelets decreased (n=33), neutrophils decreased (n=26), WBC decreased (n=15), lymphocytes decreased (n=6), hemoglobin decreased (n=4), bicarbonate increased (n=1).

Based on electrocardiogram (ECG) results, 3 patients (1 patient in the 400 mg QD group and 2 patients in the 600 mg QD group) had a post baseline maximum Corrected QT interval using Fridericia Formula (QTcF) of ≥500 msec, and 6 patients (1 from the 5 mg group and 5 from the 600 mg group) had a maximum QTcF increase from baseline of ≥60 msec. Higher frequencies and grades of QTcF prolongation were observed at the highest dose levels (400 mg QD and 600 mg QD). All these events were asymptomatic and transient and did not result in significant clinical sequelae.

The MTD was defined as 400 mg after considering the one DLT at 600 mg (Grade 3 peripheral edema) and the high frequency of QTc prolongation observed at the 600 mg QD dose level. The Recommended Phase 2 Dose (RP2D) for glasdegib was determined to be 200 mg, based on the following factors:

- Doses of glasdegib up to 200 mg were safe and well tolerated following prolonged administration (most patients tolerated study drug for a minimum of 3 cycles in the dose range of 5-180 mg);

- At doses >200 mg, 3 patients (1 patient in the 400 mg group and 2 patients in the 600 mg group) had a post baseline maximum QTcF interval of ≥500 msec;

- An overall lower frequency of treatment related Grade 3/4 AEs was observed at doses of 200 mg or less. Over this dose range, the most commonly reported treatment related AEs were of Grade 1 or 2 severity suggesting that glasdegib is generally well tolerated in this dose range.

Although evaluation of efficacy was not the primary objective of this study, patients were evaluated for disease specific efficacy endpoints. A total of 4 MDS/CMML patients (4/7 patients: 3/6 MDS patients and 1/1 CMML patient, 57.1%) achieved stable disease or better, among whom 2 patients (2/7 patients, 28.6%) showed hematologic improvement. For the 7 MF patients, 2 patients achieved clinical improvement. For patients with AML (28 patients), 1 patient (3.6%) had morphologic complete remission with incomplete blood count recovery (CRi), 4 patients (14.3%) had partial remission with incomplete blood count recovery (PRI), and 4 patients (14.3%) had minor response (MR). Treatment failures occurred in 7 AML patients (25%) due to resistant disease. Clinical benefit (CR + CRI + PR + PRI + SD + MR) was shown in 16 AML patients (57.1%), including 7 patients (25%) with SD.

Out of the 46 patients evaluated for efficacy, 2/7 MDS/CMML patients (28.6%), 2/7 MF patients (28.6%), and 9/28 AML patients (32.1%) had an objective response.

In summary, glasdegib appears to be well tolerated with early signs of efficacy observed in all the hematologic diseases studied. Several patients with aggressive malignancies remained on trial for prolonged durations. On target AEs (eg, dysgeusia and alopecia) were observed at multiple dose levels. Taken together, this data support testing glasdegib as a combination therapy in patients with AML and MDS for whom there are few effective therapeutic options for sustained responses.

Table 5. Treatment Emergent Adverse Events with Frequency ≥5% by System Organ Class and Preferred Term

N (%) With AEs by SOC MedDRA Preferred Term[a]	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5	Missing or Unknown	Total (n = 47)
Any AEs	6 (12.8)	11 (23.4)	8 (17.0)	3 (6.4)	0	0	28 (59.6)
Gastrointestinal disorders	6 (12.8)	4 (8.5)	4 (8.5)	0	0	0	14 (29.8)
Diarrhoea	3 (6.4)	3 (6.4)	0	0	0	0	6 (12.8)
Nausea	4 (8.5)	1 (2.1)	1 (2.1)	0	0	0	6 (12.8)
Vomiting	4 (8.5)	0	1 (2.1)	0	0	0	5 (10.6)
General disorders and administration site conditions	3 (6.4)	4 (8.5)	3 (6.4)	0	0	0	10 (21.3)
Fatigue	2 (4.3)	2 (4.3)	1 (2.1)	0	0	0	5 (10.6)
Mucosal inflammation	1 (2.1)	1 (2.1)	1 (2.1)	0	0	0	3 (6.4)
Investigations	2 (4.3)	5 (10.6)	2 (4.3)	0	0	0	9 (19.1)
Electrocardiogram QT prolonged	1 (2.1)	4 (8.5)	0	0	0	0	5 (10.6)
Weight decreased	1 (2.1)	2 (4.3)	2 (4.3)	0	0	0	5 (10.6)
Metabolism and nutrition disorders	2 (4.3)	2 (4.3)	5 (10.6)	0	0	0	9 (19.1)
Decreased appetite	2 (4.3)	2 (4.3)	5 (10.6)	0	0	0	9 (19.1)
Musculoskeletal and connective tissue disorders	4 (8.5)	3 (6.4)	0	0	0	0	7 (14.9)
Muscle spasms	3 (6.4)	1 (2.1)	0	0	0	0	4 (8.5)
Nervous system disorders	7 (14.9)	6 (12.8)	0	0	0	0	13 (27.7)
Dysgeusia	7 (14.9)	6 (12.8)	0	0	0	0	13 (27.7)
Skin and subcutaneous tissue disorders	6 (12.8)	2 (4.3)	0	0	0	0	8 (17.0)
Alopecia	5 (10.6)	2 (4.3)	0	0	0	0	7 (14.9)

Source: B1371001 Full Clinical Study Report (Table 28).

Abbreviations: MedDRA = Medical Dictionary for Regulatory Activities, N/n = number of patients, QT = in electrocardiography, the time corresponding to the beginning of depolarization to repolarization of the ventricles, SOC = system organ class.

[a] MedDRA (version 16.0) coding dictionary applied.

1.2.13.2. Study B1371012: Safety Lead-In Cohort

As of 23 September 2015, twelve patients were enrolled into the safety LIC of the current study with higher risk MDS (n=7), AML (n=4), and CMML (n=1) and treated with glasdegib 100mg QD orally in combination with azacitidine 75 mg/m^2 SC daily for 7 days. As of a data cutoff date of 19 September 2015, a safety review was conducted in 11/12 patients who received at least 1 cycle of treatment. Baseline characteristics are summarized in Table 6. One additional patient was enrolled and treated after the data cut-off period (MDS IPSS-risk Intermediate-2).

The median glasdegib treatment duration was 51 days, range 23-128 days. The median relative glasdegib dose intensity was 92.0% across all cycles. The median relative azacitidine dose intensity was 98.0% across all cycles.

Table 6. Baseline Patient Characteristics

Characteristic	Glasdegib 100 mg/ Aza 75 mg/m^2 (N = 11) N (%)
Male/Female	7:4
Mean (range) age, in years	71.7 (59-89)
≥65, n (%)	8 (72.7)
Race	
White	10 (90.9)
Non-White	1 (9.1)
Disease, n (%)	
MDS IPSS high	2 (18.2)
MDS IPSS intermediate-2	4 (36.4)
AML	3 (27.3)
NP-CMML	1 (9.1)
Other*	1 (9.1)

*Erythroleukemia. IPSS, International Prognostic Scoring System; MDS, myelodysplastic syndrome; NP-CMML, non-proliferative chronic myelomonocytic leukemia; oAML, oligoblastic acute myeloid leukemia

All patients who received at least one dose of study treatment (n=11) experienced Treatment Emergent Adverse Events (TEAEs). The most frequently reported TEAEs of any grade and regardless of causality, occurring in 3 or more patients, are summarized in Table 7.

Electrocardiogram (EKG) QT prolonged (1 patient Grade 3; 3 patients Grade 1/2). Nine patients (81.8%) experienced ≥ Grade 3 TEAEs. The most frequently reported Grade ≥3 TEAEs regardless of causality, occurring in 3 or more patients were anemia (72.7%) and neutropenia (45.5%).

Table 7. Most Frequently Reported TEAEs in the Safety Lead-In Cohort (Any Grade, All Causality, in ≥ 3 Patients)

MedDRA PT[a]	N (%)
Anemia	8 (72.7%)
Constipation	8 (72.7%)
Fatigue	7 (63.6%)
Dysgeusia	6 (54.5%)
Nausea	6 (54.5%)
Neutropenia	5 (45.5%)
Dyspnea	4 (36.4%)
Electrocardiogram QT prolonged	4 (36.4%)
Pyrexia	4 (36.4%)
Vomiting	4 (36.4%)
Weight decreased	4 (36.4%)
Cough	3 (27.3%)
Diarrhea	3 (27.3%)
Injection site erythema	3 (27.3%)

Source: PHASE 1B SAFETY LEAD-IN DATA FOR STUDY B1371012 (Table 14.3.1.2.11.1)

Abbreviations: MedDRA = Medical Dictionary for Regulatory Activities, N/n = number of patients, QT = in electrocardiography, the time corresponding to the beginning of depolarization to repolarization of the ventricles, TEAE = Treatment Emergent Aderse Events.

[a.] MedDRA (version 18.1) coding dictionary applied.

Overall 7 patients (63.6%) experienced SAEs. Of these, the most frequently reported SAEs (reported in 2 patients each, 18.2%) were cellulitis, febrile neutropenia, and pyrexia. As of the data cut-off, 3 patients (27.3%) discontinued study treatment due to the following AEs (n=1 each): grade 4 cellulitis, sepsis, and septic shock not related to either study drug; grade 3 malignant lung neoplasm not related to either study drug; grade 3 QTc prolongation related to glasdegib. One patient died within 28 days of last dose of study medication due to a grade 5 acute myocardial infarction as a result of underlying coronary artery disease and cardiovascular risk factors of obesity and hypertension, deemed unrelated to either study drug by the Investigator.

The reported AEs were consistent with the individual toxicity profiles of glasdegib, azacitidine, and complications from the underlying disease itself. The addition of glasdegib to standard of care azacitidine did not appear to adversely impact azacitidine dosing nor did it result in a significant number of discontinuations due to toxicity in the subject population. An internal Pfizer review team declared the combination of glasdegib and azacitidine in the patient population as having an acceptable safety and tolerability profile, consistent with what is expected for glasdegib or azacitidine alone, and deemed acceptable to proceed to the next phase of development.

As of 23 March 2016, preliminary data showed a total of 5 patients responded: 3 patients with CR and 2 patients with mCR (of note, after the data cutoff date, the complete blood count of one of the patients with mCR had normalized, consistent with CR). Of the 4 patients with CR (including the mCR patient who became CR after the data cutoff date),

3 patients had oligoblastic AML. Of the 5 patients who responded, 4 responses occurred on or before Day 100. Of the 4 patients with CR (including the mCR patient who achieved a CR after the data cutoff date), 3 patients had AML (75% CR rate vs the historical control for azacitidine alone, 19.5%) and 1 patient had MDS (14% CR rate vs the historical control for azacitidine alone, 17%).[18,57] A further 4 patients had stable disease. At the time of the cutoff, median survival had not been reached. An evaluation of the DDI potential between glasdegib and azacitidine was conducted in this component of the study and no evidence of DDI potential was observed. (Borate et al, 2016).[45]

As of 10 March 2017, the safety LIC is complete with no patients on active treatment, 1 patient in follow-up, 4 patients withdrew from follow up, and 7 patients have died due to the following reasons deemed unrelated to study treatment by the study Investigators: Sepsis leading to Multi-organ failure, Acute myocardial infarction, Unknown (n=1 each), and Disease progression (n=4). No deaths were reported as the reason for discontinuation of study treatment, 2 deaths occurred within 28 days after last treatment dose and, 5 deaths occurred after 28 days from last dose.

Based on the acceptable safety and tolerability profile of glasdegib in combination with azacitidine and the early clinical activity seen, further investigation of this combination is warranted.

1.2.13.3. Study B1371003: Phase 1b/2 Study in Patients with AML or High-Risk MDS

This is an open-label, multicenter safety and efficacy study of glasdegib in combination with LDAC, decitabine, or intensive chemotherapy in patients with AML or high-risk MDS. This study includes two portions:

- Phase 1b: To evaluate the safety and RP2D determination of three first-line combination regimens of glasdegib plus: LDAC, decitabine, or '7+3' induction chemotherapy (cytarabine/daunorubicin).
- Phase 2: To assess the efficacy of two combination regimens:
  - A Phase 2 randomized (2:1) open-label component in unfit patients (P2 Unfit) enrolled to receive either LDAC in combination with glasdegib or LDAC alone;
  - A Phase 2 single arm component in fit patients (P2 Fit) to receive glasdegib in combination with 7+3 induction chemotherapy. Please refer to the glasdegib IB for further details on this part of the study.

Phase 1b Part

In the Phase 1b part of Study B1371003, 52 patients with AML or higher risk MDS were treated with glasdegib 100 mg or 200 mg PO Qday in combination with LDAC (n=23), decitabine (n=7), or 7 + 3 (n=22).

In Arm A (LDAC + glasdegib), 23 unfit patients were enrolled (15 males/8 females). Seventeen (17) patients received a starting glasdegib dose of 100 mg and 6 patients of 200 mg QD. No DLTs were observed. The most frequently reported treatment-related AEs in patients were nausea (n = 6, 35.3%), diarrhoea and neutropenia (n = 5, 29.4% each), and muscle spasms and dysgeusia (n = 4, 23.5% each).

In Arm B (Decitabine + glasdegib) 7 unfit patients were enrolled (5 male/2 female). Four (4) patients received glasdegib 100 mg and 3 patients received glasdegib 200 mg. No DLTs were reported. The most frequently reported treatment-related AEs of any grade were nausea (n=3, 75%), diarrhoea, thrombocytopenia, and neutropenia (n=2, 50% each). Of the AML patients treated in combination with decitabine, 2/5 (40%) responded (1 CR and 1 complete response with incomplete blood count recovery (CRi)), a similar population of newly diagnosed elderly AML patients was enrolled into a Phase 3 study of decitabine vs supportive care vs low dose cytarabine where the CR+ CRi rate was 25.6% in the decitabine only arm (Kantarjian et al, 2012).[58] Of the high-risk MDS patients treated in combination with decitabine, 2/2 achieved a response of mCR. Median OS in the combined AML and MDS patients was 4.4 months, 11.5 months (historical mOS of 7.7 months; Kantarjian et al, 2012),[58] and 34.7 months respectively in the 3 treatment arms. This arm was not evaluated in the Phase 2 component of Study B1371003.

In Arm C (Cytarabine/Daunorubicin + glasdegib), 22 fit patients were enrolled (12 males/10 females). Sixteen patients received a starting glasdegib dose of 100 mg QD and 6 patients of 200 mg QD. The most frequently reported treatment-related AEs in patients who received glasdegib 100 mg + cytarabine + daunorubicin of any grade were nausea (n =13, 81.3%), diarrhea, febrile neutropenia and muscle spasms (n = 7, 43.8% each), dysgeusia (n = 6, 37.5%), stomatitis, headache, fatigue and pyrexia (n = 5, 31.3% each), constipation, dyspepsia, vomiting, anaemia, neutropenia, white blood cell count decreased, hypocalcaemia, hypokalaemia and alopecia (n = 4, 25% each). A DLT of Grade 4 polyneuropathy, later attributed to concomitant medication, was reported at the 100 mg dose level and treatment was permanently discontinued in that patient.

Of the 45 AML patients treated in the entire Phase 1b cohort of Study B1371003, 1/20 treated patients in combination with LDAC responded (1 CR), 2/5 treated in combination with decitabine responded (1 CR, 1 complete response with incomplete blood count recovery (CRi), and 11/20 treated patients in combination with 7 + 3 responded (10 CR, 1 CRi).

Median OS (in AML and MDS patients combined) were 4.4 months (80% CI: 2.5, 6.6), 11.5 months (80% CI: 4.5, 17.4), and 34.7 months (80% CI: 14.5, Not Reached), respectively.

Of the 7 high-risk MDS patients treated in the entire Phase 1b cohort of Study B1371003, 2/3 treated in combination with LDAC responded (1 CR, 1 mCR), 2/2 treated in combination with decitabine responded (2 mCR), and 2/2 treated in combination with 7 + 3 induction chemotherapy responded (1 CR, 1 mCR).

Phase 2 Randomized Combination Part (Phase 2 Unfit)

In the Phase 2 portion of Study B1371003, a prospective, randomized (2:1), open-label clinical trial in 132 AML patients not suitable for intensive chemotherapy based on age or other risk factors, the addition of glasdegib 100 mg PO Qday to LDAC vs LDAC alone resulted in a significant improvement in OS (median 8.8 months (80% CI: 6.9, 9.9) vs 4.9 months (80% CI: 3.5, 6.0); HR 0.513 [80% CI: 0.394-0.666]; 1-sided p-value=0.0004 based on stratified log-rank test. This benefit in OS was also consistent within prespecified subgroups and supported by higher rates of complete remission in the LDAC + glasdegib arm (17% [80% CI: 11.9, 22.2] vs 2.3% [80% CI: 0.0, 5.2]). The addition of glasdegib to LDAC was well-tolerated, with 14 (16.7%) discontinuations due to adverse events. Thirteen of 84 (15%) patients were treated for at least 1 year (vs none in the LDAC alone arm). The median treatment duration was 83 days (range 3, 972 days) in the LDAC + glasdegib arm versus 47days (range 6, 239 days) in the LDAC alone arm.

The safety profile was consistent with that in elderly AML patients receiving chemotherapy, namely cytopenias and gastrointestinal (GI) side effects, and had the safety/tolerability profile of other marketed SMO inhibitors. In the LDAC + glasdegib arm, serious adverse events (SAEs) of febrile neutropenia, occurred more frequently (28.6%) than in the LDAC alone arm (19.5%); however, frequencies of pneumonias were similar between treatment arms (21.4% in the LDAC + glasdegib arm and 17.1% in the LDAC alone arm), and sepsis rates were lower in the LDAC + glasdegib arm (3.6% in the LDAC + glasdegib arm and 12.2% in the LDAC alone arm). The most common AEs in the LDAC + glasdegib arm were cytopenias and GI events, consistent with that in elderly AML patients receiving chemotherapy. Cytopenias were not accompanied with higher rates of infections or bleeding as compared to the LDAC alone arm. QTcF prolongation >500 msec (Grade 3) was less frequent in the LDAC + glasdegib arm (6%) than in the LDAC alone arm (11.8%). SMO inhibitor-associated AEs in the LDAC + glasdegib arm included dysgeusia (25%), muscle spasms (21.4%) and alopecia (10.7%). In the LDAC + glasdegib arm 28 (33%) patients were permanently discontinued due to AEs vs 20 (49%) patients in the LDAC alone arm, mostly for disease progression or infection. The most common cause of death was disease progression in both treatment arms.

The safety profile and magnitude of improvement in OS appeared to be consistent with that in other ongoing single-arm studies of glasdegib as monotherapy or in combination with other chemotherapies in other MDS and AML populations.

1.2.13.4. Study B1371005: Safety and Efficacy in an Asian Population

In the ongoing Phase 1 Study B1371005, 25 Japanese patients with selected hematologic malignancies were enrolled into three cohorts: 1) Thirteen (13) patients with AML, MDS, CMML, or MF enrolled into the open label, dose escalation monotherapy cohort and received glasdegib as a single agent at doses ranging from 25-100 mg PO Qday, 2) Six (6) patients with untreated AML or high risk MDS patients unsuitable to receive intensive induction chemotherapy received glasdegib 100 mg PO QD in combination with LDAC , and 3) Six (6) untreated AML or high risk MDS patients eligible for intensive chemotherapy enrolled in combination cohort #2 and received glasdegib 100 mg PO QD in combination with cytarabine (7days)/daunorubicin (3 days) chemotherapy.

No DLTs were observed at any dose level. The most frequently reported treatment related AEs occurring in ≥3 patients were: dysgeusia (69.2%), muscle spasms (38.5%), alopecia (30.8%), and decreased appetite (30.8%), blood creatinine phosphokinase increased (23.1%), constipation (23.1%), and diarrhea (23.1%). The safety and PK profiles in Japanese patients were consistent with what was observed in Western patients and in Study B1371001.

Preliminary efficacy data showed that 1 out of 7 AML patients achieved morphologic complete remission and 1 out of 4 MDS patients achieved marrow complete remission at the 100 mg dose level and 4 achieved SD across all dose levels (Yoshimoto et al, 2016).[46]

1.2.14. Post Allogeneic HSCT Investigator Initiated Research Study

In an ongoing IIR, single-arm study in patients with MDS, AML, or acute lymphocytic leukemia (ALL) with evidence of minimal residual disease (MRD) or other high-risk characteristics associated with a high rate of disease relapse at the time of allo HSCT, the addition of glasdegib 100 mg PO Qday post absolute neutrophil count (ANC) engraftment for up to a year resulted in 10/13 patients free of disease relapse: 12/13 patients remained alive (Gutman et al, 2015).[47] Historically, patients with measureable MRD at the time of HSCT have disease relapse rates >60%, and mOS of ~1 year. (Walter et al, 2015)[48] Araki et al, 2016)[49]

1.2.15. Summary of Azacitidine Product Profile

Azacitidine (VIDAZA®) is a chemical analogue of the cytosine nucleoside whose mechanism of action involves inhibition of DNA methyltransferase at low doses, causing hypomethylation of DNA, and direct cytotoxicity in abnormal hematopoietic cells in the bone marrow through its incorporation into DNA and ribonucleic acid (RNA) at high doses, resulting in cell death. Azacitidine was approved by the FDA in 2004 for the treatment of all subtypes of MDS according to the FAB classification. Azacitidine was approved in the EU in 2009 for the treatment of adult patients who are not eligible for hematopoietic stem cell transplantation with intermediate-2 and High-Risk MDS (per IPSS), CMML with 10-29% bone marrow blasts without myeloproliferative disorder and AML with 20-30% blasts and multi-lineage dysplasia. In 2015, the EU expanded the approval of azacitidine in AML to include adult patients aged 65 years or older who are not eligible for HSCT with >30% myeloblasts according to the WHO classification.

1.2.16. Azacitidine Toxicities

Per the VIDAZA® EU Summary of Product Characteristics (SPC), the following (very common ≥1/10) adverse reactions associated with azacitidine treatment were obtained from clinical studies and post marketing surveillance: pneumonia, nasopharyngitis, febrile neutropenia, neutropenia, leukopenia, thrombocytopenia, anemia, anorexia, decreased appetite, hypokalemia, insomnia, dizziness, headache, dyspnea, epistaxis, diarrhea, vomiting, constipation, nausea, abdominal pain, petechiae, pruritus, rash, ecchymosis, arthralgia, musculoskeletal pain, fatigue, pyrexia, asthenia, chest pain, injection site erythema, injection site pain, injection site reaction (unspecified), and weight decreased.

1.2.16.1. Azacitidine Dosing Schedule

The dosing schedule in the safety LIC is 75 mg/m^2/day SC for 7 consecutive days every 28 days. In the expansion component, azacitidine will be administered per local label or per the Investigational Product Manual (or SPC). Azacitidine may be administered by SC injection or IV infusion at the starting dose of 75 mg/m^2/day for 7 days every 28 days. Alternate dosing schedules to administer the 7 doses to accommodate patient and treatment center availability are allowed.

A trial which compared 3 different azacitidine schedules[36] showed 44% HI (22/50) for the 5-2-2 dosing schedule (95% CI, 31 to 60), another trial (AZA 001), showed 49% HI in the azacitidine arm (87/177) ($p < 0.0001$). There are no data showing that varying 7 day schedules are not equivalent, therefore, the Investigators can choose the appropriate schedule based on the standard of care at their institution.

1.2.16.2. Azacitidine Dose Modifications

For azacitidine dose modification, refer to the local label or the Investigational Product Manual (or SPC).

Complete information for azacitidine may be found in the SRSD, which for this study is the EU SPC for Vidaza®.[27]

1.2.17. Rationale for Testing Glasdegib in Combination with Azacitidine in Patients with Previously Untreated Higher-Risk MDS, AML, and CMML

The combination of glasdegib with azacitidine is proposed for testing in this therapeutic setting based on:

- Clinical and pre-clinical data suggesting a role for aberrant Hh pathway activation in MDS, AML and CMML (See Section 1.2.2 and 1.2.3);
- Non-clinical data demonstrating that glasdegib limits LSC proliferation and evidence of glasdegib synergy with chemotherapy (See Section 1.2.2);
- The acceptable safety, tolerability and pharmacokinetic profile observed for glasdegib in clinical studies in patients with hematological malignancies both as a single agent and in combination with decitabine and azacitidine (see Section 1.2.6);
- The clinical activity observed following single-agent and combination treatment with glasdegib in patients with select hematological malignancies (see Section 1.2.6);
- The glasdegib pharmacodynamic data for Hh pathway inhibition obtained in surrogate tissues from a limited number of patients (n=18) with select hematological malignancies and advanced solid tumors (see Section 1.2.13.2).

The above data along with the high unmet medical need for more effective therapies (higher response rates and hematologic improvement that translate into survival benefit) for patients with higher-risk MDS, AML, and CMML, support the evaluation of glasdegib in combination with azacitidine in this population.

1.2.18. Rationale for the Starting Dose of Gladegib

As reported in Section 1.2.13.1, the B1371001 study identified the MTD for single-agent glasdegib continuous administration as 400 mg QD, and the RP2D as 200 mg QD in patients with select hematologic malignancies.

Subsequent evaluation of potential dose levels for further studies in patients with hematologic malignancies suggested the 100 mg QD dose level (MTD -4) as the optimal starting dose of single agent glasdegib. This was supported by the following data:

- Clinical benefit observed in 16 patients in the B1371001 study (including some with a diagnosis MDS and CMML) with doses of glasdegib as low as 10 mg QD, with the highest frequency of responses being observed at ≤80 mg QD;

- GLI1 (a biomarker of Hh pathway signaling activation) expression is down regulated by ≥80% at doses of 50 mg QD and higher in surrogate (skin) tissue, suggesting there will be adequate target modulation at the 100 mg QD dose;

- Potential for increase in glasdegib plasma exposures in the presence of a strong CYP3A4 inhibitor(s) (~140% increase in AUC_{inf} and a 40% increase in the C_{max}) such as azoles which are medically necessary for management of infections in AML patients.

- Taking into consideration the observed clinical activity, safety and tolerability profile, modulation of hedgehog pathway activity in surrogate tissue, and information relating to the possible impact of a CYP3A4 inhibitor, a dose of 100 mg QD was chosen as the appropriate glasdegib starting dose for further clinical studies both as a single agent and in combination. In the randomized Phase 2 portion of Study B1371003 (Section 1.2.13.3), clincal benefit was demonstrated with LDAC ± glasdegib (100 mg Qday continuously in 132 first line AML patients. The mOS was 8.8 months (80% CI: 6.9, 9.9) vs. 4.9 months (80% CI: 3.5, 6.0) for LDAC alone, with a hazard ratio of 0.513 [80% CI: 0.394-0.666]. The safety profile of glasdegib + LDAC was generally tolerable and manageable.

- In the single arm Phase 2 portion of Study B1371003 (Section 1.2.13.3), for older AML pts receiving intensive chemotherapy, the mOS stratified by subgroup was improved by adding glasdegib. The combination of glasdegib with '7+3' was well-tolerated, with a safety profile consistent with that typically seen in AML patients receiving standard intensive chemotherapy.

These data provides additional rationale for the 100 mg QD dose of glasdegib being a safe and potentially clinically effective dose in combination with azacitadine.

1.2.19. Assessment of the Drug-Drug Interaction (DDI) Potential between Glasdegib and Azacitidine

Glasdegib has been shown to be extensively metabolized by CYP3A4 (99.8%) using human liver microsomes and hepatocytes. For azacitidine, the exact route of elimination and metabolic fate is not known in humans. One of the pathways of elimination for azacitidine appears to be deamination by cytidine deaminase principally located in the liver but also in granulocytes, the intestinal epithelium, and whole blood (Vidaza® US package insert). The potential for a DDI was considered to be low for the glasdegib and azacitidine, as enzyme systems other than CYP3A may be involved in the metabolism of azacitidine. However, since this was a combination setting for dosing of glasdegib and azacitadine, a DDI assessment was conducted in twelve subjects as part of the safety LIC. Based on preliminary PK results, there was no evidence of changes in the PKs of either glasdegib or azacitadine when dosed in combination as compared to single agent dosing.

1.2.20. Summary of Benefit-Risk Assessment

An evaluation of the anticipated risks and benefits of treatment with glasdegib in the defined patient population as required in Article 3(2)(a) of Directive 2001/20/EC (cf. Article 6(3)(b) of Directive 2001/20/EC) has been conducted.

Based on the available clinical data, the safety profile of glasdegib as a single agent and in combination administered orally on a once daily continuous dosing regimen is characterized by manageable and potentially reversible toxicities that are generally mild to moderate in severity. The key observed toxicities are: muscle spasms, dysgeusia, decreased appetite, and alopecia.

Small but significant increases in the QTc interval have been reported in non-clinical studies with glasdegib. Across the clinical program at glasdegib doses of 100 mg QD, cases of QTcF prolongation >500 msec or change in QTcF >60 msec from baseline have been reported, generally in settings of multiple confounders; causal relationship could not be determined. Specific dosing modification and additional monitoring may apply in case of prolonged QTcF (refer to Section 5.4.5.1 and Table 14). Concomitant administration of glasdegib with moderate/strong CYP3A4/5 inhibitors (Appendix 6 and Appendix 7) and drugs with known risk of Torsade de Pointes (TdP) (Appendix 5) is not recommended due to the potential for DDI to prolong the QTc interval.

In a thorough QT (TQT) study (Study B1371023), a large effect (≥20 msec, the threshold of clinical concern for cancer drugs) of glasdegib on the QTc interval was not demonstrated at therapeutic (exposure equivalent to 100 mg QD) and supratherapeutic (exposure equivalent to 200 mg QD) doses. The largest mean QTc interval change at any time point following the therapeutic dose was 8.03 msec. The upper bound of the 2-sided 90% CIs for all time-matched least squares (LS) mean differences between glasdegib and placebo was below 20 msec (the maximum 90% CI upper bound was 15.6 msec at the supratherapeutic dose). Based on PK-PD analysis in cancer patients, there was no observed relationship between glasdegib concentration and heart rate. The predicted mean change in QT interval corrected for heart rate using Fridericia's formula (QTcF) from baseline was 5.30 msec (95% CI: 4.40, 6.24) at the mean C_{max} at the therapeutic dose of 100 mg QD, and 12.1 msec (95% CI: 10.0,

14.3) at the mean supratherapeutic C_{max}. The upper bound of the 95% CI for the projected increases in QTcF were below 20 msec.

When glasdegib was combined with treatments commonly used in patients with higher risk MDS and AML who were not candidates for intensive chemotherapy (azacitidine, decitabine, and LDAC), improvements in response rates and OS in the context of historical controls were observed.

Azacitidine has been shown to prolong OS in patients with higher risk MDS[18] with an acceptable safety profile, but following treatment failure, life expectancy is short, with a mOS of <6 months. In AML patients who were not candidates for intensive chemotherapy, azacitidine has demonstrated a clinically meaningful survival benefit. Therefore, taken together with clinical and pre-clinical data suggesting a potential relevant role for the Hh pathway in myeloid malignancies, these data support the evaluation of glasdegib in combination with azacitidine in the described therapeutic setting to improve clinical outcomes with respect to treatment with single agent azacitidine.

2. STUDY OBJECTIVES AND ENDPOINTS

2.1. Objectives for the Safety Lead-In Cohort

Primary Objective

- To assess the safety and tolerability of glasdegib when administered in combination with azacitidine in patients with previously untreated Intermediate-2 or High-Risk MDS, AML with 20-30% blasts and multi-lineage dysplasia, and CMML.

Secondary Objectives

- To assess the Response Rate (RR);
- To assess other clinical efficacy measures;
- To characterize the PK of glasdegib and azacitidine alone and in combination;
- To characterize the effects of glasdegib in combination with azacitidine on QTc interval.

CCI

2.2. Endpoints for the Safety Lead-In Cohort

Primary Endpoint

- Adverse events as characterized by type, frequency, severity (as graded by National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) v.4.03), timing, seriousness and relationship to study therapy and laboratory abnormalities as characterized by type, frequency, severity (as graded by NCI CTCAE v.4.03) and timing.

Secondary Endpoints

- RR (percentage of patients achieving CR + PR) as defined by modified IWG criteria (2006) (Appendix 2);
- Other efficacy measures HI, mCR, Cytogenetic Response, and SD as defined by modified IWG criteria (2006) (Appendix 2);
- PK parameters of glasdegib and azacitidine, including but not limited to C_{max}, T_{max} and AUC;
- QTc interval.

CCI [redacted]

2.3. Objectives for the Expansion

Primary Objective

- To determine the CR rate of glasdegib when administered in combination with azacitidine in patients with previously untreated Intermediate, High, or Very High risk MDS and AML not suitable for intensive chemotherapy.

Secondary Objectives

- To assess OS;
- To assess other clinical efficacy measures;
- To assess duration of CR;

- To assess time to CR;
- To evaluate the overall safety profile of glasdegib + azacitidine;
- To evaluate the pharmacokinetic parameters of glasdegib;
- To characterize any effects of glasdegib + azacitidine on QTc interval.

CCI

[redacted]

2.4. Endpoints for the Expansion

Primary Endpoint

- CR rate for MDS patients (Appendix 2) and AML patients (Appendix 11).

Secondary Endpoints

- OS;
- For MDS cohort: disease-specific efficacy measures, such as marrow CR (mCR), Partial Remission (PR), Stable Disease (SD), Partial or Complete Cytogenetic Response, and Hematologic Improvement (HI) (Appendix 2);
- For AML cohort: disease-specific efficacy measures, such as CR with Incomplete Hematologic Recovery (CRi), Complete Remission with partial hematologic recovery (CRh), Morphologic Leukemia-Free State (MLFS), PR, and SD (Appendix 11);
- Duration of CR;
- Time to CR;

- Adverse events and laboratory abnormalities as graded by NCI CTCAE v.4.03;
- Pharmacokinetics parameters of glasdegib;
- QTc interval.

CCI [redacted]

3. STUDY DESIGN

3.1. Study Overview

This multi-center, open-label Phase 1b study is designed to evaluate the safety, efficacy, PK, and PD of glasdegib when combined with azacitidine in patients with previously untreated Higher-Risk MDS, AML, and CMML. The Phase 1b study includes two components: (a) a safety LIC, and (b) an expansion phase with two cohorts.

3.2. Safety Lead-In Cohort

As of 23 September 2015, a safety LIC of 12 patients with previously untreated Intermediate-2 or High-Risk MDS per IPSS (n=7), AML with 20-30% blasts and multi-lineage dysplasia (n=3), erythroleukemia (n=1), and CMML (n=1) were enrolled and received open-label treatment with glasdegib at a starting dose of 100 mg given orally once/day in combination with azacitidine at the starting dose of 75 mg/m^2/day given SC for 7 consecutive days every 28 days. An evaluation of the DDI potential between glasdegib and azacitidine was performed. See Section 7 for a detailed description of the study assessments. An internal safety review team reviewed the LIC data after each patient had received at least 4 weeks of treatment and determined that the safety profile of glasdegib in combination with azacitidine in the defined population was consistent with what is expected for glasdegib or azacitidine alone with no unexpected toxicities identified, therefore the combination was deemed acceptable to proceed to the next phase of development.

3.3. Expansion

Patients with previously untreated Intermediate, High, or Very High risk MDS per IPSS-R (n=30) or patients with AML who are not candidates for intensive chemotherapy (n=30) will receive glasdegib 100 mg orally once/day in combination with azacitidine per local label or per the Investigational Product Manual (or SPC). Azacitidine may be administered by SC injection or IV infusion at the starting dose of 75 mg/m^2/day for 7 days every 28 days. Alternate dosing schedules to administer the 7 doses to accommodate subject and treatment center availability are allowed.

The attribution of 'not being candidates' for intensive chemotherapy will be determined by the Investigator based on the patient's baseline eligibility, comorbidities and other factors according to 2017 ELN recommendations. The primary objective of the expansion component is to demonstrate that the CR rate of the combination treatment in each patient population is reasonably better than the historical CR rate for azacitidine alone in that population using a Bayesian decision criteria allowing early stopping for futility.

Patients in the expansion MDS and AML cohorts will be enrolled continuously. The CR rate among the MDS and AML patients will be continuously monitored throughout the expansion component. After a certain number of patients have been enrolled in each cohort (Table 8 and Table 9, respectively) and observed for at least 28 weeks for the expansion MDS cohort and 24 weeks for the expansion AML cohort, the Sponsor will conduct a review of the CR rate within each expansion cohort to determine if the minimum number of responses are achieved to continue enrollment into that cohort. If the minimum number of CRs in any group is not achieved, then study enrollment will stop for futility. If the study is stopped for futility, patients on active treatment that are deriving clinical benefit will continue on study treatment until they meet the criteria for discontinuation (Section 3.3.1). The Bayesian prior parameter assumptions for each cohort are based on glasdegib combination study data in the respective populations, while prior assumption for control groups are based on historical control data.[56]

Analysis of specific safety criteria will be performed to evaluate stopping enrollment for a specifc cohort when there is at least 70% probability that the toxicity rate of any of the below pre-defined safety events of interest in that cohort is above 25% (Section 9.7.2):

- Treatment-related deaths that occur during study treatment through 28 days following the last dose of any study treatment, or the beginning of another anti-cancer therapy, whichever occurs first.

- Drug-induced liver injury (Hy's Law cases), confirmed as detailed in Section 8.6.2, that occurs during study treatment through 28 days following the last dose of any study treatment, or the beginning of another anti-cancer therapy, whichever occurs first.

- Grade ≥3 non-hematologic treatment-related AEs in the first cycle of treatment that have failed to recover to baseline or ≤ Grade 1 within 21 days from when the second cycle is due to start (corresponding to recovery before or/on Day 49 of the first cycle) and required permanent discontinuation of study treatment.
- Grade 4 treatment-related neutropenia (ANC <500/mm^3) lasting ≥42 days from the start of cycle 1 in the presence of bone marrow hypoplasia without evidence of active AML or MDS.

A safety event of interest is defined as any of the above deemed related to glasdegib and /or azacitidine as assessed by the investigator. All AEs will be classified according to CTCAE version 4.03.

The safety stopping criteria will be applied within a cohort (AML or MDS) starting when at least 10 patients have completed the required follow-up period (28/24 weeks for MDS/AML respectively) and applied continuously afterwards. Enrollment will continue unless the stopping boundary is crossed (Table 10). The same stopping criteria will be used for the AML and MDS cohorts; however, the two cohorts will be analyzed independently.

Table 8. MDS Efficacy Decision Criteria

# Patients with mature response data (inclusive)	Stop expansion MDS enrollment if there are this many responses total:
1-9	No stop
10-13	≤2
14-16	≤3
17-20	≤4
21-24	≤5
25-27	≤6
28-29	≤7
30	Full enrollment

Table 9. AML Efficacy Decision Criteria

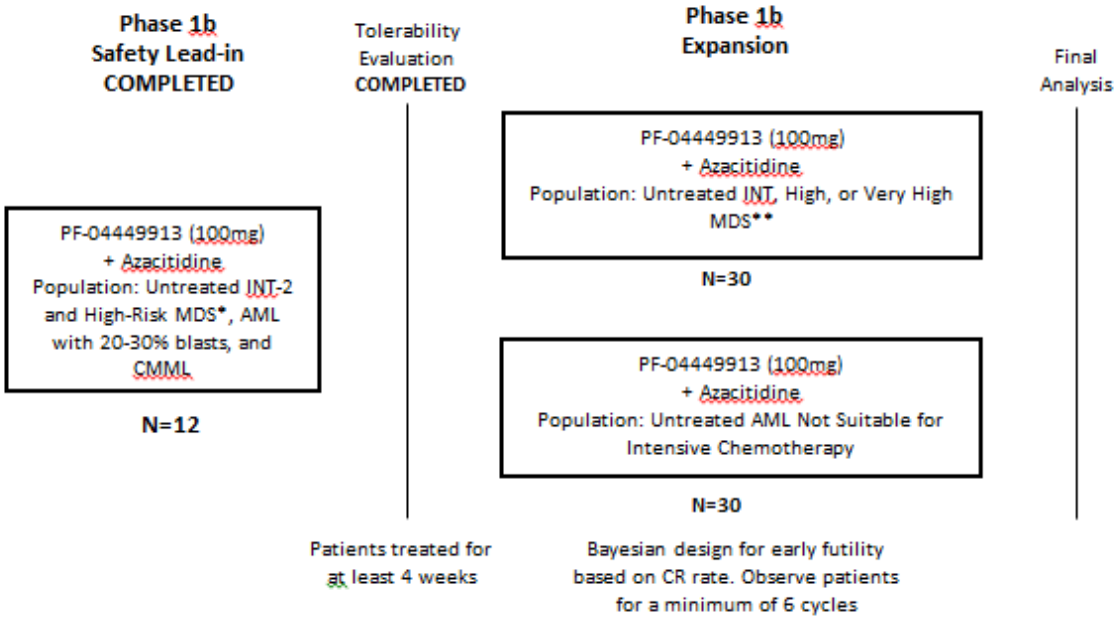
# Patients with mature response data (inclusive)	Stop expansion AML enrollment if there are this many responses total:
1-10	No stop
11-13	0
14-17	≤1
18-20	≤2
21-23	≤3
24-27	≤4
28-29	≤5
30	Full enrollment

Table 10. Safety Decision Criteria

# Patients*	Stop cohort enrollment if there are this many patients with any pre-defined safety events of interest**
1-9	No stopping
10-12	≥4
13-16	≥5
17-20	≥6
21-23	≥7
24-27	≥8
28-30	≥9

*Patients who have completed the required follow-up period (ie, 28/24 weeks for MDS/AML respectively) or patients who have experienced any pre-defined safety events of interest within the required follow-up period will be counted.
**A weak prior of Beta (0.5,0.5) was used in the calculation.

Figure 3. Schematic of Study Design



*MDS patients enrolled in the Safety Lead-In component must have Intermediate-2 or High-Risk disease according to IPSS. MDS patients enrolled in the Expansion component must have Intermediate, High, or Very High risk disease acoording to IPSS-R.

3.3.1. Study Treatments

Treatment will be administered in 28-day cycles. Glasdegib will be administered at the starting dose of 100 mg orally once/day and continuously in combination with azacitidine.

Safety Lead-In Cohort

The safety lead-in cohort has been completed.

- All patients will be administered glasdegib, 100 mg orally once/day and continuously;
- Azacitidine will be administered SC at the starting dose of 75 mg/m^2/day on a continuous schedule from Day 1 to Day 7 of each cycle (Schedule 1). Patients with >30% BM blasts OR a rapidly progressive increase in the proportion of BM blasts at any point during the course of treatment must discontinue the study drug combination and enter follow up.

Expansion

- All patients will be administered glasdegib 100 mg orally once daily and continuously;
- Azacitidine will be administered per local label or per the Investigational Product Manual (or SPC). Azacitidine may be administered by SC injection or IV infusion at the starting dose of 75 mg/m^2/day for 7 days every 28 days. Alternate dosing schedules to administer the 7 doses to accommodate patient and treatment center availability are allowed.

Since responses to azacitidine may require 4-6 cycles of administration to emerge, treatment with the study drug combination should be continued for at least 6 cycles, or until death, unacceptable toxicity, or patient refusal whichever occurs first. If documentation of disease progression occurs within the first 6 cycles of study treatment the patient **SHOULD NOT** be withdrawn from study treatment if, in the Investigator's judgment, the patient is still likely to receive clinical benefit. Treatment with the study drug combination should be continued beyond 6 cycles of treatment until objective disease progression or relapse, unacceptable toxicity, patient refusal or death, whichever occurs first. Treatment should also be continued beyond 6 cycles if patients demonstrate reasonable evidence of clinical benefit, defined as HI or better in patients enrolled into the safety LIC, SD + HI or better in MDS patients enrolled to the expansion, and not meeting the criteria for disease progression for AML patients enrolled into the expansion.

If glasdegib is permanently discontinued for reasons other than objective disease progression, patient refusal, or consent withdrawal, single-agent treatment with azacitidine may be continued if, in the Investigator's judgment, a clinical benefit has been observed and following discussion between the Investigator and Sponsor.

In cases of unacceptable toxicity or pregnancy, the patient must be withdrawn from study drug combination and entered into the follow-up phase.

When study treatment with both drugs (glasdegib and azacitidine) is permanently discontinued, patients will enter into the follow-up phase. Patients receiving at least one dose of study treatment will be followed up for survival for up to 2 years from the first visit of the last patient enrolled in the expansion component of the study, or until death, lost to follow-up, or consent withdrawal.

3.3.2. Study Assessments Summary

Patients will be followed for efficacy throughout the study by means of bone marrow aspirates. Following study entry, bone marrow biopsies will only be required if adequate bone marrow aspirates are not obtained. A CR or PR response needs to be confirmed at least 4 weeks following the BM evaluation by assessing the stability of improved counts on PB, an additional bone marrow confirmatory specimen is not required (applies to all patients in the safety LIC and only MDS patients in the expansion component).

CCI [redacted] Transfusional support (red blood cells and platelets) will also be recorded. Timely and complete (bone marrow AND peripheral blood counts) disease assessments at screening and during the study, whenever clinically indicated, are essential. Failure to perform any of the required disease assessments will result in the inability to determine disease status for that time point and may weaken the conclusions of the study.

Safety assessments (laboratory, instrumental and clinical) and PK assessments will be performed regularly during the active treatment period in both components of the study.

DDI assessments were performed in the safety LIC only.

CCI [redacted]

Please refer to the Schedule of Activities for the Safety Lead-in Cohort and the Schedule of Activities for the Expansion: MDS and AML Patients for a complete list of assessments to be performed on patients in the study.

4. PATIENT SELECTION

This study can fulfill its objectives only if appropriate patients are enrolled. The following eligibility criteria are designed to select patients for whom protocol treatment is considered appropriate. All relevant medical and non-medical conditions should be taken into consideration when deciding whether this protocol is suitable for a particular patient. These criteria must also be met prior to dosing on Cycle 1 Day 1. No exceptions will be granted.

4.1. Inclusion Criteria

Patient eligibility must be reviewed and documented by an appropriate member of the investigator's study team before patients are included in the study.

Patients must meet all the following inclusion criteria to be eligible for enrollment into the study:

4.1.1. Safety Lead-in Cohort

The safety lead-in cohort has been completed.

1. Morphologically confirmed diagnosis of one of the following:

   a. MDS according to the WHO 2008 classification (Appendix 1), and bone marrow blasts ≥5%;

   b. AML with 20-30 % BM blasts and multi-lineage dysplasia, according to WHO 2008 classification(Appendix 1), WBC <20x10^9/L;CMML according to the WHO 2008 classification (Appendix 1**)** and BM blasts between 10% - 19% and WBC <13x10^9/L.

2. MDS patients must have Intermediate-2 (1.5 to 2.0 points) or High-Risk (≥2.5 points) disease according to the International Prognostic Scoring System 1997 (IPSS).

3. MDS patients must have normal levels of vitamin B12 within the institutional range of normal as determined within 28 days of study entry.

4. AML patients with 20-30% BM blasts and multi-lineage dysplasia, must have stable blast counts per Investigator's judgment.

5. Clinical indication for treatment with azacitidine for MDS, AML or CMML.

6. Eastern Cooperative Oncology Group (ECOG) Performance Status ≤2. See Appendix 9.

7. ≥18 years of age.

8. Adequate Renal Function:

   - Serum creatinine ≤1.5 x upper limit of normal (ULN);

   OR

   - Estimated creatinine clearance ≥60 ml/min (calculated using the standard method for the institution).

9. Adequate Liver Function:

- Total serum bilirubin ≤1.5 x ULN (unless the bilirubin is principally unconjugated and there is strong suspicion of sub-clinical hemolysis or the patient has documented Gilbert's disease);
- Aspartate transaminase (AST) and Alanine transaminase (ALT) ≤2.5 x ULN;
- Alkaline phosphatase ≤2.5 x ULN.

10. Serum amylase or lipase <1.5 x ULN.
11. Serum or urine pregnancy test (for female patients of childbearing potential) with a minimum sensitivity of 25 IU/L or equivalent units of human chorionic gonadotropin (HCG) negative at screening.
12. Male and female patients of childbearing potential and at risk for pregnancy must agree to use two highly effective method(s) of contraception throughout the study and for 90 days after the last dose of azacitidine and the last dose of glasdegib or placebo, whichever occurs later.
13. Female patients who are not of childbearing potential (ie, meet at least 1 of the following criteria):
    a. Have undergone a documented hysterectomy and/or bilateral oophorectomy;
    b. Have medically confirmed ovarian failure; or
14. Achieved postmenopausal status, defined as follows: cessation of regular menses for at least 12 consecutive months with no alternative pathological or physiological cause; status may be confirmed by having a serum follicle stimulating hormone (FSH) level within the laboratory's reference range for postmenopausal women.
15. Evidence of a personally signed and dated informed consent document indicating that the patient (or a legally acceptable representative) has been informed of all pertinent aspects of the study.
16. Patients who are willing and able to comply with scheduled visits, treatment plans, laboratory tests and other procedures (including BM assessments).

4.1.2. Expansion

Patients must meet all the following inclusion criteria to be eligible for enrollment into the expansion cohorts:

1. Patients must have previously untreated MDS or AML according to the WHO 2016 classification. (Appendix 17).
    a. The following AML patients will be included:

- AML arising from MDS or another antecedent hematologic disease (AHD).
- AML after previous cytotoxic therapy or radiation (secondary AML).

b. MDS patients must have Intermediate (>3 to 4.5 points), High-Risk (>4.5 – 6) or Very High-Risk (>6 points) disease according to the Revised International Prognostic Scoring System 2012 (IPSS-R). (Appendix 10).

- CMML patients according to the WHO 2016 classification (Appendix 17) are included in the MDS cohort.
- MDS/MPN, unclassifiable patients according to the WHO 2016 classification (Appendix 17) are included in the MDS cohort.

2. Clinical indication for treatment with azacitidine for MDS or AML.

3. ≥18 years of age.

4. Adequate organ function as defined by the following:

- Total serum bilirubin ≤2 x ULN (unless the bilirubin is principally unconjugated and there is strong suspicion of sub-clinical hemolysis or the patient has documented Gilbert's disease);
- Aspartate transaminase (AST) and Alanine transaminase (ALT) ≤3 x ULN, excluding patients with liver function abnormalities due to underlying malignancy;
- Estimated creatinine clearance ≥30 mL/min as calculated using the standard method for the institution.

5. Serum or urine pregnancy test (for female patients of childbearing potential) with a minimum sensitivity of 25 IU/L or equivalent units of human chorionic gonadotropin (HCG) negative at screening.

6. Male and female patients of childbearing potential and at risk for pregnancy must agree to use at least (1) highly effective method(s) of contraception throughout the study and for 180 days after the last dose of azacitidine and the last dose of glasdegib, whichever occurs later.

7. Female patients who are not of childbearing potential must meet at least 1 of the following criteria:

a. Have undergone a documented hysterectomy and/or bilateral oophorectomy;

b. Have medically confirmed ovarian failure; or

c. Achieved postmenopausal status, defined as follows: cessation of regular menses for at least 12 consecutive months with no alternative pathological or physiological cause; status may be confirmed by having a serum follicle stimulating hormone (FSH) level within the laboratory's reference range for postmenopausal women.

All other female patients (including female patients with tubal ligations) are considered to be of childbearing potential.

8. Evidence of a personally signed and dated informed consent document indicating that the patient (or a legally acceptable representative) has been informed of all pertinent aspects of the study.

9. Patients who are willing and able to comply with scheduled visits, treatment plans, laboratory tests and other procedures (including BM assessments).

4.2. Exclusion Criteria

4.2.1. Safety Lead-in Cohort

The safety lead-in cohort has been completed.

Patients with any of the following may not be included in the study:

1. Patients with AML who are candidates for standard induction chemotherapy as first line treatment.

2. Therapy-related (secondary to radiation or chemotherapy) MDS or AML.

3. Prior hypomethylating agents or cytotoxic chemotherapy for MDS, AML or CMML (prior immunosuppressive therapy and hydroxyurea are permitted provided that treatment is stopped within 8 and 2 weeks from study entry, respectively).

4. Previous hematopoietic stem cell transplant.

5. Prior treatment with a licensed or experimental smoothened inhibitor (SMOi) and/or hypomethylating agent (HMA).

6. Participation in a clinical study involving an investigational drug(s) (Phases 1-4) within 4 weeks prior to study entry.

7. Major surgery or radiation within 12 weeks prior to study entry.

8. Patients known to be refractory to platelet or packed red cell transfusions as per institutional guidelines, or who are known to refuse or who are likely to refuse blood product support.

9. Treatment with hematopoietic growth factors including: erythropoietin, granulocyte colony stimulating factor (G-CSF), and granulocyte macrophage colony stimulating factor (GM-CSF), or thrombopoietin receptor agonists within 3 weeks prior to study entry.

10. Any ongoing medical condition requiring chronic use of moderate to high dose steroids (defined as ≥10 mg/day of prednisone or equipotent dose of another corticosteroid).

11. Any anti-cancer treatment within 2 weeks prior to study entry.

12. Current use or anticipated requirement for drugs that are known strong CYP3A4/5 inducers (Appendix 4).

13. Diagnosis of any malignant disease other than MDS, AML or CMML within the prior 12 months, with the exception of adequately treated: (i) in-situ carcinomas, (ii) basal or squamous cell carcinoma, or (iii) non-melanoma skin cancer.

14. Known malabsorption syndrome or other condition that may impair the absorption of the study drug (eg, gastrectomy, lap band, Crohn's disease) and inability or unwillingness to swallow tables or capsules.

15. Patients with active, uncontrolled bacterial, fungal or viral infection, including hepatitis B (HBV), hepatitis C (HCV), known human immunodeficiency virus (HIV), or acquired immunodeficiency syndrome (AIDS) related illness.

16. Known uncontrolled central nervous system (CNS) involvement.

17. Known moderate to severe chronic obstructive pulmonary disease, interstitial lung disease, or pulmonary fibrosis.

18. Prior history of chronic liver disease (eg, chronic alcoholic liver disease, autoimmune hepatitis, sclerosing cholangitis, primary biliary cirrhosis, hemachromatosis, hepatic tumors, non-alcoholic steatohepatitis [NASH]).

19. Any one of the following ongoing or in the previous 6 months: myocardial infarction, congenital long QT syndrome, Torsades de pointes, arrhythmias (including sustained ventricular tachyarrhythmia), right or left bundle branch block and bifascicular block, unstable angina, coronary/peripheral artery bypass graft, symptomatic congestive heart failure (CHF New York Heart Association class III or IV), cerebrovascular accident, transient ischemic attack or symptomatic pulmonary embolism; as well as bradycardia defined as <50 bpms.

20. Active cardiac dysrhythmias of NCI CTCAE Grade ≥2 (eg, atrial fibrillation) or QTcF interval >470 msec.

21. Pregnant or breastfeeding female patients.

22. Patients who are investigational site staff members directly involved in the conduct of the study and their family members, site staff members otherwise supervised by the investigator, or patients who are Pfizer employees directly involved in the conduct of the study.

23. Documented or suspected hypersensitivity to azacitidine or mannitol.

24. Other severe acute or chronic medical or psychiatric conditions, including recent (within the past year) or active/ongoing suicidal ideation or behavior, or laboratory abnormalities that may increase the risk associated with study participation or investigational product administration or may interfere with the interpretation of study results and that in the judgment of the investigator, would make the patient inappropriate for entry into the study.

4.2.2. Expansion Cohorts

Patients with any of the following may not be included in the study:

1. Acute Promyelocytic Leukemia (APL) patients (French-American-British [FAB] M3 classification) with t(15;17) or APL with promyelocytic leukemia/retinoic acid receptor alpha (PML-RARA) (WHO 2016 classification).

2. Patients with a t(9:22) cytogenetic translocation (AML with BCR-ABL1) as a sole abnormality.

3. Patients with AML who are candidates for standard induction chemotherapy as first line treatment.

4. Patients with known active CNS leukemia.

5. Prior treatment with a smoothened inhibitor (SMOi) and/or hypomethylating agent.

6. Participation in a clinical study involving an investigational drug(s) (Phases 1-4) within 4 weeks prior to study entry.

7. Major surgery or radiation within 12 weeks prior to study entry for safety LIC, 4 weeks in the expansion component.

8. Patients known to be refractory to platelet or packed red cell transfusions as per institutional guidelines, or who are known to refuse or who are likely to refuse blood product support.

9. Current use or anticipated requirement for drugs that are known strong CYP3A4/5 inducers.

10. Diagnosis of any active malignancy on treatment with the exception of adequately treated: (i) in-situ carcinomas, (ii) basal or squamous cell carcinoma, or (iii) non-melanoma skin cancer. Other prior or concurrent malignancies will be considered on a case-by-case basis.

11. Known malabsorption syndrome or other condition that may impair the absorption of the study drug (eg, gastrectomy, lap band, Crohn's disease) and inability or unwillingness to swallow tablets or capsules.

12. Patients with an active, life threatening or clinically significant uncontrolled systemic infection.

13. Current drug or alcohol abuse.

14. Any one of the following ongoing or in the previous 6 months: myocardial infarction, congenital long QT syndrome, Torsades de pointes, symptomatic arrhythmias (including sustained ventricular tachyarrhythmia), left bundle branch block or bifascicular block, unstable angina, coronary/peripheral artery bypass graft, symptomatic congestive heart failure (CHF New York Heart Association class III or IV), cerebrovascular accident, transient ischemic attack or symptomatic pulmonary embolism; as well as bradycardia defined as <50 bpms.

15. QTc interval >470 msec using the Fredericia correction (QTcF).

16. Pregnant or breastfeeding female patients.

17. Patients who are investigational site staff members directly involved in the conduct of the study and their family members, site staff members otherwise supervised by the investigator, or patients who are Pfizer employees directly involved in the conduct of the study.

18. Documented or suspected hypersensitivity to azacitidine or mannitol.

19. Other severe acute or chronic medical or psychiatric conditions, including recent (within the past year) or active/ongoing suicidal ideation or behavior, or laboratory abnormalities that may increase the risk associated with study participation or investigational product administration or may interfere with the interpretation of study results and that in the judgment of the investigator, would make the patient inappropriate for entry into the study.

4.3. Lifestyle Guidelines

In this study, male subjects who are able to father children and female subjects who are of childbearing potential will receive azacitidine, a compound that has been shown to cause congenital malformations in animals and glasdegib, a compound which has been associated with teratogenic risk. Subjects who are, in the opinion of the investigator, sexually active and at risk for pregnancy with their partner(s) must agree to use at least 1 highly effective

form of contraception throughout the study and for at least 180 days after the last dose of investigational product. Male subjects must, additionally, use a condom to prevent potential transmission of investigational product in seminal fluid. The investigator or his or her designee, in consultation with the subject, will confirm that the subject has selected at least 1 appropriate method of contraception for the individual subject and his/her partner(s) from the list of permitted contraception methods (see below) and will confirm that the subject has been instructed in their consistent and correct use. At time points indicated in the Table 3 Schedule of Activities for the Expansion: MDS and AML Patients, the investigator or designee will inform the subject of the need to use at least 1 highly effective method of contraception consistently and correctly and document the conversation, and the subject's affirmation, in *the subject's* chart. In addition, the investigator or designee will instruct the subject to call immediately if the selected contraception method is discontinued or if pregnancy is known or suspected in the subject or partner(s).

Highly effective methods of contraception are those that, alone or in combination, result in a failure rate of less than 1% per year when used consistently and correctly (ie, perfect use) and include the methods described in Table 11.

Table 11. Methods of Birth Control

Highly effective (failure rate <1% if used consistently and correctly) low user dependency	**Highly effective (failure rate <1% if used consistently and correctly) high user dependency**
• Progestogen only contraceptive implant; • Intrauterine hormone releasing system (IUS); • Intrauterine device (IUD); • Bilateral tubal occlusion.	Combined hormonal contraception (estrogen and progestogen) • Oral; • Intravaginal; • Transdermal; • Injectable.
Vasectomized partner: A vasectomized partner is a highly effective form of contraception provided they are the sole male partner of the women of child bearing potential and the absence of sperm has been confirmed. If not an additional highly effective method of contraception should be used.	Progestogen only hormonal contraception • Oral; • Injectable.

4.4. Sunlight Exposure

Patients will be advised to report any reaction to sun exposed skin. In addition, special precautions will be taken to limit any potential photo irritation effect, by minimizing the patients' exposure to light including high intensity ultraviolet b (UVb) sources such as tanning beds, tanning booths and sunlamps. Patients should be advised to apply sunscreen/sunblock daily.

4.5. Sponsor's Qualified Medical Personnel

The contact information for the sponsor's appropriately qualified medical personnel for the study is documented in the study contact list located in the Study Reference Manual.

To facilitate access to appropriately qualified medical personnel on study-related medical questions or problems, patients are provided with a contact card. The contact card contains, at a minimum, protocol and investigational compound identifiers, patient study numbers, contact information for the investigational site, and contact details for a help desk in the event that the investigational site staff cannot be reached to provide advice on a medical question or problem originating from another healthcare professional not involved in the patient's participation in the study. The help desk number can also be used by investigational staff if they are seeking advice on medical questions or problems; however, it should only be used in the event that the established communication pathways between the investigational site and the study team are not available. It is therefore intended to augment, but not replace, the established communication pathways between the investigational site and the study team for advice on medical questions or problems that may arise during the study. The help desk number is not intended for use by the patient directly, and if a patient calls that number, he or she will be directed back to the investigational site.

5. STUDY TREATMENTS

5.1. Allocation to Treatment

5.1.1. Safety Lead-In Cohort and Expansion

During both components of the study, allocation of patients to treatment groups will proceed through the use of an Interactive Response Technology (IRT) System [Interactive Web Response (IWR)/Interactive Voice Response (IVR)]. The site personnel (study coordinator or specified designee) will be required to enter or select information including but not limited to the user's identification (ID) and password, protocol number and the date of birth of the patient. The site personnel will then be provided with a treatment assignment and dispensable unit (DU) or container number when drug is being supplied via the IRT. The IRT system will provide a confirmation report containing the patient number and DU or container number assigned. The confirmation report must be stored in the site's files.

There is a 24 hour a day, 365 days a year IRT helpdesk available for any questions or issues. The study-specific IRT reference manual will provide the contact information and further details on the use of the IRT. Note: The IRT is the source of the patient number. The IRT system will provide the patient number at the end of the first IRT patient transaction.

In the Safety LIC and expansion, allocation to treatment will occur in an open label fashion.

5.2. Patient Compliance

For glasdegib, all patients will maintain patient dosing diaries throughout the study which will record the date of administration and all regular, missed, changed, or delayed doses.

Patients are required to return all bottles, unused study drug and the patient dosing diary, at each cycle and at End of Treatment visit for compliance assessment and drug accountability. The number of tablets returned by the patient at the end of the cycle will be counted, documented and recorded.

For azacitidine provided by the Sponsor, the site should complete the required dosage Preparation Record located in the Study Reference Manual. The use of the Preparation Record is preferred but it does not preclude the use of an existing appropriate clinical site documentation system. The existing clinical site's documentation system should capture all pertinent/required information on the preparation and administration of the dose including the methodology used to calculate the patient body surface area. This may be used in place of the Preparation Record after approval from the Sponsor.

5.3. Drug Supplies

5.3.1. Formulation and Packaging

5.3.2. Glasdegib

Glasdegib will be supplied by Pfizer Worldwide Research and Development as 25 mg and 100 mg tablets for oral administration. Supplies will be labeled according to local regulatory requirements.

Glasdegib will be packaged in high-density polyethylene (HDPE) bottles and should be handled with care. Each bottle will contain enough medication for a 28-day cycle of daily dosing, plus an additional amount to cover the time between site visits. Patients should be instructed to keep their medication in the bottles provided and not transfer it to any other containers and return the bottles to the site at the next study visit. Site personnel must ensure that patients clearly understand the directions for self-medication.

Investigational product should be dispensed by an appropriately qualified and experienced member of the study staff (eg, physician, nurse, physician’s assistant, practitioner, or pharmacist) as allowed by local, state, and institutional guidance.

5.3.3. Azacitidine

Azacitidine 25 mg/mL powder for suspension for injection will be used in this study. Please refer to the local package insert (or SPC) or the investigational product manual for detailed formulation, preparation and IV and SC administration instructions.

Only qualified personnel who are familiar with procedures that minimize undue exposure to them and to the environment should undertake the preparation, handling, and safe disposal of chemotherapeutic agents.

5.4. Administration

5.4.1. General Guidelines

Both study drugs are administered in 28-day cycles. Cycle duration maybe extended beyond 28 days to allow resolution of toxicities related to study treatments. It is suggested that sites contact the patients via phone during the first week of Cycle 1 and anytime there is a dose reduction just to confirm that the patient adequately understands the dosing instructions.

Glasdegib will be self-administered by the patient at home, unless otherwise specified. Glasdegib will be administered orally with approximately 8 ounces (240 mL) of water and should be taken in the morning, at the same time each day. Tablets must not be crushed or cut; they must be swallowed whole, not manipulated or not chewed prior to swallowing. Patients should be instructed to self-administer their medication in the morning at approximately the same time each day and to not take more than the prescribed dose at any time. If a patient forgets to take their dose at the regularly scheduled time, and if less than 10 hours have passed since the scheduled dosing time, that dose should be taken as soon as possible. If more than 10 hours have passed since the scheduled dosing time, the dose should be skipped and the patient should continue on their normal dosing schedule. If a patient misses a day's dose entirely, they must be instructed not to "make it up" the next day. If a patient vomits any time after taking a dose, they must be instructed not to "make it up," but to resume subsequent doses the next day as prescribed. If a patient inadvertently takes 1 extra dose during a day, the patient should not take the next dose of glasdegib. The patient will be reminded **NOT** to take their dose at home on clinic days but to bring their bottle(s) and patient dosing diary into clinic so that glasdegib may be administered there.

Patients requiring glasdegib dose reduction(s) will be administered multiples of 25 mg tablets and should continue taking the glasdegib at the same time each morning at the dose prescribed by the Investigator (ie, 75 mg QD and 50 mg QD in the form of three or two 25 mg tablets respectively). In situations where clinical benefit is observed, glasdegib can be reduced below 50 mg QD upon Sponsor approval.

Dose modifications are discussed in Section 5.4.5.

5.4.2. Safety Lead-In Cohort

The safety lead-in cohort has been completed.

- Azacitidine will be administered SC daily at a dose of 75 mg/m^2/day on Days 1-7 (every 28 days). No other dosing schedule is permitted.

- Glasdegib will be orally administered daily and continuously. In Cycle 1 only, administration of glasdegib will commence on Day 2 of the cycle (C1D2) to permit DDI evaluation. The starting dose will be 100 mg.

- Dose modifications are discussed in Section 5.4.5.

5.4.3. Expansion

- Azacitidine will be administered per local label or per the Investigational Product Manual (or SPC). Azacitidine may be administered by SC injection or IV infusion at the starting dose of 75 mg/m^2/day for 7 days every 28 days. Alternate dosing schedules to administer the 7 doses to accommodate patient and treatment center availability are allowed.

- Glasdegib will be orally administered daily and continuously. The starting dose will be 100 mg daily.

Dose modifications are discussed in Section 5.4.5.

5.4.4. Treatment Duration

Since responses to azacitidine may require 4-6 cycles of administration to emerge, treatment with the study drug combination should be continued for at least 6 cycles, or until death, unacceptable toxicity, or patient refusal whichever occurs first. If documentation of disease progression occurs within the first 6 cycles of study treatment the patient **SHOULD NOT** be withdrawn from study treatment if, in the Investigator's judgment, the patient is still likely to receive clinical benefit. In the safety LIC, patients with >30% BM blasts OR a rapidly progressive increase in the proportion of BM blasts at any point during the trial, must discontinue the study drug combination and enter follow-up.

Treatment with the study drug combination should be continued beyond 6 cycles of treatment until objective disease progression or relapse, death, unacceptable toxicity, or patient refusal whichever occurs first. Treatment should also be continued beyond 6 cycles if patients demonstrate reasonable evidence of clinical benefit, defined as HI or better in patients enrolled into the safety LIC, SD + HI or better in MDS patients enrolled to the expansion, and not meeting the criteria for disease progression for AML patients enrolled into the expansion.

If glasdegib is permanently discontinued for reasons other than objective disease progression, patient refusal, or consent withdrawal, single-agent treatment with azacitidine may be continued if, in the Investigator's judgment, a clinical benefit has been observed and following discussion between the Investigator and Sponsor.

In cases of unacceptable toxicity or pregnancy, the patient must be withdrawn from study drug combination and entered into the follow-up phase of the study.

When study treatment with both drugs (glasdegib and azacitidine) is permanently discontinued, patients will enter into the follow-up phase.

5.4.5. Dose Modifications

Every effort should be made to administer the study drug treatment according to the planned dose and schedule.

In the event of significant toxicity, dosing must be interrupted, delayed and/or reduced as outlined below. In the event of multiple toxicities, dose modification should be based on the worst toxicity observed. Patients must be instructed to notify investigators at the first occurrence of any adverse symptom/s.

Dose modifications may occur in three ways:

- **Within a cycle**: Dosing interruption until adequate recovery followed by dose reduction (if required) of glasdegib during a given treatment cycle.
- **Between cycles:** The next treatment cycle may be delayed if toxicity from the preceding cycle persists.
- **In the next cycle**: Dose reduction may be required based on toxicities experienced in the previous cycle.

A cycle is determined by the azacitidine administration schedule. A cycle is 28 days, but will be extended if there are dose delays or modifications for azacitidine. Azacitidine administration should not be interrupted if glasdegib dosing is interrupted for toxicity.

If start of glasdegib administration in the next cycle is delayed due to toxicities potentially attributable to glasdegib, azacitidine administration should not be delayed, and the day when azacitidine administration occurs will be counted as Day 1 of the next cycle for both study drugs.

5.4.5.1. Glasdegib

Glasdegib does not need to be delayed or dose reduced for hematologic toxicity deemed unrelated/unlikely related to glasdegib by the Investigator.

Patients experiencing Grade 3 or 4 non-hematological toxicities potentially attributable to glasdegib should have their glasdegib treatment interrupted regardless of when it occurs in the cycle until the toxicity resolves or returns to baseline or ≤Grade 1, as described in Table 13. If these parameters have not been met following >28 consecutive days of dose interruption, glasdegib should be permanently discontinued. If glasdegib treatment is permanently discontinued, patients may continue single agent treatment with azacitidine, if according to the investigator's judgment a clinical benefit has been observed, and following discussion between the investigator and the sponsor.

Appropriate follow-up assessments should be implemented until adequate recovery (toxicity resolves or returns to baseline) occurs.

Depending on when the adverse event resolved, treatment interruption may lead to the patient missing all subsequent planned doses of glasdegib within the cycle. If the AE leading to

treatment interruption recovers within the same cycle, re-commencement of dosing in that cycle is allowed. The need for a dose reduction at the time of treatment resumption should be based on the criteria outlined in Table 13, unless specifically agreed otherwise following discussion between the Investigator and the Sponsor. If a dose reduction for glasdegib is applied in the same cycle, the patient must return to the clinic to receive a new supply of drug. Glasdegib doses omitted for toxicity will not be replaced within that cycle (eg, cycles will not be prolonged beyond the 28 days in order to make up for any missed glasdegib doses during that cycle).

Glasdegib may be interrupted or permanently discontinued for any reason as per good clinical practice. In the event of glasdegib treatment interruption for reasons other than treatment-related toxicity (eg, elective surgery) for a duration >28 days, the details of treatment resumption will be determined in consultation with the Sponsor.

Dose reduction of glasdegib by 1 or, if necessary, 2 dose levels (Table 12) will be allowed depending on the type and severity of toxicity encountered. **NOTE**: In the specific situations where clinical benefit is observed, glasdegib can be reduced below 50 mg QD upon Sponsor approval. All dose modifications/adjustments must be clearly documented in the patient's notes and case report form (CRF).

Once the glasdegib dose has been reduced, all subsequent cycles should be administered at that dose level, unless further dose reduction is required. Dose re-escalation is not allowed. Deviations from any of the dose modifications must be discussed and agreed with the Sponsor Medical Monitor.

Table 12. Available Dose Levels

Glasdegib (mg QD)
100
75
50
25 *

* **NOTE**: If clinical benefit is observed, glasdegib may be reduced below 50 mg QD following Sponsor approval.

Dose modifications for treatment-related non-hematologic toxicities (excluding QTc prolongation, muscle spasms, and myalgia) are outlined in Table 13.

Table 13. Dose Modifications for Non Hematologic Toxicities (Excluding QTc Prolongation, Muscle Spasms, and Myalgia)

Toxicity (NCI CTCAE version 4.03)	Glasdegib
≥ Grade 3 toxicity (Nausea, vomiting, and/or diarrhea must persist at ≥ Grade 3 (despite maximal appropriate medical therapy) to require dose modification)	Hold glasdegib until toxicity has recovered to ≤ Grade 1. **First episode**: Decrease by 1 dose level **Second episode**: Decrease by 1 dose level **Third episode**: Permanently discontinue
Potential drug induced liver injury/Hy's Law (as defined in Section 8.6.2)	Interrupt glasdegib dosing. If an alternative cause is found, restarting of glasdegib at the same dose may be considered.
Confirmed drug induced liver injury/Hy's Law (as defined in Section 8.6.2)	Glasdegib should be permanently discontinued.

Patients should be closely monitored for potential cardiovascular symptoms. Appropriate monitoring should include clinical examinations, vital signs, routine ECGs, and AE monitoring. In case of QTc prolongation, concomitant conditions such as electrolyte imbalances, hypoxia, or use of medications affecting the QT interval should be ruled out and/or corrected. In case of clinically significant toxicities, glasdegib administration should be interrupted and the dose reduced as indicated in Table 14.

Concomitant administration of glasdegib with moderate/strong CYP3A4/5 inhibitors (Appendix 6 and Appendix 7) and drugs with known risk of Torsade de Pointes (TdP) (Appendix 5) is not recommended due to the potential for drug-drug interaction to prolong the QTc interval. However, if it is medically necessary for patients to use these medications please refer to Section 7.6 for monitoring procedures. All protocol specified QTcF prolongation-related exclusion criteria must be followed. Investigators must be aware of the QTcF-prolonging potential of all medications that patients on study are taking, and should take appropriate action when clinically indicated. Given the potential for QTcF prolongation, the measurement and immediate correction of electrolyte abnormalities such as potassium

and magnesium, and of other reversible causes of QTcF prolongation such as hypoxia, are especially important. In the event that the QTcF interval is prolonged beyond 480 ms (CTCAE v.4.03 ≥ Grade 2), Table 14 must be referenced and actioned. Additional ECG and cardiac consultation should be obtained if clinically indicated.

Table 14. Glasdegib Dose Modifications for mean QTcF (mQTcF) Prolongation

CTCAE v 4.03	Grade 1	Grade 2	Grade 3**	Grade 4
Electrocardiogram QT corrected (QTc) interval prolonged*	450-480 msec	481-500 msec	≥501 msec at least two separate ECGs	QTc >= 501 or >60 msec change from baseline and Torsade de pointes or polymorphic ventricular tachycardia or signs/symptoms of serious arrhythmia

*The severity of QTc prolongation assessment is to be done by calculating a mean QT of 3 consecutive ECGs performed approximately 2 minutes (but no longer than 5 minutes) apart by using the Fridericia correction method (mQTcF).
** If mQTcF is ≥501 msec, continuous ECG monitoring and cardiology consultation are required.

		Grade			
Category	Requirement	1	2	3	4
ECG monitoring	Continuous ECG monitoring and cardiology consultation for mQTcF ≥501 msec			x	x
Initial glasdegib action	Discontinue and do not re-challenge.				x
	Interrupt treatment		x	x	
	Continue at same level	x			
General management	Assess and correct electrolyte abnormalities.	x	x	x	x
	Withhold any concomitant medications (if possible) that may cause QTc prolongation.		x	x	x
Resume glasdegib dosing	At prior dose if mQTcF returns to ≤470 msec and to within 20 msec of baseline in 7 days and if no prior dose interruption related to mQTcF prolongation has occurred		x	x	
	At one lower dose level if mQTcF returns to ≤470msec and to within 20 msec of baseline between 7-14 days and if no prior dose interruption related to mQTcF prolongation has occurred		x	x	
	At one lower dose level if mQTcF returns to ≤470 msec and to within 20 msec of baseline in 14 days if one prior dosing interruption related to mQTcF prolongation has occurred		x		
Management after dose resumed	An ECG should be repeated and mQTcF re-assessed approximately 7 days after glasdegib dosing resumption following interruption for a mQTcF prolongation		x	x	

Table 14. Glasdegib Dose Modifications for mean QTcF (mQTcF) Prolongation

Discontinue glasdegib permanently	The mQTcF prolongation does not return to ≤470 msec and to within 20 msec of baseline after 14 days		x	x	
	The Grade ≥2 mQTcF prolongation recurs after one dose reduction related to mQTcF prolongation		x	x	
	The Grade ≥3 mQTcF prolongation recurs after one prior dosing interruption related to mQTcF prolongation has occurred			x	
	If at any time during the 14 day window that glasdegib is stopped due to QTcF prolongation the patient has a confirmed mean QTcF interval >515 msec or becomes symptomatic		x	x	

Dose modifications for glasdegib in case of drug class related AEs are outlined in Table 15.

Table 15. Dose Modifications for Glasdegib in Case of Drug Class Related AEs

Muscle Spasms or Myalgia	Grade 1	Grade 2	Grade 3
Glasdegib	Continue at same dose level. Administer oral rehydration solutions containing electrolytes.[a] Consider other appropriate interventions (eg, anti-spasmodics) as per institutional guidelines. Evaluate levels of: CK, Vit B6, Vit D, ferritin, transferin and electrolytes (Na, K, Mg, Ca and P).[b] If CK is elevated, evaluate urine and serum myoglobin, CK isoenzymes, and serum creatinine.	Continue at same dose level. Administer oral re-hydration salts containing electrolytes.[a] Consider other appropriate interventions (eg, anti-spasmodics) as per institutional guidelines. Evaluate levels of: CK, Vit B6, Vit D, ferritin, transferin and electrolytes (Na, K, Mg, Ca and P).[b] If CK is elevated, evaluate urine and serum myoglobin, CK isoenzymes, and serum creatinine. If event persists, hold dose until resolution to Grade ≤1. Upon resolution, restart at prior dose, or for prolonged muscle spasms, consider reducing dose by one dose level.	Hold dose. Administer oral re-hydration salts containing electrolytes.[a] Consider other appropriate interventions (eg, anti-spasmodics) as per institutional guidelines. Evaluate levels of: CK, Vit B6, Vit D, ferritin, transferin and electrolytes (Na, K, Mg, Ca and P).[b] If CK is elevated, evaluate urine and serum myoglobin, CK isoenzymes, and serum creatinine. Upon resolution to Grade ≤1, restart study treatment at next lower dose level. If the event does not resolve within 3 weeks to Grade ≤1, at the discretion of the Investigator the dose may be restarted at the next lower dose level or the patient may be permanently discontinued from study treatment.

Abbreviations: CK creatinine kinase; Vit vitamin; Na sodium; K potassium; Mg magnesium; Ca calcium; P phosphorous.

a. Electrolyte replacement drinks should include Na, K, Mg, Ca and P. Consideration should be given to ensuring adequate hydration prior to bedtime, and whenever fluid intake is decreased for a prolonged duration.
b. Labs may be drawn as unscheduled assessments between protocol visits.
In the event of alopecia or dysgeusia, investigator discretion should be applied with respect to dose interruption and/or dose reduction of glasdegib as preliminary analysis of available clinical data suggests that these events are not dose dependent.

5.4.5.2. Azacitidine

For azacitidine dose modification, refer to the local package insert (or SPC) or Investigational Product Manual.

5.5. Drug Storage

The investigator, or an approved representative, eg, pharmacist will ensure that all investigational products, including any comparative agents and/or marketed products are stored in a secured area with controlled access under recommended storage conditions and in accordance with applicable site and regulatory requirements.

Storage conditions stated in the SRSD (IB for glasdegib and EU SPC for Vidaza®[27]) will be superseded by the storage conditions stated in the labeling.

Glasdegib should be stored as described on the drug label. Note that the storage conditions in any study documentation will be superseded by the storage conditions stated on the product label. Patients should be instructed to keep their medication in its original container. Returned medication should be stored at the clinical site separately from medication that needs to be dispensed.

Azacitidine will be stored according to the labeled storage conditions.

Investigators and site staff are reminded to check temperatures daily (ie, manually or by using alarm systems to alert of any excursions) and ensure that thermometers are working correctly as required for proper storage of investigational products. These include thermometers for both the room storage and refrigerator storage. Any temperature excursions should be reported to the sponsor.

The investigational product(s) must be stored as indicated. Deviations from the storage requirements, including any actions taken, must be documented and reported to the sponsor. Once a deviation is identified, the investigational product must be quarantined and not used until the sponsor provides documentation of permission to use the investigational product.

Site systems must be capable of measuring and documenting (for example, via a log), at a minimum, daily minimum and maximum temperatures for all site storage locations (as applicable, including frozen, refrigerated and/or room temperature products). This should be captured from the time of investigational product receipt throughout study. Even for continuous monitoring systems, a log or site procedure which ensures active daily evaluation for excursions should be available. The operation of the temperature monitoring device and storage unit (for example, refrigerator), as applicable, should be regularly inspected to ensure it is maintained in working order.

Any excursions from the product label storage conditions should be reported upon discovery. The site should actively pursue options for returning the product to labeled storage conditions, as soon as possible. Deviations from the storage requirements, including any actions taken, must be documented and reported to the sponsor.

Once a temperature excursion is identified, the investigational product must be quarantined and not used until the sponsor provides documentation of permission to use the investigational product. Specific details regarding information the site should report for each excursion will be provided to the site.

Site staff will instruct patients on the storage requirements for take home medications including how to report temperature excursions.

5.6. Drug Accountability

The investigator's site must maintain adequate records documenting the receipt, use, loss, or other disposition of the drug supplies. At each dispensing visit (Cycle 2 Day 1, Cycle 3 Day 1, etc. or when there is a dose reduction), all unused or partially used bottles must be returned by patients to the Investigator. The number of tablets returned by the patient at the end of the cycle will be counted, documented and recorded.

The sponsor or designee will provide guidance on the destruction of unused investigational product (eg, at the site). If destruction is authorized to take place at the study site, the investigator must ensure that the materials are destroyed in compliance with applicable environmental regulations, institutional policy, and any special instructions provided by sponsor or designee and all destruction must be adequately documented.

5.7. Concomitant Treatment(s)

All concomitant medications and treatments must be recorded in the CRF. Any prior treatment received within 28 days prior to study entry (including hematopoietic growth factor receptor agonists: erythropoietin, granulocyte colony stimulating factor (G-CSF), romiplostim, eltrombopag) will be recorded in the CRF.

In addition, any transfusion (red blood cells or platelets) within 8 weeks prior to screening should be recorded in the CRF.

All prior immunosuppressive therapy (eg, cyclosporine) used to treat MDS, or all prior cyto-reduction therapy (eg, hydroxyurea) used to treat AML or CMML, will be recorded regardless of when they were received by the patient. Information collected will include dates of use, best treatment response and the reasons for stopping therapy.

Every concomitant treatment, blood products, growth factors, as well as interventions, required by the patients during the active study treatment (and up to 28 days following last study drug administration or until initiation of another anti-cancer treatment) and the reason for its administration must be recorded on the CRF.

All concomitant medications the patient is currently receiving must be reviewed by the Sponsor prior to enrollment in the safety LIC. Study entry criteria are defined in Section 4.

5.7.1. Restricted or Prohibited Concomitant Medications

The following medications are not allowed during the active study treatment period:

- Agents used to treat AML or MDS; for control of rapidly progressing leukemia, hydroxyurea and/or leukopheresis may be used before and for up to 1 week after the first dose of glasdegib;
- Investigational agents;

- CYP3A4/5 Inducers: A drug-drug interaction study in health subjects with the strong CYP3A4 inducer, rifampin, resulted in a 70% decrease in plasma exposures (AUC_{inf}) and a 35% decrease in peak plasma concentration (C_{max}) of a single 100-mg oral dose of glasdegib. Therefore co-administration of glasdegib and moderate/strong CYP3A4/5 inducers is not permitted. A comprehensive list of moderate/strong CYP3A4/5 inducers is provided in Appendix 4. However, if you are uncertain whether a concomitant medication is contraindicated, you should contact the Sponsor study team.

The following medications have use restrictions during the active study treatment period:

- CYP3A4/5 Inhibitors: In vitro studies with human liver microsomes and recombinant CYP enzymes indicated that glasdegib metabolism is primarily mediated by the drug-metabolizing enzyme CYP3A4/5. Clinically, there is likelihood that glasdegib plasma concentrations may be increased in the presence of co-administered inhibitors of the CYP3A4/5 enzymes. In a healthy volunteer study, ketoconazole, a potent CYP3A4/5 inhibitor, produced a 2.4-fold increase in plasma exposure and a 1.4-fold increase in peak plasma concentration of glasdegib. Therefore a potential exists for drug-drug interactions with CYP3A4/5 inhibitors, and co-administration of glasdegib in combination with moderate/strong CYP3A4/5 inhibitors is not recommended. Selection of concomitant medication with no or minimal CYP3A4/5 inhibition potential is recommended. Moderate/strong CYP3A4/5 inhibitors (Appendix 6 and Appendix 7) should be used with caution and only if considered medically necessary. If a moderate/strong CYP3A4/5 inhibitor is to be initiated in addition to glasdegib, the guidance provided in Section 7.6 and dose modifications for QT prolongation per Table 14 must be followed.

- Drugs with a known risk of Torsade de pointes (TdP): Glasdegib has been shown to have the potential to prolong the QTc interval in pre-clinical studies and at doses >200 mg (see Section 1.2.20 for summary of TQT study). While the glasdegib dose being evaluated in this study is 100 mg, the concomitant administration of glasdegib and drugs with a known risk of Torsade de pointes should be avoided whenever possible. A list of such drugs is provided in Appendix 5. Use of these drugs is not recommended unless there are no alternatives. If a TdP drug is to be initiated in addition to glasdegib, the guidance provided in Section 7.6 and dose modifications for QT prolongation per Table 14 must be followed.

- QT prolonging medications (without a risk of TdP) should be avoided whenever possible.

- Concomitant administration of multiple moderate/strong CYP3A4/5 inhibitors, TdP drugs, and/or QT prolonging medications (without a risk of TdP) is not recommended and must be discussed with the Sponsor Medical Monitor.

5.7.2. Permitted Concomitant Medications

5.7.2.1. Best Supportive Therapy

Best Supportive Therapy (BST) administration is permitted according to Institutional guidelines for all patients on study. BST will be provided by the site and may vary depending on the patient's signs and symptoms, site current practice, and country practice. It includes medications and supportive measures that may palliate disease-related symptoms, improve quality of life and treat bacterial, fungal or viral infections. BST may include:

- Blood transfusions;
- Platelet transfusions;
- Antibiotics;
- Anti-fungal agents;
- Anti-viral agents.

5.7.2.2. Hematopoietic Growth Factors

Hematopoietic growth factors (eg, G-CSF, GM-CSF) may be used according to local practice and guidelines.

5.7.2.3. Anti-Emetic and Anti-Diarrheal Therapy

Patients should be pre-medicated with anti-emetics for nausea and vomiting before each dose of azacitidine in all cycles according to local practice and guidelines.

Primary prophylaxis of diarrhea is permitted at the Investigator's discretion. The choice of the prophylactic drug is up to the investigator assuming the drug is not contraindicated as described in Section 5.7.1.

5.7.3. Surgery

Caution is advised on theoretical grounds for any surgical procedures during the study. The appropriate interval of time between surgery and glasdegib required to minimize the risk of impaired wound healing and bleeding has not been determined. Stopping glasdegib is recommended at least 7 days prior to surgery. Post-operatively, the decision to reinitiate glasdegib treatment is up to the Investigator with Sponsor approval and should be based on a clinical assessment of satisfactory wound healing and recovery from surgery.

6. STUDY PROCEDURES

6.1. Screening

Screening can be accomplished over one or multiple visits over a 4-week period (28 days), unless specifically noted otherwise (ie, bone marrow sample collection). Protocol specific tests or procedures not considered standard of care can only be done after the patient has signed the Informed Consent document. The Informed Consent document may be signed up to 60 days prior to study entry.

See the Schedule of Activities for the Safety Lead-in and the Schedule of Activities for the Expansion: MDS and AML Patients for a complete list of assessments and procedures to be collected during the screening visit.

6.2. Study Period

See the Schedule of Activities for the Safety Lead-in and the Schedule of Activities for the Expansion: MDS and AML Patients for a detailed list of the assessments and procedures to be collected. Study entry is defined as when the patient is enrolled into the IRT system. Patients must be enrolled into the IRT system prior to receiving first dose of study drug.

All assessments on Cycle 1 Day 1 should be collected pre-dose, unless documented otherwise.

6.3. End of Treatment Visit

The End of Treatment Visit should be scheduled as soon as possible once a patient has been withdrawn from study drug. For a detailed list of assessments and procedures to be completed please refer to the Schedule of Activities for the Safety Lead-in and the Schedule of Activities for the Expansion: MDS and AML Patients.

6.4. Follow-up

The first follow up contact should occur at least 28 days, and no more than 35 days after the last dose of study drug to capture any potential adverse events (refer to Section 8.2) and to confirm appropriate contraception usage (refer to Section 4.3). Contact with the patient may be done via phone. For a detailed list of assessments and procedures to be completed please refer to the Schedule of Activities for the Safety Lead-in and the Schedule of Activities for the Expansion: MDS and AML Patients.

In cases of unacceptable toxicity or pregnancy, the patient must be withdrawn from study drug combination and entered into the follow-up phase of the study.

Patients who permanently discontinue both study drugs (azacitidine and glasdegib) for any reason (except death, or withdrawal of patient consent) will enter into the follow-up phase.

Patients continuing to experience toxicity following discontinuation of treatment will continue to be followed minimally every 4 weeks until resolution or determination, in the clinical judgment of the Investigator, that no further improvement is expected.

Patients enrolled in the safety LIC, which has been completed, will be contacted every 3 months to confirm survival status, and to collect information on any new anti-cancer therapy initiated. Telephone calls are acceptable and patients will be followed up to the time of death or consent withdrawal. Patients starting the study long-term follow up phase with ≤30% BM blasts should also have disease assessments (BM aspirate and PB sampling) until blasts are >30% or until initiation of another anti-cancer therapy.

Patients enrolled in the expansion component will be contacted every 3 months to confirm survival status, and to collect information on any new anti-cancer therapy initiated. Date of post-treatment disease progression recorded in the source notes will be collected. CCI [redacted]
Patients receiving at least one dose of study treatment will be followed for survival for up to 2 years from the first visit of the last patient enrolled in the expansion component, or until death, lost to follow-up, or consent withdrawal.

Patients may withdraw from the study at any time at their own request, or they may be withdrawn at any time at the discretion of the Investigator or Sponsor for safety or behavioral reasons or the inability of the patient to comply with the protocol required schedule of study visits or procedures at a given study site.

Reasons for permanent discontinuation of study drug combination treatment may include:

- Objective disease progression or relapse (unless it happens during the first 6 cycles of treatment or the patient according to the Investigator's judgment, can derive a clinical benefit). In the safety LIC, patients with >30% BM blasts OR a rapidly progressive increase in the proportion of BM blasts at any point during the trial must discontinue the study drug combination and enter follow-up;
- Global deterioration of health status;
- Unacceptable toxicity;
- Need for more than 2 dose level reductions of azacitidine;
- Need for cycle start delay >28 days due to persistent drug combination related toxicity, unless the patient is receiving obvious clinical benefit and after discussion between the Sponsor and the Investigator;
- Lost to follow-up;
- Patient refused further treatment (follow-up permitted by the patient);
- Withdrawal of patient consent (cessation of follow-up);
- Pregnancy;
- Start of another anti-cancer treatment;

- Study terminated by Sponsor;
- Death.

Reasons for withdrawal from study may include:

- Study terminated by Sponsor;
- Lost to follow-up;
- Withdrawal of patient consent for any further contact;
- Death.

If a patient does not return for a scheduled visit, every effort should be made to contact the patient. All attempts to contact the patient and information received during contact attempts must be documented in the patient's medical record. In any circumstance, every effort should be made to document patient outcome, if possible. The Investigator should inquire about the reason for withdrawal, request that the patient return all unused investigational product(s), request that the patient return for a final visit, if applicable, and follow up with the patient regarding any unresolved AEs.

If the patient withdraws from the study, and also withdraws consent for disclosure of future information, no further study specific evaluations should be performed, and no additional data should be collected. The Sponsor may retain and continue to use any data collected before such withdrawal of consent.

7. ASSESSMENTS

Every effort should be made to ensure that the protocol-required tests and procedures are completed as described. However, it is anticipated that from time to time there may be circumstances, outside of the control of the investigator, which may make it unfeasible to perform the test. In these cases the investigator will take all steps necessary to ensure the safety and well-being of the patient. When a protocol-required test cannot be performed, the investigator will document the reason for this and any corrective and preventive actions that they have taken to ensure that normal processes are adhered to as soon as possible. The study team must be informed of these incidents in a timely manner.

7.1. Pregnancy Testing

For female patients of childbearing potential, a serum or urine pregnancy test, with sensitivity of at least 25 mIU/mL, will be performed on two occasions prior to starting study therapy - once at the start of screening and once at the baseline visit, immediately before investigational product administration. Following a negative pregnancy result at screening, appropriate contraception (defined in Section 4.3) must be commenced and a further negative pregnancy result will then be required at the baseline visit before the patient may receive the investigational product. Pregnancy tests will also be routinely repeated at every cycle during the active treatment period, at the end of study treatment, and additionally whenever one

menstrual cycle is missed or when potential pregnancy is otherwise suspected. In the case of a positive confirmed pregnancy, the patient will be withdrawn from administration of study drug combination and enter into the Follow-up phase. Additional pregnancy tests may also be undertaken if requested by Institutional Review Boards (IRBs)/Ethic Committees (ECs) or if required by local regulations.

7.2. Adverse Events

Assessment of AEs will include the type, incidence, severity (graded by the NCI CTCAE version 4.03) timing, seriousness, and relatedness. Additional information regarding AE and Serious AE (SAE) reporting is provided in Section 8.

7.3. Laboratory Safety Assessments

Hematology, blood chemistry, coagulation and urinalysis assessments will be drawn at the time points described in the Schedule of Activities for the Safety Lead-in and the Schedule of Activities for the Expansion: MDS and AML Patients and will be analyzed by the site/Investigator at local laboratories. Laboratory certifications and normal ranges with units must be provided to the Sponsor.

If hematology [Complete blood count (CBC) with differentials] is obtained within 3 days of scheduled blood draw, the collection need not be repeated. For those patients achieving a CR or PR, a CBC should be done at least 4 weeks after the BM assessment in order to confirm response (applies to all patients in the safety LIC and only MDS patients in the expansion component). Hematology tests may be repeated also as clinically indicated.

If blood chemistry or coagulations are obtained within 3 days of scheduled blood draw, the collection need not be repeated.

If a urinalysis was obtained within 3 days of the scheduled collection, it should not be repeated. For urinalysis, dipstick is acceptable. Microscopic analyses should be done if abnormal results (ie, the presence of protein or blood).

See Appendix 8 for list of required tests.

7.4. Transfusions

All red blood cell and platelet transfusions, including the date of each transfusion and number of red blood cell or platelet units transfused must be recorded while the patient is on treatment. Transfusion histories for the 8 weeks prior to screening must also be recorded in the CRF. Note that the number of units (not the number of bags) must be recorded.

7.5. Vital Signs and Physical Examination

Vital signs will include blood pressure and heart rate (to be recorded in sitting position). Patients will have a physical exam (PE) including an examination of major body systems (includes general appearance, head, neck, lungs, heart, abdomen, musculoskeletal, extremities, skin, lymph nodes, neurological), measurement by palpation of spleen and liver, weight, height and assessment of ECOG status. If PE obtained within 48 hours of previous

assessments, the evaluation need not be repeated. Height need not be recorded after the first measurement at screening. Weight must be recorded at Screening, Day 1 of each cycle, and End of Treatment.

7.6. Triplicate (12-Lead) ECGs

See Table 2 (for LIC) and Table 4 (for expansion) for the specific time points of ECG collection, and Table 14 for dose modification related to management of QTcF prolongation.

Triplicate 12-lead (with a 10-second rhythm strip) tracing will be performed for ECGs at every timepoint. It is preferable that the machine used has a capacity to calculate the standard intervals automatically. The acceptable mean on treatment upper limit of QTc interval will be using the Fridericia (QTcF) correction method. At each time point 3 consecutive supine ECGs will be performed approximately 2 minutes (but no longer than 5 minutes) apart, to determine the mean QTcF interval. The sites will be provided with a simple calculation tool that will allow for real-time assessment of mean QTcF values from the triplicate QT and heart rate measurements.

If Grade 3 mean QTcF (mQTcF) prolongation occurs (mQTcF ≥501 msec), continuous ECG monitoring and cardiology specialist evaluation and guidance are required.

The acceptable mean on-treatment upper limit of QTcF interval is 480 msec. If any patient has a mean pre- or post-dose QTcF value >480 msec, please refer to Table 14 of the protocol for detailed instructions on management of QTcF prolongation and handling dose delays and dose modifications for glasdegib.

When matched with PK sampling, every effort should be made to perform the ECGs before each PK sample drawing such that the PK sample is collected at the nominal time (ie, the timing of the PK collections over rides the timing of the ECG collections). A 15-min window for each ECG collection is allowed around the nominal ECG time point.

7.7. Efficacy Assessments

7.7.1. Response Criteria

Disease response, measured from baseline through the End of Treatment, will be evaluated using IWG Modified Response Criteria (Appendix 2) for all patients in the Safety Lead-In cohort and for the MDS patients in the Expansion. The 2017 ELN Response Criteria will be applied to all AML patients in the Expansion (Appendix 11).

CR with partial hematologic recovery (CRh) will be assessed for the AML Expansion Cohort. CRh is defined as CR but with ANC >$0.5x10^9$/L and platelets >$50x10^9$/L.

CCI [redacted]

CCI [redacted]

7.7.3. Bone Marrow Biopsies and Aspirates

Please see the Schedule of Activities for the Safety Lead-in and the Schedule of Activities for the Expansion: MDS and AML Patients (footnote 16) for specific assessment timepoints for BM biopsy and aspirate collection. A CR or PR need to be confirmed at least 4 weeks after the BM evaluation by assessing the stability of improved counts on PB according to the IWG criteria; the need for an additional marrow confirmatory specimen is not required (applies to patients enrolled in the safety LIC and MDS patients enrolled in the expansion).

The importance of timely and complete disease assessments (including BM and PB assessments) at screening and during the study, whenever clinically indicated, cannot be understated. Failure to perform any of the required disease assessments will result in the inability to determine disease status for that time point and have the potential to weaken the conclusions of this study.

7.7.4. Pharmacokinetics Assessments

Every effort must be made to obtain the PK samples at the scheduled nominal time relative to dosing. However, PK samples obtained within 10% of the nominal time (eg, within 6 minutes of a 60 minute sample) will be considered protocol compliant, and the exact time of the sample collection should be noted on the CRF. The pre-dose PK sample should be collected within 30 minutes prior to administration of the drug. If a scheduled blood sample collection cannot be completed for any reason, the missed sample time may be rescheduled with agreement of clinical investigators, patient and sponsor.

PK samples will be assayed using a validated analytical method in compliance with Pfizer standard operating procedures. Details regarding the collection, processing, storage and shipping of the blood samples will be provided in the laboratory manual.

7.7.4.1. Glasdegib (Safety Lead-In Cohort and Expansion)

Blood samples (1.5 mL whole blood sufficient to provide a minimum of 0.6 mL of plasma) will be collected for PK analysis of glasdegib as outlined in the PK flowcharts (see Table 2 and Table 4).

7.7.4.2. Azacitidine (Safety LIC Only)

Blood samples (2 mL whole blood sufficient to provide a minimum of 1 mL of plasma) will be collected for PK analysis of azacitidine (and possibly metabolites) as outlined in the PK flowchart (see Table 2).

CCI [redacted]

CCI

[redacted]

CCI

[redacted]

CCI

[redacted]

CCI

[redacted]

CCI [redacted]

CCI [redacted]

- [redacted]
- [redacted]
- [redacted]
- [redacted]

CCI [redacted]

[redacted]

CCI [redacted]

[redacted]

CCI [redacted]

[redacted]

CCI [redacted]

CCI [redacted]

CCI [redacted]

CCI [redacted]

8. ADVERSE EVENT REPORTING

8.1. Adverse Events

All observed or volunteered AEs regardless of treatment group or suspected causal relationship to the investigational product(s) will be reported as described in the following sections.

For all AEs, the investigator must pursue and obtain information adequate both to determine the outcome of the AE and to assess whether it meets the criteria for classification as a serious adverse event (SAE) requiring immediate notification to Pfizer or its designated representative. For all AEs, sufficient information should be obtained by the investigator to determine the causality of the AE. The investigator is required to assess causality. Follow-up by the investigator may be required until the event or its sequelae resolve or stabilize at a level acceptable to the investigator, and Pfizer concurs with that assessment.

As part of ongoing safety reviews conducted by the sponsor, any non-serious AE that is determined by the sponsor to be serious will be reported by the sponsor as an SAE. To assist in the determination of case seriousness, further information may be requested from the investigator to provide clarity and understanding of the event in the context of the clinical study.

8.2. Reporting Period

The time period for actively eliciting and collecting AEs and SAEs ("active collection period") for each subject begins from the time that the subject provides informed consent, which is obtained prior to the subject's participation in the study (ie, prior to undergoing any study-related procedure and/or receiving investigational product), through and including 28 calendar days after the last administration of the investigational product.

For subjects who are screen failures, the active collection period ends when screen failure status is determined.

All SAEs occurring in a subject during the active collection period are to be reported to Pfizer Safety on the Clinical Trial (CT) Serious Adverse Event (SAE) Report Form. SAEs occurring in a patient after the active reporting period has ended should be reported to Pfizer if the investigator becomes aware of them; at a minimum, all SAEs that the investigator believes have at least a reasonable possibility of being related to investigational product are to be reported to Pfizer.

During the active collection period, both non-serious AEs and SAEs are recorded on the CRF.

Follow-up by the investigator may be required until the event or its sequelae resolve or stabilize at a level acceptable to the investigator, and Pfizer concurs with that assessment.

If a subject begins a new anticancer therapy, the recording period for non-serious AEs ends at the time the new treatment is started; however, SAEs must continue to be recorded on the CRF during the above-indicated active collection period.

Death must be reported if it occurs during the SAE reporting period after the last dose of investigational product, irrespective of any intervening treatment.

8.3. Definition of an Adverse Event

An AE is any untoward medical occurrence in a clinical investigation patient administered a product or medical device; the event need not necessarily have a causal relationship with the treatment or usage. Examples of AEs include but are not limited to:

- Abnormal test findings;
- Clinically significant symptoms and signs;
- Changes in physical examination findings;
- Hypersensitivity;
- Drug abuse;
- Drug dependency.

Additionally, they may include the signs or symptoms resulting from:

- Drug overdose;
- Drug withdrawal;
- Drug misuse;
- Drug interactions;
- Extravasation;
- Exposure during pregnancy (EDP);
- Exposure via breastfeeding;
- Medication error;
- Occupational exposure;

- Worsening of signs and symptoms of the malignancy under study should be reported as AEs in the appropriate section of the CRF. Disease progression assessed by measurement of malignant lesions on radiographs or other methods should not be reported as AEs.

8.4. Medication Errors

Medication errors may result, in this study, from the administration or consumption of the wrong product, by the wrong patient, at the wrong time, or at the wrong dosage strength. Such medication errors occurring to a study participant are to be captured on the medication error case report form (CRF) which is a specific version of the adverse event (AE) page, and on the SAE form when appropriate. In the event of medication dosing error, the sponsor should be notified immediately.

Medication errors are reportable irrespective of the presence of an associated AE/SAE, including:

- Medication errors involving patient exposure to the investigational product;
- Potential medication errors or uses outside of what is foreseen in the protocol that do or do not involve the participating patient.

Whether or not the medication error is accompanied by an AE, as determined by the investigator, the medication error is captured on the medication error version of the adverse event (AE) page and, if applicable, any associated AE(s) are captured on an AE CRF page.

8.5. Abnormal Test Findings

The criteria for determining whether an abnormal objective test finding should be reported as an AE are as follows:

- Test result is associated with accompanying symptoms; and/or
- Test result requires additional diagnostic testing or medical/surgical intervention; and/or
- Test result leads to a change in study dosing or discontinuation from the study, significant additional concomitant drug treatment, or other therapy; and/or
- Test result is considered to be an AE by the investigator or sponsor.

Merely repeating an abnormal test, in the absence of any of the above conditions, does not constitute an AE. Any abnormal test result that is determined to be an error does not require reporting as an AE.

8.6. Serious Adverse Events

An SAE is any untoward medical occurrence at any dose that:

- Results in death;
- Is life-threatening (immediate risk of death);
- Requires inpatient hospitalization or prolongation of existing hospitalization;
- Results in persistent or significant disability/incapacity (substantial disruption of the ability to conduct normal life functions);
- Results in congenital anomaly/birth defect.

Progression of the malignancy under study (including signs and symptoms of progression) should not be reported as an SAE unless the outcome is fatal within the safety reporting period. Hospitalization due to signs and symptoms of disease progression should not be reported as an SAE. If the malignancy has a fatal outcome during the study or within the safety reporting period, then the event leading to death must be recorded as an AE and as an SAE with CTCAE Grade 5 (see Section 8.8 on Severity Assessment).

Medical and scientific judgment is exercised in determining whether an event is an important medical event. An important medical event may not be immediately life-threatening and/or result in death or hospitalization. However, if it is determined that the event may jeopardize the patient or may require intervention to prevent one of the other AE outcomes the important medical event should be reported as serious.

Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasias or convulsions that do not result in hospitalization; or development of drug dependency or drug abuse.

8.6.1. Protocol-Specified Serious Adverse Events

There are no protocol-specified SAEs in this study. All cases of Grade >2 mQTcF prolongation regardless of causality and treatment arm must be reported as an SAE for up to 28 calendar days after the last dose of study drug administered. All SAEs will be reported by the investigator as described in previous sections, and will be handled as SAEs in the safety database (see the section on Serious Adverse Event Reporting Requirements).

8.6.2. Potential Cases of Drug-Induced Liver Injury

Abnormal values in aspartate aminotransferase (AST) and/or alanine aminotransferase (ALT) levels concurrent with abnormal elevations in total bilirubin level that meet the criteria outlined below in the absence of other causes of liver injury are considered potential cases of drug-induced liver injury (potential Hy's law cases) and should always be considered important medical events.

The threshold of laboratory abnormalities for a potential case of drug-induced liver injury depends on the patient's individual baseline values and underlying conditions. Patients who present with the following laboratory abnormalities should be evaluated further to definitively determine the etiology of the abnormal laboratory values:

- Patients with AST or ALT and total bilirubin baseline values within the normal range who subsequently present with AST or ALT values ≥3 times the upper limit of normal (X ULN) concurrent with a total bilirubin value ≥2 X ULN with no evidence of hemolysis and an alkaline phosphatase value ≤2 X ULN or not available.

- For patients with preexisting ALT **OR** AST **OR** total bilirubin values above the ULN, the following threshold values should be used in the definition mentioned above:

    - For patients with preexisting AST or ALT baseline values above the normal range: AST or ALT values ≥2 times the baseline values and ≥3 X ULN, or ≥8 X ULN (whichever is smaller).

    Concurrent with

    - For patients with preexisting values of total bilirubin above the normal range: Total bilirubin level increased from baseline by an amount of at least 1 X ULN **or** if the value reaches ≥3 X ULN (whichever is smaller).

The patient should return to the investigational site and be evaluated as soon as possible, preferably within 48 hours from awareness of the abnormal results. This evaluation should include laboratory tests, detailed history, and physical assessment. The possibility of hepatic neoplasia (primary or secondary) should be considered.

In addition to repeating measurements of AST and ALT, laboratory tests should include albumin, creatine kinase, total bilirubin, direct and indirect bilirubin, gamma-glutamyl transferase, prothrombin time (PT)/ international normalized ratio (INR), and alkaline phosphatase. A detailed history, including relevant information, such as review of ethanol, acetaminophen, recreational drug and supplement consumption, family history, occupational exposure, sexual history, travel history, history of contact with a jaundiced person, surgery, blood transfusion, history of liver or allergic disease, and work exposure, should be collected. Further testing for acute hepatitis A, B, or C infection and liver imaging (eg, biliary tract) may be warranted. All cases confirmed on repeat testing as meeting the laboratory criteria defined above, with no other cause for liver function test (LFT) abnormalities identified at the time, should be considered potential Hy's law cases irrespective of availability of all the results of the investigations performed to determine etiology of the abnormal LFTs. Such potential Hy's law cases should be reported as SAEs.

A potential Hy's law case becomes a confirmed case only after all results of reasonable investigations have excluded an alternative etiology.

8.7. Hospitalization

Hospitalization is defined as any initial admission (even less than 24 hours) in a hospital or equivalent healthcare facility or any prolongation of an existing admission. Admission also includes transfer within the hospital to an acute/intensive care unit (eg, from the psychiatric wing to a medical floor, medical floor to a coronary care unit, or neurological floor to a tuberculosis unit). An emergency room visit does not necessarily constitute a hospitalization; however, the event leading to the emergency room visit should be assessed for medical importance.

Hospitalization does not include the following:

- Rehabilitation facilities;
- Hospice facilities;
- Respite care (eg, caregiver relief);
- Skilled nursing facilities;
- Nursing homes;
- Same-day surgeries (as outpatient/same-day/ambulatory procedures).

Hospitalization or prolongation of hospitalization in the absence of a precipitating, clinical AE is not in itself an SAE. Examples include:

- Admission for treatment of a preexisting condition not associated with the development of a new AE or with a worsening of the preexisting condition (eg, for workup of persistent pre-treatment laboratory abnormality);
- Social admission (eg, patient has no place to sleep);
- Administrative admission (eg, for yearly physical examination);
- Protocol-specified admission during a study (eg, for a procedure required by the study protocol);
- Optional admission not associated with a precipitating clinical AE (eg, for elective cosmetic surgery);
- Hospitalization for observation without a medical AE;
- Preplanned treatments or surgical procedures. These should be noted in the baseline documentation for the entire protocol and/or for the individual patient;
- Admission exclusively for the administration of blood products.

Diagnostic and therapeutic noninvasive and invasive procedures, such as surgery, should not be reported as AEs. However, the medical condition for which the procedure was performed should be reported if it meets the definition of an AE. For example, an acute appendicitis that begins during the AE reporting period should be reported as the AE and the resulting appendectomy should be recorded as treatment of the AE.

8.8. Severity Assessment

AEs will be reported using concise medical terminology (verbatim) as well as the Common Terminology Criteria (CTC) term for Adverse Events (Version 4.03, Publish Date: June 14, 2010, http://ctep.cancer.gov/reporting/ctc.html)) listed in the Cancer Therapy Evaluation Program.

The investigator may use the following definitions of Severity in accordance with CTCAE Version 4.03 to describe the maximum intensity of the adverse event.

GRADE	Clinical Description of Severity
0	No change from normal or reference range (this grade is not included in the Version 4.03 CTCAE document but may be used in certain circumstances.)
1	MILD adverse event
2	MODERATE adverse event
3	SEVERE adverse event
4	LIFE-THREATENING consequences; urgent intervention indicated
5	DEATH RELATED TO adverse event

Note the distinction between the severity and the seriousness of an AE. A severe event is not necessarily an SAE. For example, a headache may be severe (interferes significantly with the patient's usual function) but would not be classified as serious unless it met one of the criteria for SAEs, listed above.

8.9. Causality Assessment

The investigator's assessment of causality must be provided for all AEs (serious and non-serious); the investigator must record the causal relationship in the CRF, as appropriate, and report such an assessment in accordance with the SAE reporting requirements if applicable. An investigator's causality assessment is the determination of whether there exists a reasonable possibility that the investigational product caused or contributed to an AE; generally the facts (evidence) or arguments to suggest a causal relationship should be provided. If the investigator does not know whether or not the investigational product caused the event, then the event will be handled as "related to investigational product" for reporting purposes, as defined by the sponsor (see the section on Reporting Requirements). If the investigator's causality assessment is "unknown but not related to investigational product," this should be clearly documented on study records.

In addition, if the investigator determines that an SAE is associated with study procedures, the investigator must record this causal relationship in the source documents and CRF, as appropriate, and report such an assessment in accordance with the SAE reporting requirements, if applicable.

8.10. Exposure During Pregnancy

For both unapproved/unlicensed products and for marketed products, an exposure during pregnancy occurs if:

1. A female becomes, or is found to be, pregnant either while receiving or having been exposed (eg, because of treatment or environmental exposure) to the investigational product; or the female becomes, or is found to be pregnant after discontinuing and/or being exposed to the investigational product;

   An example of environmental exposure would be a case involving direct contact with a Pfizer product in a pregnant woman (eg, a nurse reports that she is pregnant and has been exposed to chemotherapeutic products).

2. A male has been exposed (eg, because of treatment or environmental exposure) to the investigational product prior to or around the time of conception and/or is exposed during his partner's pregnancy.

If a study patient or study patient's partner becomes or is found to be pregnant during the study patient's treatment with the investigational product, the investigator must submit this information to the Pfizer drug safety unit on a Serious Adverse Event (SAE) Report Form and Exposure During Pregnancy (EDP) supplemental form, regardless of whether an SAE has occurred. In addition, the investigator must submit information regarding environmental exposure to a Pfizer product in a pregnant woman (eg, a patient reports that she is pregnant and has been exposed to a cytotoxic product by inhalation or spillage) using the EDP supplemental form. This must be done irrespective of whether an AE has occurred and within 24 hours of awareness of the exposure. The information submitted should include the anticipated date of delivery (see below for information related to termination of pregnancy).

Follow-up is conducted to obtain general information on the pregnancy and its outcome for all EDP reports with an unknown outcome. The investigator will follow the pregnancy until completion (or until pregnancy termination) and notify Pfizer of the outcome as a follow-up to the initial EDP supplemental form. In the case of a live birth, the structural integrity of the neonate can be assessed at the time of birth. In the event of a termination, the reason(s) for termination should be specified and, if clinically possible, the structural integrity of the terminated fetus should be assessed by gross visual inspection (unless preprocedure test findings are conclusive for a congenital anomaly and the findings are reported).

If the outcome of the pregnancy meets the criteria for an SAE (ie, ectopic pregnancy, spontaneous abortion, intrauterine fetal demise, neonatal death, or congenital anomaly [in a live-born baby, a terminated fetus, an intrauterine fetal demise, or a neonatal death]), the investigator should follow the procedures for reporting SAEs.

Additional information about pregnancy outcomes that are reported as SAEs follows:

- Spontaneous abortion includes miscarriage and missed abortion;
- Neonatal deaths that occur within 1 month of birth should be reported, without regard to causality, as SAEs. In addition, infant deaths after 1 month should be reported as SAEs when the investigator assesses the infant death as related or possibly related to exposure to the investigational product.

Additional information regarding the exposure during pregnancy may be requested by the investigator. Further follow-up of birth outcomes will be handled on a case-by-case basis (eg, follow-up on preterm infants to identify developmental delays). In the case of paternal exposure, the investigator will provide the study patient with the Pregnant Partner Release of Information Form to deliver to his partner. The investigator must document in the source documents that the patient was given the Pregnant Partner Release of Information Form to provide to his partner.

8.11. Occupational Exposure

An occupational exposure occurs when during the performance of job duties, a person (whether a healthcare professional or otherwise) gets in unplanned direct contact with the product, which may or may not lead to the occurrence of an adverse event.

An occupational exposure is reported to the drug safety unit within 24 hours of the investigator's awareness, using the SAE Report form, regardless of whether there is an associated AE/SAE. Since the information does not pertain to a patient enrolled in the study, the information is not reported on a Case Report Form (CRF), however a copy of the completed SAE Report form is maintained in the investigator site file.

8.12. Withdrawal Due to Adverse Events

Withdrawal due to AEs should be distinguished from withdrawal due to other causes, according to the definition of AE noted earlier, and recorded on the appropriate AE CRF page. When a patient withdraws because of an SAE, the SAE must be reported in accordance with the reporting requirements defined below.

8.13. Eliciting Adverse Event Information

The investigator is to report all directly observed AEs and all AEs spontaneously reported by the study patient/legally acceptable representative. In addition, each study patient/legally acceptable representative will be questioned about AEs.

8.14. Reporting Requirements

Each AE is to be assessed to determine if it meets the criteria for SAEs. If an SAE occurs, expedited reporting will follow local and international regulations, as appropriate.

8.14.1. Serious Adverse Event Reporting Requirements

If an SAE occurs, Pfizer Safety is to be notified within 24 hours of investigator awareness of the event.

In particular, if the SAE is fatal or life-threatening, notification to Pfizer must be made immediately, irrespective of the extent of available AE information. This time frame also applies to additional new information (follow-up) on previously forwarded SAE reports as well as to the initial and follow-up reporting of exposure during pregnancy, exposure via breastfeeding and occupational exposure cases.

In the rare event that the investigator does not become aware of the occurrence of an SAE immediately (eg, if an outpatient study patient initially seeks treatment elsewhere), the investigator is to report the event within 24 hours after learning of it and document the time of his or her first awareness of the AE.

For all SAEs, the investigator is obligated to pursue and provide information to Pfizer in accordance with the time frames for reporting specified above. In addition, an investigator may be requested by Pfizer to obtain specific additional follow up information in an expedited fashion. This information collected for SAEs is more detailed than that captured on the AE CRF. In general, this will include a description of the AE in sufficient detail to allow for a complete medical assessment of the case and independent determination of possible causality. Information on other possible causes of the event, such as concomitant medications, vaccines, and/or illnesses, must be provided. In the case of a patient death, a summary of available autopsy findings must be submitted as soon as possible to Pfizer or its designated representative.

8.14.2. Non-serious Adverse Event Reporting Requirements

All AEs will be reported on the AE page(s) of the CRF. It should be noted that the form for collection of SAE information is not the same as the AE CRF. Where the same data are collected, the forms must be completed in a consistent manner. For example, the same AE term should be used on both forms. AEs should be reported using concise medical terminology on the CRFs as well as on the form for collection of SAE information.

8.14.3. Sponsor's Reporting Requirements to Regulatory Authorities

AE reporting, including suspected unexpected serious adverse reactions will be carried out in accordance with applicable local regulations.

9. DATA ANALYSIS/STATISTICAL METHODS

A detailed methodology for summary and statistical analysis of the data collected in this study will be documented in a Statistical Analysis Plan will be maintained by the Sponsor. The document may modify the plans outlined in the protocol; however, any major modifications of the primary endpoint definition and/or its analysis will also be reflected in a protocol amendment.

9.1. Sample Size Determination

9.1.1. Safety Lead-In Cohort

Approximately 10 patients will be included in the single-arm open-label Phase 1 LIC. This sample size provides at least 80% probability to observe at least one AE if the true incidence of the AE in the population is at least 15%.

9.1.2. Expansion

In the expansion phase, two cohorts of patients (MDS and AML respectively) will be enrolled, approximately 30 patients each. Based on the Bayesian decision rule (Section 3.3), a minimum of 10 and a maximum of 30 patients will be needed. For the MDS cohort, with a maximum of 30 patients, the maximum width of the exact 2-sided 95% confidence intervals (CI) for CR will be ≤0.374. For the AML cohort, with a maximum of 30 patients, the maximum width of the exact 2-sided 95% CI for CR will be ≤0.374.

9.2. Analysis Populations

9.2.1. Full Analysis Set (FAS)

The FAS will include all enrolled patients in the respective cohort (LIC, expansion MDS, and expansion AML cohort separately), who received at least one dose of any study treatment (glasdegib or azacitidine). This will be the primary analysis population for evaluating efficacy endpoints and patient characteristics.

9.2.2. Safety Analysis Set

The safety analysis set will include all patients who receive at least one dose of any study treatment (glasdegib or azacitidine). It will be the primary analysis population for evaluating treatment administration/compliance and safety endpoints.

9.2.3. PK Analysis Set

The PK concentration analysis set is defined as all patients who are treated and who have at least 1 value of analyte concentration of glasdegib or azacitidine available. The PK parameter analysis set is defined as all patients who are treated and who have at least 1 of the PK parameters of interest.

CCI [redacted]

9.3. Efficacy Analysis

Efficacy analyses will use the FAS. They will be reported for the safety LIC, the expansion MDS cohort, and expansion AML cohort separately. All CI for binary endpoint will use the exact method, unless otherwise stated.

9.3.1. Complete Response

The proportion of patients achieving CR is the primary endpoint for the expansion cohorts. The endpoint of CR will be analyzed when the endpoint is mature in the specific expansion cohort.

A confirmation of response (peripheral blood only) is required 4 weeks after the first assessment per IWG 2006 for MDS patients. The final analyses for MDS cohorts will be performed after all patients in the expansion MDS cohort have been followed for at least 28 weeks (to allow for confirmation of response per IWG 2006). No confirmation is needed for the expansion AML cohort. The final anslyses for the AML cohort will be performed after all patients in this cohort have been followed for at least 24 weeks.

The proportion and two-sided 95% CI of patients achieving CR will be provided separately for the two expansion cohorts.

9.3.2. Response Rate

The proportion of patients achieving response (CR+PR) is a secondary endpoint for the safety LIC. A confirmation of response (Peripheral Blood only) is required 4 weeks after the first assessment per IWG 2006. The final analyses will be conducted after all patients in the safety LIC have been followed for 28 weeks (to allow for confirmation of response per IWG 2006). The proportion and two-sided 95% CI (using exact method) of patients achieving response (CR+PR) will be provided for the safety LIC.

9.3.3. Overall Survival (Expansion)

Overall survival (OS) is defined as the time from date of first study treatment to date of death due to any cause. Patients last known to be alive will be censored at the date of last contact.

OS will be analyzed and displayed graphically for each expansion cohort separately using the Kaplan-Meier method. The median event time for each expansion cohort and corresponding two-sided 95% CI will be provided. The Kaplan-Meier estimate of survival probabilities at 12, 18, and 24 months and their two-sided 95% CI (using log-log transformation and back-transformation) will be provided for each arm separately.

First, OS will be analyzed when the primary endpoint of CR is analyzed in the respective expansion cohort. A follow-up analysis of updated OS will be conducted when the study concludes. OS is defined as the date of the first dose of any of the study medications to the date of death from any cause.

9.3.4. Duration of Response

Duration of Response (DoR) is only defined in MDS patients or AML patients achieving a CR in the expansion component. DoR is defined as the duration from date of first achieving CR to the date of disease progression (relapse) after CR, or death due to any cause. Patients last known to be alive who are free from disease progression or relapse after CR are censored at the date of the last assessment that verifies their disease status. The minimum DoR is 4 weeks for MDS patients by definition (CR must last at least 4 weeks to qualify as such per Appendix 2).

DoR will be analyzed and displayed graphically for each expansion cohort separately using the Kaplan-Meier method. The median DoR and corresponding two-sided 95% CI will be provided.

9.3.5. Time to Response

Time to response (TTR) is only defined for patients in the expansion component who have ever achieved response on study as the time from date of the first dose of study drug to date of the first documentation of response (CR+PR). Note that response needs to be confirmed for MDS patients by definition (CR must last at least 4 weeks to qualify as such per Appendix 2).

TTR will be analyzed and displayed graphically for each cohort seperately using the Kaplan-Meier method. The median TTR and corresponding two-sided 95% CI will be provided.

9.3.6. Other Efficacy Measures

Additional efficacy measure of interest for the safety LIC and expansion MDS cohort include marrow CR (mCR), partial remission (PR), stable disease (SD), partial or complete cytogentic response, and hematolgic improvement (HI). Additional efficacy measures of interest for the expansion AML cohort include CR with incomplete hematologic recovery (CRi), complete remission with partial hematologic recovery (CRh), morphologic leukemia-free state (MLFS), PR, SD, Cytogenetic CR (CRc), and molecular CR (CRm) per Appendix 11.

The proportion of patients ever achieving each of the endpoints for the respective cohort will be estimated with two-sided 95% CI respectively.

CCI [redacted]

CCI [redacted]

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CCI [redacted]

[redacted]

CCI [redacted]

[redacted]

CCI [redacted]

CCI [redacted]

9.4. Safety Analysis

Summary and analysis of the safety parameters will include all patients in the safety analysis set. They will be reported separately for the safety LIC and each cohort in the expansion, as well as all three cohorts pooled.

9.4.1. Adverse Events

9.4.2. Analysis of Primary Endpoint of Safety Lead-in Cohort

Overall safety profile and tolerability will be characterized by type, frequency, severity, timing, and relationship to study therapy of adverse events and laboratory abnormalities.

Adverse events will be classified using the MedDRA classification system. The severity of the toxicities will be graded according to the NCI CTCAE version 4.03.

In all summaries, emphasis will be placed on treatment emergent adverse events (TEAEs), namely, those with initial onset or that worsen in severity after the first dose of study drug. Adverse events will be summarized by the frequency of patients experiencing treatment emergent adverse events corresponding to body systems and MedDRA preferred term and by worst NCI CTCAE (version 4.03) grade. Summaries will also be provided of treatment related TEAEs, namely, those judged by the investigator to be related or likely related to study drug.

Adverse events leading to death or discontinuation of study treatment, events classified as NCI CTCAE version 4.03 Grade 3 or higher, study drug related events, and serious adverse events will be considered with special attention. Adverse events reporting, including suspected unexpected serious adverse reactions, will be carried out in accordance with applicable local regulations.

9.4.3. Analysis of Secondary Endpoint of Expansion Component

Overall safety profile will be characterized by type, frequency, severity, timing, and relationship to study therapy of adverse events and laboratory abnormalities.

Adverse events will be classified using the MedDRA classification system. The severity of the toxicities will be graded according to the NCI CTCAE version 4.03.

In all summaries, emphasis will be placed on treatment emergent adverse events (TEAEs), namely, those with initial onset or that worsen in severity after the first dose of study drug. Adverse events will be summarized by the frequency of patients experiencing treatment emergent adverse events corresponding to body systems and MedDRA preferred term and by worst NCI CTCAE (version 4.03) grade. Summaries will also be provided of treatment related TEAEs, namely, those judged by the investigator to be related or likely related to study drug.

Adverse events leading to death or discontinuation of study treatment, events classified as NCI CTCAE version 4.03 Grade 3 or higher, study drug related events, and serious adverse events will be considered with special attention. Adverse events reporting, including suspected unexpected serious adverse reactions, will be carried out in accordance with applicable local regulations.

9.4.4. Laboratory Test Abnormalities

The number and percentage of patients who experienced laboratory test abnormalities will be summarized according to worst toxicity grade observed for each lab assay, graded according to NCI CTCAE version 4.03. The analyses will summarize laboratory tests both on the entire study period and by cycle (Cycle 1 and Cycles beyond 1). Shift tables will be provided to examine the distribution of laboratory toxicities.

For laboratory tests without CTC grade definitions, results will be categorized as normal, abnormal or not done.

9.4.5. Baseline Characteristics

Patient characteristics at the time of study entry will be summarized in frequency tables and descriptive statistics will be provided for quantitative variables for the full analysis set (see Section 9.2 for definitions of study populations).

9.4.6. Electrocardiogram Analysis

The QT measurements corrected by heart rate (QTc) will be used for the data analysis and interpretation. QTcF is planned to be the primary analysis method for the QTc endpoint. In addition a study-specific correction method (QTcS) and QTcB may also be evaluated for the QTc evaluable patients. The most appropriate correction method that eliminates any QT vs. RR relationship may be chosen after review of the data.

9.4.7. Summary and Categorical Analysis of Electrocardiogram Findings

The analysis of ECG results will be based on patients with both baseline and on-treatment ECG data. All ECGs obtained during the study will be evaluated for safety. ECG collected prior to the first day of dosing will be considered the baseline ECG.

ECG measurements (an average of the triplicate measurements) will be used for the statistical analysis and all data presentations. Any data obtained from ECGs repeated for safety reasons after the nominal time-points will not be averaged along with the preceding

triplicates. Interval measurements from repeated ECGs will be included in the outlier analysis as individual values obtained at unscheduled time points.

Data will be summarized and listed for QT, HR, RR, PR, QRS, QTcF and QTcB in the safety LIC and expansion cohorts. Individual QTc (all evaluated corrections) intervals will be listed by time. The most appropriate correction factor will be selected and used for the following analyses of central tendency and outliers and used for the study conclusions.

Descriptive statistics (n, mean, median, standard deviation, minimum, and maximum) will be used to summarize the absolute QTc value and changes from baseline in QTc after treatment, and by treatment and time point. For each patient by treatment the maximum change from baseline will be calculated as well as the maximum post-baseline value across time-points. Outlier analysis of the QTc data will be conducted and summarized as follows:

- The number of patients with maximum change from baseline in QTc (<30, 30-<60, and ≥60 msec);
- The number of patients with maximum post-dose (post-baseline) QTc (≤450, >450-≤480, >480- ≤500, and >500 msec);
- PR changes from baseline ≥25% and absolute values >200 msec;
- QRS changes from baseline ≥25% and absolute values >110 msec;
- Number and percentage of individuals with abnormal ECG findings.

Shift tables will be provided for baseline versus worst on study QTc (one or more correction method will be used) using Maximum CTCAE Grade. Tables of ECG abnormality at baseline (yes, no, not done: (n, %)) will also be provided. Patients experiencing clinically-relevant morphological ECG changes will be summarized (including frequency and percentage).

9.4.8. Exposure-QTc Analysis

Linear mixed effect modeling to quantify the relationship between plasma concentrations of glasdegib and QTc interval will be performed. Additionally, the adequacy of the model fit to the assumption of linearity and the impact on quantifying the concentration response relationship will be explored including diagnostic evaluation. CCI [redacted]

The exposure-QTc analyses will be reported in a separate document. CCI [redacted]

CCI [redacted]

9.6. Pharmacokinetic Analysis

9.6.1. PK Parameters

Descriptive statistics will be provided for the following PK parameters in tabular form by analyte, cycle and day: n, mean, SD, CV, median, minimum, maximum, geometric mean and its associated CV.

For the safety LIC, standard plasma PK parameters including the observed maximum plasma concentration (C_{max}), time to maximum plasma concentration (T_{max}), and area under the plasma concentration versus time curve (AUC) for each drug (and metabolite if relevant), will be estimated using non-compartmental analysis. If data permit or if considered appropriate, plasma trough concentration (C_{trough}), average plasma concentration (C_{ave}) will be estimated. For the expansion component, the plasma trough concentration (C_{trough}) will be reported.

9.6.2. PK Concentrations

For drug concentrations, individual values and descriptive statistics (n, mean, SD, CV, median, minimum, maximum, geometric mean and its associated CV) will be presented by cycle, day of assessment, and nominal time in tabular form.

For the Phase 1 safety LIC, individual patient and median profiles of the concentration-time data will be plotted by dose, cycle and day using nominal times. Median profiles will be presented on both linear-linear and log-linear scales.

9.6.3. Evaluation of Drug-Drug Interaction Potential (Safety LIC)

The primary PK parameters, AUC and Cmax, will be utilized to estimate the effect of co-administration of glasdegib and azacitidine on the PK of either glasdegib or azacitidine. Note that these endpoints are **not** applicable in the expansion component.

Glasdegib AUC and Cmax when administered alone (Cycle 1/Day 15) will be compared to Cycle 1/Day 7 AUC and Cmax, when administered in combination with azacitidine. A similar assessment will be performed to determine the effect of glasdegib on azacitidine. The AUC and Cmax on Cycle 1 Day 1 when azacitidine is administered alone will be compared to Cycle 1/Day 7 AUC and Cmax when azacitidine is administered in combination with glasdegib. The geometric mean ratios and its 90% confidence intervals (if data permit) for the PK parameters may be generated if considered appropriate, since the study is not statistically powered for such an analysis.

9.6.4. Population Pharmacokinetic Analysis or PK/PD Modeling

PK and PD data from this study may be analyzed using modeling approaches and may also be pooled with data from other studies to investigate any causal relationship between glasdegib exposure and CCI significant safety endpoints. The results of these analyses, if performed, may be reported separately.

9.7. Interim Analyses

9.7.1. Futility Analyses

A Bayesian decision rule (Section 3.3) will be used to continuously monitor CR rate without holding enrollment in the expansion component to allow early stopping of the study for futility. The decision rule is to stop enrollment for a specific expansion cohort if the posterior probability of the CR rate in study treatment is no more than 0.2 higher than historical azacitidine is greater than 95% in an expansion cohort, ie, Pr (glasdegib+Aza response < historical Aza reponse + 0.2) >0.95. The prior distribution assumptions for the Bayesian model are as follow: for MDS cohort, we assume a prior distribution of Beta(1,6) for the study treatment (based on data from MDS patients accumulated in the safety LIC [1 out of 7 MDS patients achieved CR]), and a prior distribution of Beta(15,75) by discounting historical CR rate by half (AZA 001 trial); for the AML cohort, a prior distribution of Beta(4,4) for the study treatment (based on pooled data on AML patients from the B1371003 study [1 out of 4 AML patients achieved CR] and the LIC [3 out of 4 AML patients achieved CR]), and a prior distribution of Beta(23.5,97) by discounting historical CR rate by half.[57] The Multc Lean software (Version 2.1.0) developed by MD Anderson Cancer Center is used (https://biostatistics.mdanderson.org/softwaredownload/SingleSoftware.aspx?Software_Id=12), which properly models variability in historical control that is more often than not ignored. Stopping for toxicity is not modeled.

The Bayesian decision rule applies once the minimum number of patients (ie, 10) in each expansion cohort has achieved the required follow-up duration (ie, 28 weeks for the expansion MDS cohort and 24 weeks for the expansion AML cohort). The enrollment to the respective expansion cohort will be stopped if the minimum number of responders in that expansion cohort is not achieved (Table 8 for expansion MDS cohort, and Table 9 for expansion AML cohort in Section 3.3). For instance, if there are no more than 4 responders in the first 17 patients who have achieved 28 weeks follow-up, the enrollment into the expansion MDS cohort should be stopped for futility.

9.7.2. Safety Stopping Analyses

Analysis of specific safety criteria will be performed to evaluate stopping enrollment for a specifc cohort when there is at least 70% probability that the toxicity rate of any of the pre-defined safety events of interest (Section 3.3) in that cohort is above 25%.

The safety stopping criteria will be applied within each cohort (AML or MDS) starting when at least 10 patients have completed the required follow-up period (28/24 weeks for MDS/AML respectively) and applied continuously afterwards. Enrollment will continue

unless the stopping boundary is crossed (Table 10 in Section 3.3). Patients who have completed the required follow-up period or patients who have experienced any pre-defined safety events of interest within the required follow-up period will be included in the safety decision making. The same stopping criteria will be used for the AML and MDS cohorts; however, the two cohorts will be analyzed independently.

9.8. Data Monitoring Committee

This study will use an external data monitoring committee (EDMC). The EDMC will be responsible for ongoing monitoring of the safety of subjects in the study according to the charter. The recommendations made by the EDMC to alter the conduct of the study will be forwarded to Pfizer for final decision. Pfizer will forward such decisions, which may include summaries of aggregate analyses of endpoint events and of safety data that are not endpoints, to regulatory authorities, as appropriate. An EDMC will be convened to monitor safety in the study at least once per year.

10. QUALITY CONTROL AND QUALITY ASSURANCE

During study conduct, Pfizer or its agent will conduct periodic monitoring visits to ensure that the protocol and Good Clinical Practices (GCPs) are being followed. The monitors may review source documents to confirm that the data recorded on CRFs are accurate. The investigator and institution will allow Pfizer monitors/auditors or its agents and appropriate regulatory authorities direct access to source documents to perform this verification.

The study site may be subject to review by the institutional review board (IRB)/ethics committee (EC), and/or to quality assurance audits performed by Pfizer, or companies working with or on behalf of Pfizer, and/or to inspection by appropriate regulatory authorities.

It is important that the investigator(s) and their relevant personnel are available during the monitoring visits and possible audits or inspections and that sufficient time is devoted to the process.

11. DATA HANDLING AND RECORD KEEPING

11.1. Case Report Forms/Electronic Data Record

As used in this protocol, the term CRF should be understood to refer to either a paper form or an electronic data record or both, depending on the data collection method used in this study.

A CRF is required and should be completed for each included patient. The completed original CRFs are the sole property of Pfizer and should not be made available in any form to third parties, except for authorized representatives of Pfizer or appropriate regulatory authorities, without written permission from Pfizer.

The investigator has ultimate responsibility for the collection and reporting of all clinical, safety and laboratory data entered on the CRFs and any other data collection forms (source documents) and ensuring that they are accurate, authentic / original, attributable, complete, consistent, legible, timely (contemporaneous), enduring and available when required. The

CRFs must be signed by the investigator or by an authorized staff member to attest that the data contained on the CRFs is true. Any corrections to entries made in the CRFs or source documents must be dated, initialed and explained (if necessary) and should not obscure the original entry.

In most cases, the source documents are the hospital's or the physician's patient chart. In these cases data collected on the CRFs must match the data in those charts.

In some cases, the CRF, or part of the CRF, may also serve as source documents. In these cases, a document should be available at the investigator's site as well as at Pfizer and clearly identify those data that will be recorded in the CRF, and for which the CRF will stand as the source document.

11.2. Record Retention

To enable evaluations and/or audits from regulatory authorities or Pfizer, the investigator agrees to keep records, including the identity of all participating patients (sufficient information to link records, eg, CRFs and hospital records), all original signed informed consent/assentdocuments, copies of all CRFs, safety reporting forms, source documents, and detailed records of treatment disposition, and adequate documentation of relevant correspondence (eg, letters, meeting minutes, and telephone call reports). The records should be retained by the investigator according to International Conference on Harmonization (ICH), according to local regulations, or as specified in the clinical study agreement (CSA), whichever is longer.

If the investigator becomes unable for any reason to continue to retain study records for the required period (eg, retirement, relocation), Pfizer should be prospectively notified. The study records must be transferred to a designee acceptable to Pfizer, such as another investigator, another institution, or an independent third party arranged by Pfizer. Investigator records must be kept for a minimum of 15 years after completion or discontinuation of the study or for longer if required by applicable local regulations.

The investigator must obtain Pfizer's written permission before disposing of any records, even if retention requirements have been met.

12. ETHICS

12.1. Institutional Review Board (IRB)/Ethics Committee (EC)

It is the responsibility of the investigator to have prospective approval of the study protocol, protocol amendments, informed consent/assent documents, and other relevant documents, eg, recruitment advertisements, if applicable, from the IRB/EC. All correspondence with the IRB/EC should be retained in the investigator file. Copies of IRB/EC approvals should be forwarded to Pfizer.

The only circumstance in which an amendment may be initiated prior to IRB/EC approval is where the change is necessary to eliminate apparent immediate hazards to the patients. In that event, the investigator must notify the IRB/EC and Pfizer in writing immediately after the implementation.

12.2. Ethical Conduct of the Study

The study will be conducted in accordance with legal and regulatory requirements, as well as the general principles set forth in the International Ethical Guidelines for Biomedical Research Involving Human Patients (Council for International Organizations of Medical Sciences 2002), Guidelines for Good Clinical Practive (GCP) (ICH 1996), and the Declaration of Helsinki (World Medical Association 1996 & 2008).

In addition, the study will be conducted in accordance with the protocol, the ICH guideline on GCP, and applicable local regulatory requirements and laws.

12.3. Patient Information and Consent

All parties will ensure protection of patient personal data and will not include patient names or other identifiable data in any reports, publications or other disclosures, except where required by laws.

When study data is compiled for transfer to Pfizer and other authorized parties, patient names, address, birth date and other identifiable data will be replaced by a numerical code consisting of a numbering system provided by Pfizer in order to de-identify the study patient. The study site will maintain a confidential list of patients who participated in the study linking their numerical code to the patient's actual identity. In case of data transfer, Pfizer will maintain high standards of confidentiality and protection of patient personal data consistent with applicable privacy laws.

The informed consent/assent document must be in compliance with ICH GCP, local regulatory requirements, and legal requirements including applicable privacy laws.

The informed consent/assent document(s) used during the informed consent process must be reviewed by the sponsor, approved by the IRB/EC before use, and available for inspection.

The investigator must ensure that each study patient, or his or her legally acceptable representative, is fully informed about the nature and objectives of the study and possible risks associated with participation.

Whenever consent is obtained from a patient's legally acceptable representative, the patient's assent (affirmative agreement) must subsequently be obtained when the patient has the capacity to provide assent, as determined by the IRB/EC. If the investigator determines that a patient's decisional capacity is so limited he/she cannot reasonably be consulted, as permitted by the IRB/EC and consistent with local regulatory and legal requirements, then the patient's assent may be waived with source documentation of the reason assent was not obtained. If the study patient does not provide his/her own consent, the source documents must record why the patient did not provide consent (eg, minor, decisionally impaired adult),

how the investigator determined that the person signing the consent was the patient's legally acceptable representative, the consent signer's relationship to the study patient (eg, parent, spouse) and that the patient's assent was obtained, or waived. If assent is obtained verbally it must be documented in the source documents.

The investigator, or a person designated by the investigator, will obtain written informed consent from each patient or the patient's legally acceptable representative before any study-specific activity is performed unless a waiver of informed consent has been granted by an IRB/EC. The investigator will retain the original of each patient's signed consent/assent document.

12.4. Patient Recruitment

Advertisements approved by ethics committees and investigator databases may be used as recruitment procedures.

12.5. Reporting of Safety Issues and Serious Breaches of the Protocol or ICH GCP

In the event of any prohibition or restriction imposed (ie, clinical hold) by an applicable competent authority in any area of the world, or if the investigator is aware of any new information that might influence the evaluation of the benefits and risks of the investigational product, Pfizer should be informed immediately.

In addition, the investigator will inform Pfizer immediately of any urgent safety measures taken by the investigator to protect the study patients against any immediate hazard, and of any serious breaches of this protocol or of ICH GCP that the investigator becomes aware of.

13. DEFINITION OF END OF TRIAL

End of Study in all participating countries is defined as Last Patient Last Visit.

14. SPONSOR DISCONTINUATION CRITERIA

Premature termination of this study may occur because of a regulatory authority decision, change in opinion of the IRB/EC, drug safety problems, or at the discretion of Pfizer. In addition, Pfizer retains the right to discontinue development of glasdegib at any time.

If a study is prematurely terminated or discontinued, Pfizer will promptly notify the investigator. After notification, the investigator must contact all participating patients and the hospital pharmacy (if applicable) within 14 days. As directed by Pfizer, all study materials must be collected and all CRFs completed to the greatest extent possible.

15. PUBLICATION OF STUDY RESULTS

15.1. Communication of Results by Pfizer

Pfizer fulfills its commitment to publicly disclose clinical trial results through posting the results of studies on www.clinicaltrials.gov (ClinicalTrials.gov), the European Clinical Trials Database (EudraCT), and/or www.pfizer.com, and other public registries in accordance with applicable local laws/regulations.

In all cases, study results are reported by Pfizer in an objective, accurate, balanced, and complete manner and are reported regardless of the outcome of the study or the country in which the study was conducted.

www.clinicaltrials.gov

Pfizer posts clinical trial US Basic Results on www.clinicaltrials.gov for Pfizer-sponsored interventional studies conducted in patients that evaluate the safety and/or efficacy of a Pfizer product, regardless of the geographical location in which the study is conducted. US Basic Results are submitted for posting within 1 year of the primary completion date for studies in adult populations or within 6 months of the primary completion date for studies in pediatric populations.

Primary completion date is defined as the date that the final patient was examined or received an intervention for the purposes of final collection of data for the primary outcome, whether the clinical study concluded according to the prespecified protocol or was terminated.

EudraCT

Pfizer posts EU Basic Results on EudraCT for all Pfizer-sponsored interventional studies that are in scope of EU requirements. EU Basic Results are submitted for posting within 1 year of the primary completion date for studies in adult populations or within 6 months of the primary completion date for studies in pediatric populations.

www.pfizer.com

Pfizer posts Public Disclosure Synopses (clinical study report synopses in which any data that could be used to identify individual patients has been removed) on www.pfizer.com for Pfizer-sponsored interventional studies at the same time the US Basic Results document is posted to www.clinicaltrials.gov.

15.2. Publications by Investigators

Pfizer has no objection to publication by an investigator of any information collected or generated by the investigator, whether or not the results are favorable to the investigational drug. However, to ensure against inadvertent disclosure of confidential information or unprotected inventions, the investigator will provide Pfizer an opportunity to review any proposed publication or other type of disclosure before it is submitted or otherwise disclosed.

The investigator will provide manuscripts, abstracts, or the full text of any other intended disclosure (poster presentation, invited speaker or guest lecturer presentation, etc.) to Pfizer at least 30 days before they are submitted for publication or otherwise disclosed. If any patent action is required to protect intellectual property rights, the investigator agrees to delay the disclosure for a period not to exceed an additional 60 days.

The investigator will, on request, remove any previously undisclosed confidential information (other than the study results themselves) before disclosure.

If the study is part of a multicenter study, the investigator agrees that the first publication is to be a joint publication covering all centers. However, if a joint manuscript has not been submitted for publication within 12 months of completion or termination of the study at all participating sites, the investigator is free to publish separately, subject to the other requirements of this section.

For all publications relating to the study, the institution will comply with recognized ethical standards concerning publications and authorship, including Section II - "Ethical Considerations in the Conduct and Reporting of Research" of the Uniform Requirements for Manuscripts Submitted to Biomedical Journals, http://www.icmje.org/index.html#authorship, established by the International Committee of Medical Journal Editors.

Publication of study results is also provided for in the CSA between Pfizer and the institution. In this section entitled Publications by Investigators, the defined terms shall have the meanings given to them in the CSA.

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Appendix 1. 2008 WHO Classification of Myelodysplastic Syndromes (MDS)*

Appendix 1 applies ONLY to patients in the lead-in cohort which has been completed.

Disease	Blood findings	BM findings
Refractory cytopenia with unilineage dysplasia (RCUD): (refractory anemia [RA]; refractory neutropenia [RN]; refractory thrombocytopenia [RT])	Unicytopenia or bicytopenia* No or rare blasts (< 1%)†	Unilineage dysplasia: ≥ 10% of the cells in one myeloid lineage < 5% blasts < 15% of erythroid precursors are ring sideroblasts
Refractory anemia with ring sideroblasts (RARS)	Anemia No blasts	≥ 15% of erythroid precursors are ring sideroblasts Erythroid dysplasia only < 5% blasts
Refractory cytopenia with multilineage dysplasia (RCMD)	Cytopenia(s) No or rare blasts (< 1%)† No Auer rods $< 1 \times 10^9$/L monocytes	Dysplasia in ≥ 10% of the cells in ≥ 2 myeloid lineages (neutrophil and/or erythroid precursors and/or megakaryocytes) < 5% blasts in marrow No Auer rods ± 15% ring sideroblasts
Refractory anemia with excess blasts-1 (RAEB-1)	Cytopenia(s) < 5% blasts† No Auer rods $< 1 \times 10^9$/L monocytes	Unilineage or multilineage dysplasia 5%-9% blasts† No Auer rods
Refractory anemia with excess blasts-2 (RAEB-2)	Cytopenia(s) 5%-19% blasts‡ Auer rods ±‡ $< 1 \times 10^9$/L monocytes	Unilineage or multilineage dysplasia 10%-19% blasts‡ Auer rods ±‡
Myelodysplastic syndrome—unclassified (MDS-U)	Cytopenias < 1% blasts†	Unequivocal dysplasia in < 10% of cells in one or more myeloid lineages when accompanied by a cytogenetic abnormality considered as presumptive evidence for a diagnosis of MDS (see Table 6) < 5% blasts
MDS associated with isolated del(5q)	Anemia Usually normal or increased platelet count No or rare blasts (< 1%)	Normal to increased megakaryocytes with hypolobated nuclei < 5% blasts Isolated del(5q) cytogenetic abnormality No Auer rods

*Bicytopenia may occasionally be observed. Cases with pancytopenia should be classified as MDS-U.

†If the marrow myeloblast percentage is < 5% but there are 2% to 4% myeloblasts in the blood, the diagnostic classification is RAEB-1. Cases of RCUD and RCMD with 1% myeloblasts in the blood should be classified as MDS-U.

‡Cases with Auer rods and < 5% myeloblasts in the blood and less than 10% in the marrow should be classified as RAEB-2. Although the finding of 5% to 19% blasts in the blood is, in itself, diagnostic of RAEB-2, cases of RAEB-2 may have < 5% blasts in the blood if they have Auer rods or 10% to 19% blasts in the marrow or both. Similarly, cases of RAEB-2 may have < 10% blasts in the marrow but may be diagnosed by the other 2 findings, Auer rod+ and/or 5% to 19% blasts in the blood.

Vardiman, JW, Thiele, J, Arber, D, et al. The 2008 revision of the World Health Organization (WHO) classification of myeloid neoplasms and acute leukemia: rationale and important changes. Blood 2009; 114(5):937-51. * Only applies to MDS patients enrolled into the safety lead-in component of the study.

Appendix 2. IWG Criteria: Response Criteria and Progression Definitions for Myelodysplasia***

Response Criteria (responses CR, PR, mCR must last at least 4 weeks)	**Peripheral Blood**				**Bone Marrow Blasts (BMB) (%)**	**Other**
	Hgb(g/dL)	Neutrophils (L)	Platelets (L)	Blasts (%)		
Complete Remission (CR)**	≥11	≥1 x 10^9	≥100 x 10^9	0	≤5	Normal maturation of all cell lines, note if has persistent dysplasia
Partial Remission (PR)**					Decreased by ≥50% but still >5%	All CR criteria if abnormal before treatment except BMB
Marrow CR (mCR)	If hematologic improvement (HI) response, note in addition to Marrow CR				≤5% & decreased by ≥50%	
Stable Disease*						Failure to achieve PR & no evidence of progression*
Failure						Death, or disease progression: worsening cytopenia, increase in % BM blasts, progression to a more advanced MDS FAB subtype
Relapse after (m)CR or PR					ICH	At least one of the following: Return to pre-treatment BMB % Decrement of ≥50% from maximum remission/response levels in granulocytes or platelets Reduction in Hgb ≥1.5g/dL or transfusion dependence

Cheson BD, Greenberg PL, Bennett JM et al. Clinical application and proposal for modification of the international working group (IWG) response criteria in myelodysplasia. Blood 2006; 108(2) 419-25.

*SD must last >8 weeks but response is documented regardless of duration.

**Stability of the improved counts is sufficient to define CR or PR without the need to repeat a second BM.

***This criteria will be applied to MDS patients enrolled in the Safety Lead-In and Expansion components of the study and patients with AML with 20-30% blasts and multi-lineage dysplasia and CMML without proliferative disorder enrolled into the Safey Lead-In component of the study.

Additional Response Criteria for Myelodysplasia***

Cytogenetic Response	
Complete	Disappearance of chromosomal abnormality with no appearance of new ones
Partial	≥50% reduction of chromosomal abnormality
Disease Progression **For patients with % blasts at screening:**	
<5% bone marrow blasts	≥50% increase to >5% bone marrow blasts
5-10% bone marrow blasts	≥50% increase to >10% bone marrow blasts
11-20% bone marrow blasts	≥50% increase to >20% bone marrow blasts
21-30% bone marrow blasts	≥50% increase to >30% bone marrow blasts
For all categories, any of:	At least 50% decrease from maximum remission/response in granulocytes or platelets Reduction in Hgb by ≥2 g/dL Transfusion dependence

Proposed modified IWG Myelodysplasia Response Criteria for Hematologic Improvement (HI)**

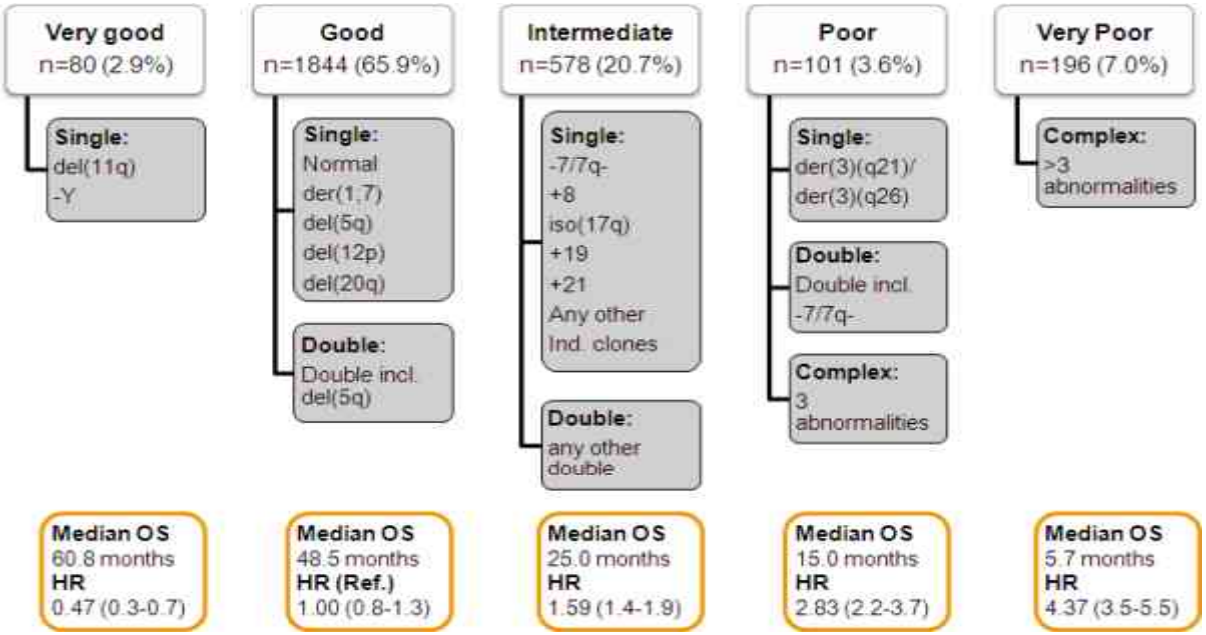
Erythroid response (pre-treatment <11g/dL)*	Hgb increase by ≥1.5 g/dL Relevant reduction of units of RBC transfusions by an absolute number of at least 4 RBC transfusions/8 weeks as compared to the pretreatment transfusion number in the previous 8 weeks (only RBC transfusions given for Hb ≤9 g/dL pretreatment will count in the RBC transfusion evaluation).
Platelet Response (pretreatment <100 x10^9/L)*	Absolute increase of ≥30 x10^9/L if starting with >20 x 10^9/L platelets Increase from <20 x 10^9/L to >20 x10^9/L and by at least 100%
Neutrophil Response (pretreatment <1 x 10^9/L)*	At least a 100% increase and an absolute increase >0.5 x10^9/L
Progression or relapse after HI in the absence of another explanation	At least one of the following: • At least 50% decrease from maximum response levels in granulocytes or platelets; • Reduction in Hgb by ≥1.5g/dL; • Transfusion dependence.

*Pretreatment counts averages of at least 2 measurements (not influenced by transfusions) ≥1 week apart.

** Hematologic Improvement must last ≥ 8 weeks and is derived based on lab data entered in the database.

***This criteria will be applied to MDS patients enrolled in the Safety Lead-In and Expansion components of the study and patients with oligoblastic AML and CMML without proliferative disorder enrolled into the Safey Lead-In component of the study.

Appendix 3. Myelodysplastic Syndromes: 2014 Update on Diagnosis, Risk-Stratification, and Management*



* Applies to MDS patients enrolled in the Safety Lead-In and Expansion components of the study and patients with AML with 20-30% blasts and multi-lineage dysplasia and CMML without proliferative disorder enrolled into the Safey Lead-In component of the study.

Source: Schanz J, Tüchler H, et al. New comprehensive cytogenetic scoring system for primary myelodysplastic syndromes (MDS) and oligoblastic acute myeloid leukemia after MDS derived from an international database merge. J Clin Onc 2012; 30:820-29.

Figure from Garcia-Manero G. Myelodysplastic syndromes: 2014 update on diagnosis, risk stratification, and management. American Journal of Hematology 2014; 89(1):97-108.

Appendix 4. Strong CYP3A4/5 Inducers

Strong CYP3A4/5 Inducers	
Inducer	**Therapeutic Class**
Rifampin	Antibiotics
Rifabutin	Antibiotics
Avasimibe	Antilipedimics
Phenytoin	Anticonvulsants
Carbamazepine	Anticonvulsants
Phenobarbital	Anticonvulsants
Enzalutamide	Antiandrogens
St. John's Wort	Herbal Medications
Mitotane	Antineoplastic
Moderate CYP3A4/5 Inducers	
Inducer	Therapeutic Class
Semagacestat	Alzheimers
Efavirenz	Non-nucleoside Reverse Transcriptase Inhibitors (NNRTI)
Bosentan	Endothelin Receptor Antagonist
Genistein	Food Product
Thioridazine	Antipsychotics
Naficillin	Antibiotics
Talviraline	NNRTI
Lopinavir	Protease Inhibitor
Modafinil	Psychostimulant
Etravirine	NNRTI
Lersivirine	NNRTI

Source: University of Washington Drug Interaction Database. "Copyright University of Washington 1999-2015, UW Metabolism and Transport Drug Interaction Database, accessed: May 2017".

Appendix 5. List of Drugs with Known Risk of Torsade de Pointes

The following drugs are known to have the risk of Torsade de Pointes due to QTc prolongation and their current use in combination with glasdegib is not recommended. If any of these drugs are considered to be medically necessary, then they should be used with caution in combination with glasdegib.

Generic Name	Drug Class	Therapeutic Use	Route
Amiodarone	Anti-arrhythmic	Abnormal heart rhythm	oral,injection
Anagrelide	Phosphodiesterase 3 inhibitor	Thrombocythemia	oral
Arsenic trioxide	Anti-cancer	Leukemia	injection
Astemizole (Off US mkt)	Antihistamine	Allergic rhinitis	oral
Azithromycin	Antibiotic	Bacterial infection	oral,injection
Bepridil (Off US mkt)	Anti-anginal	Heart pain	oral
Chloroquine	Anti-malarial	Malaria infection	oral
Chlorpromazine	Anti-psychotic / Anti-emetic	Schizophrenia/ nausea	oral, injection, suppository
Cilostazol	Phosphodiesterase 3 inhibitor	Intermittent claudication	oral
Ciprofloxacin	Antibiotic	Bacterial Infection	oral, injection
Cisapride (Off US mkt)	GI stimulant	Heartburn	oral
Citalopram	Anti-depressant, SSRI	Depression	oral
Clarithromycin	Antibiotic	Bacterial infection	oral
Disopyramide	Anti-arrhythmic	Abnormal heart rhythm	oral
Dofetilide	Anti-arrhythmic	Abnormal heart rhythm	oral
Domperidone (Not on US mkt)	Anti-nausea	Nausea	oral,injection, suppository
Donepezil	Cholinesterase inhibitor	Dementia	oral
Dronedarone	Anti-arrhythmic	Atrial Fibrillation	oral
Droperidol	Anti-psychotic / Anti-emetic	Anesthesia adjunct, nausea	injection
Erythromycin	Antibiotic	Bacterial infection; increase GI motility	oral, injection
Escitalopram	Anti-depressant, SSRI	Major depression/ Anxiety disorders	oral
Flecainide	Anti-arrhythmic	Abnormal heart rhythm	oral
Fluconazole	Anti-fungal	Fungal infection	oral, injection
Gatifloxacin (Off US mkt)	Antibiotic	Bacterial infection	oral, injection

Generic Name	Drug Class	Therapeutic Use	Route
Grepafloxacin (Off market worldwide)	Antibiotic	Bacterial infection	oral
Halofantrine	Anti-malarial	Malaria infection	oral
Haloperidol	Anti-psychotic	Schizophrenia, agitation	oral, injection
Ibutilide	Anti-arrhythmic	Abnormal heart rhythm	injection
Levofloxacin	Antibiotic	Bacterial infection	oral, injection
Levomethadyl (Off US mkt)	Opiate	Pain control, narcotic dependence	oral
Mesoridazine (Off US mkt)	Anti-psychotic	Schizophrenia	oral
Methadone	Opiate	Pain control, narcotic dependence	oral, injection
Moxifloxacin	Antibiotic	Bacterial infection	oral, injection
Ondansetron	Anti-emetic	Nausea, vomiting	oral, injection
Pentamidine	Antibiotic	Pneumocystis pneumonia	injection, inhaled
Pimozide	Anti-psychotic	Tourette's tics	oral
Probucol (Off US mkt)	Antilipemic	Hypercholesterolemia	oral
Procainamide (Oral off US mkt)	Anti-arrhythmic	Abnormal heart rhythm	injection
Propofol	Anesthetic	Anesthesia	injection
Quinidine	Anti-arrhythmic	Abnormal heart rhythm	oral, injection
Sevoflurane	Anesthetic, general	Anesthesia	inhaled
Sotalol	Anti-arrhythmic	Abnormal heart rhythm	oral
Sparfloxacin (Off US mkt)	Antibiotic	Bacterial infection	oral
Sulpiride (Not on US mkt.)	Anti-psychotic, atypical	Schizophrenia	oral
Terfenadine (Off US mkt)	Antihistamine	Allergic rhinitis	oral
Thioridazine	Anti-psychotic	Schizophrenia	oral
Vandetanib	Anti-cancer	Thyroid cancer	oral

US mkt = United States Market.

Source: Credible Meds.org (http://crediblemeds.org/healthcare-providers/drug-list/?rf=All). TdP risk category filtered on Drugs with known TdP risk. Assessed 11 October 2015.

Appendix 6. Strong CYP3A4/5 Inhibitors

Strong CYP3A4/5 Inhibitors	
Inhibitor	**Therapeutic Class**
Ketoconazole	Antifungal
Itraconazole	Antifungal
Voriconazole	Antifungal
Posaconazole	Antifungal
Troleandomycin	Antibiotics
Clarithromycin	Antibiotics
Telithromycin	Antibiotics
Mibefradil	Calcium Channel Blocker
Conivaptan	Diuretics
Nefazodone	Antidepressants
Cobicistat	--
Indinavir/Ritonavir	Protease Inhibitors
Tipranavir/Ritonavir	Protease Inhibitors
Ritonavir	Protease Inhibitors
Indinavir	Protease Inhibitors
Nelfinavir	Protease Inhibitors
Saquinavir	Protease Inhibitors
Saquinavir/Ritonavir	Protease Inhibitors
Lopinavir/Ritonavir	Protease Inhibitors
Telaprevir	Antivirals
Boceprevir	Antivirals
Danoprevir/Ritonavir	Antivirals
Elvitegravir/Ritonavir	Antivirals
LCL161	Cancer treatment
Idelalisib	Kinase Inhibitors
Grapefruit Juice DS	Food Products

Source: University of Washington Drug Interaction Database. "Copyright University of Washington 1999-2015. UW Metabolism and Transport Drug Interaction Database, accessed: 11 October 2015."

Appendix 7. Moderate CYP3A4/5 Inhibitors

Moderate CYP3A4/5 Inhibitors	
Inhibitor	**Therapeutic Class**
Fluconazole	Antifungals
Erythromycin	Antibiotics
Ciprofloxacin	Antibiotics
Diltiazem	Calcium Channel Blockers
Verapamil	Calcium Channel Blockers
Dronedarone	Antiarrhythmics
Aprepitant	Antiemetics
Casopitant	Antiemetics
Netupitant	Antiemetics
Tofisopam	Benzodiazepines
Cyclosporine	Immunosuppressant
Schisandra sphenanthera	Herbal Medication
ACT-178882	Renin Inhibitor
Cimetidine	H2 Receptor Antagonist
FK1706	Central Nervous System Agent
Faldaprevir	Antivirals
Crizotinib	Kinase Inhibitor
Nilotinib	Kinase Inhibitor
Atazanivir/Ritonavir	Protease Inhibitor
Darunavir	Protease Inhibitor
Darunavir/Ritonavir	Protease Inhibitor
Atazanavir	Protease Inhibitor
Amprenavir	Protease Inhibitor
Imatinib	Antineoplastic agent
Grapefruit Juice	Food Products

Source: University of Washington Drug Interaction Database. "Copyright University of Washington 1999-2015. UW Metabolism and Transport Drug Interaction Database, accessed: 11 October 2015."

Appendix 8. Laboratory Assessments

Hematology	Blood Chemistry	Urinalysis (microscopic analysis)	Coagulation Tests
Hemoglobin	ALT	If urine dipstick is positive for protein, perform urinalysis (U/A) with microscopic. If U/A with microscopic shows ≥2+ protein, collect 24-hour urine for protein.	aPTT
Platelets	AST	Urine dipstick for urine blood: If positive, collect a U/A with microscopic (unless hematuria can be explained by local bleeding such as menses).	INR
WBC	Alk Phos	Specific Gravity	
Neutrophils	Sodium	PH	
Lymphocytes	Potassium	Protein	
Monocytes	Magnesium	Glucose	
Eosinophils	Chloride	RBC	
Basophils	Calcium	WBC	
Bands	Total Bilirubin	Ketones	
Blast Count	BUN or Urea	Leukocyte Esterase	
	Creatinine	Casts	
	Uric Acid	Crystals	
	Glucose (non-fasting)	Nitrate	
	Albumin		
	Total Protein		
	Phosphorus		
	LDH		
	CPK		
	Bicarbonate		
	B12*		

* Applies to Safety Lead-In patients only: Needed only at Screening Visit only for eligibility requirement.

Appendix 9. Eastern Cooperative Oncology Group Performance Status

ECOG PERFORMANCE STATUS*

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

* Oken, M.M., Creech, R.H., Tormey, D.C., Horton, J., Davis, T.E., McFadden, E.T., Carbone, P.P.: Toxicity And Response Criteria Of The Eastern Cooperative Oncology Group. Am J Clin Oncol 5:649-655, 1982.

By the Eastern Cooperative Oncology Group, Robert Comis M.D., Group Chair.

Appendix 10. IPSS-R Classification System for Myelodysplastic Syndromes*

Prognostic variable	0	0.5	1	1.5	2	3	4
Cytogenetics	Very Good		Good		Intermediate	Poor	Very Poor
Bone Marrow Blast %	≤2		>2 to <5		5-10	>10	
Hemoglobin	≥10		8 to <10	<8			
Platelets	≥100	50-<100	<50				
ANC	≥0.8	<0.8					

Risk Category	**Risk Score**
Very Low	≤1.5
Low	>1.5-3
Intermediate	>3-4.5
High	>4.5-6
Very High	>6

Adapted from Greenberg PL et al. Revised International Prognostic Scoring System for Myelodysplastic Syndromes. Blood 2012; 120(12) 2454-2465.
*Only applies to MDS patients enrolled in the Expansion component of the study.

Appendix 11. 2017 ELN Response Criteria for Acute Myeloid Leukemia

Response Criteria	*Neutrophils (µL)*	*Platelets (µL)*	*Bone Marrow Blasts (%)*	*Other*
Complete Remission without Minimal Residual Disease (CR_{MRD-})				If studied pretreatment, CR with negativity for a genetic marker by RT qPCR, or CR with negativity by multiparameter flow cytometry
Morphologic Complete Response (CR)	≥1,000	≥100,000	<5; no peripheral blasts; no blasts with Auer rods	No EMD; Transfusion independent
Complete Remission with partial hematologic recovery (CRh)[1]	>500	>50,000	<5; no peripheral blasts; no blasts with Auer rods	No EMD; Not qualifying for CR
Morphologic CR with incomplete blood count recovery (CRi)	<1,000 **-or-**	<100,000	<5; no peripheral blasts; no blasts with Auer rods	No EMD; Either neutrophils **or** platelets not recovered; Not qualifying for CRh
Morphologic leukemia-free state (MLFS)	<1,000 **-and-**	<100,000	<5; no blasts with Auer rods	No EMD; Neutrophils **and** platelets not recovered; BM not merely "aplastic"; BM cellularity must be 10%, or 200 cells enumerated; Not qualifying for CRi
Partial remission (PR)	≥1,000	≥100,000	blasts decrease to 5-25 and ≥50% decrease from pretreatment	Blasts ≤5% if Auer rod positive
Stable Disease (SD)				Absence of CR_{MRD-}, CR, CRh, CRi, PR, MLFS and criteria for PD not met. Should last at least 3 months.

Progressive Disease (PD)			>50% increase in blasts from pretreatment (if baseline is <30% blasts, must have at least 15% increase; or >70% blasts for ≥3 months; no improvement in ANC (>0.5 x 10^9/L [500 μL], and/or platelet count to >50 x 10^9/L [50 000 μL nontransfused]; or > 50% increase in peripheral blasts (WBC count x % blasts) to >25 x 10^9/L (25000 μL); or new EMD	
Relapse				
Hematologic relapse (after CRMRD-, CR, CRi)			Bone marrow blasts >5%; or Reappearance of blasts in the blood; or Development of EMD	
Molecular Relapse (after CRMRD-)			If studied pretreatment, reoccurrence of MRD as assessed by RT-qPCR or multiparameter flow cytometry	
Treatment Failure				
Primary refractory disease	For Non Intensive: Treatment Failure is defined as failure to achieve CR or CRh following up to 6 cycles of study treatment.			
Death in aplasia	Deaths occurring ≥7 days following completion of initial treatment while cytopenic; with an aplastic or hypoplastic bone marrow obtained within 7 days of death, without evidence of persistent leukemia.			
Death from indeterminate cause	Deaths occurring before completion of therapy, or <7 days following its completion or deaths occurring ≥7 days following completion of initial therapy with no blasts in the blood, but no bone marrow examination available.			

ANC=Absolute neutrophil count; WBC=white blood cell; EMD=extramedullary disease.

There is no minimum requirement for bone marrow cellularity or hemoglobin concentration for response criteria.

Composite from Cheson, BD, Bennett JM, Kopecky KJ, et al. Revised recommendations of the International Working group for diagnosis, standardization of response criteria, treatment on outcomes and reporting standards for therapeutic trials in acute myeloid leukemia. J Clin Oncol 2003; 21(24)4642-4649[40] and Döhner H, Estey E, Grimwade D, et al. Diagnosis and management of AML in adults: 2017 ELN recommendations from an international expert panel. Blood 2017;129(4): 424-47.[42]

[1]CRh is not part of the 2017 ELN recommendations, but is a required assessment for this study.

Appendix 12. 2016 WHO Classification of Myelodysplastic Syndromes

Name	Dysplastic lineages	Cytopenias*	Ring sideroblasts as % of marrow erythroid elements	BM and PB blasts	Cytogenetics by conventional karyotype analysis
MDS with single lineage dysplasia (MDS-SLD)	1	1 or 2	<15%/<5%†	BM <5%, PB <1%, no Auer rods	Any, unless fulfills all criteria for MDS with isolated del(5q)
MDS with multilineage dysplasia (MDS-MLD)	2 or 3	1-3	<15%/<5%†	BM <5%, PB <1%, no Auer rods	Any, unless fulfills all criteria for MDS with isolated del(5q)
MDS with ring sideroblasts (MDS-RS)					
MDS-RS with single lineage dysplasia (MDS-RS-SLD)	1	1 or 2	≥15%/≥5%†	BM <5%, PB <1%, no Auer rods	Any, unless fulfills all criteria for MDS with isolated del(5q)
MDS-RS with multilineage dysplasia (MDS-RS-MLD)	2 or 3	1-3	≥15%/≥5%†	BM <5%, PB <1%, no Auer rods	Any, unless fulfills all criteria for MDS with isolated del(5q)
MDS with isolated del(5q)	1-3	1-2	None or any	BM <5%, PB <1%, no Auer rods	del(5q) alone or with 1 additional abnormality except −7 or del (7q)
MDS with excess blasts (MDS-EB)					
MDS-EB-1	0-3	1-3	None or any	BM 5%-9% or PB 2%-4%, no Auer rods	Any
MDS-EB-2	0-3	1-3	None or any	BM 10%-19% or PB 5%-19% or Auer rods	Any
MDS, unclassifiable (MDS-U)					
with 1% blood blasts	1-3	1-3	None or any	BM <5%, PB = 1%,‡ no Auer rods	Any
with single lineage dysplasia and pancytopenia	1	3	None or any	BM <5%, PB <1%, no Auer rods	Any
based on defining cytogenetic abnormality	0	1-3	<15%§	BM <5%, PB <1%, no Auer rods	MDS-defining abnormality
Refractory cytopenia of childhood	1-3	1-3	None	BM <5%, PB <2%	Any

*Cytopenias defined as: hemoglobin, <10 g/dL; platelet count, $<100 \times 10^9$/L; and absolute neutrophil count, $<1.8 \times 10^9$/L. Rarely, MDS may present with mild anemia or thrombocytopenia above these levels. PB monocytes must be $<1 \times 10^9$/L

†If *SF3B1* mutation is present.

‡One percent PB blasts must be recorded on at least 2 separate occasions.

§Cases with ≥15% ring sideroblasts by definition have significant erythroid dysplasia, and are classified as MDS-RS-SLD.

Arber DA, Orazi A, Hasserjian R, et al. The 2016 revision to the World Health Organization classification of myeloid neoplasms and acute leukemia. Blood 2016;127(20):2391-405.

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Appendix 16. 2017 ELN AML Risk Stratification by Genetics

Risk category*	Genetic abnormality
Favorable	t(8;21)(q22;q22.1); *RUNX1-RUNX1T1*
	inv(16)(p13.1q22) or t(16;16)(p13.1;q22); *CBFB-MYH11*
	Mutated *NPM1* without *FLT3*-ITD or with *FLT3*-ITD^{low}†
	Biallelic mutated *CEBPA*
Intermediate	Mutated *NPM1* and *FLT3*-ITD^{high}†
	Wild-type *NPM1* without *FLT3*-ITD or with *FLT3*-ITD^{low}† (without adverse-risk genetic lesions)
	t(9;11)(p21.3;q23.3); *MLLT3-KMT2A*‡
	Cytogenetic abnormalities not classified as favorable or adverse
Adverse	t(6;9)(p23;q34.1); *DEK-NUP214*
	t(v;11q23.3); *KMT2A* rearranged
	t(9;22)(q34.1;q11.2); *BCR-ABL1*
	inv(3)(q21.3q26.2) or t(3;3)(q21.3;q26.2); *GATA2,MECOM(EVI1)*
	−5 or del(5q); −7; −17/abn(17p)
	Complex karyotype,§ monosomal karyotype‖
	Wild-type *NPM1* and *FLT3*-ITD^{high}†
	Mutated *RUNX1*¶
	Mutated *ASXL1*¶
	Mutated *TP53*#

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

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

†Low, low allelic ratio (<0.5); high, high allelic ratio (≥0.5); semiquantitative assessment of *FLT3*-ITD allelic ratio (using DNA fragment analysis) is determined as ratio of the area under the curve "*FLT3*-ITD" divided by area under the curve "*FLT3*-wild type"; recent studies indicate that AML with *NPM1* mutation and *FLT3*-ITD low allelic ratio may also have a more favorable prognosis and patients should not routinely be assigned to allogeneic HCT.[57-59,77]

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

§Three or more unrelated chromosome abnormalities in the absence of 1 of the WHO-designated recurring translocations or inversions, that is, t(8;21), inv(16) or t(16;16), t(9;11), t(v;11)(v;q23.3), t(6;9), inv(3) or t(3;3); AML with *BCR-ABL1*.

‖Defined by the presence of 1 single monosomy (excluding loss of X or Y) in association with at least 1 additional monosomy or structural chromosome abnormality (excluding core-binding factor AML).[116]

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

#*TP53* mutations are significantly associated with AML with complex and monosomal karyotype.[37,66-69]

From: Döhner H, Estey E, Grimwade D, et al. Diagnosis and management of AML in adults: 2017 ELN recommendations from an international expert panel. Blood 2017;129(4): 424-47.[42]

Appendix 17. 2016 WHO Classification of Myeloid Neoplasms and Acute Leukemia

Myeloproliferative neoplasms (MPN)
Chronic myeloid leukemia (CML), *BCR-ABL1*$^{+}$
Chronic neutrophilic leukemia (CNL)
Polycythemia vera (PV)
Primary myelofibrosis (PMF)
PMF, prefibrotic/early stage
PMF, overt fibrotic stage
Essential thrombocythemia (ET)
Chronic eosinophilic leukemia, not otherwise specified (NOS)
MPN, unclassifiable
Mastocytosis
Myeloid/lymphoid neoplasms with eosinophilia and rearrangement of *PDGFRA*, *PDGFRB*, or *FGFR1*, or with *PCM1-JAK2*
Myeloid/lymphoid neoplasms with *PDGFRA* rearrangement
Myeloid/lymphoid neoplasms with *PDGFRB* rearrangement
Myeloid/lymphoid neoplasms with *FGFR1* rearrangement
Provisional entity: Myeloid/lymphoid neoplasms with PCM1-JAK2
Myelodysplastic/myeloproliferative neoplasms (MDS/MPN)
Chronic myelomonocytic leukemia (CMML)
Atypical chronic myeloid leukemia (aCML), *BCR-ABL1*$^{-}$
Juvenile myelomonocytic leukemia (JMML)
MDS/MPN with ring sideroblasts and thrombocytosis (MDS/MPN-RS-T)
MDS/MPN, unclassifiable
Myelodysplastic syndromes (MDS)
MDS with single lineage dysplasia
MDS with ring sideroblasts (MDS-RS)
MDS-RS and single lineage dysplasia
MDS-RS and multilineage dysplasia
MDS with multilineage dysplasia
MDS with excess blasts
MDS with isolated del(5q)
MDS, unclassifiable
Provisional entity: Refractory cytopenia of childhood

Myeloid neoplasms with germ line predisposition
Acute myeloid leukemia (AML) and related neoplasms
AML with recurrent genetic abnormalities
AML with t(8;21)(q22;q22.1);*RUNX1-RUNX1T1*
AML with inv(16)(p13.1q22) or t(16;16)(p13.1;q22);*CBFB-MYH11*
APL with *PML-RARA*
AML with t(9;11)(p21.3;q23.3);*MLLT3-KMT2A*
AML with t(6;9)(p23;q34.1);*DEK-NUP214*
AML with inv(3)(q21.3q26.2) or t(3;3)(q21.3;q26.2); *GATA2, MECOM*
AML (megakaryoblastic) with t(1;22)(p13.3;q13.3);*RBM15-MKL1*
Provisional entity: AML with BCR-ABL1
AML with mutated *NPM1*
AML with biallelic mutations of *CEBPA*
Provisional entity: AML with mutated RUNX1
AML with myelodysplasia-related changes
Therapy-related myeloid neoplasms
AML, NOS
AML with minimal differentiation
AML without maturation
AML with maturation
Acute myelomonocytic leukemia
Acute monoblastic/monocytic leukemia
Pure erythroid leukemia
Acute megakaryoblastic leukemia
Acute basophilic leukemia
Acute panmyelosis with myelofibrosis
Myeloid sarcoma
Myeloid proliferations related to Down syndrome
Transient abnormal myelopoiesis (TAM)
Myeloid leukemia associated with Down syndrome

Blastic plasmacytoid dendritic cell neoplasm
Acute leukemias of ambiguous lineage
Acute undifferentiated leukemia
Mixed phenotype acute leukemia (MPAL) with t(9;22)(q34.1;q11.2); *BCR-ABL1*
MPAL with t(v;11q23.3); *KMT2A* rearranged
MPAL, B/myeloid, NOS
MPAL, T/myeloid, NOS
B-lymphoblastic leukemia/lymphoma
B-lymphoblastic leukemia/lymphoma, NOS
B-lymphoblastic leukemia/lymphoma with recurrent genetic abnormalities
B-lymphoblastic leukemia/lymphoma with t(9;22)(q34.1;q11.2);*BCR-ABL1*
B-lymphoblastic leukemia/lymphoma with t(v;11q23.3);*KMT2A* rearranged
B-lymphoblastic leukemia/lymphoma with t(12;21)(p13.2;q22.1); *ETV6-RUNX1*
B-lymphoblastic leukemia/lymphoma with hyperdiploidy
B-lymphoblastic leukemia/lymphoma with hypodiploidy
B-lymphoblastic leukemia/lymphoma with t(5;14)(q31.1;q32.3) *IL3-IGH*
B-lymphoblastic leukemia/lymphoma with t(1;19)(q23;p13.3);*TCF3-PBX1*
Provisional entity: B-lymphoblastic leukemia/lymphoma, BCR-ABL1–like
Provisional entity: B-lymphoblastic leukemia/lymphoma with iAMP21
T-lymphoblastic leukemia/lymphoma
Provisional entity: Early T-cell precursor lymphoblastic leukemia
Provisional entity: Natural killer (NK) cell lymphoblastic leukemia/lymphoma

Arber DA, Orazi A, Robert, H, et.al. The 2016 revision to the World Health Organization classification of myeloid neoplasms and acute leukemia. *Blood*. 2016; 127 (20): 2391-2405.

Appendix 18. France Appendix

This appendix applies to study sites located in France.

1. GCP Training

Prior to enrollment of any subjects, the investigator and any sub-investigators will complete the Pfizer-provided Good Clinical Practice training course ("Pfizer GCP Training") or training deemed equivalent by Pfizer. Any investigators who later join the study will complete the Pfizer GCP Training or equivalent before performing study-related duties. For studies of applicable duration, the investigator and sub-investigators will complete Pfizer GCP Training or equivalent every three years during the term of the study, or more often if there are significant changes to the ICH GCP guidelines or course materials.

2. Investigational Product

No subjects or third-party payers will be charged for investigational product.

3. Inspections

The investigator(s) will notify Pfizer or its service provider immediately of any regulatory inspection notification in relation to the study. Furthermore, the investigator will cooperate with Pfizer or its service provider to prepare the study site for the inspection and will allow Pfizer or its service provider (if not prohibited by law) to be present during the inspection. The study site and investigator will promptly resolve any discrepancies that are identified between the study data and the subject's medical records. The investigator will promptly provide copies of the inspection findings to Pfizer or its service provider. Before response submission to the regulatory authorities, the investigator will provide Pfizer or its service provider with an opportunity to review and comment on responses to any such findings.