CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

210656Orig1s000

CLINICAL REVIEW(S)

Clinical Review
Kelly Norsworthy, MD
NDA 210656
Daurismo® (glasdegib)

CLINICAL REVIEW

Application Type	NDA Type 1
Application Number(s)	210656 (Original-1)
Priority or Standard	Priority
Submit Date(s)	4/27/2018
Received Date(s)	4/27/2018
PDUFA Goal Date	12/27/2018
Division/Office	Division of Hematology Products / Office of Hematology and Oncology Products
Reviewer Name(s)	Kelly Norsworthy, MD
Review Completion Date	9/27/2018
Established/Proper Name	Glasdegib
(Proposed) Trade Name	Daurismo®
Applicant	Pfizer
Dosage Form(s)	Film-coated tablet 100 mg
Applicant Proposed Dosing Regimen(s)	100 mg orally, once daily
Applicant Proposed Indication(s)/Population(s)	(b) (4) [redacted]
Recommendation on Regulatory Action	Full approval for revised indication
Recommended Indication(s)/Population(s) (if applicable)	DAURISMO is a hedgehog pathway inhibitor indicated, in combination with low-dose cytarabine, for the treatment of newly-diagnosed acute myeloid leukemia (AML) in adults.

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Glossary

AC	advisory committee
AE	adverse event
AHD	antecedent hematologic disease
ALP	alkaline phosphatase
ALT	alanine aminotransferase
ANC	absolute neutrophil count
AR	adverse reaction
ARDS	acute respiratory distress syndrome
AST	aspartate aminotransferase
BLA	biologics license application
BM	bone marrow
BPCA	Best Pharmaceuticals for Children Act
BRF	Benefit Risk Framework
CBC	complete blood count
CBER	Center for Biologics Evaluation and Research
CDER	Center for Drug Evaluation and Research
CDRH	Center for Devices and Radiological Health
CDTL	Cross-Discipline Team Leader
CFR	Code of Federal Regulations
CI	confidence interval
CMC	chemistry, manufacturing, and controls
CMML	chronic myelomonocytic leukemia
CMP	comprehensive metabolic panel
COSTART	Coding Symbols for Thesaurus of Adverse Reaction Terms
CPK	creatine phosphokinase
CR	complete remission
CRc	cytogenetic complete response
CRF	case report form
CRi	complete remission with incomplete blood count recovery
CRm	molecular complete response
CRO	contract research organization
CRT	clinical review template
CSR	clinical study report
CSS	Controlled Substance Staff
CV	coefficient of variation
DDI	drug-drug interaction

DLI	donor lymphocyte infusion
DLT	dose-limiting toxicity
DMC	data monitoring committee
ECG	electrocardiogram
ECOG PS	Eastern Cooperative Oncology Group performance status
eCTD	electronic common technical document
ETASU	elements to assure safe use
FAERS	FDA adverse event reporting system
FAS	full analysis set
FDA	Food and Drug Administration
FDAAA	Food and Drug Administration Amendments Act of 2007
FDASIA	Food and Drug Administration Safety and Innovation Act
GCP	good clinical practice
GRMP	good review management practice
Hh	Hedgehog
HiDAC	high-dose cytarabine
HMA	hypomethylating agent
HR	hazard ratio
HSCT	hematopoietic stem cell transplantation
ICH	International Council for Harmonization
ICM	ischemic cardiomyopathy
IND	Investigational New Drug Application
ISE	integrated summary of effectiveness
ISS	integrated summary of safety
ITT	intent to treat
IVRS	interactive voice response system
IWG	International Working Group
LDAC	low-dose cytarabine
MAD	maximum administered dose
MDS	myelodysplastic syndrome
MedDRA	Medical Dictionary for Regulatory Activities
MF	myelofibrosis
MI	myocardial infarction
mITT	modified intent to treat
MLFS	morphologic leukemia-free state
MR	minor response
MTD	maximum tolerated dose
NCI-CTCAE	National Cancer Institute-Common Terminology Criteria for Adverse Event
NDA	new drug application
NME	new molecular entity
NR	not reached

OCS	Office of Computational Science
OPQ	Office of Pharmaceutical Quality
OS	overall survival
OSE	Office of Surveillance and Epidemiology
OSI	Office of Scientific Investigation
PBRER	Periodic Benefit-Risk Evaluation Report
PD	pharmacodynamics
PI	prescribing information or package insert
PK	pharmacokinetics
PMC	postmarketing commitment
PMR	postmarketing requirement
PP	per protocol
PPI	patient package insert
PR	partial remission
PREA	Pediatric Research Equity Act
PRi	partial remission with incomplete blood count recovery
PRO	patient reported outcome
PSUR	Periodic Safety Update report
PT	preferred terms
Ptc	Patched
PVC	premature ventricular contraction
REMS	risk evaluation and mitigation strategy
RP2D	recommended phase 2 dose
R/R	relapsed or refractory
SAE	serious adverse event
SAP	statistical analysis plan
SAS	safety analysis set
SD	stable disease
SGE	special government employee
SMO	Smoothened
SMQ	Standardized MedDRA Queries
SOC	standard of care
TdP	Torsades de Pointes
TEAE	treatment emergent adverse event
TESAE	treatment emergent serious adverse event

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1. Executive Summary

1.1. Product Introduction

Pfizer submitted NDA 210656 for glasdegib (Daurismo®), also known as PF-04449913, a new molecular entity (NME) (b) (4) Glasdegib is a potent small molecule inhibitor of Smoothened (SMO), a key protein in the Hedgehog (Hh) signaling pathway.

The applicant's proposed indication is (b) (4) The proposed dosing schedule for patients with AML is 100 mg administered orally once daily continuously as long as the patient is deriving clinical benefit.

1.2. Conclusions on the Substantial Evidence of Effectiveness

I conclude that the information submitted by the Applicant has provided substantial evidence for the effectiveness of glasdegib, in combination with low-dose cytarabine (LDAC), for the treatment of adult patients with newly-diagnosed AML and supports regular approval of this indication. This conclusion is based on the results of a single randomized, phase 2, add-on, controlled study in patients ≥ 55 years with newly-diagnosed AML, which demonstrated an overall survival (OS) advantage in patients who received glasdegib in addition to LDAC compared with LDAC alone (HR 0.46, P=0.0002). The study included patients with high-risk MDS, but only 16 randomized patients had high-risk MDS, which was insufficient to draw conclusions on efficacy in this patient population. The applicant provided data from studies of glasdegib monotherapy in patients with newly-diagnosed and relapsed/refractory AML, which showed no evidence of clinical benefit of monotherapy in these indications, supporting a limitation of use.

1.3. Benefit-Risk Assessment

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Benefit-Risk Integrated Assessment

Glasdegib is a small molecule that inhibits Smoothened, a key protein in the Hedgehog signaling pathway. The applicant's proposed indication evaluated in this review i (b) (4) The benefit-risk assessment supports regular approval of glasdegib, in combination with low-dose cytarabine (LDAC) for the treatment of adults with newly-diagnosed AML. (b) (4)

The efficacy of glasdegib is primarily based on the results of a single, phase 2, randomized, open-label study that compared glasdegib, administered at 100 mg by mouth once daily continuously in combination with LDAC (cytarabine 20 mg subcutaneously twice daily on days 1 to 10 of each 28-day cycle) until disease progression or unacceptable toxicity, to LDAC alone in patients age 55 years and older with newly-diagnosed AML. A total of 115 patients with AML (77 on the glasdegib+LDAC arm and 38 on the LDAC arm) were evaluated on this study, which found that glasdegib yielded a statistically significant OS advantage (HR=0.46, p=0.0002). Median OS was 8.3 months (95% CI 4.4-12.2 months) on the glasdegib+LDAC arm and 4.5 months (95% CI 1.9-5.7 months) on the LDAC arm. Rates of complete remission (CR) were also higher on the glasdegib+LDAC arm (18% vs 3%). Although the pivotal study was conducted in patients age ≥ 55 years meeting at least one of a) age ≥ 75 years, b) performance status = 2, c) serum creatinine > 1.3 mg/dL, and d) severe cardiac disease, efficacy data can be extrapolated to a younger patient population, given no biologic basis to suspect lesser responses. Certain younger patients with AML may not be considered for treatment with intensive chemotherapy, based on comorbidities or poor performance status, which may make them appropriate for glasdegib+LDAC therapy. Thus, a broad indication for adults with newly-diagnosed AML is recommended, leaving the decision to treat to the physician and patient. Data from studies of glasdegib monotherapy in patients with newly-diagnosed or relapsed/refractory AML show toxicity without substantial clinical activity and resulted in a limitation of use statement in the product label.

The safety database for glasdegib consists of 469 patients exposed to glasdegib across 13 studies in patients with AML, patients with other hematologic malignancies, solid tumors, and healthy volunteers. In general, glasdegib appears well-tolerated. Most fatal adverse events (AEs) occurred on studies of patients with AML and were less frequent on the glasdegib+LDAC arm than the LDAC arm on the pivotal study. These events were primarily due to cardiac causes and infection, which are common causes of treatment-related mortality in an elderly comorbid AML patient population. The most frequent serious adverse reaction was febrile neutropenia. Common adverse reactions (>20%) included fatigue, bleeding, febrile neutropenia, musculoskeletal pain, nausea, edema, dyspnea, decreased appetite, dysgeusia, and mucositis. The incidence of QTc prolongation observed with glasdegib warrants a recommendation to monitor ECGs and electrolytes, particularly in patients

with cardiac disease and those taking medications known to prolong the QTc interval and CYP3A4 inhibitors. As animal reproductive studies noted fetal anomalies and fetal loss secondary to glasdegib, I recommend a boxed warning for embryo-fetal toxicity.

Benefit-Risk Dimensions

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	• There were 21,380 new cases of AML and 10,590 deaths from AML in the United States in 2017. AML occurs in all age groups, but is primarily a disease of older adults, with a median age at diagnosis of 67 years. • AML is universally fatal without treatment, with a median survival of approximately two months.	AML is a fatal disease
Current Treatment Options	• Non-intensive regimens for newly-diagnosed AML yield CR rates of 15-20% and median OS of 4-10 months. • Only LDAC and gemtuzumab ozogamicin (median OS 4-5 months) have demonstrated a survival advantage over supportive care therapies for patients with newly-diagnosed AML.	Current standard of care regimens are insufficient, and more effective therapies are needed.
Benefit	• Study B1371003 was a randomized, open-label, add-on study of glasdegib in combination with LDAC in patients with newly-diagnosed AML. • The glasdegib+LDAC arm had a statistically significant improvement in OS (HR 0.46, p=0.0002).	Glasdegib 100 mg daily continuously in combination with cytarabine 20 mg subcutaneously twice daily on days 1 to 10 of each 28-day cycle until disease progression or unacceptable toxicity improves survival in patients with newly-diagnosed AML compared to standard low-dose cytarabine therapy.

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Dimension	Evidence and Uncertainties	Conclusions and Reasons
Risk and Risk Management	• Fatal toxicities occurred in 7% of patients on the glasdegib+LDAC arm compared to 12% of patients on the LDAC arm. • The most frequent serious adverse reaction was febrile neutropenia. • Common adverse reactions (>20%) include fatigue, bleeding, febrile neutropenia, musculoskeletal pain, nausea, edema, dyspnea, decreased appetite, dysgeusia, and mucositis. • Glasdegib can cause QTc prolongation and ventricular arrhythmias • Glasdegib causes fetal anomalies and fetal loss in animal reproductive studies. • Glasdegib is toxic and fails to produce clinical responses when administered as monotherapy to patients with AML.	The overall safety profile of glasdegib is acceptable for patients with AML. The prescribing information will include a boxed warning with information about risk of embryo-fetal toxicity and a warning and precaution for QTc prolongation. There will be a limitation of use statement that glasdegib should not be used as monotherapy in AML.

1.4. Patient Experience Data

Patient Experience Data Relevant to this Application (check all that apply)

□	The patient experience data that was submitted as part of the application include:	Section where discussed, if applicable
	□ Clinical outcome assessment (COA) data, such as	
	□ Patient reported outcome (PRO)	
	□ Observer reported outcome (ObsRO)	
	□ Clinician reported outcome (ClinRO)	
	□ Performance outcome (PerfO)	
	□ Qualitative studies (e.g., individual patient/caregiver interviews, focus group interviews, expert interviews, Delphi Panel, etc.)	
	□ Patient-focused drug development or other stakeholder meeting summary reports	
	□ Observational survey studies designed to capture patient experience data	
	□ Natural history studies	
	□ Patient preference studies (e.g., submitted studies or scientific publications)	
	□ Other: (Please specify)	
□	Patient experience data that were not submitted in the application, but were considered in this review:	
	□ Input informed from participation in meetings with patient stakeholders	
	□ Patient-focused drug development or other stakeholder meeting summary reports	
	□ Observational survey studies designed to capture patient experience data	
	□ Other: (Please specify)	
x □	Patient experience data was not submitted as part of this application.	

2. Therapeutic Context

2.1. Analysis of Condition

AML is a heterogeneous group of hematopoietic neoplasms characterized by a clonal proliferation of myeloid precursors with limited ability to differentiate into more mature myeloid cells. These blasts replace normal hematopoietic tissue in the bone marrow (BM), resulting in low red blood cell, platelet, and/or white blood cell counts. According to the National Cancer Institute's SEER database, it is estimated that there were 21,380 new cases of AML and 10,590 deaths from AML in the United States in 2017. AML occurs in children and adults of all ages, but is primarily a disease of older adults, with a median age at diagnosis of 67 years. AML is more common in men than women (5.2 vs 3.6 new cases per 100,000 persons per year) and does not have a strong racial or ethnic predilection (Howlader N 2017). AML is universally fatal without treatment, with a median survival of approximately two months (Oran & Weisdorf 2012).

Newly diagnosed AML in older patients is difficult to treat. Cure rates for adults ≥ 65 years with AML are < 10% (Walter & Estey 2015). Co-morbidities and advanced age often prevent the successful administration of potentially-curative intensive chemotherapy and hematopoietic stem cell transplantation (HSCT). Thus, treatment options for older adults consist of less intensive therapies, or simply, best supportive care with antibiotics, transfusions, and hydroxyurea for count control.

2.2 Analysis of Current Treatment Options

With the exception of a rare subtype of AML called acute promyelocytic leukemia (APL), which is frequently curable with retinoic acid and arsenic trioxide and will be excluded from further discussion in this review, combination chemotherapy regimens with or without HSCT are a mainstay of therapy for patients with AML. A list of chemotherapy agents with FDA approval for the treatment of AML are provided in Table 1. In patients who can tolerate intensive therapy, cytarabine and daunorubicin or idarubicin induction (the so-called "7+3" regimen) followed by high-dose cytarabine (HiDAC) consolidation is frequently used. This regimen results in complete remission (CR) rates of 60-70% and 2-year OS of approximately 50% in patients < 60 years of age (Fernandez et al. 2009). However, older patients (age ≥ 60) fare less well, with CR rates of approximately 50% and 2-year OS of approximately 20% (Estey 2007).

Recent developments in newly-diagnosed patients with AML eligible for intensive chemotherapy include the recent FDA approvals for midostaurin in combination with 7+3 and HiDAC consolidation for patients with FLT3-mutated AML and Vyxeos® ([daunorubicin and cytarabine] liposome injection) for the treatment of adults with therapy-related AML or AML with myelodysplasia-related changes. Both drugs led to improvements in OS compared to standard 7+3.

In patients who are not candidates for intensive remission therapy or decline intensive therapy, National Comprehensive Cancer Network guidelines recommend low-intensity therapy (hypomethylating agents [HMA] preferred or LDAC), gemtuzumab ozogamicin (GO) for CD33

positive patients, enasidenib for IDH-2 mutated AML, ivosidenib for IDH-1 mutated AML, or best supportive care with hydroxyurea and transfusion support ("National Comprehensive Cancer Network. Acute Myeloid Leukemia (Version 2.2018)"). HMAs (azacitidine and decitabine) and LDAC result in CR rates of 15-20% and median OS of roughly 4-10 months (Burnett et al. 2007; Dombret et al. 2015; H. M. Kantarjian et al. 2012). Only LDAC has led to a demonstrable survival benefit compared to hydroxyurea with or without all-trans retinoic acid (Burnett et al. 2007). Both HMAs failed to demonstrate a survival benefit compared to investigator's choice regimens (Dombret et al. 2015; H. M. Kantarjian et al. 2012).

GO recently received FDA approval as monotherapy for the treatment of adult patients with newly-diagnosed CD33-positive AML based on a survival benefit compared to best supportive care (median OS 4.9 vs 3.6 months; hazard ratio [HR] 0.69 [95% CI 0.53-0.90]) (Jen et al. 2018). CR rate with GO was 17/111 (15%) (Amadori et al. 2016). Other recent approvals in the AML space include enasidenib and ivosidenib for the treatment of adults with relapsed or refractory (R/R)-AML with an IDH2 or an IDH1 mutation, respectively. Although the approvals were for R/R AML, the NCCN guidelines include enasidenib and ivosidenib as options for newly-diagnosed patients with an IDH2 or IDH1 mutation based on preliminary results in the frontline setting (DiNardo et al. 2018; Pollyea et al. 2017). CR rate in 37 patients with previously untreated IDH2-mutated AML with enasidenib was 19% with median duration of CR not reached (95% CI 3.7, NR). Median OS was 10.4 months (95% CI 5.7, 15.1). CR rate in 34 patients with previously untreated IDH1-mutated AML with ivosidenib was 21% with a median duration of CR not reached (95% CI 5.6, NR). It is not known how the enasidenib and ivosidenib results compare to the other available treatment options for adults with newly-diagnosed IDH2 and IDH1-mutated AML.

In conclusion, although multiple novel therapies have recently emerged for the treatment of newly-diagnosed AML, treatment of older and co-morbid patients with AML remains problematic and with poor long-term outcomes. There is still a clear need for new treatments for patients with AML who cannot tolerate intensive chemotherapy.

Table 1: Currently Available Treatments for Acute Myeloid Leukemia

Agent	Excerpted Indication
Azacitidine	Indicated for myelodysplastic syndrome (MDS), including refractory anemia with excess blasts in transformation (i.e., 20-30% blasts), which is now classified as AML per contemporary classification systems
Cyclophosphamide	Indicated for the treatment of leukemias
Cytarabine	Indicated in combination with other approved anticancer drugs for induction in acute non-lymphocytic leukemia of adults and children
Daunorubicin	Indicated in combination with other approved anticancer drugs for remission induction in acute non-lymphocytic leukemia of adults
Daunorubicin and cytarabine liposome injection	Indicated for the treatment of adults with newly-diagnosed therapy-related AML or AML with myelodysplasia-related changes

Decitabine	Indicated for myelodysplastic syndrome (MDS), including refractory anemia with excess blasts in transformation (i.e., 20-30% blasts), which is now classified as AML per contemporary classification systems
Dexamethasone	For the palliative management of leukemias and lymphomas
Doxorubicin	Doxorubicin has been used successfully to produce regression in disseminated neoplastic conditions, including acute myeloblastic leukemia
Enasidenib	Indicated for the treatment of adults with relapsed or refractory AML with an IDH2 mutation
Gemtuzumab ozogamicin	Indicated for the treatment of newly-diagnosed CD33-positive AML in adults and indicated for the treatment of relapsed or refractory CD33-positive AML in adults and pediatric patients 2 years and older.
Hydrocortisone	For palliative management of leukemias and lymphomas in adults, acute leukemia of childhood.
Idarubicin	Indicated in combination with other approved anti-leukemic drugs for the treatment of AML in adults
Ivosidenib	Indicated for the treatment of adults with relapsed or refractory AML with an IDH1 mutation
Methylprednisolone	For palliative management of leukemias and lymphomas in adults, acute leukemia of childhood
Midostaurin	Indicated for newly diagnosed, FLT3+ AML in combination with standard cytarabine and daunorubicin induction and cytarabine consolidation.
Mitoxantrone	Indicated in combination with other approved drug(s) in the initial therapy of acute non-lymphocytic leukemia in adults
Prednisone	For palliative management of leukemias and lymphomas in adults, acute leukemia of childhood
Thioguanine	Indicated for remission induction and remission consolidation treatment of acute non-lymphocytic leukemias, with higher remission rates in combination with other chemotherapy agents
Vincristine	Indicated in acute leukemia

3. Regulatory Background

3.1. U.S. Regulatory Actions and Marketing History

Glasdegib is not currently marketed in the United States.

3.2. Summary of Presubmission/Submission Regulatory Activity

The trials included in this application were conducted under IND 105453, which was submitted on August 14, 2009. The IND has never been placed on clinical hold.

A Type B End of Phase 1 face-to-face meeting was held on 5/6/2014 to discuss the clinical development plan for glasdegib and to obtain FDA feedback on the design of the randomized

controlled study to potentially support registration of glasdegib (b) (4)

A Type C teleconference meeting was held on 11/13/2014 (b) (4)

A Type B face-to-face meeting was held on 7/22/2015 (b) (4)

A Type C teleconference meeting was held on 4/27/2016 to discuss and reach agreement on the proposed clinical development plan to support registration for the proposed indication of adult patients (b) (4)

FDA provided written responses for a Type C meeting on 11/22/2016 with feedback on the potential of Study B1371003, which showed a survival benefit for glasdegib+LDAC compared to LDAC alone, to support registration for the treatment of AML in combination with LDAC. FDA indicated that, in general, a positive randomized controlled trial that isolates the treatment effect of a new drug is appropriate to support submission of a marketing application, but that approval would be a review issue.

A Type B Pre-Phase 3 face-to-face meeting was held on 3/31/2017 where FDA provided feedback on the proposed phase 3 trial, Study B1371019, which will randomize patients intended for intensive therapy to 7+3 vs 7+3+glasdegib and patients intended for non-intensive therapy to azacitidine vs azacitidine+glasdegib.

A Type B face-to-face meeting was held on 4/27/2017 where FDA provided feedback on the proposed stability strategy in support of the registration of glasdegib in combination with LDAC as a treatment for de novo AML in elderly patients who are not suitable for intensive induction chemotherapy.

The FDA granted Orphan Drug Designation to glasdegib for the treatment of AML on June 28, 2017 (designation number 17-5855).

A Type B teleconference meeting was held on 7/24/2017 where FDA provided feedback on the content and format of an upcoming NDA for glasdegib for the treatment of AML. The Sponsor proposed submission of the NDA during the first quarter of 2018.

A Type C face-to-face meeting was held on 8/24/2017 to obtain FDA's advice and agreement on CMC strategies to pursue during commercial development.

The FDA granted Orphan Drug Designation to glasdegib for the treatment of MDS on October 20, 2017 (designation number 17-6086).

A Type C face-to-face meeting was held on 12/6/2017 to obtain FDA's advice and agreement on CMC strategies to pursue during commercial development and for the preparation of the upcoming NDA.

This NDA was submitted on April 27, 2018, in its entirety, using a data cut date of January 3, 2017. The Applicant requested priority review, which was granted by the FDA on June 22, 2018. The Applicant provided updated safety data on all patients treated with glasdegib at the time of the 4-month safety update, using a data cut date of March 13, 2018. This was agreed to by the FDA at the time of the pre-NDA meeting.

3.3. Foreign Regulatory Actions and Marketing History

Glasdegib is not currently available in any foreign markets.

4. Significant Issues from Other Review Disciplines Pertinent to Clinical Conclusions on Efficacy and Safety

4.1. Office of Scientific Investigations (OSI)

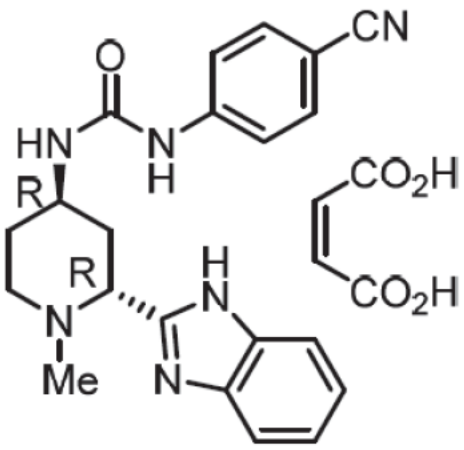
Given that the highest number of randomized patients at any one site was only 8, the clinical team recommended against inspections of clinical sites. A review of efficacy across the higher volume sites did not reveal that any one site could skew the efficacy results. Review of efficacy and safety across sites was limited by the small patient numbers by site and 2:1 randomization.

The applicant (Pfizer) was audited. Inspection review identified two regulatory deficiencies related to: failure to ensure proper monitoring of the study and ensure the study is conducted in accordance with the protocol and/or investigational plan (particularly regarding serious adverse event [SAE] reporting from Site 1033 with n=8 patients) and failure to describe transfer of obligations to a contract research organization in writing before the effective dates (i.e., delay in administrative documentation). A Form 483 was issued to Pfizer describing these deficiencies. Given that the pivotal portion of Study B1371003 was conducted at 38 different trial sites, these findings, while serious, are not likely to significantly impact the results of the clinical trial.

4.2. Product Quality

Glasdegib is supplied as an immediate-release film-coated tablet containing 100 mg of glasdegib (also available as a 25 mg tablet). It is intended for oral administration. Early clinical trials used tablets containing glasdegib (b) (4) salt drug substance. However, the physical properties and stability were not acceptable for the commercial product. Thus, the

commercial product uses a maleate salt form of the drug substance, which has improved physical properties and stability. The molecular formula for glasdegib is $C_{25}H_{26}N_6O_5$ (drug) $C_4H_4O_4$ (maleate). The molecular weight is 490.51 Daltons (as the maleate). The chemical structure of glasdegib maleate is shown below:



No product quality concerns were identified on preliminary CMC review, and approval is recommended.

4.3. Clinical Microbiology

Not applicable.

4.4. Nonclinical Pharmacology/Toxicology

In rats and dogs, glasdegib administered orally caused toxicities in multiple organ systems. The organ systems involved were kidneys (rat and dog), liver (dog only), and rat only in growing bone, growing teeth, testis, and peripheral nerve. Additional findings in rats and dogs included significant weight loss and decreased food consumption, alopecia and/or and skin irritation/inflammation, and tremors/twitching (muscle and/or whole body). In rats, minimal to mild hypercellularity of BM, which corresponded with decreased red cell mass and increased reticulocytes in peripheral blood, and/or minimal to mid decreased cellularity of lymphoid tissues was observed. The red cell loss was thought to be a consequence of the oral ulcerations, hemorrhage, and dental changes observed in rats. Lastly, a single dose safety pharmacology study in dogs identified QTc prolongation as a toxicity.

Glasdegib was found to be teratogenic at the lowest doses tested in rats and rabbits in embryofetal developmental toxicity studies. Glasdegib was not genotoxic based on a standard

battery of assays for mutagenicity and clastogenicity. Carcinogenicity studies have not been conducted given the intended treatment of patients with cancer. Fertility studies with glasdegib have not been conducted given the intended treatment of patients with advanced cancer.

The preclinical pharmacology/toxicology reviewer recommended approval.

4.5. Clinical Pharmacology

Mechanism of action: Glasdegib is a potent small molecule inhibitor of Smoothened (SMO), a key protein in the Hedgehog (Hh) signaling pathway. The Hh pathway is activated by the binding of Hh ligand to the transmembrane receptor, Patched (Ptc). In the absence of ligand, Ptc suppresses the Hh signaling cascade by inhibiting the activity of SMO, a second transmembrane protein. Binding of Hh ligand to Ptc alleviates repression of SMO, allowing it to transduce the signal to the cytoplasm resulting in activation of zinc finger transcription factor, Gli 1. Gli1 translocates to the nucleus and activates transcription of target genes including Gli1 and Ptc (McMillan & Matsui 2012). Activation of the Hh pathway, leading to upregulation of Gli1, has been implicated in hematologic malignancies.

Absorption: Absolute bioavailability of glasdegib is about 77%. T_{max} ranged from about 0.75 to 4.1 hours. After single and multiple doses ranging from 5 to 640 mg, the drug displayed dose-proportional pharmacokinetics (PK). Steady-state was reached by 8 days with daily dosing and accumulation was roughly 2.5-fold. There was no notable food effect; AUC decreased by about 15% with a high-fat meal.

Distribution: Glasdegib is about 91% plasma protein bound. The volume of distribution was 188 L. Glasdegib is a substrate of P-gp and BCRP.

Metabolism: Glasdegib is present as 69% unchanged drug in plasma. Metabolites are not active. The primary CYP enzymes involved in the oxidative metabolism of glasdegib are CYP3A4 (60-80%) and CYP2C8 (2-20%). For the minor glucuronidation pathway, UGT1A9 was the predominant enzyme. The plasma elimination half-life of glasdegib at a dose of 100 mg was 17.4 hours, supporting daily dosing.

Excretion: Glasdegib was eliminated via the liver and kidneys, with 42% in feces (21% as unchanged) and 49% in urine (17% as unchanged).

Drug-drug interactions (DDIs): A 40% increase in glasdegib C_{max} and a 140% increase in glasdegib AUC_{inf} were noted in a DDI study conducted with the strong CYP3A4 inhibitor ketoconazole. A 35% decrease in glasdegib C_{max} and a 70% decrease in glasdegib AUC_{inf} were noted in a clinical DDI study conducted with rifampin, a strong CYP3A4 inducer.

Specific populations: Population PK analyses showed no effects of age, sex, weight, race, and mild-moderate renal and hepatic impairment.

Effects on QT: A thorough QT study showed a mean change in QTcF from baseline of 13.4 ms (90% CI 11.2, 15.6) at a single dose of 300 mg. Concentration-QT analysis showed a mean change in QTcF from baseline of 5.3 ms (95% CI 4.4, 6.2) at 100 mg qday and 12.1 ms (95% CI 1, 14.3) at the mean supratherapeutic (2-fold higher) Cmax.

Recommended phase 2 dose (RP2D): The first-in-human study in patients with hematologic malignancies identified the maximum tolerated dose (MTD) to be 400 mg. Activity in AML was observed across a broad range of doses (10 to 600 mg). Inhibition of GLI1 expression was > 90% at ≥ 100 mg and ≥ 80% at 50 mg. Thus, a dose of 100 mg dose was chosen as a safe and biologically effective dose, allowing for higher glasdegib exposures in combination with strong CYP3A4 inhibitors.

Clinical pharmacology reviewers determined that the evidence of effectiveness and the proposed dose and regimen were sufficiently supported by the application and recommended approval.

4.6. Devices and Companion Diagnostic Issues

Not applicable.

4.7. Consumer Study Reviews

The Division of Medication Error Prevention and Analysis (DMEPA) reviewed the proposed Prescribing Information (PI) and the proposed carton and vial labels. DMEPA has not identified any significant issues that would interfere with product approval.

5. Sources of Clinical Data and Review Strategy

5.1. Table of Clinical Studies

The Applicant submitted clinical study reports or summaries (ongoing trials) from 13 clinical trials of glasdegib and SAEs and death reports from 2 investigator-initiated trials (Table 2). Of the commercial studies, 3 were studies of glasdegib in combination with intensive chemotherapy, LDAC, decitabine, or azacitidine for treatment-naïve AML, high-risk MDS, or chronic myelomonocytic leukemia (CMML), 3 were studies of glasdegib monotherapy in select hematologic malignancies, solid tumors, or MF, and 7 were studies performed in healthy volunteers. The investigator-initiated trials include an ongoing monotherapy trial in high-risk acute leukemia patients post-transplant and a completed trial of glasdegib monotherapy in patients with R/R MDS or CMML. Raw datasets for clinical review were submitted for all 13 commercial studies. See Table 2 for further details.

Table 2: Listing of Clinical Trials Relevant to this NDA

Trial*	Trial Design (Primary Endpoint)	Regimen, Schedule, Route	Treatment Duration	No. Enrolled	Population	Countries and No. Centers
Pivotal Study						
1003	Phase 1B/2 study of glasdegib in combination with LDAC versus LDAC alone (Arm A, phase 2 cohort - OS), decitabine (Arm B, phase 1b - safety), intensive chemotherapy (Arm C, phase 2 cohort - CR rate), in patients with AML or high-risk MDS	Arm A: LDAC 20 mg subcut BID Days 1-10 of 28-day cy ± glasdegib 100 mg qday continuously for 1 year Arm B: Decitabine 20 mg/m^2 days 1-5 of 28-day cy + glasdegib 100 mg qday starting day 2 then continuously for 1 year Arm C: "7+3" induction followed by HiDAC consolidation + glasdegib 100 mg daily for 1-2 cy induction, 2-4 cy consolidation, and up to 6 cy maintenance	Indefinitely if clinical benefit with tolerable toxicity	255 (Arm A phase 1b N=23, phase 2 N=132 [88 LDAC+G, 44 LDAC]; Arm B phase 1b N=7; Arm C, phase 1b N=22, phase 2 N=71)	Untreated AML and high-risk MDS patients not eligible for intensive chemo (Arms A and B) or eligible for intensive chemo (Arm C)	Canada: 2 Germany: 10 Italy: 4 Poland: 3 Spain: 8 US: 21
Studies to Support Efficacy and Safety						
1001	Phase 1, open-label study of glasdegib monotherapy for hematologic malignancies (Safety)	Glasdegib 5-600 mg PO qday continuously	Indefinitely if clinical benefit with tolerable toxicity	47	Newly diagnosed and R/R AML (n=28), MDS (n=6), CMML (n=1), CML (n=5), MF (n=7)	Italy: 1 US: 3

Trial*	Trial Design (Primary Endpoint)	Regimen, Schedule, Route	Treatment Duration	No. Enrolled	Population	Countries and No. Centers
1005**	Phase 1 trial of glasdegib monotherapy in Japanese patients with hematologic malignancies and in combination with LDAC, azacitidine, or intensive chemotherapy in patients with AML or high-risk MDS (safety)	Monotherapy: Glasdegib 25-100 mg PO qday continuously Non-intensive: LDAC 20 mg subcut BID Days 1-10 of 28 day cy + glasdegib 100 mg qday continuously Intensive: "7+3" induction followed by HiDAC consolidation + glasdegib 100 mg daily for 1-2 cy induction, 2-4 cy consolidation, and up to 6 cy maintenance	Indefinitely if clinical benefit with tolerable toxicity	25 (glasdegib N=13; LDAC+ glasdegib N=6; 7+3+ glasdegib N=6)	Newly-diagnosed and R/R AML (n=17), MDS (n=6), CMML (n=1), MF (n=1)	Japan: 7
1012**	Phase 1B trial of glasdegib in combination with azacitidine in patients with untreated high-risk MDS, AML with 20-30% blasts, or CMML (safety, CR rate)	Azacitidine 75 mg/m^2/day days 1-7 of 28-day cy + glasdegib 100 mg PO qday continuously	Until PD or toxicity	12	Untreated high-risk MDS (n=7), AML (n=4), CMML (n=1)	Belgium: 1 Canada: 2 UK: 1 US: 9
Studies to Support Safety in Patients With Cancer						
1002	Phase 1 trial of glasdegib monotherapy in solid tumors (safety)	Glasdegib 80-640 mg PO qday continuously	Indefinitely if clinical benefit with tolerable toxicity	23	Advanced/ metastatic solid tumors	US: 3
1013	Phase 2 double-blind randomized study of glasdegib versus placebo in patients with MF previously treated with ruxolitinib (safety, spleen volume reduction)	Glasdegib 100 mg PO qday continuously	Until PD or toxicity	21	MF previously treated with ruxolitinib	Japan: 3 US: 7
WS2233 096***	Investigator-initiated phase 2 trial of glasdegib for acute leukemia post-HSCT maintenance	Glasdegib 100 mg qday continuously starting around day +80 post-HSCT	Up to 1 year	29	AML or ALL post-HSCT with high risk of relapse	US: 2

Trial*	Trial Design (Primary Endpoint)	Regimen, Schedule, Route	Treatment Duration	No. Enrolled	Population	Countries and No. Centers
WI171861***	Investigator-initiated phase 2 trial of glasdegib in patients with R/R MDS or CMML	Glasdegib 100-200 mg qday continuously	Up to 4 cycles	35	R/R MDS or CMML	US: 1
Studies to Support Safety in Healthy Volunteers						
1022	Randomized, single dose crossover study to compare bioavailability of 2 formulations (bioavailability)	Glasdegib 50 mg IV x 1 or glasdegib 100 mg PO x 1	2 doses (1 of each)	12	Healthy volunteers	US: 1
1014	Randomized study to estimate bioavailability of 4 formulations and to evaluate effect of food and proton pump inhibitor (bioavailability)	Glasdegib 100 mg PO x 1 (4 formulations) ± rabeprazole 40 mg qday days -5 to 1	4 doses (1 of each)	35	Healthy volunteers	US: 1
1026	Randomized study to establish bioequivalence of phase 2 formulation to (b) (4) formulation and to estimate effect of food and proton pump inhibitor (bioequivalence)	Glasdegib 100 mg PO x 1 (2 formulations) ± rabeprazole 40 mg qday days -6 to 1	3 doses (1 of each)	24	Healthy volunteers	US: 1
1010	Open-label study to estimate the effects of food and drug-drug interaction potential of ketaconazole (PK)	Glasdegib 200 mg PO x 1 ± ketoconazole 400 mg qday days 1-7 (glasdegib day 4)	3 doses	14	Healthy volunteers	US: 1
1015	Open-label, fixed-sequence, 2-period study to investigate the effect of multiple doses of rifampin on glasdegib (PK)	Glasdegib 100 mg PO x 1 ± rifampin 600 mg PO days -5 to 0	2 doses	12	Healthy volunteers	US: 1
1009	Open-label single radiolabeled dose study to investigate the absorption, metabolism, and excretion of glasdegib (PK)	Glasdegib 100 mg PO with 100 µCi [^{14}C]PF-04449913 x 1	Single dose	6	Healthy volunteers	US: 1
1023	Randomized, 4-way crossover, double blind, placebo and moxifloxacin-controlled study (QTc)	Glasdegib 150 mg PO x 1, 300 mg PO x 1, moxifloxacin 400 mg PO x 1, placebo x 1	2 doses	36	Healthy volunteers	Belgium: 1

*Trial names truncated for commercial trials, which all begin with "B137."

**Study ongoing; summary provided.
***Investigator-initiated studies; SAEs and deaths provided.
Source: FDA synopses of individual studies provided by the Applicant in Module 2.7.6.
Abbreviations: BID, twice a day; chemo, chemotherapy; CR, complete remission; cy, cycles; G, glasdegib; HiDAC, high dose cytarabine; LDAC, low dose cytarabine; mono, monotherapy; OS, overall survival; PO, oral; subcut, subcutaneously.

5.2. Review Strategy

The key materials used for the review of efficacy and safety include:

- NDA 210656
- Relevant published literature
- Relevant information in the public domain

The review of efficacy was primarily based on analysis of newly-diagnosed AML patients treated on the randomized phase 2 portion of Study B1371003 and supported as follows:

- Summarized efficacy data from Study B1371005 was used to support the analysis of the patient population covered by the proposed indication
- Efficacy data from Studies B1371003 and B1371005 were used to support the analysis of dose selection in combination with LDAC
- Efficacy data from Studies B1371001 and B1371005 were used to justify a limitation of use

Results from all 15 trials listed in Table 2 were used to support the analysis of safety. Review emphasis was placed on safety data from the phase 2 randomized portion of Study B1371003, but this was supported as follows:

- Pooled safety data in patients treated with glasdegib in combination with LDAC from all phases of B1371003 and B1371005 by dose were used to support the analysis of dose selection in combination with LDAC
- Pooled safety data from Studies B1371001, B1371005, and B1371013 to investigate the safety of glasdegib monotherapy in patients with hematologic malignancies by dose
- Pooled safety data from Studies B1371005 and B1371013 to investigate the safety of glasdegib monotherapy in hematologic malignancies at the RP2D
- Summarized safety data from Study B1371002 to investigate the safety of glasdegib monotherapy in patients with solid tumors
- Pooled safety data from all trials of glasdegib monotherapy in healthy volunteers was used look for potential safety signals

All major efficacy and safety analyses were reproduced or audited. Summaries of data and statistical analyses by the reviewer were performed using JMP 12.0 (SAS Institute, Inc., Cary, NC), and Excel 2016 (Microsoft, Redmond, WA). MedDRA Adverse Events Diagnostic 1.8 (MAED) (FDA, Silver Spring, MD) was used to look for safety signals. See the statistician's review for analyses of efficacy endpoints.

6. Review of Relevant Individual Trials Used to Support Efficacy

6.1. Study B1371003

6.1.1. Study Design

Overview and Objective

Study B1371003 is a phase 1B/2, open-label, international, multi-center trial that evaluated the safety and efficacy of glasdegib administered in combination with first-line treatment regimens for AML and high-risk MDS. Phase 1B evaluated the safety and RP2D of glasdegib with the three first-line combination regimens; Arm A with LDAC, Arm B with decitabine, and Arm C with 7+3. Phase 2 assessed the efficacy of two combination regimens; 7+3 plus glasdegib in patients who were able to receive intensive chemotherapy and LDAC plus glasdegib in the patients who were unable to receive intensive chemotherapy (pivotal portion). The remainder of this Section will describe only Arm A of Phase 1B and the randomized phase 2 pivotal portion of the trial (LDAC ± glasdegib), given that the other cohorts are irrelevant to the proposed indication.

The primary objective of phase 1B was to determine the MTD and RP2D of glasdegib in combination with LDAC when administered to adults with previously untreated AML or high-risk MDS. The primary endpoint was first cycle dose limiting toxicities (DLTs). The primary objective of the randomized phase 2 pivotal portion of the trial was to compare OS of glasdegib + LDAC versus LDAC alone in patients with previously untreated AML or high-risk MDS. The primary efficacy endpoint was OS.

Secondary objectives included safety and tolerability, pharmacodynamics (PD), PK, clinical efficacy measures, and effects on the QTc interval. Secondary efficacy endpoints included CR rate, CR with incomplete blood count recovery (CRi), morphologic leukemia-free state (MLFS), partial remission (PR), PR with incomplete blood count recovery (PRi), minor response (MR), stable disease (SD), cytogenetic complete response (CRc), and molecular complete response (CRm). They also defined marrow CR and partial cytogenetic response for MDS patients.

Trial Design

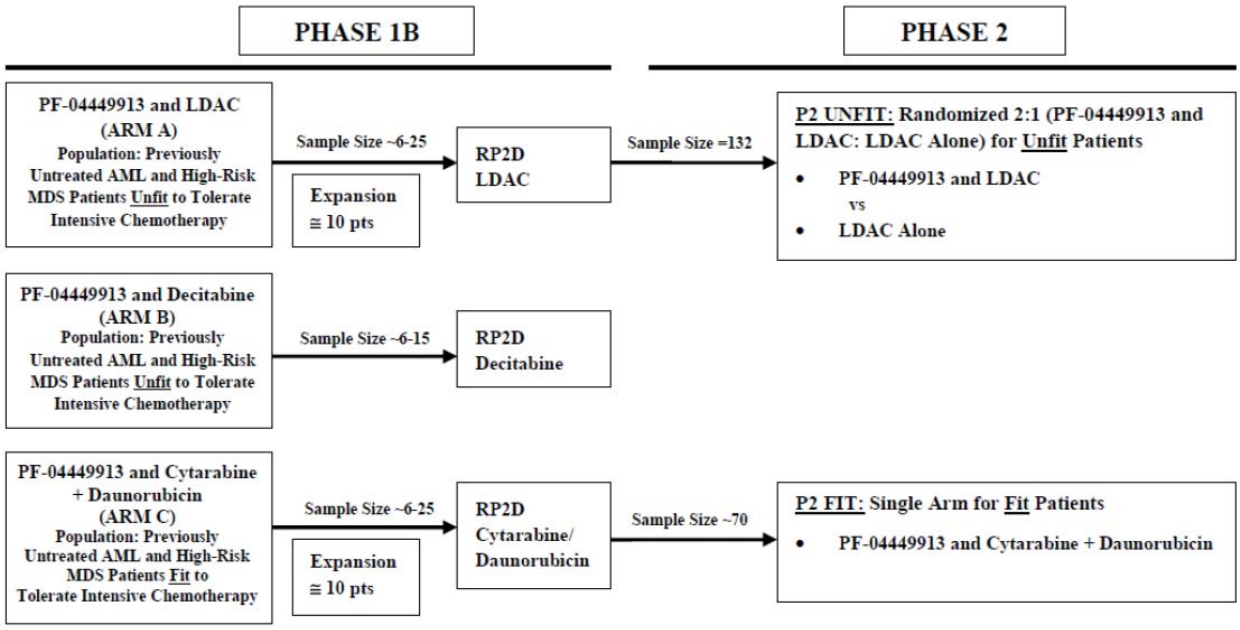
Treatment with glasdegib in combination with LDAC could continue for up to 1 year (12 cycles) from the start of therapy or until disease progression or relapse, patient refusal or unacceptable toxicity, whichever comes first. Patients who completed a year (12 cycles) with LDAC were considered to have completed the trial. Patients who completed the maximum number of cycles on study treatment, demonstrated clinical benefit with manageable toxicity, and were willing to continue receiving the assigned treatment were given the opportunity to do so upon agreement between Investigator and Sponsor pending study drug availability.

In phase 1B, there were 3 parallel arms – Arms A, B, and C (see Figure 1). For each arm, a 3+3 dose escalation design was applied in 3-6 patient cohorts until the identification of the MTD or

maximum administered dose (MAD) was determined in combination with each standard therapy. The starting dose of glasdegib was 100 mg qday based on safety, efficacy, PD, and PK data from Study B1371001. Once the MTD and MAD was established, they planned to expand Arm A by approximately 10 patients at the MTD, MAD, or a lower dose to further characterize the safety and tolerability profile and better define the RP2D of the combination.

Once the combination RP2D was defined in Arm A, they opened enrollment to the phase 2, open-label, pivotal portion of the trial. They randomized 132 patients 2:1, stratified by prognosis (poor vs good/intermediate per ELN 2010 guidelines (Dohner et al. 2010)), to LDAC ± glasdegib. There was one planned interim futility analysis.

Figure 1: Schematic of Trial Design



Source: Module 5.3.5.1, Clinical Study Report, Figure 1

To characterize the effects of glasdegib on the QTc interval when administered in combination with LDAC, approximately 30 evaluable patients from the glasdegib + LDAC arm of the randomized phase 2 study underwent additional ECG assessments.

Eligibility criteria (summarized):

Inclusion –

1. AML or RAEB-2 high-risk MDS newly diagnosed according to WHO 2008 and previously

untreated. Eligible patients with MDS and AML arising from an antecedent hematologic disease (AHD) or MDS may have had one prior regimen with commercially available agents (e.g. azacitidine or decitabine) for the treatment of their prior hematologic disease. The patients may not have had prior therapy for their AML.

2. Patients in the P2 "Unfit" arm must have had a known cytogenetic profile at study entry
3. AML patients include de-novo, AML evolving from MDS or other AHD and AML after previous cytotoxic therapy or radiation (secondary AML).
4. For a diagnosis of AML, BM blast count of 20% or more is required.
    a. For AML defined by cytogenetic aberrations t(8;21), inv(16) or t(16;16) and some cases of erythroleukemia the proportion of BM blasts may be <20%.
    b. In AML FAB M6a (erythroid leukemia) ≥ 20% of non-erythroid cells in the bone marrow must be leukemic blasts and ≥ 50% of the cells are erythroid precursors.
    c. In AML with monocytic or myelomonocytic differentiation, monoblasts and promonocytes, but not abnormal monocytes, are counted as blast equivalents.
5. For a diagnosis of high-risk MDS RAEB-2 the patient must have 10-19% BM blasts.
6. Age ≥ 18 years for patients on phase 1B and phase 2 "fit" arm and age ≥ 55 years for patients enrolled on the phase 2 "unfit" arms.
7. Eastern Cooperative Oncology Group performance status (ECOG PS) of 0, 1, or 2.
8. Patients with AML or high-risk MDS who have one or more of the criteria below are considered "unfit" for intensive chemotherapy (H. Kantarjian et al. 2006) and are eligible for phase 1B Arms A and B or Phase 2 "unfit" arms:
    a. Age ≥ 75 years
    b. ECOG of 2
    c. Serum creatinine > 1.3 mg/dL
    d. Severe cardiac disease (e.g. left ventricular ejection fraction < 45% by multi-gated acquisition or echocardiography at screening)
9. Adequate organ function defined as the following:
    a. Serum aspartate aminotransferase (AST) and serum alanine aminotransferase (ALT) ≤ 3 x upper limit of normal (ULN), or AST and ALT ≤ 5 x ULN if liver function abnormalities are due to underlying malignancy.
    b. Total serum bilirubin ≤ 2 x ULN (except patients with documented Gilbert's syndrome).
    c. Serum creatinine ≤ 1.5 x ULN or estimated creatinine clearance ≥ 60 mL/min as calculated using the method standard for the institution.
10. All anti-cancer treatments (unless specified) discontinued ≥2 weeks from study entry
    a. Hydroxyurea or leukapheresis may be used before and for up to 1 week after the first dose of glasdegib
    b. Patients with controlled CNS leukemia (documented by 2 consecutive assessments of 0 blast counts in the cerebrospinal fluid) and who are still receiving intrathecal therapy at study entry are eligible and will continue to receive intrathecal therapy

11. Resolved acute effects of prior therapy to baseline severity or ≤ grade 1 except for adverse events (AEs) not constituting a safety risk by investigator judgement.
12. Serum/urine pregnancy test (for females of childbearing potential) that is negative at screening and immediately prior to initiation of the first dose of treatment.
13. Males and females of childbearing potential must agree to use a highly effective method of contraception throughout the study and for at least 180 days after the last dose of assigned treatment. A patient is of childbearing potential if, in the opinion of the investigator, he/she is biologically capable of having children and is sexually active.
14. Signed informed consent document
15. Willingness and ability to comply with the study treatment plan

Exclusion -

1. APL or patients with a t(9;22) translocation.
2. Hyperleukocytosis (leukocytes ≥ 30 x 10^9/L) at study entry. These patients may be treated with hydroxyurea or receive leukapheresis treatment according to routine practice and enroll in the study when the leukocyte count falls below 30 x 10^9/L.
3. Patients known to be refractory to platelet or packed red blood cell transfusions or patients who refuse blood support.
4. Patients with an active malignancy, with exceptions including non-melanoma skin cancer, cervical carcinoma in situ, and other malignancies on a case-by-case basis.
5. Myocardial infarction, congenital long QT syndrome, torsades de pointes (TdP), or clinically significant ventricular arrhythmias currently or in the previous 6 months.
6. QTc interval > 470 msec using the Fridericia (QTcF).
7. Patients with active, life-threatening or clinically significant uncontrolled systemic infection.
8. Patients with known and active central nervous system leukemia.
9. Known human immunodeficiency virus or acquired immunodeficiency syndrome-related illness or active Hepatitis B or C infection.
10. Known malabsorption syndrome or other condition that may impair absorption of study medication.
11. Major surgery or radiation within 4 weeks of starting therapy.
12. Prior treatment with a Hedgehog inhibitor at any time or an investigational agent for the treatment of an AHD.
13. Prior treatment of primary diagnosis or AHD with cytarabine.
14. Hypersensitivity to cytarabine (not including drug fever or exanthema).
15. Concurrent treatment with any investigational or approved oncology agents.
16. Concurrent herbal preparations.
17. Current use at the time of study entry or anticipated need for drugs that are known strong CYP3A4/5 inducers.
18. Current drug or alcohol abuse.

19. Other severe acute or chronic medical or psychiatric condition or laboratory abnormality that may increase the risk associated with study participation or investigational product administration or may interfere with the interpretation of study results and, in the judgment of the investigator, would make the patient inappropriate for entry into this study.
20. Patients who are investigational site staff members or relatives of those site staff members or patients who are Pfizer employees directly involved in the conduct of the trial.
21. Pregnant females; breastfeeding females; males and females of childbearing potential not using highly effective contraception or not agreeing to continue highly effective contraception for at least 180 days after last dose of investigational product; males and females of childbearing potential not using two (2) methods of highly effective contraception or not agreeing to continue two (2) methods of highly effective contraception for at least 180 days after last dose of investigational product.
22. Recent or active suicidal ideation or behavior.

Treatment plan:

LDAC was given at a dose of 20 mg subcutaneously twice daily in the morning and evening about 12 hours apart for 10 consecutive days of each 28-day cycle. For phase 1B, glasdegib started on day 3 for PK assessment purposes, but continued with no interruptions thereafter. Planned dose levels for glasdegib are shown in Table 3 below. Intra-patient dose escalation of glasdegib was not allowed.

Table 3: Glasdegib Planned Dose Levels for Escalation and De-Escalation

Dose Level	PF-04449913 Potential Dose Levels (mg)
-1	50
1*	100
2	200

* Starting dose. In Phase 2, dose cannot be escalated to 200 mg.

Source: Module 5.3.5.1, Protocol B1371003, Table 9

Reviewer comments: The choice of dose levels on Study B1371003 is sound based on the first-in-human study in patients with hematologic malignancies that showed 1) an MTD of 400 mg, 2) activity in AML across a broad range of doses (10 to 600 mg), and 3) inhibition of GLI1 expression > 90% at ≥ 100 mg and ≥ 80% at 50 mg.

For patients randomized to the treatment arm on phase 2, glasdegib was given orally with plenty of water with or without food at a dose of 100 mg once daily and continuously in 28-day

cycles starting on day 1 of each cycle. Treatment with LDAC ± glasdegib continued until disease progression or relapse, patient refusal or unacceptable toxicity.

Glasdegib was given in the morning at approximately the same time as the first LDAC subcutaneous injection on days they were dosed together. On days that glasdegib was dosed alone, it was given in the morning at about the same time each day. Tablets were to be swallowed whole and not chewed. If a patient missed a day's dose entirely, they were instructed not to make it up the next day. If a patient vomited any time after taking a dose, they were instructed not to make it up, but to resume subsequent doses the next day as prescribed. If a patient inadvertently took 1 extra dose of glasdegib, patients were instructed to not take the next dose of glasdegib.

LDAC could be administered either on an outpatient or inpatient basis, per institutional guidelines. If given on an outpatient basis, the patient would be provided instructions as to how to correctly self-administer the subcutaneous injection of LDAC from the participating institution. The patient was to be reminded not to self-administer their dose at home on clinic days, but instead to bring the LDAC into clinic so that it may be administered by staff.

In phase 1B, DLTs were evaluated during Cycle 1 of treatment and were defined as any of the following events that were considered by the Investigator to be possibly related to glasdegib:

- Grade ≥ 3 non-hematologic toxicity (uncontrolled despite optimal medical management [e.g. nausea, vomiting, and diarrhea]), excluding grade ≥ 3 infection, fever (including febrile neutropenia), infusion related AEs, electrolyte abnormalities and ALT/AST elevation that returns to grade ≤ 1 or baseline within 7 days.
    - In an asymptomatic patient, grade ≥ 3 QTc prolongation will first require repeat testing, re-evaluation by a qualified person, and correction of reversible causes such as electrolyte abnormalities, concomitant medications that may cause QTc prolongation, or hypoxia for confirmation. If, after correction of any reversible causes, the grade 3 prolongation persists, then the event would be considered a DLT.
- Prolonged myelosuppression lasting longer than 42 days from the point of detection, defined as absolute neutrophil count (ANC) < 500/μL or platelets < 10 x10^9/L with a normal BM (<5% blasts and no evidence of disease or dysplasia).
- Inability to deliver at least 80% of the planned study doses for all agents in a combination due to non-hematologic toxicities.
- Delay of > 28 days in receiving the next scheduled cycle due to persisting non-hematologic toxicities.

The RP2D was determined based on the dose below or equal to the corresponding MTD or MAD upon review of overall Phase 1B safety, tolerability, efficacy, PK, and PD data.

Reasons for discontinuation from study treatment included the following:

- Need for treatment delay for > 28 days due to ongoing study treatment related non-hematologic toxicity (or > 42 days for prolonged study treatment related myelosuppression) unless the patient was demonstrating clinical benefit as agreed by the investigator and sponsor
- Need for more dose reductions than allowed
- Objective disease progression or relapse
- Global deterioration of health status
- Unacceptable toxicity
- Lost to follow-up
- Patient refused further treatment
- Study terminated by Sponsor
- Death
- Completed

Study assessments:

History and physical exam, including height, weight, and performance status were collected at the time of screening (within 28 days prior to dosing). Screening laboratory assessments consisted of complete blood counts with differential (CBC), a comprehensive metabolic panel (CMP), coagulation studies, urinalysis, and urine or serum pregnancy test in women of childbearing potential. In addition, screening triplicate 12-lead electrocardiograms (ECGs) were performed on the LDAC+glasdegib arm.

Physical exams were repeated on days 1, 10, and 21 of cycle 1 and then on day 1 of subsequent cycles. CBCs, CMPs, and assessment of AEs were repeated on days 1, 10, and 21 of cycle 1 and days 1 and 15 of cycles 2-6. For cycles 7 and beyond, labs and AEs were only assessed on day 1 of each cycle.

For patients not assigned to ECG Sub-Study, ECGs were repeated: a) Cycle 1, Day 1 at pre-dose, 1 and 4 hours post-dose; b) Cycle 1, Day 10 at 1 and 4 hours post-dose; c) On Day 1 of Cycles 2 and 3 at 1 and 4 hours post-dose; and d) End of Treatment. For patients assigned to the ECG Sub-Study, the following triplicate 12-lead ECGs were repeated approximately 2 minutes apart using provided ECG machine: a) Cycle 1, Day -1 at 0, 1, 2, 4, and 6 hours; b) Cycle 1, Day 1 at pre-dose, 1 and 4 hours post-dose; c) Cycle 1, Day 10 at pre-dose, 1, 2, 4, and 6 hours post-dose; d) On Day 1 of Cycles 2 and 3 at 1 and 4 hours post-dose; and e) End of Treatment. Starting time for 12-lead ECGs on Cycle 1, Day -1 and Cycle 1, Day 10 were the same and all subsequent ECGs were time-matched.

Peripheral blood was collected for PK assessments in consenting patients at the following time points:

- Cycle 1, Day 1 at pre-dose, 1 and 4 hours post-dose
- Cycle 1, Day 10 at pre-dose, 1, 2, 4, and 6 hours post-dose
- Cycles 2-5, Day 1 at pre-dose, 1 and 4 hours post-dose

Table 4: Schedule of Assessments Phase 2 Unfit

	Screening	Cycle 1 (28 –day cycle)				Even Cycle*		Odd Cycle*			
Protocol Activity	**Within 28 days Prior to Dosing**	**Day -1****	**Day 1**	**Day 10**	**Day 21 (±2 days)**	**Day 1 (±2 days)**	**Day 15 (±2 days)**	**Day 1 (±2 days)**	**Day 15 (±2 days)**	**End of Txt/ Withdrawal**	**Post Txt Follow up[23]**
Baseline documentation											
Informed Consent[1]	X										
Medical/Oncologi History[2]	X										
ECOG Status[3]	X		X			X		X		X	
Safety Labs/Measurements											
Vital Signs (BP and pulse)***	X		X	X	X	X		X		X	
Physical Examination[4]	X		X	X	X	X		X		X	
CBC with differential[5]	X		X	X	X	X	X	X	X	X	
Blood Chemistry[6]	X		X	X	X	X	X	X	X	X	
Urinalysis with micro[7]	X		X			X		X		X	
PT/PTT or aPTT)/INR***	X		X			X		X		X	
Pregnancy test[8]	X		X			X		X		X	
Triplicate 12 – lead ECG[9] **(LDAC + PF-04449913 arm only)**	X	X	X	X		X		X		X	
Other Clinical Assessments											
Adverse Event Monitoring[10]			X	X	X	X	X	X	X	X	X
Review Prior/Concomitant Medications and Treatments[11]	X		X	X	X	X	X	X	X	X	X
Recording of red cell and platelet transfusions[20]	X		X	X	X	X	X	X	X	X	
Drug Compliance[12]			X	X	X	X	X	X	X	X	
Study Treatments[22]											
PF-04449913 Dosing[13]			Days 1 to 28			Days 1 to 28		Days 1 to 28			
LDAC Dosing[14]			Days 1 to 10			Days 1 to 10		Days 1 to 10			
Special Laboratory Studies											
Blood samples for PF-04449913 PK **(LDAC + PF-04449913 arm only)**[15]			X	X		X		X			
Blood samples for biomarkers[16]			X	X						X	
Bone marrow for clinical staging and for biomarkers[17] (±7 days from Day 1)	X					X (C6 and C12)		X (C3 and C9)		X	
Survival Follow-up[18]											X

	Screening	Cycle 1 (28 –day cycle)				Even Cycle*		Odd Cycle*			
Protocol Activity	**Within 28 days Prior to Dosing**	**Day -1****	**Day 1**	**Day 10**	**Day 21 (±2 days)**	**Day 1 (±2 days)**	**Day 15 (±2 days)**	**Day 1 (±2 days)**	**Day 15 (±2 days)**	**End of Txt/ Withdrawal**	**Post Txt Follow up[23]**
Immunophenotyping and Cytogenetics[19]	X					X (C6 and C12)		X (C3 and C9)		X	
Retained Pharmacogenomic Samples[21]	X										

Source: Module 5.3.5.1, Protocol B1371003, Table 2

A BM aspiration was required within 14 days of the screening period, on cycle 3 day 1 (± 7 days), every third cycle thereafter, within 14 days of achieving initial hematologic recovery in the peripheral blood (ANC>1000/µL and platelet≥100,000/µL), end of treatment, and per investigator discretion. BM aspirate and biopsy were required at screening and cycle 3 day 1 for both local clinical staging and centralized biomarker assessments. Thereafter, only aspirates were required for all patients and biopsies were optional unless required for clinical staging (e.g. dry tap). Aspirates were collected and frozen at each BM evaluation. Quantitative immunophenotyping and cytogenetics were conducted locally for all patients using any

scheduled or unscheduled bone marrow samples collected during study participation.

All red cell and platelet transfusions, including date of each transfusion and number of red cell units transfused, were recorded while on treatment. For patients with MDS, the transfusion history was required to be provided for 8-weeks prior to the start of study therapy.

A follow-up visit was planned for at least 28 days, and no more than 35 days, after discontinuation of treatment for review of concomitant medications and assessment for resolution of any treatment related toxicity. AE information and concomitant medications were collected for up to 42 days after the last dose of study drug if treatment was stopped for prolonged myelosuppression. Telephone contact was acceptable unless a visit was needed for safety follow-up. AE grading was per Common Terminology Criteria for Adverse Events version 4.0.

For all randomized patients, survival status was collected every month for the first 2 months after discontinuation of study treatment and every 2 months thereafter until death or 4 years from each patient's first dose (or from time of randomization if treatment was not started). They also collected data on subsequent anticancer therapy and whether the patient underwent a HSCT. Telephone contact was considered acceptable for these assessments.

Compliance was monitored using diaries for the first 2 cycles only to include missed or changed doses or significantly delayed doses. Dates of all missed doses were to be recorded. Patients were required to return all bottles and unused study medications (and patient dosing diaries for the first 2 cycles) at each cycle and at the end of treatment for compliance assessment. LDAC compliance was also assessed if LDAC was self-administered. The number of tablets, syringes, or vials returned by the patient at the end of the cycle were counted, documented, and recorded.

Dose modifications and management of toxicity:

In the event of study treatment related toxicity, dosing could be delayed and/or dose reduced:

- Doses of glasdegib that were held or missed during any cycle due to glasdegib-related toxicities were not made up (e.g. cycles would not be prolonged beyond the 28th calendar day).
- Glasdegib could be dose reduced during any cycle.
- No dose reductions were permitted in cycle 1 for any of the backbone chemotherapeutic agents.
- After cycle 1, if a toxicity was attributed to the backbone chemotherapy and not to glasdegib, chemotherapeutics could be delayed or reduced, while glasdegib dosing could be continued.
- Missed doses of backbone chemotherapy could be made up if the investigator

considered it appropriate according to standard practice.

- Cycles could be extended to a maximum of 56 days for non-hematologic toxicity, or to a maximum of 70 days if due to hematologic toxicity. Glasdegib dosing could continue if observed toxicity was not deemed related to glasdegib.
- If a treatment interruption continued beyond day 28 of the cycle for any agent, then the day when full treatment (all agents in the combination) was restarted would be counted as day 1 of the next cycle for all agents.
- In a subsequent cycle, dose reductions were based on the worst toxicity in the previous cycle.
- A study treatment related continuous treatment interruption or delay of >28 days for non-hematologic toxicity or >42 days for prolonged myelosuppression defined as ANC <500/µL or platelet count <10 x10^9/L in a normal bone marrow with <5% blasts and no evidence of disease or dysplasia, would result in permanent discontinuation from treatment, unless the patient demonstrated clinical benefit as agreed by the Investigator and Sponsor.

Table 5 below includes dose modification criteria for treatment-related toxicities, excluding QTc prolongation.

Table 5: Dose Modification Criteria for Treatment-Related Toxicities, Excluding QTc Prolongation

Drug	Toxicity	Grade 1	Grade 2	Grade 3	Grade 4
PF-04449913	Non Hematologic	Continue at the same dose level.	Continue at the same dose level. If persistent (at least 7 days) and not responding to optimal medical management, withhold dose until toxicity is grade ≤1, then resume treatment at the same dose level or reduce the dose by 1 level at the discretion of the investigator.	Withhold dose until toxicity is grade ≤1, or has returned to baseline, then resume treatment at the same dose level or reduce the dose by 1 level at the discretion of the investigator) (=Nausea, vomiting or diarrhea must persist at Grade 3 or 4 despite maximal medical therapy to require dose modification).	Withhold dose until toxicity is grade ≤1, or has returned to baseline, then reduce the dose by 1 level and resume treatment, or discontinue at the discretion of the investigator. (Nausea, vomiting or diarrhea must persist at Grade 3 or 4 despite maximal medical therapy to require dose modification).
PF-04449913	Hematologic – myelosuppression lasting **≤42 days**	If ANC <500/μL or platelet count <10 x10^9/L for ≤42 days in a normal bone marrow with <5% blasts and no evidence of disease or dysplasia, withhold dose until toxicity is grade ≤2, or has returned to baseline, then reduce the dose by 1 level and resume treatment, or discontinue at the discretion of the investigator.			
PF-04449913	Hematologic – prolonged myelosuppression lasting **>42 days**	If ANC <500/μL or platelet count <10 x10^9/L in a normal bone marrow with <5% blasts and no evidence of disease or dysplasia **for >42 days**, discontinue treatment			
PF-04449913	Delay of more than 28 days for non-hematologic toxicity	Discontinue treatment			

Drug	Toxicity	Grade 1	Grade 2	Grade 3	Grade 4
LDAC	Non Hematologic	Continue at the same dose level.	Continue at the same dose level. If persistent (at least 7 days) and not responding to optimal medical management, withhold dose until toxicity is grade ≤1, then resume treatment at the same dose level or reduce the dose by 1 level at the discretion of the investigator.	Withhold dose until toxicity is grade ≤1, or has returned to baseline, then resume treatment at the same dose level or reduce the dose by 1 level at the discretion of the investigator (Nausea, vomiting or diarrhea must persist at Grade 3 or 4 despite maximal medical therapy to require dose modification).	Withhold dose until toxicity is grade ≤1, or has returned to baseline, then reduce the dose by 1 level and resume treatment, or discontinue at the discretion of the investigator. (Nausea, vomiting or diarrhea must persist at Grade 3 or 4 despite maximal medical therapy to require dose modification).
LDAC	Hematologic – myelosuppression lasting **≤42 days**	If ANC <500/μL or platelet count <10 x10^9/L for **≤42 days** in a normal bone marrow with <5% blasts and no evidence of disease or dysplasia, withhold dose until toxicity is grade ≤2, or has returned to baseline, then resume treatment at same dose level or reduce the dose by 1 level and resume treatment, or discontinue at the discretion of the investigator.			
LDAC	Hematologic – prolonged myelosuppression lasting **>42 days**	If ANC <500/μL or platelet count <10 x10^9/L in a normal bone marrow with <5% blasts and no evidence of disease or dysplasia **for >42 days**, discontinue treatment			
LDAC	Delay of more than 28 days for non-hematologic toxicity	Discontinue treatment			

Source: Module 5.3.5.1, Protocol B1371003, Table 7

Table 6 below includes management guidelines for QTc prolongation. Patients were permanently discontinued from therapy for grade 4 QTc prolongation. For grades 2 and 3 QTc prolongation, dose interruption and possible dose reduction was recommended.

Table 6: Dose Modification Criteria for QTc Prolongation

Category	Requirement	Grade 1	Grade 2	Grade 3	Grade 4
ECG monitoring	Continuous ECG monitoring and cardiology consultation for mQTcF ≥501 msec			x	x
Initial treatment action	Discontinue and do not re-challenge.				x
	Interrupt treatment		x	x	
	Continue at same level	x			
General management	Assess for and correct electrolyte abnormalities.	x	x	x	x
	Withhold any concomitant medications if possible that may cause QTc prolongation.		x	x	x
Resume 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 treatment dosing resumption following interruption for a mQTcF prolongation		x	x	
Discontinue treatment 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 treatment is stopped due to QTcF prolongation the patient has a confirmed mean QTcF interval >515 msec or becomes symptomatic		x	x	

Source: Module 5.3.5.1, Protocol B1371003, Table 8

Concomitant administration of glasdegib with moderate/strong CYP3A4/5 inhibitors and drugs with a known risk of TdP were not recommended. However, if it was medically necessary for patients to use these medications, they included extra monitoring. Prior to the start of a moderate/strong CYP3A4/5 inhibitor or TdP drug, ECGs were performed pre-glasdegib and 1 and 4 hours post-glasdegib dose. In addition, ECGs were to be performed on day 2 or 3 and on days 5, 6, or 7 pre-glasdegib dose, 1 and 4 hours post-glasdegib dose. They were also to perform additional ECG testing as appropriate, perform routine electrolyte monitoring, and

implement timely electrolyte correction, followed by appropriate rechecking of values. When there was an urgent need to start a moderate/strong CYP3A4/5 inhibitor or TdP drug, the Investigator was to consider temporarily interrupting glasdegib dosing and implement the additional monitoring procedures as soon as reasonably possible.

If required, the dose of glasdegib was reduced from 100 mg to 50 mg (dose level -1). LDAC doses could be reduced to 15 mg (dose level -1) or 10 mg (dose level -2). Once a patient had a dose reduction for a study drug-related toxicity, the dose was not re-escalated. If patients required dose reduction beyond the lowest dose, they were withdrawn from treatment.

Patients were advised to report any reaction to sun exposed skin. Special precautions were to be taken to limit potential photo irritation by minimizing patients' exposure to light, including high sensitivity UVb sources such as tanning beds, tanning booths, and sunlamps. Patients were advised to apply sunscreen/sunblock daily.

Caution was advised on surgery based on theoretical grounds for impaired wound healing. Stopping glasdegib was recommended at least 1 week prior to elective surgery. Postoperatively, the decision to reinitiate glasdegib treatment should be based on a clinical assessment of satisfactory wound healing and recovery from surgery.

Concomitant medications:

Concomitant treatment considered necessary for the patient's well-being could be given at the discretion of the treating physician. Based on interaction with moderate/strong CYP3A4 inhibitors, co-administration of glasdegib with moderate/strong CYP3A4 inhibitors was not recommended. However, such medications could be used with caution and only if considered medically necessary. Co-administration with CYP3A4/5 inducers was not permitted unless approved by the Sponsor based on possible induction of glasdegib metabolism. Given the potential for glasdegib to prolong the QTc interval, the concomitant administration of glasdegib with drugs with known risk of TdP was not recommended unless there were no alternatives. QT prolonging drugs without a risk of TdP should be avoided whenever possible.

Patients who were part of the ECG sub-study were prohibited from taking TdP medications until cycle 1 day 11 to avoid confounding effects of these drugs on the QTc assessments and analysis.

Prior or concurrent treatment with a Hh inhibitor or concurrent treatment with other investigational agents not specified in the protocol was not permitted. All anti-cancer treatments were to be discontinued at least 2 weeks from study entry.

Use of low dose dexamethasone was allowed. Patients with controlled central nervous system leukemia and who were still receiving intrathecal therapy at study entry were considered

eligible and could continue to receive intrathecal therapy. Patients with high circulating blasts could receive hydroxyurea or leukopheresis to reduce their blast count for up to 1 week in Cycle 1 after the first dose of glasdegib. Continuation beyond that time needed approval by the Sponsor. Suggestions for management of tumor lysis syndrome were provided, including the use of intravenous hydration, use of allopurinol or rasburicase, and correction of electrolytes.

Infection prophylaxis was recommended for patients with ANC < 500. Antimicrobial agents could be chosen at the discretion of the local institutional guidelines. However, suggested antifungals were caspofungin or micafungin or anidulafungin or amphotericin B; suggested antibiotics were sparfloxacin or levofloxacin; suggested antivirals were acyclovir or valacyclovir.

Primary prophylactic use of granulocyte-colony stimulating factors/granulocyte-macrophage colony stimulating factors was not permitted during cycle 1, but they could be used to treat treatment emergent complicated neutropenia as indicated by the American Society of Clinical Oncology or institutional guidelines. Erythropoietin could be used at the investigator's discretion for the supportive treatment of emergent anemia, but prophylactic use was discouraged.

Study Endpoints

Phase 1B Portion –

Primary endpoint:

- First cycle DLTs

Secondary endpoints:

- Type, incidence, severity (graded by the National Cancer Institute CTCAE version 4.0), timing, seriousness, and relatedness of AEs
- PD biomarkers
- PK parameters of glasdegib and LDAC
- CR/CRi
- OS
- QTc interval

Phase 2 Portion –

Primary endpoint:

- OS

Secondary endpoints:

- CR

- CRi, MLFS, PR, PRi, MR, SD, CRc, and CRm for AML patients
- Marrow CR, PR, SD, partial or complete cytogenetic response, and CRi for MDS patients
- Type, incidence, severity (graded by the National Cancer Institute CTCAE version 4.0), timing, seriousness, and relatedness of AEs
- PD biomarkers
- PK parameters of glasdegib
- QTc interval

OS was defined as the duration from the date of randomization to the date of death from any cause. Patients not known to have died at the last follow-up were censored on the date they were last known to be alive.

Assessment of response was made using response criteria for MDS (Cheson et al. 2006) and AML (Cheson et al. 2003) as defined by the disease specific International Working Groups. Complete response / remission (CR) was defined as all the following:

- Peripheral blood: ANC ≥ 1,000/µL, platelet count ≥ 100,000/µL, and adequate erythroid recovery so that RBC transfusions were not necessary (time frame not defined)
- BM: no Auer rods and < 5% blasts with spicules present
- No extramedullary leukemia

Reviewer comments: Note that responses less than a CR were not considered as relevant for the purposes of the efficacy evaluation, given that CRi and lesser responses may not indicate benefit to patients.

Complete response with incomplete blood count recovery (CRi) was defined as: < 5% blasts in the BM, no extramedullary disease, but either ANC < 1000/µL or platelets < 100,000/µL.

Morphologic leukemia-free state was defined as: < 5% blasts in the BM with spicules and no Auer rods, flow cytometry negative, no extramedullary disease, but ANC < 1000/µL and platelets < 100,000/µL.

Partial remission (PR) was defined as: ANC ≥ 1,000/µL, platelet count ≥ 100,000/µL, but the BM may contain 5-25% blasts, if decreased by ≥ 50% from baseline. Blasts could be ≤ 5% if Auer rods present.

All patient files and BM aspirate and biopsy slides needed to be available for source verification and peer review.

Statistical Analysis Plan

The safety analysis set (SAS) for each drug combination included all enrolled patients who

received at least one dose of any study medication. The full analysis set (FAS) included all enrolled patients of the Phase 1B portion who received at least one dose of study medication and all randomized patients of the phase 2 portion. The FAS was used for efficacy analyses.

In dose escalation, the protocol analysis set was evaluable for MTD. These patients received at least one dose of glasdegib and of LDAC and did not have major treatment deviations during the DLT monitoring period. Major deviations include, but are not limited to, administration of < 80% of the planned dose during the DLT monitoring period of glasdegib or LDAC for reasons other than drug-related toxicity.

The PK concentration population was all treated patients who had a least 1 concentration of any of the study drugs. The PK parameter analysis population was defined as all treated patients with at least 1 of the PK parameters of interest for any of the study drugs. The PD analysis population included all enrolled patients in the respective Phase 1B and 2 portion who received at least one dose of glasdegib and had at least one PD parameter from the corresponding assay sample with a baseline and an adequate post-treatment assessment. For those PD parameters only measured at baseline, this analysis set only included patients with at least one baseline PD measurement.

For Phase 1B Arm A, it was expected that 6-15 evaluable patients would be required for dose escalation and up to 10 patients would be enrolled into the expansion component of Arm A. Statistics were descriptive.

For the randomized phase 2 cohort, the historical median OS for LDAC was 5 months and the expected median OS for glasdegib + LDAC was 8 months, resulting in an expected HR=0.625. Based on the 2:1 randomization, a planned accrual period of about 13 months, a follow-up period of approximately 6 months, a 1-sided log-rank test with alpha=0.1 (type I error) and one futility analysis when 46 OS events were observed (50% information, rho(1) beta spending function), a total of 92 OS events would provide 80% power to detect this difference between the two arms. A total of 132 patients (88 in the LDAC+glasdegib arm and 44 in the LDAC arm) would be randomized.

There was an interim futility analysis planned when a total of 46 OS events were observed. The rho(1) spending function as used as the beta-spending function. If exactly 46 OS events were observed at the interim analysis, the futility boundary would be crossed if the observed HR >0.92. The stopping probability was 61% if HR-1 and 10% if HR=0.625, respectively. The futility boundary would be calculated accordingly using the chosen spending function and number of observed OS events at the interim analysis. The final analysis for the randomized cohort was planned when a total of 92 OS events were observed.

The efficacy endpoints of interest included hematologic response (CR, CRi) and OS. The point

estimate and 80% CI would be provided for the proportion of patients with CR at any time on study and for the proportion of responders by treatment arm. As a secondary analysis, the proportion of patients with CR/CRi achieved at any time on study, as well as its 80% CI, would also be summarized for each arm at the time of the final analysis. Similar analysis could be provided for other hematologic response categories such as PR/PRi and SD.

For OS analyses, the point estimate and 80% CI of median survival time would be estimated using the Kaplan-Meier method. Median estimates were done by treatment arm. The hazard ratio of and 80% CI of OS would be estimated using Cox proportional hazard regression stratified by prognosis (poor, good/intermediate). OS between the arms would be compared with a 1-sided stratified log-rank test at the α=0.1 overall significance level. The survival probability at 6 months for each arm were estimated using the Kaplan-Meier method. A sensitivity analysis of survival probability at 12 months for each arm could also be provided.

The primary analyses for efficacy endpoints would be based on derived response, and the secondary analyses based on investigator data. The interim analyses were based on investigator's assessments.

Safety analyses were descriptive.

For the phase 1B portion, an external Data Monitoring Committee was not established. During this portion, Pfizer procedures for periodic safety review were 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. Procedures included surveillance for serious adverse events (SAEs) according to regulatory guidelines and discussions between the Investigators and the Sponsor of AEs and laboratory test alterations seen at each dose level in an on-going manner at regular teleconferences and/or meetings to determine the safety profile and risk/benefit ratio and decide if further enrollment was appropriate.

For the phase 2 portion of the study, an Internal Review Committee (IRC) was established. The Internal Oncology Business Unit -Safety Data Monitoring Committee is a single, project-independent advisory group established to enhance the early detection of potential safety signals in clinical trials. The activities of this committee were intended to be complementary and supplemental to existing Pfizer safety risk management processes. The Internal Oncology Business Unit -Safety Data Monitoring Committee functioned as the IRC. In addition to safety data review, they also reviewed interim efficacy data. When reviewing interim efficacy data, the IRC made recommendations to the Head of Clinical Development Medical Affairs, as would be the case for an external data monitoring committee review.

Protocol Amendments

The date of the first patient visit was on June 27, 2012. The last patient on phase 2 began therapy on October 19, 2015, with 132 patients randomized. The study was revised a total of 5 times between activation and finalization in February of 2016. Key protocol revisions are summarized as follows:

- Amendment 1 (effective May 15, 2012) added an ECG substudy of 30 patients from the glasdegib+LDAC arm who would undergo additional ECG assessments. Also, added a requirement for bone marrow slides to be available for central review.
- Amendment 2 (effective November 1, 2012) modified the study to be a phase 1B/2 study allowing the efficacy evaluation of glasdegib in combination with LDAC and 7+3 in the randomized phase 2 portion and the single arm phase 2 portion, respectively. Also, added requirement for safety and efficacy review of study results by an internal review committee. Added a restriction of enrollment to patients ≥ 55 years in the phase 2 randomized portion.
- Amendment 3 (effective March 26, 2014) added that the RP2D for phase 2 was confirmed as glasdegib 100 mg qday. Exclusion criteria for prohibited concomitant medications (CYP3A4 inhibitors, narrow therapeutic index CYP3A4 substrates and P-glycoprotein inhibitors/inducers) was removed. Fasting restrictions were removed. Added creatine phosphokinase (CPK) at select timepoints. Independent BM pathology review was removed.
- Amendment 5 (effective February 8, 2016) removed phase 2 secondary endpoints cumulative incidence of relapse, relapse free survival, event free survival, cumulative incidence of death, and hematologic improvement (MDS patients only). Added requirement for survival follow-up for randomized patients that did not start treatment. Added monitoring of potential cardiovascular symptoms and guidance on the use of moderate/strong CYP3A4/5 inhibitors or drugs with a known risk of TdP as concomitant therapy. Updated Protocol-Specified Serious Adverse Events to include SAE reporting of all cases of > Grade 2 mQTcF prolongation regardless of causality for up to 28 calendar days after the last dose of study drug administered.

No major changes were made to the eligibility criteria or response criteria over the course of the study.

6.1.2. Study Results

Compliance with Good Clinical Practices

The applicant provided attestation that this study was conducted in accordance with U.S. regulations governing the protection of human subjects, institutional review boards, and the obligations of clinical investigators in accordance with good clinical practice (GCP).

Financial Disclosure

A summary of financial disclosures for Study B1371003 is provided in the appendix (Section 13.2). The applicant submitted financial disclosure information from 100% of investigators. Four primary investigators and 13 sub-investigators had financial disclosures. The four PIs had financial disclosures ranging in value from $65,651.45 to $404,240.00 for speaker honoraria, research and development grants, research collaborations, and consulting. The most patients randomized at any one of these four sites was (b) (6) The total number of patients randomized to all four sites was (b) (6) The 13 sub-I financial disclosures ranged in value from $28,198.00 to $389,392.09. The most patients randomized at any one of these sites was (b) (6) The total number of patients randomized to all 13 sites was (b) (6) A total of (b) (6) patients were treated at any site with any investigator declaring a financial disclosure. Removal of all (b) (6) patients from the primary analysis did not substantially affect the result. Thus, enrollment of patients by these investigators does not appear to have biased the outcome of the study.

Patient Disposition

On phase 1B, 20 patients with newly-diagnosed AML were treated with glasdegib 100 mg (n=15) or 200 mg (n=5) qday in combination with LDAC. FDA did not consider the 3 patients with high-risk MDS for analyses of efficacy given the limited patient numbers. Disposition on phase 1B of Study B1371003 is shown below in Table 7. Discontinuations for primary disease were higher on the 200 mg qday cohort and discontinuations for adverse event were higher on the 100 mg qday cohort, although numbers were small.

Table 7: Study B1371003 Phase 1B – Disposition of Patients

	Glasdegib 100 mg qday+LDAC	Glasdegib 200 mg qday+LDAC	Total
Received treatment	**N=15**	**N=5**	**N=20**
Therapy ongoing	0	0	0
Discontinued therapy	15 (100%)	5 (100%)	20 (100%)
Adverse event	6 (40%)	0	6 (30%)
Primary disease	5 (33%)	4 (80%)	9 (45%)
Global deterioration health	2 (13%)	0	2 (10%)
Death	1 (7%)	1 (20%)	2 (10%)
Refused further follow-up	1 (7%)	0	1 (5%)

Source: FDA analysis

A total of 132 patients with newly-diagnosed AML or high-risk MDS were randomized on phase 2 of Study B1371003 to either glasdegib+LDAC (n=88) or LDAC alone (n=44). Based on only 16 randomized patients with high-risk MDS (10 to glasdegib+LDAC arm, 6 to LDAC arm), FDA considered only the newly-diagnosed AML patient population for efficacy analyses for the purposes of labeling.

Reviewer comments: A total 16 patients with high-risk MDS on the randomized phase 2 study,

with ≤ 10 patients per treatment arm is not sufficient for a claim of efficacy in high-risk MDS. Therefore, FDA excluded the subgroup of high-risk MDS patients from efficacy analyses for the purposes of labeling.

A total of 116 randomized patients (FAS) were recorded to have AML, but FDA could not confirm an AML diagnosis in Subject (b) (6). This subject was randomized to the glasdegib+LDAC arm and had 16% BM blasts recorded on day -7. Per the case report form (CRF), the marrow sample was insufficient and extramedullary disease was not present. Given that the Applicant could not provide conclusive evidence of AML, FDA considered a total of 115 patients (**FDA FAS**) with newly-diagnosed AML randomized to Study B1371003, with 77 patients randomized to glasdegib+LDAC and 38 patients randomized to LDAC alone. Of these 115 patients, 5 (3 glasdegib+LDAC, 2 LDAC) were never treated due to being randomized in error (n=4, 2 on each arm) or receiving more than one prior regimen for an AHD (n=1, combination arm). Thus, a total of 110 patients with confirmed newly-diagnosed AML were randomized and treated (**FDA SAS**) with either glasdegib+LDAC (n=74) or LDAC (n=36).

Table 8 shows the number of patients that received any portion of study therapy and the reasons for treatment discontinuation in the FDA FAS. FDA considered deaths under the primary reason for discontinuation (i.e., either primary disease or adverse event).

Table 8: Study B1371003 – Disposition of Patients in FDA FAS

	Glasdegib+LDAC (n=77)	LDAC (n=38)	Total (n=115)
Received treatment	74 (96%)	36 (95%)	110 (96%)
Therapy ongoing	3 (4%)	0	3 (3%)
Discontinued therapy	71 (92%)	36 (95%)	107 (93%)
Primary disease	37 (48%)	17 (45%)	53 (46%)
Adverse event	23 (30%)	15 (39%)	39 (34%)
Physician/patient decision	5 (6%)	2 (5%)	7 (6%)
Global deterioration health	3 (4%)	2 (5%)	5 (4%)
HSCT/DLI	2 (3%)	0	2 (2%)
Protocol violation	1 (1%)	0	1 (1%)

Source: FDA analysis
Abbreviations: DLI, donor lymphocyte infusion; HSCT, hematopoietic stem cell transplantation.

Reviewer comments: It is notable that the only patients remaining on therapy are on the combination arm. Slightly more patients on the glasegib+LDAC arm discontinued due to primary disease. However, as seen in Section 8.2.1, patients on the glasdegib+LDAC arm were on therapy for a longer duration. Even still, it is notable that more patients on the LDAC arm discontinued therapy due to an AE, compared to the glasdegib+LDAC arm. Lastly, 2 patients on the glasdegib+LDAC arm discontinued therapy to pursue HSCT (Subject (b) (6)) or DLI (Subject (b) (6)), whereas no patients on the LDAC arm proceeded to transplantation.

Protocol Violations/Deviations

A total of 1,272 protocol deviations were reported for 111 AML patients on the randomized phase 2 portion of Study B1371003. The majority (1,212 deviations, 95%) were considered by the applicant to be minor deviations. The most frequent minor deviations were laboratory (772 deviations affecting 105 patients), procedures/tests (269 deviations affecting 89 patients), and study drug (e.g. missed doses) (63 deviations affecting 27 patients).

Major protocol deviations occurred in 43% of the study patients, with a lower frequency on the glasdegib+LDAC arm (Table 9). A total of 21 patients (18%) had major deviations in safety reporting; the majority due to delayed SAE reporting. Twenty patients (17%) had a major deviation in randomization - other; the majority because they were not stratified correctly at randomization in the interactive voice response system (IVRS). Other major deviations included inclusion/exclusion criteria, study drug, and informed consent issues. The one patient with an inclusion/exclusion issue on the glasdegib+LDAC arm was randomized but not treated (AHD with more than one prior regimen) and the 4 patients on the LDAC arm had an active malignancy at study entry (n=2, signet ring cell carcinoma and bladder cancer not resolved), white count ≥ 30 x 10^9/L at study entry (n=1), and did not meet any unfit criteria (n=1). Study drug issues on the glasdegib+LDAC arm included increasing the dose after a reduction due to progressive AML, overdose (took 13 25-mg tabs), crushed drug in PEG tube, and over dose (6 pills too many between days 10 and 21 of cycle 1). As none of the major deviations were likely to bias the study in favor of the glasdegib+LDAC arm, all patients, including those with major protocol deviations were included in the FDA's analysis of efficacy endpoints.

Table 9: Randomized Phase 2 Study B1371003 – Major Protocol Deviations

	Glasdegib+LDAC (n=77)	LDAC (n=38)	Total (n=115)
Major protocol deviation	**30 (39%)**	**20 (53%)**	**50 (43%)**
Safety reporting	12 (16%)	9 (24%)	21 (18%)
Randomization - Other	14 (18%)	6 (16%)	20 (17%)
Inclusion/exclusion	1 (1%)	4 (11%)	5 (4%)
Study drug	4 (6%)	1 (3%)	5 (4%)
Informed consent issues	1 (1%)	2 (5%)	3 (3%)

Source: FDA analysis

Table of Demographic Characteristics

Phase 1B of Study B1371003 enrolled more men (n=12, 60%) than women (n=8, 40%), which is typical of the AML patient population. Most of the study subjects were white (n=17, 85%). The median age of study participants was 77 (range 60-85).

Demographic information from the patients on the randomized phase 2 portion of Study

B1371003 is summarized in Table 10. There were more men than women on both treatment arms, consistent with the demographics of AML. However, the treatment arms were somewhat imbalanced with respect to gender, with more female patients on the LDAC arm (39% vs 23%). ECOG performance status was slightly higher and the representation in North America was higher on the glasdegib+LDAC arm. The median age of the patients enrolled on this study (76 years) is older than the median age of patients with previously untreated AML in the United States (Noone AM 2018). The eligibility criteria specified that patients must be ≥ 55 years at study entry. The study had a limited representation of non-white patients and ethnicity was not recorded.

Table 10: Study B1371003 – Patient Demographics in the FDA FAS

	Glasdegib+LDAC (n=77)	LDAC (n=38)	Total (n=115)
Sex			
Female	18 (23%)	15 (39%)	33 (29%)
Male	59 (77%)	23 (61%)	82 (71%)
Age (years)			
Median	77	76	76
Min, Max	64, 92	58, 83	58, 92
ECOG Performance Status			
0	10 (13%)	3 (8%)	13 (11%)
1	25 (32%)	17 (45%)	42 (37%)
2	41 (53%)	18 (47%)	59 (51%)
Missing	1 (1%)	0	1 (1%)
Median (range)	2 (0-2)	1 (0-2)	2 (0-2)
Eligibility criteria			
Age ≥ 75 years	47 (61%)	23 (61%)	70 (61%)
Baseline creatinine > 1.3 mg/dL	15 (19%)	5 (13%)	20 (17%)
ECOG performance status = 2	41 (53%)	18 (47%)	59 (51%)
Severe cardiac disease	51 (66%)	20 (53%)	71 (62%)
Race			
White	75 (97%)	38 (100%)	113 (98%)
Black	1 (1%)	0	1 (1%)
Asian	1 (1%)	0	1 (1%)
Ethnicity			
Unknown or not reported	77 (100%)	38 (100%)	115 (100%)
Region			
North America	27 (35%)	7 (18%)	34 (30%)
United States	19 (25%)	6 (16%)	25 (24%)
Canada	8 (10%)	1 (3%)	9 (9%)
Europe	50 (65%)	31 (82%)	81 (70%)

Source: FDA analysis

Other Baseline Characteristics (e.g., disease characteristics, important concomitant drugs)

Phase 1B of Study B1371003 had 6/20 (30%) patients with de novo AML, with 5/15 in the 100 mg cohort and 1/5 in the 200 mg cohort. The remaining 14 (70%) had secondary AML, with 10/15 in the 100 mg cohort and 4/5 in the 200 mg cohort. Three (15%) patients had favorable ELN 2010 risk, all on the 100 mg cohort. Ten (50%) had intermediate-I or intermediate-II risk, with 5 in each dose cohort. Seven (35%) had poor risk disease, all on the 100 mg cohort. Two patients had a FLT3-ITD mutation, both on the 100 mg cohort.

Characteristics of the AML in patients on the phase 2 portion of Study B1371003 at baseline are displayed in Table 11 below. The incidence of secondary AML was similar across treatment arms, but the subtypes of secondary AML varied slightly in that 5% more patients on the LDAC arm had a prior MPN and 5% more patients on the glasdegib+LDAC arm had therapy-related AML. Similar numbers of patients had prior HMA therapy on both arms. ELN 2010 risk classification showed more patients with intermediate-I and intermediate-II risk on the glasdegib+LDAC arm and more patients with favorable and adverse risk on the LDAC arm. Stratification factors grouped good and intermediate risk categories from the ELN 2010 guidelines together and there was a higher number of patients in this category on the glasdegib+LDAC arm. This imbalance is likely due to the major protocol violations of incorrect stratification at randomization in the IVRS (n=17). Numbers of patients with FLT3 and NPM1 mutations were similar across the treatment arms. No patient had a TP53 mutation. FAB classifications were relatively similar across treatment arms.

Table 11: Study B1371003 FDA FAS – Baseline Disease Characteristics

	Glasdegib+LDAC (n=77)	LDAC (n=38)	Total (n=115)
Clinical onset of AML			
De novo[1]	39 (51%)	18 (47%)	57 (50%)
MDS-related	28 (36%)	15 (39%)	43 (37%)
Myeloproliferative neoplasm-related	5 (6%)	4 (11%)	9 (8%)
Therapy-related	6 (8%)	1 (3%)	7 (6%)
Prior HMA	11 (14%)	7 (18%)	18 (16%)
ELN risk			
Favorable	5 (6%)	3 (8%)	8 (7%)
Intermediate-I	27 (35%)	11 (29%)	38 (33%)
Intermediate-II	20 (26%)	8 (21%)	28 (24%)
Adverse	25 (32%)	16 (42%)	41 (36%)
Stratification factors (CRF)			
Good/intermediate cytogenetic risk	52 (68%)	22 (58%)	74 (64%)
Poor cytogenetic risk	25 (32%)	16 (42%)	41 (36%)
FLT3 mutated	7 (9%)	4 (11%)	11 (10%)
NPM1 mutated	7 (9%)	2 (5%)	9 (8%)
Leukemia classification (FAB subtype)			

M0 – Undifferentiated AML	6 (8%)	1 (3%)	7 (6%)
M1 – AML without maturation	9 (13%)	4 (11%)	13 (12%)
M2 – AML with maturation	13 (18%)	5 (14%)	18 (17%)
M4 – Acute myelomonocytic leukemia	6 (8%)	4 (11%)	10 (9%)
M5 – Acute monocytic leukemia	2 (3%)	2 (6%)	4 (4%)
M6 – Acute erythroid leukemia	1 (1%)	1 (3%)	2 (2%)
M7 – Acute megakaryoblastic leukemia	0	0	0
Missing	35 (49%)	19 (53%)	54 (50%)

Source: FDA analysis
[1]Includes a patient that the Applicant coded as secondary AML, given that this patient just had a monoclonal gammopathy of undetermined significance (Subject (b) (6)).

Reviewer comments: A large proportion of patients on this trial had secondary AML, which is reflective of the older patient population. Prior HMA use, a poor prognostic indicator, was similar but slightly higher on the LDAC arm. ELN risk indicated slightly more favorable risk patients on the LDAC arm, but less adverse risk patients. Given the major protocol violations, there is a slight imbalance towards good/intermediate risk cytogenetics and molecular studies on the glasdegib+LDAC arm versus the LDAC arm. Sensitivity analyses will be needed to determine any impact on efficacy endpoints.

Treatment Compliance, Concomitant Medications, and Rescue Medication Use

Please see Section 8.2.1 for an analysis of exposure to the study drugs.

Concomitant medications were collected throughout the treatment period on Study B1371003. Of 115 total patients in the FDA FAS, concomitant medications were recorded for 112 (97%) patients from the time of randomization.

The most frequently used (in >40% of patients on the glasdegib+LDAC arm) concomitant medications were allopurinol, furosemide, paracetamol, levofloxacin, and ondansetron.

The use of concomitant CYP3A4 inhibitors and inducers was of particular interest due to the PK of glasdegib (see Section 4.5 of this review for further details). Moderate or strong CYP3A4 inhibitors were used in 72 (63%) of patients, with 50 (65%) on the glasdegib+LDAC arm and 22 (58%) on the LDAC arm. The most frequently used moderate or strong CYP3A4 inhibitors on the glasdegib+LDAC vs LDAC arms, respectively, were ciprofloxacin (33% vs 16%), fluconazole (30% vs 40%), posaconazole (17% vs 8%), and voriconazole (17% vs 8%). Only one patient on Study B1371003, treated on the glasdegib arm, used a moderate or strong CYP3A4 inducer (phenytoin and carbamazepine).

Hematopoietic growth factor use during therapy was generally balanced across both treatment arms. Filgrastim, lenograstim, or granulocyte colony stimulator factor were used in 6 (8%) of patients on the glasdegib+LDAC arm and 4 (11%) of patients on the LDAC arm. Darbepoetin

alfa, epoetin alfa, or erythropoietin were used by 2 (3%) patients on the glasdegib+LDAC arm and one patient (3%) on the LDAC arm.

Efficacy Results – Primary Endpoint

The primary efficacy endpoint of phase 1B was the rate of CR/CRi. Results are displayed by dose and overall in Table 12 below. No responses were seen in the 100 mg cohort and only one CR response was seen in the 200 mg cohort. There were no CRi responses. Note that the median duration of therapy on phase 1B was only 30.5 days (range 1 to 377); median 27 days on the 100 mg cohort and 57 days on the 200 mg cohort.

Table 12: Study B1371003 Phase 1B – Responses

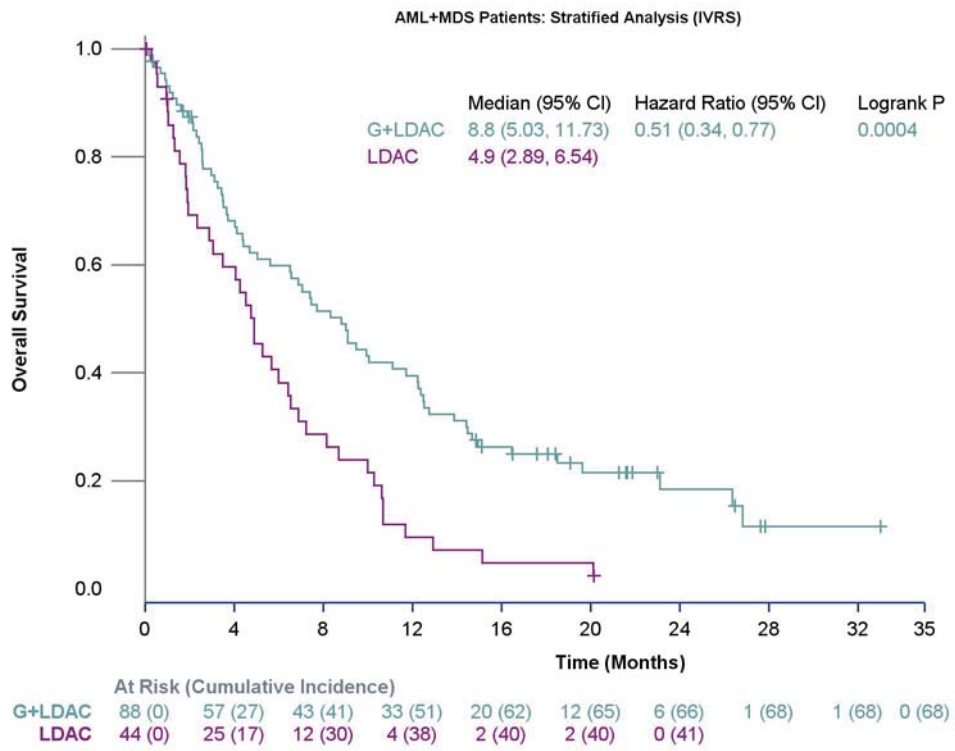
	Glasdegib 100 mg + LDAC (n=15)	Glasdegib 200 mg + LDAC (n=5)	Total (n=20)
CR+CRi rate [95% CI]	0	1 (20%) [0.5, 72]	1 (5%) [0.9, 24]
CR rate [95% CI]	0	1 (20%) [0.5, 72]	1 (5%) [0.9, 24]

Source: FDA analysis

Reviewer comments: The low responses seen on phase 1B may be related to the high rate of discontinuations early in therapy.

The primary endpoint of the phase 2 randomized portion of Study B1371003 was OS for the FAS population including AML and MDS patients. Stratification was per the IVRS-based cytogenetic risk information. There was a statistically significant difference (p=0.0004) in OS that favored glasdegib+LDAC treatment arm, with a hazard ratio of 0.51 (95% CI: 0.34, 0.77) (Figure 2).

Figure 2: Study B1371003 FAS – Overall Survival

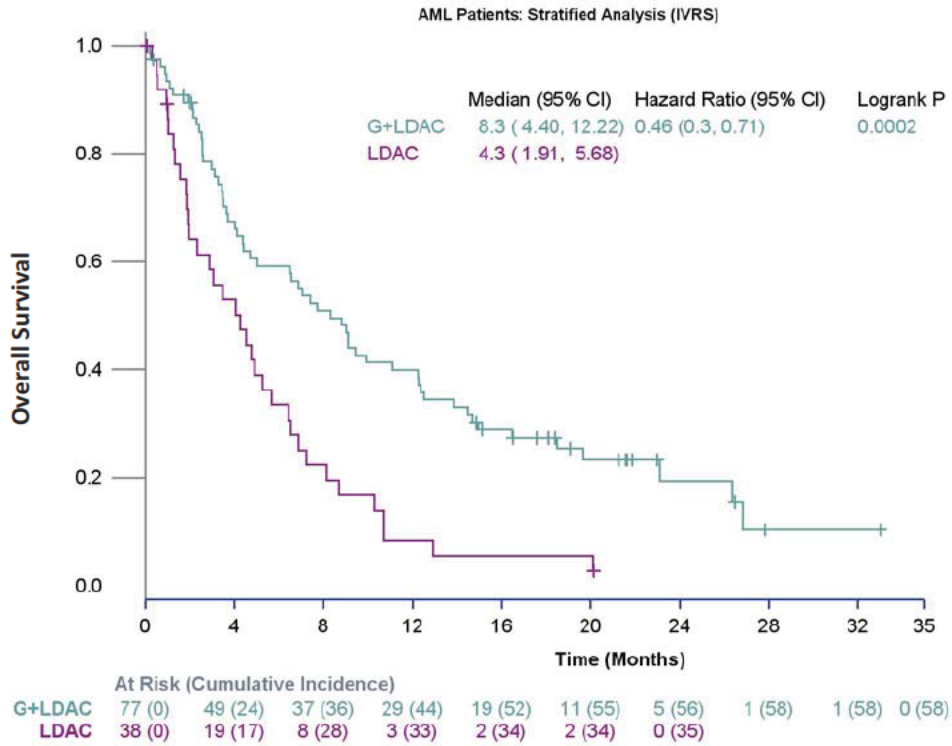


Source: FDA statistical reviewer analysis

Reviewer comments: The Figure above demonstrates that the study met its primary endpoint in the FAS population, as per the Statistical Analysis Plan. The remainder of the analyses will consider the AML subgroup only, as relevant to the labeled indication.

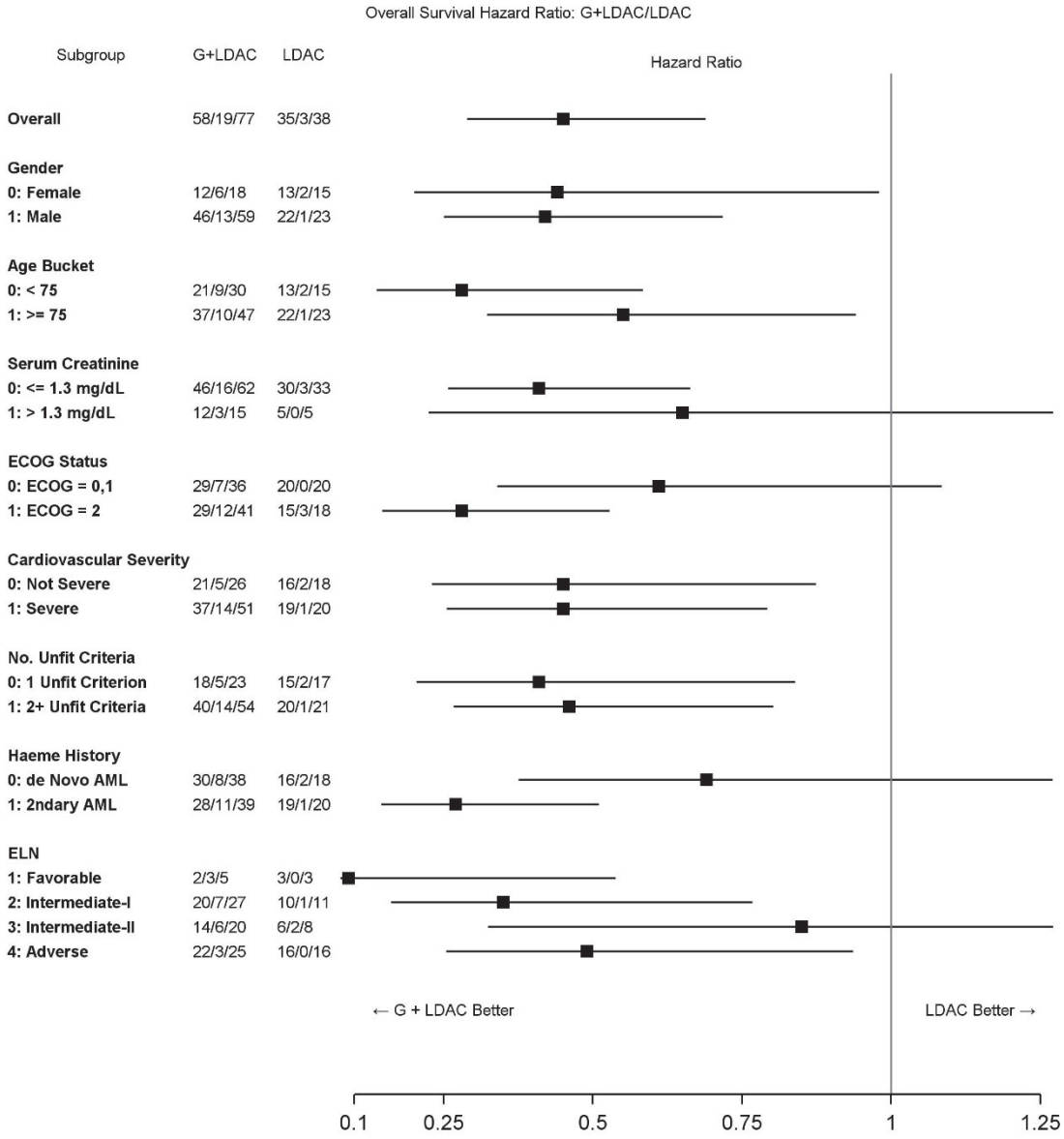
For the FDA FAS population, including AML patients only, the median time from the date of randomization to data cut-off date (January 3, 2017) was 23 months in both groups, with a minimum of 15 months and a maximum of 35 (LDAC) to 36 (glasdegib+LDAC) months in both groups. The FDA identified 93 death events, 58 (75%) on the glasdegib+LDAC arm and 35 (92%) on the LDAC arm. The remaining patients (n=22) were censored. The minority of the censored patients (4, 18%) had a date of last contact after the data cut-off date and were thus censored on the data cut-off date. The other 18 patients (82%) had a date of last contact prior to the data cut-off date and were thus censored on the date of last contact. There was a statistically significant difference (p=0.0002) in OS that favored glasdegib+LDAC treatment arm, with a hazard ratio of 0.46 (95% CI: 0.3, 0.71) (Figure 3).

Figure 3: Study B1371003 FDA FAS – Overall Survival



Source: FDA statistical reviewer analysis

Figure 4: Study B1371003 – Subpopulation Analysis of the Primary Endpoint*



Source: FDA statistical reviewer analysis
*Note that values in the treatment columns have the format A/B/C, where A = number of events, B = number censored, and C = total number of patients.

None of the baseline demographic or disease characteristics had a significant effect on OS, as per Figure 4 above. There was a trend toward a greater treatment effect in younger patients, lower serum creatinine, ECOG 2, secondary AML, and favorable/intermediate-I risk AML.

Only one patient with a CRi underwent first HSCT post-treatment (Subject (b) (6)) and one

with a CR underwent DLI (Subject [redacted]), both on the glasdegib+LDAC arm. Thus, transplantation was not considered a relevant factor in the assessment of efficacy.

Data Quality and Integrity

The quality of the submission was sufficient to evaluate and review the data. The clinical reviewer audited a sample of case report forms from Study B1371003 for consistency with datasets and patient narratives; the quality and integrity of the data required to evaluate the primary endpoint was acceptable.

Efficacy Results – Secondary and other relevant endpoints

A key secondary endpoint was CR rate, defined as per Cheson et al 2003. Other secondary endpoints included CRi and lesser response rates. A summary of response rates is provided in Table 13.

Table 13: Study B1371003 FDA FAS – Results of Secondary Efficacy Endpoints

	Glasdegib+LDAC (n=77)	LDAC (n=38)
CR rate [95% CI]	14 (18%) [10, 29]	1 (3%) [7e-04, 14]
Median time to CR (months)[1] [range]	1.9 [1.2, 5.6]	5.6
Median duration of CR (months) [range]	9.8 [0.03, 27.6]	3.0
CR/CRi rate [95% CI]	19 (25%) [16, 36]	2 (5%) [1, 18]

Source: FDA analysis
[1]Measured from the first day of treatment

Reviewer comments: The CR rate on the glasdegib+LDAC arm is notably higher than the LDAC arm. Median time to CR was 2 months on the glasdegib+LDAC arm, with an upper range of almost 6 months. Therefore, the label should specify that patients continue therapy for up to 6 months in the absence of toxicity or disease progression.

Based on subgroup analyses done by the statistical reviewer (see statistical review), none of the baseline demographic or disease characteristics had a significant effect on CR rate.

Dose/Dose Response

As seen in Table 12 above, there was only one CR response in Phase 1B of Study B1371003. The one CR response was out of 5 patients on the 200 mg glasdegib+LDAC cohort, whereas no responses were seen in the 15 patients on the 100 mg glasdegib+LDAC cohort. When

considering all patients treated (phase 1B [n=15] and phase 2 FDA SAS [n=74]) on Study B1371003 with 100 mg glasdegib+LDAC (n=89), the CR rate was 16% (95% CI 9-25%).

Reviewer comments: Given the similar CR rates of 16% amongst all AML patients treated with glasdegib 100 mg + LDAC on Study B1371003 versus 20% in the small sample size of patients treated with glasdegib 200 mg + LDAC, there does not appear to be a significant dose response. However, the small sample size on the 200 mg dose cohort limits any strong conclusions.

With the exception of dose reductions and treatment interruptions, all patients on the glasdegib+LDAC arm of the randomized phase 2 portion of Study B1371003 received 100 mg glasdegib daily. See the clinical pharmacology review for an evaluation of exposure-response.

Durability of Response

See Table 13 in the section Efficacy Results – Secondary and other relevant endpoints above. CR rate was relatively durable at 6.5 months (range 2.7-24.3 months), compared to only 3 months for the one CR on the LDAC arm.

Persistence of Effect

Not applicable. There is no data to support persistence of a treatment effect after treatment is stopped.

Additional Analyses Conducted on the Individual Trial

Not applicable.

6.2 Study B1371005

6.2.1 Study Design

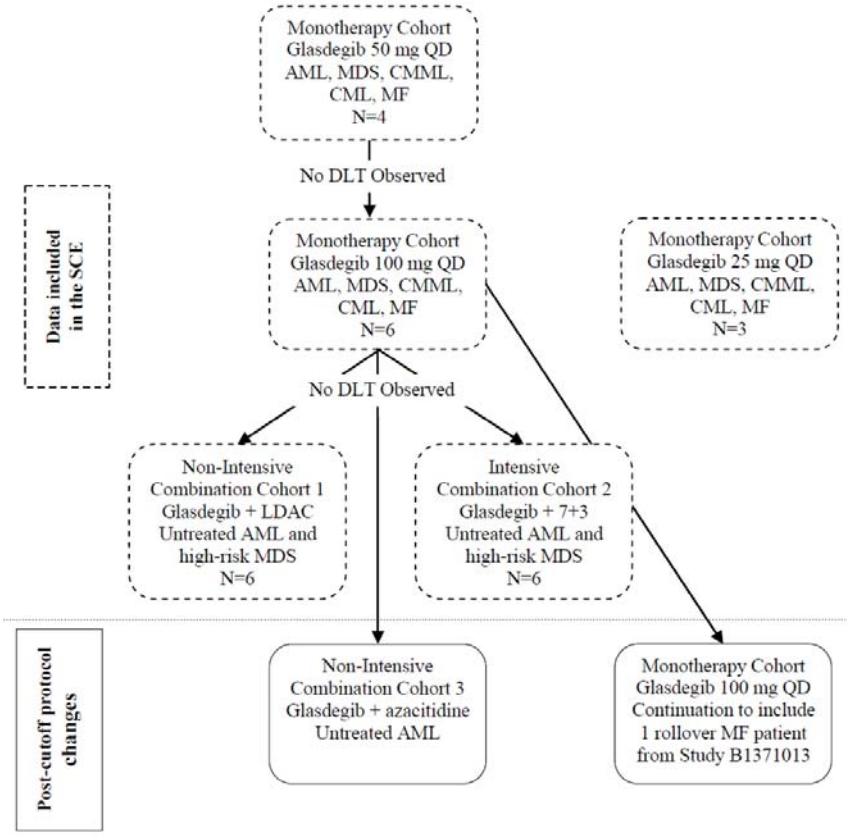
Overview and Objective

Study B1371005 is an ongoing, open-label, multi-center Japanese Phase 1 study of glasdegib given first as a single agent, then in combination with chemotherapy (LDAC or 7+3 as of the cutoff date of 2/20/2017) to patients with hematologic malignancies, including AML and high-risk MDS. The study is primarily a safety and tolerability study, but some efficacy assessments were performed. After the data cutoff, the protocol was amended to add an expansion cohort of a combination of glasdegib and azacitidine and include a rollover patient to the monotherapy cohort. Assessment of response was the same as for Study B1371003.

Trial Design

The trial schema for Study B1371005 is provided in Figure 5. Adult patients with ECOG performance status 0-2 and with advanced hematologic malignancies who were refractory, resistant or intolerant to prior therapies were eligible. For the combination therapy arms, pre-defined criteria for the non-intensive populations were as described for Study B1371003.

Figure 5: Study ADE02T – Trial Schema



Source: Summary of Clinical Efficacy Figure 3

FDA focused on the AML patient population on Study B1371005, including both the monotherapy cohorts and the glasdegib+LDAC cohort. Similar to Study B1371003, glasdegib was administered orally daily on a continuous basis. On the combination arms, glasdegib was given at a dose of 100 mg daily. LDAC was administered at a dose of 20 mg subcutaneously twice daily on days 1-10 of the 28-day cycles. Treatment with glasdegib was to be continued for up to 12 cycles or until disease progression or relapse, patient withdrawal, or unacceptable toxicity (whichever came first).

Patients were continuously monitored for AEs and had blood counts and serum chemistries at least 2 to 4 times per month. Triplicate ECGs were obtained weekly during the first cycle and

then monthly thereafter. Response assessments were performed on day one of every even cycle. Response was evaluated using standard International Working Group (IWG) criteria (Cheson et al, JCO 2003).

6.2.2 Study Results

Compliance with Good Clinical Practices

The Applicant provided attestation that this study was conducted in accordance with U.S. regulations governing the protection of human subjects, institutional review boards, and the obligations of clinical investigators in accordance with good clinical practice (GCP).

Financial Disclosure

A summary of financial disclosures for Study B1371005 is provided. All investigators disclosed that they had no financial interests in the product.

Patient Disposition

A total of 25 subjects enrolled on Study B1371005. FDA focused on the 11 patients with AML on both the monotherapy cohorts (n=7) and the glasdegib+LDAC cohort (n=4). A summary of patient disposition in listed in Table 14.

Table 14: Study B1371005 – Disposition of Patients with AML Treated with Glasdegib±LDAC

	Glasdegib 25 mg	Glasdegib 50 mg	Glasdegib 100 mg	Glasdegib 100 mg + LDAC
Received treatment	**N=1**	**N=2**	**N=4**	**N=4**
Therapy ongoing	0	0	0	0
Discontinued therapy	1 (100%)	2 (100%)	4 (100%)	4 (100%)
Adverse event	0	0	1 (25%)	0
Primary disease	1 (100%)	0	3 (75%)	2 (50%)
Death	0	2 (100%)	0	0
Other/Unknown	0	0	0	2 (50%)

Source: FDA analysis

Demographic Characteristics

B1371005 enrolled 5 women (45%) and 6 men (55%) with AML to the relevant cohorts. All patients were Asian. The median age was 72 (range 49-81) years. Most patients (9, 82%) were ≥ 65 years.

Other Baseline Characteristics

Most patients (6/11, 55%) had secondary AML. The one patient allocated to the 25 mg cohort had intermediate-II risk cytogenetics, both in the 50 mg cohort had adverse risk, 3 of 4 on the 100 mg cohort had intermediate I/II risk, and one had adverse risk. Of the 4 patients on the glasdegib+LDAC cohort, one had missing cytogenetics, 2 had intermediate-II, and one had adverse. All patients on the glasdegib+LDAC cohort were newly-diagnosed, whereas the monotherapy cohorts included patients with R/R AML, with a mean of 1.1 years (range 0.3-3.1 years) from their first histopathological diagnosis.

Efficacy Results - Primary Endpoint

The primary efficacy endpoint of Study B1371005 was the rate of objective response. Results are displayed in Table 15 below. No CR responses were seen in the lower dose monotherapy cohorts and there was only one response in the 100 mg cohort in a patient with *de novo* AML, leading to an overall CR rate of 14% in the 7 AML patients treated with monotherapy. Out of 4 patients treated with glasdegib+LDAC, the CR rate was 25%.

Table 15: Study B1371005 AML Patients – Responses

	Glasdegib monotherapy				
	25 mg (n=1)	50 mg (n=2)	100 mg (n=4)	All doses (n=7)	Glasdegib 100 mg +LDAC (n=4)
CR rate [95% CI]	0	0	1 (25%) [0.6, 81]	1 (14%) [3, 51]	1 (25%) [0.6, 81]

Source: FDA analysis

Reviewer comments: There was only one response among patients treated with glasdegib monotherapy. Will need to assess monotherapy responses in Study B1371001 as well to see if a monotherapy indication is justified.

Data Quality and Integrity - Reviewers' Assessment

The quality of the submission was sufficient to evaluate and review the data. The quality and integrity of the data required to evaluate the primary efficacy endpoint was acceptable.

6.3 Study B1371001

6.3.1 Study Design

Overview and Objective

Study B1371001 was a first in human, phase 1, multi-center study of glasdegib monotherapy in patients with hematologic malignancies. The primary study goals were safety, tolerability, PK, PD, and determining the RP2D. Secondary endpoints included overall response, time to

progression, duration of response, and progression free survival. Response criteria for patients with AML were defined in the same way as on Study B1371003.

Trial Design

Adult patients with ECOG performance status 0-2 and with advanced hematologic malignancies who were refractory, resistant or intolerant to prior therapies, or for whom standard therapies were not anticipated to result in a durable response, were eligible. Patients must have been able, in the investigator's opinion, to receive at least 3 cycles of treatment. FDA focused on the AML patient population on Study B1371001.

The starting glasdegib dose was 5 mg qday administered in a continuous regimen. Dose escalation up to 600 mg was done in 3-6 patient cohorts up to identification of the MTD or the dosing cap.

Patients were continuously monitored for adverse events and had blood counts and serum chemistries at least 2 to 4 times per month. Triplicate ECGs were obtained weekly during the first cycle and then monthly thereafter. Response assessments were performed on day one of every even cycle. Response was evaluated using standard IWG criteria (Cheson et al, JCO 2003).

6.3.2 Study Results

Compliance with Good Clinical Practices

The Applicant provided attestation that this study was conducted in accordance with U.S. regulations governing the protection of human subjects, institutional review boards, and the obligations of clinical investigators in accordance with good clinical practice (GCP).

Financial Disclosure

The Applicant submitted financial disclosure information for Study B1371001. Four investigators reported payments, with 3 of the 4 being from one site that enrolled (b) (4) of patients. In total, the 3 investigators received over $900,000 for honorarium, research and development grants, consulting, and advisory boards. The remaining investigator received $98,040 for science administration. No financial interests or arrangements were reported for the remaining investigators.

Patient Disposition

A total of 47 subjects enrolled on Study B1371001. FDA focused on the 28 patients with AML. A summary of AML patient disposition is listed in Table 16.

Table 16: Study B1371001 – Disposition of Patients with AML Treated with Glasdegib

	5 mg	10 mg	20 mg	40 mg	80 mg	120 mg	180 mg	270 mg	400 mg	600 mg
Treated	**N=1**	**N=2**	**N=2**	**N=1**	**N=5**	**N=2**	**N=2**	**N=4**	**N=7**	**N=2**
Therapy ongoing	0	0	0	0	0	0	0	0	0	0
Discontinued	1	2	2	1	5	2	2	4	7	2
Adverse event	0	1	2	0	1	0	0	2	2	0
Primary disease	1	1	0	0	1	0	0	1	0	1
Death	0	0	0	0	1	0	1	0	1	0
Other/Unknown	0	0	0	1	2	2	1	1	4	1

Source: FDA analysis

Demographic Characteristics

B1371001 enrolled 11 women (39%) and 17 men (61%) with AML. The majority (75%) were Caucasian, 4 (14%) were Hispanic, and 3 (11%) were Black. The median age was 69 (range 25-89) years. Most patients (17, 61%) were ≥ 65 years.

Other Baseline Characteristics

A total of 11/28 (39%) patients had secondary AML due to either MDS (n=8) or another AHD (n=3). Most patients had R/R AML, with a mean of 1.3 years (range 0-7.3 years) from their first histopathological diagnosis.

Efficacy Results - Primary Endpoint

The primary efficacy endpoint of Study B1371001 was the rate of overall response, which included CR, CRi, and other lesser responses. Out of the 28 patients with AML, there were no CR responses. One patient out of 28 (4%) had a CRi; this patient was in the 80 mg dose cohort.

Reviewer comments: There were no CR responses out of 28 AML patients treated with glasdegib monotherapy, at doses ranging from 5 mg to 600 mg on Study B1371001. Thus, glasdegib does not appear to be effective as monotherapy for the treatment of R/R AML.

Data Quality and Integrity - Reviewers' Assessment

The quality of the submission was sufficient to evaluate and review the data. The quality and integrity of the data required to evaluate the primary efficacy endpoint was acceptable.

7 Integrated Review of Effectiveness

7.2 Assessment of Efficacy Across Trials

7.2.1 Primary Endpoints

Glasdegib, administered at 100 mg by mouth once daily continuously in combination with LDAC 20 mg subcutaneously bid on days 1-10 of a 28-day cycle in patients with newly-diagnosed AML, confers a survival advantage when compared to LDAC alone (HR 0.46 p=0.0002). Median OS was 8.3 months on the combination therapy arm compared to only 4.3 months on the LDAC arm.

Review comments: OS is the gold standard clinical efficacy endpoint for AML and glasdegib+LDAC showed a significant improvement in median OS over LDAC, a standard of care therapy for patients with newly-diagnosed AML. It is notable that LDAC is not commonly used for newly-diagnosed AML based on cross trial comparisons suggesting superiority of HMA therapy. However, HMA therapies have never shown an OS advantage over LDAC in a randomized trial. The median OS of 8.3 months with glasdegib+LDAC is similar to the median OS of 8-10 months with decitabine and azacitidine (H. M. Kantarjian et al. 2012; Dombret et al. 2015).

7.2.2 Secondary and Other Endpoints

In the pivotal study, the rate of complete response was also higher on the glasdegib+LDAC arm, revealing consistent benefit of glasdegib in combination with LDAC in newly-diagnosed AML.

Reviewer comments: CR rate was 18% with glasdegib+LDAC, which was significantly higher than the CR rate of 3% on the LDAC arm. It is notable that the CR rate with glasdegib+LDAC is similar to the 16-20% CR rates seen with decitabine and azacitidine (H. M. Kantarjian et al. 2012; Dombret et al. 2015).

Data from Studies B1371005 and B1371001 demonstrated only one CR out of 35 patients treated with glasdegib monotherapy, with doses ranging from 5 to 600 mg daily. Most patients (21; 60%) received glasdegib doses of ≥ 100 mg daily. Thus, the single agent activity of glasdegib is limited in patients with AML.

7.2.3 Subpopulations

On the pivotal study, none of the baseline demographic or disease characteristics had a significant effect on OS, but there was a trend toward a greater treatment effect in younger patients, those with lower serum creatinine, ECOG 2, secondary AML, and good/intermediate-I risk AML. See Figure 4 above.

7.2.4 Dose and Dose-Response

Phase 1B of Study B1371003 was the only dose-ranging study of glasdegib in combination with LDAC in patients with newly-diagnosed AML. As summarized in Section 6.1.2, there was only one CR response out of 20 patients on Phase 1B. The one CR response was out of 5 patients on the 200 mg glasdegib+LDAC cohort, whereas no responses were seen in the 15 patients on the 100 mg glasdegib+LDAC cohort. When considering all patients treated on Study B1371003 with 100 mg glasdegib+LDAC (n=89), the CR rate was 16% (95% CI 9-25%), thus similar to the 20% CR rate out of the 5 patients treated at the 200 mg dose. Considering also the 4 patients treated with glasdegib 100 mg + LDAC on Study B1371005 (1 of 4 had a CR), the pooled response rate for the 100 mg dose of glasdegib + LDAC across trials was 15/93 (16%, 95% CI 9-25%).

Reviewer comments: Given the similar CR rates of 16% amongst all AML patients treated with glasdegib 100 mg + LDAC on Studies B1371003 and B1371005 versus 20% in the small sample size of patients treated with glasdegib 200 mg + LDAC, there does not appear to be a significant dose response. However, the small sample size on the 200 mg dose cohort limits strong conclusions.

Based on the monotherapy experience with glasdegib, there was no observable dose response in patients with R/R AML given that only one patient experienced a CR at a dose of 100 mg daily.

7.2.5 Onset, Duration, and Durability of Efficacy Effects

Most of the CRs that were observed on Study B1371003 occurred after roughly 2 cycles of therapy, with a range from approximately 1 to 6 months. Median duration of response was almost 10 months with range from <1 to almost 28 months. There was only one CR response on the LDAC arm, which occurred after almost 6 months and lasted only 3 months.

Reviewer comments: Given that patients may take up to 6 months of therapy to respond, the label should include instructions to continue therapy for up to 6 months in the absence of toxicity or disease progression to allow adequate time for response.

7.3 Additional Efficacy Considerations

7.3.1 Considerations on Benefit in the Postmarket Setting

While patients who enroll on clinical trials tend to differ in various ways from the broader population of patients with cancer, there is no indication that efficacy would be lower in patient populations underrepresented on Study B1371003. Given that the therapy is oral, it will be important for prescribers to monitor compliance closely.

7.3.2 Other Relevant Benefits

Not applicable.

7.4 Integrated Assessment of Effectiveness

The efficacy of glasdegib+LDAC in AML has been established, based primarily on the results of a single randomized, phase 2 study in patients age 55 and older with at least one of age 75 and older, creatinine greater than 1.3 mg/dL, ECOG performance status of 2, and severe cardiac disease with newly-diagnosed AML, in which patients who received 100 mg daily of glasdegib in combination with LDAC had longer OS than patients who received LDAC alone (HR 0.46 p=0.0002). The median OS estimates demonstrated an almost doubling of survival (8.3 months on the combination therapy arm compared to only 4.3 months on the LDAC arm).

Reviewer comments: Although the pivotal portion of Study B1371003 was restricted to patients age ≥ 55 years, the (b) (4) ***indication to include adult patients*** (b) (4) (b) (4) ***is justified*** (b) (4) ***There is no biological reason to expect different efficacy results when this therapy is used in younger patients. The decision to treat patients with a less intensive therapy regimen such as glasdegib+LDAC should be left to the combined decision making of the physician and patient.***

The dose and regimen used in the pivotal study are supported by the data from Studies B1371003 and Study B1371005, in which patients who received doses of glasdegib 100 mg daily in combination with LDAC experienced similar responses to those with glasdegib 200 mg daily.

Data from Studies B1371005 and B1371001 demonstrate lack of efficacy of glasdegib as monotherapy in patients with AML and support a limitation of use statement in the product label.

8 Review of Safety

8.1 Safety Review Approach

Although review emphasis was placed on safety data from the randomized portion of Study B1371003, results from all 15 trials listed in Table 2 were used to support the analysis of safety.

The primary analyses were based on the safety analysis set (**SAS**) in the phase 2 randomized portion of Study B1371003. Analyses were performed on all treated patients in the SAS, which included 84 patients (75 AML, 9 MDS) on the LDAC + glasdegib arm and 41 patients (36 AML, 5 MDS) on the LDAC alone arm. Although the numbers were small in the MDS patient population, safety results were overall comparable between the AML and MDS patient populations, leading to both populations being analyzed in composite. Selected analyses, for example exposure,

focused on the AML patient population alone.

Pooled safety data from trials of glasdegib monotherapy and the two trials of glasdegib in combination with LDAC are summarized where relevant in Section 8.4. These additional safety sets are described as follows:

- Glasdegib+LDAC pool (n=113): Safety data in patients treated with glasdegib in combination with LDAC from all phases of B1371003 and B1371005 were pooled and analyzed by dose (100 mg [n=107] vs 200 mg [n=6]) to support the analysis of dose selection in combination with LDAC
- Heme monotherapy pool (n=81): Safety data from Studies B1371001 (n=47), B1371005 (n=13), and B1371013 (n=21) were pooled by dose to investigate the safety of glasdegib monotherapy in patients with hematologic malignancies
- Heme monotherapy RP2D pool (n=27): Safety data were pooled from Studies B1371005 (n=6) and B1371013 (n=21) using glasdegib monotherapy in hematologic malignancies at the RP2D
- Solid set (n=23): Safety data were summarized across dose levels from Study B1371002 using glasdegib monotherapy in patients with solid tumors
- Healthy volunteer set (n=136): Safety data from all trials of glasdegib monotherapy in healthy volunteers were pooled and analyzed

Two studies for which databases were not available were also considered relevant for the proposed indication. Patients with high-risk acute leukemia post-HSCT on Study WS2233096 (n=29) as well as 35 patients with R/R MDS or CMML on Study WI171861 were exposed to glasdegib monotherapy on these studies. They are not included in the pooled analyses, but SAEs and deaths were reviewed.

Particular attention was paid to known drug class side effects of Hh pathway inhibitors. Vismodegib and sonidegib are Hh pathway inhibitors approved for the treatment of patients with basal cell carcinoma. Both have boxed warnings for embryo-fetal toxicity and warnings and precautions regarding blood donation (both drugs) and semen donation (vismodegib). In addition, vismodegib has a warning for premature fusion of the epiphyses and sonidegib has a warning for musculoskeletal adverse reactions (ARs). Other drug class side effects include muscle spasms, alopecia, dysgeusia, fatigue, musculoskeletal pain, myalgias, weight loss, nausea, vomiting, diarrhea, increased creatinine, and increased CPK.

Furthermore, premature fusion of the epiphyses has been reported in pediatric patients exposed to vismodegib, which was predicted based on toxicology studies in animals for both vismodegib and sonidegib. Glasdegib toxicity studies in rats also showed adverse changes in growing bone and teeth (see Section 4.4). To further review bone and tooth toxicities of the approved Hh pathway inhibitors and gain insight into what might be seen with glasdegib, FDA performed a review of the FDA Adverse Event Reporting System (FAERS) database for

vismodegib and sonidegib.

Using Empirica Signal, FDA searched the FAERS database for vismodegib and sonidegib as of 8/29/2018 using the following high level terms: Bone and joint infections (excl arthritis), Bone disorders NEC, Bone related signs and symptoms, Dental and periodontal infections and inflammations, Dental developmental disorders and anomalies, Dental disorders NEC, Dental pain and sensation disorders, Dental pulp disorders, Dental surface disorders, Epiphyseal disorders, Fracture complications, Fractures NEC, Gingival discolourations, Gingival disorders NEC, Gingival haemorrhages, Gingival infections, Gingival pains, Limb fractures, Metabolic bone disorders, Pelvic fractures, Skull and face fractures, Spinal column fractures, Thoracic cage fractures non-spinal, and Tooth missing. The search returned 30 results, summarized in Table 17 below.

Table 17: FAERS Results Vismodegib and Sonidegib Bone and Tooth AEs

Preferred term	Vismodegib (N=28)	Sonidegib (N=2)
Bone pain	9	1
Tooth loss	5	0
Epiphyses premature fusion	3	0
Poor dental condition	3	0
Tooth disorder	2	0
Bone cyst	1	0
Fracture	1	0
Spinal pain	1	0
Teething	1	0
Tooth discolouration	1	0
Upper limb fracture	1	0
Vertebral column mass	0	1

Source: FDA analysis

Most of the events in FAERS occurred in association with vismodegib, likely due to its approval over 3 years before sonidegib. PTs that occurred in 2 or more patients in the FAERS search were bone pain, tooth loss, epiphyses premature fusion, poor dental condition, and tooth disorder. The events of epiphyses premature fusion occurred in children with ages 2 to 8 years. Age data was known for 3 patients with tooth loss or poor dental condition (70 to 79 years).

Reviewer comments: Given the toxicology studies showing effects on growing bone and evidence of premature fusion in children treated with vismodegib, there is concern for use of glasdegib in children until more data are available.

8.2 Review of the Safety Database

8.2.1 Overall Exposure

A total of 469 patients were exposed to glasdegib across the glasdegib clinical development program (Table 18). A total of 333 patients and 136 healthy volunteers have been exposed to glasdegib.

Table 18: Glasdegib Safety Population

Clinical Trial Groups	Glasdegib (N=469)	LDAC (N=41)
Controlled trials conducted for this indication[1]	84	41
Uncontrolled trials conducted for this indication[2]	29	0
Uncontrolled trials conducted for other malignant indications[3]	220	0
Healthy volunteers[4]	136	0

Source: FDA analysis
[1] Randomized Phase 2 Study B1371003
[2] Phase 1B Study B1371003 (glasdegib+LDAC arms), Study B1371005 (glasdegib+LDAC arm)
[3] Phase 1B Study B1371003 (glasdegib + 7+3 arms, glasdegib+decitabine arm), Study B1371005 (glasdegib monotherapy arms, glasdegib+ 7+3 arm), Studies B1371001, B1371002, B1371012, and B1371013
[4] Studies B1371009, B1371010, B1371014, B1371015, B1371022, B1371023, and B1371026

A summary of exposure to glasdegib on the randomized phase 2 Study B1371003 (n=84), in the pooled patient safety database (n=333), and in healthy volunteers (n=136) is provided in Table 19. In the randomized phase 2 Study B1371003, the median duration of exposure to glasdegib+LDAC was 2.7 months (mean 6.8 months), with a maximum exposure time of 42.1 months. The median duration of exposure to LDAC on Study B1371003 was 1.6 months (mean 2.2 months), with a maximum exposure time of 7.9 months. In the pooled patient safety database, the median duration of exposure was 2.2 months (mean 4.5 months), with a maximum duration of exposure of 42.1 months. In the healthy volunteer database, the median duration of exposure to glasdegib was 0.6 months (mean 0.7 months), with a maximum exposure time of 1.4 months. Five patients, all on the phase 2 randomized Study B1371003, were exposed to glasdegib for greater than 2 years.

Table 19: Duration of Exposure[1] to Glasdegib and LDAC in the Patient Safety Population

	Median (range)	0-3 months	>3 to 6 months	>6 to 12 months	> 12 months
Pivotal Study, glasdegib + LDAC arm (n=84)	2.7 (0.1, 42.1)	45 (54%)	7 (8%)	18 (21%)	14 (17%)
Pivotal Study, LDAC arm (n=41)	1.6 (0.2, 7.9)	29 (71%)	9 (22%)	3 (7%)	0
Pooled patient safety database (n=333)	2.2 (0, 42.1)	211 (63%)	42 (13%)	50 (15%)	30 (9%)
Pooled healthy volunteers (n=136)	0.6 (0, 1.4)	136 (100%)	0	0	0

Source: FDA analysis
[1] Irrespective of dose or regimen

Given that the median duration of exposure to glasdegib+LDAC on the pivotal portion of Study B1371003 was longer than that the LDAC alone arm, FDA performed an analysis to determine the time frame during which most patients on the LDAC arm were treated. The 25% and 75% quantiles for exposure to LDAC were 0.3 and 3.1 months, respectively.

Reviewer comments: It is notable that the median duration of exposure to LDAC on the pivotal Study B1371003 was over one month less than the median duration of exposure to glasdegib+LDAC. This will impact safety analyses since safety should be assessed on both treatment arms during the same time frame. Given that 75% of patients on the LDAC alone arm were treated for at least 3 months, safety between the treatment arms will be compared during the first 90 days of therapy. Safety will also need to be determined on the glasdegib+LDAC arm beyond the first 90 days of therapy to see if new or increased events occur after this time frame.

Seventy-two percent (n=241) of the patients in the patient safety database received a total of 100 mg of glasdegib daily, the same dose administered on the pivotal Study B1371003 (Table 20). Another 59 (18%) received >100 mg daily and 33 (10%) received <100 mg daily. Most healthy volunteers also received 100 mg glasdegib orally daily, with only 6 receiving 50 mg of the IV formulation and 50 receiving glasdegib tablets at a dose of > 100 mg daily.

Table 20: Planned Total Daily Dose of Glasdegib in the Patient Safety Population

Planned total daily dose[1]	Randomized Study B1371003 (n=84)	Patient safety database (n=333)	Healthy volunteer database[2] (n=136)
5 mg	0	3	0
10 mg	0	3	0
20 mg	0	4	0
25 mg	0	3	0
40 mg	0	4	0
50 mg	0	4	6[3]
80 mg	0	12	0
100 mg	84	241	83
120 mg	0	3	0
150 mg	0	0	18
160 mg	0	4	0
180 mg	0	3	0
200 mg	0	15	14
270 mg	0	5	0
300 mg	0	0	18
320 mg	0	7	0

400 mg	0	9	0
600 mg	0	5	0
640 mg	0	8	0

Source: FDA analysis
[1] Starting dose listed for healthy volunteer trials
[2] Note that 3 subjects [redacted] (b) (6) each enrolled on 2 separate healthy volunteer trials. Therefore, the sum of the numbers in the column is 139 since those patients were counted twice.
[3] IV formulation of glasdegib

FDA performed an analysis of treatment intensity on both the glasdegib+LDAC and LDAC arms of the pivotal Study B1371003 (Table 21).

Table 21: Treatment Intensity on Pivotal Study B1371003

Cycle	Glasdegib+LDAC (N=84)	Dose intensity glasdegib < 80%	Dose intensity LDAC < 80%	LDAC (N=41)	Dose intensity LDAC < 80%
1	84	15 (18%)	4 (5%)	41	4 (10%)
2	68	13 (19%)	10 (15%)	28	1 (4%)
3	48	6 (13%)	3 (6%)	18	1 (6%)
4	39	6 (15%)	3 (8%)	12	0
5	34	4 (12%)	1 (3%)	8	1 (13%)
6	34	4 (12%)	0	5	0
7	32	3 (9%)	0	3	0
8	30	3 (10%)	0	2	1 (50%)
9	26	4 (15%)	1 (4%)	2	0
10	20	4 (20%)	0	0	-
11	17	2 (12%)	0	0	-
12	15	0	1 (7%)	0	-
> 12	13	<1 (<8%)	<1 (<8%)	0	-

Reviewer comments: Treatment intensity was good, with ≥ 80% of patients receiving ≥ 80% of the planned doses of glasdegib and LDAC per cycle. The LDAC arm had good overall dose intensity as well.

8.2.2 Relevant characteristics of the safety population:

Demographic information for patients enrolled on the pivotal portion of Study B1371003 as well as those that comprise the pooled patient safety database and the healthy volunteer trials are summarized in Table 22. For the randomized phase 2 Study B1371003, the demographics of the safety population on the glasdegib+LDAC and LDAC arms are very similar to those of the efficacy population. The two arms of the study are well-balanced, except that the LDAC arm vs the glasdegib+LDAC arm had more females (41% vs 21%) and less patients from North America

(17% vs 37%). The demographics of the pooled safety database differed from Study B1371003 in that median age was younger, more patients had ECOG performance status of 0, there were more minority patients, and more patients from the United States. The healthy volunteer population differed in that it was mostly male, with a much lower median age, similar proportion of white and black patients, more Hispanic patients, and all from the United States.

Table 22: Demographics of the Safety Population

	Study B1371003 Glasdegib+LDAC (n=84)	Study B1371003 LDAC (n=41)	Pooled Safety Database[1] (n=333)	Healthy Volunteers (n=136)
Sex				
Female	18 (21%)	17 (41%)	113 (34%)	1 (1%)
Male	66 (79%)	24 (59%)	220 (66%)	135 (99%)
Age (years)				
Mean	76	75	68	37
Median	77	76	69	36
Min, Max	63, 92	58, 83	25, 92	19, 55
ECOG Performance Status[2]				
0	9 (11%)	3 (7%)	79 (24%)	-
1	34 (40%)	16 (39%)	163 (49%)	-
2	41 (49%)	22 (54%)	65 (20%)	-
3	0	0	1 (0.3%)	-
Missing	0	0	25 (8%)	-
Race				
White	81 (96%)	41 (100%)	263 (79%)	55 (40%)
Asian	2 (2%)	0	42 (13%)	2 (1%)
Black	1 (1%)	0	16 (5%)	63 (46%)
Hispanic	0	0	11 (3%)	0
American Indian or Alaska	0	0	1 (0.3%)	1 (1%)
Unknown	0	0	0	15 (11%)
Ethnicity				
Unknown	41 (100%)	41 (100%)	275 (83%)	14 (10%)
Hispanic or Latino	0	0	0	19 (14%)
Not Hispanic or Latino	0	0	58 (17%)	103 (76%)
Region				
North America	31 (37%)	7 (17%)	259 (78%)	136 (100%)
United States	23 (27%)	6 (15%)	249 (75%)	136 (100%)
Canada	8 (10%)	1 (2%)	10 (3%)	0
Non-North America	53 (63%)	34 (83%)	74 (22%)	0
Weight Group				
< 55 kg	2 (2%)	3 (7%)	17 (5%)	0
55-100 kg	77 (92%)	37 (90%)	276 (83%)	0
> 100 kg	5 (6%)	1 (2%)	38 (11%)	0
Missing	0	0	2 (0.6%)	136 (100%)

Source: FDA analysis
[1] Includes patients treated with glasdegib only
[2] Not relevant for the healthy volunteers

8.2.3 Adequacy of the safety database:

The size of the safety database is adequate to provide a reasonable estimate of ARs that may be observed with glasdegib, and the duration of treatment is adequate to allow assessment of ARs over time. The pivotal portion of Study B1371003 randomized glasdegib+LDAC against LDAC alone. Study B1371003 and the safety pool are representative of typical patients with AML, other malignancies, and healthy volunteers that participate on clinical trials, with the exception that Study B1371003 included older AML patients due to its inclusion criteria. However, non-white patients are under-represented on Study B1371003 compared to the overall AML population in the United States. Please see section 8.3.1 for a discussion of the quality of the safety database.

8.3 Adequacy of Applicant's Clinical Safety Assessments

8.3.1 Issues Regarding Data Integrity and Submission Quality

There were no major issues regarding data quality or the quality of the overall submission that had an effect on the safety review.

8.3.2 Categorization of Adverse Events

Adverse events (AE) were coded using the latest MedDRA version 19.1. AEs were graded by the investigators in the CRF using the NCI-CTCAE for AEs version 4.0.

The FDA compared the verbatim AE term with the MedDRA preferred term (PT) for all AEs reported on the pivotal Study B1371003 and did not identify any irregularities. The applicant utilized selected grouped PTs in their analyses. The FDA grouped related PTs for all analyses; a listing of these grouped terms can be found in Appendix 13.3. Standard MedDRA Query (SMQ) analysis was performed using MAED, and no additional safety signals were identified beyond those discussed below.

8.3.3 Routine Clinical Tests

See Section 6 for a description of the frequency of clinical assessments for the studies conducted in patients with AML. The frequency of clinical assessments in the other studies included in the safety pool varied but were adequate to assess the risks of serious safety events.

8.4 Safety Results

8.4.1Deaths

The FDA identified 28 deaths among the 270 subjects exposed to glasdegib in the pooled datasets listed in Table 23. Most deaths occurred more than 28 days after the last dose of glasdegib (40 subjects, 15%), leaving 28 (10%) on-treatment deaths.

Table 23: Deaths in the Safety Pool

Population / Treatment	On or within 28 days of last dose of glasdegib	More than 28 days after last dose of glasdegib
Glasdegib+LDAC pool (N=113)	33 (29%)	53 (47%)
Heme monotherapy pool (N=81)	10 (12%)	9 (11%)
Monotherapy solids (N=23)	3 (13%)	1 (4%)
Healthy volunteers (N=136)	0	0
Total (N=353)	46 (13%)	63 (18%)

Source: FDA analysis

The applicant identified the underlying malignancy as the cause of death in 35 of the 46 on-treatment deaths (76%) in subjects exposed to glasdegib. The other reported causes of on-treatment death in 2 or more patients were dyspnea/respiratory failure (3 subjects) and pneumonia (2 subjects).

The FDA identified 104 deaths among the 125 total subjects on the randomized phase 2 portion of Study B1371003 who received at least one dose of glasdegib or LDAC (Table 24). Most deaths occurred more than 28 days after the last dose of glasdegib+LDAC (39 subjects) or LDAC (23 subjects).

Table 24: Randomized Phase 2 Study B1371003 – Deaths

Category	Glasdegib+LDAC (N=84)	LDAC (N=41)
Total deaths	64 (76%)	40 (98%)
30-day mortality[1]	5 (6%)	5 (12%)
60-day mortality[1]	10 (12%)	13 (32%)
On-treatment deaths[2]	25 (30%)	17 (41%)
Fatal ARs	6 (7%)	5 (12%)
Primary disease	19 (23%)	10 (24%)
Intercurrent condition	0	2 (5%)

Source: FDA analysis
[1]Within 30 or 60 days following the first dose of therapy
[2]On or within 28 days after the last dose of therapy

The FDA reviewed individual patient narratives from the remaining 42 subjects to confirm the cause of on-treatment deaths. Narratives were not available for deaths that occurred more

than 28 days after the last dose of glasdegib or LDAC. In general, the narratives were well written.

Of the 25 on-treatment deaths on the glasdegib+LDAC arm, causes of death were primary disease (n=19) or fatal ARs (n=6) including sudden death (n=2), cardiac arrest (n=1), myocardial infarction (MI) (n=1), pneumonia (n=1), and unknown (n=1). Of the 17 on-treatment deaths on the LDAC arm, causes of death were primary disease (n=10), fatal ARs (n=5) including sepsis/septic shock (n=3) and pneumonia (n=2), or intercurrent condition (n=2) including MI/cardiogenic shock (n=1) and sepsis (n=1). FDA agreed with the Sponsor's assessment of causality for most deaths, except for the 7 listed in Table 25 below.

Table 25: Randomized Phase 2 Study B1371003 – FDA-Adjudicated Deaths At Least Possibly Related to Treatment Within 28 Days That Were Discrepant with Applicant Adjudication

Arm	Subject	Death Day	Days since last dose	FDA Root COD	Investigator Root COD
LDAC+glasdegib	(b) (6)	(b) (6)	2	AR (MI)	Intercurrent illness (MI)
LDAC+glasdegib	(b) (6)		7	AR (Cardiac arrest)	Intercurrent illness (coronary artery disease)
LDAC+glasdegib	(b) (6)		22	AR (Pneumonia)	Primary disease
LDAC	(b) (6)		19	AR (Sepsis)	Primary disease
LDAC	(b) (6)		10	AR (Septic shock)	Primary disease
LDAC	(b) (6)		17	AR (Pneumonia)	Primary disease
LDAC	(b) (6)		22	AR (Pneumonia)	Primary disease

Source: FDA analysis
Abbreviations: AR, adverse reaction; COD, cause of death; MI, myocardial infarction
[1]The subject presented following a fall and died of suspected ICH, but this was unconfirmed by imaging due to patient preference for no further intervention.

Narratives for patients listed in Table 25 with deaths at least possibly related to treatment, when discrepant with the Applicant's assessment, are listed below by treatment arm.

Glasdegib+LDAC arm

Subject (b) (6): 85-year-old man with AML a history of hypertensive heart disease, arterial hypertension, and chronic obstructive pulmonary disease. On day (b) (6) the patient died of a heart attack at home. No autopsy was performed. The event was considered unrelated by the investigator. Earlier ECGs did not show signs of QTc prolongation.

Reviewer comments: While the patient did have hypertensive heart disease, he did not have a known history of coronary artery disease. Furthermore, the MI occurred relatively early on during therapy. Cannot rule out the possibility that the MI could have been related to study

therapy.

Subject (b) (6): 80-year-old man diagnosed with AML with a history of arterial hypertension, hypertensive heart disease, coronary artery disease status post angioplasty and stent placement, cardiac insufficiency, slightly restricted systolic dysfunction, first degree atrioventricular block, atrial fibrillation, stage II chronic renal failure, and obesity. On study day (b) (6), the patient became unconscious in a shopping center and was diagnosed with Grade 4 ventricular fibrillation by paramedics. After defibrillation, the patient had sinus rhythm and normal cardiac function. Testing did not identify MI or any cause of the ventricular fibrillation. Computed tomography scan showed an unstable fracture of the 12th thoracic vertebra and the patient was stabilized surgically (he had known Bechterew's disease). Cranial CT showed hypoxic damage of the brain. The last doses of glasdegib and LDAC were received earlier on the day of the event. Previous ECGs showed no clinically significant results, but the last ECG was done almost a month before the event. The day following the event of ventricular fibrillation, the patient was ventilated but without sedation, and extubated a day later. On day (b) (6) the patient was transferred from the ICU to the cardiac unit for cardioverter-defibrillator implantation. That day, the patient became asystolic on telemetry and resuscitation was initiated, but not successful. The patient died due to asystole. The SAE was reported as Grade 5 cardiac arrest. The reason for asystolic arrest was unknown. Per the investigator, there was a reasonable possibility that the event Grade 4 ventricular fibrillation was related to glasdegib as well as LDAC. However, the Applicant did not attribute ventricular fibrillation to the study treatment. In the opinion of the investigator and Applicant, there was not a reasonable possibility that the event of grade 5 asystolic arrest was related to study treatment. Instead, the Applicant felt that the patient's medical history with ongoing coronary artery disease might be considered an alternative explanation for the reported event in this elderly patient.

Reviewer comments: This patient had a notable cardiac history and all previous ECGs were normal. However, the most recent ECG was almost a month prior to the event. The patient was not started on any new suspect concomitant medications within the 1-2 months prior to the event. Given that he experienced grade 4 ventricular fibrillation the same day as his last dose of glasdegib and LDAC, it is at least possibly related to treatment. Although the patient had a significant cardiac history, he did not carry a history of ventricular arrhythmia prior to being on the study treatment. Furthermore, there was no evidence of acute ischemia or heart failure based on the records. Following the event of ventricular fibrillation, the patient died from cardiac arrest. The death is at least possibly related to study therapy.

Subject (b) (4) 77-year-old woman with AML and history of hypertension, dyspnea, and weakness. On day (b) (6) of glasdegib+LDAC, the patient presented with symptoms of pneumonia and the study drugs were temporarily withheld due to symptoms of fever and dyspnea. Treated with antibiotics and lasix. Had persistent fevers and worsening dyspnea. Developed grade 4 hypotension due to sepsis and grade 4 respiratory distress. Antibiotics were broadened, but the

patient continued to deteriorate and died due to pneumonia. The white blood cell count increased from 10 on day (b) (6) to 28.7 on day (b) (6), but blasts decreased from 30% to 14%. ANC increased from 320 to 14920. The death was considered unrelated by the Investigator and Sponsor. The patient had 96% BM blasts at baseline. Although the patient had a high burden of disease at baseline, she developed the pneumonia early on in her treatment course, without objective evidence of progressive disease in the peripheral blood prior to her death.

LDAC arm

Subject (b) (4): 78-year-old woman with AML and history of increased coagulation test, peripheral edema, diarrhea, dyspnea on exertion, epistaxis, pyrexia, arrhythmia, hypertension, and infection. At baseline had 65% circulating blasts. The patient stopped therapy due to refusal for reason other than an AE. Died 7 days later of sepsis. Not related per the Sponsor. However, blasts decreased to 0% on day (b) (6). Therefore, there was no clear PD and cannot rule out a drug related side effect.

Subject (b) (4): 73-year-old man with AML and history of MI, pseudomembranous colitis, tumor lysis syndrome, hypertension, impaired fasting glucose, and left ventricular failure. He had 16% circulating blasts at baseline. On day (b) (6), he was admitted for dyspnea and fever and diagnosed with grade 4 septic shock. Chest x-ray showed pneumonia. Despite intensive treatment, the patient died due to septic shock. His last CBC showed 2.9% circulating blasts. The death was considered unrelated per the Applicant and Investigator. However, given no signs of disease progression, FDA considers the event of fatal septic shock to be at least possibly related LDAC.

Subject (b) (4): 70-year-old man with AML with hypertension, cardiac ischemia, and type 2 diabetes mellitus who was randomized to the LDAC arm. On day (b) (6), the patient was admitted to a local hospital for pneumonia, which led to cardiopulmonary failure. During the last study visit, PD was not observed. The event was considered not related per the Applicant. In the absence of evidence of PD, this event is considered at least possibly related to LDAC.

Subject (b) (6): 77-year-old woman with AML with arteriosclerosis and diabetes. On day (b) (6) of LDAC therapy, she was admitted for grade 4 pneumonia. Antibiotics were started, but her condition progressively worsened and she died of pneumonia. The event was considered unrelated to LDAC by the Investigator and Applicant. The white blood cell count increased to 32.7 on day (b) (6) but ANC increased to over 8000, and there were no peripheral blasts. The patient had 78.5% BM blasts at baseline, but there were no blasts in the peripheral blood throughout therapy. Therefore, in the absence of evidence to support PD, the fatal pneumonia is considered at least possibly related to LDAC.

Notwithstanding agreement with the Sponsor on causality, the two sudden deaths on the glasadegib+LDAC arm were evaluated in more detail. Subject (b) (6) died suddenly almost a month after the last dose of study therapy. PD was suspected by the investigator, but not proven. There was no evidence of QT prolongation. Subject (b) (6) had a heart murmur at the start of the trial, and on day (b) (6) he was admitted with edema, and found to have signs of heart failure and aortic stenosis on echocardiogram. The investigator thought it was unlikely that the aortic stenosis developed after starting therapy. The patient was last seen in the clinic on cycle 9 day (b) (6) with no complaints. Four days later, he had diarrhea and was weak, went to the emergency room, and came home a few hours later. Two days later, he died at home. The investigator thought the sudden death was not related, but the Applicant could not exclude an association. This patient had grade 2 QTc prolongation during cycle 2 in the setting of concomitant ciprofloxacin and fluconazole, but the QTc prolongation resolved on subsequent readings.

Reviewer comments: Causes of death on both treatment arms were typical for an elderly and co-morbid AML patient population. However, the sudden deaths on the glasdegib+LDAC arm did raise some concern. A fatal arrhythmia or other cardiac dysfunction related to therapy could not be completely excluded, but other causes could have contributed, including the underlying disease.

8.4.2Serious Adverse Events

A treatment-emergent SAE (TESAE) occurring within 28 days after the last dose of glasdegib was reported for 64 (76%) of the 84 patients on the LDAC+glasdegib arm and 32 (78%) of the 41 patients on the LDAC alone arm. The most frequently occurring (≥ 2%) TESAEs on the glasdegib+LDAC arm included febrile neutropenia (29%), pneumonia (24%), hemorrhage (12%), QT interval prolongation (10%), anemia (7%), sepsis (7%), fatigue (4%), renal insufficiency (4%), cardiac failure (2%), fall (2%), fungal infection (2%), hyponatremia (2%), muscle spasms (2%), and myocardial ischemia (2%).

Considering only the first 90 days on therapy, TESAEs occurred in 52 (62%) of 84 patients on the combination arm and 28 (68%) on the LDAC alone arm. The most frequently occurring (≥ 5%) TESAEs during the first 90 days of therapy are included in Table 26 below.

Table 26: TESAEs (≥ 5%) in first 90 days of therapy on randomized phase 2 study B1371003

PT[1]	Glasdegib+LDAC (n=84)	LDAC (n=41)
Febrile neutropenia	**21 (25%)**	**5 (12%)**
Pneumonia	11 (13%)	8 (20%)
Hemorrhage	5 (6%)	2 (5%)

Source: FDA analysis
[1] Includes grouped terms (see Appendix 13.3)
Note: All-cause TESAEs ≥ 2% more frequent on the glasdegib+LDAC arm are indicated in bold font.

The only SAEs occurring ≥ 2% more frequently on the glasdegib+LDAC arm than the LDAC alone arm were febrile neutropenia (25% vs 12%), QT prolongation grouped term (4.8% [3 patients with syncope, 1 with cardiac arrest] vs 0%), anemia (4% vs 0%), fatigue (2% vs 0%), renal insufficiency (2% vs 0%), and hyponatremia (2% vs 0%).

Beyond 90 days, SAEs on the glasdegib+LDAC arm that were ≥ 5% were pneumonia (10%) and hemorrhage (6%). Hemorrhage events included 4 patients with ICH and one with gastrointestinal hemorrhage. One case was fatal and related to the primary disease (Subject (b) (6)), whereas the other cases were grade 3-4 in severity. The incidence of febrile neutropenia after 90 days was less at 4%.

Analysis of SAEs in the other safety pools and the two investigator-initiated trials (Study WI171861 and Study WS2233096) did not reveal additional safety signals. There was only one patient in the healthy volunteer set (on Study B1371010) who developed an SAE of accelerated idioventricular rhythm following glasdegib 200 mg treatment. Maximum QTcF was 434 msec and the event was classified as unrelated to treatment. The narrative is detailed below.

Subject (b) (4): A 29-year-old black man participated in the heathy volunteer food effect/DDI Study B1371010. He was given a single dose of glasdegib 200 mg orally. Tmax for the study drug was 1-2 hours. He was on no concomitant medications and had no known medical problems besides a remote leg fracture. ECGs 1, 2, and 4 hours post-dose were normal, but premature ventricular contractions (PVCs) were seen on the ECG 6 hours post-dose. As a precaution, continuous cardiac monitoring was initiated and revealed multiple PVCs, with increasing frequency and duration. Electrolytes, including magnesium were normal. Given an increase in PVCs/nonsustained ventricular tachycardia, the patient was transferred to the emergency room and admitted for further evaluation and monitoring. He was given aspirin. He was noted to have ventricular ectopy, specifically PVCs and accelerated idioventricular rhythm. Echocardiogram was normal. The subject reported considerable exercise, and did not have any symptoms, excluding mild, atypical, non-specific chest discomfort lasting seconds at the time of hospital transfer. The Applicant concluded that the presentation was suggestive of incidental findings of ventricular ectopy in a young healthy individual with an athletic heart.

Reviewer comments: Despite the lack of correlation with the Tmax, the occurrence of PVCs and accelerated idioventricular rhythm post-single dose of glasdegib in a healthy young man is concerning and at least possibly related to study drug administration.

8.4.3Dropouts and/or Discontinuations Due to Adverse Effects

Overall, 95/125 (76%) of treated subjects had a dose interruption, dose reduction, or permanent discontinuation due to an AE (Table 27), with 67/84 (80%) on the glasdegib+LDAC arm and 28/41 (68%) on the LDAC arm.

Table 27: Treatment Interruptions, Reductions, or Withdrawals

	Glasdegib+LDAC (N=84)	LDAC (N=41)
Interruption	47 (56%)	13 (32%)
Dose reduction	22 (26%)	0
Withdrawal	29 (35%)	18 (44%)
Any of the above	67 (80%)	28 (68%)

Source: FDA analysis

The most common TEAEs leading to interruption of glasdegib and/or LDAC are shown in Table 28 in decreasing order. The table includes only those events that occurred in > 2% of subjects on the glasdegib+LDAC arm of the pivotal Study B1371003. Of interruptions on the glasdegib+LDAC arm, 30 included both agents, 33 included glasdegib alone, and 7 included LDAC alone.

Table 28: TEAEs Leading to Dose Interruption

Preferred Term[1]	Glasdegib+LDAC (N=84)	LDAC (N=41)
Febrile neutropenia	14 (17%)	1 (2%)
Pneumonia	8 (10%)	3 (7%)
Hemorrhage	6 (7%)	0
Fatigue	5 (6%)	1 (2%)
Anemia	4 (5%)	0
Muscle spasms	4 (5%)	0
Pyrexia	4 (5%)	0
QT interval prolongation	4 (5%)	0
Renal insufficiency	4 (5%)	0
Neutropenia	3 (4%)	3 (7%)

Source: FDA analysis
[1] Includes grouped terms (see Appendix 13.3)

The grouped term QT interval prolongation leading to dose interruptions included PTs of electrocardiogram QT prolonged (n=2), syncope (n=1), and ventricular fibrillation (n=1).

The most common TEAE leading to dose reductions of glasdegib and/or LDAC are shown in Table 29 in decreasing order. The table includes only those events that occurred in > 1 subject on the pivotal Study B1371003. Of patient dose reductions on the glasdegib+LDAC arm, 4 included both agents, 11 included glasdegib alone, and 10 included LDAC alone.

Table 29: TEAEs Leading to Dose Reductions

Preferred Term[1]	Glasdegib+LDAC (N=84)	LDAC (N=41)
Muscle spasms	4 (5%)	0
Fatigue	3 (4%)	0
Febrile neutropenia	3 (4%)	0
QT interval prolongation	3 (4%)	0
Anemia	2 (2%)	0
Thrombocytopenia	2 (2%)	0

Source: FDA analysis
[1] Includes grouped terms (see Appendix 13.3)

The grouped term QT interval prolongation leading to dose reductions included PTs of electrocardiogram QT prolonged (n=2) and loss of consciousness (n=1).

The most common TEAEs leading to dose discontinuations of glasdegib and/or LDAC are shown in Table 30**Error! Reference source not found.** in decreasing order. The table includes only those events that occurred in > 1 subject on the pivotal Study B1371003. Most discontinuations on the glasdegib+LDAC arm led to discontinuation of both agents (n=25), whereas only 4 patients discontinued glasdegib alone. No patients on the glasdegib+LDAC arm discontinued LDAC alone.

Table 30: Randomized Study B1371003 – AEs Leading to Discontinuation in ≥ 2 Patients

Preferred Term[1]	Glasdegib+LDAC (N=84)	LDAC (N=41)
Pneumonia	5 (6%)	1 (2%)
QT interval prolongation	4 (5%)	0
Sepsis	3 (4%)	2 (5%)
Febrile neutropenia	3 (4%)	2 (5%)
Myocardial ischemia	2 (2%)	2 (5%)
Nausea	2 (2%)	0
Renal insufficiency	2 (2%)	1 (2%)

Source: FDA analysis
[1] Includes grouped terms (see Appendix 13.3)

Discontinuations due to pneumonia were more frequent on the glasdegib+LDAC arm. However, it is notable that 3 of the 5 cases of pneumonia on the glasdegib+LDAC arm occurred on days 329 to 789 of therapy, far beyond the 90-day window during which most LDAC patients remained on therapy. The grouped term QT interval prolongation leading to discontinuation included PTs of sudden death (n=2), cardiac arrest (n=1), and electrocardiogram QT prolonged (n=1).

Patients on the glasdegib+LDAC arm who discontinued glasdegib alone and continued on LDAC

had events of cardiac arrest, decreased appetite, MI, and ICH.

Reviewer comments: Discontinuations due to AEs were more common overall on the LDAC arm. The most common reasons for discontinuation on the glasdegib+LDAC arm were not unexpected for an elderly AML patient population and were similar to those seen on the LDAC arm, with the exception of pneumonia, QT interval prolongation grouped term (including 2 sudden deaths), and nausea. The sudden deaths are reviewed under Section 8.4.1 above.

8.4.4Significant Adverse Events

QT prolongation

QT interval prolongation is an ADR that has been associated with glasdegib, based on both nonclinical and clinical safety findings. The applicant found that QT interval prolongation occurred in 7/107 (7%) patients in the glasdegib 100 mg + LDAC pool (n=107), 7/84 (8%) on the glasdegib+LDAC arm, and 1/41 (2%) on the LDAC arm of the randomized Study B1371003 SAS. Grade 3-4 QTc prolongation occurred in 3/84 (4%) of patients on the glasdegib+LDAC arm and in 1/41 (2%) of patients on the LDAC arm. As per Section 8.4.3, 5% of subjects on the glasdegib+LDAC arm had a dose interruption and 4% had a dose reduction due to the grouped term QT interval prolongation (2% each had a dose interruption or reduction due to the PT electrocardiogram QT prolonged). Four (5%) subjects discontinued glasdegib+LDAC due to the grouped term QTc prolongation (2 sudden deaths, 1 cardiac arrest, and one electrocardiogram QT prolonged).

The Interdisciplinary Review Team reviewer conducted an analysis of ECG intervals in subjects treated on the pivotal Study B1371003. The analysis only included patients in the safety population with a baseline ECG. The results of the analysis are shown in Table 31.

Table 31: Maximum Postbaseline Absolute QTcF Intervals

QTcF Category	Glasdegib+LDAC (N=83)	LDAC (N=17)
QTcF maximum postbaseline value		
< 450 msec	46 (55%)	8 (47%)
450 to < 480 msec	29 (35%)	4 (24%)
480 to < 500 msec	3 (4%)	3 (18%)
> 500 msec	5 (6%)	2 (12%)
QTcF maximum increase from baseline		
< 30 msec	60 (72%)	12 (71%)
30 to < 60 msec	19 (23%)	4 (24%)
> 60 msec	4 (5%)	1 (6%)

Source: FDA Interdisciplinary Review Team analysis

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Kelly Norsworthy, MD
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Glasdegib is a CYP3A4 substrate as per the results of their DDI study B1371010. Thus, concomitant use of glasdegib with moderate/strong CYP3A4 inhibitors may increase glasdegib concentrations, which may increase the risk of QT interval prolongation (see Section 4.5 for details).

FDA performed an analysis of grade 3 or higher events using the grouped term QT prolongation, consisting of the Torsade de Pointes/QT prolongation SMQ (Narrow) and PT Seizure in the first 90 days of therapy on both treatment arms of the pivotal portion of Study B1371003. Of the 84 patients on the glasdegib+LDAC arm, 7 (8%) had a QT prolongation PT, including electrocardiogram QT prolonged (n=3), syncope (n=3), and cardiac arrest (n=1). Of the 41 patients on the LDAC arm, 3 (7%) had a QT prolongation PT, including electrocardiogram QT prolonged (n=1), syncope (n=1), and loss of consciousness (n=1).

The one case of grade 4 cardiac arrest occurred in Subject (b) (6):

This was an 83-year-old man with AML with a history of hypoxia, atrial fibrillation, increased creatinine, cerebrovascular disorder, chronic kidney disease, fatigue, hypertension, and proteinuria who was randomized to the glasdegib+LDAC arm. On day (b) (6) of treatment, the patient was hospitalized for grade 4 neutropenic fever and was started on intravenous antibiotics. Fevers continued, and a blood culture was positive for Candida tropicalis, resulting in the addition of fluconazole. On day (b) (6), computed tomography of the chest showed small to moderate bilateral pleural effusions with overlying opacities due to atelectasis or pneumonia. On day (b) (6), the patient developed grade 4 ARDS and grade 3 hypertension and was placed on noninvasive positive pressure ventilation. He received steroids and furosemide. ECG revealed atrial fibrillation with rapid ventricular response. The patient recovered and was transferred out of the intensive care unit. However, he was permanently withdrawn from therapy on day (b) (6) due to failure to respond and poor performance status. On day (b) (6) the patient was found unresponsive, with midline catheter removed, and a large collection of blood noted. Code blue was called, and CPR was initiated. A femoral pulse was palpated but blood pressure was not measurable. The patient was given 3 rounds of epinephrine and intravenous fluids. He was ultimately started on pressors and transferred back to the intensive care unit. Hemoglobin dropped from 9.2 g/dL to 6.7 g/dL within 24 hours and 3 units of blood were transfused. ECG showed sinus bradycardia with first degree AV block and left bundle branch block. The patient was transferred out of the unit the next day. ECG results did not reveal any QTc prolongation. On day (b) (6) disease evaluation showed 61% marrow blasts, consistent with treatment failure. The patient was discharged 4 days later with hospice support and died about a month later.

Reviewer comments: This case of cardiac arrest was in the context of an elderly patient with underlying atrial fibrillation who developed infections and anemia in the setting of persistent AML unresponsive to the therapy. It is unlikely that the event was related to glasdegib.

On the pivotal portion of Study B1371003, there were 2 (2%) of patients on the glasdegib+LDAC arm and none on the LDAC arm with a TEAE under the ventricular arrhythmia grouped term (see Appendix 13.3). Broadening the search to the glasdegib 100 mg + LDAC pool (including Study B1371003 phase 1B), three patients out of 107 (3%) had a ventricular arrhythmia. All had AML; two patients had ventricular tachycardia (Grade 2) and one patient had ventricular fibrillation (Grade 4). Case narratives are as follows.

Subject (b) (4): 80-year-old man with AML with history of prostatectomy, prolonged aPTT/PT, aphthous ulcer, and hypertension. The patient was enrolled in the phase 2 randomized portion of Study B1371003 and was randomized to the combination arm. On study day (b) (6) the patient was noted to have grade 2 QTc prolongation (mQTcF 466), which resolved on day (b) (6) On day (b) (6) the patient was again noted to have grade 2 QTc prolongation (mQTcF 481), but no action was taken with glasdegib or LDAC. On day (b) (6) grade 2 QT prolongation worsened to grade 3 (mQTcF 504), resulting in permanent discontinuation of study therapy. On day (b) (6) the patient experienced grade 2 ventricular tachycardia, which resolved on the same day. Mean QTcF was up to 530 on study day (b) (6) The event QTc prolonged continued as of the last ECG recorded, with mQTcF 472 msec on study day (b) (6) Mean QTcF at baseline was 453 msec. Concomitant medications included ondansetron, fluconazole then voriconazole then posaconazole, and moxifloxacin then levofloxacin. The investigator considered the AEs of ECG QT prolongation to be related to glasdegib.

Reviewer comments: The event of grade 2 ventricular tachycardia is likely related to the glasdegib given the clear correlation between the start of therapy and QTc prolongation.

Subject (b) (4): 85-year-old man with AML with a history of MDS, AST/ALT elevation, atrial fibrillation, dyspnea, fluid retention, and hypertension. He was enrolled on phase 1B of Study B1371003 and treated with glasdegib and LDAC. On day (b) (6) the patient experienced diarrhea, confusion, dehydration, and weakness and was admitted for the management of grade 3 weakness and grade 4 clostridium difficile sepsis. He was treated with intravenous fluids, ceftriaxone, and vasopressors. Study medications were permanently discontinued in response to these events and disease progression. On day (b) (6) the patient experienced grade 2 ventricular tachycardia, grade 3 febrile neutropenia, and grade 2 lethargy. The patient was discharged to hospice care 6 days later. The patient died of disease progression. Ventricular tachycardia was ongoing at the time of death. The investigator considered the ventricular tachycardia to be related to the clostridium difficile sepsis.

Reviewer comments: Given the disease progression and sepsis, this event of ventricular tachycardia is unlikely related to glasdegib+LDAC.

Subject (b) (4): Case of ventricular fibrillation detailed under Section 8.4.1.

Reviewer comments: The event of grade 4 ventricular fibrillation was considered at least possibly related to treatment.

The median time from the first dose of glasdegib+LDAC to the first event of electrocardiogram QT prolonged was 29 days (range 7-57 days). The only event on the LDAC arm occurred at 10 days. The median time from the first dose of glasdegib+LDAC to the first event of grade 3 or higher electrocardiogram QT prolonged was 31 days (range 15-57).

Reviewer comment: There is evidence to suggest that glasdegib has the potential to delay ventricular repolarization. I agree to include QTc prolongation in Warnings and Precautions in the PI. I recommend adding that ventricular arrhythmias have occurred. Given that the TEAEs of electrocardiogram QT prolonged occurred in the first 2 months of therapy, will recommend monitoring ECGs for at least the first 2 months. In addition, will include that certain patients (e.g. those with cardiac disease or on a concomitant CYP3A4 inhibitor) should undergo more frequent monitoring.

8.4.5Treatment Emergent Adverse Events and Adverse Reactions

Pivotal trial

Treatment-emergent adverse events (TEAE) occurring either on study treatment or within 28 days after discontinuation of study treatment on the randomized portion of Study B1371003 are summarized by system organ class (SOC) in Table 32. Given that a minority of patients on the LDAC arm received greater than 90 days of treatment, FDA focused its analyses of TEAEs on the first 90 days of therapy on both arms. Events on the glasdegib+LDAC arm beyond 90 days of therapy were analyzed separately to determine any new safety signals.

All but two patients on the study experienced a TEAE in the first 90 days, which is expected for the patient population (82 [98%] on the glasdegib+LDAC arm and 41 [100%] on the LDAC arm). Most experienced a grade 3 or higher TEAE in first 90 days as well (73 [87%] on the glasdegib+LDAC arm and 37 [90%] on the LDAC arm).

SOCs in which the frequency of AEs of any grade was ≥ 2% higher in the glasdegib+LDAC arm included the nervous system (Δ30%), metabolism and nutrition (Δ19%), musculoskeletal and connective tissue (Δ17%), skin & subcutaneous tissue disorders (Δ14%), cardiac (Δ11%), general & administrative site conditions (Δ10%), investigations (Δ9%), renal and urinary (Δ9%), injury, poisoning & procedural (Δ6%), eye disorders (Δ4%), gastrointestinal (Δ4%), psychiatric (Δ4%), and blood & lymphatic system (Δ2%).

Table 32: Study B1371003 – TEAE Occurring in ≥ 10% of Patients by SOC First 90 Days

	Glasdegib (n=84)		LDAC (n=41)	
System Organ Class	**All grades**	**Grade 3+**	**All grades**	**Grade 3+**
General & administrative site conditions	60 (71%)	21 (25%)	25 (61%)	8 (20%)
Gastrointestinal	56 (67%)	10 (12%)	26 (63%)	3 (7%)
Blood & lymphatic system	55 (65%)	54 (64%)	26 (63%)	26 (63%)
Investigations	46 (55%)	25 (30%)	19 (46%)	10 (24%)
Infections and infestations	42 (50%)	22 (26%)	22 (54%)	14 (34%)
Nervous system	42 (50%)	9 (11%)	8 (20%)	2 (5%)
Metabolism and nutrition	39 (46%)	13 (15%)	11 (27%)	3 (7%)
Musculoskeletal and connective tissue	39 (46%)	3 (4%)	12 (29%)	1 (2%)
Skin & subcutaneous tissue disorders	36 (43%)	3 (4%)	12 (29%)	1 (2%)
Respiratory, thoracic & mediastinal	35 (42%)	11 (13%)	21 (51%)	7 (17%)
Psychiatric	20 (24%)	1 (1%)	8 (20%)	1 (2%)
Vascular disorders	19 (23%)	6 (7%)	13 (32%)	0
Cardiac	18 (21%)	7 (8%)	4 (10%)	2 (5%)
Renal and urinary	18 (21%)	7 (8%)	5 (12%)	2 (5%)
Injury, poisoning & procedural	15 (18%)	2 (2%)	5 (12%)	2 (5%)
Eye disorders	9 (11%)	1 (1%)	3 (7%)	0

Source: FDA analysis

The SOC with the greatest increase on the glasdegib+LDAC arm vs the LDAC arm was Nervous system. The most common PTs/grouped terms (see Appendix 13.3) on the glasdegib+LDAC arm under this SOC were dysgeusia (18, 21%), dizziness (15, 18%), headache (10, 12%), and syncope/presyncope/loss of consciousness (7, 8%). The most common PTs on the LDAC arm included headache (4, 10%), dizziness (3, 7%), and syncope/loss of consciousness (3, 7%).

Reviewer comments: The increased incidence of nervous system SOC AEs appears to be driven primarily by the increased cases of dysgeusia and dizziness on the glasdegib+LDAC arm.

TEAEs occurring either on study treatment or within 28 days after discontinuation of study treatment on randomized Study B1371003 within the first 90 days of therapy are summarized by PT in Table 34. TEAEs, regardless of grade, occurring in at least 10% of patients are included in the table.

Table 33: Randomized Study B1371003 – TEAEs in ≥ 10% of Patients on the Glasdegib+LDAC Arm in the First 90 Days of Therapy by PT

Preferred Term[1]	Glasdegib+LDAC (n=84)		LDAC (n=41)	
	All grades	Grade 3+	All grades	Grade 3+
Anemia	36 (43%)	34 (40%)	17 (41%)	15 (37%)
Fatigue	**30 (36%)**	**12 (14%)**	**13 (32%)**	**3 (7%)**
Hemorrhage	30 (36%)	5 (6%)	17 (41%)	5 (12%)
Febrile neutropenia	**26 (31%)**	**26 (31%)**	**9 (22%)**	**9 (22%)**
Musculoskeletal pain	**25 (30%)**	**2 (2%)**	**7 (17%)**	**1 (2%)**
Thrombocytopenia	**25 (30%)**	**25 (30%)**	**11 (27%)**	**10 (24%)**
Nausea	**24 (29%)**	**1 (1%)**	**5 (12%)**	**1 (2%)**
Edema	**25 (30%)**	**0**	**8 (20%)**	**1 (2%)**
Dyspnea	19 (23%)	9 (11%)	10 (24%)	3 (7%)
Decreased appetite	**18 (21%)**	**1 (1%)**	**3 (7%)**	**1 (2%)**
Dysgeusia	**18 (21%)**	0	**1 (2%)**	0
Mucositis	18 (21%)	1 (1%)	5 (12%)	0
Constipation	17 (20%)	1 (1%)	5 (12%)	0
Rash	**17 (20%)**	**2 (2%)**	**3 (7%)**	**1 (2%)**
Abdominal pain	16 (19%)	0	5 (12%)	0
Pneumonia	16 (19%)	13 (15%)	10 (24%)	9 (22%)
Renal insufficiency	**16 (19%)**	**4 (5%)**	**4 (10%)**	**0**
Cough	15 (18%)	0	6 (15%)	1 (2%)
Diarrhea	15 (18%)	3 (4%)	9 (22%)	0
Dizziness	**15 (18%)**	**1 (1%)**	**3 (7%)**	**0**
Pyrexia	15 (18%)	1 (1%)	9 (22%)	1 (2%)
Vomiting	15 (18%)	2 (2%)	4 (10%)	1 (2%)
Muscle spasms	**13 (15%)**	**0**	**2 (5%)**	**0**
Atrial arrhythmia	11 (13%)	3 (4%)	3 (7%)	1 (2%)
QT interval prolonged	11 (13%)	3 (4%)	4 (10%)	1 (2%)
Hypokalemia	11 (13%)	3 (4%)	5 (12%)	0
Weight decreased	**11 (13%)**	**0**	**1 (2%)**	**0**
Chest pain	**10 (12%)**	**1 (1%)**	**1 (2%)**	**0**
Headache	10 (12%)	0	4 (10%)	1 (2%)
Hyponatremia	**9 (11%)**	**5 (6%)**	**0**	**0**
White blood cell count decreased	**9 (11%)**	**9 (11%)**	**2 (5%)**	**1 (2%)**

Source: FDA analysis

[1] Includes grouped terms (see Appendix 13.3)

Note: All-cause TEAEs ≥ 10% more frequent on the glasdegib+LDAC arm and grade ≥ 3 TEAEs ≥ 5% more frequent on the glasdegib+LDAC arm are indicated in bold print.

Although it was not ≥ 10% in incidence, the typical Hh inhibitor class side effect of alopecia was seen in 5 (6%) of patients on the glasdegib+LDAC arm, compared to no patients on the LDAC

arm. Furthermore, FDA performed an analysis of dental disorders and fractures (see Appendix 13.3 for grouped terms) given the expected toxicities to bone and teeth based on rat toxicology studies (Section 4.4). Four (5%) of patients on the glasdegib+LDAC arm had a dental disorder compared to no patients on the LDAC arm. PTs included loose tooth (n=2) and toothache (n=2). Five (6%) of patients on the glasdegib+LDAC arm had a fracture compared to no patients on the LDAC arm. PTs included femur fracture, foot fracture, fracture, patella fracture, spinal fracture, and thoracic vertebral fracture. Three patients had grade 3 fractures (femur fracture, fracture, patella fracture, and spinal fracture).

Reviewer comments: Many of the typical Hh inhibitor class side effects were seen with glasdegib+LDAC at a greater number than the LDAC alone arm (for either all-grade or grade 3+ TEAEs). These included musculoskeletal pain, muscle spasms, dysgeusia, fatigue, weight loss, nausea, vomiting, diarrhea, and renal insufficiency.

Other side effects that were more common on the glasdegib+LDAC arm included febrile neutropenia, thrombocytopenia, edema, decreased appetite, rash, dizziness, chest pain, hyponatremia, and white blood cell count decreased.

Side effects more common on the LDAC arm included hemorrhage and pneumonia, likely due to its lesser treatment effect.

I recommend including the laboratory related ARs (e.g. anemia, renal insufficiency) in a separate table in the PI based on the raw lab data in the first 90 days of therapy. The remainder of the TEAEs in the Table above are considered ARs of glasdegib, with the exception of atrial arrhythmia (see Section 8.4.8).

Events on the glasdegib+LDAC arm beyond 90 days of therapy were analyzed separately (Table 34). A total of 53/84 (63%) of patients on the glasdegib+LDAC arm experienced any grade TEAE and 36/84 (43%) experienced a grade 3 or higher TEAE after 90 days of therapy. TEAEs, regardless of grade, occurring in at least 10% of patients are included in the table below.

Table 34: Randomized Study B1371003 – TEAEs in ≥ 10% of Patients on the Glasdegib+LDAC Arm by PT Beyond 90 Days

	Glasdegib+LDAC (n=84)	
PT[1]	All grades	Grade 3+
Diarrhea	15 (18%)	2 (2%)
Anemia	14 (17%)	11 (13%)
Decreased appetite	14 (17%)	2 (2%)
Hemorrhage	14 (17%)	5 (6%)
Muscle spasms	14 (17%)	4 (5%)
Fatigue	13 (15%)	3 (4%)

	Glasdegib+LDAC (n=84)	
PT[1]	All grades	Grade 3+
Pyrexia	13 (15%)	1 (1%)
Neutropenia	11 (13%)	8 (10%)
Thrombocytopenia	11 (13%)	10 (12%)
Nausea	10 (12%)	1 (1%)
Pneumonia	10 (12%)	9 (11%)
Dysgeusia	9 (11%)	0

Source: FDA analysis
[1] Includes grouped terms (see Appendix 13.3)

The incidence of diarrhea, decreased appetite, and pyrexia were similar before and after 90 days of therapy on the glasdegib+LDAC arm. For the TEAEs of anemia, hemorrhage, fatigue, thrombocytopenia, nausea, pneumonia, and dysgeusia, incidence dropped after 90 days of therapy. Incidence of muscle spasms increased after 90 days.

Reviewer comments: All-grade and grade 3 or higher TEAEs were less common overall following 90 days of therapy. However, some notable Hh drug class side effects persisted, including diarrhea, fatigue, dysgeusia, and muscle spasms. Most side effects were either similar or lower in incidence following 90 days of therapy, but the incidence of muscle spasms increased slightly, which is consistent with the lab analysis of CPK in Section 8.4.6 below.

Glasdegib+LDAC pool

An analysis of TEAEs by dose was performed on the glasdegib+LDAC pool, including patients treated with glasdegib in combination with LDAC from all phases of B1371003 and B1371005 (glasdegib 100 mg + LDAC [n=107] and glasdegib 200 mg + LDAC [n=6]). All-grade and grade 3+ TEAEs in ≥ 10% of the patients by dose are listed in Table 35 below.

Table 35: Glasdegib+LDAC Pool – AEs Occurring in ≥ 10% of Patients

	Glasdegib 100 mg + LDAC (n=107)		Glasdegib 200 mg + LDAC (n=6)	
Preferred Term[1]	All grades	Grade 3+	All grades	Grade 3+
Hemorrhage	**45 (42%)**	**10 (9%)**	**4 (67%)**	**0**
Anemia	44 (41%)	41 (38%)	1 (17%)	1 (17%)
Fatigue	**42 (39%)**	**19 (18%)**	**2 (33%)**	**2 (33%)**
Febrile neutropenia	**39 (36%)**	**39 (36%)**	**3 (50%)**	**3 (50%)**
Nausea	**38 (36%)**	**2 (2%)**	**4 (67%)**	**1 (17%)**
Thrombocytopenia	34 (32%)	34 (32%)	1 (17%)	1 (17%)
Diarrhea	33 (31%)	5 (5%)	2 (33%)	0
Musculoskeletal pain	**33 (31%)**	**4 (4%)**	**2 (33%)**	**1 (17%)**
Edema	32 (30%)	0	1 (17%)	0
Muscle spasms	**32 (30%)**	**5 (5%)**	**3 (50%)**	**1 (17%)**

Pyrexia	**32 (30%)**	**2 (2%)**	**1 (17%)**	**1 (17%)**
Constipation	**30 (28%)**	**1 (1%)**	**3 (50%)**	**0**
Decreased appetite	**30 (28%)**	**3 (3%)**	**2 (33%)**	**1 (17%)**
Dysgeusia	**30 (28%)**	**0**	**4 (67%)**	**0**
Pneumonia	30 (28%)	25 (23%)	1 (17%)	0
Rash	**28 (26%)**	**2 (2%)**	**3 (50%)**	**0**
Abdominal pain	27 (25%)	1 (1%)	1 (17%)	0
Cough	26 (24%)	0	1 (17%)	0
Dyspnea	26 (24%)	11 (10%)	0	0
Mucositis	26 (24%)	2 (2%)	2 (33%)	0
Renal insufficiency	**24 (22%)**	**6 (6%)**	**3 (50%)**	**0**
Neutropenia	23 (22%)	18 (17%)	0	0
Weight decreased	**20 (19%)**	**2 (2%)**	**1 (17%)**	**1 (17%)**
Dizziness	**19 (18%)**	**1 (1%)**	**2 (33%)**	**0**
QT interval prolongation	19 (18%)	13 (12%)	0	0
Vomiting	**19 (18%)**	**2 (2%)**	**2 (33%)**	**1 (17%)**
Chest pain	16 (15%)	3 (3%)	0	0
Atrial arrhythmia	15 (14%)	3 (3%)	1 (17%)	0
Hepatic injury	15 (14%)	5 (5%)	1 (17%)	0
Hypokalemia	**15 (14%)**	**5 (5%)**	**3 (50%)**	**1 (17%)**
Sepsis	15 (14%)	12 (11%)	1 (17%)	0
Headache	14 (13%)	0	1 (17%)	0
White blood cell count decreased	14 (13%)	12 (11%)	0	0
Hyponatremia	13 (12%)	6 (6%)	0	0
Hypotension	**13 (12%)**	**4 (4%)**	**3 (50%)**	**2 (33%)**
Insomnia	13 (12%)	0	0	0
Fall	**11 (10%)**	**1 (1%)**	**2 (33%)**	**2 (33%)**

Source: FDA analysis
[1] Includes grouped terms (see Appendix 13.3)
Note: All-cause TEAEs ≥ 10% more frequent on the glasdegib 200 mg + LDAC arm and grade ≥ 3 TEAEs ≥ 5% more frequent on the glasdegib 200 mg + LDAC arm are indicated in bold print.

Reviewer comments: The results of this analysis demonstrate that many TEAEs were more common in patients treated with glasdegib 200 mg + LDAC than in patients treated with glasdegib 100 mg + LDAC. Not surprisingly, many of the TEAEs more common in patients treated with 200 mg glasdegib + LDAC included Hh class side effects including fatigue, nausea, musculoskeletal pain, muscle spasms, dysgeusia, renal insufficiency, weight loss, and vomiting. Given the small patient population in the 200 mg glasdegib+LDAC cohort of Study B1371003, it is not possible to draw any firm conclusions on TEAEs that were less common in this cohort. Overall, the AE profile appears to be more manageable with glasdegib 100 mg + LDAC, supporting the selection of this lower dose in combination with LDAC.

Heme monotherapy pool

Safety data from Studies B1371001 (n=47), B1371005 (n=13), and B1371013 (n=21) were pooled by dose to investigate the safety of glasdegib monotherapy in patients with hematologic malignancies. All-grade TEAEs in ≥ 10% of patients, with at least 2 or more patients with each TEAE by dose, are listed in Table 36 below.

Table 36: Glasdegib Heme Monotherapy Pool by Dose (mg) – AEs Occurring in ≥ 10% of Patients

PT[1]	5 (n=3)	10 (n=3)	20 (n=4)	25 (n=3)	40 (n=4)	50 (n=4)	80 (n=8)	100 (n=27)	120 (n=3)	180 (n=3)	270 (n=5)	400 (n=9)	600 (n=5)
Dysgeusia	0	0	1 (25%)	1 (33%)	2 (50%)	3 (75%)	3 (38%)	18 (67%)	0	1 (33%)	1 (20%)	3 (33%)	2 (40%)
Muscle spasms	0	0	0	1 (33%)	0	3 (75%)	2 (25%)	15 (56%)	1 (33%)	0	2 (40%)	3 (33%)	1 (20%)
Alopecia	0	1 (33%)	1 (25%)	0	1 (33%)	2 (50%)	1 (13%)	10 (37%)	0	0	1 (20%)	2 (22%)	2 (40%)
Decreased appetite	0	0	1 (25%)	0	3 (75%)	3 (75%)	1 (13%)	10 (37%)	2 (67%)	1 (33%)	2 (40%)	6 (67%)	4 (80%)
Fatigue	0	2 (67%)	4 (100%)	0	3 (75%)	2 (50%)	2 (25%)	9 (33%)	3 (100%)	1 (33%)	4 (80%)	4 (44%)	4 (80%)
Musculoskeletal pain	0	2 (67%)	1 (25%)	0	4 (100%)	2 (50%)	3 (38%)	9 (33%)	3 (100%)	0	2 (40%)	4 (44%)	2 (40%)
Rash	1 (33%)	0	1 (25%)	0	2 (50%)	2 (50%)	1 (13%)	8 (30%)	1 (33%)	0	1 (20%)	0	0
Constipation	2 (67%)	0	1 (25%)	0	2 (50%)	3 (75%)	2 (25%)	6 (22%)	0	0	0	2 (22%)	1 (20%)
Pyrexia	0	0	2 (50%)	1 (33%)	1 (33%)	3 (75%)	1 (13%)	6 (22%)	0	1 (33%)	3 (60%)	1 (11%)	2 (40%)
Weight decreased	0	1 (33%)	0	0	0	2 (50%)	1 (13%)	6 (22%)	1 (33%)	0	1 (20%)	2 (22%)	2 (40%)
Anemia	2 (67%)	2 (67%)	4 (100%)	0	0	1 (25%)	4 (50%)	5 (19%)	0	0	1 (20%)	1 (11%)	2 (40%)
Hyperuricemia	1 (33%)	0	0	0	0	0	0	5 (19%)	1 (33%)	0	0	0	2 (40%)
Thrombocytopenia	3 (100%)	0	1 (25%)	0	1 (33%)	2 (50%)	3 (38%)	4 (15%)	1 (33%)	0	1 (20%)	0	2 (40%)
Hemorrhage	2 (67%)	2 (67%)	1 (25%)	1 (33%)	1 (25%)	3 (75%)	6 (75%)	4 (15%)	2 (67%)	3 (100%)	2 (40%)	3 (33%)	1 (20%)
Abdominal pain	0	0	1 (25%)	0	2 (50%)	2 (50%)	2 (25%)	4 (15%)	1 (33%)	0	1 (20%)	6 (67%)	4 (80%)
Cough	0	0	1 (25%)	0	0	1 (25%)	1 (13%)	4 (15%)	0	0	1 (20%)	1 (11%)	1 (20%)
Dyspnea	1 (33%)	0	1 (25%)	0	2 (50%)	0	2 (25%)	4 (15%)	1 (33%)	2 (67%)	2 (40%)	3 (33%)	3 (60%)
Nausea	0	0	1 (25%)	1 (33%)	2 (50%)	1 (25%)	1 (13%)	4 (15%)	1 (33%)	3 (100%)	1 (20%)	6 (67%)	2 (40%)
Edema	2 (67%)	1	2 (50%)	1 (33%)	2 (50%)	1 (25%)	2 (25%)	3 (11%)	1 (33%)	0	1 (20%)	3 (33%)	3 (60%)
Dehydration	1 (33%)	0	1 (25%)	0	0	1 (25%)	2 (25%)	3 (11%)	0	0	1 (20%)	4 (44%)	1 (20%)
Diarrhea	1 (33%)	1 (33%)	0	0	2 (50%)	3 (75%)	1	3 (11%)	1 (33%)	0	3 (60%)	5 (56%)	2 (40%)
Hepatic injury	0	0	1 (25%)	0	0	1 (25%)	1 (13%)	3 (11%)	0	1 (33%)	2 (40%)	2 (22%)	0
Neutropenia	1 (33%)	0	1 (25%)	0	0	0	1 (13%)	3 (11%)	0	0	0	0	0
QT interval	1 (33%)	0	0	0	0	0	0	3 (11%)	0	0	1 (20%)	4	3

PT[1]	5 (n=3)	10 (n=3)	20 (n=4)	25 (n=3)	40 (n=4)	50 (n=4)	80 (n=8)	100 (n=27)	120 (n=3)	180 (n=3)	270 (n=5)	400 (n=9)	600 (n=5)
prolongation												(44%)	(60%)
Upper respiratory tract infection	0	1 (33%)	0	2 (67%)	1 (25%)	1 (25%)	1 (13%)	3 (11%)	0	0	1 (20%)	0	0
Blood CPK increased	0	0	0	1 (33%)	0	0	0	2 (7%)	0	0	0	0	0
Chest pain	0	0	0	0	0	1 (25%)	0	2 (7%)	0	0	0	1 (11%)	1 (20%)
Dizziness	0	1 (33%)	0	0	0	0	0	2 (7%)	1 (33%)	0	0	1 (11%)	2 (40%)
Dry mouth	1 (33%)	0	1 (25%)	0	0	0	1 (13%)	2 (7%)	0	0	0	1 (11%)	0
Fall	1 (33%)	0	0	0	0	1 (25%)	0	2 (7%)	0	0	0	0	0
Herpesvirus infection	0	0	1 (25%)	0	0	0	0	2 (7%)	0	0	0	0	1 (20%)
Insomnia	0	0	0	0	0	0	0	2 (7%)	0	0	0	2 (22%)	1 (20%)
Mucositis	1 (33%)	0	0	0	1 (25%)	1 (25%)	3 (38%)	2 (7%)	2 (67%)	1 (33%)	1 (20%)	4 (44%)	2 (40%)
Dental disorder	0	2 (67%)	0	1 (33%)	0	1 (25%)	0	1 (4%)	1 (33%)	0	0	1 (11%)	0
Confusion	1 (33%)	0	0	0	0	0	0	1 (4%)	0	0	0	1 (11%)	0
Failure to thrive	0	0	0	0	0	0	0	1 (4%)	0	0	0	1 (11%)	0
Fungal infection	0	0	0	1 (25%)	0	0	2 (25%)	1 (4%)	1 (33%)	1 (33%)	0	2 (22%)	0
Gastroesophageal reflux disease	0	0	0	0	0	0	1 (13%)	1 (4%)	0	0	0	0	1 (20%)
Headache	0	0	0	0	0	1 (25%)	1 (13%)	1 (4%)	1 (33%)	0	1 (20%)	5 (56%)	0
Hyperglycemia	0	0	1 (25%)	0	0	0	1 (13%)	1 (4%)	0	0	1 (20%)	2 (22%)	0
Hypersensitivity	0	0	0	1 (25%)	0	1 (25%)	0	1 (4%)	1 (33%)	0	0	0	1 (20%)
Hypoalbuminemia	0	0	0	0	0	1 (25%)	0	1 (4%)	0	0	1 (20%)	0	0
Hypokalemia	1 (33%)	0	0	0	0	2 (50%)	0	1 (4%)	0	0	1 (20%)	1 (11%)	1 (20%)
Leukocytosis	1 (33%)	1 (33%)	1 (25%)	0	1 (33%)	1 (25%)	5 (63%)	1 (4%)	0	0	1 (20%)	1 (11%)	1 (20%)
Mental status changes	0	0	0	0	0	0	0	1 (4%)	0	0	1 (20%)	1 (11%)	0
Pneumonia	1 (33%)	0	1 (25%)	2 (67%)	1 (25%)	0	2 (25%)	1 (4%)	0	1 (33%)	0	1 (11%)	1 (20%)
Respiratory failure	0	0	1 (25%)	0	0	0	0	1 (4%)	1 (33%)	0	2 (40%)	1 (11%)	0
Vomiting	0	1 (33%)	0	0	2 (50%)	0	2 (25%)	1 (4%)	2 (67%)	1 (33%)	1 (20%)	4 (44%)	1 (20%)
Anxiety	0	0	0	0	0	0	0	0	0	0	0	2 (22%)	1 (20%)
Pollakiuria	2 (67%)	0	0	0	0	0	0	0	0	0	0	0	0
Atrial arrhythmia	0	0	0	1 (25%)	0	0	0	0	0	0	1 (20%)	2 (22%)	2 (40%)
Cellulitis	1 (33%)	0	1 (25%)	0	0	0	0	0	2 (67%)	0	1 (20%)	0	0
Febrile neutropenia	0	1 (33%)	2 (50%)	0	0	0	2 (25%)	0	1 (33%)	2 (67%)	1 (20%)	3 (33%)	1 (20%)
Hypertension	0	0	1 (25%)	0	0	0	0	0	1 (33%)	0	0	1	1

PT[1]	5 (n=3)	10 (n=3)	20 (n=4)	25 (n=3)	40 (n=4)	50 (n=4)	80 (n=8)	100 (n=27)	120 (n=3)	180 (n=3)	270 (n=5)	400 (n=9)	600 (n=5)
												(11%)	(20%)
Hypomagnesemia	1 (33%)	0	0	0	1 (33%)	0	1 (13%)	0	0	0	0	1 (11%)	1 (20%)
Hypophosphatemia	1 (33%)	0	0	0	0	1 (25%)	1 (13%)	0	0	0	2 (40%)	1 (11%)	0
Hypotension	0	0	0	0	0	0	0	0	0	1 (33%)	0	0	1 (20%)
Neuropathy	0	0	0	0	0	0	1 (13%)	0	0	1 (33%)	0	0	0
Palpitations	0	0	1 (25%)	0	0	0	0	0	0	0	0	0	2 (40%)
Renal insufficiency	0	0	0	0	1 (25%)	2 (50%)	1 (13%)	0	0	0	2 (40%)	1 (11%)	2 (40%)
Sepsis	1 (33%)	0	2 (50%)	1 (33%)	0	0	2 (25%)	0	1 (33%)	2 (67%)	2 (40%)	1 (11%)	0
Urinary tract infection	0	0	1 (25%)	0	0	1 (25%)	0	0	1 (33%)	0	0	2 (22%)	2 (40%)
Ventricular arrhythmia	0	0	0	0	0	0	0	0	0	0	0	0	2 (40%)

Source: FDA analysis
[1] Includes grouped terms (see Appendix 13.3)

Reviewer comments: There was no clear dose response with febrile neutropenia, indicating that this TEAE was more likely disease-related, as opposed to treatment-related.

Interestingly, dental issues were noted starting from very low dose levels, which is consistent with the predicted effects on bone and teeth in the rat toxicology studies (Section 4.4). The total incidence across doses was 7/81 (9%). PTs included dental caries, loose tooth, sensitivity of teeth, tooth fracture, and toothache.

Drug class related side effects, such as fatigue, musculoskeletal pain, muscle spasms, alopecia, diarrhea, dysgeusia, nausea, vomiting, weight loss, and renal insufficiency were relatively common across dose levels, but without a clear dose toxicity relationship. Of note, across dose levels, the incidence of alopecia was 21 (26%), which is higher than the incidence of 6% seen on the glasdegib+LDAC arm of the pivotal Study B1371003.

TEAEs that appeared to increase with dose included decreased appetite, arrhythmias, and QT interval prolongation.

Solid tumor monotherapy

Safety data from Study B1371002 (n=23) were analyzed to investigate the safety of glasdegib monotherapy in patients without hematologic malignancies. All-grade and grade 3 or higher TEAEs in ≥ 10% of patients are listed in Table 37 below. All dose levels, including 80 mg (n=4), 160 mg (n=4), 320 mg (n=7), and 640 mg (n=8) were pooled for this analysis.

Table 37: Glasdegib Solids Monotherapy Pool – AEs Occurring in ≥ 10% of Patients

	Glasdegib+LDAC (n=23)	
PT[1]	All grades	Grade 3+
Dysgeusia	15 (65%)	0
Fatigue	14 (61%)	1 (4%)
Decreased appetite	10 (43%)	1 (4%)
Diarrhea	10 (43%)	0
Nausea	9 (39%)	0
Abdominal pain	8 (35%)	3 (13%)
Dehydration	8 (35%)	2 (9%)
Dizziness	8 (35%)	1 (4%)
Hepatic injury	7 (30%)	2 (9%)
Alopecia	6 (26%)	0
Muscle spasm	6 (26%)	0
Musculoskeletal pain	6 (26%)	0
Vomiting	6 (26%)	0
Constipation	5 (22%)	1 (4%)
Dyspnea	5 (22%)	1 (4%)
Rash	5 (22%)	0
Insomnia	4 (17%)	0
Chills	3 (13%)	0
Cough	3 (13%)	0
Hyperglycemia	3 (13%)	1 (4%)
Hyponatremia	3 (13%)	3 (13%)
Hypotension	3 (13%)	0
Palpitations	3 (13%)	0
QT interval prolongation	3 (13%)	3 (13%)
Renal insufficiency	3 (13%)	0
Upper respiratory tract infection	3 (13%)	0
Weight decreased	3 (13%)	0

Source: FDA analysis
[1] Includes grouped terms (see Appendix 13.3)

Reviewer comments: Again, we can see the common theme of dysgeusia, fatigue, decreased appetite, nausea/vomiting, abdominal pain, dehydration, dizziness, alopecia, musculoskeletal pain/muscle spasms, QT interval prolongation, renal insufficiency, and weight decreased. In addition, we continue to see hyponatremia as a side effect, which will be explored further in Section 8.4.6.

Given that the monotherapy trials indicate a higher incidence of alopecia than reported on Study B1371003, I recommend inclusion of this ADR in Section 6.1 of the PI.

Lastly, it is notable that hematologic toxicities were not common in the solid tumor patient

population.

Healthy volunteers

Lastly, safety data from the healthy volunteer Studies B1371009 (n=6), B1371010 (n=14), B1371014 (n=35), B1371015 (n=12), B1371022 (n=12), B1371023 (n=36), and B1371026 (n=21) were pooled and analyzed to investigate the safety of glasdegib monotherapy in healthy individuals. Dose levels of glasdegib ranged from 50 mg to 300 mg. All grade TEAEs and moderate grade TEAEs in > 1 subject are listed in Table 38 below.

Table 38: Glasdegib Healthy Volunteer Studies – AEs Occurring in > 1 of Patients

	Glasdegib+LDAC (n=136)	
PT[1]	**All grades**	**Moderate grade**
Headache	17 (13%)	2 (1%)
Chromaturia	12 (9%)	0
Rash	9 (7%)	0
Hemorrhage	8 (6%)	1 (1%)
Abdominal pain	7 (5%)	0
Diarrhea	7 (5%)	0
Musculoskeletal pain	5 (4%)	3 (2%)
Vomiting	4 (3%)	2 (1%)
Chest pain	3 (2%)	0
Hepatic injury	3 (2%)	2 (1%)
Mucositis	3 (2%)	0
Ocular discomfort	3 (2%)	0
Abnormal dreams	2 (1%)	0
Dental disorder	2 (1%)	0
Dizziness	2 (1%)	0
Fatigue	2 (1%)	0
Muscle spasm	2 (1%)	1 (1%)
Palpitations	2 (1%)	1 (1%)
Presyncope	2 (1%)	1 (1%)

Source: FDA analysis
[1] Includes grouped terms (see Appendix 13.3)

Of 136 healthy volunteers treated with glasdegib, 72 (53%) experienced any TEAE and 13 (10%) experienced a moderate TEAE.

Reviewer comments: Based on the healthy volunteer data, headache, mucositis, and hepatic injury appear to be true ADRs of glasdegib. Hepatic injury will be addressed in Section 8.4.6 below.

The dental disorders included PTs of tooth fracture and toothache. Given that dental disorders have been seen across studies, I recommend that the PI include dental disorders in Section 6, even though the incidence was below the 10% cutoff for Study B1371003.

Of note, the AE of chromaturia was identified only in healthy patients treated with rifampin, which has a known effect on body fluid discoloration. Therefore, chromaturia is not a true ADR of glasdegib.

Of note, the hemorrhage grouped term included PTs of ecchymosis, epistaxis, hemotochezia, hemoptysis, and vessel puncture site bruise/hematoma/hemorrhage in the healthy volunteers. Bleeding appears to be a true ADR of glasdegib, although the incidence was lower on the glasdegib+LDAC arm of the randomized Study B1371003, compared to the LDAC arm.

Again, we see the same ADRs of rash, abdominal pain, nausea, vomiting, diarrhea, musculoskeletal pain, muscle spasms, and fatigue.

8.4.6Laboratory Findings

For standard clinical laboratory test results, the applicant provided summaries of shifts in toxicity grade from baseline to worst treatment-emergent value. The following observations were made on laboratory parameters of interest in the phase 2 portion of Study B1371003.

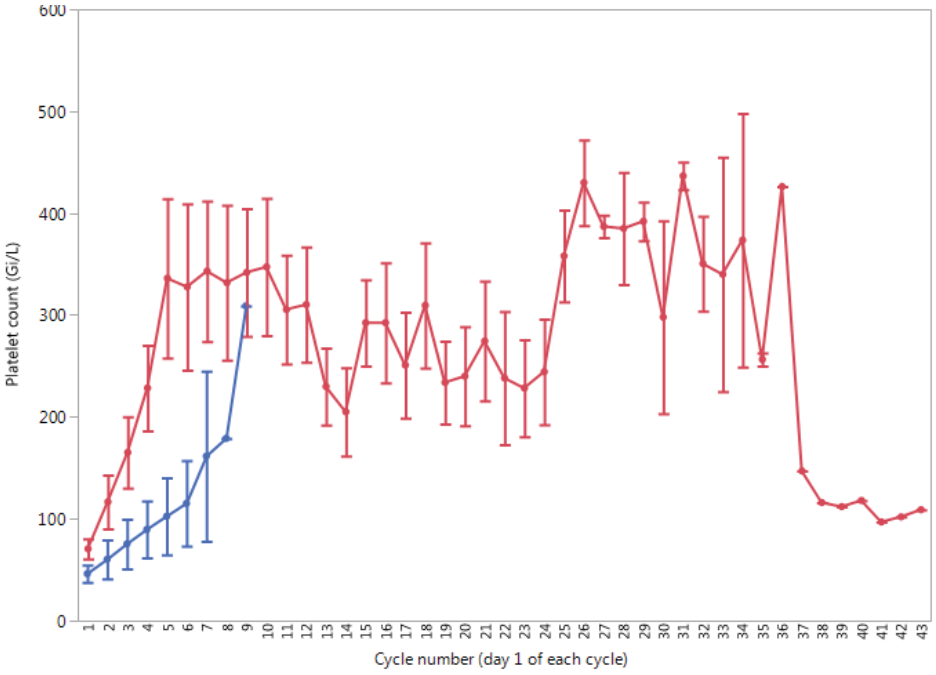
Complete blood count results

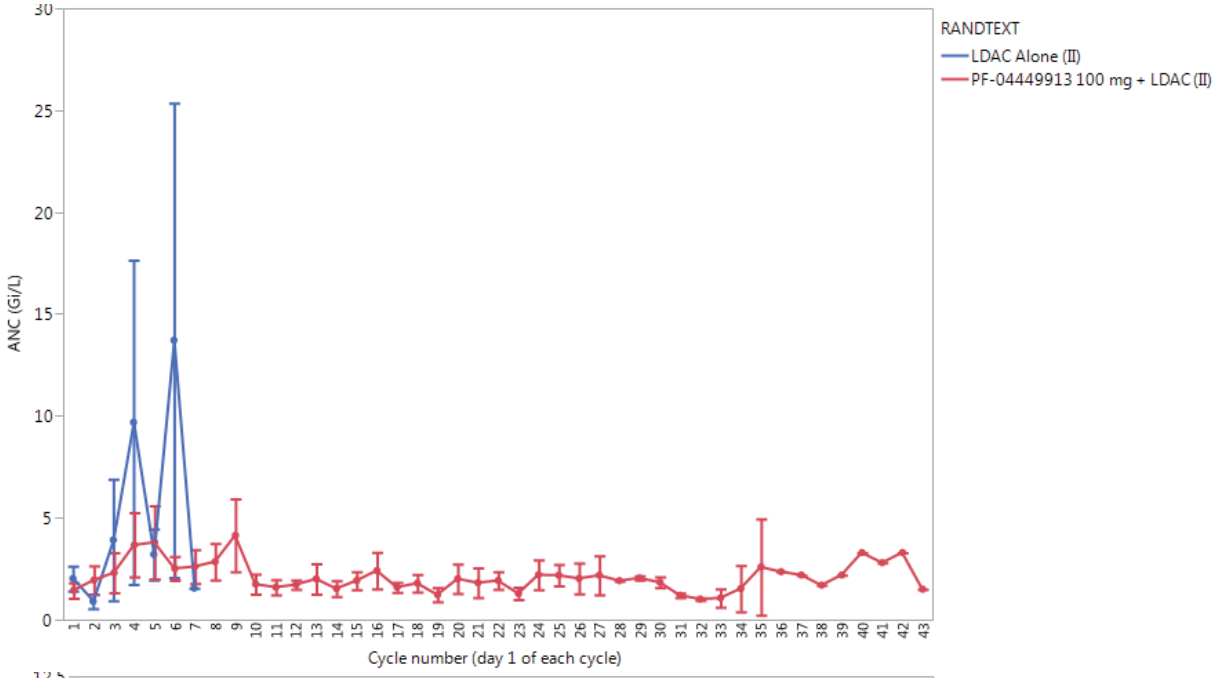
- All-grade anemia and thrombocytopenia occurred in 100% of patients on both the glasdegib+LDAC arm and the LDAC arm
- Shifts from grade ≤ 2 anemia to grade 3 were seen in 63% of patients on both arms
- Shifts from grade ≤ 2 platelet count decreased to grade 3 were seen in 11% of patients on the glasdegib+LDAC arm and 5% on the LDAC arm. Shifts to grade 4 were seen in 32% of patients on the glasdegib+LDAC arm and 20% on the LDAC arm.
- Lymphocyte count decreased in 85% of patients on the glasdegib+LDAC arm vs 68% of patients on the LDAC arm
- Shifts from grade ≤ 2 lymphocyte count decreased to grade 3 were seen in 26% of patients on the glasdegib+LDAC arm and 20% on the LDAC arm. Shifts to grade 4 were seen in 9% on the glasdegib+LDAC arm and 3% on the LDAC arm.
- Lymphocyte count increased in 21% of patients on the glasdegib+LDAC arm vs 33% of patients on the LDAC arm
- Shifts from grade ≤ 2 lymphocyte count increased to grade 3 were seen in 7% of patients on the glasdegib+LDAC arm and 3% on the LDAC arm.
- Neutrophil count decreased in 95% of patients on the glasdegib+LDAC arm vs 88% of patients on the LDAC arm

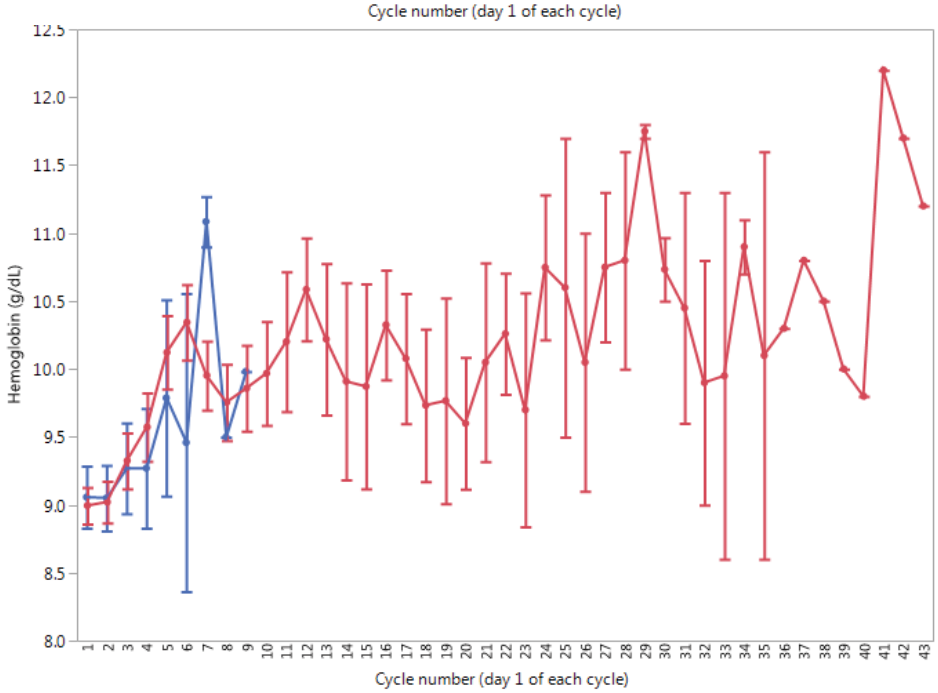
- Shifts from grade ≤ 2 neutrophil count decreased to grade 3 were seen in 7% of patients on the glasdegib+LDAC arm and 8% on the LDAC arm. Shifts to grade 4 were seen in 17% on the glasdegib+LDAC arm and 20% on the LDAC arm.
- WBC decreased in 88% of patients on the glasdegib+LDAC arm v 83% of patients on the LDAC arm
- Shifts from grade ≤ 2 WBC count decreased to grade 3 were seen in 20% of patients on the glasdegib+LDAC arm and 35% on the LDAC arm. Shifts to grade 4 were seen in 16% on the glasdegib+LDAC arm and 15% on the LDAC arm.

FDA performed an analysis of changes in hematologic parameters over time in the lab value versus cycle in Figure 6.

Figure 6: Mean (±SE) Platelets (Gi/L), ANC (Gi/L), and Hemoglobin (g/L) for Study B1371003







Reviewer comments: The hematologic lab value versus time graphs are biased because over time, the denominator is enriched for patients who are responding to glasdegib+LDAC. However, it appears that there is no significant treatment-related adverse impact of glasdegib+LDAC on blood counts.

FDA performed an analysis of ANC and platelet recovery in responders (Table 39). No patients

on either arm met the definition of prolonged neutropenia, defined as neutrophils < 0.5 Gi/L lasting past cycle day 42 in the absence of active leukemia. Two patients out of 14 (14%) on the glasdegib+LDAC arm had an ANC of < 0.5 Gi/L for over 42 days, but neither had documented absence of leukemia yet at that time. Furthermore, two patients on the glasdegib+LDAC arm had platelets < 50 Gi/L for over 42 days, but again, neither had documented absence of leukemia yet at that time.

Table 39: Median (Range) Time in Days to Count Recovery in Patients with CR Response on Pivotal Study B1371003

Parameter	Glasdegib+LDAC (n=14)	LDAC (n=1)
ANC > 0.5 Gi/L	32 (21-57)[1]	10
ANC > 1 Gi/L	37 (21-61)[1]	30
Platelets > 50 Gi/L	23 (10-140)	23
Platelets > 100 Gi/L	33 (21-170)	23

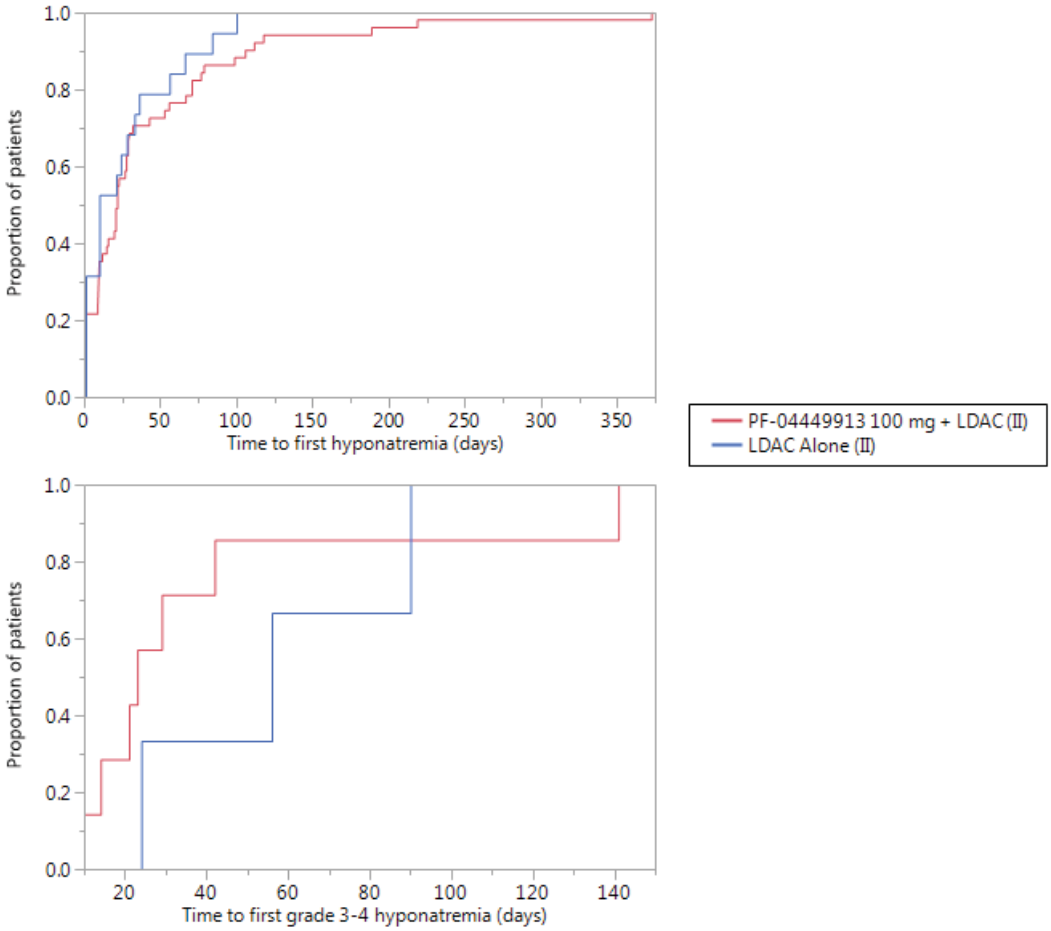
FDA Analysis
[1]Subject (b) (6) never dropped their ANC below 1 Gi/L and was excluded from the analysis.

Reviewer comments: The time to ANC and platelet recovery with glasdegib+LDAC is favorable for a non-intensive AML therapy. The LDAC arm only had one CR response, so comparison to the LDAC arm does not provide much information.

Hyponatremia

- Time to first all-grade hyponatremia occurred at median of 22 days (95% CI 10-29 days) on the combination arm versus 10 days (95% CI 1-33) on the LDAC alone arm.
- Time to first grade 3-4 hyponatremia occurred at median of 23 days (95% CI 10-42 days) on the combination arm versus 56 days (95% CI 24-90) on the LDAC alone arm.

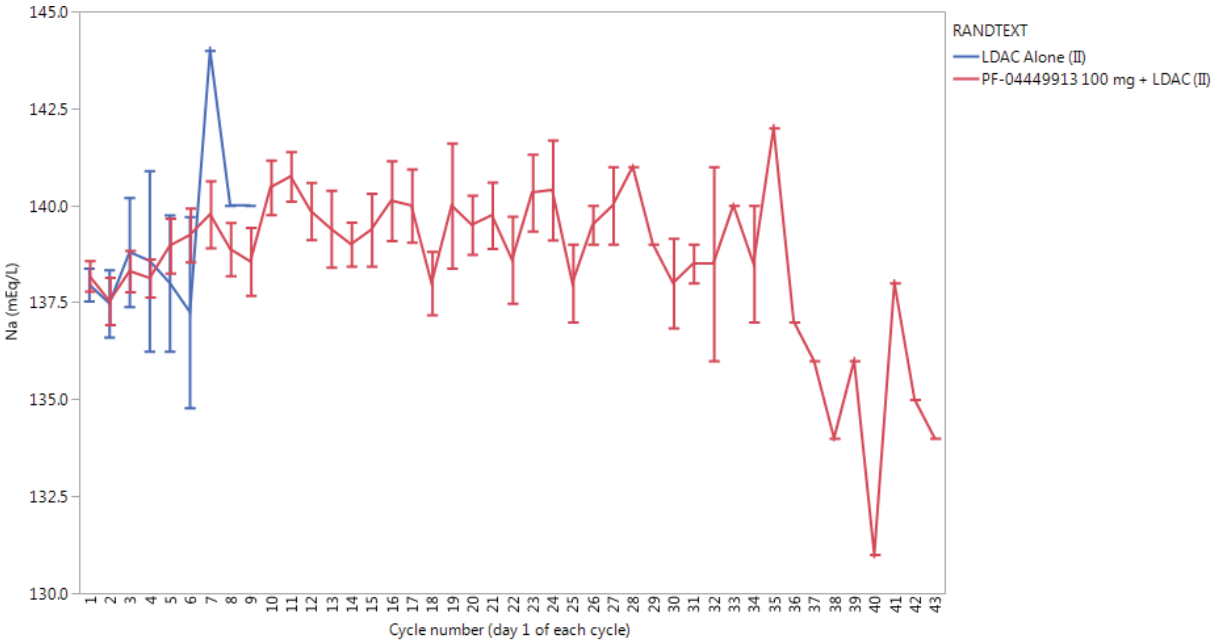
Figure 7: Time to First All-Grade and Grade 3+ Hyponatremia on Study B1371003



Source: FDA analysis

- Of 81 patients on the combination arm with post-baseline sodium data, 63% experienced all-grade decreases in sodium versus 44% of the 39 patients on the LDAC arm
- Grade 3-4 decreases in sodium occurred in 7% of patients on the combination arm versus 8% of patients on the LDAC arm
- Mean sodium levels were roughly stable over the course of therapy, as seen in Figure 8 below, except for one patient late in the course of therapy

Figure 8: Mean (± SE) Sodium (mg/dL) Over Time on Study B1371003



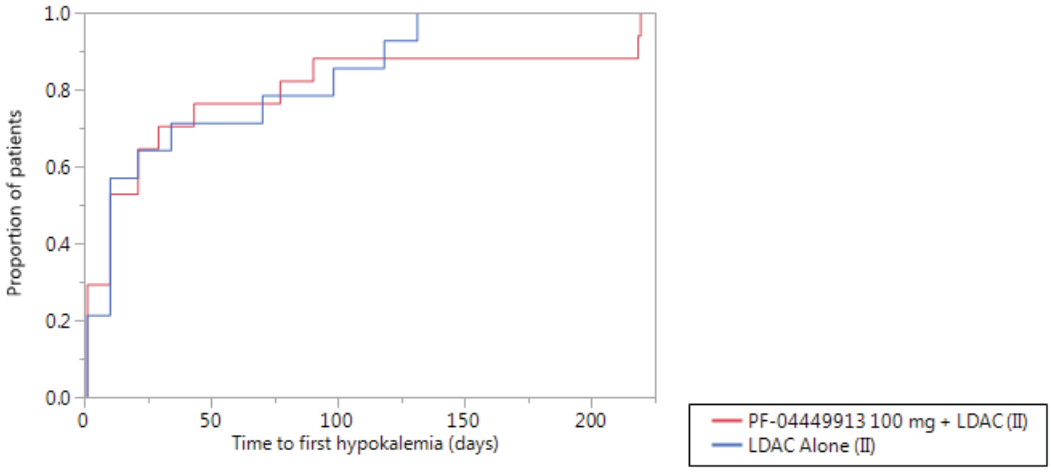
Source: FDA analysis

Reviewer comments: Time to first all-grade and grade 3+ hyponatremia was within 1-2 months of starting therapy. Levels remained relatively constant over the course of therapy. Sodium levels should be routinely monitored for at least the first 2 months of therapy.

Hypokalemia

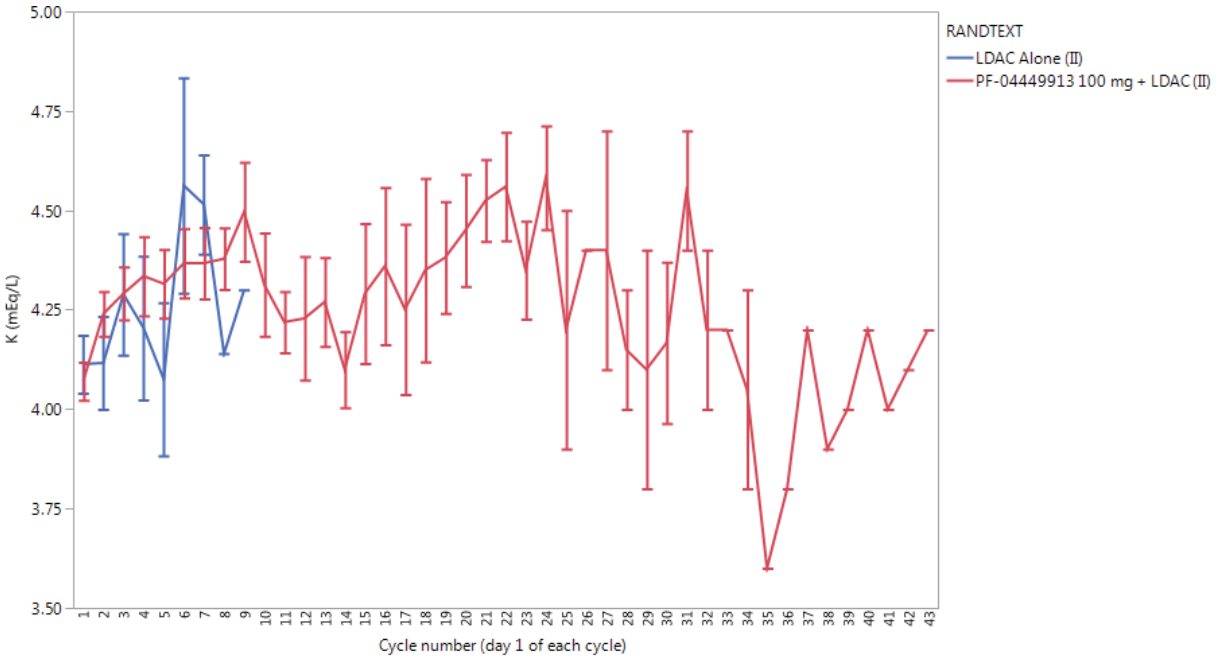
- Time to first all-grade hypokalemia occurred at median of 10 days (95% CI 1-43 days) on the combination arm versus 10 days (95% CI 1-70) on the LDAC alone arm.
- Grade 3-4 hypokalemia only occurred in 1 patient per arm at 136 days on the combination arm and 131 days on the LDAC alone arm.

Figure 9: Time to First All-Grade Hypokalemia on Study B1371003



- Of 81 patients on the combination arm with post-baseline potassium data, 17% experienced all-grade decreases in potassium versus 30% of 40 patients on the LDAC arm
- Grade 3-4 decreases in potassium occurred in 1% of patients on the combination arm versus 3% of patients on the LDAC arm
- Mean potassium levels remained above 4 over the course of the trial, as seen in Figure 10 below, except for one patient late in the course of therapy

Figure 10: Mean (± SE) Potassium (mg/dL) Over Time on Study B1371003



Source: FDA analysis

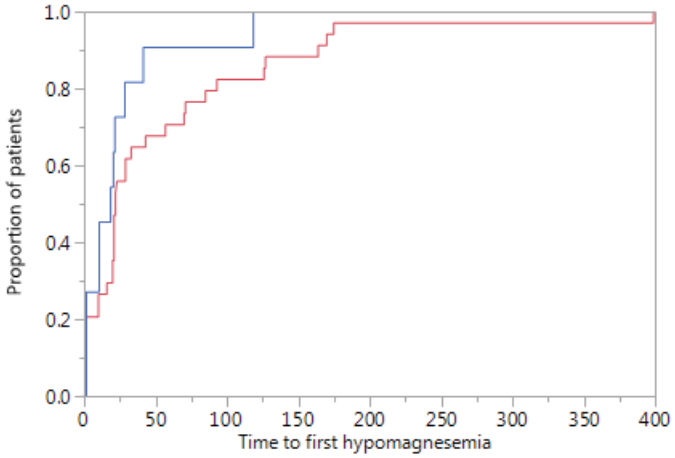
FDA comments: The median time to first decrease in potassium on the combination arm was

within 1 month, but the first grade 3-4 elevation (only 1 patient) was not until after the fourth month of therapy. Notwithstanding, mean levels were mostly above 4 over the course of therapy. Given the potential for QTc prolongation with glasdegib, it may be prudent to monitor potassium for at least the first 3 months of therapy.

Hypomagnesemia

- Time to first all-grade hypomagnesemia occurred at median of 22 days (95% CI 20-43 days) on the combination arm versus 18 days (95% CI 1-28) on the LDAC alone arm.
- Grade 3-4 hypomagnesemia only occurred in 1 patient per arm at 263 days on the combination arm and 256 days on the LDAC alone arm.

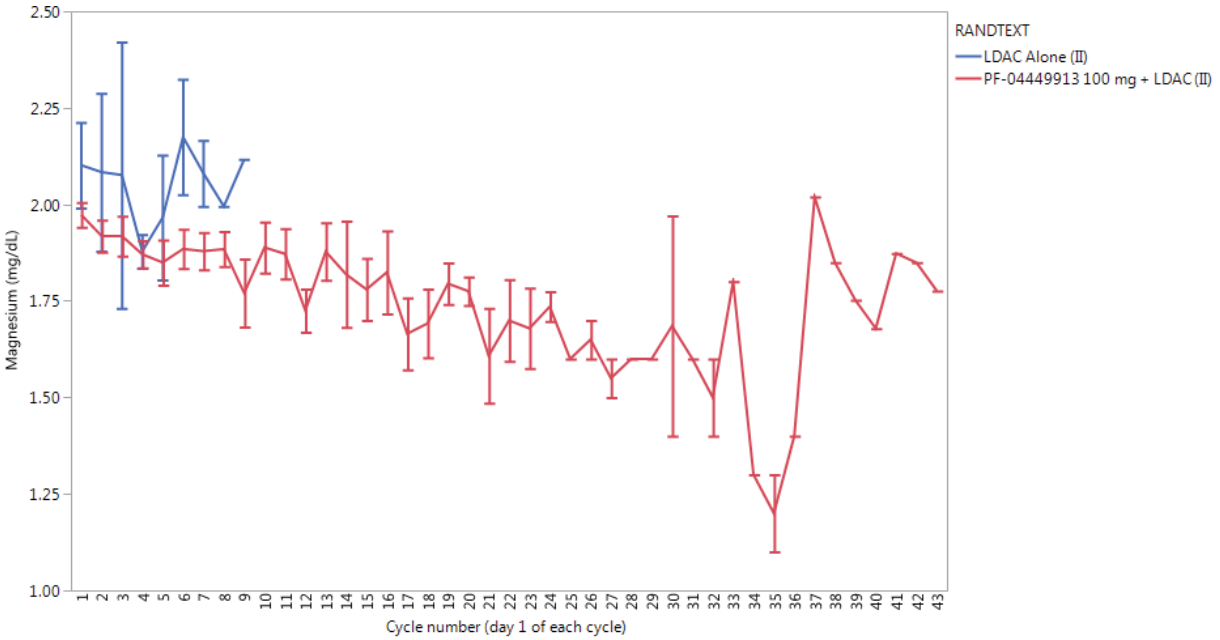
Figure 11: Time to First All-Grade Hypomagesemia on Study B1371003



Source: FDA analysis

- Of 81 patients on the combination arm with post-baseline magnesium data, 42% experienced all-grade decreases in magnesium versus 26% of 39 patients on the LDAC arm.
- Grade 3-4 decreases in magnesium occurred in 1% of patients on the combination arm versus 3% of patients on the LDAC arm.
- Mean magnesium levels were mostly below 2 mg/dL over the course of the trial, as seen in Figure 12 below.

Figure 12: Mean (± SE) Magnesium (mg/dL) Over Time on Study B1371003

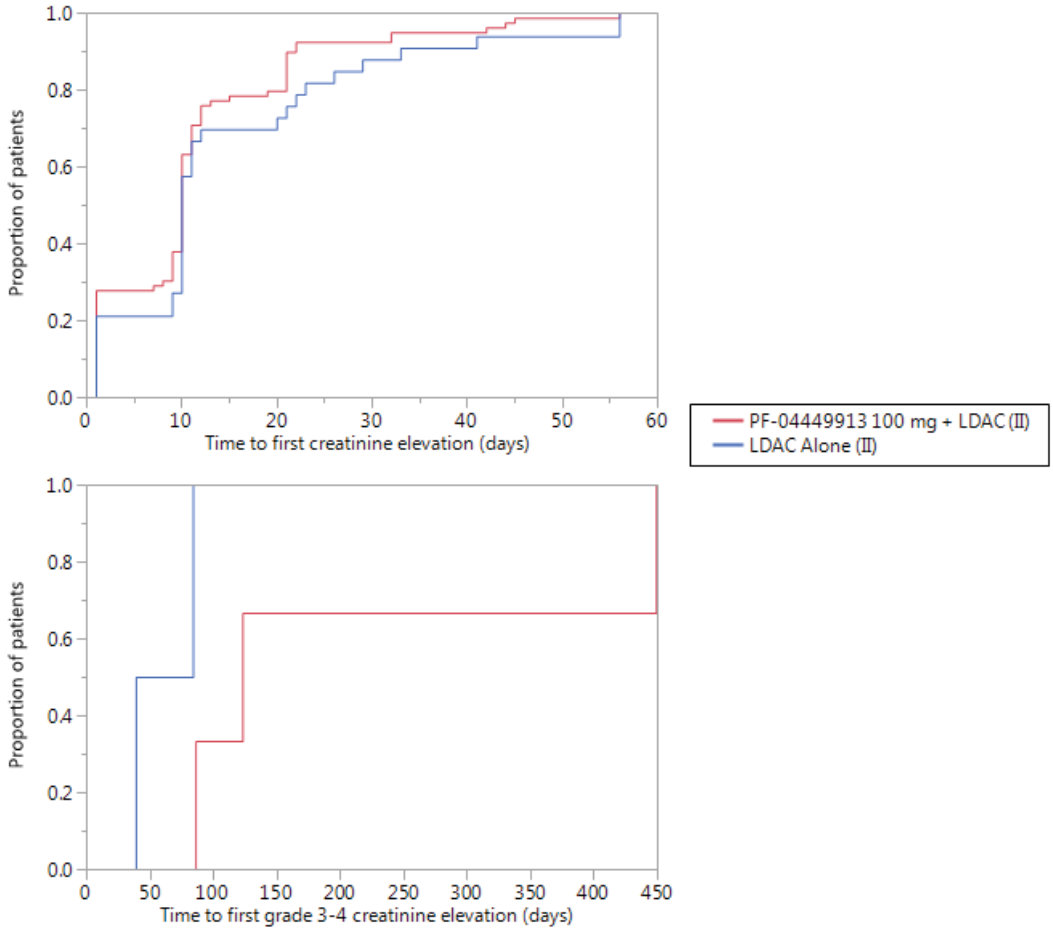


Reviewer comments: Time to first event of all-grade hypomagnesemia was within the first month or 2 of therapy. Only one patient had a grade 3 decrease in magnesium on both arms. However, it is concerning that mean magnesium levels were lower on the treatment arm over the course of therapy, with most mean levels on day 1 of each cycle being below 2 mg/dL. Monitoring monthly electrolytes, including magnesium levels, may be prudent given the risk of QTc prolongation with glasdegib.

Creatinine

- Time to first creatinine elevation above the upper range of normal was a median of 10 days (95% CI 10-11 days) on the combination therapy arm and also 10 days on the LDAC arm
- Time to first grade 3+ creatinine elevation was a median of 123 days (95% CI 86-449 days) on the combination therapy arm versus 62 days (95% CI 39-84 days) on the LDAC arm

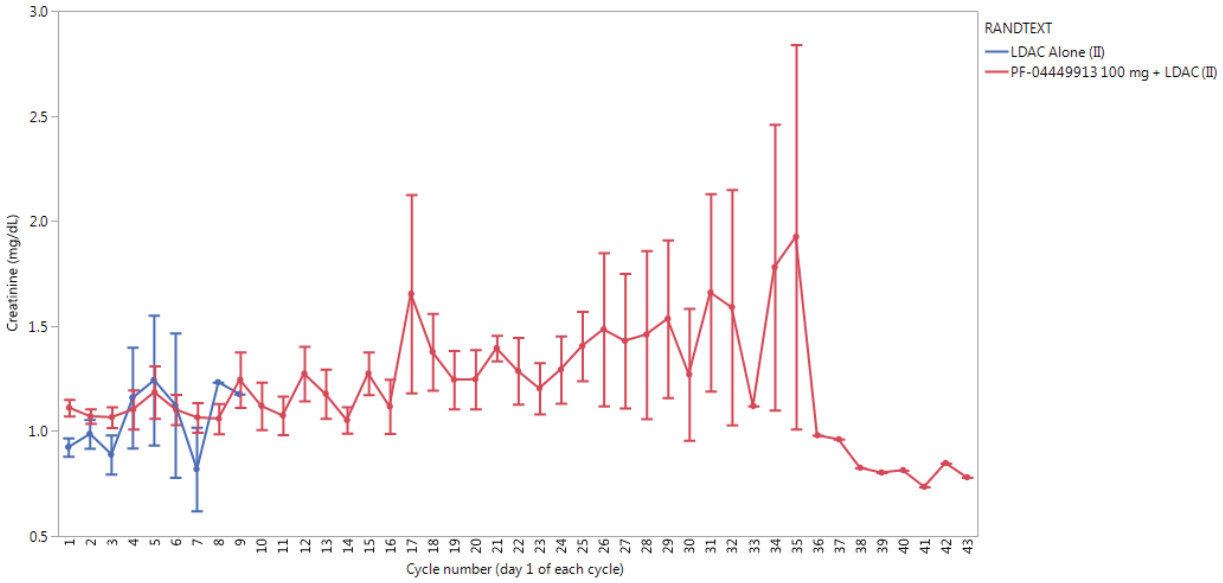
Figure 13: Time to First All-Grade and Grade 3+ Creatinine Elevation on Study B1371003



Source: FDA analysis

- Of 81 patients on the combination arm with post-baseline creatinine data, 96% experienced all-grade elevations in creatinine versus 80% of the 40 patients on the LDAC arm.
- Grade 3-4 elevations in creatinine occurred in 3.7% of patients on the combination arm versus 5% of patients on the LDAC arm.
- Mean creatinine levels were elevated at various time points over the course of therapy, as seen in Figure 14 below.

Figure 14: Mean (± SE) Creatinine (mg/dL) Over Time on Study B1371003



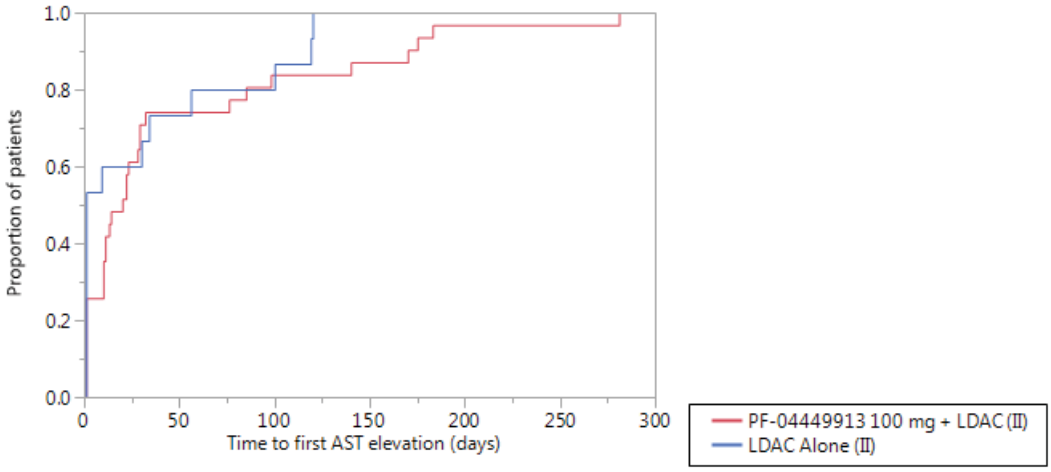
Source: FDA analysis

Reviewer comments: While the time to first creatinine elevation was only 10 days, the time to first grade 3+ creatinine elevation was much longer at 123 days. This matches the data in Figure 14 ***above showing elevations in mean creatinine throughout the course of therapy. Therefore, once monthly monitoring while on therapy would be prudent.***

AST

- Time to first AST elevation above the upper limit of normal was a median of 20 days (95% CI 10-29 days) on the combination therapy arm and 1 day (95% CI 1-34 days) on the LDAC arm.
- Grade 3-4 AST elevation only occurred in 2 patients on the combination arm at 32 and 191 days. No patients on the LDAC alone arm had a grade 3-4 elevation in AST.

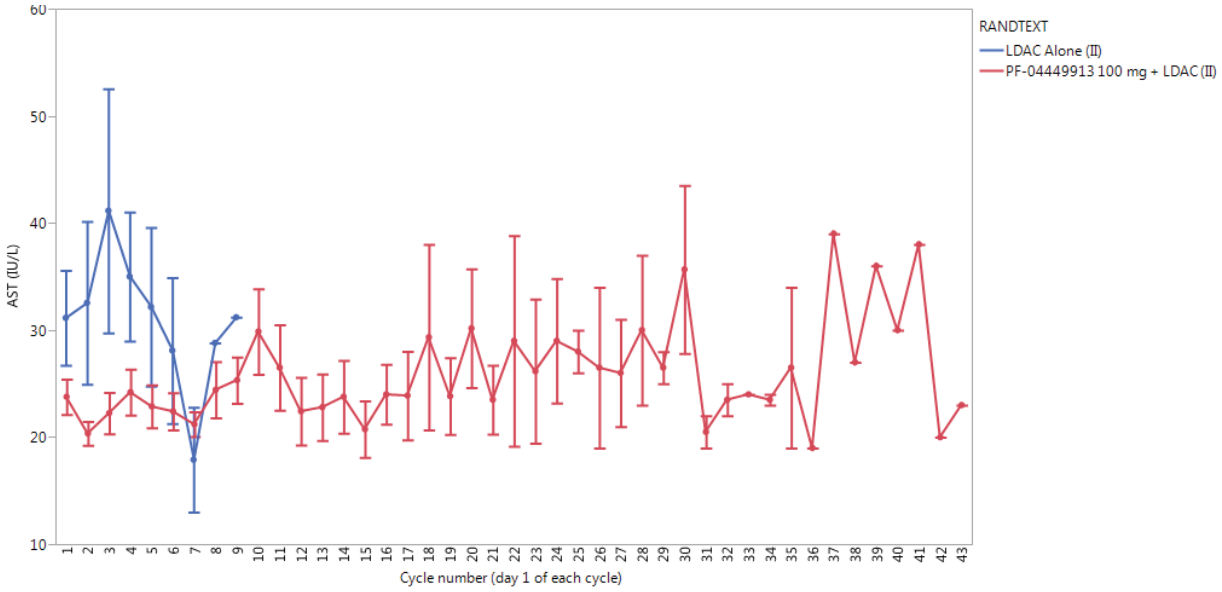
Figure 15: Time to First All-Grade AST Elevation on Study B1371003



Source: FDA analysis

- Of 80 patients on the combination arm with post-baseline AST data, 36% experienced all-grade elevations in AST versus 30% of the 40 patients on the LDAC arm.
- Grade 3-4 elevations in AST occurred in 3% of patients on the combination arm versus 0% of patients on the LDAC arm.
- Mean AST levels were relatively consistent over the course of therapy, as seen in Figure 16 below.

Figure 16: Mean (± SE) AST (IU/L) Over Time on Study B1371003

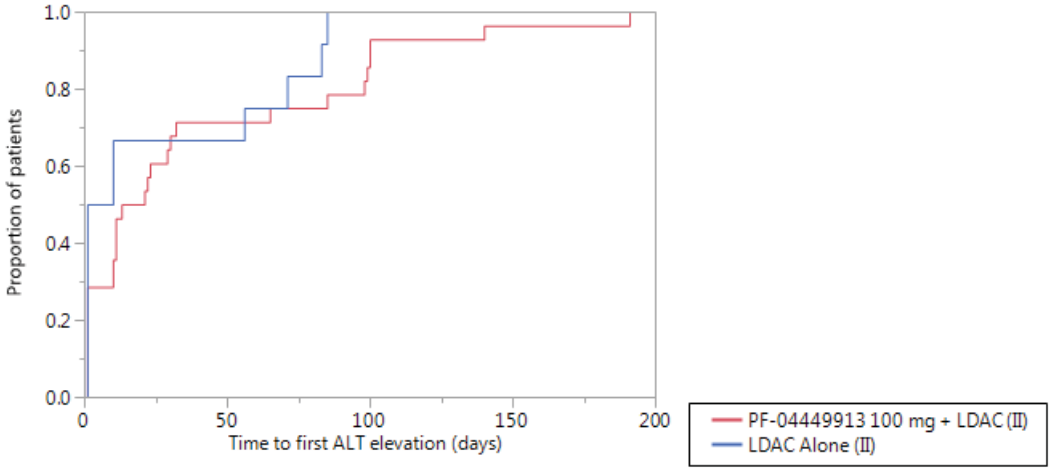


Source: FDA analysis

ALT

- Time to first ALT elevation above the upper limit of normal was a median of 17 days (95% CI 10-30 days) on the combination therapy arm and 6 days (95% CI 1-71 days) on the LDAC arm.
- Grade 3-4 ALT elevation only occurred in 2 patients on the combination arm at 91 and 163 days. One patient on the LDAC alone arm had a grade 3-4 elevation in ALT at 30 days.

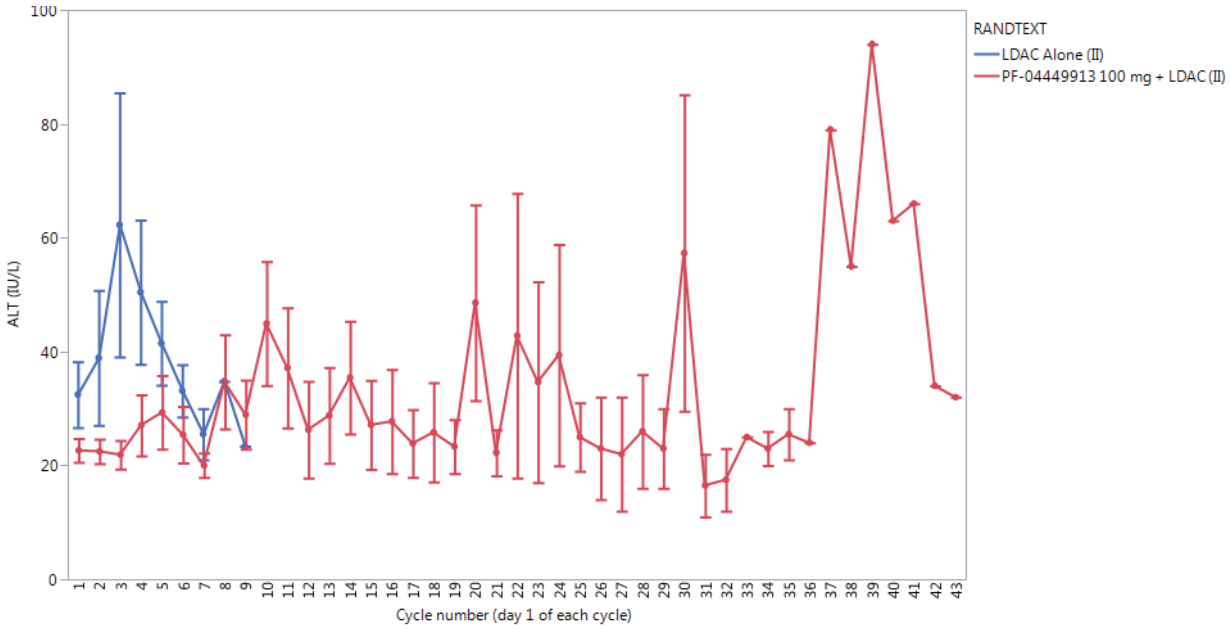
Figure 17: Time to First All-Grade ALT Elevation on Study B1371003



Source: FDA analysis

- Of 80 patients on the combination arm with post-baseline ALT data, 31% experienced all-grade elevations in ALT versus 28% of the 40 patients on the LDAC arm.
- Grade 3-4 elevations in ALT occurred in 3% of patients on both the combination arm and the LDAC arm.
- Mean ALT levels were relatively consistent over the course of therapy, as seen in Figure 18 below.

Figure 18: Mean (± SE) ALT (IU/L) Over Time on Study B1371003

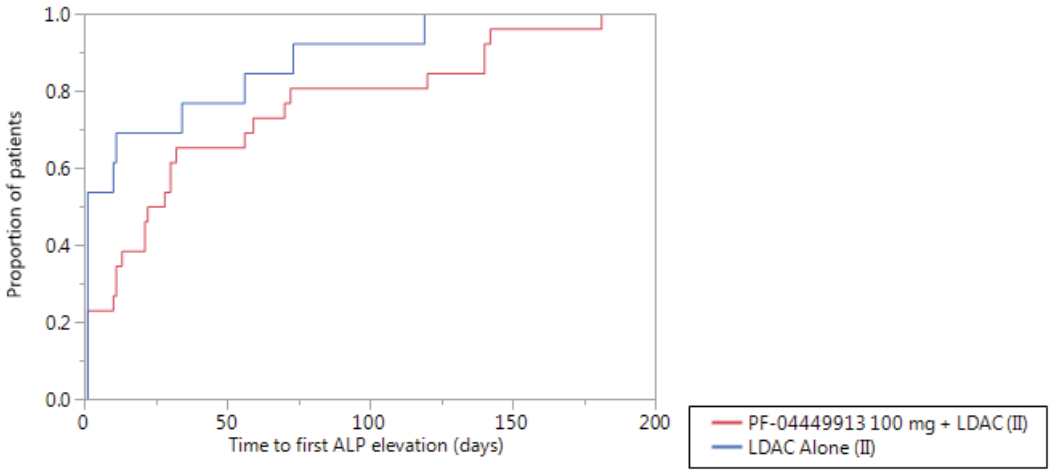


Source: FDA analysis

Alkaline Phosphatase (ALP)

- Time to first ALP elevation above the upper limit of normal was a median of 25 days (95% CI 11-56 days) on the combination therapy arm and 1 day (95% CI 1-34 days) on the LDAC arm.
- No patients on the combination arm and only 1 patient on the LDAC arm had a grade 3-4 elevation in ALP. The patient on the LDAC arm had the elevation on day 63.

Figure 19: Time to First All-Grade ALP Elevation on Study B1371003



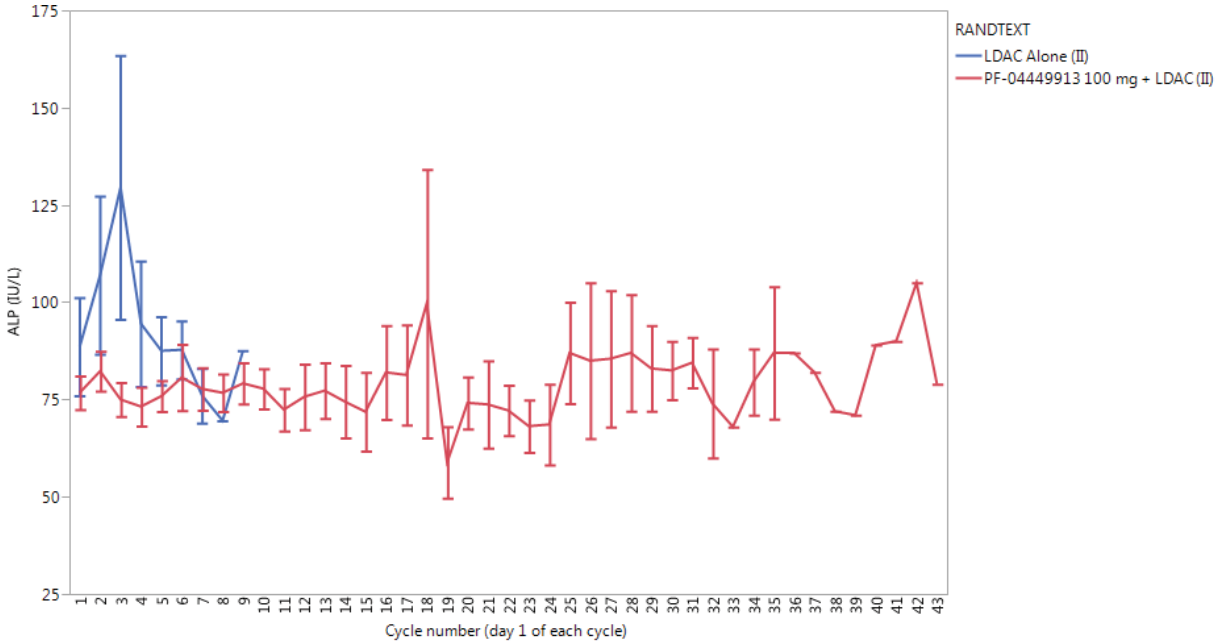
Source: FDA analysis

- Of 80 patients on the combination arm with post-baseline ALP data, 29% experienced all-

grade elevations in ALP versus 30% of the 40 patients on the LDAC arm.

- Grade 3-4 elevations in ALP occurred in 0% of patients on both the combination arm and 3% of patients on the LDAC arm.
- Mean ALP levels were relatively consistent over the course of therapy, as seen in Figure 20 below.

Figure 20: Mean (± SE) ALP (IU/L) Over Time on Study B1371003

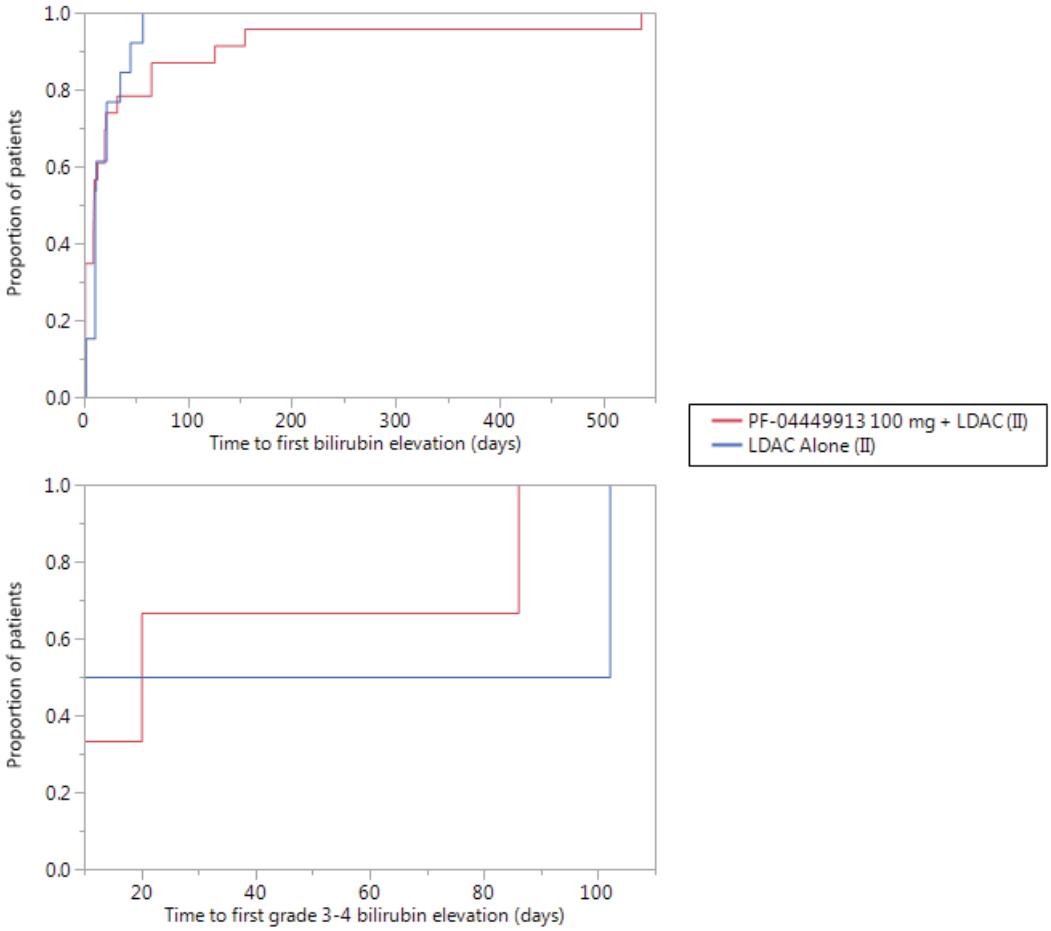


Source: FDA analysis

Bilirubin

- Time to first total bilirubin elevation was a median of 10 days (95% CI 1-20 days) on the combination therapy arm and 10 days (95% CI 10-21 days) on the LDAC arm.
- Time to first grade 3+ bilirubin elevation was a median of 20 days (95% CI 10-86 days) on the combination therapy arm versus 56 days (95% CI 10-102 days) on the LDAC arm.

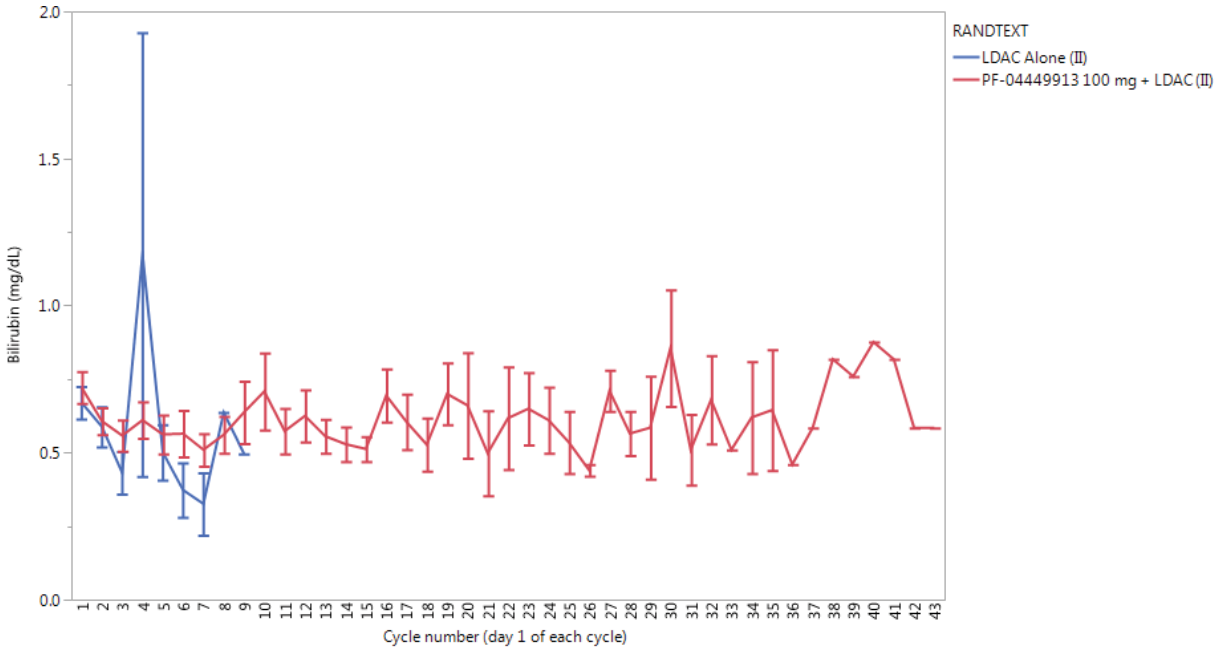
Figure 21: Time to First All-Grade and Grade 3+ Bilirubin Elevation on Study B1371003



Source: FDA analysis

- Of 80 patients on the combination arm with post-baseline total bilirubin data, 29% experienced all-grade elevations in bilirubin versus 33% of the 39 patients on the LDAC arm.
- Grade 3-4 elevations in bilirubin occurred in 4% of patients on the combination arm and 5% of patients on the LDAC arm.
- Mean bilirubin levels were relatively consistent over the course of therapy, as seen in Figure 22 below.

Figure 22: Mean (± SE) Bilirubin (IU/L) Over Time on Study B1371003



Source: FDA analysis

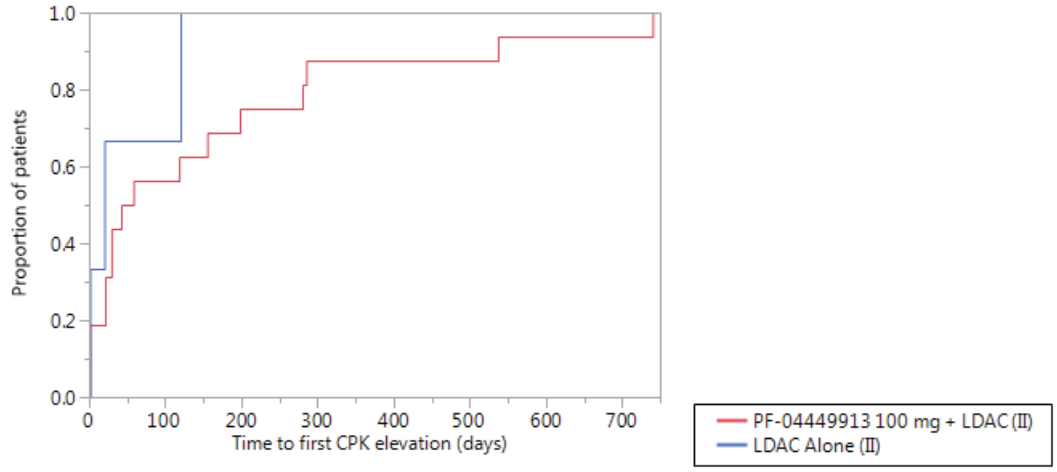
Reviewer comments: Median time to first elevation in liver function tests occurred within the first month of treatment on the combination therapy arm. Mean liver function test levels were relatively stable, without signs of clinically significant elevations over the course of therapy. Therefore, would only recommend monitoring liver function tests for at least the first month of therapy.

Of note, there were no Hy's law cases on the pivotal Study B1371003.

CPK

- Time to first total CPK elevation was a median of 50 days (95% CI 21-198 days) on the combination therapy arm and 20 days (95% CI 1-120 days) on the LDAC arm.
- No grade 3-4 elevations in CPK occurred on either treatment arm.

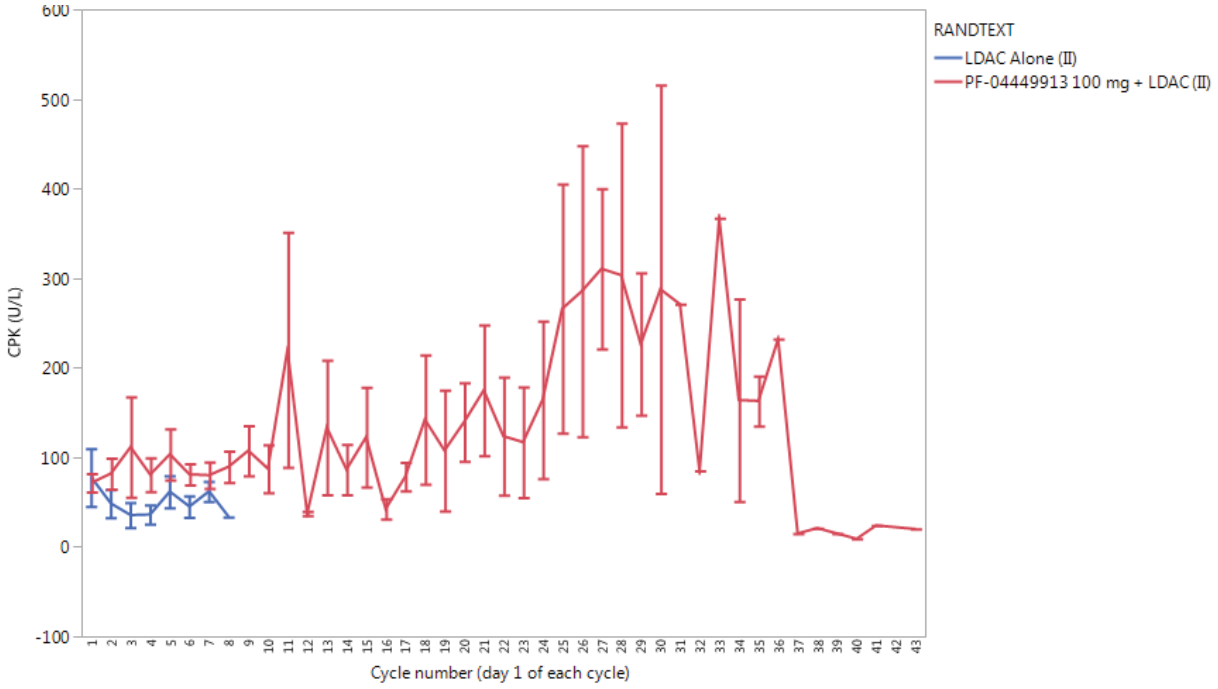
Figure 23: Time to First All-Grade and Grade 3+ CPK Elevation on Study B1371003



Source: FDA analysis

- Of 51 patients on the combination arm with post-baseline total CPK data, 28% experienced all-grade elevations in CPK versus 11% of the 19 patients on the LDAC arm.
- The maximum CPK observed on the combination therapy arm was 988 U/L.
- Mean CPK levels appeared to increase slightly over the course of therapy, as seen in Figure 24 below.

Figure 24: Mean (± SE) CPK (IU/L) Over Time on Study B1371003



Source: FDA analysis

Reviewer comments: It is concerning that CPK elevations occurred over the course of therapy and appeared to increase over time. However, no grade 3-4 elevations occurred. Therefore, I do not think that routine monitoring is required, but I agree with inclusion of this lab abnormality in Section 6 of the label. Should include instructions in Section 2 to do reflexive testing in patients with muscle cramping/pain.

8.4.7Vital Signs

The applicant did not identify any unexpected trends or clinically meaningful post-baseline findings in vital sign parameters. The most common AEs (≥ 5%) associated with vital signs on the glasdegib+LDAC arm vs LDAC arm on pivotal Study B1371003 were pyrexia (18% vs 22%), hypotension (6% vs 10%), and weight decreased (13% vs 2%).

Clinically significant changes in blood pressure and heart rate were not observed (Study B1371003 CSR Table 14.3.4.2.2.1.2). However, consistent with the common ADR of weight decreased, the mean weight in kg decreased by 1.3 kg from baseline on the glasdegib+LDAC arm vs 0.2 kg on the LDAC arm. After 2 cycles, the mean change was -2.8 vs -1.6 kg, respectively. Following 3 cycles, the mean change was -4.3 vs -2.2 kg. Following 6 cycles, the mean change was -4.8 vs +0.2 kg.

Reviewer comments: Based on the frequent ADR of weight decreased, supported by the vital sign data, I agree with the Applicant's proposal to include weight decreased in Section 6 of the PI.

8.4.8Electrocardiograms (ECGs)

ECGs on the pivotal Study B1371003 were obtained at least at baseline, on cycle 1 day 1 (pre-dose, 1 and 4 hours post-dose), cycle 1 day 10 (1 and 4 hours post-dose), cycles 2 and 3 day 1 (1 and 4 hours post-dose), and at the end of treatment.

Atrial arrhythmias (grouped term in Appendix 13.3) occurred at any time (before or after 90 days of therapy) in 12 (14%) of patients on the glasdegib+LDAC arm of pivotal Study B1371003 and in 3 (7%) of patients on the LDAC arm. PTs for atrial arrhythmias on the glasdegib+LDAC arm were atrial fibrillation (n=6), bradycardia (n=4), tachycardia (n=3), sinus tachycardia (n=2), bradycardia (n=2), and sinus bradycardia (n=2).

Reviewer comments: The findings of atrial arrhythmia are similar to what would be expected in the underlying patient population. No safety signal was identified for atrial arrhythmias on review of adverse events related to ECG findings.

Ventricular arrhythmias (grouped term in Appendix 13.3) on the pivotal portion of Study

B1371003 occurred in 2 (2%) of patients on the glasdegib+LDAC arm and none on the LDAC arm. A detailed analysis of these cases was presented in Section 8.4.4.

8.4.9QT

A detailed review of QT prolongation and ventricular arrhythmias is provided in Section 8.4.4 above.

8.4.10 Immunogenicity

Not applicable.

8.5 Analysis of Submission-Specific Safety Issues

8.5.1Embryo-fetal toxicity

Glasdegib was found to be teratogenic at the lowest doses tested in rats and rabbits in embryofetal developmental toxicity studies (Section 4.4). Thus, it will be important to notify prescribers that glasdegib should not be administered to pregnant women. FDA agrees with the Applicant's proposal to include a boxed warning for embryo-fetal toxicity. See Section 8.8.2 for further details.

8.5.2Musculoskeletal toxicity

Musculoskeletal pain, myalgias, and increased CPK are drug class effects of Hh inhibitors, and glasdegib is no exception. On pivotal Study B1371003, without regard to timing (before or after 90 days of therapy), 32 (38%) of patients on the glasdegib+LDAC arm reported musculoskeletal pain (4% grade ≥ 3) compared to 8 (20%) of the patients on the LDAC arm (5% grade ≥ 3). PTs for the grade 3 or higher events included back pain (n=2) and myalgia (n=1).

Similarly, 20 (24%) of the patients on the glasdegib+LDAC arm reported muscle spasms (5% grade ≥ 3) compared to 2 (5%) of the patients on the LDAC arm (0% ≥ grade 3). The muscle spasms increased beyond 90 days of therapy, with the incidence before and after 90 days on the glasdegib+LDAC arm 15% and 17% (0% and 5% grade ≥ 3), respectively.

While the musculoskeletal events were generally low-grade and did not prompt study treatment discontinuations, prescribers should be aware of these ADRs and consider checking CPK based on results presented in Section 8.4.6.

8.6 Safety Analyses by Demographic Subgroups

As the majority of patients on pivotal Study B1371003 were Caucasian, safety was not analyzed

by race or ethnicity. Furthermore, as most patients on the study were over age 65 years, an analysis of safety below and above the age of 65 years could not be conducted.

The Applicant conducted an analysis of TEAEs on pivotal Study B1371003 in patients < 75 (n=34) and ≥ 75 years (n=50) and found that the following TEAEs were > 10% more common in patients ≥ 75: constipation (32% vs 15%), decreased appetite (40% vs 24%), pneumonia (36% vs 18%), weight decreased (26% vs 9%), and rash (20% vs 6%). The following TEAEs were > 10% more common in patients < 75 years: anemia (53% vs 40%), diarrhea (35% vs 22%), vomiting (29% vs 16%), and WBC decreased (24% vs 10%). On the LDAC arm, TEAEs > 10% more common in patients ≥ 75 were as follows: pyrexia (29% vs 12%), thrombocytopenia (33% vs 18%), fatigue (25% vs 12%), headache (17% vs 6%), and decreased appetite (17% vs 6%).

The Applicant also conducted an analysis of TEAEs on pivotal Study B1371003 by sex. There were 66 male and 18 female patients on the glasdegib+LDAC arm and 24 male and 17 female patients on the LDAC alone arm. On the glasdegib+LDAC arm, TEAEs >10% more common in women than men were as follows: diarrhea (44% vs 23%), anemia (56% vs 42%), nausea (61% vs 29%), pyrexia (44% vs 23%), thrombocytopenia (50% vs 26%), hyponatremia (28% vs 9%), hypokalemia (22% vs 12%), vomiting (33% vs 18%), WBC count decreased (33% vs 11%), abdominal pain (28% vs 14%), dyspnea (39% vs 21%), neutrophil count decreased (22% vs 11%), hypomagnesaemia (22% vs 6%), and back pain (28% vs 5%). On the LDAC arm, events >10% more common in women included: anemia (53% vs 33%), nausea (24% vs 4%), fatigue (29% vs 13%), thrombocytopenia (35% vs 21%), headache (24% vs 4%), vomiting (24% vs 0%), insomnia (12% vs 0%), dizziness (18% vs 4%), and sepsis (12% vs 4%).

The following TEAEs were > 10% more common in men than women on the glasdegib+LDAC arm: constipation (29% vs 11%), muscle spasms (27% vs 6%), and insomnia (11% vs 0%). The following TEAEs were > 10% more common in men than women on the LDAC arm: pneumonia (29% vs 18%) and dyspnea (38% vs 12%).

Reviewer comments: Safety by demographic subgroups showed that selected AEs were greater in patients over age 75, which may be expected for an older patient population (e.g. decreased appetite, pneumonia). However, certain AEs were more frequent in younger patients as well. Firm conclusions cannot be made based on the small sample size.

The analysis of safety by sex is limited by the smaller number of women on the glasdegib+LDAC arm. However, the trend appears to be more AEs in women than men with both glasdegib+LDAC and LDAC therapy. No firm conclusions on a true difference in safety by sex can be drawn from these analyses.

8.7 Specific Safety Studies/Clinical Trials

No studies or trials were conducted to evaluate a specific safety concern.

8.8 Additional Safety Explorations

8.8.1 Human Carcinogenicity or Tumor Development

Glasdegib was not genotoxic based on a standard battery of assays for mutagenicity and clastogenicity. Carcinogenicity studies have not been conducted given the intended treatment of patients with cancer (Section 4.4). Neoplasms (identified using the Neoplasms, Benign, Malignant and Unspecified SOC) were rare on pivotal Study B1371003. One patient (1%) on the glasdegib+LDAC arm and 2 (5%) on the LDAC arm developed a neoplasm. The one patient on the glasdegib+LDAC arm developed a basal cell carcinoma and the 2 patients on the LDAC arm developed a squamous cell carcinoma of skin and signet-ring cell carcinoma. Based on these data, no secondary cancer safety signal was identified.

8.8.2 Human Reproduction and Pregnancy

Similar to the other agents in the Hh inhibitor drug class, glasdegib was found to be embryotoxic, fetotoxic, and teratogenic in animals. However, there are no clinical data on the use of glasdegib in pregnant women. Fertility studies with glasdegib have not been conducted given the intended treatment of patients with advanced cancer. FDA agrees with the Applicant's proposal to include embryo-fetal toxicity as a boxed warning.

Reviewer comments: Based on the significant embryo-fetal concerns with the drug class and animal studies, I agree with the plan for a boxed warning for embryo-fetal toxicity. In addition, I recommend a post-marketing requirement (PMR) for a pregnancy pharmacovigilance study, similar to those required for the Hh inhibitors vismodegib and sonidegib.

8.8.3 Pediatrics and Assessment of Effects on Growth

The Applicant was granted Orphan Designation for glasdegib for the treatment of patients with AML and is therefore exempt from pediatric studies under the Pediatric Research Equity Act (PREA). There is no data on the safety of glasdegib in children. Furthermore, in repeat-dose toxicity studies in rats, oral administration of glasdegib resulted in adverse changes in growing bone, teeth, and testis. Effects on bone consisted of partial to complete closure of the epiphyseal plate. Effects in growing incisor teeth included degeneration/necrosis of ameloblasts, and complete tooth loss with oral ulceration. Furthermore, an investigation into post-marketing bone/tooth AEs with approved Hh inhibitors is detailed in Section 8.1.

Reviewer comments: Based on animal data suggesting detrimental effects of glasdegib on growth, (b) (4)
I agree with the Sponsor's inclusion of the cautionary animal data in Section 8.4 of the PI.

8.8.4 Overdose, Drug Abuse Potential, Withdrawal, and Rebound

The applicant did not provide any reported cases of overdose of glasdegib in the AML population. The highest dose of glasdegib studied in patients (n=8) was 640 mg on a continuous schedule in patients with solid tumors. The AEs most commonly reported at single doses > 270 mg were constipation, decreased appetite, diarrhea, dizziness, dysgeusia, dyspnea, fatigue, headache, and nausea (Study B1371002 Table 14.3.1.2.11.1 and B1371001 Table 14.3.1.2.11.2).

Analysis of TEAEs by dose in the heme monotherapy pool (Section 8.4.5) revealed a higher incidence of the grouped term QT interval prolongation with higher doses of glasdegib. Furthermore, in Study B1371001, 3 patients (1 patient in the 400 mg arm and 2 patients in the 600 mg arm) had a postbaseline maximum QTcF interval of ≥500 msec and in Study B1371002, 1 patient in the 320 mg arm had postbaseline QTcF interval ≥500 msec. Thus, FDA agrees with the Sponsor's proposal to recommend symptomatic management of glasdegib overdose and ECG monitoring in Section 10 of the PI.

Glasdegib does not have abuse potential.

8.9 Safety in the Postmarket Setting

8.9.1 Safety Concerns Identified Through Postmarket Experience

Not applicable.

8.9.2 Expectations on Safety in the Postmarket Setting

Safety in the postmarket setting is expected to be similar to that observed on the clinical trials reviewed in this Application.

8.9.3 Additional Safety Issues From Other Disciplines

No additional safety issues were identified by other disciplines.

8.10 Integrated Assessment of Safety

The primary data in support of safety for the proposed indication came from the randomized phase 2 portion of Study B1371003, in which 84 patients with previously untreated AML were exposed to glasdegib+LDAC and 41 were exposed to LDAC alone. The median duration of exposure to glasdegib+LDAC on this study was 2.7 months, with a maximum exposure time of 42.1 months. Data from an additional 249 patients and 136 healthy volunteers who were exposed to glasdegib across the development program were included in the integrated safety database.

Major safety events on the pivotal Study B1371003 are displayed in Table 40.

Table 40: Major Safety Events on Pivotal Study B1371003

Safety Event	Glasdegib+LDAC (N=84)	LDAC (N=41)
Total deaths	64 (76%)	40 (98%)
On-treatment deaths[1]	25 (30%)	17 (41%)
On-treatment fatal ARs[1]	6 (7%)	5 (12%)
30-day mortality[2]	5 (6%)	6 (15%)
TEAEs	84 (100%)	41 (100%)
TEAEs first 90 days	82 (98%)	41 (100%)
TEARs[3] first 90 days	78 (93%)	33 (80%)
TEAEs > 90 days	53 (63%)	--
TEARs[3] > 90 days	39 (46%)	--
Gr ≥ 3 TEAEs	78 (93%)	40 (98%)
Gr ≥ 3 TEAEs first 90 days	73 (87%)	37 (90%)
Gr ≥ 3 TEARs[3] first 90 days	52 (62%)	25 (61%)
Gr ≥ 3 TEAEs > 90 days	36 (43%)	--
Gr ≥ 3 TEARs[3] > 90 days	22 (26%)	--
TESAEs	64 (76%)	32 (78%)
TESARs[3]	50 (60%)	18 (44%)
All-cause discontinuation	81 (96%)	41 (100%)
TEAE with discontinuation	29 (35%)	18 (44%)
TEAR[3] with discontinuation	15 (18%)	5 (12%)

FDA Analysis
[1] On or within 28 days after the last dose of therapy
[2] Within 30 days following the first dose of therapy
[3] Includes all non-laboratory TEAEs in Table 33 except for atrial arrhythmia. Also includes ARs of alopecia, dental disorder, and fractures.

The study population was monitored for deaths, SAEs, common AEs, and common laboratory

tests. A thorough QT study was conducted. A total of 25 (30%) patients on the glasdegib+LDAC arm died during or within 28 days after study treatment, compared to 17 (41%) on the LDAC alone arm. The most frequent cause of death on both treatment arms was the primary disease. Treatment-related fatal ARs on the glasdegib+LDAC arm included sudden death, cardiac arrest, MI, pneumonia, and unknown (suspected ICH). Causes of treatment-related death on the LDAC arm were predominately caused by infection.

Glasdegib+LDAC was generally well-tolerated. The most common non-laboratory treatment-emergent ARs in the first 90 days of treatment (incidence ≥ 20% and ≥ 2% more frequent on the glasdegib+LDAC arm) were fatigue, febrile neutropenia, musculoskeletal pain, nausea, edema, decreased appetite, dysgeusia, mucositis, constipation, and rash. The most frequent Grade 3/4 ARs (incidence ≥ 10% and ≥ 2% more frequent on the glasdegib+LDAC arm) were fatigue, febrile neutropenia, and dyspnea. The most frequent serious AR in the first 90 days of therapy was febrile neutropenia, which occurred at a higher rate on the glasdegib+LDAC (25%) versus the LDAC arm (12%).

Muscle spasms were more noticeable beyond 90 days of therapy, with 17% incidence of all-grade muscle spasms and 5% incidence of grade 3 or higher muscle spasms. Other non-laboratory ARs occurring in ≥ 10% of the patients in the glasdegib+LDAC arm beyond 90 days of therapy were decreased appetite (17%), hemorrhage (17%), fatigue (15%), pyrexia (15%), nausea (12%), pneumonia (12%), and dysgeusia (11%). Most of these events were mild-moderate in severity, except for pneumonia (11% grade ≥ 3).

Discontinuation due to AR occurred in 18% of patients on the glasdegib+LDAC arm versus 12% on the LDAC alone arm. The most frequent ARs leading to discontinuation on the glasdegib+LDAC arm were pneumonia (6%), QT interval prolongation (5%), febrile neutropenia (4%), and nausea (2%).

Analysis of the glasdegib+LDAC pool from all phases of Study B1371003 and B1371005 supported the dose of 100 mg glasdegib in combination with LDAC given lower incidences in many TEAEs compared to patients treated with 200 mg glasdegib in combination with LDAC. The heme monotherapy pool, including Studies B1371001, B1371005, and B1371013, provided insight into TEAEs by dose level in patients treated with single agent glasdegib. TEAEs that appeared to increase with dose included decreased appetite, arrhythmias, and QT interval prolongation. Solid tumor monotherapy data from Study B1371002 demonstrated a lack of notable hematologic toxicities yet reported a higher incidence in alopecia than seen on Study B1371003. Lastly, the healthy volunteer data demonstrated evidence to support headache, mucositis, hepatic injury, bleeding, and dental disorders as ADRs of glasdegib.

Overall, given the historically poor survival in older patients with newly-diagnosed AML, the level of toxicity observed with glasdegib+LDAC is acceptable for the clinical benefit observed.

9 Advisory Committee Meeting and Other External Consultations

This Application was not presented to the Oncologic Drug Advisory Committee or any other external consultants.

10 Labeling Recommendations

10.1 Prescription Drug Labeling

The following are recommended major changes to the glasdegib PI proposed by the applicant based on this review:

- **1 INDICATIONS AND USAGE:** [redacted] (b) (4) Add a limitation of use: glasdegib should not be used as monotherapy in patients with AML.
- **2 DOSAGE AND ADMINISTRATION:** Add information on LDAC dosing.
- **2 DOSAGE MODIFICATION:** Add monitoring guidelines for labs and ECGs. Adjust dose modifications to more closely match the protocol.
- **5 WARNINGS AND PRECAUTIONS:** Add advice not to donate blood or blood products while taking glasdegib based on embryo-fetal toxicity concerns. Add information on ventricular arrhythmias in patients treated with glasdegib under "QTc Interval Prolongation."
- **6 ADVERSE REACTIONS:** Modify the tables of ARs and laboratory abnormalities to include only the first 90 days of therapy for better comparison between the treatment arms. Preferred terms should be grouped.
- **14 CLINICAL STUDIES:** [redacted] (b) (4)

10.2 Nonprescription Drug Labeling

Not applicable.

11 Risk Evaluation and Mitigation Strategies (REMS)

Given the favorable safety profile of glasdegib, there are no additional risk management strategies beyond recommended labeling. The Division of Risk Management in the Office of Surveillance and Epidemiology concurs with this assessment.

12 Postmarketing Requirements and Commitments

The Hh inhibitor drug class includes significant risks of teratogenicity. Glasdegib is embryotoxic, fetotoxic, and teratogenic in animals. Other approved smoothened inhibitors (vismodegib and sonidegib) had PMRs for pregnancy pharmacovigilance studies. I recommend a similar PMR for glasdegib using the proposed wording below.

A Pregnancy Pharmacovigilance Study to evaluate pregnancy outcomes and infant outcomes following exposure to Daurismo (glasdegib). This study will include a mechanism to collect, classify, and analyze data on direct exposures (women exposed to Daurismo (glasdegib) as treatment) and indirect exposures (women exposed to Daurismo (glasdegib) through the seminal fluid of a male partner). The Pregnancy Pharmacovigilance Study will be initiated and functioning at the time of product launch. There will be interim annual reporting of the data collected from the study. The study, at a minimum, will include the following key elements (see the Guidance for Industry Establishing Pregnancy Exposure Registries for a detailed description of these elements):

- Data collection of prospective and retrospective data points, adequate to produce informative, reliable data outcomes.

- Data analysis utilizing descriptive statistics for summarizing data that will fully capture outcomes of concern. Data collected prospectively analyzed separate from data collected retrospectively.

- Description of procedures including the patient recruitment, along with healthcare provider awareness of potential safety risk and existence of this study, and the monitoring of pregnancy and infant outcomes.

Each annual interim and final report should constitute a stand-alone report of cumulative pregnancy and infant outcomes data.

Desired milestones:

Annual Interim Report for nine years:	November 2019
	November 2020
	November 2021
	November 2022
	November 2023
	November 2024
	November 2025
	November 2026
	November 2027
Trial Completion:	November 2028
Final Report Submission:	November 2029

Reviewer comments: The PMR wording above was drafted by this reviewer and was only preliminary at the time this review was completed.

13 Appendices

13.1 References

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13.2 Financial Disclosure

Covered Clinical Study (Name and/or Number): Studies B1371001, B1371002, B1371003, B1371005, B1371009, B1371010, B1371012, B1371013, B1371023, B1371026

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from Applicant)
Total number of investigators identified: 868		
Number of investigators who are Sponsor employees (including both full-time and part-time		

employees): 15		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 25		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: 0 Significant payments of other sorts: 25 Proprietary interest in the product tested held by investigator: 0 Significant equity interest held by investigator in Sponsor of covered study: 0		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes ☒	No ☐ (Request details from Applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes ☒	No ☐ (Request information from Applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) 0		
Is an attachment provided with the reason:	Yes ☒	No ☐ (Request explanation from Applicant)

13.3 Grouped Preferred Terms

Grouped Term	Preferred Terms/Standardized MedDRA Queries
Abdominal pain	Abdominal discomfort, Abdominal pain, Abdominal pain lower, Abdominal pain upper, Abdominal tenderness, Gastrointestinal pain
Anemia	Anaemia, Anaemia of malignant disease, Erythropenia, Haematocrit decreased, Haemoglobin decreased, Red blood cell count decreased
Atrial arrhythmia	Arrhythmia, Arrhythmia supraventricular, Atrial fibrillation, Atrial flutter, Atrial tachycardia, Bradycardia, Junctional ectopic tachycardia, Nodal arrhythmia, Paroxysmal arrhythmia, Sinus arrhythmia, Sinus bradycardia, Sinus tachycardia, Supraventricular extrasystoles, Supraventricular tachyarrhythmia, Supraventricular tachycardia, Tachycardia, Tachycardia paroxysmal

Grouped Term	Preferred Terms/Standardized MedDRA Queries
Cardiac failure	Acute left ventricular failure, Cardiac failure, Cardiac failure acute, Cardiac failure congestive, Cardiac failure high output, Cor pulmonale, Diastolic dysfunction, Left ventricular dysfunction, Left ventricular failure, Systolic dysfunction
Cellulitis	Anorectal cellulitis, Breast cellulitis, Catheter site cellulitis, Cellulitis, Cellulitis of male external genital organ, Cellulitis orbital, Erysipelas, Injection site cellulitis, Periorbital cellulitis, Vaginal cellulitis, Vulval cellulitis
Chest pain	Angina pectoris, Chest discomfort, Chest pain, Non-cardiac chest pain
Clostridial infection	Clostridial infection, Clostridium colitis, Clostridium difficile colitis, Clostridium difficile infection
Conduction disorder	Atrioventricular block, Atrioventricular block complete, Atrioventricular block first degree, Atrioventricular block second degree, Bundle branch block right, Paroxysmal atrioventricular block
Cough	Cough, Productive cough, Upper airway cough syndrome
Dental disorder	Dental caries, Loose tooth, Sensitivity of teeth, Tooth fracture, Toothache
Diarrhea	Colitis, Diarrhea, Enteritis, Enterocolitis, Gastroenteritis, Neutropenic colitis
Dysgeusia	Dysgeusia, Hypogeusia, Ageusia
Dyspnea	Acute respiratory failure, Bronchospasm, Dyspnoea, Dyspnoea exertional, Hypoxia, Respiratory failure, Respiratory rate increased
Edema	Face oedema, Fluid overload, Fluid retention, Generalized oedema, Oedema, Oedema peripheral, Peripheral swelling, Swelling face
Eye irritation	Dry eye, Eye irritation, Eye pain, Eye pruritus, Keratitis
Fatigue	Asthenia, Fatigue
Fractures	Femur fracture, Foot Fracture, Fracture, Patella fracture, Spinal fracture, Thoracic vertebral fracture
Fungal infection	Anal candidiasis, Anal fungal infection, Aspergilloma, Aspergillosis oral, Aspergillus infection, Bladder candidiasis, Bronchopulmonary aspergillosis, Candida infection, Candida sepsis, Central nervous system fungal infection, Cerebral aspergillosis, Cerebral candidiasis, Cerebral fungal infection, Cryptococcal fungaemia, Fungaemia, Fungal infection, Fungal skin infection, Gastrointestinal candidiasis, Gastrointestinal fungal infection, Genital infection fungal, Hepatic candidiasis, Hepatosplenic candidiasis, Hepatic infection fungal, Mucocutaneous candidiasis, Nasal candidiasis, Oesophageal candidiasis, Oral candidiasis, Oral fungal infection, Oro-pharyngeal aspergillosis, Oropharyngeal candidiasis, Peritoneal candidiasis, Pneumonia fungal, Respiratory moniliasis, Sinusitis fungal, Splenic candidiasis, Splenic infection fungal, Systemic candida, Tongue fungal infection, Upper respiratory fungal infection, Vulvovaginal candidiasis, Vulvovaginal mycotic infection
Headache	Headache, Sinus headache
Hemorrhage	SMQ (narrow) for Haemorrhages (excl laboratory terms)

Grouped Term	Preferred Terms/Standardized MedDRA Queries
Hepatic injury	Acute hepatic failure, Acute on chronic liver failure, Acute yellow liver Atrophy, Alanine aminotransferase abnormal, Alanine aminotransferase increased, Allergic hepatitis, Ammonia abnormal, Ammonia increased, Ascites, Aspartate aminotransferase abnormal, Aspartate aminotransferase increased, Asterixis, Biliary ascites, Biliary cirrhosis, Biliary fibrosis, Bilirubin Conjugated abnormal, Bilirubin conjugated increased, Bilirubin excretion disorder, Biopsy liver abnormal, Blood bilirubin abnormal, Blood bilirubin increased, Blood bilirubin unconjugated increased, Cholestatic liver injury, Chronic hepatic failure, Chronic hepatitis, Coagulation factor decreased, Computerized tomogram liver abnormal, Drug-induced liver injury, Hepatic Cirrhosis, Hepatic congestion, Hepatic encephalopathy, Hepatic enzyme abnormal, Hepatic enzyme increased, Hepatic failure, Hepatic fibrosis, Hepatic function abnormal, Hepatic infiltration eosinophilic, Hepatic necrosis, Hepatic steato-fibrosis, Hepatic steatosis, Hepatitis, Hepatitis acute, Hepatitis cholestatic, Hepatitis fulminant, Hepatitis toxic, Hepatocellular injury, Hepatorenal failure, Hepatorenal syndrome, Hepatotoxicity, Hyperbilirubinaemia, Hypertransaminasaemia, Hypoalbuminaemia, Hypocoagulable state, Icterus index increased, International normalized ratio increased, Jaundice, Jaundice cholestatic, Jaundice hepatocellular, Liver disorder, Liver function test abnormal, Liver function test increased, Liver injury, Liver scan abnormal, Mixed liver injury, Portal hypertension, Steatohepatitis, Subacute hepatic failure, Transaminases abnormal, Transaminases increased, Ultrasound liver abnormal, Venoocclusive liver disease
Herpesvirus infection	Genital herpes, Herpes simplex, Herpes simplex pneumonia, Herpes virus infection, Herpes zoster, Oral herpes, Varicella zoster virus infection
Hyperbilirubinemia	Bilirubin conjugated increased, Blood bilirubin increased, Blood bilirubin unconjugated increased, Hyperbilirubinaemia, Jaundice
Hyperglycaemia	Diabetes mellitus, Hyperglycaemia
Hypersensitivity	Anaphylactic reaction, Drug eruption, Drug hypersensitivity, Erythema multiforme, Hypersensitivity, Urticaria
Hypoalbuminemia	Blood albumin decreased, Hypoalbuminaemia
Hypotension	Blood pressure decreased, Blood pressure systolic decreased, Hypotension, Orthostatic hypotension
Injection site reaction	Injection site erythema, Injection site extravasation, Injection site haematoma, Injection site irritation, Injection site pain, Injection site pruritus, Injection site rash, Injection site reaction, Injection site swelling
Leukoencephalopathy	Acute disseminated encephalomyelitis, Encephalomyelitis, Encephalopathy, Leukoencephalomyelitis, Leukoencephalopathy, Posterior reversible Encephalopathy syndrome, Progressive multifocal leukoencephalopathy, Toxic encephalopathy, Toxic leukoencephalopathy

Grouped Term	Preferred Terms/Standardized MedDRA Queries
Mucositis	Anal inflammation, Anal ulcer, Anorectal discomfort, Aphthous ulcer, Gingival pain, Gingivitis, Glossitis, Laryngeal discomfort, Laryngeal inflammation, Laryngeal pain, Mouth ulceration, Mucosal inflammation, Mucosal pain, Oesophageal pain, Oesophageal ulcer, Oesophagitis, Oral mucosal blistering, Oral mucosal blistering, Oral pain, Oropharyngeal pain, Pharyngeal inflammation, Proctalgia, Proctitis, Stomatitis, Vaginal inflammation
Muscle spasm	Muscle contractions involuntary, Muscle spasms, Muscle spasticity, Muscle tightness, Muscle twitching
Musculoskeletal pain	Arthralgia, Back pain, Bone pain, Musculoskeletal chest pain, Musculoskeletal discomfort, Musculoskeletal disorder, Musculoskeletal pain, Musculoskeletal stiffness, Myalgia, Neck pain, Pain in extremity
Myocardial ischemia	Acute myocardial infarction, Myocardial infarction, Myocardial ischaemia, Troponin increased, Troponin I increased, Troponin T increased
Neuropathy	Acute motor axonal neuropathy, Acute motor-sensory axonal neuropathy, Acute polyneuropathy, Ataxia, Axonal neuropathy, Bickerstaff's encephalitis, Biopsy peripheral nerve abnormal, Burning feet syndrome, Burning sensation, Cerebellar ataxia, Cerebral ataxia, Chronic inflammatory demyelinating polyradiculoneuropathy, Demyelinating polyneuropathy, Gait disturbance, Guillain-Barre syndrome, Loss of proprioception, Lumbosacral plexopathy, Miller Fisher syndrome, Mononeuritis, Mononeuropathy, Multifocal motor neuropathy, Myelopathy, Nerve conduction studies abnormal, Nerve degeneration, Neuritis, Neuromuscular toxicity, Neuromyopathy, Neuronal neuropathy, Neuropathic muscular atrophy, Neuropathy peripheral, Paresthesia, Peripheral motor neuropathy, Peripheral nerve palsy, Peripheral nerve paresis, Peripheral sensorimotor neuropathy, Peripheral sensory neuropathy, Polyneuropathy, Polyneuropathy idiopathic progressive, Polyneuropathy in malignant disease, Sensorimotor disorder, Sensory disturbance, Sensory loss, Toxic neuropathy
Pneumonia	Atypical pneumonia, Lung infection, Pneumonia, Pneumonia aspiration, Pneumonia bacterial, Pneumonia klebsiella
Pneumonitis	Acute interstitial pneumonitis, Pneumonitis, Pulmonary toxicity, Pneumonitis chemical
Pulmonary edema	Acute pulmonary oedema, Non-cardiogenic pulmonary oedema, Pulmonary congestion, Pulmonary oedema
QT prolongation	Torsade de Pointes/QT prolongation SMQ (Narrow) and PT Seizure
Rash	Acute febrile neutrophilic dermatosis, Butterfly rash, Dermatitis, Dermatitis acneiform, Dermatitis allergic, Dermatitis bullous, Dermatitis contact, Dermatitis exfoliative, Dermatitis exfoliative generalised, Dermatitis psoriasiform, Drug eruption, Erythema, Exfoliative rash, Macule, Pruritus, Pruritus generalised, Rash, Rash erythematous, Rash generalised, Rash Macular, Rash maculo-papular, Rash papular, Rash pruritic, Rash pustular, Rash vesicular, Skin erosion, Skin exfoliation, Skin reaction, Skin ulcer, Toxic skin eruption, Urticaria

Grouped Term	Preferred Terms/Standardized MedDRA Queries
Renal insufficiency	Acute kidney injury, Acute phosphate nephropathy, Acute prerenal failure, Anuria, Azotaemia, Blood creatinine increase, Continuous haemodiafiltration, Dialysis, Glomerular filtration rate decreased, Haemodialysis, Haemofiltration, Hypercreatininaemia, Hyponatriuria, Nephropathy toxic, Oliguria, Peritoneal dialysis, Prerenal failure, Renal disorder, Renal failure, Renal impairment, Renal tubular disorder
Reproductive toxicity	Termination of pregnancy and risk of abortion SMQ (Narrow), Fertility Disorders SMQ (Narrow and Broad), Foetal Disorders (narrow and broad), Neonatal Disorders (narrow and broad) Congenital, Familial and Genetic Disorders SMQ (Narrow), Lactation related topics (including neonatal exposure through breast milk) SMQ (Narrow), and PTs Exposure during pregnancy, Exposure during breast feeding, Exposure via father, Exposure via body fluid, Foetal exposure during pregnancy, Foetal exposure timing unspecified, Maternal exposure before pregnancy, Maternal exposure during pregnancy, Maternal exposure
Respiratory failure	Acute respiratory distress syndrome, Acute respiratory failure, Cardiopulmonary failure, Cardio-respiratory arrest, Respiratory arrest, Respiratory failure
Sepsis	Abdominal sepsis, Acinetobacter bacteraemia, Bacillus bacteraemia, Bacteraemia, Bacterial sepsis, Bacteroides bacteraemia, Biliary sepsis, Brucella sepsis, Burkholderia cepacia complex sepsis, Campylobacter sepsis, Citrobacter sepsis, Clostridium bacteraemia, Corynebacterium bacteraemia, Corynebacterium sepsis, Cronobacter bacteraemia, Device related sepsis, Enterobacter bacteraemia, Enterobacter sepsis, Enterococcal bacteraemia, Enterococcal infection, Enterococcal sepsis, Escherichia bacteraemia, Escherichia infection, Echerichia sepsis, Granulicatella bacteraemia, Haemophilus bacteraemia, Helicobacter sepsis, Intestinal sepsis, Klebsiella bacteraemia, Klebsiella sepsis, Listeria sepsis, Meningococcal bacteraemia, Meningococcal sepsis, Micrococcal sepsis, Neutropenic infection, Neutropenic sepsis, Nocardia sepsis, Pelvic sepsis, Pneumococcal bacteraemia, Pneumococcal sepsis, Post procedural sepsis, Pseudomonal bacteraemia, Pseudomonal sepsis, Pulmonary sepsis, Salmonella bacteraemia, Salmonella sepsis, Sepsis, Sepsis syndrome, Septic shock, Serratia bacteraemia, Serratia sepsis, Shewanella algae bacteraemia, Staphylococcal bacteraemia, Staphylococcal infection, Staphylococcal sepsis, Stenotrophomonas infection, Stenotrophomonas sepsis, Streptococcal bacteraemia, Streptococcal sepsis, Urosepsis, Wound sepsis, Yersinia bacteraemia, Yersinia sepsis

Grouped Term	Preferred Terms/Standardized MedDRA Queries
Thrombosis	Brachiocephalic vein thrombosis, Cavernous sinus thrombosis, Cerebral venous thrombosis, Deep vein thrombosis, Device related thrombosis, Intracranial venous sinus thrombosis, Jugular vein thrombosis, Ovarian vein thrombosis, Portal vein thrombosis, Portosplenomesenteric venous thrombosis, Pulmonary embolism, Pulmonary thrombosis, Pulmonary venous thrombosis, Renal vein thrombosis, Splenic vein thrombosis, Subclavian vein thrombosis, Superior sagittal sinus thrombosis, Thrombosis, Thrombosis in device, Thrombosis mesenteric vessel, Transverse sinus thrombosis, Venous thrombosis
Upper respiratory tract infection	Acute sinusitis, Chronic sinusitis, Laryngitis, Nasopharyngitis, Pharyngitis, Pharyngitis streptococcal, Rhinitis, Sinusitis, Tonsillitis, Upper respiratory tract infection, Upper respiratory tract infection bacterial, Viral upper respiratory tract infection
Urinary tract infection	Cystitis, Escherichia urinary tract infection, Kidney infection, Pyelonephritis, Renal abscess, Urinary tract infection, Urinary tract infection bacterial, Urinary tract infection enterococcal, Urinary tract infection pseudomonal
Ventricular arrhythmia	Extrasystoles, Torsade de pointes, Ventricular arrhythmia, Ventricular extrasystoles, Ventricular fibrillation, Ventricular tachyarrhythmia, Ventricular tachycardia
Visual impairment	Cataract, Diplopia, Hypermetropia, Myopia, Vision blurred, Visual acuity reduced, Visual impairment
Vomiting	Retching, Vomiting

Amadori, S, S Suciu, D Selleslag, F Aversa, G Gaidano, M Musso, L Annino, A Venditti, MT Voso, C Mazzone, D Magro, P De Fabritiis, P Muus, G Alimena, M Mancini, A Hagemeijer, F Paoloni, M Vignetti, P Fazi, L Meert, SM Ramadan, R Willemze, T de Witte, & F Baron. (2016). Gemtuzumab Ozogamicin Versus Best Supportive Care in Older Patients With Newly Diagnosed Acute Myeloid Leukemia Unsuitable for Intensive Chemotherapy: Results of the Randomized Phase III EORTC-GIMEMA AML-19 Trial. J Clin Oncol, 34(9), 972-979.

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/s/

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09/27/2018

DONNA PRZEPIORKA
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he secondary review comments are incorporated in the Cross-Discipline Team Leader Review.