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APPLICATION NUMBER:

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CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

Office of Clinical Pharmacology Integrated Review

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Submitssion Date(s)	April 27, 2018
Priority or Standard	Priority
PDUFA Goal Date	December 27, 2018
Generic Name	Glasdegib
Brand Name	Daurismo
Dosage Form and Strength	Tablet, 25 mg and 100 mg
Route of Adminstration	Oral
Pharmacologic Class	Hegdehog pathway inhibitor
Applicant Proposed Indication(s)/Population(s)	(b) (4)
Applicant	Pfizer
Associated Applications	None
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1 Executive Summary

The Applicant seeks approval of DAURISMO (glasdegib) (b) (4) The proposed DAURISMO dosing regimen is 100 mg orally once daily, with or without food.

The efficacy and safety of glasdegib in combination with LDAC in untreated patients with AML who were ineligible for intensive chemotherapy (n=116) was supported by the randomized (2:1), active-controlled (LDAC alone) Trial B1371003. Treatment with glasdegib in combination with LDAC resulted in a statistically significant improvement in overall survival (OS) as compared with LDAC alone. The most common adverse reactions (incidence ≥20%) are fatigue, bleeding, febrile neutropenia, musculoskeletal pain, nausea, edema, dyspnea, decreased appetite, dysgeusia, mucositis, constipation, and rash.

The Clinical Pharmacology section of the NDA is supported by the evaluations and analyses of single and repeat dose pharmacokinetics (PK) of glasdegib, effect of food on glasdegib PK, bioequivalence of glasdegib formulations, glasdegib exposure-response relationship for efficacy and safety, population PK, drug-drug interactions (DDI) between glasdegib and cytochrome P450 (CYP) 3A modulators and acid reducing agents, and potential for QT/QTc prolongation.

Based on the efficacy and safety results in the registration trial, the proposed DAURISMO dosing regimen of 100 mg orally once daily with the dose reduction schema in the event of adverse reactions is reasonable. There was no evident exposure-response (ER) relationship for OS in patients with AML or MDS who received a dose of 100 mg once daily, at an exposure (cumulative area under the curve in cycle 1) range of 56 to 1223 µg•h/mL. Exposure-safety relationships were significant for dysgeusia, muscle spasms, renal toxicity, and QTc interval prolonged; however, adverse events (AEs) were Grade ≤2 for dysgeusia and the incidence of serious or Grade 3/4 muscle spasms and renal toxicity was low.

The key review questions focused on dose recommendations for patients taking concomitant strong CYP3A inhibitors and QT-prolonging drugs, and for patients with hepatic and renal impairment. No dose adjustment of DAURISMO is recommended with co-administration of strong CYP3A inhibitors and QT-prolonging drugs. The population PK analyses did not identify clinically important covariates influencing glasdegib PK, including mild hepatic impairment and mild to moderate renal impairment; no dose adjustment is recommended for patients with mild hepatic impairment and mild to moderate renal impairment.

1.1.Recommendations

The proposed DAURISMO dosing regimen of 100 mg orally once daily with the dose reduction schema in the event of adverse reactions is acceptable. From a Clinical Pharmacology standpoint, the NDA is approvable provided the Applicant and the FDA reach an agreement regarding the labeling language.

Review Issue	Recommendations and Comments
Pivotal or supportive evidence of effectiveness†	Trial B1371003 (phase 2, patients with AML who were ineligible for intensive chemotherapy) demonstrated an improvement in median OS in the DAUSIRMO + LDAC arm compared to LDAC alone.
General dosing instructions	100 mg orally once daily, with or without food
Dosing in patient subgroups (intrinsic and extrinsic factors)	• No dose adjustments are recommended in patients with mild hepatic impairment and mild-to-moderate renal impairment, and co-administration with strong CYP3A inhibitors, QT prolonging drugs, and acid reducing agents. • Avoid coadministration of strong CYP3A inducers.
Labeling	• No dose adjustment is necessary with concomitant use of a strong CYP3A inhibitor. Consider alternative therapies that are not strong CYP3A inhibitors or monitor for increased risk of adverse reactions, including QTc interval prolongation. • Avoid co-administration of strong CYP3A inducers. • Avoid co-administration of QTc prolonging drugs or replace with alternative therapies. If co-administration of a QTc prolonging drug is unavoidable, monitor patients for increased risk of QTc interval prolongation. • No dose adjustment is necessary with gastric acid reducing agents. • No dose adjustment is necessary in patients with mild hepatic impairment and mild to moderate renal impairment. The PK and safety of DAURISMO in patients with moderate and severe hepatic impairment and severe renal impairment have not been studied.
Bridge between the to-be-marketed and clinical trial formulations	Yes. The to-be-marketed formulation ((b) (4) tablet) was found to be bioequivalent to the (b) (4) salt formulation ((b) (4) tablet) used in the registration trial (1003) and dose escalation studies (1001, 1002). In addition, the (b) (4) (b) (4) formulations used in a supportive trial (1005) in patients and pertinent clinical pharmacology studies (1014,

	1015) were found to be bioequivalent to the (b) (4) tablet.

1.2.Postmarketing Requirements and Commitments

The Applicant is requested to conduct the following clinical pharmacology studies as a postmarketing requirement (PMR) or postmarketing commitment (PMC). The PMR/PMC studies will be included in the Approval letter with milestones agreed upon after negotiation with the Applicant.

PMC or PMR	Key Issue(s) to be Addressed	Rationale	Key Considerations for Design Features
☐ PMC ☒ PMR	Determination of an appropriate glasdegib dose for patients with moderate to severe hepatic impairment.	42% of the administered dose (20% as unchanged glasdegib) was recovered in the feces, indicating that hepatic elimination is the major elimination pathway.	Single dose of glasdegib in otherwise healthy subjects with moderate to severe hepatic impairment compared to healthy subjects.
☐ PMC ☒ PMR	Determination of an appropriate glasdegib dose for patients with severe renal impairment.	49% of the administered dose (17% as unchanged glasdegib) was recovered in the urine.	Single dose of glasdegib in otherwise healthy subjects with severe renal impairment compared to healthy subjects.
☒ PMC ☐ PMR	Determination of an appropriate glasdegib dose for patients with co-administration of a moderate CYP3A4 inducer.	Coadministration of rifampin (a strong CYP3A4 inducer) decreased glasdegib AUC by 70% (90% CI:67, 74) and C_{max} by 36% (90% CI: 27, 43) as compared with glasdegib alone.	Single dose of glasdegib with and without coadministration of repeat doses of a moderate CYP3A4 inducer in healthy subjects. Alternatively, use of a PBPK modeling approach to assess the magnitude of decreased drug exposure and to determine appropriate dosing recommendations may be acceptable.

2 Summary of Clinical Pharmacology Assessment

2.1. Pharmacology and Clinical Pharmacokinetics

Glasdegib (molecular weight of 375 g/mol as free base) is an inhibitor of transmembrane protein, Smoothened, which plays a vital role in the hedgehog signaling pathway.

The following is a summary of the clinical pharmacokinetics (PK) and pharmacodynamics (PD) of glasdegib:

Pharmacodynamics

GLI1 expression was inhibited by ≥90% at doses ≥100 mg, and about ≥80% at 50 mg following administration of glasdegib once daily over the dose range of 25 mg to 640 mg.

Pharmacokinetics

Systemic exposure was dose proportional over the dose range of 5 mg to 600 mg in patients with hematologic malignancies after a single dose and at steady-state. Steady-state was achieved by 8 days, with a median accumulation ratio of 1.25- to 2.5-fold following glasdegib once daily dosing.

At 100 mg once daily dosing, the geometric mean (%CV) of glasdegib C_{max} was 1252 (44%) ng/mL and AUC_{tau} was 17210 (54%) ng•hr/mL at steady state in patients with AML.

Absorption
The absolute bioavailability (90% confidence intervals (CI)) of glasdegib is 77% (72, 83). The median T_{max} at steady-state across visits ranged from 1.3 to 1.8 hours following once daily oral dosing of glasdegib in patients with AML.

Effect of Food: A high-fat meal, high-calorie meal (total 800-1000 calories: 500-600 fat calories, 250 carbohydrate calories and 150 protein calories) decreased glasdegib $AUC_{0\text{-}inf}$ by 16% and C_{max} by 31%. Median T_{max} was delayed by 0 to 3 hours in the different food effect studies.

Distribution
Glasdegib was 90% bound to human plasma proteins in vitro. The human blood-to-plasma concentration ratio was 1.38. The geometric mean apparent volume of distribution (V_d/F) of glasdegib at steady-state was 283 L.

Elimination
The mean terminal elimination half-life (%CV) of glasdegib was 17.4 (19%) to 26.5 (15%) hours in patients with hematologic malignancies. The geometric mean (% CV) apparent clearance (CL/F) was 6.3 L/hr (43%). The mean apparent clearance of glasdegib was higher in healthy subjects compared to patients with cancer.

Metabolism: Glasdegib is primarily metabolized by CYP3A (60-80%), with minor contributions by CYP2C8 (2-20%) and UGT1A9 in vitro. The metabolic pathways include N-demethylation glucuronidation, oxidation, and dehydrogenation. Unchanged glasdegib (69%) was the major circulating component. No active metabolites were detected in plasma.

Excretion: Following a single 100 mg oral dose of ^{14}C-glasdegib, 42% of the dose was recovered in feces (20% of dose as unchanged drug) and 49% of the dose was recovered in urine (17% of dose as unchanged drug).

Specific Populations

Age (25-92 years), sex, race or ethnicity (234 White, 16 Black, 9 Asian, and 11 Hispanic), body weight (43.5 to 145.6 kg), mild hepatic impairment (total bilirubin ≤ ULN and AST > ULN, or total bilirubin 1-1.5 x ULN and any AST) or mild to moderate renal impairment (creatinine clearance [CLcr] 30-89 mL/min) did not have clinically meaningful effects on the PK of glasdegib. The effect of moderate (total bilirubin 1.5-3 x ULN and any AST) and severe (total bilirubin > 3 x ULN and any AST) hepatic impairment or severe renal impairment (CLcr 15-29 mL/min) on glasdegib pharmacokinetics is unknown.

Drug Interactions Studies

Effect of Strong CYP3A4 Inhibitors on Glasdegib:

Co-administration of ketoconazole (a strong inhibitor of CYP3A4: 400 mg daily for 7 days) with single dose of DAURISMO (200 mg) increased the glasdegib AUC_{inf} by 2.4-fold (90% CI: 2.1, 2.7) and C_{max} by 1.4-fold (90% CI: 1.2, 1.6).

Effect of Strong CYP3A4 Inducers on Glasdegib:

Co-administration of rifampin (a strong inducer of CYP3A4: 600 mg daily for 11 days) with single dose of DAURISMO (100 mg) decreased glasdegib AUC_{inf} by 70% (90% CI: 66, 74) and C_{max} by 35% (90% CI: 27, 43).

Effect of Gastric Acid Reducing Agents on Glasdegib:

Co-administration of rabeprazole (a proton pump inhibitor: 40 mg daily for 6 days) with a single dose of DAURISMO (100 mg on Day 7) did not alter glasdegib AUC_{inf} (1.01; 90% CI: 0.9, 1.1) but decreased C_{max} by 19% (90% CI: 8, 29).

In Vitro Studies

Effect of Glasdegib on Cytochrome P450 (CYP) Substrates

Glasdegib does not inhibit CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, or CYP3A, and does not induce CYP1A2, CYP2B6, and CYP3A in vitro.

Effect of Transporters on Glasdegib

Glasdegib is a substrate of P-glycoprotein (P-gp) and breast cancer resistance protein (BCRP).

Effect of Glasdegib on Transporters:

Glasdegib inhibits P-gp, BCRP, multidrug and toxin extrusion (MATE) protein 1, and MATE-2K, but not organic anion transporting polypeptide (OATP)1B1, OATP1B3, organic anion transporter (OAT)1, OAT3, organic cation transporter (OCT)2 in vitro.

2.2.General Dosing and Therapeutic Individualization

2.2.1. General Dosing

The Applicant proposes DAURISMO dosing regimen of 100 mg orally once daily, with or without food.

The proposed DAURISMO dosing regimen was evaluated in untreated patients with AML who were ineligible for intensive chemotherapy (n=116) in Phase 2 of Trial B1371003. The dosing regimen was chosen based on the maximum tolerated dose (MTD) of 400 mg once daily, safety, and dose modification results of glasdegib with LDAC in the dose escalation phase of Trial B1371003, pharmacodynamic (PD) data on down-regulation of GLI-1 expression, and the results of the DDI study showing approximately 2-fold increase in glasdegib exposure with co-administration of a strong CYP3A4 inhibitor (ketoconazole).

Food did not affect glasdegib exposure; therefore, DAURISMO is recommended to be administered without regards to food.

2.2.2. Therapeutic Individualization

CYP3A modulators, QT-prolonging drugs, and acid reducing agents:

- Avoidance of co-administration of strong CYP3A inducers is recommended as glasdegib exposure was decreased by ~70% with a strong CYP3A inducer.
- No dose adjustments are recommended with strong CYP3A inhibitors. Alternative therapies that are not strong CYP3A4 inhibitors during treatment with DAURISMO are recommended. If unavoidable, patients should be monitored for increased risk of adverse reactions including QTc interval prolongation. This recommendation is based on the following:
  a) No dose adjustments are recommended due to adequate safety margin with the recommended dose of 100 mg once daily, which is 4-fold lower than the maximum tolerated dose of 400 mg once daily.
  b) No apparent differences in serious AEs and Grade 3/4 AEs with strong CYP3A inhibitors versus no CYP3A inhibitors in Trial B1371003 (Phase 1 & 2, patients ineligible for intensive chemotherapy). Grade 5 AEs were lower with strong CYP3A inhibitors versus no CYP3A inhibitors.
  c) AEs were mostly managed by dose interruptions.
  d) Incidence of dose discontinuations and dose reductions due to AEs were low.
  e) Glasdegib exhibits concentration dependent QT-prolongation. Most of the glasdegib C_{max} concentrations at 100 mg once daily with strong CYP3A inhibitors were below the ΔQTcF of 10 ms (based on concentration-ΔQTcF relationship), with almost all Cmax concentrations below the 20 ms cut-off.
  f) Alternative therapies that are not strong CYP3A4 inhibitors during treatment with DAURISMO are recommended as a precaution because strong CYP3A4 inhibitors increased glasdegib exposure by up to 2.4-fold.

g) Strong CYP3A inhibitors cannot always be avoided in patients with AML who require azole anti-fungal therapy. 60% of patients in the registration trial were taking CYP3A inhibitors, of which half of them received strong CYP3A inhibitors.
h) Several of the azole anti-fungal drugs that are strong CYP3A inhibitors are also QT prolonging and patients should be monitored for increased risk of adverse reactions including QTc interval prolongation if strong CYP3A4 inhibitors are unavoidable.

- Avoidance of co-administration of QTc prolonging drugs with DAURISMO or replacing with alternative therapies are recommended. If co-administration of a QTc prolonging drug is unavoidable, it is recommended to monitor patients for increased risk of QTc interval prolongation. If QTc interval is >500 ms, dose interruption is recommended until QTc interval is <481 ms followed by dose reduction to 50 mg once daily. These recommendations are based on the following:
  a) 75% of patients in the registration trial were on concomitant QT-prolonging drugs.
  b) Serious and Grade ≥3 cardiac-related AEs[1] were higher in patients in the Glasdegib+LDAC arm, with ~80% of these patients taking QT-prolonging drugs.
  c) 5% of patients had fatal Grade 5 cardiac-related AEs in the Glasdegib+LDAC arm , of which 3 patients had either no concomitant medication or concomitant medications were stopped >6 months prior to the events.
  d) AEs were mostly managed by dose interruptions.
  e) 15% of the patients with Grade ≥3 QT-prolongation were dose reduced per protocol in Trial B1371003 (Phase 2, patients ineligible for intensive chemotherapy).
- No dose adjustments are recommended with acid reducing agents (ARA) as glasdegib exposure was not affected by rabeprazole, a proton pump inhibitor.

Organ impairment: No dose adjustments are recommended for patients with mild hepatic impairment (total bilirubin ≤ ULN and AST > ULN, or total bilirubin 1-1.5 x ULN and any AST) or mild to moderate renal impairment (creatinine clearance [CLcr] 30-89 mL/min) as there was no clinically meaningful changes in glasdegib PK in these patient populations compared to subjects with normal hepatic function and normal renal function (CLcr ≥90 mL/min). The safety of mild hepatic impairment and mild to moderate renal impairment was comparable to normal hepatic function and normal renal function. The PK and safety of glasdegib in patients with moderate (total bilirubin 1.5-3 x ULN and any AST) and severe (total bilirubin > 3 x ULN and any AST) hepatic impairment are sparse, and patients with severe renal impairment (CLcr 15-29 mL/min) have not been studied.

2.3. Outstanding Issues

- The PK and safety of glasdegib in patients with severe renal impairment and moderate to severe hepatic impairment have not been studied; therefore PMR studies are requested to determine an appropriate glasdegib dose for patients with severe renal impairment and for patients with moderate to severe hepatic impairment.
- The PK and potential decrease in efficacy of glasdegib in patients requiring concomitant use of a moderate CYP3A4 inducer have not been studied; therefore, a PMC clinical trial is requested to determine dosing recommendations in patients requiring concomitant

use of a moderate CYP3A4 inducer. Alternatively, a PBPK modeling approach to assess the magnitude of decreased glasdegib exposure and determine appropriate dosing recommendations may be acceptable.

2.4. Summary of Labeling Recommendations

The Office of Clinical Pharmacology recommends the following labeling concepts to be included in the final package insert:

- Modify Section 7 to include recommendation for concomitant use of QT-prolonging drugs. Include a table for drug interactions with DAURISMO and strong CYP3A modulators and QT-prolonging drugs, instead of the proposed text.
- (b) (4)
- Modify Section 12.2 to include that glasdegib shows concentration-dependent QT prolongation, and describe the results of the thorough QT study, excluding the moxifloxacin results.

Section 12.3

- Revise format per FDA's current clinical pharmacology labeling guidance.
- Include information on time to steady-state levels and accumulation ratio.
- Include description of high fat meal, and the impact of food on C_{max}.
- (b) (4)
- Modify 'Specific Populations' sub-section, to state that glasdegib PK is not affected by age, race, sex, body weight, mild hepatic impairment, and mild-to-moderate renal impairment. Population PK showed no clinically meaningful changes in glasdegib PK with changes in CLcr ≥30 mL/min and with mild hepatic impairment. Only 3 patients with moderate hepatic impairment, one patient with severe hepatic impairment, and no patient with severe renal impairment were included in the population PK analysis. The effect of moderate (total bilirubin 1.5 - 3 x ULN and any AST) and severe (total bilirubin > 3 x ULN and any AST) hepatic impairment or severe renal impairment (CLcr 15-29 mL/min) on glasdegib pharmacokinetics is unknown.
- State that glasdegib is a substrate of P-glycoprotein (P-gp) and breast cancer resistance protein (BCRP) in vitro
- State that in vitro studies indicate that glasdegib inhibits P-gp, BCRP, multidrug and toxin extrusion (MATE) 1, and MATE-2K , but does not inhibit CYP1A, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, CYP3A, organic anion transporter (OAT)1, OAT3, organic cation transporter (OCT)2, organic anion transporting polypeptide (OATP)1B1, and OATP1B3. Also, state that glasdegib does not induce CYP1A2, CYP2B6, and CYP3A in vitro.

3 Comprehensive Clinical Pharmacology Review

3.1. Overview of the Product and Regulatory Background

General Pharmacology and Pharmacokinetic Characteristic

The PK parameters listed in Table 1 are from the clinical pharmacology studies in healthy subjects and patients.

Table 1: Summary of General Pharmacology and Pharmacokinetic Characteristics of Glasdegib

Pharmacology	
Mechanism of Action	Glasdegib (molecular weight of 375 g/mol as free base, 491 g/mol as maleate salt): • is an inhibitor of Smoothened. • IC_{50} 7.7 nM based on competitive binding assay • Inhibits (IC_{50} 5 nM) sonic hedgehog-induced pathway activation in cell based assay.
Active Moieties	No active metabolites. Unchanged glasdegib was the major circulating component in plasma (69%). N-desmethyl and N-glucuronide metabolites of glasdegib accounted for 8% and 7% of the circulating radioactivity, respectively. Other metabolites in plasma individually accounted for <5% of circulating radioactivity.
QT Prolongation	Glasdegib inhibited hERG current with an IC_{50} of 2.8 µM (1049 ng/mL) in vitro, i.e., 9-fold > mean unbound C_{max} of 113 ng/mL (300 nM). Glasdegib exhibited concentration-dependent QT prolongation. Thorough QT study (1023) showed that the placebo-corrected, baseline-adjusted QTc interval change (ΔΔQTcF) at therapeutic and supratherapeutic levels were 8 ms (90% CI: 6, 10) & 10 ms (90% CI: 11, 16), respectively, in healthy subjects.
General Information	
Bioanalysis	Glasdegib was measured using validated LC-MS/MS assay methods.
Healthy vs. Patients	Higher mean apparent oral clearance (CL/F) (%CV) in healthy subjects versus patients: 12 (31%) L/hr (Study B1371026) versus 6.3 (43%) L/hr in patients.
Drug Exposure at Steady State Following the Therapeutic Dosing Regimen	The following table provides a summary of PK of glasdegib at steady-state following daily glasdegib dosing with LDAC in patients with AML/MDS:

PK Parameter	**At Cycle 1/Day 10 after 100 mg Once Daily**	
	Phase 1a (n=13)	**Phase 2** (n=41)
$AUC_{0\text{-}tau}$, ng·h/mL	15020 (49)	17210 (54)
C_{max}, ng/m	1074 (63)	1252 (44)
C_{avg}, ng/mL	554 (71)	718 (54)
C_{trough}, ng/mL	270 (73)	427 (80)
Median T_{max} (hr)	1.8	1.7
Source: Tables 32 & 38, Study B1371003		

Dose Proportionality	AUCinf and Cmax after a single dose and AUCtau and Cmax after once daily dosing, were approximately dose proportional over the range of 5 mg to 600 mg in

	patients with hematologic malignancies. 90% CI included 1 (Study B1371001).
Accumulation	The median observed accumulation ratio (Rac) for glasdegib ranged from 1.2 to 2.5 in patients with hematologic malignancies and solid tumors.
Variability	Following a single dose of 100 mg of [redacted] (b) (4) tablets, the inter-subject variability (%CV) for glasdegib C_{max} was 23% to 30% and AUC_{inf} was 25 to 31% (Study 1026, 1014) under fasted state and C_{max} was 28% to 34% and AUC_{inf} was 20 to 30% under fed conditions (Study B1371026, 1014).
Absorption	
Bioavailability	77%
Median T_{max}	1.3 to 1.8 hours across visits in AML patients (Study B1371003)
Food effect [a] (Fed/fasted)	With a high fat, high-calorie meal (total 800-1000 calories: 500-600 fat calories, 250 carbohydrate calories and 150 protein calories), glasdegib AUC_{0-inf} decreased by 16%, and Cmax by 31%. Median T_{max} was delayed by 0 to 3 hours with food (Studies B1371010, 1014, 1026).
Distribution	
Volume of Distribution	Mean Vd/F of 283 L.
Plasma Protein Binding	The mean fu of glasdegib was 0.09
Blood to Plasma Ratio	Mean Cb/Cp of glasdegib in human was 1.38.
As Substrate of Transporters	• Substrate of P-glycoprotein (P-gp) & breast cancer resistance protein (BCRP). • Not a substrate of organic anion transporting polypeptide (OATP1B1, OATP1B3), organic anion transporter (OAT1, OAT3), organic cation transporter (OCT2), and multidrug and toxin extrusion proteins (MATE1, MATE2K).
Elimination	
Terminal Elimination Half-Life	The arithmetic mean (%CV) elimination half-life ($t_{1/2}$) of glasdegib was 17.4 (19%) to 26.5 (15%) hours (B1371001). The mean (%CV) apparent clearance (CL/F) of glasdegib is 6.3 L/h (43%) (popPK).
Metabolism	
Fraction Metabolized (% dose)	N-desmethyl metabolite of glasdegib was the most abundant metabolite in urine and feces, accounting for 16.8% and 9.2% of dose respectively. Other metabolites in the excreta individually accounted for <5% of dose.
Primary Metabolic Pathway(s)	Primary metabolic pathways for glasdegib included N-demethylation, glucuronidation, oxidation, and dehydrogenation. Primarily metabolized by CYP3A4 (60% to 80%), with minor contribution by CYP2C8 (2 to 20%) and UGT1A9.
Excretion	
Primary Excretion Pathways (% dose) ±SD	In 6 healthy subjects administered 100 mg (~100 µCi) of ^{14}C-glasdegib, and collection of plasma samples up to 144 hrs and urine and fecal samples up to 288 h: • Feces: 42% ± 2% (20% as unchanged drug). • Urine: 49% ± 2% (17% as unchanged drug). Recovery was 90%.
Interaction liability (Drug as Perpetrator)	

Inhibition/Induction of Metabolism	• Clinical studies with a single dose of glasdegib show that glasdegib AUC_{inf} increased by 2.4-fold (90% CI: 2.1, 2.7) with ketoconazole, a strong CYP3A inhibitor, and decreased by 70% (90% CI: 64, 74) with rifampin, a strong CYP3A inducer. • In vitro data suggests that glasdegib is unlikely to inhibit CYP1A2, 2B6, 2C8, 2C9, 2C19, 2D6, or 3A4/5 at clinically relevant concentrations. • Clinical study with a single dose of glasdegib showed that rabeprazole, a PPI increased glasdegib AUC_{inf} by 1.01-fold (90% CI: 0.9, 1.1) with (b) (4) tablets. • In human hepatocytes, glasdegib did not induce CYP1A2, CYP2B6, or CYP3A4 at concentrations that were >33x the steady-state unbound C_{max}. • Inhibit UGT1A1 and UGT1A9 activities (unbound IC_{50} values of 3.9 and 20 μM) in vitro, but little or no inhibition of UGTs 1A4, 1A6, 2B7, and 2B15 (IC_{50} >131 μM).
Inhibition/Induction of Transporter Systems	Glasdegib inhibits P-gp, BCRP, MATE-1, and MATE-2K, but not OATP1B1, OATP1B3, OAT1, OAT3, OCT2 in vitro.

*PK parameters are presented as geometric mean (%CV) or median (minimum, maximum) unless otherwise noted

3.2. Clinical Pharmacology Questions

3.2.1. Does the clinical pharmacology program provide supportive evidence of effectiveness?

Yes, the clinical pharmacology information was adequate to provide supportive evidence of effectiveness of glasdegib on overall survival in patients with AML/MDS. The Clinical Pharmacology program, including the exposure-response analysis provided in Appendix 4.6.2, supported the following:

- The selected daily 100 mg for patients with AML was supported by the efficacy and safety results of the active-controlled Trial B1371003.
- Significant exposure-response relationship was identified for safety endpoints, including dysgeusia, muscle spasms, renal toxicity, and QT interval prolonged.
- However, the incidence of glasdegib dose reduction and discontinuations were low, and adverse reactions were mostly managed by dose interruptions and dose delays.
- No exposure-response relationship for overall survival (OS) at the 100 mg once daily dose in Trial B1371003 (Phase 2, patients who were ineligible for intensive chemotherapy).

3.2.2. Is the proposed dosing regimen appropriate for the general patient population for which the indication is being sought?

Yes, the proposed dosing regimen of 100 mg orally once daily, without regards to food, appears appropriate for the indicated patient population based on the available efficacy and safety data. The Applicant selected the 100 mg dose for the following reasons:

- doses up to 400 mg once daily (maximum tolerated dose) were well tolerated in the dose escalation phase in patients with hematologic malignancies,
- 100 mg glasdegib+LDAC had similar safety profile as LDAC alone

- there was low incidence of dose delays/discontinuations in dose escalation phase of Study B1371003 (Phase 1b, Arm A),
- inhibition of GLI1 expression was ≥90% at doses of ≥100 mg based on PD data,
- there is adequate safety margin to account for a 2-fold increase in glasdegib exposure with strong CYP3A inhibitors based on DDI study with ketoconazole,
- efficacy and safety data from the active-controlled phase of registration Trial B1371003 (Phase 2, patients who were ineligible for intensive chemotherapy). Less than 10% of the patients were discontinued due to adverse reactions during the study. Discontinuation and dose reduction, due to any adverse reactions in the Glasdegib+LDAC arm were low.
- exposure-safety analyses based on data from Trial B1371003 (Phase 2, patients who were ineligible for intensive chemotherapy) indicates increase in toxicity with increasing exposure (Appendix 4.6.2.2). Therefore, the dose of 100 mg is predicted to be associated with lower toxicity compared to 200 mg.

Also, food has no effect on the bioavailability of DAURISMO.

3.2.3. Is an alternative dosing regimen or management strategy required for subpopulations based on intrinsic patient factors?

No. Based on the results of the population PK analysis (Appendix 4.6.1), hepatic impairment was not a significant covariate and glasdegib PK were similar between patients with mild hepatic impairment (total bilirubin ≤ ULN and AST > ULN, or total bilirubin 1-1.5 x ULN and any AST: n=26) and normal hepatic function (n=217). However, the effect of moderate and severe hepatic impairment is unknown, as only 3 patients with moderate and 1 patient with severe hepatic impairment were included during clinical development. Also, while population PK analysis indicated that CLcr was a significant covariate (glasdegib clearance was decreased by <30%), there was no clinically meaningful difference in PK with moderate (CLcr 30 to <60 mL/min: n=61) renal impairment, compared to patients with normal renal function (CLcr ≥90 mL/min: n=105). Also, glasdegib PK were similar between patients with mild (CLcr 60 to <90 mL/min: n=142) renal impairment and patients with normal renal function (Appendix 4.6.1, Figure 7). Therefore, a lower dose is not recommended for patients with mild hepatic impairment and mild to moderate renal impairment. However, the effect of severe renal impairment (CLcr 15-29 mL/min) has not been studied during clinical development. The safety of mild hepatic impairment was comparable to normal hepatic function (Appendix 4.4, Table 22), and safety and efficacy of mild to moderate renal impairment were comparable to normal renal function (Appendix 4.4, Table 24 and Table 25).

Age (25-92 years), sex, race or ethnicity (235 Whites, 16 Blacks, 9 Asians and 11 Hispanics), body weight (43.5 to 145.6 kg), had no clinically meaningful effect on the PK of glasdegib (Appendix 4.6.1).

3.2.4. Are there clinically relevant food-drug or drug-drug interactions, and what is the appropriate management strategy?

Yes. A management strategy is required for the coadministration of strong CYP3A modulators and QT-prolonging drugs. A description of possible interactions of glasdegib with CYP3A modulators and QT-prolonging drugs will be included in the labeling.

Drug-Drug Interactions

Effects of Other Drugs on Glasdegib

Strong CYP3A Inducers
Avoid concomitant use of strong inducers. This recommendation was based on the decrease of ~70% in glasdegib exposure (AUC_{inf}) with a strong CYP3A inducer (Appendix 4.3, Table 11).

Strong CYP3A Inhibitors
Drug interaction studies indicated that glasdegib AUC_{inf} increases up to 2.4-fold and C_{max} by 1.4-fold with a strong CYP3A inhibitor (Appendix 4.3, Table 11).

There were no restrictions for the use of CYP3A inhibitors in Trial B1371003 and ~60% of the patients were treated with CYP3A inhibitors, of which half of them were on strong CYP3A inhibitors. As fungal infections are a common cause of morbidity and mortality in the AML population, patients may require azole-antifungal agents that are CYP3A inhibitors during therapy. In Trial B1371003 (Phase 1 & 2, patients who were ineligible for intensive chemotherapy), the steady-state trough concentrations were 1.5-fold higher with strong CYP3A inhibitors compared to no CYP3A inhibitors, and no discernable safety signals were observed with strong CYP3A inhibitors (Appendix 4.3, Table 13 and Table 14). In addition, dose reductions (15%) and discontinuations (9%) due to AEs were low in the trial and majority of the AEs were managed by dose interruptions (Appendix 4.3,Table 18).

Also, most antifungal drugs have the potential for QT-prolongation, and glasdegib exhibits concentration-dependent QT prolongation. In patients not eligible for intensive chemotherapy in Trial B1371003, there was higher incidence of cardiac-related events in the Glasdegib+LDAC arm. Nonetheless, majority of the concentrations at the C_{max} range were below the $\Delta\Delta$QTcF of 10 ms and majority were within 20 ms cut-off based the concentration-$\Delta\Delta$QTcF relationship (Appendix 4.3, Figure 3). Majority of the AEs were managed by dose interruptions (Appendix 4.3, Table 18).

A lower starting dose is not recommended based on available data; however, due to the potential for increase in glasdegib exposure, drugs that do not strongly inhibit CYP3A activity should be considered. Alternatively, patients taking strong CYP3A inhibitors should be closely monitored for ARs, including the risk for QT-prolongation. No PMR is necessary to assess the impact of moderate CYP3A inhibitors on the tolerability as no discernable safety signal were observed with strong CYP3A inhibitors in Trial B1371003.

QT-Prolonging Drugs

Avoid co-administration of QTc prolonging drugs. Alternately, if coadministration of a QTc prolonging drug is unavoidable, monitor patients for increased risk of QTc interval prolongation. If QTc interval >500 ms, interrupt DAURISMO dose until QTc interval is < 481 ms, and resume DAURISMO at a lower dose of 50 mg. The rationale for these recommendations is as follows:

In Trial B1371003 (Phase 2, patients who were ineligible for intensive chemotherapy), 75% of patients were on concomitant QT-prolonging drugs, including fluoroquinolones (i.e., levofloxacin, ciprofloxacin) or antiemetics (i.e., ondansetron). In addition, the majority of patients on QT-prolonging drugs also received azole-antifungals that have QT-prolonging potential. Patients with serious and Grade ≥3 QT-related AEs were higher in the Glasdegib+LDAC arm, and 80% of these patients were on QT-prolonging drugs (Appendix 4.3, Table 17). 5% of patients had fatal Grade 5 cardiac-related AEs, of which 3 patients had either no concomitant medication or concomitant medications were stopped >6 months prior to the events. AEs were mostly managed by dose interruptions (Appendix 4.3, Table 18). 15% of the patients were dose reduced per protocol for QT-prolongation (i.e., Grade ≥3).

Effect of Glasdegib

On Transporters: In vitro, glasdegib has the potential to inhibit P-gp (IC_{50} >33 µM) and BCRP (IC_{50} 4.6 µM), MATE-1 (IC_{50} 4.9 µM) and MATE-2K (IC_{50} 1.2 µM). This may translate into clinically relevant inhibition at the dose of 100 mg for P-gp and BCRP (i.e., I_{gut}/IC_{50} >11), and MATE-1 and MATE-2K ($I_{max,u}/IC_{50}$ >0.02 f) , according to the FDA guidance for drug interaction studies (2017) (Appendix 4.3,Table 20).

Food-Drug Interactions

No dose adjustment is recommended with food.

Glasdegib $AUC_{0\text{-}inf}$ decreased by 16% and C_{max} by 31% with a high-fat meal (Appendix 4.2, Table 5). In the registration trial, DAURISMO was administered without regards to food.

3.2.5. Does glasdegib PK support the proposed dose reduction strategy?

The proposed DAURISMO dose reduction to a minimum of 50 mg in the event of adverse reactions including QT-prolongation were based on dose reductions per protocol in Study B1371003. At 50 mg once daily, mean steady-state trough concentrations exceed the IC_{50} for inhibition of Smoothened and sonic hedgehog-induced pathway activation.

3.2.6. Does this drug prolong the QT or QTc interval?

Glasdegib is associated with a concentration-dependent QTc prolongation (Appendix 4.3, Figure 4) (DARRTS ID 4305856). In a thorough QT study in 36 healthy subjects, the largest placebo-corrected, baseline-adjusted QTc interval change (ΔΔQTcF) was 8 ms (90% CI: 6, 10

ms) with a single dose of 150 mg (therapeutic levels at the recommended dose) and 13 ms (90% CI: 11, 16 ms) with a single dose of 300 mg (2-fold therapeutic concentrations).

4 Appendices

4.1.General Information

Table 2: Listing of clinical pharmacology studies

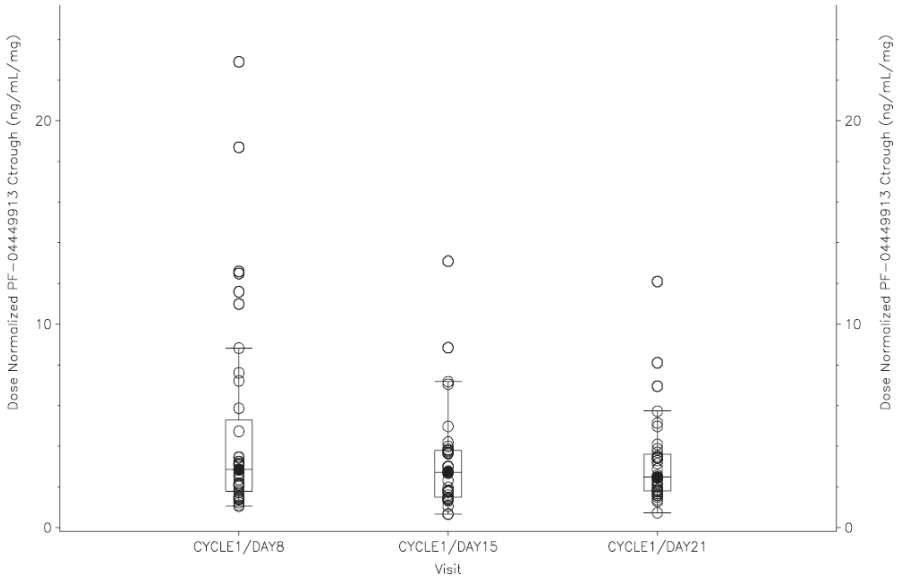
Study Type	Study Number	Formulation	Study Description
Single Dose Studies	B1371009	Oral Soln	Mass balance study in Healthy Subjects
	B1371022	(b) (4)	Absolute BA study in Healthy Subjects
Bioavailability and Food Effect	B1371010		Food effect study in Healthy Subjects
	B1371014		Relative BA study and food effect study (b) (4) in Healthy Subjects
	B1371026		Relative BE and food effect (FCH) study in Healthy Subjects
Drug-Drug Interaction Studies	B1371010		Drug-drug interaction study with strong CYP3A inhibitor, ketoconazole in Healthy Subjects
	B1371015		Drug-drug interaction study with strong CYP3A inducer, rifampin in Healthy Subjects
	B1371014		PPI study in Healthy Subjects
	B1371026		PPI study in Healthy Subjects
Thorough QT	B1371023		Thorough QT study of single 100 mg & 300 mg doses of glasdegib in healthy subjects
Multiple Dose in Patients	B1371001		Phase 1 study in hematologic malignancies (monotherapy) Fast ± 2 hr dose
	B1371002		Phase 1 study in solid tumors (monotherapy) Fast ± 2 hr dose
	B1371003		Phase 1b/2 dose escalation/expansion study in AML & HR-MDS Phase 1b: Fast ± 2 hr dose. Phase: w/ or w/o food
	B1371005		Phase 1 study in Japanese patients with hematologic malignancies (monotherapy) and in AML & HR-MDS as combination therapy. Cycle1: Fast ± 2 hr dose. Cycle ≥2: w/ or w/o food
	B1371012		Phase 1b study (combination of glasdegib with azacitidine) in patients with previously untreated intermediate-2 or HR MDS, AML or CML w/ or w/o food
	B1371013		Phase 2 study of glasdegib versus placebo, in patients with myelofibrosis previously treated with one or more Janus Kinase inhibitors w/ or w/o food
	B1371019		Phase 3 study of chemotherapy in combination with glasdegib versus chemotherapy in combination with placebo in adult patients with previously untreated AML w/ or w/o food

(b) (4) ADME = absorption, distribution, metabolism, and excretion, BA = bioavailability, CYP = cytochrome P450, PD = pharmacodynamic, P-gp = P-glycoprotein, PK = pharmacokinetic.
Source: Clinical Pharmacology Summary, Module 2.7.2

Single and Multiple Dose Pharmacokinetics, and Dose Proportionality

Following once daily glasdegib dosing in patients with hematologic malignancies in dose escalation Study (B1371002), steady state was achieved by Day 8 (Figure 1). Glasdegib PK was dose proportional between 5 mg and 600 mg after a single dose and at steady state (Day 21) following once daily dosing (Figure 2). The 90% CIs for the slopes of the log-log regression included a value of 1 for both glasdegib Cmax and AUC after single and multiple oral administrations (Table 3). There was up to 2.5-fold accumulation of glasdegib exposure at steady state.

Figure 1: Box plots of dose normalized glasdegib trough concentrations by visit in Study 1001

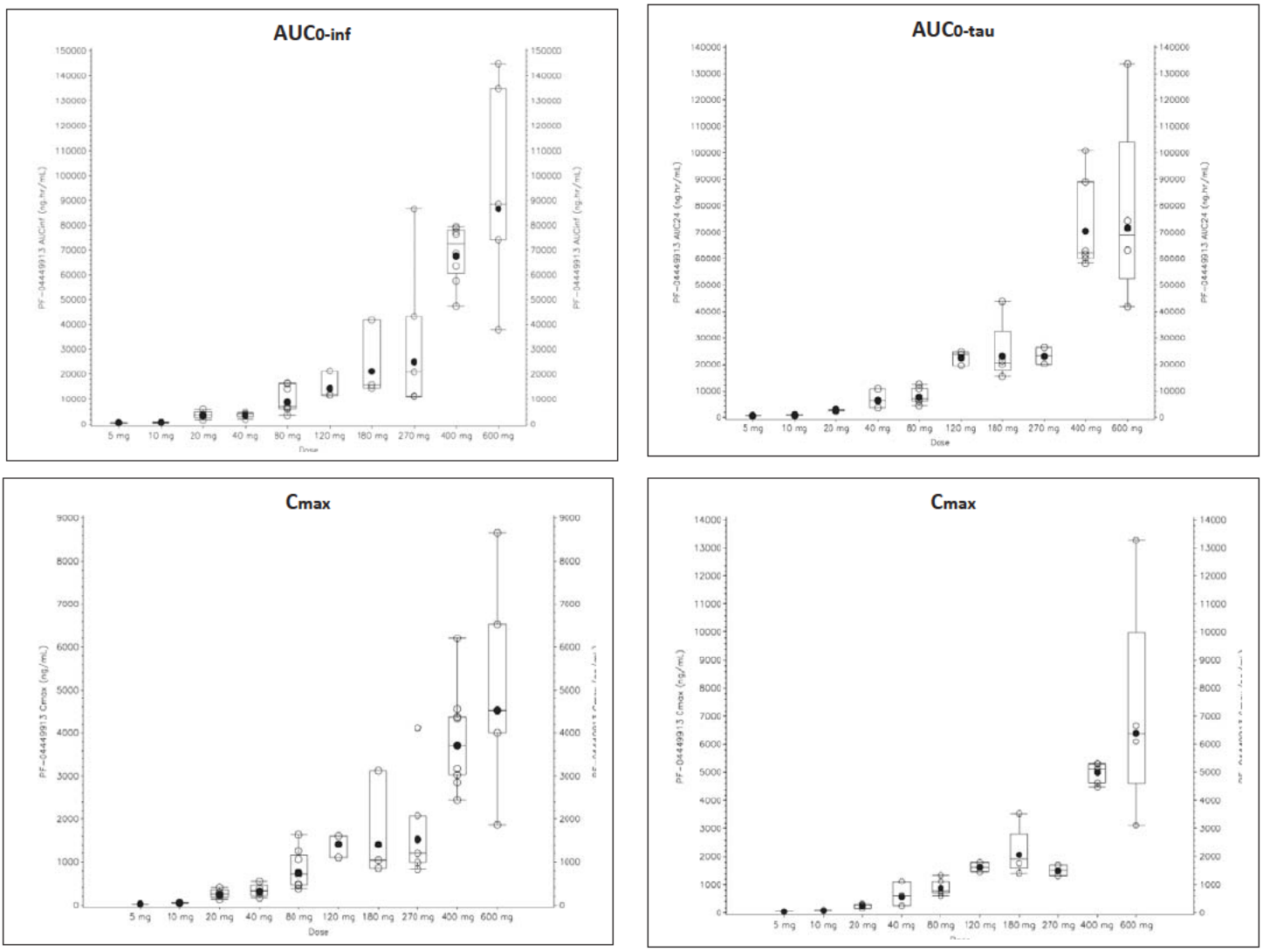


Source: Tables 14.4.4.10, Study B1371001

Table 3: Dose proportionality of glasdegib PK in patients with hematologic malignancies in Study-1001

	Dose Proportionality, Slope (90% CI)	
PK Parameter	**Single Dose**	**Steady State**
$AUC_{0\text{-}inf}$, ng·h/mL	1.05 (0.96, 1.14)	--
$AUC_{0\text{-}tau}$, ng·h/mL	--	1.07 (0.995, 1.15)
C_{max}, ng/mL	1.01 (0.92, 1.09)	1.03 (0.96, 1.11)
Racc	--	1.25-2.5
Source: Table 20, Study B1371001, and Figures 19 & 20, SCP		

Figure 2: Box plots of Geometric mean AUC (top) and Cmax (bottom) between 5 and 600 mg after single dose (left) and multiple dose (right) in Study 001



Source: Tables 14.4.4.1, 14.4.4.2, 14.4.4.5, 14.4.4.6 of Study 1001

The PK parameters after 100 mg once daily administration in patients with AML/MDS are listed in Table 4.

Table 4: PK parameters at steady state after daily 100 mg dose in AML/MDS patients in Study B1371003

PK Parameter	At Cycle 1/Day 10 after 100 mg Once Daily	
	Phase 1a (n=13)	Phase 2 (n=41)
$AUC_{0\text{-}tau}$, ng·h/mL	15020 (49)	17210 (54)
C_{max}, ng/mL	1074 (63)	1252 (44)
C_{avg}, ng/mL	554 (71)	718 (54)
C_{trough}, ng/mL	270 (73)	427 (80)
Median Tmax (hr)	1.8	1.7
Source: Tables 32 & 38, Study B1371003		

Inter-subject variability

Following a single dose of 100 mg of [redacted] (b) (4) tablets in healthy subjects, the inter-subject variability (%CV) of glasdegib under fasted conditions for glasdegib Cmax was 23% to 30% and AUC_{inf} was 25 to 31% (Studies B1371010, 1026, 1014) under fasted state. The variability under fed conditions were similar: Cmax was 28% to 34% and AUCinf was 20 to 30% (Studies B1371010, 1026, 1014).

4.2.Absorption, Distribution, and Elimination

Absorption

Glasdegib is rapidly absorbed in the fasted state with a median time to peak concentration (Tmax) of 0.5 to 4.1 hour following a 100 mg oral once daily in patients with AML.

Absolute BA

Glasdegib has an absolute bioavailability of 77% (Table 5).

B1371022: Open-label, single dose, randomized, 2-period, 2-treatment, 2-sequence, crossover study of oral (100 mg) and IV (50 mg as 50 mL of 1 mg/mL over 1.25 hours) glasdegib in 12 healthy adult volunteers under fasting condition (at least 6-day washout). PK sampling up to 96 hour post-dose.

Table 5: Point estimates and 90% confidence intervals of pharmacokinetic parameters with a intravenous and oral glasdegib formulations.

Comparison	Geometric Mean Ratio (90% CI)		Median T_{max}
	$AUC_{0\text{-}inf}$ (ng*hr/mL)	Cmax (ng/mL)	Oral/IV
Study B1371022 (n=12)			
100 mg Oral vs 50 mg IV	0.77 (0.72, 0.83)	0.77 (0.72, 0.83)	1.2
Fed-Hi: High fat meal, Fed-Std: standard meal, and Fast: fasted state, Japan=Japanese			

Table 6: Pharmacokinetic parameters of intravenous and oral glasdegib formulations

PK parameter (unit)	AUCinf (ng*hr/mL)	Cmax (ng/mL)	T_{max}† (hr)	$T_{1/2}$‡ (hr)

Study B1371022 (n=12*)				
Oral (100 mg, [redacted])	4879 (38)	665 (27)	1 (1-1.3)	13.78 ±2.97
IV (50 mg)	7628 (38)	668 (28)	1.5 (1-4)	14.26 ±2.45

†median (min, max), ‡ arithmetic mean (%CV)
Source: Study 1022

Bioequivalence

The to-be-marketed formulation [redacted] and clinical formulations, [redacted] were bioequivalent to original [redacted] salt clinical formulation (Table 7).

The bioequivalence were evaluated in the following studies:

- Study B1371014: randomized (1:1:1:1), open-label, 4-group, 12-sequence 6-treatment incomplete block study in 36 healthy subjects. Each treatment sequence consisted of 4 treatment periods. Each subject received 4 treatments with a washout period of at least 7 days. Day 6 in Periods 1, 2 and 3 could be Day 0 of the following period. PK were collected over 120 hour in both periods.
- Study B1371026: randomized, open label, 4- treatment, 3-period, 4-sequence study in 24 healthy volunteers. Subjects were randomized to 1 of 4 treatment sequences, with each treatment sequence consisted of 3 treatment periods with a washout period of at least 7 days between successive glasdegib doses. Periods 1 and 2 evaluated the bioequivalence. PK were collected over 96 hour in both periods.

Table 7: Point estimates and 90% confidence intervals of pharmacokinetic parameters under fasted state

Comparison	Geometric Mean Ratio (90% CI)			Median T_{max}
	$AUC_{0\text{-}inf}$ (ng*hr/mL)	$AUC_{0\text{-}t}$ (ng*hr/mL)	C_{max} (ng/mL)	[redacted]
Study B1371014 (n=34)				
[redacted] vs [redacted] (100 mg)	1.05 (1.01, 1.09)	1.05 (1.01, 1.09)	1.07 (1.02, 1.13)	1.00
[redacted] vs [redacted] (100 mg)	1.08 (1.04, 1.12)	1.08 (1.04, 1.12)	1.08 (1.01, 1.15)	1.50
Study B1371026 (n=24)				
[redacted] vs [redacted] (100 mg)	1.04 (1.00, 1.09)	1.04 (1.00, 1.09)	1.02 (0.96, 1.07)	0.50

Fed-Hi: High fat meal, and Fast: fasted state,

Table 8: Pharmacokinetic parameters of a single dose of glasdegib under fasted state

PK parameter (unit)	$AUC_{0\text{-}inf}$ (ng*hr/mL)	$AUC_{0\text{-}t}$ (ng*hr/mL)	C_{max} (ng/mL)	T_{max}† (hr)	$T_{1/2}$‡ (hr)
Study B1371014 (n=34, n=14*)					
Fasted (100 mg, [redacted])	8333 (26)	8239 (27)	712.9 (23)	1 (0.5-3)	16.0 (25.6%)
Fasted (100 mg, [redacted])	8871 (25)	8760 (30)	772 (25)	1 (0.5-3)	16.0 (17.5%)
Fasted (100 mg, [redacted])	9051 (30)	8957 (30)	775 (28)	1.5 (0.5-4)	15.1 (15.9%)
Study B1371026 (n=24)					
Fasted (100 mg, [redacted])	8368 (31)	8275 (31	764 (30)	2 (0.5-4)	15.0 (20%)
Fasted (100 mg [redacted])	8704 (30)	8612 (30)	561 (33)	3 (1-6)	15.2 (21.1%)

†median (min, max), ‡ arithmetic mean (%CV)
Source: Study1010, 1014, 1026

Food Effect

Food had no effect on glasdegib exposure (Table 9). In the pivotal trial supporting the proposed indications, DAURISMO was administered with or without food. The Applicant recommended administration of DAURISMO with or without food.

The effect of food on glasdegib PK was evaluated in the following four, single dose (2x 20 mg) studies in healthy subjects using the [redacted] (b) (4) tablet formulations:

- Study B1371010: open label, 2-sequence, 3-period, 3-treatment, single dose (200 mg), crossover study with a 8-day washout between periods in 14 healthy subjects (effect of ketoconazole was a coprimary objective). Periods 1 and 2 evaluated food effect, and blood samples for PK were collected over 120 hour in both periods.
- Study B1371014: randomized (1:1:1:1), open-label, 4-group, 12-sequence 6-treatment incomplete block study in 36 healthy subjects. Each treatment sequence consisted of 4 treatment periods. Each subject received 4 treatments with a washout period of at least 7 days. Day 6 in Periods 1, 2 and 3 could be Day 0 of the following period. PK were collected over 120 hour in both periods
- Study B1371026: randomized, open label, 4- treatment, 3-period, 4-sequence study in 24 healthy volunteers. Subjects were randomized to 1 of 4 treatment sequences, with each treatment sequence consisted of 3 treatment periods with a washout period of at least 7 days between successive glasdegib doses. Periods 2 and 3 evaluated the food effect. PK were collected over 96 hour in both periods

A high-calorie, high-fat meal (approximately 800-1000 calories: 500-600 fat calories, 250 carbohydrate calories and 150 protein calories) was used in Studies 1010, 1014 and 1026, consistent with the recommendations in the Food Effect FDA Guidance for Industry. Food was consumed within 30 minutes and study drug taken within 15 minutes of meal completion.

Table 9: Point estimates and 90% confidence intervals of pharmacokinetic parameters with a high-fat meal or a low-fat meal versus under a fasted state

Comparison	Geometric Mean Ratio (90% CI)		Median T_{max}
	$AUC_{0\text{-}inf}$ (ng*hr/mL)	**C_{max} (ng/mL)**	**Fed/Fast**
Study B1371010 (n=14)			
Fed-Hi vs Fast (200 mg, [redacted] (b) (4))	0.87 (0.78, 0.97)	0.66 (0.56, 0.78)	4.00
Study B1371014 (n=34 & 13)			
Fed-Hi vs Fast (100 mg, [redacted] (b) (4))	0.86 (0.81, 0.92)	076 (0.65, 0.88)	1.35
Study B1371026 (n=12)			
Fed-Hi vs Fast (100 mg, [redacted] (b) (4))	0.84 (0.76, 0.91)	0.69 (0.62, 0.77)	1.50
Fed-Hi: High fat meal, and Fast: fasted state			

Administration of a single 100 mg or 200 mg dose of glasdegib with a high-fat, high-calorie meal in healthy subjects resulted in ≤ 16% decrease in $AUC_{0\text{-}inf}$ and < 34% decrease in C_{max}

(Table 9). The median Tmax with food was delayed by a median of 0 to 3 hours compared to fasted conditions (Table 10).

Table 10: Pharmacokinetic parameters of a single dose of glasdegib with a high-fat meal under a fasted state

PK parameter (unit)	AUCinf (ng*hr/mL)	Cmax (ng/mL)	T_{max}† (hr)	$T_{1/2}$‡ (hr)
Study B1371010 (n=13)				
Fasted (200 mg, (b) (4))	15390 (26)	1204 (27)	1 (0.5-2)	18.32±1.30
Fed (200 mg, (b) (4))	13510 (35)	807 (41)	4 (2-6)	18.58±1.58
Study B1371014 (n=34, n=13*)				
Fasted (100 mg, (b) (4))	9051 (30)	775 (28)	1.5 (0.5-4)	15.10±2.42
Fed (100 mg, (b) (4))*	8059 (20)	576 (34)	2 (0.5-4)	17.28±2.48
Study B1371026 (n=24, n=12*)				
Fasted (100 mg (b) (4))	8704 (30)	561 (33)	3 (1-6)	15.20±3.22
Fed (100 mg, (b) (4))*	7927 (24)	587 (27)	3 (1.5-6)	16.08±2.67

* Refer to Appendix 4.4 for cross-validation issues
†median (min, max), ‡ arithmetic mean (%CV)
Source: Study A001-005, -018 & -017, and G000-010

Distribution:

Glasdegib is 90% bound to human plasma proteins, including human serum albumin and alpa-1 acid glycoprotein, in vitro.

The mean ratio of whole blood total radioactivity to the plasma total radioactivity at 4, 24 and 48 hours postdose were 1.362, 1.362 and 1.490, respectively. The mean ratio of the RBC total radioactivity to the plasma total radioactivity was at 4, 24, and 48 hours postdose, were 1.793, 1.786, and 2.074, respectively.

Elimination

The elimination half-life of glasdegib is ~19 hours.

An open-label, mass balance study (PK-901) was conducted in healthy volunteers (n=6) with a single oral dose (100 mg) of glasdegib [^{14}C] oral suspension. PK samples were collected up to 144 hours. Additional blood samples for whole blood analysis for total radioactivity were collected at 4, 24, 48 and 72 hour postdose. Urine samples were collected from 12 hours pre-dose, and 24 hour intervals up to 288 hours. The excretion of radioactivity in feces was monitored at Day 0 through predose on Day 1 and up to 288 hours.

Unchanged glasdegib was the major component of human plasma, accounting for 69% (mean of all 6 subjects) of the total dose, and human excreta accounting for 37% of the total dose. The mean renal clearance was 1.97 L/hr. The arithmetic mean terminal t½ (standard deviation) was 18.58 ±3.3671 hours for plasma glasdegib.

Metabolism

In humans, the primary metabolic pathways of glasdegib were comprised of N-demethylation, glucuronidation, oxidation, and dehydrogenation. In plasma, the N-desmethyl (M3) and N-glucuronide (M8) metabolites of glasdegib accounted for 7.9% and 7.2% of the circulating radioactivity, respectively. Other metabolites in plasma individually accounted for <5% of circulating radioactivity. The N-desmethyl metabolite of glasdegib was the most abundant metabolite in urine and feces, accounting for 16.8% and 9.2% of dose respectively. The N-glucuronide metabolite of glasdegib was observed in urine, accounting for 4.2% of dose. The other metabolites in the excreta individually accounted for <5% of dose.

CYP3A4 is the predominant isoform responsible for the metabolism of glasdegib (60-80%: Study 112959). CYP2C8 accounted for 2-20% of overall activity in vitro. Based on the combined results from hepatocytes (Studies 081555 and 112959), CYP3A accounted for inhibition 76% and CYP2C8 accounted for 15% inhibition of the enzyme kinetics. In pooled HLM and rCYP assays, CYP3A4 was the predominant CYP enzyme involved in the metabolism of glasdegib (1 uM) to M1, M2, M3, and M9 accounting for 60% to 80% of the overall metabolism. Minor contributions by CYP2C8 (2% to 20%), CYP2C9 (<1%) and CYP1A2 (<1%) were also observed

Excretion

High ^{14}C recovery (91%) was achieved in the mass balance study. The radioactivity in the urine was 49% ± 2% and in the feces was 42% ± 2% of dose recovered. Unchanged glasdegib accounted for 17% of the total dose in urine and 20% of the total dose in feces.

4.3. In Vivo Drug Interaction Studies

Fungal infections are a common cause of morbidity and mortality in patients with AML. For this reason, majority of patients with AML on chemotherapy are prescribed anti-fungals. The most commonly prescribed antifungals are strong CYP3A inhibitors. Two dedicated *in vivo* studies, retrospective PK analysis and safety analysis from the pivotal trial, and population PK analysis were submitted to evaluate the potential interaction of glasdegib with strong CYP3A inhibitors and inducers.

Strong CYP3A inhibitor can increase glasdegib exposures up to 2-fold based on the results of a dedicated DDI study, retrospective PK analysis in the registration trial, and population PK analysis. Also available safety data in Trial B1371003 suggests no discernable safety signals with strong CYP3A inhibitors in the Glasdegib+LDAC arm.

Glasdegib exhibits concentration dependent QT-prolongation. Majority of the azole-antifungals are also QT-prolonging. In addition, QT-prolonging drugs were frequently used in Trial B1371003 often with azole-antifungals. Strong CYP3A inhibitors in the dedicated DDI study increased mean C_{max} levels increased by 1.4 fold whereas the retrospective PK analysis in Trial B1371003 indicated a 1.2-fold increase in mean C_{max} levels with strong

CYP3A inhibitor. Majority of C_{max} in the registration trial were within ΔΔQTcF of 10 ms. An 1.4-fold increase in Cmax levels is not expected to have a major impact on the outcome of the analysis. Serious and Grade 5 cardiac-related AEs were higher in the Glasdegib+LDAC arm.

Majority of AEs were managed by dose interruptions in Trial B1371003, and the incidence of dose reductions and discontinuations were low.

Based on the above findings and since strong CYP3A inhibitors cannot be avoided in AML population due potential for fungal infection, it will be recommended that adverse reactions and the risk of QT-prolongation be monitored when DAURISMO is used with strong CYP3A inhibitors.

A strong CYP3A4 inducer decreased glasdegib exposure by ~90% in the dedicated trial. Therefore, it will be recommended that patients avoid the use of DAURISMO with drugs that are strong inducers of CYP3A in the labeling.

Drug-Drug Interactions

Effects on Glasdegib

Effect of Strong CY3A Inhibitors

Management strategy is required for the co-administration of strong CYP3A modulators.

DDI Studies:
The effect of ketoconazole (a strong CYP3A4 inhibitor), on glasdegib PK was evaluated in an open label, 2-sequence, 3-period, 3-treatment, single dose (200 mg), crossover study (B1371010) with a 8-day washout between periods in 14 healthy subjects. In Period 3, all subjects received a fixed regimen of daily doses (400 mg) of ketoconazole from Days 1 to 7 and a single dose (200 mg) of glasdegib was co-administered on Day 4. The blood samples for PK were collected at predose on Day 4, and up to 144 hours post dose.

The effects of rifampin (a strong CYP3A inducer) on glasdegib PK were evaluated in a 2-period, fixed-sequence study (Study B1371015). In Periods 1 and 2, a single dose (100 mg) of glasdegib was administered on Day 1. In Period 2, all subjects also received 600 mg oral daily doses of rifampin from Day -6 to Day 4. The blood samples for PK were collected at predose and up to 96 hours post dose in both periods

Table 11: Point estimates and 90% confidence intervals of pharmacokinetic parameters in the presence of Strong CYP3A modulators

Comparison	Geometric Mean Ratio (90% CI)		Median T_{max}
	AUC_{0_inf} (ng*hr/mL)	C_{max} (ng/mL)	Glas+drug/Glas
Study B1371010 (n=13) - Ketoconazole			
Glasdegib+Keto vs Keto (200 mg)	2.40 (2.15,2.68)	1.40 (1.23, 1.58)	0.5
Study B1371015 (n=12) -Rifampin			
Glasdegib+Rifam vs Rifam (200 mg)	0.30 (0.26, 0.34)	0.64 (0.57, 0.73)	0.83
Keto=ketoconazole, Rifam=rifampin Source:			

Table 12: Pharmacokinetics of glasdegib in the presence of Strong CYP3A modulators

PK parameter (unit)	AUCinf (ng*hr/mL)	Cmax (ng/mL)	T_{max}† (hr)	$T_{1/2}$‡ (hr)
Study B1371010 (n=13) - Ketoconazole				
Fasted (200 mg)	15390 (26)	1204 (27)	1 (0.5-2)	18.32 ±1.30
Fast+Keto (200 mg)	36900 (29)	1681 (24)	2 (0.5-4)	19.98 ±2.02
Study B1371015 (n=12) -Rifampin				
Fasted (200 mg)	8145 (23)	703.2 (19)	1.50 (1.00-4.05)	13.39±2.76
Fast+Rifampin (200 mg)	2416 (25)	455.0 (26)	1.25 (1.00-2.07)	5.112±1.06

†median (min, max), ‡ arithmetic mean (%CV)
Source:

PK and Safety in Study B1731003 (Arm A of Phase 1 and Phase 2):

There were no restrictions for the use of CYP3A inhibitors in the Trial B1371003. As fungal infections are a common cause of morbidity and mortality in AML population, 58% of patients were on CYP3A inhibitors, of which roughly half (27%) were taking strong CYP3A inhibitors in Arm A of Phase 1b and Phase 2 (Non-intensive) of Trial B1371003. Steady state trough concentrations ($C_{trough,ss}$) were collected on on C1D10, C1D21, and C2-5D1 in Arm A of Phase 1 and on C1D10 and C2D1 in Phase 2 (unfit) following 100 mg glasdegib once daily . Comparison of observed $C_{trough,ss}$ in patients who received glasdegib+LDAC in Trial B1371003 (Arm A of Phase 1b, and Phase 2) revealed that mean $C_{trough,ss}$ levels in patients during strong CYP3A inhibitor use (including a week after CYP3A inhibitor use) was 1.5-fold higher compared to $C_{trough,ss}$ levels when no CYP3A inhibitors were administered (Table 13). However, this analysis may be confounded as the time of administration of CYP3A inhibitors were not recorded, instead only the start and stop dates of CYP3A inhibitor use were recorded.

Table 13: Effect of CYP3A inhibitors on glasdegib trough concentrations at steady state in B1371003.

	Ctrough,ss (ng/mL)		
	No CYP3A	**Moderate CYP3A†**	**Strong CYP3A†**
N	56	19	17
Mean (%CV)*	365 (81%)	281 (322%)	550 (123%)
Median	355	381	638
Min	41	0.444	40
Max	3480	1860	4870

*geometric mean and CV
†during administration of CYP3A inhibitor (not including the first day of use) and up to 7 days after CYP3A inhibitor use

The safety profile indicates any grade adverse events (AE), serious AEs, and Grade 3/4 AEs were similar between the two arms in patients with no CYP3A inhibitors (Table 14). Serious and Grade 3/4 AEs were higher in the Glasdegib+LDAC arm compared to LDAC, however, serious, Grade 3/4, and Grade 5 AEs were similar for moderate and strong CTP3A inhibitors

in the Glasdegib+LDAC arm. Also, Grade 5 AEs were higher in patients without CYP3A inhibitors compared to with CYP3A inhibitors: the higher incidence of Grade 5 AEs in the patients with no CYP3A inhibitors appears to result from infections (pneumonia, sepsis).

Table 14: Safety profile (all causality) and dose modifications in the presence and absence of CYP3A inhibitors in Study B1371003 (Patients ineligible for intensive chemoptherapy)

	Glasdegib+LDAC			LDAC		
All Causality	**No CYP3A**	**Moderate CYP3A**	**Strong CYP3A**	**No CYP3A**	**Moderate CYP3A**	**Strong CYP3A**
Patients Evaluable for Adverse Events	**40**	**43**	**30**	**19**	**17**	**11**
# of Adverse Events	**488**	**519**	**475**	**73**	**100**	**202**
Evaluable Patients with	**%**	**%**	**%**	**%**	**%**	**%**
Adverse Events	100	86	93	100	71	73
Serious Adverse Events*	55	65	77	53	29	37
Grade 3/4 Adverse Events	82	77	90	90	65	55
Grade 5 Adverse Events *	20	2	3	26	0	9

CYP3A= CYP3A inhibitors, DR= dose reduction, Temp. Discont.=temporary discontinuation
*does not include disease progression
Source: Tables 1.1.d.1, 1.1.d.2, 1.1.d.3, 2.2.1, 2.2.2, IR response 6/25/18, SDN 8, and Tables 3.1, 3.2, 3a.1, 3a.2, 3b.1, 3b.2, IR Response 7/20/18, SDN 13.

Effect of Other Enzyme Modulators:

Glasdegib metabolism was negligible with recombinant UGT enzymes (rUGT) 1A1, 1A3, 1A4, 1A6, 1A7, 1A8, 1A9, 1A10, 2B4, 2B7, 2B10, 2B15, and 2B17 (Studies 163216, 050630 and YDP/003/281).

Effect of Gastric Acid Reducing Agents

There was no effect of acid reducing agents on glasdegib exposure (Table 15).

The effect of acid reducing agents was evaluated in the following studies:

- Study B1371014: randomized (1:1:1:1), open-label, 4-group, 12-sequence 6-treatment incomplete block study in 36 healthy subjects. Each treatment sequence consisted of 4 treatment periods. The effect of rabeprazole, a proton pump inhibitor was evaluated in Period 4 using the (b) (4) glasdegib formulation.
- Study B1371026: randomized, open label, 4- treatment, 3-period, 4-sequence study in 24 healthy volunteers. Subjects were randomized to 1 of 4 treatment sequences, with each treatment sequence consisted of 3 treatment periods with a washout period of at least 7 days between successive glasdegib doses. Period 3 evaluated the effect of rabeprazole using the (b) (4) glasdegib formulation.

Table 15: Point estimates and 90% confidence intervals of pharmacokinetic parameters in the presence of proton pump inhibitors

Comparison	Geometric Mean Ratio (90% CI)		Median T_{max}
	AUC_{0_inf} (ng*hr/mL)	C_{max} (ng/mL)	Glas+drug/Glas
Study B1371014 (n=34 & 13) -PPI			
No PPI vs PPI (100 mg, (b) (4))	1.12 (1.03, 1.22)	0.87 (0.76, 1.00)	1.33
Study B1371026 (n=24 vs 12) -PPI			
No PPI vs PPI (100 mg, (b) (4))	1.00 (0.93, 1.09)	0.81 (0.71, 0.92)	1.50
Fed-Hi: High fat meal, Fed-Std: standard meal, and Fast: fasted state, Japan=Japanese			

Table 16: Pharmacokinetics of glasdegib in the presence of proton pump inhibitors

PK parameter (unit)	AUCinf (ng*hr/mL)	Cmax (ng/mL)	T_{max}† (hr)	$T_{1/2}$‡ (hr)
Study B1371014 (n=34, n=14*)				
Fasted (100 mg, (b) (4))	9051 (30)	775 (28)	1.5 (0.5-4)	
Fast-PPI (100 mg, (b) (4))*	9908 (35)	690 (31)	2 (1-6)	
Study B1371026 (n=24, n=12*)				
Fasted (100 mg, (b) (4)	8704 (30)	561 (33)	3 (1-6)	
Fast-PPI (100 mg, (b) (4))*	8110 (42)	155 (38)	8 (3 - 24)	
†median (min, max), ‡ arithmetic mean (%CV)				

Effect on QT Prolongation

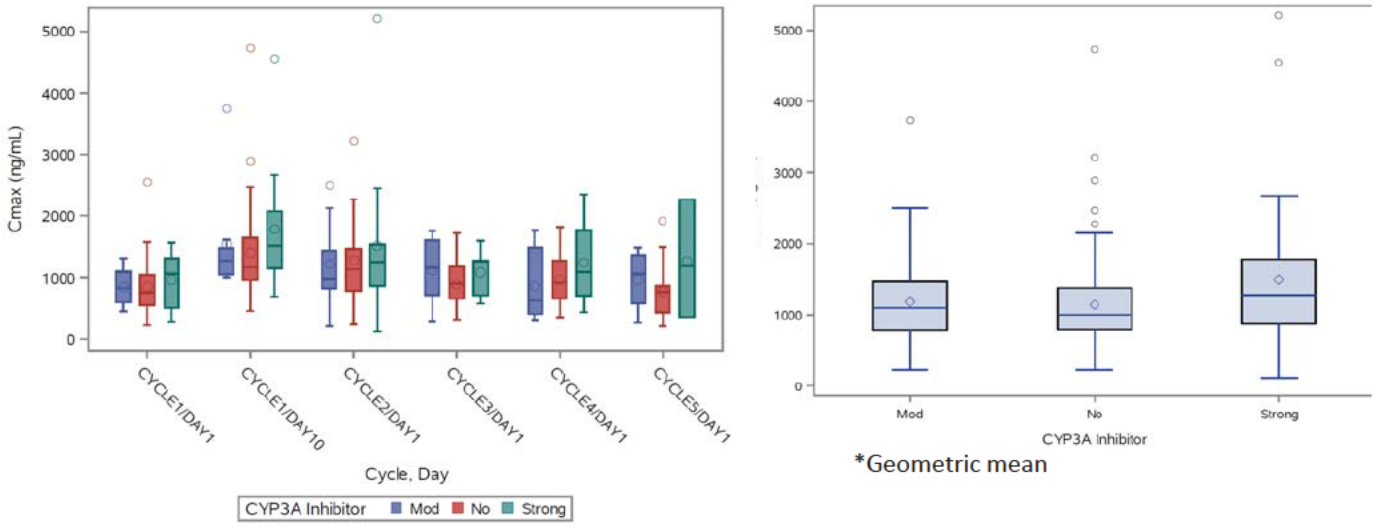
Effect of Strong CY3A Inhibitors

Retrospective analysis of PK data in Trial B1371003, indicated that the mean Cmax concentrations at steady state in patients with strong CYP3A inhibitors was 1.2-fold higher compared to that in the absence of CYP3A inhibitors. The safety profile in patients taking strong CYP3A inhibitors was not unusual compared to patients not taking CYP3A inhibitors. Majority of maximum post-dose concentrations at steady state in patients taking moderate or strong CYP3A inhibitors were within the ΔΔQTcF of 10 ms.

Steady state post-dose concentrations were collected on 0.5, 1, 2, 4, 6, and 24 hour post-dose on C1D10 and C1D21, and on 1 hour post-dose on C2-5D1 in Phase 1 (Arm A) and at 1, 2, 4, and 6 hour post-dose on C1D10 and on 1 and 4 hour post-dose on C2D1 in Phase 2 (non-intensive) following 100 mg glasdegib once daily in Study B1731003.

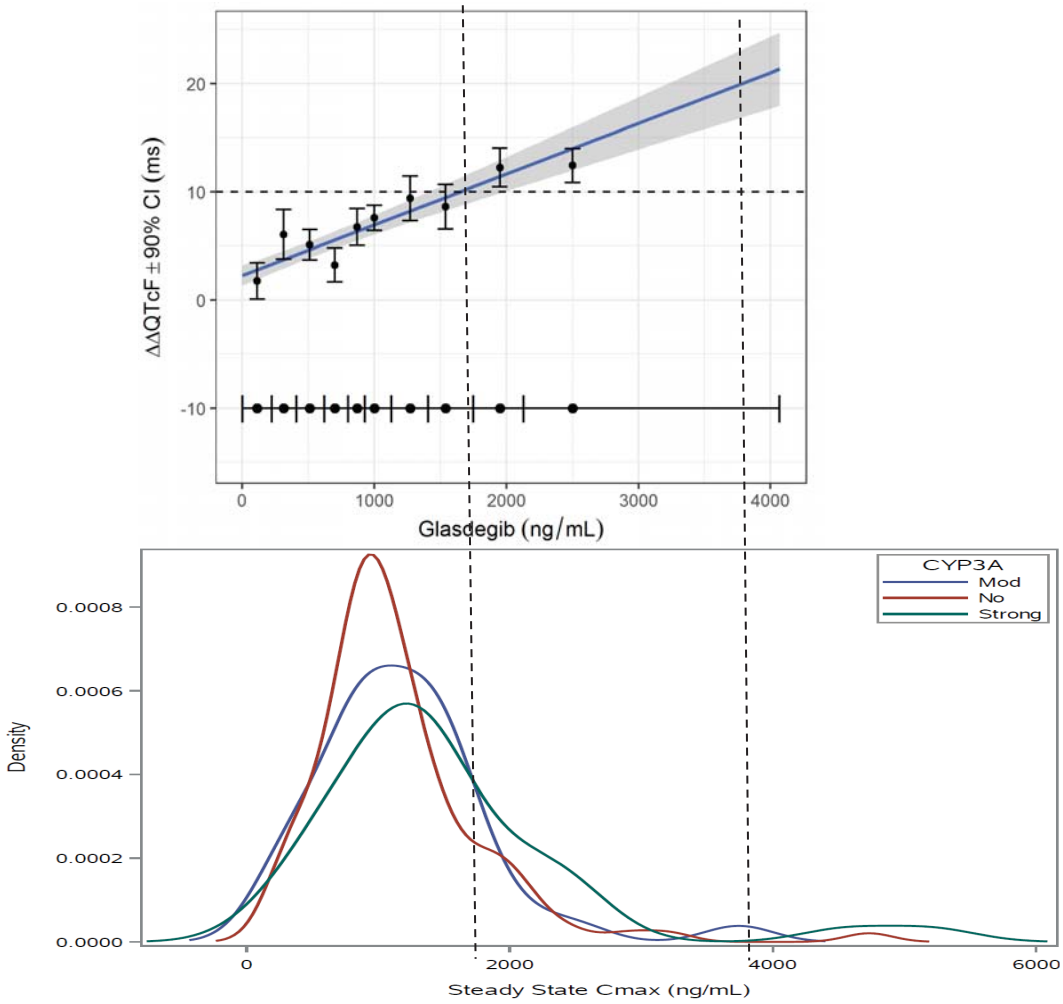
Evaluation of the maximum post-dose concentrations was used as a measure of Cmax, as glasdegib median Tmax is expected between 1-2 hours post-dose. The mean maximum post-dose concentrations at steady state in the presence of strong CYP3A inhibitors was 1.2-fold higher compared to that in the absence of CYP3A inhibitors (Figure 4:, right), with a range of 1 to 1.5-fold increase in exposure across visits (Figure 4:, left). This is within the range of the 1.4-fold increase in Cmax observed with ketoconazole in the DDI study. The difference in results may have arisen as the time of administration of CYP3A inhibitors were not recorded in Study B1371003, only the start and stop dates of CYP3A inhibitor use were recorded.

Figure 3: Mean concentrations at the Cmax range by visit (left) and at steady state across visits (right) in the presence and absence of CYP3A inhibitor in Study B1731003 (Patients ineligible for intensive chemoptherapy).



As shown in Figure 4, the majority of maximum post-dose concentrations at steady state in patients taking moderate or strong CYP3A inhibitors were within the ΔΔQTcF of 10 ms, and almost all concentrations were within the 20 ms cut-off. A 1.4-fold increase in Cmax levels is not expected to have a major impact on the outcome of the analysis.

Figure 4: Placebo-corrected change in baseline of QT interval (ΔΔQTcF)-glasdegib concentration relationship (top: from QT-IRT review) and density plots of steady state Cmax concentrations with CYP3A inhibitor use from Study B1731003 (bottom).



The serious and Grade 5 cardiac-related events were higher in the Glasdegib+LDAC arm (Table 17) in Trial B1371003. Five patients had fatal Grade 5 AEs, including 2 sudden deaths (ID [redacted]), 1 cardiac arrest (ID [redacted]) and 2 myocardial infarctions (ID [redacted] in Phase 1b, and ID [redacted]) in Glasdegib+LDAC arm. Of which, 3 patients (ID [redacted]) had no concomitant medications or concomitant medications were stopped > 6 months prior to the events. No action was taken for majority of the patients with cardiac events, and dose was interrupted or discontinued in 6 patients with Grade ≥3 cardiac events in the Glasdegib+LDAC arm.

Table 17: QT-related adverse events in the presence of QT-prolonging drugs in Study B1371003 (Phase 1, Arm A; Phase 2, Unfit)

	Number of Patients (%)	
	Glasdegib+LDAC (n=101)	**LDAC (n=41)**
With Cardiac Events	**19**	**10**

Serious AEs	10			0		
Grade 3-4	10			7		
Grade 5	5			0		
Dose Interruptions	3			0		
Discontinuations	4			0		
Dose Reduction	1			0		
No Action Taken	12			10		
	QT-prolonging + CYP3A Inhibitor (†)		**Only QT-Prolong**	**QT-prolonging + CYP3A inhibitor (†)**		**Only QT-Prolong**
	Strong	**Moderate**		**Strong†**	**Moderate**	
With Cardiac Events	5 (3)	5 (5)	4	2 (2)	2 (2)	2 (2)
Serious AEs	3 (2)	3 (3)	3	0	0	0
Grade 3-4	5 (2)	3 (3)	3	0	2	2
Grade 5*	0	1 (1)	1	0	0	0
Dose Interruptions	0	2 (2)	0	0	0	0
Discontinuations	1	2 (2)	2	0	0	0
Dose Reduction	0	1 (1)	0	0	0	0
No Action Taken	4 (3)	5 (5)	4	2 (2)	2 (2)	2 (2)

QT-Prolong=QT-Prolonging drugs
†represents only CYP3A inhibitor administered that are QT-prolonging at the time of event.
* Grade 5 events for Patients (b) (6) (Death) and (b) (6) (Cardiac arrest) not included, as the events occurred >6 months after concomitant medications were stopped.
Source: CSR 1003, Tables 16.2.7.1.1 & 16.2.7.1.3, and SDN 8 & 13.

Further, the use of CYP3A inhibitors with QT-prolonging drugs and the use of only QT-prolonging drugs were compared in patients with cardiac events (Table 17). For any grade, Grade 3/4, and serious events, the number of patients taking strong or moderate CYP3A inhibitors at the time of cardiac-related events were similar in the Glasdegib+LDAC arm. No patients with Grade 5 cardiac events were on strong CYP3A inhibitors: one patient was on moderate CYP3A inhibitors and the other was on only QT-prolonging drugs at the time of events in the Glasdegib+LDAC arm. Also, except for one patient, dose modifications were limited to patients taking either moderate CYP3A inhibitors with QT-prolonging drugs or only QT-prolonging drugs.

Glasdegib Dose Modifications with Concomitant Drugs

Majority of the AEs were managed by glasdegib dose interruptions with CYP3A inhibitors and/or QT prolonging drugs (Table 18). There were 1 to 8 dose interruptions per patient. Time to first dose interruption started in Cycles 3 or later, and the mean duration of interruption was short (10-12 days). The incidence of glasdegib dose reduction (1 % to 13%) and dose discontinuations (none to 7%) due to AEs were low.

Table 18: Dose Modifications due to AEs with CYP3A inhibitors and/or QT prolonging drugs

Dose Modifications	**Patients**	**Mean (Median: range), Days**

		Time to 1st Event	Event Duration
With CYP3A inhibitors			
Dose Reduction	2%	65 (65: 41, 89)	493 (493: 327, 659)
Dose Interruptions	9%	81 (22: 10, 254)	12 (7: 2, 35)
Dose Discontinuation	2%	--	--
With CYP3A inhibitors + QT-Prolonging Drugs			
Dose Reduction	13%	120 (76: 30, 377)	210 (54: 15, 659)
Dose Interruptions	38%	63 (29: 2, 323)	11 (7: 1, 49)
Dose Discontinuation	7%	--	--
With only QT-Prolonging Drugs			
Dose Reduction	1%	254	9
Dose Interruptions	9%	74 (29: 5, 308)	10 (6: 1, 22)
Dose Discontinuation	0	--	--
Source: Applicant's 7/20/18 response to Information Request, SDN 13 (Tables 4c.1, 4c.2, & 4c.3,)			

Effect of Glasdegib

On CYP Inhibition:

Glasdegib does not inhibit CYP1A, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, CYP2E1, or CYP3A in vitro (Table 19).

Table 19: IC_{50} and calculated R_1 values for glasdegib inhibition of CYP activities in human liver microsomes

CYP Enzyme	Substrate	Glasdegib IC_{50} (µM)	Positive Control	R_1 value $1+(I_{max,u}/K_i)$
CYP1A2	Phenacetin	> 94	Furafylline ()†, α-Naphthoflavone ()‡	1.0
CYP2B6	Bupropion	> 94	Orphenadrine, Phencyclidine	1.0
CYP2C8	Amodiaquine†, Paclitaxel‡	82	Montelukast, Gemfibrozil	1.0
CYP2C9	Tolbutamide	> 94	Sulfaphenazole, Tienilic acid	1.0
CYP2C19	S-Mephenytoin	> 94	Modafinil, *S*-Fluoxetine	1.0
CYP2D6	Dextromethorphan	88	Quinidine, Paroxetine	1.0
CYP3A	Midazolam Nifedipine Testosterone	> 94 > 94 > 94	Ketoconazole, Troleandomycin	1.0

Calculation of glasdegib R_1 values based on maximal steady-state concentration of 1252 ng/mL or 3.3 µM [I_{max}]. Fraction unbound = 10%= 0.10
K_i assumed to be $IC_{50}/2$ for competitive inhibition for those CYP enzymes without an experimental K_i value
Source: XT135086.

Glasdegib did not show TDI or MDI of CYPs 1A2, 2B6, 2C8, 2C9, 2C19, 2D6 or 3A4/5 at concentrations up to 100 µM.

Mechanistic static modeling, predicts an AUCR of 1.02 following co-administration of glasdegib with substrates of CYP3A4/5 which is <1.25.

On UGT Inhibition:
In the absence of 2% BSA, glasdegib total IC_{50} was >131 µM for inhibition of UGT1A4, 1A6, 1A9, 2B7, or 2B15 catalyzed activities, and IC_{50} of 9.5 µM for UGT1A1. In the presence of 2% BSA, glasdegib total IC_{50} >131 µM for UGTs 1A4, 1A6, 2B7, and 2B15 (R1 <1.02), and with unbound IC_{50} of 3.9 (R1=1.15) and 20 µM (R1=1.03) for UGT1A1 and UGT1A9 activity, respectively. Per Applicant, the predicted AUCR values were <1.25 following co-administration of glasdegib with sensitive substrates of UGT1A1 (AUCR=1.15) and UGT1A9 (AUCR=1.03).The current FDA DDI guidance does not have criteria for UGT inhibition of investigational drug.

Per FDA guidance an enzyme is considered significant if the enzyme is responsible for > 25% of the drug's elimination based on the in vitro phenotyping studies and human PK data. Per the ADME study, glucuronide metabolites contributed to <10% of dose in plasma and ~5% in urine.

On CYP Induction:
1 to 30 µM of glasdegib did not induce CYP3A4 (mRNA or enzyme activity: midazolam as substrate) and CYP2B6 (mRNA or enzyme activity: bupropion as substrate) in 3 lots of hepatocytes. In the initial study, glasdegib up to 100 µM also did not induce CYP3A4 and CYP1A2 mRNA and enzymatic activity but low cell viability was noted at concentrations above 10 µM (135232 & XT133102). Nonetheless, the potential for glasdegib to induce CYP3A, 2B6 and 1A2 is low, as the maximum observed glasdegib plasma concentrations in clinical trials were ≤ 3.3 µM.

On Transporter Inhibition:

Glasdegib has the potential to inhibit P-gp and BCRP (I_{gut}/IC_{50} >11), and MATE1 and MATE-2K ($I_{max,u}/IC_{50}$ >0.02) at clinically relevant concentrations per the current FDA DDI guidance (2017) (Table 20).

Table 20: IC_{50} and calculated R values for glasdegib inhibition of transporters

Transporter	Substrate	Glasdegib IC_{50} (µM)	I_{gut}/IC_{50}	$I_{max,u}/IC_{50}$	1+ $((f_{u,p} \times I_{in,max})/IC_{50})$ [b]
P-gp	Digoxin	>33	32	--	--
BCRP	Pitavastatin	4.6	232	--	--
OCT1	--	--	--	<0.1	--
OCT2	Metformin	>50	--	<0.1	--
OAT1	PAH	>50	--	<0.1	--
OAT3	Estrone 3–sulfate	>50	--	<0.1	--
MATE1	Metformin	4.9	--	0.06	--
MATE2K	Metformin	1.2	--	3.6	--
OATP1B1	Rosuvastatin	26	--	--	<1.1
OATP1B3	Rosuvastatin	26	--	--	<1.1

I_{gut}=Dose/250 mL = 0.4 mg/mL = 1067 µM

[b] $I_{in,max}$ = (Imax + (Fa x Fg x Ka x Dose))/Qh/R_B

Where Imax = 3.3 µM or 1252 ng/mL, $f_{u,p}$ = 0.10, Fa=1, Fg=1, Ka=0.001/min, Dose=100 mg, Qh=97 L/hr = 1616mL/min, and R_B=1.4,

Source: *Study 154108,

Substrates of Glasdegib

Transporters:

Glasdegib is a substrate of P-gp and BCRP. Greater than 2-fold uptake of glasdegib was observed in P-gp- and BCRP-expressing cells, and efflux ratio (ER) in the presence of a P-gp or BCRP inhibitor decreased to <50% of the ER in the absence of inhibitor (Table 21).

Table 21: Evaluation of glasdegib as substrate of transporters in vitro

CYP Enzyme	Inhibitor	Glasdegib		Control Probes	Control Probes	
		Efflux or Uptake Ratio$^{\Delta}$	% Inhibition		Efflux or Uptake Ratio$^{\Delta}$	% Inhibition
P-gp*	Cyclosporine CP-100256	15-27§ (1 -30 µM)	96-97% §	N/A	N/A	N/A
BCRP**	Ko144	33§ (0.5 µM)	94% §	N/A	N/A	N/A
OATP1B1 & 3†	Rifamycin SV	--	0%$^{\Delta}$ (1 µM)	1 µM Rosuvastatin	--	48%
OAT1‡	--	1.5 & 1.2$^{\Delta}$ (1 & 10 µM)	-	2 µM P-aminohippurate	71	--
OAT3‡	--	2 & 1.7$^{\Delta}$ (1 & 10 µM)	--	2 µM estrone-3-sulfate	29	
OCT2‡	--	0.3$^{\Delta}$ (1 & 10 µM)	--	50 µM Metformin	40	
MATE1‡	--	0.3 & 0.2$^{\Delta}$ (1 & 10 µM)	--	50 µM Metformin	13	
MATE2K‡	---	0.9 & 0.7$^{\Delta}$ (1 & 10 µM)	--	50 µM Metformin	8	

§Per FDA DDI guidance, substrate if efflux ratio ≥2 in P-gp or BCRP expressing cells and % inhibition >50%
$^{\Delta}$Per FDA DDI guidance, substrate if overexpressing/wild-type uptake ratio ≥2 and % inhibition >50%
Source: *131858, **101906, †150827, ‡15351

Glasdegib is not a substrate of OATP1B1, OATP1B3, OAT1, OAT3, OCT2, MATE-1 and MATE-2K. Less than 2-fold uptake of glasdegib was observed in OAT1, OAT3, OCT2, MATE-1 and MATE-2K -expressing cells compared to those in wild-type cells, and in the presence of a OATP1B1/OATP1B3 inhibitor, there was no inhibition of uptake ratio.

4.4. Specific Populations

No dose adjustment is recommended for age (20-94 years), sex, race or ethnicity (234 White, 16 Black, 9 Asian, and 11 Hispanic), body weight (43.5 to 145.6 kg), mild hepatic impairment (HI) and mild to moderate renal impairment (RI) as these factors did not affect the PK of glasdegib (Appendix 4.6.1).

Hepatic Impairment

A lower starting dose is not recommended for patients with mild to moderate HI based on the available PK, safety and efficacy data. The effect of severe HI on PK of glasdegib has not been evaluated, and safety and efficacy data in this population is limited.

The effect of HI on PK evaluated by population PK analysis indicates that hepatic impairment was not a significant covariate (Appendix 4.6.1). However, only 3 patients with moderate HI and 1 patient with severe HI were evaluated. In addition, safety of glasdegib in patients with mild HI was comparable to patients with normal hepatic function (Table 22) in Study B1731003 (patients who are ineligible for intensive chemotherapy): only 2 patients were evaluated for moderate HI. The efficacy estimation for mild and moderate HI may not be reliable due limited sample size (Table 23)

Renal Impairment

A lower starting dose is not recommended for patients with mild and moderate RI (CLcr ≥ 30 mL/min). The effect of severe RI on PK of glasdegib has not been evaluated.

49% of the administered dose is recovered in urine, with 17% as unchanged drug. No dedicated RI study was conducted. Population PK analysis that included patients with mild and moderate RI, showed that CLcr (as surrogate for renal function) was a significant covariate, however, the reduction in glasdegib clearance with moderate impairment (CLcr 30-59 mL/min) was not clinically meaningful (Appendix 4.6.1). The effect of severe RI (CLcr < 30 mL/min) was not studied. The safety and efficacy of mild and moderate RI were comparable to normal renal function in Study B1731003 (patients ineligible for intensive chemotherapy) (Table 24 and Table 25)

Table 22: Safety summary of hepatic impairment (HI) in the Glasdegib+LDAC arm in Trial B1371003 (patients ineligible for intensive chemotherapy)

Patients	N	%AE	% Grade 3/4	% Grade 5	% SAE	%AE → TD	%AE → DI	%AE → DR
Normal	80	100	89	30	78	37	55	15
Mild HI	17	100	94	41	82	24	59	18
Moderate HI	2	100	50	0	50	0	0	0

AE= adverse event, SAE=serious AE, PD=treatment discontinuation, TD=temporary discontinuation, DI = dose interruption
Source: Table 3.2.5, Response to IR, 6/25/18, SDN 8

Table 23: Overall Survival (OS) in patients with hepatic impairment in Trial B1371003

	Glasdegib+LDAC	Median OS (80% CI)
Normal	N=80	9 [7, 12]
Mild HI (B1)	N=11	4 [3, 7]
Mild HI (B1)	N=6	6 [5, 15]
Moderate HI	N=2	. [10, .]

Source: Figure 3.1.3, Response to IR, 6/25/18, SDN 8

Table 24: Safety summary of renal impairment (RI) in the Glasdegib+LDAC arm in Trial B1371003 (patients ineligible for intensive chemotherapy)

Patients	N	%AE	% Grade 3/4	% Grade 5	% SAE	%AE → PD	%AE → TD	%AE → DR
Normal	16	100	94	44	69	44	56	19
Mild RI	39	100	90	31	82	39	49	10
Moderate RI	45	100	87	24	77	36	53	18

AE= adverse event, SAE=serious AE, PD=treatment discontinuation, TD=temporary discontinuation, DI = dose interruption,
Source: Table 3.2.6, Response to IR, 6/25/18, SDN 8

Table 25: Overall Survival (OS) in patients with renal impairment in Trial B1371003

	Glasdegib+LDAC	Median OS (80% CI)
Normal	N=16	7 [4 , 13]

	Glasdegib+LDAC	Median OS (80% CI)
Mild RI	N=45	7 [4, 10]
Moderate RI	N=39	8 [5, 11]
Source: Figure 3.1.4, Response to IR, 6/25/18, SDN 8		

4.5. Summary of Bioanalytical Method Validation and In-Study Performance

Method Validation

The Applicant used a liquid-liquid extraction with tandem mass spectrometric detection (LC/MS/MS) for quantitation of glasdegib in human plasma. Two bioanalytical methods were used for the estimation of glasdegib in human plasma. The initial method covered a range of 0.2 to 200 ng/mL (Method B1379001), and the method was later modified to include a reduced sample extraction volume (from 100 µL to 50 µL) and a broader quantitative range (to 3.00 to 3000 ng/mL) (Method B1379008). The bioanalytical methods were validated as described in Table 26.

Table 26: Method validation parameters

Validation Parameters	**B1379001**	**B1379008**
Facility	(b) (4)	(b) (4)
Analyte	Glasdegib	
Internal Standard	D4-glasdegib-d4	
Detection	LC/MS/MS	
Extraction	Liquid-liquid	
Range	0.200 to 200 ng/mL	3.00 to 3000 ng/mL
Inter/Intra-assay Precision	≤7%	≤7%
Inter/Intra-assay Accuracy	≤ 3%	≤ 10%
Stock stability for galsdegib Stock stability for S	96 days at -10°C to -30°C, 6 hrs at RT	105 days at -10°C to -30°C 6 hrs at RT
Bench-top stability	• 53 hours at RT • 49 hours at 45°C	23 hours at 15°C -30°C
Refrigerated stability	25 hours at 2°C -8°C	4 hours at 2°C -8C (b) (4) and maleate forms)
Long-term Stability*	• 372 days at -10°C to -30°C† • 1277 days at -60°C to -80°C‡	• 279 days ((b) (4)) & 386 days (Maleate) at -20°C • 575 days at -70°C ((b) (4) and maleate forms)
Dilution samples stability	482 days at -10°C to -30°C and at -60°C to -80°C‡	
Free-ze-Thaw Stability	6 cycles‡	5 cycles
Processed Extract stability:.	87 hrs at 2°C -8°C	143 hrs at 2°C -8°C
Reinjection stability:	90 hours at 2°C to 8°C	150 hours at 2°C to 8°C
Hemolysis	No effect	
Whole blood stability	2 hrs at RT & wet ice‡	2 hrs at 15°C -30°C & Wet ice

		([(b) (4)] and maleate forms)
Dilution	10x dilution	10x dilution
Assay used in Clinical Studies	B1371001, B1371002, B1371003, B1371009, and B1371010	B1371005, 1012, 1014, 1015, 1022, 1023, and 1026

†Addendum 1, ‡Addendum 2, RT=room temperature

*Glasdegib was found to be unstable when stored for 496 to 1277 days at -10°C to -30°C (degradation by >15 to 55%).

In-Study Assay Performance:

In Studies B1371001, B1371002, B1371003, B1371009, and B1371010, the precision was ≤11% and accuracy was ≤14%. In Studies B1371005, B1371012, B1371014, B1371015, B1371022, B1371023, and B1371026 the precision was ≤7% and accuracy was ≤11%.. Majority (≥ 80%) of the analytical runs in the studies were successful. The incurred sample reanalysis (ISR) was performed in all studies, and were within acceptable limits (≥67% of samples within 20% different).

The study samples were handled within the validated storage and handling conditions, except the maximum long-term storage in the following studies were longer than the validated range (i.e., 372 days at -10°C to -30°C):

Table 27: Long-term storage deviations

Study	1st enroll & last subject compl	Analysis dates	Comments
1001	3/3/10-2/27/13	4/6 to 8/12/13	Max storage 814 days at -10 to -30C. Report states that only 6 samples were outside the 372 day limit.
1002	5/11/11 – 12/28/12	7/20/11-4/11/13	Report states that max storage 406 days at -10 to -30C, > 372 day limit at -10 to -30 or 279 days @ -20C Report states that only 5 samples were outside the 372 day limit. D
1003	6/27/12- 1/3/17	121/24/12 to 8/14/17	Report states that max storage 966 days at -20 to -70C, within the 1277 day at -60 to 80C, but > 372 day limit at -10 to -30 or 279 days @ -20C.

Per the Applicant's response, only 42 glasdegib plasma PK samples in studies B1371001, B1371002 and B1371003 (Arm A Phase 1b, and Phase 2, unfit) were analyzed beyond established long-term stability (372 days at -10°C to -30°C). This represents ~5% of total samples analyzed. Per Applicant, the PK profiles for patients [(b) (6)], and [(b) (6)] were in-line with the other profiles that were assayed within known stability limits, for each treatment group. Hence, the impact of these small number of out-of-stability PK samples on the glasdegib PK parameter estimates is likely negligible.

Cross-Validation

The two bioanalytical methods were not cross-validated. Nonetheless, the studies used for population PK analysis were analyzed with the same method (B1379001). The clinical pharmacology studies B1371010, B1371014, B1371015, B1371022, B1371023, and

B1371026, that used method B1379008, are standalone studies and are not affected by the lack of cross-validation. The reliability of data from Study B1371005 (using method B1379008) for comparison against Study 1003 (using method B1379001) is questionable due to the lack of cross validation.

4.6. Pharmacometrics Review

4.6.1. Population PK

A population PK model was developed by Applicant based on pooling data from two Phase 1 studies, Studies B1371001 and B1371002, and one Phase 1b/2 study, B1371003. B1371001 was a Phase 1 dose escalation study of glasdegib administered orally as a single agent to adults with select hematologic malignancies. A total of 47 subjects were enrolled in the study with the dose range of 5 to 600 mg once daily. PK samples were collected at the following time points:

- Lead-in period Day -6: Pre-dose, 0.5, 1, 2, 4, 8, 24, 48, 96 and 120 hours post dose.
- Cycle 1 Day 1: Pre-dose and 1 hour post dose.
- Cycle 1 Day 5: Pre-dose.
- Cycle 1 Day 8: Pre-dose, 1 and 4 hours post dose.
- Cycle 1 Day 15: Pre-dose and 1 hour post dose.
- Cycle 1 Day 21: Pre-dose and 0.5, 1, 2, 4, 8, and 24 hours post dose.
- Cycles 2-5 Day 1: Pre-dose and 1 hour post dose.
- Cycles 6 and above Day 1 and EOT: 1 hour post dose.

B1371002 was a Phase 1 dose escalation study of glasdegib administered orally as a single agent to adult patients with diagnosis of select advanced/metastatic solid tumors that were either resistant to standard therapy, for which no standard therapy was available, or that was inappropriate for standard treatment. A total of 23 subjects were enrolled in the study with the dose range of 80 to 640 once daily. PK samples were collected at the following time points:

- Cycle 1 Day 1: Pre-dose and 1, 2, 4, 6, 10, and 24 hours post dose.
- Cycle 1 Day 8 and Day 15: Pre-dose and 2 hours post dose.
- Cycle 1 Day 25: Pre-dose and 1, 2, 4, 10, 24, 48, 72, and 96 hours post dose.
- Cycles 2-8 Day 1 and EOT: Pre-dose and 2 hours post dose.

B1371003 was a Phase 1b/2 safety and efficacy study of glasdegib in combination with intensive chemotherapy (cytarabine/daunorubicin,7+3), Low-Dose Cytarabine (LDAC), or decitabine in previously untreated patients with acute myeloid leukemia (AML) or high risk myelodysplastic syndrome (MDS). In the Phase 1b portion, 52 subjects were enrolled in the study with doses of 100 mg or 200 mg. In the Phase 2 portion, 132 (including 44 patients without glasdegib) and 71 subjects were enrolled with a dose of 100 mg once daily for fit

(intensive) arm and unfit (non-intensive) arm, respectively. PK samples were collected at the following time points:

- Phase 1b 100/200 mg glasdegib + LDAC Cycle 1 Day 3: Pre-dose, 0.5, 1 and 4. Cycle 1 Days 10 and 21: Pre-dose, 0.5, 1, 2, 4, 6, and 24. Cycles 2+ Day 1: Pre-dose and 1.
- Phase 1b 100/200 mg glasdegib + decitabine Cycle 1 Day 2: Pre-dose, 1 and 4. Cycle 1 Day 10: Pre-dose, 0.5, 1, 2, 4, 6, and 24. Cycle 2 Day 1: Pre-dose, 0.5, 1, 2, 6, and 24. Cycles 3+ Day 1: Pre-dose and 1. Phase 1b and Phase 2 100/200 mg glasdegib +7+3 Lead-in Day -3: Pre-dose and 1. Induction Cycle Day 3: Pre-dose, 0.5, 1, 6, and 24. Induction Cycle Day 10: Pre-dose, 0.5, 1, 4, 6, and 24e. All Consolidation and Maintenance cycles: 1.
- Phase 2 100 mg glasdegib +LDAC Cycle 1 Day 1: Pre-dose, 0.5, 1, and 4. Cycle 1 Day 10: Pre-dose, 1, 2, 4, and 6. Cycle 2+ Day 1: Pre-dose, 1 and 4.

The observed data for each continuous demographic or safety laboratory variable are summarized in Table 28 for all patients (N = 272). The number (%) of individuals for each categorical variable level are summarized in Table 29.

Table 28: Summary of Continuous Variables

Variable	Study	N	Nm	Mean (Stdev)	Median (Range)
Age (years)	B1371001	47	0	64.13 (13.75)	69.00 (25.00-89.00)
	B1371002	23	0	58.22 (13.02)	61.00 (27.00-76.00)
	B1371003	202	0	69.01 (11.44)	70.50 (27.00-92.00)
	Overall	272	0	67.25 (12.40)	69.00 (25.00-92.00)
Baseline Albumin (g/dL)	B1371001	47	0	3.76 (0.55)	3.80 (2.40-4.90)
	B1371002	23	1	3.90 (0.54)	4.05 (2.60-4.60)
	B1371003	202	3	3.66 (2.19)	3.60 (0.00-33.00)
	Overall	272	4	3.70 (1.90)	3.67 (0.00-33.00)
Baseline ALT (U/L)	B1371001	47	0	33.11 (51.89)	23.00 (5.00-348.00)
	B1371002	23	1	26.50 (23.15)	19.50 (6.00-116.00)
	B1371003	202	1	24.89 (18.00)	20.00 (5.00-166.00)
	Overall	272	2	26.45 (27.43)	20.00 (5.00-348.00)
Baseline AST (U/L)	B1371001	47	0	31.85 (52.90)	20.00 (10.00-364.00)
	B1371002	23	1	31.41 (30.60)	23.50 (8.00-150.00)
	B1371003	202	4	23.77 (12.78)	21.00 (8.00-107.00)
	Overall	272	5	25.82 (26.29)	21.00 (8.00-364.00)
Baseline Bilirubin (mg/dL)	B1371001	47	0	0.68 (0.61)	0.50 (0.10-4.24)
	B1371002	23	1	0.70 (0.41)	0.60 (0.30-1.80)
	B1371003	202	0	0.68 (0.35)	0.60 (0.02-2.30)
	Overall	272	1	0.68 (0.41)	0.60 (0.02-4.24)
Baseline Creatinine Clearance (mL/min)	B1371001	47	0	91.04 (33.14)	86.10 (38.60-224.75)
	B1371002	23	1	94.79 (30.40)	94.25 (46.55-148.95)
	B1371003	202	0	84.17 (33.35)	78.17 (31.36-238.35)
	Overall	272	1	86.22 (33.17)	80.92 (31.36-238.35)
Baseline Hemoglobin (g/dL)	B1371001	47	0	9.52 (1.36)	9.40 (6.90-14.60)
	B1371002	23	1	13.10 (1.90)	12.80 (9.20-17.20)
	B1371003	202	0	9.00 (1.15)	8.80 (6.90-13.80)
	Overall	272	1	9.43 (1.68)	9.00 (6.90-17.20)
Baseline Body Mass Index (kg/m^2)	B1371001	47	0	25.24 (5.23)	23.74 (16.99-45.25)
	B1371002	23	0	27.74 (6.54)	27.28 (17.18-43.82)
	B1371003	202	0	28.31 (5.10)	27.38 (17.06-46.74)
	Overall	272	0	27.73 (5.36)	27.14 (16.99-46.74)
Baseline Percent Bone Marrow Blasts	B1371001	47	8	41.75 (32.69)	37.00 (0.00-100.00)
	B1371002	23	23	None	None
	B1371003	202	11	44.87 (24.58)	39.50 (10.00-100.00)
	Overall	272	42	44.34 (26.08)	39.25 (0.00-100.00)
Baseline Body Surface Area (m^2)	B1371001	47	0	1.84 (0.21)	1.87 (1.42-2.35)
	B1371002	23	0	1.88 (0.22)	1.82 (1.50-2.37)
	B1371003	202	0	1.93 (0.21)	1.92 (1.44-2.54)
	Overall	272	0	1.91 (0.21)	1.90 (1.42-2.54)
Baseline Serum Creatinine (mg/dL)	B1371001	47	0	0.84 (0.24)	0.78 (0.48-1.69)
	B1371002	23	1	0.92 (0.24)	0.86 (0.60-1.30)
	B1371003	202	0	0.99 (0.28)	0.94 (0.47-1.91)
	Overall	272	1	0.96 (0.28)	0.90 (0.47-1.91)
Baseline White Blood Cells ($10^9/L$)	B1371001	47	0	9.11 (11.46)	4.40 (0.40-48.50)
	B1371002	23	1	6.34 (2.08)	6.45 (2.40-11.60)
	B1371003	202	0	35.49 (411.21)	2.83 (0.40-5850.00)
	Overall	272	1	28.55 (355.03)	3.60 (0.40-5850.00)
Baseline Weight (kg)	B1371001	47	0	73.35 (16.03)	71.80 (43.50-117.30)
	B1371002	23	0	78.87 (19.23)	73.80 (47.00-127.40)
	B1371003	202	0	81.99 (16.72)	80.15 (47.50-145.60)
	Overall	272	0	80.23 (17.08)	78.59 (43.50-145.60)
Baseline Height (cm)	B1371001	47	0	170.41 (9.73)	170.70 (152.40-193.00)
	B1371002	23	0	168.69 (8.51)	169.90 (153.40-185.40)
	B1371003	202	0	170.06 (9.12)	170.20 (145.00-188.00)
	Overall	272	0	170.00 (9.16)	170.20 (145.00-193.00)

Source: Applicant's population PK report, Page 33, Table 7

Table 29: Summary of Categorical Variables

Variable	Category	Total	B1371001	B1371002	B1371003
N		272	47	23	202
Patient Status	Hematologic	249 (92%)	47 (100%)	0 (0%)	202 (100%)
	Solid tumor	23 (8%)	0 (0%)	23 (100%)	0 (0%)
Formulation	di-HCl small	121 (44%)	47 (100%)	23 (100%)	51 (25%)
	di-HCl large	151 (56%)	0 (0%)	0 (0%)	151 (75%)
Fed/Fasted Status	Fasted	110 (40%)	36 (77%)	23 (100%)	51 (25%)
	Fed	1 (0%)	1 (2%)	0 (0%)	0 (0%)
	Fasted or Fed	161 (59%)	10 (21%)	0 (0%)	151 (75%)
CYP3A inhibitor use[a]	No CYP3A inhibitor used	154 (57%)	32 (68%)	21 (91%)	101 (50%)
	Moderate CYP3A inhibitor used	62 (23%)	8 (17%)	2 (9%)	52 (26%)
	Strong CYP3A inhibitor used	56 (21%)	7 (15%)	0 (0%)	49 (24%)
PPI use[a]	No PPI used	147 (54%)	29 (62%)	18 (78%)	100 (50%)
	PPI used	125 (46%)	18 (38%)	5 (22%)	102 (50%)
Sex	Male	181 (67%)	28 (60%)	14 (61%)	139 (69%)
	Female	91 (33%)	19 (40%)	9 (39%)	63 (31%)

Variable	Category	Total	B1371001	B1371002	B1371003
Race	White	235 (86%)	38 (81%)	18 (78%)	179 (89%)
	Black	16 (6%)	4 (9%)	0 (0%)	12 (6%)
	Asian	9 (3%)	1 (2%)	3 (13%)	5 (2%)
	Hispanic	11 (4%)	4 (9%)	2 (9%)	5 (2%)
	Other	1 (0%)	0 (0%)	0 (0%)	1 (0%)
Baseline Renal Impairment Grade	A (Normal)	106 (39%)	21 (45%)	15 (65%)	70 (35%)
	B (Mild)	103 (38%)	22 (47%)	3 (13%)	78 (39%)
	C (Moderate)	62 (23%)	4 (9%)	4 (17%)	54 (27%)
	D (Severe)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
	Missing	1 (0%)	0 (0%)	1 (4%)	0 (0%)
Baseline Hepatic Impairment Grade	A (Normal)	220 (81%)	39 (83%)	16 (70%)	165 (82%)
	B1 (Mild)	26 (10%)	4 (9%)	3 (13%)	19 (9%)
	B2 (Mild)	17 (6%)	3 (6%)	3 (13%)	11 (5%)
	C (Moderate)	3 (1%)	0 (0%)	0 (0%)	3 (1%)
	D (Severe)	1 (0%)	1 (2%)	0 (0%)	0 (0%)
	Missing	5 (2%)	0 (0%)	1 (4%)	4 (2%)
Treatment	Monotherapy	70 (26%)	47 (100%)	23 (100%)	0 (0%)
	Glasdegib with LDAC	106 (39%)	0 (0%)	0 (0%)	106 (52%)
	Glasdegib with decitabine	7 (3%)	0 (0%)	0 (0%)	7 (3%)
	Glasdegib with 7+3	89 (33%)	0 (0%)	0 (0%)	89 (44%)

Source: Applicant's population PK report, Page 34, Table 8

A 2-compartment first order absorption model with body weight allometric scaling adequately characterized glasdegib PK. Baseline percent bone marrow blasts (BPBL), standardized creatinine clearance (WNCL) (calculated using baseline creatinine clearance x (70/body weight) to remove the dependence on body weight as body weight is already a covariate on CL/F), and use of moderate or strong cytochrome P450 (CYP)3A inhibitors were significant covariates on CL/F. Tumor type (ie, solid tumors) was a significant covariate on Vp/F and Q.
The final model parameters are presented in Table 30.

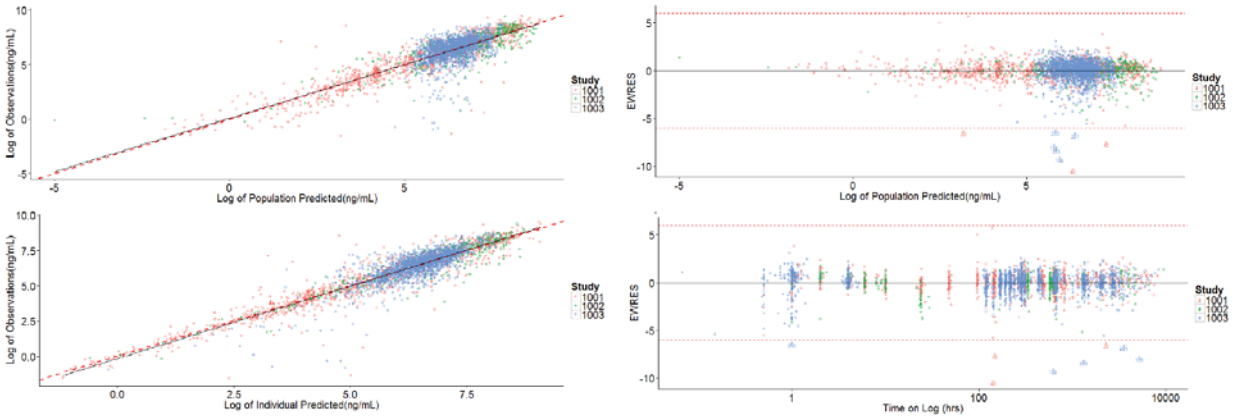
Table 30: Final Model Final Parameter Estimates

	Final Model			Bootstrap	
Parameter	Estimate	RSE(%)	Shrinkage(%)	Median	95% CI
$\theta_{CL\ (L/h)}$	6.274	6.419	-	6.231	(5.5663 ; 6.8050)
$\theta_{V_c\ (L)}$	3.318	23.712	-	3.517	(1.8699 ; 5.5490)
$\theta_{V_p\ (L)}$	279.213	90.048	-	296.041	(80.0941 ; 1090.4500)
$\theta_{Q\ (L/h)}$	1.288	46.596	-	1.576	(0.8962 ; 2.5709)
$\theta_{ka\ (h^{-1})}$	0.060	5.032	-	0.061	(0.0554 ; 0.0718)
$\theta_{Res.\ Error\ for\ Heme}$	0.657	5.22	-	0.657	(0.5915 ; 0.7326)
$\theta_{Res.\ Error\ for\ Solid}$	0.595	6.955	-	0.593	(0.5137 ; 0.6790)
$\theta_{CYP_{mod}\ on\ CL}$	-0.173	59.358	-	-0.178	(-0.3743 ; 0.0894)
$\theta_{CYP_{strong}\ on\ CL}$	-0.303	36.639	-	-0.308	(-0.5268 ; -0.0576)
$\theta_{WNCL\ on\ CL}$	0.406	23.324	-	0.410	(0.2226 ; 0.5976)
$\theta_{Solid\ tumor\ on\ Q}$	-0.653	24.415	-	-0.693	(-0.9143 ; -0.2670)
$\theta_{Solid\ tumor\ on\ V_p}$	-0.825	14.568	-	-0.814	(-0.9498 ; -0.2992)
$\theta_{BPBL\ on\ CL}$	-0.004	34.539	-	-0.004	(-0.0060 ; -0.0007)
IIV	Estimate	CV(%)	Shrinkage(%)	Median	95% CI
ω^2_{CL}	0.185	42.978	16.217	0.179	(0.1355 ; 0.2439)
$\omega^2_{V_c}$	4.637	215.335	22.624	4.631	(2.9009 ; 7.1604)
$\omega^2_{V_p}$	1.272	112.805	69.145	1.607	(0.1798 ; 4.5281)
ω^2_{Q}	0.433	65.783	62.870	0.357	(0.0323 ; 0.7359)
ω^2_{ka}	0.018	13.516	70.694	0.012	(0.0017 ; 0.0445)
OFV	1471.574	-	-	1444.066	-

Source: Applicant's population PK report, Page 46, Table 12

The goodness of fit plot is shown in Figure 5.

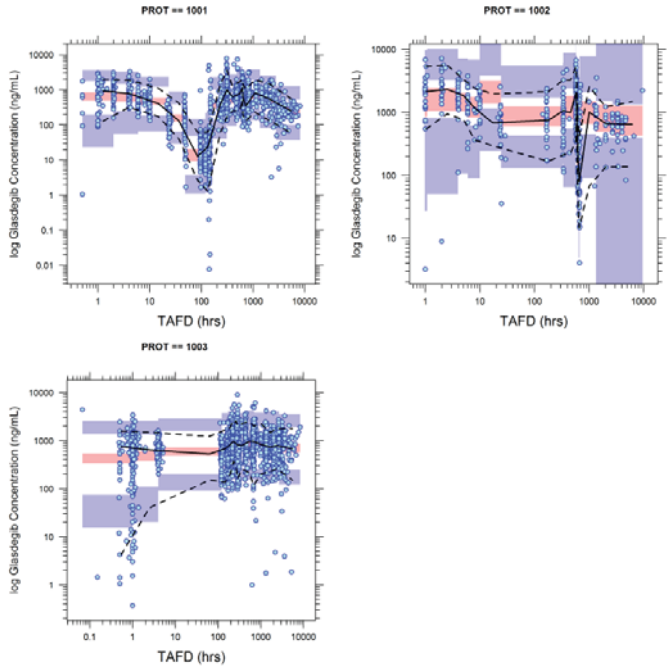
Figure 5: Goodness of Fit for Glasdegib



Source: Applicant's population PK report, Pages 48-50, Figures 7-9

A prediction corrected VPC was performed using the final model and the results are displayed in Figure 6 by study.

Figure 6: Final Model Prediction-corrected Visual Predictive Check



Source: Applicant's population PK report, Page 52, Figure 11

Baseline body weight was incorporated on CL/F and Q in the base model as a fixed effect using the scaling factor exponent of 0.75, and using the scaling factor exponent of 1 on Vc/F and Vp/F. Relative to the typical value of CL/F of 6.274 L/h for a 70 kg individual, CL/F decreased by approximately 10% for a 61.24 kg (10^{th} percentile) individual. For a 102.1 kg (90^{th} percentile) individual, CL/F increased by approximately 33% compared to a 70 kg individual. In terms of volume, at the 10^{th} percentile body weight, volume (ie, Vc/F and Vp/F) decreased by about 13%. At the 90^{th} percentile body weight, volume increased by

about 46%. The effect of BWT on clearance and volume is not considered clinically significant and dose adjustment based on body weight is not warranted.
The effect of BPBL was statistically significant on CL/F using a linear function as follows:

$$Cl/F = 6.274 \times (1 - 0.004 \times (BPBL - 38.20))$$

Relative to the typical value of CL/F of 6.274 L/h, CL/F increased by approximately 9% for an individual with 15% BPBL (10th percentile). CL/F decreased by approximately 17% for an individual with 83% BPBL (90th percentile). Although the inclusion of BPBL on CL/F was statistically significant, the effect of BPBL is not considered to be clinically relevant and dose adjustment based on this laboratory value is not warranted.
The effect of moderate or strong CYP3A inhibitor use was significant on CL/F, as described by the linear function:

$$CL/F = 6.274 \times (1 - 0.173 \times CYP_{moderate}) \times (1 - 0.303 \times CYP_{strong})$$

The list of moderate and strong CYP3A inhibitors and proton pump inhibitors (PPIs) is presented in the Table 31.
Table 31: A list of moderate and strong CYP3A inhibitors and PPIs

Strong CYP3A4/5 Inhibitors		Moderate CYP3A4/5 Inhibitors		Proton Pump Inhibitors
Ketoconazole	Lopinavir/Ritonavir	Fluconazole	Cimetidine	Omeprazole
Itraconazole	Telaprevir	Erythromycin	FK1706	Rabeprazole
Voriconazole	Boceprevir	Ciprofloxacin	Faldaprevir	Lansoprazole
Posaconazole	Danoprevir/Ritonavir	Diltiazem	Crizotinib	Pantaprazole
Troleandomycin	Elvitegravir/Ritonavir	Verapamil	Nilotinib	Esomeprazole
Clarithromycin	LCL161	Dronedarone	Atazanivir/Ritonavir	Dexlansprazole
Telithromycin	Idelalisib	Aprepitant	Darunavir	
Mibefradil	Grapefruit Juice DS	Casopitant	Darunavir/Ritonavir	
Conivaptan	Ritonavir	Netupitant	Atazanavir	
Nefazodone	Indinavir	Tofisopam	Amprenavir	
Cobicistat	Nelfinavir	Cyclosporine	Imatinib	
Indinavir/Ritonavir	Saquinavir	Schisandra sphenanthera	Grapefruit Juice	
Tipranavir/Ritonavir	Saquinavir/Ritonavir	ACT-178882		

Source: Applicant's population PK report, Page 86

Concomitant use of moderate and strong CYP3A inhibitors with glasdegib were estimated to reduce glasdegib CL/F by approximately 17% and 30%, respectively. The magnitude of glasdegib CL/F decrease in this population PK analysis was not as high as the magnitude of decrease observed in B1371010 (58% reduction with ketoconazole). B1371010 was a controlled study conducted in healthy subjects where ketoconazole was dosed at 400 mg QD for 7 days with glasdegib dosed on day 4 to ensure maximum inhibition of CYP3A at the time of glasdegib dosing. On the other hand, the population PK analysis dataset included data captured in oncology patients from clinical studies with intermittent use of moderate and strong CYP3A inhibitors for varying periods of time. This may be more clinically representative of the use of these inhibitors in the real world setting and their impact,

where patients may be dosed with CYP3A inhibitors for a few days as needed resulting in different degrees of CYP3A inhibition. Given the already existing clinical experience with CYP3A inhibitor use in the AML and MDS patient population in B1371003, taking CYP3A inhibitors is not expected to pose a safety risk to patients. Therefore, no dose adjustment is warranted with concomitant CYP3A inhibitor use.

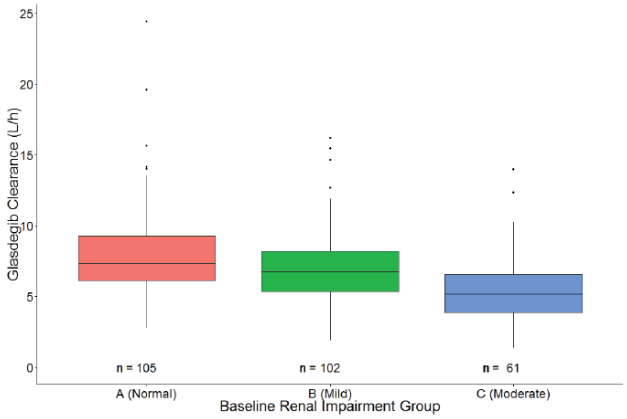
The effect of WNCL was statistically significant on glasdegib CL/F using a power function as follows:

$$CL/F = 6.274 \times (\frac{WNCL}{71.23})^{0.406}$$

Relative to the typical value of CL/F of 6.274 L/h for a patient with WNCL of 71.23 mL/min, CL/F decreased by approximately 16% for an individual with reduced WNCL of 46.9 mL/min (10^{th} percentile). CL/F increased by approximately 19% for an individual with WNCL of 109.6 mL/min (90^{th} percentile).

No patients had baseline severe renal impairment. The median CL/F for moderate renal impairment patients is 4.8 L/h, which is approximately a 26% decrease from normal renal function patients. While the median CL/F in patients with moderate renal impairment was numerically lower than in patients with normal renal function, there was significant overlap in the range of individual CL/F values between the two groups. Therefore, while the inclusion of WNCL on CL/F was statistically significant, the effect on CL/F is not expected to pose a safety risk and dose adjustment based on baseline renal impairment status for mild and moderate renal impairment is not required.

Figure 7: Glasdegib Clearance by Renal Impairment Group



Source: Applicant's population PK report, Page 62, Figure 18

Reviewer's comments: the reviewer has verified the population PK model independently. The population PK model appears to be reasonable. No additional covariate was identified. Baseline aspartate aminotransferase (AST) and baseline total bilirubin (BIL) were not identified as covariates for CL. However, limited data were available for patients with moderate (n=3) and severe (n=1) hepatic impairment, the effects of hepatic impairment

upon glasdegib PK may not be conclusive. In addition, in current population PK model, the impact of strong CYP3A inhibitor on CL may not represent the worst-case scenarios since strong CYP3A inhibitor was a group of CYP3A inhibitors that given intermittently.

4.6.2. Exposure-response analysis

4.6.2.1. Exposure-response analysis for efficacy

A Cox regression analysis of overall survival (OS) was conducted for all randomized patients of the Phase 2 non-intensive portion of Study B1371003 (Table 32).

Table 32: Phase 2 AML/MDS Non-Intensive Overall Survival

	Glasdegib 100 mg + LDAC	LDAC alone	HR [80% CI]
Number of patients	88	44	
Deaths (%)	68 (77.3)	41 (93.2)	
Censored (%)	20 (22.7)	3 (6.8)	
Kaplan-Meier estimates of time-to-event (months) 50% [80% CI][a]	8.8 [6.9, 9.9]	4.9 [3.5, 6.0]	
Cox proportional HR[b]			0.513 [0.394, 0.666]
p-value[c]			0.0004

Source: Applicant's exposure-response for efficacy report, Page 21, Table 2

An exposure-response (ER) analysis for efficacy was conducted by Applicant in phase 2 AML/MDS patients who were not suitable for intensive chemotherapy with available OS data and who were randomized to receive LDAC with or without glasdegib. The population PK was used to derive the summary measures of exposure, i.e., area under the curve (AUC) and maximum observed concentration (Cmax). The analysis included 84 patients with at least one PK sample who were randomized to receive glasdegib + LDAC and 44 patients who were randomized to receive LDAC alone.

The observed data for each continuous demographic or baseline safety laboratory variable are summarized in Table 33.

Table 33: Summary of Continuous Variables

Variable	Treatment Arm	N	Nm	Mean (Stdev)	Median (Min-Max)
Age (years)	Glasdegib + LDAC	88	0	76.17 (6.22)	77.00 (63.00-92.00)
	LDAC	44	0	74.52 (4.89)	75.00 (58.00-83.00)
	Overall	132	0	75.62 (5.85)	76.00 (58.00-92.00)
Baseline ALT (IU/L)	Glasdegib + LDAC	88	2	22.09 (16.15)	18.00 (5.00-90.00)
	LDAC	44	1	29.67 (31.55)	17.00 (4.00-152.00)
	Overall	132	3	24.62 (22.64)	17.00 (4.00-152.00)
Baseline AST (IU/L)	Glasdegib + LDAC	88	3	23.72 (13.09)	20.00 (8.00-73.00)
	LDAC	44	1	30.28 (24.49)	21.00 (7.00-111.00)
	Overall	132	4	25.92 (17.93)	20.50 (7.00-111.00)
Baseline Percent Peripheral Blasts	Glasdegib + LDAC	88	15	15.50 (21.97)	4.00 (0.00-91.00)
	LDAC	44	8	16.07 (22.68)	5.00 (0.00-85.00)
	Overall	132	23	15.69 (22.10)	4.00 (0.00-91.00)
Baseline Creatinine Clearance (mL/min)	Glasdegib + LDAC	88	1	66.66 (22.52)	60.16 (31.36-148.60)
	LDAC	44	1	73.00 (23.62)	69.34 (39.60-139.25)
	Overall	132	2	68.76 (22.99)	65.01 (31.36-148.60)
Baseline Neutrophils (10^9/L)	Glasdegib + LDAC	88	17	1.46 (2.99)	0.41 (0.00-14.14)
	LDAC	44	7	12.58 (63.87)	0.80 (0.00-390.00)
	Overall	132	24	5.27 (37.50)	0.52 (0.00-390.00)
Baseline Percent Bone Marrow Blasts	Glasdegib + LDAC	88	6	46.15 (25.56)	40.00 (10.00-99.00)
	LDAC	44	5	46.54 (25.98)	40.00 (10.50-95.00)
	Overall	132	11	46.28 (25.59)	40.00 (10.00-99.00)
Baseline White Blood Cells (10^9/L)	Glasdegib + LDAC	88	1	73.16 (626.58)	2.60 (0.40-5850.00)
	LDAC	44	0	39.10 (205.51)	3.61 (1.20-1370.00)
	Overall	132	1	61.72 (523.41)	2.85 (0.40-5850.00)
Baseline Weight (kg)	Glasdegib + LDAC	88	0	78.80 (13.43)	79.05 (47.50-116.40)
	LDAC	44	0	77.34 (14.28)	78.55 (51.89-118.00)
	Overall	132	0	78.31 (13.68)	79.00 (47.50-118.00)

Source: Applicant's exposure-response for efficacy report, Page 27, Table 4

The number (%) of individuals for each categorical variable level are summarized in Table 34.

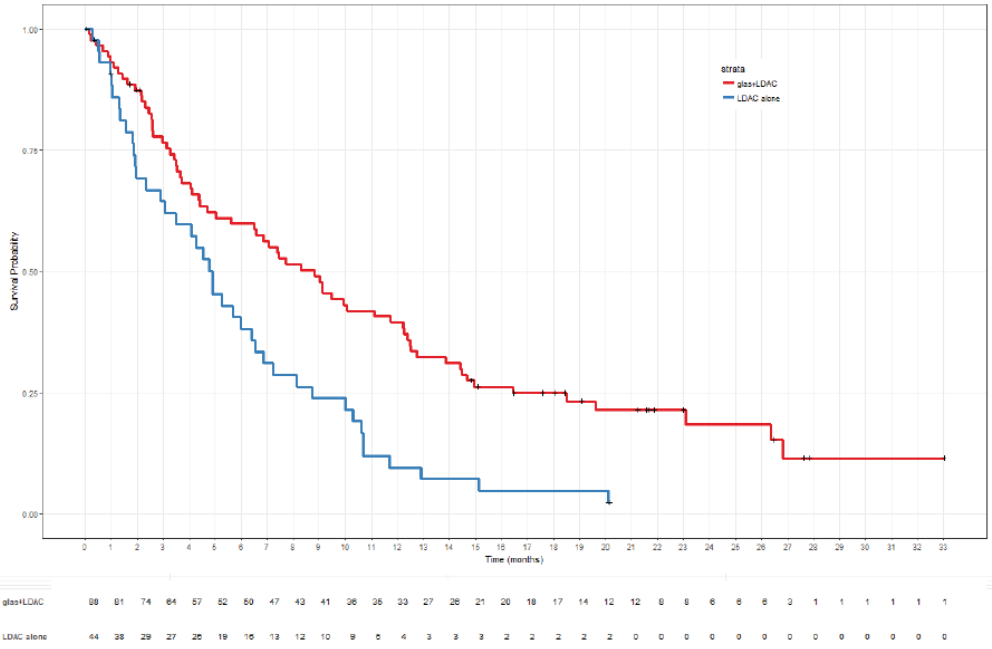
Table 34: Summary of Categorical Variables

Variable	Category	Total	Glasdegib + LDAC	LDAC
N		132	88	44
Sex	Male	95 (72%)	69 (78%)	26 (59%)
	Female	37 (28%)	19 (22%)	18 (41%)
Race	White	129 (98%)	85 (97%)	44 (100%)
	Black	1 (1%)	1 (1%)	0 (0%)
	Asian	2 (2%)	2 (2%)	0 (0%)
Disease	AML	116 (88%)	78 (89%)	38 (86%)
	MDS	16 (12%)	10 (11%)	6 (14%)
Disease History	de novo	68 (52%)	46 (52%)	22 (50%)
	Secondary	64 (48%)	42 (48%)	22 (50%)
Cytogenetic Risk	Good/Intermediate	77 (58%)	52 (59%)	25 (57%)
	Poor	55 (42%)	36 (41%)	19 (43%)
Prior Treatment with Hypomethylating Agent	No	108 (82%)	73 (83%)	35 (80%)
	Yes	24 (18%)	15 (17%)	9 (20%)
Baseline ECOG Performance Status	0	14 (11%)	11 (12%)	3 (7%)
	1	47 (36%)	29 (33%)	18 (41%)
	2	70 (53%)	47 (53%)	23 (52%)
	NA	1 (1%)	1 (1%)	0 (0%)

Source: Applicant's exposure-response for efficacy report, Page 29, Table 5

The observed OS data is presented in Figure 8 by treatment arm.

Figure 8: Kaplan Meier Plot by Treatment Arm



Source: Applicant's exposure-response for efficacy report, Page 30, Figure 2

For the glasdegib E-R analysis, a range of exposure parameters were selected for evaluation:

- Cycle 1 first dose Cmax (CMAX1)
- End of Cycle 1 Cmax (C1CMAXL)
- End of Cycle 1 Cmin (C1CMINL)
- Cycle 1 cumulative AUC (C1AUC)
- Cycle 1 Cavg (C1CAVG)
- Average area under the plasma concentration-time profile over the dosing interval (AUCAV)
- Overall Cavg (CUCAVG)

The exposure metrics are summarized in Table 35.

Table 35: Summary of Exposure Metrics

Exposure Metric	N	Mean (Stdev)	Median (Min-Max)
Cycle 1 First Dose C_{max} (ng/mL)	84	578.84 (338.74)	596.00 (0.83-1437.80)
End of Cycle 1 C_{max} (ng/mL)	84	1291.94 (714.21)	1112.90 (275.32-3612.50)
Cycle 1 Cumulative AUC (h*ng/mL)	84	625139.18 (343306.41)	572525.00 (54368.00-1797600.00)
Cycle 1 C_{avg} (ng/mL)	84	993.72 (535.65)	912.16 (161.93-3505.40)
End of Cycle 1 C_{min} (ng/mL)	84	719.61 (545.31)	571.03 (4.89-2762.00)
Average AUC_{tau} (h*ng/mL)[a]	84	18344.41 (10644.41)	16269.80 (2927.87-61527.33)
Overall C_{avg} (ng/mL)[b]	84	897.03 (510.81)	778.33 (218.45-3505.40)

Source: Applicant's exposure-response for efficacy report, Page 31, Table 6

Exponential, Weibull, and log-logistic distributions were explored for the base model and compared. Based on the non-significant change in objective function value (OFV) with the Weibull and log-logistic models, the exponential distribution time-to-event (TTE) model was selected as the final base model. The following covariates were evaluated, and the results showed that no exposure metrics were found to be significant and no other covariate was found to be significant.

Table 36: Covariates Evaluated in the Exposure-Response Analysis

Category	Covariates
Treatment	Prior treatment with hypomethylating agent
Demographic	Sex, age, baseline weight, race
Disease characteristics	AML or MDS, de novo or secondary disease, cytogenetic risk, and baseline ECOG performance status
Baseline laboratory values	Creatinine clearance, AST[a,b], WBC[a,b], percent bone marrow blasts[a], percent peripheral blasts[a]

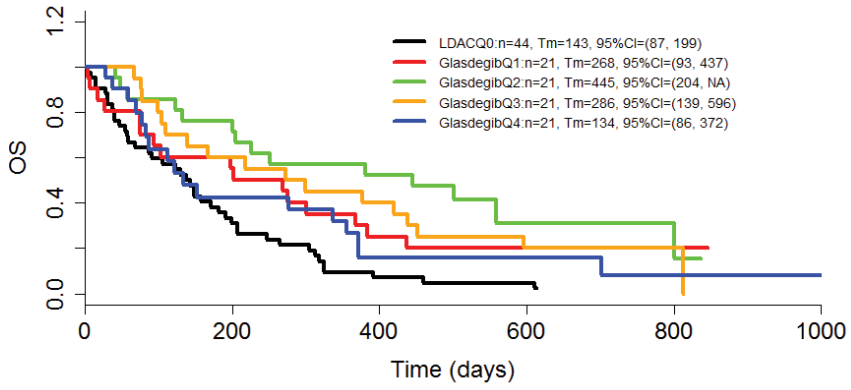
Source: Applicant's exposure-response for efficacy report, Page 45, Table 13

The final model survival function is described by:

$$S(t) = e^{-0.00249 \cdot t}$$

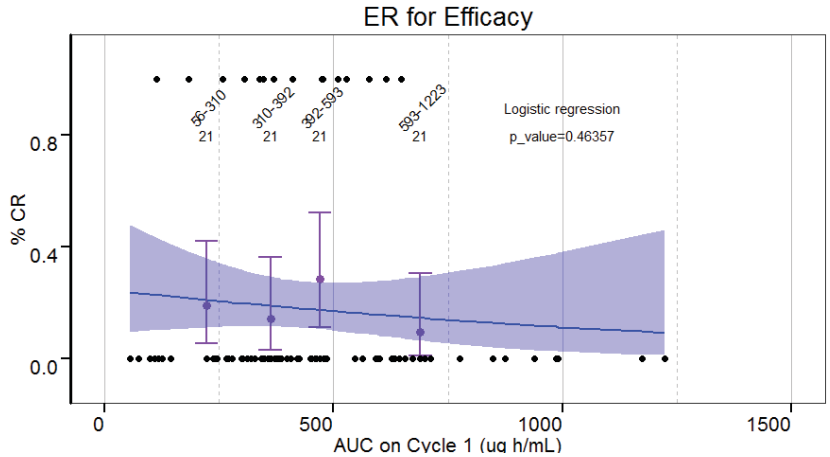
Reviewer' comments: An independent exposure-response analyses for OS and complete response (CR) were conducted by the Reviewer in AML or DMS patients (N=84). No significant exposure-response relationship between OS or CR and exposure was identified (Figure 9 and Figure 10). Similar results were derived for AML patients only (N=75) as shown in Figure 11 and Figure 12. No additional covariate was identified. It is worth noting that the exposure-response analysis was conducted based on data from Phase 2 portion with only one dose, which was 100 mg with an exposure range of 56 to 1223 ug·h/mL. In addition, the dose modifications following the 1st cycle would compromise the power to identify a E-R relationship if there were one.

Figure 9: Exposure-response relationship between cumulated AUC at first cycle and OS in AML or DMS patients.



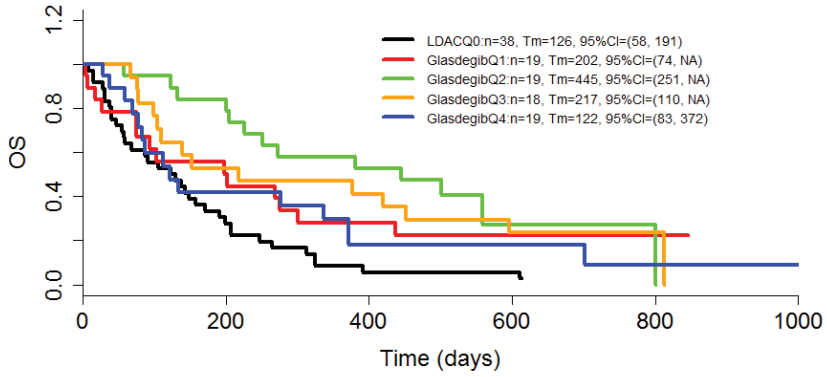
Source: Reviewer's independent analysis

Figure 10: Exposure-response relationship between cumulated AUC at first cycle and CR in AML or DMS patients.



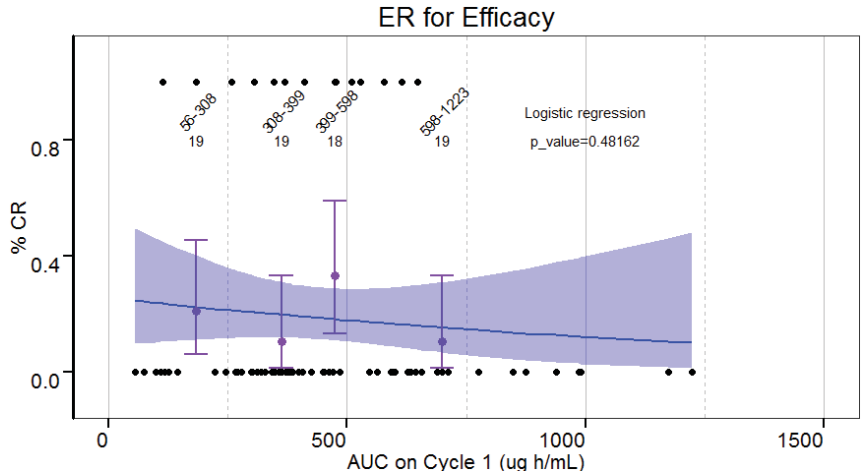
Source: Reviewer's independent analysis

Figure 11: Exposure-response relationship between cumulated AUC at first cycle and OS in AML patients.



Source: Reviewer's independent analysis

Figure 12: Exposure-response relationship between cumulated AUC at first cycle and CR in AML patients.



Source: Reviewer's independent analysis

In Phase 1b portion, 17 patients received 100 mg glasdegib plus LDAC and 6 patients received 200 mg glasdegib plus LDAC. The overall death rate was 88.2% vs 100% with median time to event of 3.4 and 9.3 months for 100 and 200 mg, respectively. The higher dose only showed numerical longer time to event but not survival rate considering the small sample size. The dose-response relationship provided limited information to support the higher dose. Notably, the overall death rate was 77.3% with median time to event of 8.8 month for 100 mg glasdegib plus LDAC in the Phase 2 portion (N=88).

4.6.2.2. Exposure-response analysis for safety

An exposure-response (ER) analysis for safety was conducted by Applicant in patients Studies B1371001, B1371002 and B1371003. The safety endpoints included dysgeusia, muscle spasms, renal toxicity, and QT interval prolonged. The exposure metrics were generated by population PK model and listed below:

- Cmax, minimum predicted concentration (Cmin), average concentration calculated using the cumulative AUC over the period of time (Cavg) and area under the curve (AUC) up to the day of the event
- Cmax, Cmin, Cavg and AUC prior to dose on Day 1 of Cycle 2. The exposure metrics calculated for this time period will be referred as Cycle 1 exposure

Only patients who received at least 1 dose of glasdegib in the pooled data analysis for whom the safety endpoint and dose information were available were considered for these analyses (N=272). On studies B1371001 and B1371002 patients were treated with single agent glasdegib (N=70), on study B1371003, 106 patients were treated with glasdegib in combination with low-dose cytarabine (LDAC), 7 patient were treated with glasdegib in combination with decitabine, 89 patients were treated with glasdegib in combination with daunorubicin (DNR) and cytarabine (Ara-C). A summary of the frequency of the safety endpoints by Study treatment and Grade is shown in Table 37.

Table 37: Summary of Adverse Terms by Study Treatment and per Grade

Variable	Category	B1371001 Monotherapy	B1371002 Monotherapy	B1371003 G+LDAC	B1371003 G+Decitabine	B1371003 G+DNR/Ara-C	Total	B1371003 LDAC only
N		47	23	106	7	89	272	41
DYSGEUSIA	Grade 0	34 (72.3%)	8 (34.8%)	76 (71.7%)	4 (57.1%)	59 (66.3%)	181 (66.5%)	40 (97.6%)
	Grade 1	7 (14.9%)	14 (60.9%)	18 (17%)	2 (28.6%)	19 (21.3%)	60 (22.1%)	0 (0%)
	Grade 2	6 (12.8%)	1 (4.3%)	12 (11.3%)	1 (14.3%)	11 (12.4%)	31 (11.4%)	1 (2.4%)
MUSCLE SPASMS	Grade 0	27 (57.4%)	14 (60.9%)	60 (56.6%)	4 (57.1%)	44 (49.4%)	149 (54.8%)	37 (90.2%)
	Grade 1	12 (25.5%)	6 (26.1%)	15 (14.2%)	1 (14.3%)	26 (29.2%)	60 (22.1%)	3 (7.3%)
	Grade 2	5 (10.6%)	3 (13%)	23 (21.7%)	2 (28.6%)	13 (14.6%)	46 (16.9%)	1 (2.4%)
	Grade 3	3 (6.4%)	0 (0%)	8 (7.5%)	0 (0%)	4 (4.5%)	15 (5.5%)	0 (0%)
	Grade 4	0 (0%)	0 (0%)	0 (0%)	0 (0%)	1 (1.1%)	1 (0.4%)	0 (0%)
	Missing	0 (0%)	0 (0%)	0 (0%)	0 (0%)	1 (1.1%)	1 (0.4%)	0 (0%)
RENAL TOXICITY	Grade 0	35 (74.5%)	18 (78.3%)	80 (75.5%)	4 (57.1%)	59 (66.3%)	196 (72.1%)	35 (85.4%)
	Grade 1	6 (12.8%)	1 (4.3%)	13 (12.3%)	1 (14.3%)	18 (20.2%)	39 (14.3%)	3 (7.3%)
	Grade 2	6 (12.8%)	4 (17.4%)	7 (6.6%)	1 (14.3%)	10 (11.2%)	28 (10.3%)	2 (4.9%)
	Grade 3	0 (0%)	0 (0%)	5 (4.7%)	0 (0%)	2 (2.2%)	7 (2.6%)	1 (2.4%)
	Grade 4	0 (0%)	0 (0%)	1 (0.9%)	1 (14.3%)	0 (0%)	2 (0.7%)	0 (0%)
QT INTERVAL PROLONGED	Grade 0	39 (83%)	21 (91.3%)	98 (92.5%)	7 (100%)	80 (89.9%)	245 (90.1%)	40 (97.6%)
	Grade 1	2 (4.3%)	0 (0%)	2 (1.9%)	0 (0%)	1 (1.1%)	5 (1.8%)	0 (0%)
	Grade 2	6 (12.8%)	0 (0%)	3 (2.8%)	0 (0%)	4 (4.5%)	13 (4.8%)	0 (0%)
	Grade 3	0 (0%)	2 (8.7%)	2 (1.9%)	0 (0%)	4 (4.5%)	8 (2.9%)	1 (2.4%)
	Grade 4	0 (0%)	0 (0%)	1 (0.9%)	0 (0%)	0 (0%)	1 (0.4%)	0 (0%)

Source: Applicant's exposure-response for efficacy report, Page 41, Table 11

The frequencies of Grade 3 and Grade 4 for the safety endpoints for muscle spasms, renal toxicity and QT interval prolonged were very low. Therefore, Grade 3 and Grade 4 were grouped and the ordinal categorical endpoints were studied as Grade 0 to Grade 2 and Grade ≥3. To model the severity of the selected safety endpoints, an ordinal logistic regression model was used with a logit link function to identify potential correlations between glasdegib exposure and safety ordinal grades.

Dysgeusia

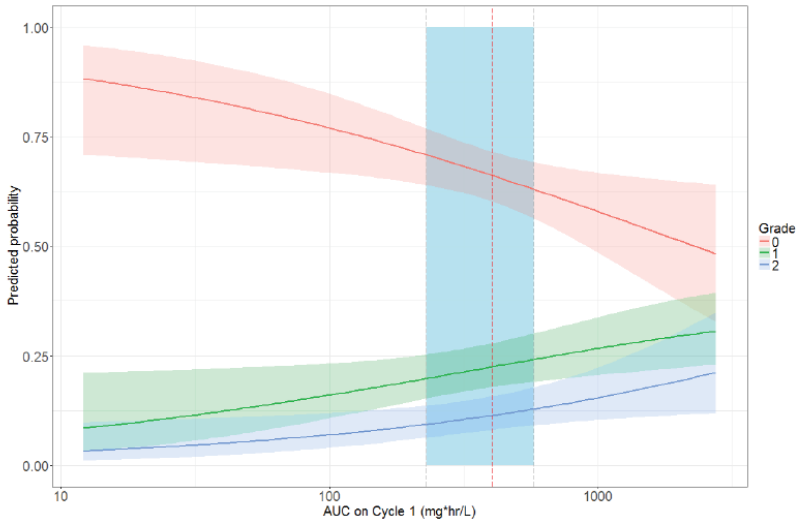
The natural logarithmic value of AUC on Cycle 1 was selected as the most significant glasdegib exposure variable related to dysgeusia events. No additional covariate was identified for the exposure-response analysis. Table 38 tabulates parameter estimates or coefficients and the odds ratio. Figure 13 shows the predicted probability of gysgeusia by grade. The predicted probability of a given dysgeusia Grade>0 increases with increasing glasdegib exposure.

Table 38: Ordinal Logistic Regression Parameter Estimates for Dysgeusia

Endpoint (n/N)	Coefficients	Estimate	95% CI	z-Value	Probability >|z|
DYSGEUSIA 272/272	Intercept-Grade 0 to 1	2.9916	(1.087-4.8962)	3.0786	0.0021
	Intercept-Grade 1 to 2	4.3758	(2.432-6.3196)	4.4122	<0.0001
	Log of AUC on Cycle 1 (mg*hr/L)	0.3867	(0.0728-0.7006)	2.4148	0.0157
	Odds Ratio				
	Log of AUC on Cycle 1 (mg*hr/L)	1.4721	(1.0755-2.0150)		
	Loglik	AIC	Iter(Convergence)	Gradient	Cond.number
	-228.60	463.19	5(0)	<0.001	4500.0

Source: Applicant's exposure-response for efficacy report, Page 47, Table 13

Figure 13: Predicted Probability of Dysgeusia by Grade



The red dotted vertical line represents the geometric mean value of AUC on Cycle 1 simulated from patients in the analysis dataset at a dose of 100 mg QD. The blue shaded area represents the geometric mean value ± the coefficient of variation (CV) of the geometric mean value.
Source: Applicant's exposure-response for efficacy report, Page 48, Figure 6

Muscle spasms

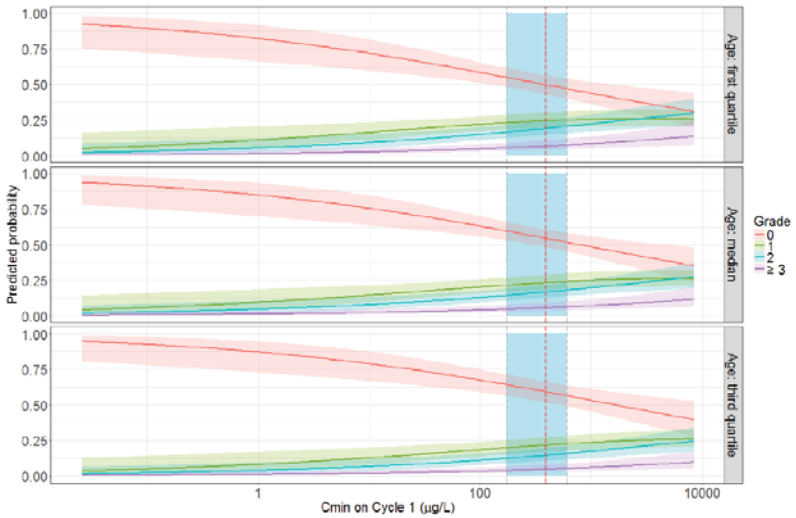
The natural logarithmic value of Cmin on Cycle 1 was selected as the most significant glasdegib exposure variable of muscle spasms events. Other than Cmin on cycle 1, age was identified as a significant covariate for the exposure-response relationship. Table 39 tabulates parameter estimates or coefficients and the odds ratio. Predicted probabilities as a function of Cmin on Cycle 1 and age are shown in Figure 14. The predicted probability of a given muscle spasms Grade>0 increases with increasing glasdegib exposure and decreases with age.

Table 39: Ordinal Logistic Regression Parameter Estimates for Muscle Spasms

Endpoint (n/N)	Coefficients	Estimate	95% CI	z-Value	Probability >|z|
MUSCLE SPASMS	Intercept-Grade 0 to 1	-0.1486	(-1.4877 - 1.1905)	-0.2175	0.8278
271/272	Intercept-Grade 1 to 2	0.9175	(-0.4257 - 2.2607)	1.3388	0.1806
	Intercept-Grade 2 to ≥ 3	2.4954	(1.0948 - 3.8959)	3.4922	0.0005
	Log of Cmin (μg/L) on Cycle 1	0.2577	(0.1126 - 0.4029)	3.4809	0.0005
	Age (years)	-0.0271	(-0.0457 - -0.0085)	-2.8506	0.0044
	Odds Ratio				
	Log of Cmin (μg/L) on Cycle 1	1.2940	(1.1192-1.4962)		
	Age (years)	0.9733	(0.9553-0.9915)		
	Loglik	AIC	Iter(Convergence)	Gradient	Cond.number
	-297.60	605.20	5(0)	<0.001	460000.0

Source: Applicant's exposure-response for efficacy report, Page 54, Table 18

Figure 14: Predicted Probability of Muscle Spasms by Grade



Source: Applicant's exposure-response for efficacy report, Page 55, Figure 11

Renal toxicity

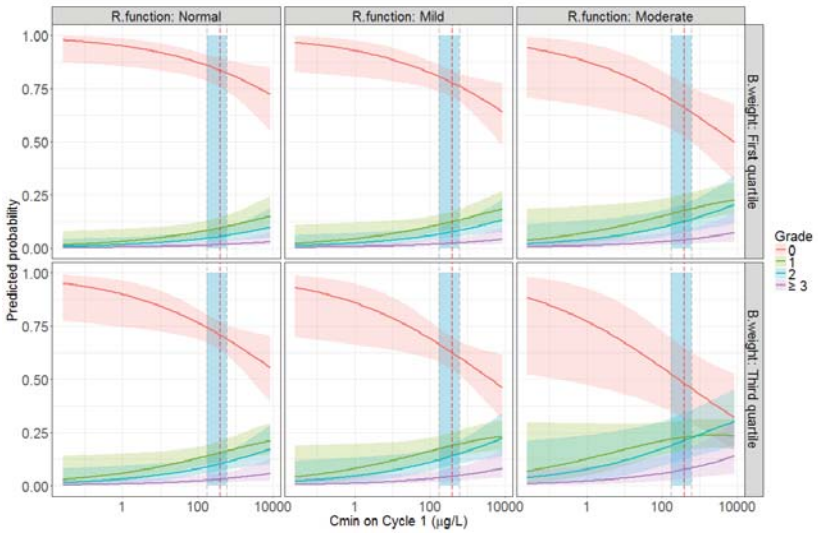
The natural logarithmic value of Cmin on Cycle 1 was selected as the most significant glasdegib exposure variable of renal toxicity events. Other than Cmin on Cycle 1, baseline body weight and baseline creatinine clearance were identified as significant covariates for the exposure-response relationship. Table 40 tabulates parameter estimates or coefficients and the odds ratio. Predicted probabilities as a function of Cmin on Cycle 1, baseline body weight, and baseline creatinine clearance are shown in Figure 15. The predicted probability of a given renal toxicity Grade>0 increases with increasing glasdegib exposure and baseline body weight and decreases with baseline creatinine clearance.

Table 40: Ordinal Logistic Regression Parameter Estimates for Renal Toxicity

Endpoint	Coefficients	Estimate	95% CI	z-Value	Probability >|z|
RENAL TOXICITY	Intercept-Grade 0 to 1	0.4311	(-3.1055 - 3.9676)	0.2389	0.8112
272/272	Intercept-Grade 1 to 2	1.3999	(-2.1458 - 4.9456)	0.7738	0.4390
	Intercept-Grade 2 to ≥ 3	2.9893	(-0.5947 - 6.5732)	1.6348	0.1021
	Log of Cmin on Cycle 1 (μg/L)	0.2182	(0.0371 - 0.3992)	2.3619	0.0182
	BWT (kg)	0.0348	(0.0174 - 0.0523)	3.9136	0.0001
	Log of BCCL (mL/min)	-1.0562	(-1.9158 - -0.1965)	-2.4080	0.0160
	Odds Ratio				
	Log of Cmin on Cycle 1 (μg/L)	1.2438	(1.0378-1.4906)		
	BWT (kg)	1.0354	(1.0176-1.0537)		
	Log of BCCL (mL/min)	0.3478	(0.1472-0.8216)		
	Loglik	AIC	Iter(Convergence)	Gradient	Cond.number
	-222.18	456.36	6(0)	<0.001	3900000.0

Source: Applicant's exposure-response for efficacy report, Page 63, Table 23

Figure 15: Predicted Probability of Renal Toxicity by Grade



Source: Applicant's exposure-response for efficacy report, Page 55, Figure 11

QT interval prolonged

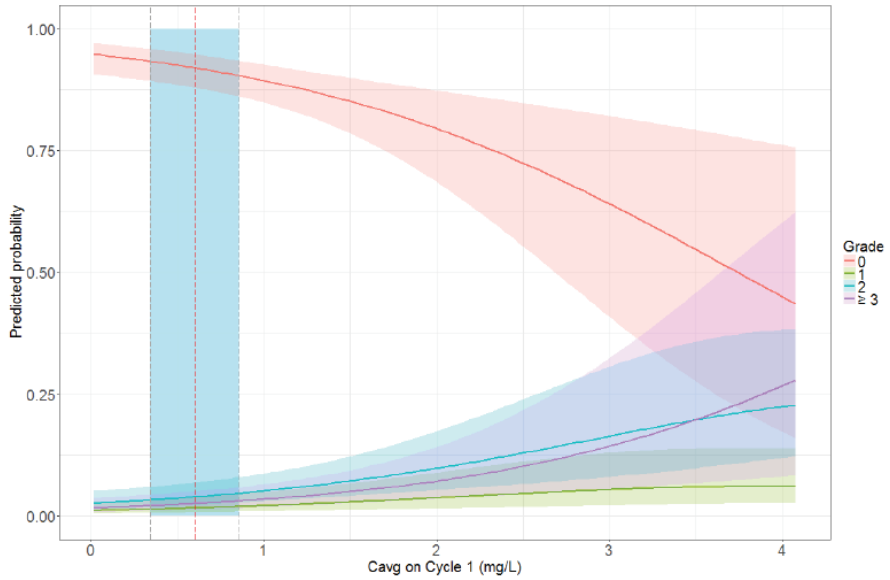
The value of Cavg on Cycle 1 was selected as the most significant glasdegib exposure variable of QT interval prolonged events. No additional covariate was identified for the exposure-response relationship. Table 41 tabulates parameter estimates or coefficients and the odds ratio. Predicted probabilities as a function of Cavg on Cycle 1 are shown in Figure 16. The predicted probability of a given QT interval prolonged Grade>0 increases with increasing glasdegib exposure.

Table 41: Ordinal Logistic Regression Parameter Estimates for QT Interval Prolonged

Endpoint	Coefficients	Estimate	95% CI	z-Value	Probability >|z|
QT INTERVAL PRO-LONGED	Intercept-Grade 0 to 1	2.9190	(2.2871-3.5509)	9.0543	<0.0001
272/272	Intercept-Grade 1 to 2	3.1599	(2.4924-3.8273)	9.2789	<0.0001
	Intercept-Grade 2 to ≥3	4.1338	(3.2808-4.9868)	9.4986	<0.0001
	Cavg on Cycle 1 (mg/L)	0.7802	(0.3337-1.2266)	3.4252	0.0006
	Odds Ratio				
	Cavg on Cycle 1 (mg/L)	2.1818	(1.3961-3.4096)		
	Loglik	AIC	Iter(Convergence)	Gradient	Cond.number
	-110.67	229.35	7(2)	<0.001	74.0

Source: Applicant's exposure-response for efficacy report, Page 74, Table 28

Figure 16: Predicted Probability of QT Interval Prolonged by Grade

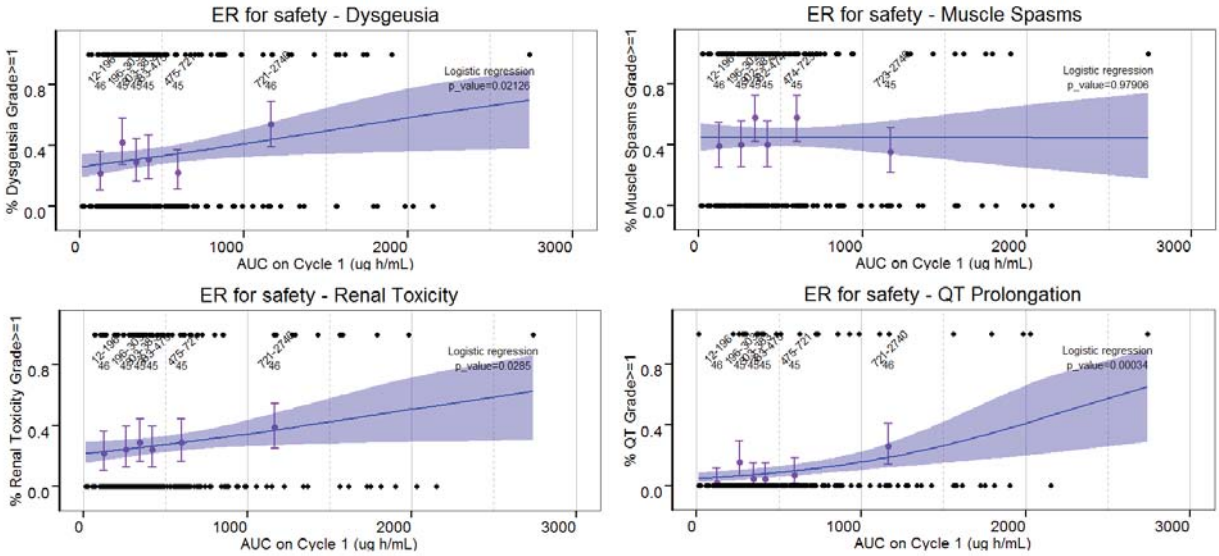


Source: Applicant's exposure-response for efficacy report, Page 75, Figure 25

Reviewer's comments: The Reviewer verified the exposure-response analysis for the safety endpoints including dysgeusia, muscle spasms, renal toxicity, and QT prolongation for Grade equals to or more than 1 only. AUC on Cycle 1 was used by the Reviewer while AUC on Cycle 1, Cmin on cycle 1, and Cavg on Cycle 1 were used by the Applicant. The ER relationship is not expected to be dramatically differed by different PK measure. The results showed that the higher probability of safety events was associated with higher exposure for dysgeusia, renal toxicity, and QT prolongations, but not for muscle spasms. Based on the exposure-response analysis for safety endpoints, the dose of 100 mg is predicted to cause less safety issues compared to the dose of 200 mg, supporting the selection of lower dose from safety perspectively. It should be noted that the exposure may be increase when the drug is co-administered with CYP3A4 inhibitor intermittently. The current exposure-response analysis

did not consider the impact of background therapy and its confounding effect via drug-drug interaction on safety.

Figure 17: Exposure-response relationship for safety endpoints



Source: Reviewer's independent analysis

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/s/

SRIRAM SUBRAMANIAM
09/27/2018

LUNING ZHUANG
09/27/2018

CHAO LIU
09/27/2018

RUBY LEONG
09/27/2018

NAM ATIQUR RAHMAN
09/27/2018
I concur.