

Absolute Oral Bioavailability of Glasdegib (PF-04449913), a Smoothened Inhibitor, in Randomized Healthy Volunteers

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Abstract

Glasdegib (PF-04449913) is an oral small-molecule inhibitor of the Hedgehog signaling pathway under development for treating myeloid malignancies. This was an open-label phase I, randomized, 2-sequence, 2-treatment, 2-period, crossover study evaluating the absolute bioavailability of glasdegib in healthy volunteers under fasting condition (NCT03270878). In period I, 12 eligible subjects received either a single oral dose of glasdegib 100 mg (tablet) or a single intravenous (IV) dose of glasdegib 50 mg. Following ≥ 6 -day washout, subjects received the treatment that they did not receive in the first period. Blood samples were collected for up to 96 hours after dosing. Drug plasma concentrations were determined by high-performance liquid chromatography–tandem mass spectrometry. Glasdegib pharmacokinetic parameters were calculated using noncompartmental analysis. The mean terminal half-life was 14.3 hours for oral tablet treatment vs 13.8 hours for glasdegib IV treatment. The absolute oral bioavailability measured as the ratios (oral/IV) of adjusted geometric mean (90% confidence interval) of dose normalized area under the plasma concentration–time curve was 77.12% (71.83%–82.81%). Two adverse events (1 mild and 1 moderate in severity) were reported by 2 subjects following oral tablet administration; these were fully resolved by the end of the study.

Keywords

absolute bioavailability, glasdegib, healthy volunteers

Glasdegib (PF-04449913) is an oral small-molecule inhibitor of the Hedgehog (Hh) signaling pathway that is being developed for treating myeloid malignancies, particularly acute myeloid leukemia (AML) and myelodysplastic syndrome.^{1–3} The Hh pathway regulates cell differentiation in developing embryos and is involved in the maintenance of neural and epithelial stem cells in adults. The Hh signaling pathway is mostly quiescent in adults and inappropriate reactivation is linked to cancer development in adults. Several chemoresistant AML cell lines overexpress components of the Hh pathway, and aberrant Hh signaling occurs in various human leukemias.⁴ In a phase II study conducted in patients with AML and high-risk myelodysplastic syndrome, the addition of glasdegib 100 mg daily to cytarabine improved overall survival compared with cytarabine alone.⁵ Glasdegib appears to be well tolerated in human trials: in a phase I dose-escalation study conducted in patients with advanced myeloid malignancies, the maximum tolerated dose of glasdegib as a single agent was 400 mg once daily (QD) and the most common treatment-related adverse events (AEs) observed were alopecia, dysgeusia, and

decreased appetite.² A different phase I study in patients with advanced solid tumor determined the maximum tolerated dose to be 320 mg QD.⁶ Based on clinical activity, biomarker modulation, and safety/tolerability data, the recommended phase II dose of glasdegib for clinical development was 100 mg QD.

Evaluating alterations in plasma exposure due to extrinsic factors is necessary to understand the implications for patient safety and intended efficacy.

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*At the time when the study was conducted.

Because glasdegib is orally administered, it is important to determine the pharmacokinetics (PK) in relation to meal consumption and concurrent medications that might impact absorption. The effect of a high-fat, high-calorie meal on the PK of glasdegib was previously evaluated, leading to the recommendation that glasdegib may be taken independently of food intake.^{7,8} The solubility of glasdegib, a weakly basic drug, is hydrogen (pH)-dependent with decreasing solubility as pH increases. Therefore, the effect of proton-pump inhibitors on the PK of glasdegib was investigated due to their ability to elevate gastric pH and frequent use in cancer patients for the treatment of concomitant conditions.⁷ The study demonstrated that proton-pump inhibitors do not have a clinically relevant effect on glasdegib following a single 100-mg dose.

Preclinical studies determined that glasdegib is primarily metabolized by cytochrome P450 (CYP) 3A4/5, and therefore the effects of a CYP3A inhibitor (ketoconazole) and inducer (rifampicin) were investigated.^{8,9} The coadministration of ketoconazole increased plasma exposure in healthy individuals (area under the plasma concentration–time curve from time 0 extrapolated to infinite time [$AUC_{0-\infty}$], ~140%; maximum plasma concentration [C_{max}], ~40% increase), with rifampicin decreasing exposure ($AUC_{0-\infty}$, ~70%; C_{max} , ~35% decrease). Together, these studies indicate that concomitant use with strong CYP3A4 inducers should be avoided, and alternative therapies that are not strong CYP3A4 inhibitors should be considered.

Poor drug bioavailability is a common reason for drug development failure. Because glasdegib is administered as an oral dose, it is of relevance to investigate the proportion of oral glasdegib reaching the systemic circulation unchanged. A previous study investigated the PK of a glasdegib oral solution compared to a tablet formulation, indicating that disintegration and dissolution do not appear to impact the absorption kinetics for the glasdegib instant-release tablet.⁷ Glasdegib had not previously been administered by the intravenous (IV) route to humans; however, results from *in vitro* blood compatibility and rabbit local tolerance studies with parenteral formulation did not suggest that glasdegib was the cause of hemolysis in human blood and/or local vascular tissue irritation. Moreover, glasdegib was well tolerated when administered as a single dose of 320 mg in patients with advanced tumors.⁶ Based on this and prior clinical experience, a single 50-mg IV dose administration with a washout period was expected to be well tolerated in healthy adult volunteers.

This study aimed to evaluate the absolute bioavailability of a single oral dose of glasdegib relative to an IV dose administered in healthy subjects. The secondary objective was to assess the safety and tolerability of both formulations in healthy subjects.

Methods

Study Design and Implementation

This was an open-label phase I, single-dose, randomized, 2-period, 2-treatment, 2-sequence, crossover study in healthy volunteers (ClinicalTrials.gov: NCT03270878). The study was conducted between September 1, 2017, and October 30, 2017.

Subjects were equally randomized to receive either a single oral dose of glasdegib 100 mg (tablet) or a single IV dose of glasdegib 50 mg (50 mL of 1 mg/mL IV solution over 1.25 hours) after an overnight fast of at least 10 hours (treatment period 1). Following a washout period of at least 6 days, in treatment period 2, subjects received the treatment that they did not receive in treatment period 1 in a way that each subject received both oral and IV glasdegib by the end of the 2 treatment periods. Subjects who withdrew from the study were not replaced unless the number of evaluable subjects was <10. The investigator assigned a number to each subject at the time of study screen. The sponsor provided a randomization schedule to the investigator and, in accordance with the randomization numbers, subjects received the study treatment regimens in the order assigned to the corresponding randomization number.

This study was conducted in compliance with the ethical principles originating in or derived from the Declaration of Helsinki and in compliance with all International Council for Harmonisation Good Clinical Practice Guidelines. The final study protocol and informed consent documentation were approved by the Institutional Review Board (IntegReview Ethical Review Board, Austin, Texas). All subjects gave written informed consent prior to participating and before any screening procedures were initiated.

Subjects

The study was conducted at a single Pfizer Clinical Research Unit (New Haven, Connecticut). The clinical laboratory sample analyses were performed at the same place. Medical and clinical monitoring of this study was delegated to personnel at the unit in accordance with local procedures. The study drug was packaged, labeled, and shipped by the study sponsor.

Eligible subjects included men and women of non-childbearing potential, aged 18 to 55 years inclusive, with a body mass index of 17.5 to 35 kg/m² for a total body weight of >50 kg, and with no relevant clinical or laboratory abnormalities. Subjects were excluded from the study if they had a history of clinically significant hematologic, renal, endocrine, pulmonary, gastrointestinal, cardiovascular, hepatic, psychiatric, neurologic, or allergic disease, or any condition possibly affecting drug absorption. Subjects were also excluded from the study if they had a history of regular alcohol

consumption exceeding 7 drinks/week for female subjects or 14 drinks/week for male subjects (1 drink = 150 mL of wine, 360 mL of beer, or 45 mL of hard liquor) within 6 months before screening. In addition, subjects with a blood pressure (BP) ≥ 140 mm Hg (systolic) or ≥ 90 mm Hg (diastolic) after at least 5 minutes of supine rest, or with an electrocardiogram (ECG) corrected QT wave interval >450 milliseconds or a QRS interval >120 milliseconds were also excluded. Subjects with a positive urine test for illicit drugs or with current use of prescription or nonprescription drugs (including dietary supplements) except acetaminophen/paracetamol (1 g/day) were also excluded. Limited use of nonprescription medications that were not believed to affect subject safety or the overall results of the study may have been permitted on a case-by-case basis. Female subjects who were pregnant or breastfeeding, and male subjects with partners currently pregnant were excluded from the study. Subjects could withdraw from the study at any time or could be withdrawn at any time at the discretion of the investigator or sponsor for safety, behavioral, or administrative reasons.

Treatment

Investigator site personnel administered the investigational drug at 8AM (± 4 hours) with ambient-temperature water to a total volume of 240 mL for oral dosing or as an IV infusion. For the oral treatment, subjects swallowed the tablet whole, and did not manipulate or chew prior to swallowing. All subjects were required to refrain from lying down (except when required for BP, pulse rate, and ECG measurements), eating, and drinking beverages other than water during the first 4 hours after glasdegib oral dosing or start of the infusion.

Pharmacokinetic Evaluation

Two-milliliter blood samples (to provide approximately 1.0 mL of plasma) were collected for PK analysis at 0, 0.75, 1, 1.25, 2, 3, 4, 6, 10, 24, 48, 72, and 96 hours after glasdegib oral dose, and at 0, 0.25, 0.5, 1, 1.5, 2, 3, 4, 6, 10, 24, 48, 72, and 96 hours after glasdegib IV dose. The blood samples for PK analysis were processed to plasma at the investigator site, shipped to the bioanalytical laboratory, and analyzed using a validated, sensitive, and specific high-performance liquid chromatography–tandem mass spectrometric method at Covance Bioanalytical Services (Shanghai, China). A 50- μ L plasma aliquot was spiked with deuterated internal standard (glasdegib- d_4), followed by addition of 10% NH_4OH (aq), extraction with 1000 μ L ethyl acetate, and centrifugation. A 400- μ L aliquot of the organic layer was evaporated to dryness under a stream of nitrogen, and the residue was reconstituted with

400 μ L of 0.1% formic acid in acetonitrile:water (25:75, v/v) and injected onto the high-performance liquid chromatography–tandem mass spectrometric system. Chromatographic separation was achieved with a Zorbax XDB-C18 (50 \times 2.1 mm, 5 μ m; Agilent Technologies, Santa Clara, California) high-performance liquid chromatography column heated to 30°C and a mobile phase gradient at a flow rate of 600 μ L/min. Mobile phase A consisted of 0.1% formic acid in water, and mobile phase B consisted of 0.1% formic acid in acetonitrile. The mobile phase composition started at 20% B for 0.4 minutes and increased linearly to 75% B over 1.6 minutes. Detection of glasdegib and the internal standard was by tandem mass spectrometry (Sciex API 4000; Applied Biosystems, Foster City, California) in multiple reaction monitoring mode using positive ion electrospray (IonSpray voltage of 3000 V and temperature at 550°C). The monitored ion transitions were m/z 375 \rightarrow 257 for glasdegib and m/z 379 \rightarrow 257 for the internal standard.

Calibration curves were linear over the range of 3 to 3000 ng/mL for glasdegib in plasma, using a weighted ($1/\text{concentration}^2$) linear regression. The lower limit of quantification of glasdegib was 3 ng/mL. PK plasma samples were stored at -70°C and assayed within the 575 days of established frozen plasma stability. Inter-assay accuracy (percent relative error) at 9, 100, and 2250 ng/mL glasdegib in quality control samples ranged from -0.9% to 1.6% . Interassay precision (percent coefficient of variation [%CV]) was $\leq 5.3\%$ across quality control levels.

Glasdegib PK parameters were calculated using non-compartmental analysis of plasma concentration–time data. Samples below the lower limit of quantification were set to 0 for analysis. Actual sample collection times were used for the PK analysis. C_{max} and time when C_{max} was reached were the observed values. AUC from time 0 to the time of the last quantifiable concentration ($\text{AUC}_{0\text{-last}}$) was determined using the linear/log trapezoidal method. $\text{AUC}_{0\text{-}\infty}$ was calculated as $\text{AUC}_{0\text{-last}} + (C_{\text{last}}/K_{\text{el}})$, where C_{last} was the predicted plasma concentration at the last quantifiable time point estimated from the log-linear regression analysis and K_{el} was the terminal phase rate constant calculated by a linear regression of the log-linear concentration–time curve. Terminal half-life was calculated as $\log_e(2)/K_{\text{el}}$. Clearance (CL) for IV dosing and apparent clearance (CL/F) for oral dosing were calculated as $\text{dose}/\text{AUC}_{0\text{-}\infty}$. Volume of distribution during the terminal phase (area) was calculated as $\text{IV dose}/K_{\text{el}}(\text{AUC}_{0\text{-}\infty})$.

Determination of Sample Size

A sample size of 12 subjects (6 per sequence) provided 90% confidence interval (CI) for the difference between treatments of ± 0.1347 on the natural logarithm scale

for AUC, with 90% coverage probability. This determination was based on an assumed within-subject standard deviation of 0.144 for $\log_e AUC_{0-\infty}$.

Safety Evaluation

AEs including adverse drug reactions, illnesses with onset during the study, exacerbation of previous illnesses, clinically significant changes in physical examination findings, and abnormal objective test findings were recorded. Serious AEs were defined as any AE resulting in death or in immediate risk of death, requiring inpatient hospitalization or prolongation of existing hospitalization, resulting in persistent or significant disability/incapacity or congenital anomaly/birth defect, or considered to be an important medical event.

Statistical Analysis

Summary profiles (mean) of the concentration–time data were plotted by treatment. For summary statistics and summary plots by sampling time, nominal PK sampling time was used. The PK concentration population was defined as all subjects randomized and treated who had at least 1 glasdegib plasma concentration in at least 1 treatment period, whereas the PK parameter analysis population was defined as all subjects randomized and treated who had at least 1 of the glasdegib PK parameters of primary interest in at least 1 treatment period. Dose normalized (dn) natural log-transformed $AUC_{0-\infty}$ ($AUC_{0-\infty(dn)}$) and $AUC_{0-last(dn)}$ were analyzed using a linear mixed-effect model with sequence, period, and treatment as fixed effects and subject within sequence as a random effect. Estimates of the adjusted mean difference (test-reference, where IV glasdegib was the reference and oral glasdegib was the test) and corresponding 90%CI were obtained from the model. The adjusted mean difference and 90%CI for the difference were exponentiated to provide estimates of the ratio of adjusted geometric means (test/reference) and 90%CI for the ratios. Absolute bioavailability was expressed as the ratio of dose-normalized adjusted geometric means of $AUC_{0-\infty}$ for oral and IV glasdegib. Safety parameters were monitored throughout the study by AE assessment, physical examination, monitoring of pulse rate, BP, and ECG.

Results

Subject Disposition and Baseline Characteristics

A total of 12 subjects were enrolled and randomized to 1 of 2 treatment sequences (6 in each sequence). All subjects ($N = 12$) were male, the mean age was 37.4 years, and 66.7% were black or African American (Table 1). Two subjects were discontinued from the study, 1 due to moderate AE, and the other subject received both

Table 1. Baseline Demographic and Clinical Characteristics

	N = 12
Male, n (%)	12 (100)
Age (y), mean (SD)	37.4 (7.9)
Race, n (%)	
White	4 (33.3)
Black or African American	8 (66.7)
Height (cm), mean (SD)	179.1 (7.2)
Weight (kg), mean (SD)	85.1 (12.2)
BMI (kg/m ²)	
Mean (SD)	26.4 (2.2)

BMI, body mass index; SD, standard deviation.

treatments but withdrew from the study due to a family emergency.

Pharmacokinetic Results

Glasdegib arithmetic mean plasma concentration–time profiles following oral tablet and IV dosing are presented in Figure 1. Time when C_{max} was reached occurred at 1.52 and 1.27 hours after oral and IV dosing, respectively (Table 2). The arithmetic mean terminal half-life was 14.3 hours for oral tablet treatment vs 13.8 hours for IV glasdegib treatment whereas CL/F and CL were 13.87 L/h and 10.84 L/h for oral tablet and IV treatment, respectively (Table 2). Individual and arithmetic mean $AUC_{0-\infty(dn)}$ and $AUC_{0-last(dn)}$ are plotted by treatment in Figure 2. Intersubject variability for glasdegib exposure expressed as %CV values was 42% for $AUC_{0-\infty}$ and 41% to 42% for AUC_{0-last} . The absolute oral bioavailability measured as the ratios (oral/IV) of dose normalized geometric mean (90%CI) of $AUC_{0-\infty(dn)}$ was 77.12% (71.83%–82.81%; Table 2).

Safety Evaluation

Of the 12 subjects who were randomized and treated, 10 subjects completed the study. A total of 2 AEs (1 mild and 1 moderate in severity) were reported by 2 subjects following oral tablet administration. The subject who developed a mild AE had an elevated alanine aminotransferase (ALT) value of 57 U/L (reference range, 0–41 U/L) on treatment period 2 day 5 (baseline value, 23 U/L). The ALT value decreased to 45 U/L the following day and to 47 U/L on treatment period 2 day 13. On treatment period 2 day 19, ALT value returned to normal (30 U/L). This subject was not discontinued from the study because the AE occurred after treatment period 2 dosing. The other subject had elevated ALT levels on treatment period 1 day 7 ($>2 \times$ upper limit of normal) after receiving oral glasdegib 100 mg). The ALT elevation peaked at $3 \times$ upper limit of normal on treatment period 1 day 10 and returned to normal on treatment period 1 day 28. This subject did not receive the

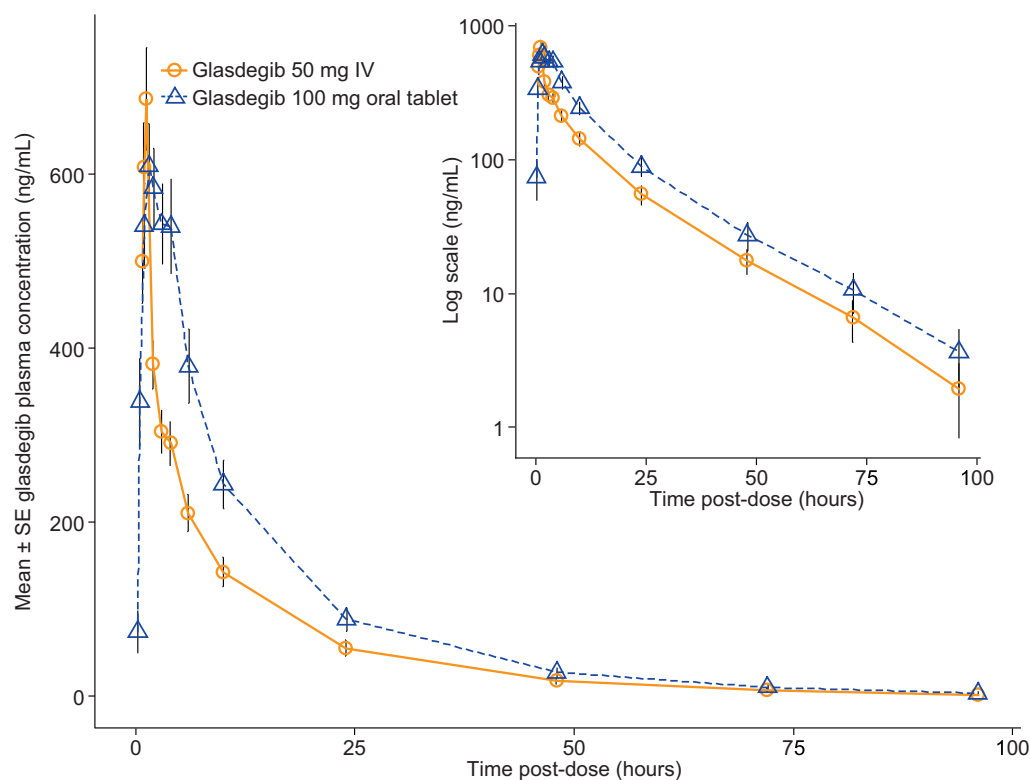


Figure 1. Arithmetic mean plasma glasdegib concentration–time profiles following a single orally administered dose or a single intravenously administered glasdegib dose. Values were calculated by setting concentration values below the lower limit of quantification (3 ng/mL) to 0.

planned glasdegib IV infusion for treatment period 2. Both AEs were resolved and considered treatment related by the investigator. No AEs were reported following glasdegib IV administration. There were no deaths, serious AEs, severe AEs, dose reductions, or temporary discontinuations. All changes observed in vital signs, ECG, and laboratory parameters were not considered clinically significant.

Discussion

This study estimated the absolute bioavailability of glasdegib after a single oral dose (100-mg tablet) relative to an IV dose (50 mg), both administered to subjects in a fasted state. As initially reported in earlier published work, data from 12 healthy subjects estimated the absolute bioavailability of oral glasdegib to be 77.12% in humans,⁹ which is above the mean absolute bioavailability observed in preclinical studies (33% in rats and 68% in dogs) and indicating that oral glasdegib was well absorbed.³

The absolute bioavailability of oral glasdegib was anticipated to be moderate based on the human mass balance (absorption, distribution, metabolism, and excretion [ADME]) study conducted in 6 healthy volunteers who received a single oral dose of 100-mg/100- μ Ci

[¹⁴C]glasdegib.¹⁰ The mean recovery of [¹⁴C]glasdegib-related radioactivity in urine was 49% (as parent and metabolites), suggesting that the oral bioavailability of glasdegib was likely to be $\geq 49\%$, ignoring any contribution of nonrenal elimination processes and assuming a low first-pass effect. Moreover, in a relative bioavailability study, the geometric mean C_{max} of glasdegib from a single 100-mg oral dose of glasdegib administered in healthy subjects as a 100-mg maleate immediate release tablet was 775.3 ng/mL.⁷ Based on these studies, it was anticipated that a 50-mg IV dose would be adequate to achieve systemic exposure that was comparable to a single 100-mg oral dose of glasdegib. As observed from the results of this study, most of the PK parameters following the oral and IV doses were remarkably similar, suggesting that oral absorption of glasdegib is not a major source of variability in PK data and oral glasdegib is highly bioavailable.

Results from the ADME study also indicated that glasdegib major route of elimination is primarily through CYP3A4 oxidation, and that contribution from the glucuronidation pathway via the uridine 5'-diphospho-glucuronosyltransferase 1-9 (UGT1A9) is only minor.¹⁰ In that study, 4.2% of the administered dose was found in the urine as N-glucuronide metabolite but not in the feces, whereas

Table 2. Summary Statistics of Plasma Pharmacokinetic Parameters by Route of Administration

Parameter (Unit)	Glasdegib 100 mg Oral Tablet	Glasdegib 50 mg IV
N	12	11
t_{\max} (h), median (range)	1.52 (1.00–4.00)	1.27 (1.00–1.27)
Arithmetic mean \pm SD		
AUC _{0-∞} (ng • h/mL)	8161 \pm 3435	5223 \pm 2206
AUC _{0-last} (ng • h/mL)	7994 \pm 3312	5115 \pm 2159
C _{max} (ng/mL)	684.2 \pm 155.4	686.8 \pm 197.2
CL/F (L/h)	13.87 \pm 4.51	N/A
CL (L/h)	N/A	10.84 \pm 3.45
V _d (area) (L)	204.6 \pm 46.1	N/A
$t_{1/2}$ (h)	14.26 \pm 2.45	13.78 \pm 2.97
Absolute oral bioavailability, % ^a	78.55 \pm 12.85	N/A
Geometric mean (geometric CV, %)		
AUC _{0-∞} (ng • h/mL)	7628 (38)	4879 (38)
AUC _{0-last} (ng • h/mL)	7488 (38)	4778 (39)
C _{max} (ng/mL)	668.0 (23)	664.6 (27)
CL/F (L/h)	13.10 (38)	N/A
CL (L/h)	N/A	10.25 (38)
V _d (area) (L)	199.6 (24)	N/A
AUC _{0-∞(dn)} (ng • h/mL/mg) ^b	76.28	98.90
AUC _{0-last(dn)} (ng • h/mL/mg) ^b	74.88	96.98
Absolute oral bioavailability, % (90%CI) ^c	77.12 (71.83–82.81)	N/A

AUC_{0-∞}, area under the plasma concentration–time profile from time 0 extrapolated to infinite time; AUC_{0-last}, area under the plasma concentration–time profile from time 0 to the time of the last quantifiable concentration (C_{last}); AUC_{0-∞(dn)}, dose normalized AUC_{0-∞}; AUC_{0-last(dn)}, dose normalized AUC_{0-last}; CI, confidence interval; C_{max}, maximum observed concentration; CL, clearance (IV infusion dosing); CL/F, apparent clearance; t_{\max} , time when C_{max} was reached; $t_{1/2}$, terminal half-life; V_d (area), volume of distribution during the terminal phase; CV, coefficient of variation; IV, intravenous; NA, not applicable; SD, standard deviation.

^aCalculated based on arithmetic mean ratios, without logarithmic transformation, of AUC_{0-∞(dn)} of the oral dose to the IV dose.

^bDose normalized geometric means from the statistical model.

^cCalculated as the ratio of the geometric means of AUC_{0-∞(dn)} of the oral dose to the IV dose.

19.5% of the administered glasdegib parent dose was recovered in the feces. However, it was unclear whether the amount recovered in the feces was entirely due to the proportion of the drug that was not absorbed or due to the back-conversion of the N-glucuronide metabolite to parent glasdegib following an enzymatic cleavage after biliary secretion. Given that UGT1A9 is a polymorphic enzyme system, it was important to understand the absolute bioavailability component, as there could be implications with regards to conducting further clinical studies to understand drug-drug interaction potential with UGT1A9 inhibitors or inducers. The results of this study show conclusively that most of the parent glasdegib recovered in the feces derives from the fraction that has not been absorbed and the contribution from the N-glucuronide metabolite reverting to parent glasdegib is likely to be minimal.

Data from this absolute bioavailability study also provided insights into the hepatic extraction of glasdegib (first-pass effect). The mean systemic plasma clearance of glasdegib following the IV administration was 13.1 L/h. The mean plasma renal clearance of glasdegib as estimated in the ADME study was 1.97 L/h¹⁰ and the plasma to whole blood partitioning of

glasdegib based on in vitro data and data from the ADME study was <1. Assuming a well-stirred model and that glasdegib is eliminated via the hepatic and renal pathways, using the hepatic blood flow of 87 L/h,¹¹ the hepatic extraction of glasdegib (estimated as hepatic blood clearance times the plasma-to-whole blood concentration ratio) was <0.3, suggesting a low first-pass effect for glasdegib.

The intersubject variability in both the CL and CL/F parameter expressed as the %CV of the geometric mean in this study was 38%. Previously reported %CV for the CL/F parameter from single oral dose evaluations of glasdegib in clinical studies ranged between 20% and 30%.^{8–10,12} The relatively high intersubject variability observed in this study was similar for both oral and IV dosing situations. The high variability noted for the clearance parameter may be due to the relatively small sample size, with a couple of subjects having lower clearance (higher AUC as noted in Figure 2).

Finally, both oral and IV glasdegib were well tolerated when administered in healthy subjects with all AEs mild/moderate in severity and fully resolved by the end of the study. In addition, none of the changes

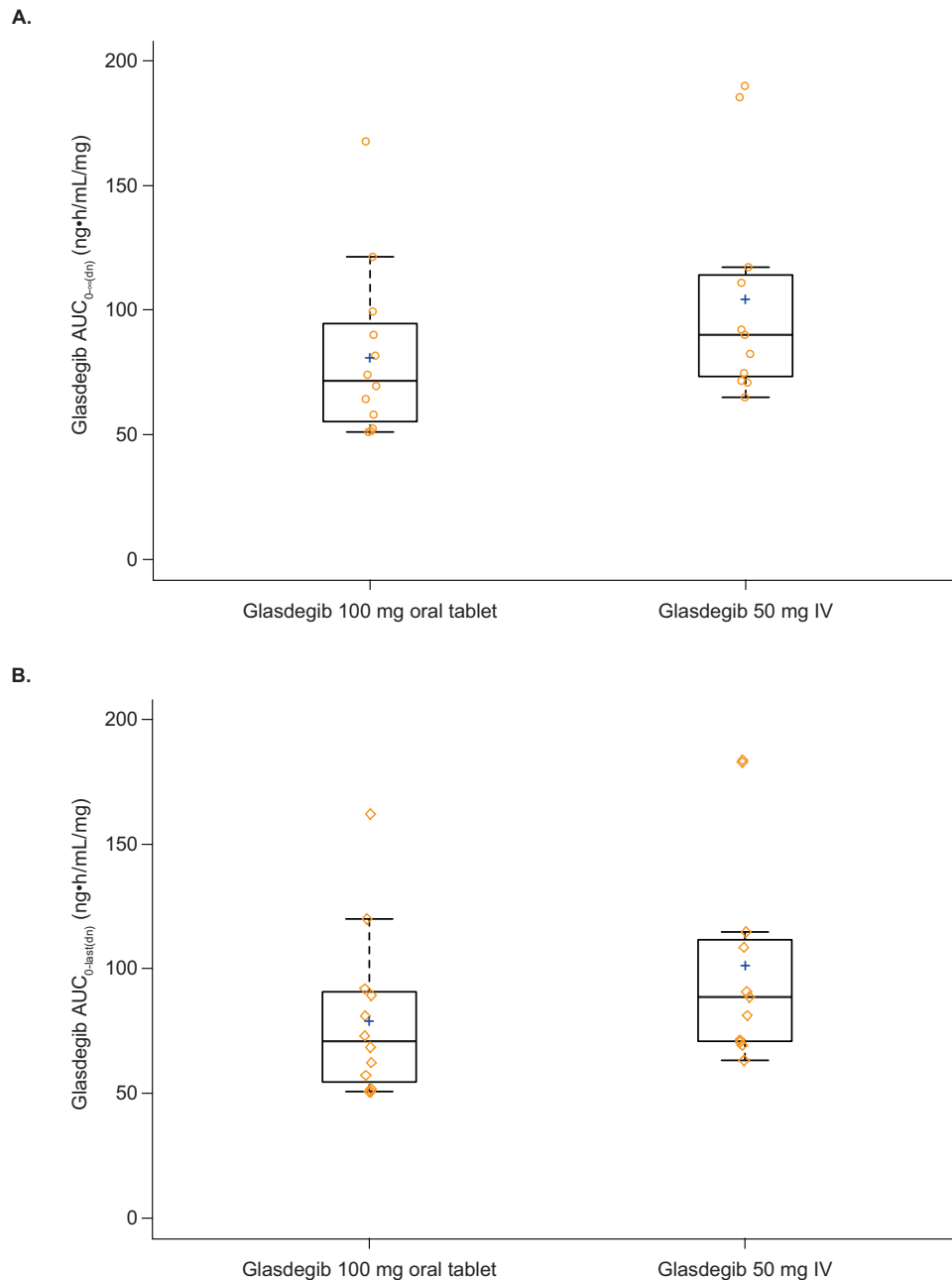


Figure 2. Individual (\circ or \diamond) and arithmetic mean (+) plasma glasdegib dose normalized $AUC_{0-\infty(dn)}$ (A) and dose normalized $AUC_{0-last(dn)}$ (B) values by treatment. Box plot provides median and 25%/75% quartiles with the bars indicating the minimum and maximum observed values within $1.5 \times$ interquartile range. $AUC_{0-\infty(dn)}$, dose normalized area under the plasma concentration–time profile from time 0 extrapolated to infinite time; $AUC_{0-last(dn)}$, dose normalized area under the plasma concentration–time profile from time 0 to the time of the last quantifiable concentration (C_{last}); IV, intravenous.

observed in vital signs, ECG, and laboratory parameters were considered clinically significant.

Conclusions

The absolute bioavailability of the oral glasdegib dose was 77.12% (90%CI, 71.83%-82.81%), indicating that more than three-quarters of the dose reached the sys-

temic circulation after oral administration. Single 100-mg oral and 50-mg IV infusion glasdegib doses were generally safe and well tolerated in healthy subjects.

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Declaration of Conflicting Interests

SMN, HB, and LBRR are employees of Pfizer and own stock in Pfizer. LY is a former employee of Pfizer and owns stock in Pfizer.

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