Original Manuscript

Clinical Pharmacology in Drug Development
2021, 10(7) 707–717

DOI: 10.1002/cpdd.897

Pharmacokinetics and Safety of Glasdegib in Participants With Moderate/Severe Hepatic Impairment: A Phase I, Single-Dose, Matched Case-Control Study

Joanna C. Masters[1], Robert R. LaBadie[2], Joanne Salageanu[3], Jerry Li[4], and Naveed Shaik[4]

Abstract

This phase I open-label trial (NCT03627754) assessed glasdegib pharmacokinetics and safety in otherwise healthy participants with moderate (Child-Pugh B) or severe (Child-Pugh C) hepatic impairment. Participants with hepatic impairment and age/weight-matched controls with normal hepatic function received a single oral 100-mg glasdegib dose under fasted conditions. The primary end points were area under the plasma concentration–time curve from time zero to infinity (AUC_{inf}) and maximum plasma concentration (C_{max}). Twenty-four participants (8/cohort) were enrolled. Glasdegib plasma exposures in moderate hepatic impairment were similar to controls, with adjusted geometric mean ratios (GMRs) of 110.8% (90% confidence interval [CI], 78.0–157.3) for AUC_{inf} and 94.8% (69.9–128.4) for C_{max} versus controls. In severe hepatic impairment, glasdegib plasma exposures were lower than controls (AUC_{inf} GMR, 75.7%; 90%CI, 51.5–111.0; C_{max} GMR, 58.0%; 90%CI, 37.8–89.0). Unbound glasdegib exposures were similar to controls for moderate ($AUC_{inf,u}$ GMR, 118.1%; 90%CI, 88.7–157.2; $C_{max,u}$ GMR, 101.1%; 90%CI, 78.4–130.3) and severe hepatic impairment ($AUC_{inf,u}$ GMR, 116.3%; 90%CI 81.8–165.5; $C_{max,u}$ GMR, 89.2%, 90%CI, 60.2–132.3). No treatment-related adverse events or clinically significant changes in laboratory values, vital signs, or electrocardiograms were observed. Together with previous findings, this suggests glasdegib dose modifications are not required based on hepatic impairment.

Keywords

acute myeloid leukemia, glasdegib, hepatic, oncology, pharmacokinetics

Acute myeloid leukemia (AML) is a rare type of cancer in which the bone marrow produces too many monocytes or granulocytes.[1] If untreated, AML usually progresses rapidly and has a very poor prognosis. Despite development in treatment options, the overall 5-year survival rate for adults in the United States is approximately 25%.[2] Outcomes remain very poor in those who are unsuitable for intensive chemotherapy because of their age or comorbidities, and unfortunately, AML occurs more commonly in older people.[1]

Various avenues into potential treatments for AML have developed from research into signaling pathways that control cell proliferation. The Hedgehog signaling pathway links the cell membrane to the nucleus, and pathway activation is essential for normal embryonic development.[3] In adults, the pathway is normally tightly regulated, but has been implicated in a number of cancers including solid tumors and leukemias.[3] Glasdegib is a potent, small-molecule, selective inhibitor of the Hedgehog signaling pathway.[4]

[1]Pharmacometrics, Pfizer Inc, La Jolla, California, USA
[2]Clinical Statistics, Pfizer Inc, Groton, Connecticut, USA
[3]Pharmacometrics, Pfizer Inc, Groton, Connecticut, USA
[4]Clinical Pharmacology, Pfizer Inc, La Jolla, California, USA

Submitted for publication 12 August 2020; accepted 23 November 2020.

Corresponding Author:
Naveed Shaik, PhD, Clinical Pharmacology, Pfizer Inc, 10555 Science Center Dr, San Diego, CA 92121
(e-mail: naveed.shaik@pfizer.com)

In the United States, glasdegib (100 mg orally once daily) is currently approved for use in combination with low-dose cytarabine for adults with newly diagnosed AML aged ≥75 years or who have comorbidities precluding intensive induction chemotherapy.[5] Glasdegib is also being studied in combination with azacitidine, or in combination with intensive induction chemotherapy in patients with newly diagnosed AML,[6,7] as well as in other types of cancer.[8]

Studies of the pharmacokinetic profile of glasdegib have demonstrated linear dose-proportional pharmacokinetics (PK).[9] Multiple clinical evaluations have been conducted to understand the absorption, distribution, metabolism, and excretion (ADME) of glasdegib in healthy trial participants and patients with cancer. Results from these evaluations indicate that the mean half-life of glasdegib is 17.4 hours at the clinical dose of 100 mg once daily, and it is moderately to highly bound to plasma proteins, with <10% unbound in plasma.[10] The results of the radiolabeled human ADME study showed that glasdegib was primarily cleared through oxidative metabolism with hepatic metabolism as the main clearance pathway; hydroxylation, *N*-desmethylation, and *N*-glucuronidation are the primary metabolic pathways before the secondary oxidation and glucuronidation processes start. The ADME study also found that cytochrome P450 (CYP) 3A4/5 was the major enzyme in glasdegib biotransformation in human hepatocytes using reaction phenotyping experiments.[10] Additional studies on drug-drug interactions showed that compared with glasdegib administered alone, the glasdegib area under the plasma concentration–time curve from time zero to infinity (AUC_{inf}) increased by 2.4-fold and the maximum plasma concentration (C_{max}) increased by 1.4-fold when ketoconazole (a strong inhibitor of CYP3A4) was coadministered with glasdegib,[11] while the glasdegib AUC_{inf} decreased by approximately 70% and C_{max} by 35% when rifampin (a strong inducer of CYP3A4) was coadministered with glasdegib.[12] Further, it was found that food with high calories and high content of fat or concurrent proton pump inhibitor treatment (rabeprazole) had a minimal effect on glasdegib exposure that was not clinically relevant.[13]

Evaluation of the impact of hepatic impairment on anticancer drugs such as glasdegib is essential, since hepatic impairment is a common comorbidity.[14] To some extent, the impact of hepatic impairment has been assessed using population pharmacokinetic analysis of data from patients in clinical trials.[15] The results demonstrated that baseline hepatic function was not a statistically significant covariate for explaining variation in glasdegib PK.[15] However, most patients in this analysis had normal hepatic function or mild hepatic impairment; therefore, while it could be concluded that mild hepatic impairment had no clinically meaningful effects on the PK of glasdegib, there was limited information for patients with moderate or severe hepatic impairment. To determine whether dose modifications are required for these groups, the current clinical trial specifically enrolled participants with moderate or severe hepatic impairment and investigated the effect on the PK and safety of glasdegib after a single oral 100-mg dose.

Methods

Overview and Ethics

This open-label, parallel-group, phase I trial enrolled participants with normal hepatic function, moderate hepatic impairment, or severe hepatic impairment. Impaired hepatic function was defined according to the modified Child-Pugh classification, as recommended for pharmacokinetic evaluation.[16,17] The study was conducted in compliance with the general principles of the Declaration of Helsinki and all International Council for Harmonisation Good Clinical Practice Guidelines. The Institutional Review Board at Orlando Clinical Research Center (Orlando, Florida) and Investigational Drug Services, University of Miami, Hospitals and Clinics, Research Pharmacy (Miami, Florida) reviewed and approved the trial protocol. All participants provided written informed consent before the study was started. The study was registered at ClinicalTrials.gov (NCT03627754) before the first participant was enrolled.

Participants

The study enrolled participants aged 18–75 years with body weight >50 kg and body mass index of 17.5–40 kg/m^2. Men and women were eligible, excluding women with childbearing potential. Participants were categorized into 1 of 3 cohorts: normal hepatic function, moderate hepatic impairment (Child-Pugh class B, score 7-9), or severe hepatic impairment (Child-Pugh class C, score 10-15). Participants in cohorts with impaired hepatic function (either severe or moderate) were enrolled first. Subsequently, participants with normal hepatic function were matched to the median values of the pooled hepatic impairment cohorts for age (within ±5 years) and weight (within ±10 kg).

For the normal hepatic function cohort, participants had to have no known or suspected hepatic impairment according to medical history or laboratory values. They also had to be otherwise healthy, with no clinically relevant abnormalities found on a detailed medical history evaluation, physical examination, electrocardiogram (ECG), or laboratory values. For the impaired hepatic function cohorts, participants were eligible if they had hepatic impairment that was clinically stable for

30 days before the study and met the modified Child-Pugh classification criteria class B or C.[18] They were required to have a diagnosis of hepatic dysfunction due to hepatocellular disease (and not secondary to any acute ongoing hepatocellular process) documented by medical history, physical examination, liver biopsy, or imaging (ultrasound, computed tomography scan, or magnetic resonance imaging).

For all participants, exclusion criteria included standard criteria for pharmacokinetic studies, such as conditions affecting drug absorption (eg, gastrectomy). In addition, participants were excluded from the normal hepatic function cohort if they had a history of regular alcohol consumption (>7 drinks/week for women or >14 drinks/week for men) within 6 months of screening; QT interval corrected for heart rate using Fridericia's formula >450 milliseconds or a QRS interval >120 milliseconds on screening ECG; use of prescription or nonprescription drugs or dietary supplements within 7 days or 5 half-lives (whichever was longer) before the glasdegib dose, except acetaminophen/paracetamol at doses of ≤1 g/day; or a history of or current positive results for hepatitis B or hepatitis C.

Participants were excluded from the hepatic impairment cohorts if they had any other clinically significant disease that contraindicated glasdegib or that may have affected glasdegib PK; hepatic carcinoma and hepatorenal syndrome or life expectancy <1 year; had undergone portacaval shunt surgery (except participants with a transjugular intrahepatic portosystemic shunt who met the Child-Pugh criteria); history of gastrointestinal hemorrhage either due to esophageal varices or peptic ulcers <1 month before study entry; or clinically significant laboratory abnormalities except for parameters influenced by hepatic impairment (including glomerular filtration rate <75 mL/min/1.73 m^2 estimated by the Modification of Diet in Renal Disease equation); presence of clinically active stage 3 or 4 encephalopathy; severe uncontrolled ascites and/or pleural effusion; screening blood pressure ≥160 mm Hg for systolic or ≥90 mm Hg diastolic; QT interval corrected for heart rate using Fridericia's formula >470 milliseconds or a QRS interval >120 milliseconds on screening ECG; or congenital long QT syndrome, medical history of torsades de pointes, or clinically significant ventricular arrhythmias. Participants were also excluded from the hepatic impairment cohorts if they had taken prescription or nonprescription drugs, dietary supplements, or food that may affect the PK of glasdegib within 7 days or 5 half-lives (whichever was longer) before the glasdegib dose, with the exception of medications that were not believed to affect participant safety and were medically necessary for the participant's hepatic disease or other comorbid conditions. In particular, participants were excluded if they had use of proton pump inhibitors within 5 days before the glasdegib dose, strong or moderate CYP3A4 inhibitors within 7 days or 5 half-lives (whichever was longer) before the glasdegib dose, or strong or moderate CYP3A4 inducers within 12 days or 5 half-lives (whichever was longer) before the glasdegib dose. In addition, participants were excluded if they took medications that could have resulted in diarrhea or had >2 bowel movements within ±12 hours of the glasdegib dose.

Trial Design

The study was conducted at 2 clinical research centers in the United States. Participants attended a screening visit to assess inclusion and exclusion criteria within 28 days before the study start on day 1. All participants were admitted the day before the glasdegib dose (day −1) and confined to the center during the study. Participants in both hepatic impairment cohorts completed safety assessments, including liver function assessments and evaluation of renal function within 24 hours before their glasdegib dosing; these assessments were not required for the cohort with normal hepatic function. On the morning of day 1, following an overnight fast of ≥10 hours, participants were administered a single oral dose of glasdegib 100 mg (tablet formulation) with approximately 240 mL of water. No food or drinks except water were allowed for 4 hours after dosing. Participants remained at the center until completion of pharmacokinetic sampling and safety assessments on the morning of day 6. A follow-up assessment was conducted by telephone 28 to 35 days after day 1.

Bioanalytical Methods

Blood samples to measure total (bound and unbound) glasdegib (2 mL to provide approximately 1 mL of plasma) were drawn before dosing and 1, 2, 3, 4, 6, 8, 12, 24, 48, 72, 96, and 120 hours after dosing. Plasma concentrations of total glasdegib were determined using a validated, sensitive, and specific high-performance liquid chromatography–tandem mass spectrometric method at Covance Bioanalytical Services (Shanghai, China).[13] The established limit of stability for samples stored at −70°C was 575 days, and all samples were analyzed within this time frame (maximum, 149 days). Deuterated glasdegib (glasdegib-d4) was used as the internal standard, and liquid-liquid extraction was carried out with ethyl acetate. The column used for high-performance liquid chromatography was Zorbax XDB-C18 (50 × 2.1 mm, 5 μm; Agilent Technologies, Santa Clara, California) with 0.1% formic acid in water as mobile phase A and 0.1% formic acid in acetonitrile as mobile phase B. The instrument for tandem mass spectrometry was Sciex API 4000 (Applied Biosystems,

Foster City, California) set in multiple reaction monitoring mode. Voltage of positive ion electrospray (IonSpray) was 3000 V, and the temperature was 550°C. The *m*/*z* monitored for glasdegib and the internal standard was 375 → 257 and 379 → 257, respectively.[13] The lower limit of quantification (LLQ) for glasdegib was 3.00 ng/mL, and calibration standard responses were linear over the range of 3 ng/mL to 3000 ng/mL, using a weighted (1/concentration^2) linear regression. For quality control samples at low, middle, and high values (9, 100, and 2250 ng/mL, respectively), interassay accuracy (percent relative error) ranged from −2.0% to 3.0%, and interassay precision (percent coefficient of variation [%CV]) was ≤6.3% across samples.

Separate blood samples to measure unbound glasdegib (10 mL to provide approximately 4 mL of plasma) were drawn before dosing and at 1, 2, and 4 hours after dosing. The mean unbound fraction (f_u) at these time points was multiplied by each time point across each participant's profile. Samples underwent equilibrium dialysis with phosphate-buffered saline (PBS). The equilibrium dialysis was carried out in an HTDialysis Device (HTDialysis LLC, Gales Ferry, Connecticut) with the molecular weight at 12,000 to 14,000 Da. PBS was used to dialyze human plasma samples containing dipotassium ethylenediaminetetraacetate. Positive control was sertraline spiked into plasma (containing dipotassium ethylenediaminetetraacetate) at 300 ng/mL. Glasdegib 100 ng/mL in human plasma was used as quality control of dialysis. The time to reach equilibrium was 6 hours. After reaching equilibrium, dialyzed plasma and dialyzed PBS were diluted with nondialyzed PBS and nondialyzed plasma, respectively, to generate plasma PBS mixed matrix samples (volume ratio of plasma to PBS, 10:40). Unbound glasdegib concentrations were determined using a validated, sensitive, and specific high-performance liquid chromatography–tandem mass spectrometric method at Covance Bioanalytical Services (Shanghai, China) as described above. For this assay measuring unbound plasma glasdegib, calibration standard responses were linear over the range of 1 ng/mL to 1000 ng/mL, using a weighted (1/concentration^2) linear regression. The LLQ for glasdegib was 1 ng/mL. For low, low-middle, middle, and high quality control samples (3, 40, 400, and 800 ng/mL, respectively), interassay accuracy (percent relative error) ranged from −2.3% to 7.3%, and interassay precision (%CV) was ≤6.4% across samples.

Sample Size

A sample size of 24 participants was considered adequate to determine any clinically meaningful impact of hepatic impairment on glasdegib PK, consistent with the United States Food and Drug Administration guidance for pharmacokinetic studies in participants with hepatic impairment.[15] Populations for analyses were prespecified as follows: pharmacokinetic concentration analyses included all participants who received the glasdegib dose and had ≥1 measurement of glasdegib concentration; pharmacokinetic parameter analyses included all participants who had ≥1 available result for a primary end point; and safety analyses included all participants who received the glasdegib dose.

Pharmacokinetic and Statistical Analyses

Glasdegib pharmacokinetic parameters were calculated using non-compartmental analysis of plasma concentration–time data for each participant in each cohort. Pfizer proprietary software (eNCA version 2.2.4) was used for calculations. Actual sample collection times were used, and samples below the LLQ were set to zero for the pharmacokinetic analysis.

The primary end points were total plasma glasdegib AUC_{inf} and the C_{max} of glasdegib. AUC_{inf} was calculated with the formula $AUC_{last} + (C_{last}/k_{el})$, where C_{last} is the predicted plasma concentration at the last quantifiable time point estimated from the log-linear regression analysis, and k_{el} is the terminal-phase rate constant calculated by a linear regression of the log-linear concentration–time curve. For C_{max}, the observed value was used. Other pharmacokinetic end points were AUC from time zero to the time of the last quantifiable concentration (AUC_{last}), apparent oral clearance (CL/F), terminal half-life, and time to C_{max}. All AUCs were calculated using the linear/log trapezoidal method. For unbound glasdegib, $AUC_{inf,u}$, $AUC_{last,u}$, and $C_{max,u}$ were calculated by multiplying f_u by the corresponding total glasdegib values.

A one-way analysis of variance model was used to compare the natural log-transformed glasdegib primary end points AUC_{inf} and C_{max} (and corresponding unbound parameters) as well as AUC_{last} and $AUC_{last,u}$ for each of the hepatic impairment cohorts (Test) with the normal hepatic function cohort (Reference). The model used the unequal variance assumption and hepatic impairment group as a fixed effect. Estimates of the adjusted mean differences (Test minus Reference) and corresponding 90% confidence intervals (CIs) were obtained from the model. The adjusted mean differences and 90%CIs were exponentiated to provide estimates of the ratio of adjusted geometric means (Test/Reference) and 90%CIs for the ratios. Analyses were performed using SAS version 9.4 (SAS Institute, Cary, North Carolina). Other pharmacokinetic end points were summarized descriptively for each impairment group.

Safety

Safety was assessed throughout the study by monitoring adverse events (AEs), laboratory values, physical examination, vital signs, ECGs, and concomitant

Table 1. Participant Characteristics

	Severe Hepatic Impairment (n = 8)	Moderate Hepatic Impairment (n = 8)	Normal Hepatic Function (n = 8)
Gender			
Female, n (%)	2 (25.0)	2 (25.0)	2 (25.0)
Age, y			
Range	50–68	53–72	58–67
Mean ± SD	61.6 ± 7.0	62.9 ± 6.9	62.6 ± 3.6
≥65, n (%)	4 (50.0)	3 (37.5)	4 (50.0)
Weight, kg			
Range	74–121	71–119	84–96
Mean ± SD	94.7 ± 14.1	95.2 ± 17.9	88.6 ± 4.3
Race, n (%)			
White	8 (100.0)	7 (87.5)	8 (100.0)
Black or African American	0	1 (12.5)	0
Ethnicity, n (%)			
Hispanic or Latino	4 (50.0)	4 (50.0)	5 (62.5)
Not Hispanic or Latino	4 (50.0)	2 (25.0)	3 (37.5)
Not reported	0	2 (25.0)	0

SD, standard deviation.
Ranges are minimum to maximum.

medication. An AE was defined as treatment emergent if onset was after the glasdegib dose until the follow-up assessment, or if severity increased in this time frame. The *Medical Dictionary for Regulatory Activities* version 22.0 coding was applied. Safety end points were analyzed descriptively. For any assessment of changes from baseline values, baseline was defined as the last predose measurement.

Results

Participants

Between November 2018 and March 2019, 24 participants were enrolled (8 participants in each hepatic function cohort). All participants received the study drug dose, completed the study, and were included in all analyses.

Participant characteristics are shown in Table 1. Characteristics were well balanced between the groups, with body weight and age within defined ranges for matching. The most frequently used concomitant medication was furosemide, which was used by all participants with impaired hepatic function.

Pharmacokinetics

Total Plasma Glasdegib. Concentration–time profiles of total plasma glasdegib for the 3 cohorts are shown in Figure 1. Following glasdegib administration, C_{max} was reached between 1 and 4 hours for all participants (Table 2). Total glasdegib plasma exposures for the moderate hepatic impairment cohort were similar to those observed for the normal hepatic function cohort (Table 3). Adjusted geometric mean ratios (GMR) were 110.8% (90%CI, 78.0–157.3) for AUC_{inf} and 94.8% (90%CI, 69.9–128.4) for C_{max}. Total plasma glasdegib exposure for the severe hepatic impairment cohort was lower than for the normal hepatic function cohort (Table 3), with a 24% reduction in AUC_{inf} (adjusted GMR, 75.7%; 90%CI, 51.5–111.0) and a 42% reduction in C_{max} (adjusted GMR, 58.0%; 90%CI, 37.8–89.0).

Individual and geometric mean AUC_{inf} and C_{max} values for total plasma glasdegib are shown in Figure 2. Between-participant variability in plasma exposure within a cohort was moderate to high, with %CV values for the geometric mean ranging from 31% to 49% for AUC_{inf} and from 26% to 59% for C_{max} (Table 2).

All hepatic function groups had comparable mean terminal half-life values, which ranged between 18.4 and 20.7 hours (Table 2). Participants with severe hepatic impairment showed a slight increase in CL/F versus normal hepatic function; this increase was not seen in those with moderate hepatic impairment.

Unbound Plasma Glasdegib. Unbound plasma glasdegib concentration–time profiles for the 3 cohorts are shown in Figure 3. In the cohort with normal hepatic function, the glasdegib f_u in plasma was 0.08 (Table 2). The moderate hepatic impairment group also had an f_u value of 0.08, while the severe hepatic impairment group had an f_u of 0.12.

No marked differences were observed in geometric mean $AUC_{inf,u}$ or $C_{max,u}$ for the moderate or severe hepatic impairment groups compared with the

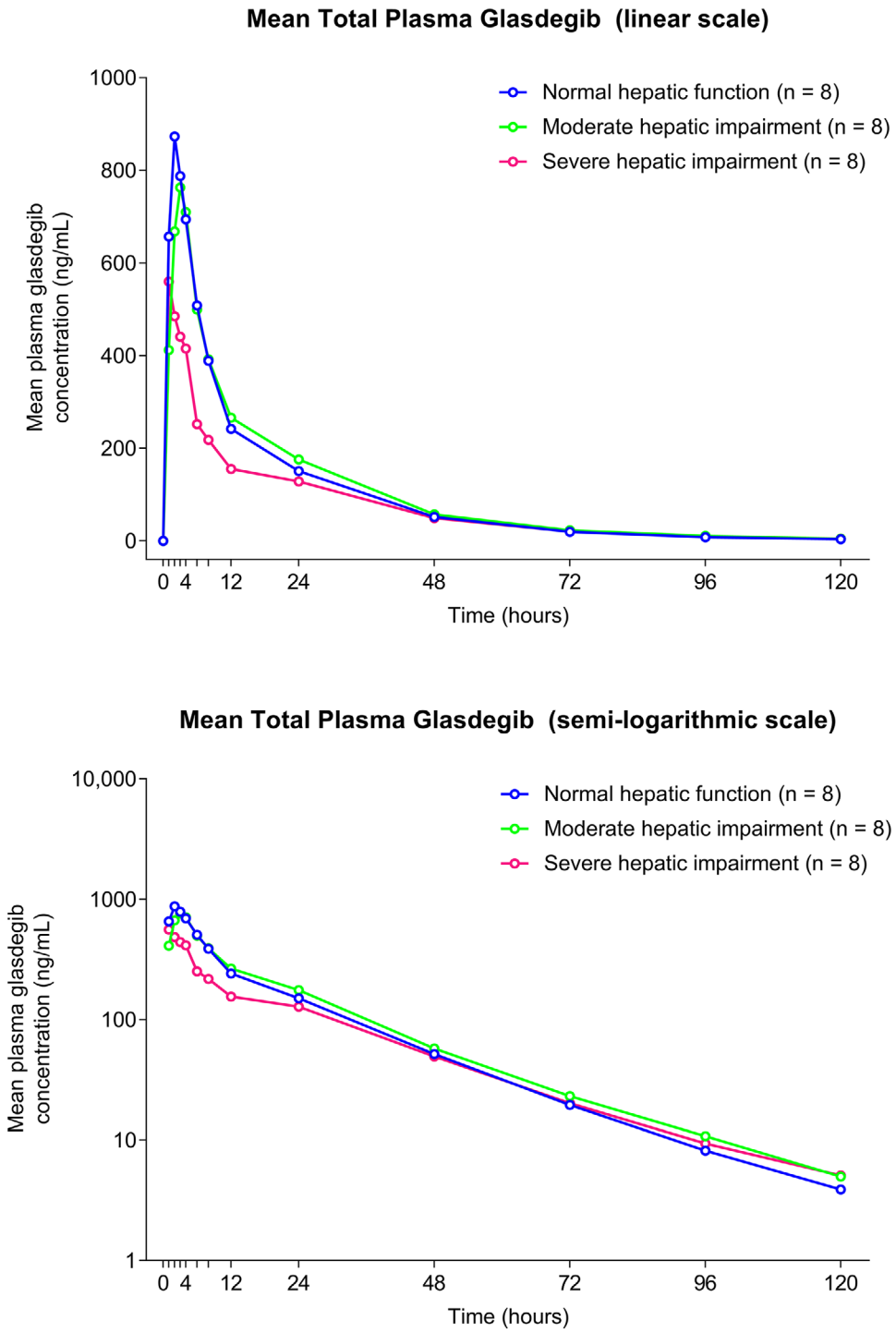

Figure 1. Plasma concentration–time profiles for total glasdegib. Concentration values below the lower limit of quantification (3 ng/mL) were set to zero.

control group (ie, the normal hepatic function group) (Table 2). Individual values for $AUC_{inf,u}$ or $C_{max,u}$ showed variability, but overlapped between groups (Figure 2). In the statistical comparison, unbound glasdegib exposures were similar to those of controls (Table 3). Relative to participants with normal hepatic function, the adjusted GMR of the unbound $AUC_{inf,u}$ was 118.1% (90%CI, 88.7–157.2) in participants with moderate hepatic impairment and 116.3% (90%CI, 81.8–165.5) in participants with severe hepatic impairment; the adjusted GMR of the peak unbound glasdegib exposure ($C_{max,u}$) was 101.1% (90%CI,

Table 2. Pharmacokinetic Parameters

		Severe Hepatic Impairment (n = 8)	Moderate Hepatic Impairment (n = 8)	Normal Hepatic Function (n = 8)
Total glasdegib				
AUC_{inf}, ng·h/mL	Arithmetic mean ± SD	8658 ± 3132	12340 ± 3498	11870 ± 6096
	Geometric mean (%CV)	8114 (42)	11880 (31)	10730 (49)
AUC_{last}, ng·h/mL	Arithmetic mean ± SD	8479 ± 3099	12200 ± 3464	11760 ± 6077
	Geometric mean (%CV)	7935 (42)	11750 (31)	10620 (50)
C_{max}, ng/mL	Arithmetic mean ± SD	612.0 ± 342.8	899.8 ± 215.7	989.9 ± 373.1
	Geometric mean (%CV)	536.3 (59)	875.9 (26)	924.4 (43)
t_{max}, h	Median (range)	1.0 (1.0–4.0)	2.5 (1.0–4.0)	1.5 (1.0–3.0)
$t_{1/2}$, h	Arithmetic mean ± SD	20.7 ± 3.5	18.4 ± 3.5	18.7 ± 1.8
CL/F, L/h	Arithmetic mean ± SD	13.3 ± 5.8	8.8 ± 2.8	10.2 ± 4.3
	Geometric mean (%CV)	12.3 (42)	8.4 (31)	9.3 (49)
Unbound glasdegib				
$AUC_{inf,u}$, ng·h/mL	Arithmetic mean ± SD	1060 ± 384	1036 ± 286	889 ± 303
	Geometric mean (%CV)	982.9 (47)	997.5 (31)	844.9 (35)
$AUC_{last,u}$, ng·h/mL	Arithmetic mean ± SD	1039 ± 379	1023 ± 278	878.9 ± 301
	Geometric mean (%CV)	962.0 (47)	985.3 (31)	834.8 (36)
$C_{max,u}$, ng/mL	Arithmetic mean ± SD	73.3 ± 36.8	75.8 ± 19.2	75.5 ± 19.1
	Geometric mean (%CV)	65.0 (58)	73.6 (27)	72.8 (31)
CL_u/F, L/h	Arithmetic mean ± SD	111.9 ± 58.1	104.6 ± 34.6	124.7 ± 43.5
	Geometric mean (%CV)	101.6 (47)	100.2 (31)	118.4 (35)
f_u	Arithmetic mean ± SD	0.12 ± 0.02	0.08 ± 0.006	0.08 ± 0.01
	Geometric mean (%CV)	0.12 (15)	0.08 (7)	0.08 (16)

AUC, area under the plasma concentration–time curve; AUC_{last}, AUC from time zero to the time of the last quantifiable concentration; AUC_{inf}, AUC from time zero to infinity; CL/F, apparent clearance of total drug from plasma; C_{max}, maximum plasma concentration; CV, coefficient of variation; f_u, fraction of unbound drug in plasma; SD, standard deviation; $t_{1/2}$, half-life; T_{max}, time to C_{max}; u, unbound.

Table 3. Pharmacokinetics of Total and Unbound Glasdegib: Statistical Comparison

	GMR (90%CI) Versus Normal Hepatic Function	
	Severe Hepatic Impairment	Moderate Hepatic Impairment
Total glasdegib		
AUC_{inf}, ng·h/mL	75.7% (51.5–111.0)	110.8% (78.0–157.3)
C_{max}, ng/mL	58.0% (37.8–89.0)	94.8% (69.9–128.4)
Unbound glasdegib		
$AUC_{inf,u}$, ng·h/mL	116.3% (81.8–165.5)	118.1% (88.7–157.2)
$C_{max,u}$, ng/mL	89.2% (60.2–132.3)	101.1% (78.4–130.3)

ANOVA, analysis of variance; AUC, area under the plasma concentration–time curve; AUC_{inf}, AUC from time zero to infinity; CI, confidence interval; C_{max}, maximum plasma concentration; GMR, geometric mean ratio; u, unbound.
GMR of hepatic impairment cohort (Test) to the normal hepatic function cohort (Reference) based on adjusted geometric means, calculated using ANOVA as described in the text.

78.4–130.3) for the moderate hepatic impairment cohort and 89.2% (90%CI, 60.2–132.3) for the severe hepatic impairment cohort. Similar values for CL_u/F were observed across all hepatic function groups (Table 2).

Safety

During this study, there were no deaths, serious AEs, severe treatment-emergent AEs, discontinuations from the study, or AEs considered treatment related by the investigator. No changes in laboratory values were considered clinically significant or reported as AEs, and there were no clinically significant changes in vital signs or ECGs. One participant (in the severe hepatic impairment cohort) reported 2 treatment-emergent AEs (fall, musculoskeletal pain); both were considered unrelated to treatment but were related to each other, with the musculoskeletal pain caused by the fall. This participant also had the only change in

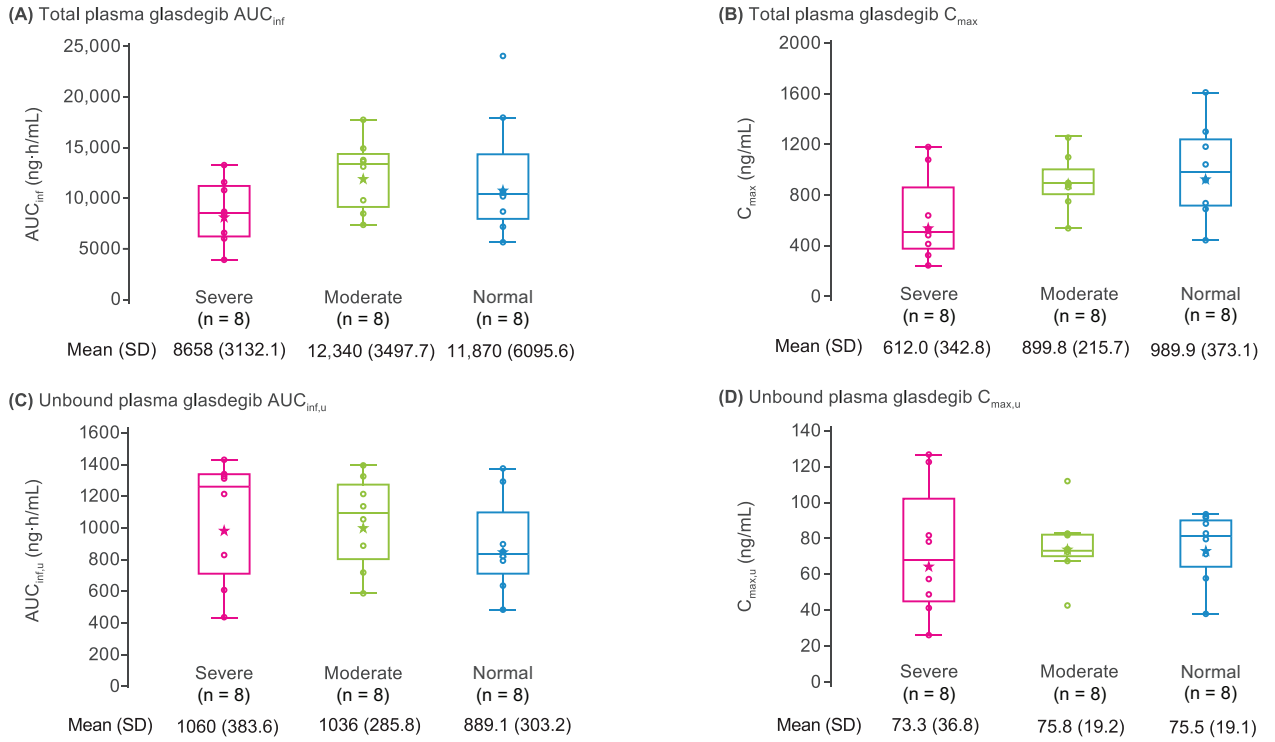

Figure 2. Individual and summary of glasdegib total and unbound AUC_{inf} and C_{max}. Circles represent individual participant values and stars represent geometric mean. Box plot provides median and 25%/75% quartiles with whiskers to the last data point within 1.5 × the interquartile range. Mean (SD) displayed numerically under box plot. AUC_{inf}, AUC from time zero to infinity; C_{max}, maximum plasma concentration; mean, arithmetic mean; SD, standard deviation; u, unbound.

concomitant medications during the study, receiving hydrocodone/paracetamol and ibuprofen for musculoskeletal pain.

Discussion

In this study, participants with normal hepatic function and those with moderate or severe hepatic impairment had substantial overlap in glasdegib pharmacokinetic parameters, indicating that there were no clinically meaningful changes in exposures. For the cohort with moderate hepatic impairment, total plasma glasdegib PK were essentially similar to those with normal hepatic function (the control cohort). For the cohort with severe hepatic impairment, total exposures were marginally lower, and CL/F was marginally higher versus controls, with individual values demonstrating substantial overlap.

The results in the cohort with severe hepatic impairment may initially seem counterintuitive for a drug that is primarily excreted via hepatic metabolism, where increased exposure might be anticipated; however, these results reflect the overall profile of glasdegib in vivo. The increase in CL/F may be explained by the 50% higher f_u in the severe impairment cohort compared with the normal function cohort (an increase that was not observed in the moderate hepatic impairment cohort). In turn, the increase in f_u in the severe hepatic impairment cohort can be explained by lower production of albumin and α_1-acid glycoprotein in the liver of these participants, as glasdegib binds moderately to both proteins.[19,20]

The higher CL/F in participants with severe hepatic impairment relative to normal hepatic function reflects the low extraction ratio of glasdegib, which has been demonstrated in studies of absolute bioavailability and ADME.[10,21] Assuming a well-stirred model, the hepatic blood clearance for glasdegib can be simplified to a product of the f_u and the intrinsic clearance. Based on this equation, study participants with severe hepatic impairment, who had a higher f_u on average, should have a higher hepatic blood clearance than the participants with normal hepatic function, if intrinsic clearance is not markedly decreased. Bioavailability is dependent on the fraction of the drug absorbed, the fraction escaping gut wall metabolism, and the fraction escaping first-pass effect. For a drug with a low extraction ratio (eg, glasdegib), one can reasonably assume the fraction of the drug absorbed and the fraction escaping gut wall metabolism are not notably affected by hepatic impairment and the fraction escaping first-pass effect is approximately 1 per the well-stirred model;

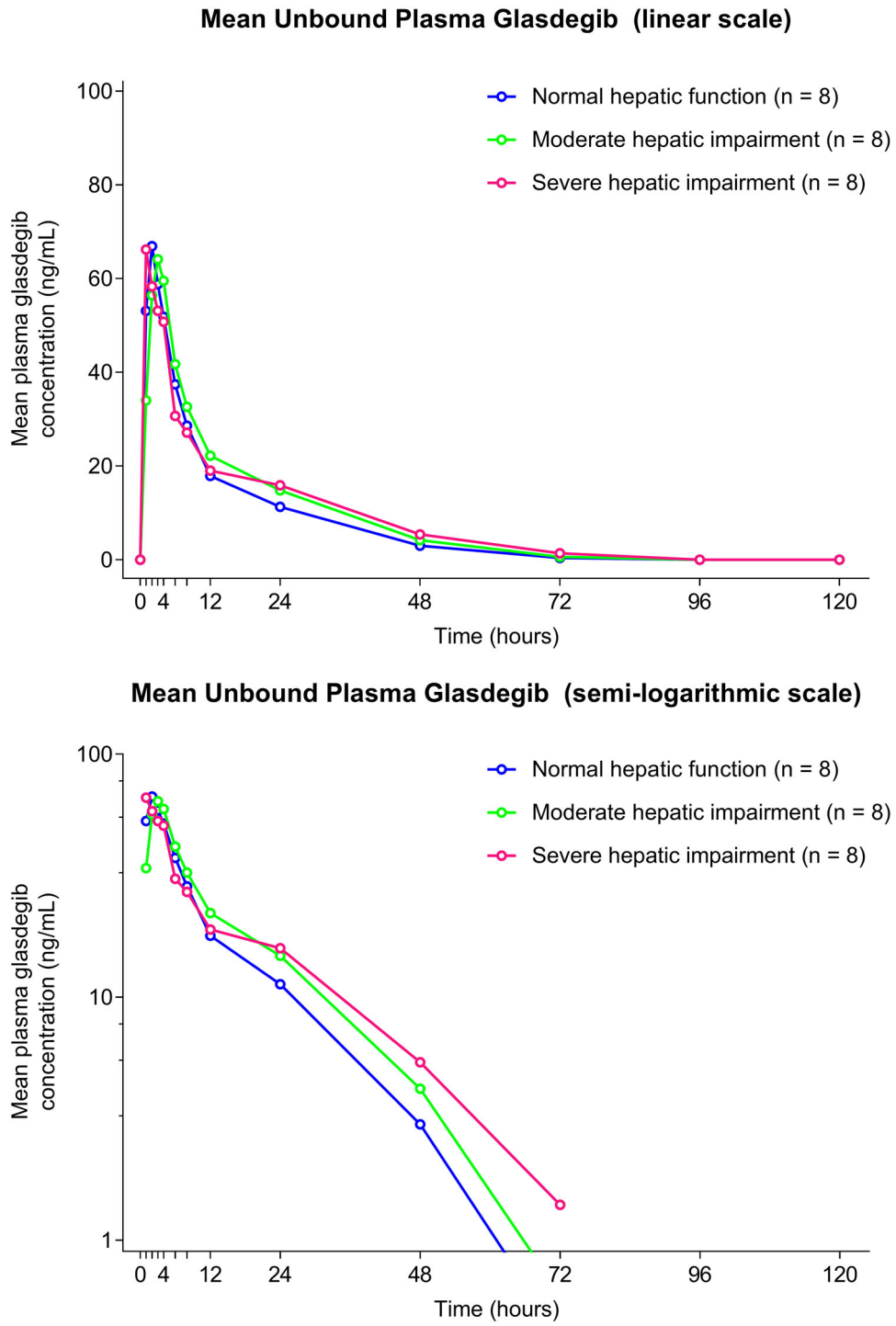

Figure 3. Plasma concentration–time profiles for unbound glasdegib. Concentration values below the lower limit of quantification (3 ng/mL) were set to zero.

this indicates that glasdegib oral bioavailability would not be markedly impacted by hepatic impairment. Therefore, CL/F is indeed expected to increase in participants with severe hepatic impairment where there is an increase in hepatic blood clearance and no change in bioavailability.

Previous publications have delved into the underpinnings of the limited practical implications of changes in protein binding, using clinical examples to refute the notion that the effective concentration of all drugs depends on f_u.[22,23] Certainly, the trend observed for glasdegib $AUC_{inf,u}$ and $C_{max,u}$ in the severe hepatic

impairment cohort is a consequence of the difference in f_u compared to the reference cohort, since values for total glasdegib AUC_{inf} and C_{max} were slightly lower in this group, demonstrating the important difference in the trend of total versus unbound drug when protein binding is impacted. Nevertheless, both the moderate and severe impairment groups had unbound glasdegib exposures similar to those of the control group. Unbound drug represents the pharmacologically active species and is therefore considered more clinically relevant, indicating that no change in dose is warranted in patients with moderate or severe impairment.

While this trial was not designed to assess long-term safety or tolerability of glasdegib, it is important to note that a single oral dose of glasdegib 100 mg was well tolerated with no treatment-related AEs reported. Furthermore, there were no discontinuations or clinically significant changes in laboratory values, vital signs, or ECGs.

The results of this study are in line with those of the previously reported population pharmacokinetic analysis for glasdegib.[15] Of 267 patients included in that analysis who had hepatic function data, 220 had normal hepatic function, 43 mild hepatic impairment, 3 moderate hepatic impairment, and 1 severe hepatic impairment.[15] Hepatic function was not a statistically significant covariate for explaining variability in glasdegib PK. Based on these results, it was concluded that glasdegib could be used without dose adjustment in patients with mild hepatic impairment, but the numbers of patients with moderate or severe impairment were too small to draw any conclusions for these groups. It should be noted that patients' hepatic function for this analysis was categorized using the National Cancer Institute Organ Dysfunction Working Group criteria, which, though it correlates with the Child-Pugh classification used in the current study, does not result in identical categorization.[24] However, since the current study included participants with greater degrees of hepatic impairment (moderate and severe) and still demonstrated no clinically meaningful impact on glasdegib exposure (notably including evaluation of free drug, the most relevant pharmacological species), it follows that mild hepatic impairment does not affect glasdegib PK, in agreement with the previous population analysis in patients.

It is acknowledged that this study has limitations, and generally these are common to all dedicated pharmacokinetic studies. The between-patient variability observed may reflect the sample size, which was chosen following regulatory guidance for the design of studies of PK in patients with impaired hepatic function.[15] While differences between groups are possible, the design protected against possible imbalances as far as was practical by matching a control group with normal hepatic function to the test groups. Furthermore, no protocol deviations occurred that precluded use of any data; therefore, all participants were included in all analyses. Thus, while the results of this study should not be overinterpreted, they are considered sufficiently robust to address the question of whether patients with hepatic impairment require dose reduction of glasdegib.

Conclusions

The results of this study demonstrate that glasdegib exposures are not altered to a clinically meaningful extent, and 100-mg single-dose glasdegib was well tolerated in participants with moderate or severe hepatic impairment. Taken together with previous findings, these data suggest that 100 mg daily remains the appropriate glasdegib dose for patients with varying degrees of liver dysfunction, and dose modifications are not required on the basis of hepatic impairment.

Acknowledgments

Medical writing support was provided by Geraldine Thompson and Shuang Li at Engage Scientific Solutions, Horsham, United Kingdom, and was funded by Pfizer.

Conflicts of Interest

All authors are employees of Pfizer. Joanna C. Masters, Robert R. LaBadie, Joanne Salageanu, and Naveed Shaik hold Pfizer stock.

Funding

This study was sponsored by Pfizer.

Data Availability Statement

Upon request, and subject to certain criteria, conditions, and exceptions (see https://www.pfizer.com/science/clinical-trials/trial-data-and-results for more information), Pfizer will provide access to individual deidentified participant data from Pfizer-sponsored global interventional clinical studies conducted for medicines, vaccines, and medical devices (1) for indications that have been approved in the United States and/or European Union or (2) in programs that have been terminated (ie, development for all indications has been discontinued). Pfizer will also consider requests for the protocol, data dictionary, and statistical analysis plan. Data may be requested from Pfizer trials 24 months after study completion. The deidentified participant data will be made available to researchers whose proposals meet the research criteria and other conditions, and for which an exception does not apply, via a secure portal. To gain access, data requesters must enter into a data access agreement with Pfizer.

References

1. Döhner H, Weisdorf DJ, Bloomfield CD. Acute myeloid leukemia. *N Engl J Med*. 2015;373(12):1136-1152.
2. American Cancer Society. *Cancer Facts & Figures 2020*. Atlanta: American Cancer Society; 2020.
3. Cortes JE, Gutzmer R, Kieran MW, Solomon JA. Hedgehog signaling inhibitors in solid and hematological cancers. *Cancer Treat Rev*. 2019;76:41-50.
4. Munchhof MJ, Li Q, Shavnya A, et al. Discovery of PF-04449913, a potent and orally bioavailable inhibitor of smoothened. *ACS Med Chem Lett*. 2012;3(2):106-111.
5. Hoy SM. Glasdegib: first global approval. *Drugs*. 2019;79(2):207-213.
6. Cortes JE, Dombret H, Merchant A, et al. Glasdegib plus intensive/nonintensive chemotherapy in untreated acute myeloid leukemia: BRIGHT AML 1019 phase III trials. *Future Oncol*. 2019;15(31):3531-3545.
7. Cortes JE, Douglas Smith B, Wang ES, et al. Glasdegib in combination with cytarabine and daunorubicin in patients with AML or high-risk MDS: phase 2 study results. *Am J Hematol*. 2018;93(11):1301-1310.
8. Sallman DA, Komrokji RS, Sweet KL, et al. A phase 2 trial of the oral smoothened inhibitor glasdegib in refractory myelodysplastic syndromes (MDS). *Leuk Res*. 2019;81:56-61.
9. Martinelli G, Oehler VG, Papayannidis C, et al. Treatment with PF-04449913, an oral smoothened antagonist, in patients with myeloid malignancies: a phase 1 safety and pharmacokinetics study. *Lancet Haematol*. 2015;2(8):e339-e346.
10. Lam JL, Vaz A, Hee B, et al. Metabolism, excretion and pharmacokinetics of [(14)C]glasdegib (PF-04449913) in healthy volunteers following oral administration. *Xenobiotica*. 2017;47(12):1064-1076.
11. Shaik MN, LaBadie RR, Rudin D, Levin WJ. Evaluation of the effect of food and ketoconazole on the pharmacokinetics of the smoothened inhibitor PF-04449913 in healthy volunteers. *Cancer Chemother Pharmacol*. 2014;74(2):411-418.
12. Shaik MN, Hee B, Wei H, LaBadie RR. Evaluation of the effect of rifampin on the pharmacokinetics of the smoothened inhibitor glasdegib in healthy volunteers. *Br J Clin Pharmacol*. 2018;84(6):1346-1353.
13. Shaik N, Hee B, Wei H, LaBadie RR. Evaluation of the effects of formulation, food, or a proton-pump inhibitor on the pharmacokinetics of glasdegib (PF-04449913) in healthy volunteers: a randomized phase I study. *Cancer Chemother Pharmacol*. 2019;83(3):463-472.
14. Krens SD, Lassche G, Jansman FGA, et al. Dose recommendations for anticancer drugs in patients with renal or hepatic impairment. *Lancet Oncol*. 2019;20(4):e200-e207.
15. Lin S, Shaik N, Martinelli G, et al. Population pharmacokinetics of glasdegib in patients with advanced hematologic malignancies and solid tumors. *J Clin Pharmacol*. 2019;60(5):605-616.
16. U.S. Department of Health and Human Services Food and Drug Administration. *Guidance for industry: pharmacokinetics in patients with impaired hepatic function: study design, data analysis, and impact on dosing and labeling; May 2003*. Silver Spring, MD: US Department of Health and Human Services Food and Drug Administration; 2003.
17. European Medicines Agency Committee for Medicinal Products for Human Use. *Guideline on the evaluation of the pharmacokinetics of medicinal products in patients with impaired hepatic function. February 2005*. London: European Medicines Agency; 2005.
18. Lewis GP, Jusko WJ. Pharmacokinetics of ampicillin in cirrhosis. *Clin Pharmacol Ther*. 1975;18(4):475-484.
19. Piafsky KM. Disease-induced changes in the plasma binding of basic drugs. *Clin Pharmacokinet*. 1980;5(3):246-262.
20. Rowland M. Protein binding and drug clearance. *Clin Pharmacokinet*. 1984;9(suppl 1):10-17.
21. Shaik N, Hee B, Liang Y, LaBadie RR. Absolute oral bioavailability of glasdegib (PF-04449913), a smoothened inhibitor, in randomized healthy volunteers. *Clin Pharmacol Drug Dev*. 2019;8(7):895-902.
22. Greenblatt DJ, Sellers EM, Koch-Weser J. Importance of protein binding for the interpretation of serum or plasma drug concentrations. *J Clin Pharmacol*. 1982;22(5-6):259-263.
23. Benet LZ, Hoener BA. Changes in plasma protein binding have little clinical relevance. *Clin Pharmacol Ther*. 2002;71(3):115-121.
24. Patel H, Egorin MJ, Remick SC, et al. Comparison of Child-Pugh (CP) criteria and NCI Organ Dysfunction Working Group (NCI-ODWG) criteria for hepatic dysfunction (HD): implications for chemotherapy dosing. *J Clin Oncol*. 2004;22(14_suppl):6051.