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Effect of Mild and Moderate Hepatic Impairment on the Pharmacokinetics, Safety, and Tolerability of a Single Dose of Oral Ivosidenib in Otherwise Healthy Participants

Bin Fan[1], David Dai[1], Marvin Cohen[2], Huansheng Xu[1], Feng Yin[1], Raj Nagaraja[1], Michelle Mobilia[1], Caroline Almon[1], Frank G. Basile[1], and Hua Yang[1]

Abstract

Ivosidenib, a small-molecule inhibitor of mutant isocitrate dehydrogenase 1, is primarily cleared by hepatic metabolism. This open-label study investigated the impact of hepatic impairment on ivosidenib pharmacokinetics (ClinicalTrials.gov: NCT03282513). Otherwise healthy participants with mild (n = 9) or moderate (n = 8) hepatic impairment (Child-Pugh score) and matched participants with normal hepatic function (n = 16) received 1 oral dose of 500-mg ivosidenib. Mild hepatic impairment had a negligible effect on total ivosidenib plasma exposure, with geometric mean ratios (90% confidence interval [CI]) of 0.933 (0.715-1.22) for maximum concentration (C_{max}) and 0.847 (0.624-1.15) for area under the plasma concentration–time curve (AUC) in participants with mild hepatic impairment versus matched controls. Moderate hepatic impairment reduced total ivosidenib exposure by 28% to 44%, with geometric mean ratios (90%CI) of 0.565 (0.419-0.763) for C_{max} and 0.716 (0.479-1.07) for AUC, although the 90%CI for AUC included 1.00. The ivosidenib unbound fraction was concentration dependent and higher in participants with mild/moderate hepatic impairment compared with matched controls. There was no apparent trend to increasing unbound C_{max} with increased hepatic impairment severity. A single 500-mg ivosidenib dose was well tolerated, with no serious or severe adverse events and no adverse events leading to discontinuation. We conclude that mild/moderate hepatic impairment did not lead to clinically relevant changes in ivosidenib exposure following a single 500-mg dose.

Keywords

hepatic impairment, ivosidenib, pharmacokinetics

Ivosidenib is an orally active small-molecule inhibitor of mutated isocitrate dehydrogenase 1 (IDH1). It is approved in the United States for the treatment of adult patients with a susceptible IDH1 mutation, as detected by a US Food and Drug Administration–approved test, with (1) relapsed or refractory acute myeloid leukemia (AML) and (2) newly diagnosed AML who are ≥75 years old or who have comorbidities that preclude use of intensive induction chemotherapy.[1,2] Cancer-associated IDH1 mutations confer a neomorphic activity on the enzyme, producing the oncometabolite D-2-hydroxyglutarate, which accumulates in the plasma of patients with mutant IDH1 AML but decreases to levels seen in healthy persons after 14 daily doses of 500-mg ivosidenib.[1]

Several clinical studies to date have shown that ivosidenib is readily absorbed and slowly eliminated after a single dose in healthy participants and in patients with advanced mutant IDH1 solid and hematologic malignancies.[1,3,4] In vitro and in vivo studies identified the liver as a primary organ involved in the clearance of ivosidenib. In vitro studies in human liver microsomes and recombinant cytochrome P450 (CYP) isoforms

[1] Agios Pharmaceuticals Inc., Cambridge, Massachusetts, USA
[2] MBC Pharma Solutions, Newtown, Pennsylvania, USA

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Corresponding Author:
Bin Fan, PhD, Agios Pharmaceuticals, Inc., 88 Sidney Street, Cambridge, MA 02139-4169
(e-mail: bfan02@hotmail.com)

Address for reprints: Agios Pharmaceuticals, Inc., 88 Sidney Street, Cambridge, MA 02139-4169

indicated that CYP3A4 plays a major role in the oxidative metabolism of ivosidenib.[5,6] An absorption, metabolism, and excretion study of radio-labeled ivosidenib in healthy male participants structurally identified 13 metabolites, 10 found in urine and 7 in feces. However, 77% of the administered dose was excreted as unchanged ivosidenib, and only unchanged ivosidenib was detected in plasma.[6] Since no circulating metabolites were observed in plasma, the pharmacological activity of metabolites was not evaluated or characterized in that or the current study. In a clinical drug-drug interaction study, a noteworthy interaction was observed when ivosidenib was coadministered with itraconazole, a strong CYP3A4 inhibitor.[3] The area under the plasma concentration–time curve (AUC) and terminal elimination half-life ($t_{\frac{1}{2}}$) of ivosidenib increased by 2.6- and 2.3-fold, respectively, indicating that hepatic metabolism via CYP3A4 is a major metabolic pathway for in vivo elimination of ivosidenib. Therefore, impaired hepatic function may also lead to increases in ivosidenib exposure.

Here, we report a study in which the primary objective was to compare the pharmacokinetics of a single 500-mg oral dose of ivosidenib in participants who had mild or moderate hepatic impairment with demographically matched participants who had normal hepatic function. Secondary objectives were to assess the safety and tolerability of a single 500-mg oral dose of ivosidenib in participants with mild or moderate hepatic impairment; explore the relationship between hepatic function (based on Child-Pugh classification) and ivosidenib pharmacokinetic parameters; and compare plasma-protein binding of ivosidenib in participants who had impaired hepatic function with participants who had normal hepatic function. An exploratory objective was to investigate potential relationships between ivosidenib pharmacokinetics and National Cancer Institute Organ Dysfunction Working Group (NCI-ODWG) criteria for hepatic dysfunction.

Methods

Study Design

In this phase 1 open-label study, participants were enrolled into 4 cohorts (approximately 8 per cohort) according to hepatic function status. Cohorts 1a and 2a included participants with mild and moderate hepatic impairment, respectively. Cohorts 1b and 2b included healthy participants with normal hepatic function who were demographically matched by sex, age (±10 years), and body mass index (±20%), such that each healthy participant in cohort 1b was matched to a participant in cohort 1a, and each healthy participant in cohort 2b was matched to a participant in cohort 2a. Cohorts 1a and 1b were enrolled before cohorts 2a and 2b. Participants were screened up to 35 days before dosing. Once assigned to a cohort, participants were admitted to the clinic the day before dosing. On day 1, all participants received a single oral dose of 500-mg ivosidenib (two 250-mg tablets taken with water) after an overnight fast. Participants with hepatic impairment remained in the clinic for ≥240 hours (day 11) after dosing, and participants with normal hepatic function remained in the clinic for 72 hours (day 4) after dosing. After discharge, all participants returned to the clinic on an outpatient basis for study assessments up to 504 hours (day 22) after dosing. An end-of-study visit was conducted on day 29 (±2).

The study was designed in accordance with the US Food and Drug Administration's Guidance for Industry for investigation of pharmacokinetics in patients with impaired hepatic function[7] and was conducted at 2 centers in the United States (DaVita Clinical Research at Lakewood, CO, and Minneapolis, MN). All procedures were performed in accordance with the ethical standards of the research committee (IntegReview IRB, Austin, TX, IRB00008463) and with the 1964 Declaration of Helsinki and its later amendments or comparable ethical standards. The trial was registered at ClinicalTrials.gov (trial identifier: NCT03282513).

Participants

All participants provided written informed consent prior to participation and were willing to comply with study requirements. Participants were male or female, aged 18 to 80 years, with a body mass index of 19 to 40 kg/m^2. Females were neither pregnant nor lactating, and both males and females had to comply with prespecified contraceptive requirements, when appropriate. Participants with hepatic impairment had to have a diagnosis of chronic (≥3 months before screening) and stable (no acute episodes of illness owing to deterioration of hepatic function within 2 months before screening) hepatic insufficiency, with a Child-Pugh score in the mild (cohort 1a) or moderate (cohort 2a) range. Evidence of liver disease was to be corroborated by liver biopsy, laparoscopy, ultrasound, magnetic resonance imaging, computed tomography scan, or documented medical history. Participants with hepatic impairment were to have current evidence or a history of ≥1 physical sign consistent with a clinical diagnosis of liver cirrhosis. Other than hepatic insufficiency with features of cirrhosis, participants were to be in good health and clinically stable, and have a stable medication regimen.

Key exclusion criteria for all participants included participation in any investigation with an experimental drug therapy or device within 30 days prior to dosing, a positive drug screen, significant new-onset illness within 2 weeks prior to dosing, or evidence of significant conditions based on medical and laboratory investigations.

Use of strong or moderate CYP3A4 inhibitors or inducers within 14 days prior to dosing was prohibited.

Pharmacokinetic Assessments

Blood samples were collected within 30 minutes prior to dosing (0 hours), and 0.5, 1, 2, 3, 4, 6, 9, 12, 24, 48, 72, 120, 168, 240, 336, and 504 hours after dosing. Blood samples for assessment of unbound ivosidenib were collected at 0, 3, 48, and 168 hours after dosing. Plasma was harvested by centrifuging blood samples at 2000 $\times$ *g* at approximately 5°C for 15 minutes, and stored at −20°C until processing. Total ivosidenib plasma concentrations were determined by a contract research organization (PPD LLC, Middleton, Wisconsin) using a validated liquid chromatography with tandem mass spectrometry (LC-MS/MS) method. A 50-μL sample aliquot was fortified with 50 μL of AGI-0018070 internal standard working solution. Analytes were isolated by protein precipitation with 400 μL of acetonitrile. A portion of the supernatant was transferred and diluted with acetonitrile/water (50:50, v/v). The final extract was analyzed on a Fortis C18 HPLC column (2.1 $\times$ 50 mm, 5 μm) with MS/MS detection; 0.1% formic acid in water and 0.1% formic acid in acetonitrile were used as mobile phases. Ion transitions 583.2–476.3 and 589.3–482.1 were monitored for ivosidenib and the internal standard, respectively, on a Sciex API3000 mass instrument with DP 60, FP 120, EP 10, CE 24, and CXP 11. This LC-MS/MS method was validated over the range 50 to 50 000 ng/mL for ivosidenib. Intra-assay precision was between 1.56% and 5.51%, and accuracy was between 2.82% and 10.0%. Interassay precision was between 2.63% and 4.67%, and accuracy was between 4.74% and 8.14%. Unbound ivosidenib plasma concentrations and percentage of unbound ivosidenib were determined by separation of unbound from total ivosidenib using an ultracentrifugation method at 500 000 g at 37°C for 6 hours (QPS LLC, Newark, Delaware). Ivosidenib concentration in the mixed matrix was measured using a qualified LC-MS/MS method with an assay range of 0.5 to 1000 ng/mL. Blank human plasma was used to develop the protein-binding method, to prepare plasma quality control samples, and to mix with the supernatant samples to produce the mixed matrix samples. Ultrafiltrate collected at the end of ultracentrifugation was mixed with plasma samples (1:1, v/v) to produce the mixed matrix samples. Ivosidenib was extracted from 50-μL aliquots of mixed matrix samples by adding internal standard in acetonitrile (50 μL of AG-0018070 at 200 ng/mL) followed by an additional 200 μL of acetonitrile. The samples were capped, vortex-mixed for 4 minutes at high speed, and centrifuged at 500 $\times$ *g* for 15 minutes. A 100-μL aliquot of the resulting supernatant from each well was mixed with 100 μL of water. The samples were analyzed by LC-MS/MS (Triple Quadrupole [API4000] mass spectrometer equipped with a Shimadzu Nexera ultra-high-performance liquid chromatography system including LC-30AD pumps, a SIL-30AC autosampler, and CTO-30A column oven).

The following pharmacokinetic parameters were calculated for total ivosidenib using noncompartmental methods: maximum observed plasma concentration (C_{max}), time to C_{max} (t_{max}), AUC from time 0 to the last measurable concentration ($AUC_{0\text{-}t}$), AUC from time 0 to 72 hours after dosing ($AUC_{0\text{-}72}$), AUC extrapolated to infinity ($AUC_{0\text{-}inf}$), $t_{\frac{1}{2}}$, and apparent total clearance (CL/F). The unbound fraction (F_u) was calculated at 3, 48, and 168 hours ($F_{u\text{-}3}$, $F_{u\text{-}48}$, and $F_{u\text{-}168}$, respectively), and the average F_u ($F_{u\text{-}avg}$) was calculated from the average of the 3 time points. Unbound C_{max} ($C_{max\_unbound}$) was calculated by multiplying the total concentration parameter (C_{max}) by the $F_{u\text{-}3}$ value.

Pharmacokinetic parameters were calculated using Phoenix WinNonlin version 6.3 (Certara USA, Inc., Princeton, New Jersey) and actual sampling times. AUC parameters were calculated using the linear-up log-down trapezoidal rule.

Safety Assessments

Safety was assessed throughout the study by monitoring adverse events (AEs), vital signs, 12-lead electrocardiograms, laboratory safety tests, and physical examinations. For participants with hepatic impairment, continuous cardiac monitoring via telemetry was also conducted for 24 hours.

Statistical Assessments and Sample Size

No formal sample size calculations were performed. The approximate total of 32 participants planned for enrollment was based upon other similar studies, and was expected to provide sufficient data to adequately assess any pharmacokinetic differences for ivosidenib in participants who had mild or moderate hepatic impairment compared with healthy control participants.

The primary analysis was the comparison of log-transformed C_{max}, $AUC_{0\text{-}t}$, and $AUC_{0\text{-}inf}$ using analysis of variance (ANOVA). The parameters for participants with mild or moderate hepatic impairment were compared with their matched participants with normal hepatic function, and point estimates of the geometric least squares mean ratio and 90% confidence intervals (CIs) presented. Secondary analyses included assessment of the relationship between severity of hepatic impairment (based on Child-Pugh score) and selected pharmacokinetic parameters evaluated using Pearson correlation analysis. Comparison of log-transformed parameters (C_{max}, $AUC_{0\text{-}t}$, and $AUC_{0\text{-}inf}$) via ANOVA, based on NCI-ODWG criteria for hepatic

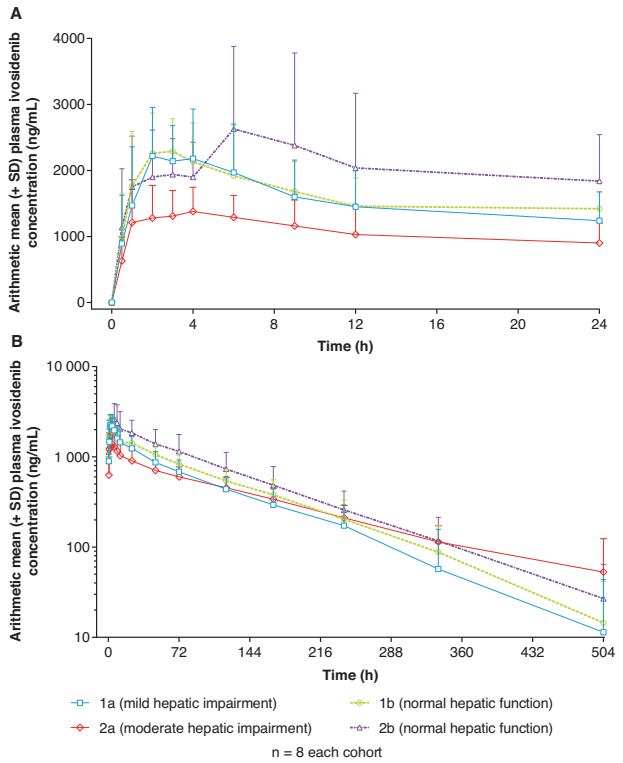

Figure 1. Arithmetic mean (+SD) total ivosidenib plasma concentration-time profile over (A) 24 hours (linear scale) and (B) 504 hours (semilog scale). SD, standard deviation.

impairment was explored (in cases for which the test group comprised ≥3 participants). Summary statistics were calculated with R version 3.4.2 (R Foundation for Statistical Computing, Vienna, Austria). No imputations were made for missing data.

All safety data were summarized descriptively by hepatic function group: mild hepatic impairment (cohort 1a), moderate hepatic impairment (cohort 2a), and normal hepatic function (cohorts 1b and 2b combined).

Results

Participant Disposition and Demographics

A total of 33 participants (9 with mild hepatic impairment, 8 with moderate hepatic impairment, and 16 with normal hepatic function) were enrolled and received a single dose of ivosidenib. One participant with mild hepatic impairment withdrew consent on day 6 and was excluded from the pharmacokinetic analysis set, as they had incomplete data and no matched control. All participants were included in the safety analysis set.

The majority of participants were male (73%) and white (79%). All participants in cohort 1a had Child-Pugh scores of 5 to 6 (mild hepatic impairment), and all participants in cohort 2b had Child-Pugh scores of 7 to 9 (moderate hepatic impairment).

Pharmacokinetic Results

Total Ivosidenib Pharmacokinetics. Total ivosidenib plasma concentrations increased rapidly after oral administration, and then declined in a multiphasic manner (Figure 1). Median t_{max} was 2 to 3 hours and was similar in all cohorts (Table 1). Arithmetic mean $AUC_{0\text{-inf}}$ values were similar for participants with mild and moderate hepatic impairment (164 000 and 167 000 ng · h/mL, respectively) but were slightly lower than both groups with normal hepatic function (192 000 and 250 000 ng · h/mL). Arithmetic mean C_{max} values were similar for participants with mild hepatic impairment and for both groups with normal hepatic function (range, 2510–3010 ng/mL); participants with moderate hepatic impairment had lower arithmetic mean C_{max} (1650 ng/mL) than the other cohorts. Variability between participants in ivosidenib exposure parameters was moderate, with the coefficient of variation (CV%) for C_{max} and AUC parameters ranging from approximately 30% to 40% in cohorts 1a, 1b, and 2a. Variability was higher in cohort 2b, with CV% ranging from 39% to 62%. Arithmetic mean estimates for $t_{\frac{1}{2}}$ appeared to increase with increasing severity of hepatic impairment, although the differences compared with matched participants with normal hepatic function were generally <2-fold. Arithmetic mean CL/F estimates were similar in participants with mild and moderate hepatic impairment, but higher (approximately 20%-40%) than both cohorts of participants with normal hepatic function.

Unbound Ivosidenib Pharmacokinetics. Unbound ivosidenib plasma concentrations were quantifiable (>0.5 g/mL) in all analyzed samples. Moderate variability between participants (CV%) was observed within cohorts in the range of approximately 15% to 54% (except at 168 hours for cohort 2b, which was higher at 70%). Unbound concentrations generally decreased over time from 3 to 168 hours after dosing, and the ranges overlapped in participants with mild or moderate hepatic impairment and participants with normal hepatic function (Figure 2). For all cohorts, arithmetic mean F_u decreased over time from 3 to 168 hours after dosing as ivosidenib concentration decreased and tended to be higher (approximately 30%-140%) in participants with hepatic impairment than in their matched participants with normal hepatic function (Table 2). However, review of the individual data suggests that the unbound ivosidenib plasma concentrations were in the same range across all cohorts at all 3 time points (Agios, data on file). Arithmetic mean $C_{max\_unbound}$ tended to be higher (approximately 30%-40%) for participants with mild or moderate hepatic impairment than for matched participants with normal hepatic function, although interestingly, the arithmetic mean $C_{max\_unbound}$ values were similar between

Table 1. Total Ivosidenib Plasma Pharmacokinetic Parameters

Parameter	Cohort 1a Mild Hepatic Impairment (n = 8)	Cohort 1b Normal Hepatic Function (n = 8)	Cohort 2a Moderate Hepatic Impairment (n = 8)	Cohort 2b Normal Hepatic Function (n = 8)
C_{max}, ng/mL	2510 (702)	2690 (674)	1650 (438)	3010 (1210)
Median (range) t_{max}, h	2.00 (2.00-4.00)	3.00 (1.00-6.00)	3.00 (1.00-12.0)	2.50 (1.00-9.00)
$AUC_{0\text{-}72}$, ng · h/mL	80 700 (26 200)	90 900 (19 000)	60 400 (17 700)	117 000 (49 200)
$AUC_{0\text{-}t}$, ng · h/mL	152 000 (61 000)	182 000 (60 100)	147 000 (46 400)	242 000 (124 000)
$AUC_{0\text{-}inf}$, ng · h/mL	164 000 (62 500)	192 000 (63 700)	167 000 (55 900)	250 000 (125 000)
$t_{\frac{1}{2}}$, h	83.3 (24.4)	77.7 (25.2)	128 (48.8)	77.9 (19.3)
CL/F, L/h	3.41 (1.20)	2.87 (0.95)	3.31 (1.13)	2.59 (1.64)

$AUC_{0\text{-}72}$, area under the concentration-time curve from time 0 to 72 h after dosing; $AUC_{0\text{-}inf}$, area under the concentration-time curve extrapolated to infinity; $AUC_{0\text{-}t}$, area under the concentration-time curve from time 0 to the last measurable concentration; CL/F, apparent total clearance; C_{max}, maximum observed plasma drug concentration; $t_{\frac{1}{2}}$, apparent terminal elimination half-life; t_{max}, time to maximum observed plasma drug concentration. Data are expressed as arithmetic mean (standard deviation) unless otherwise specified.

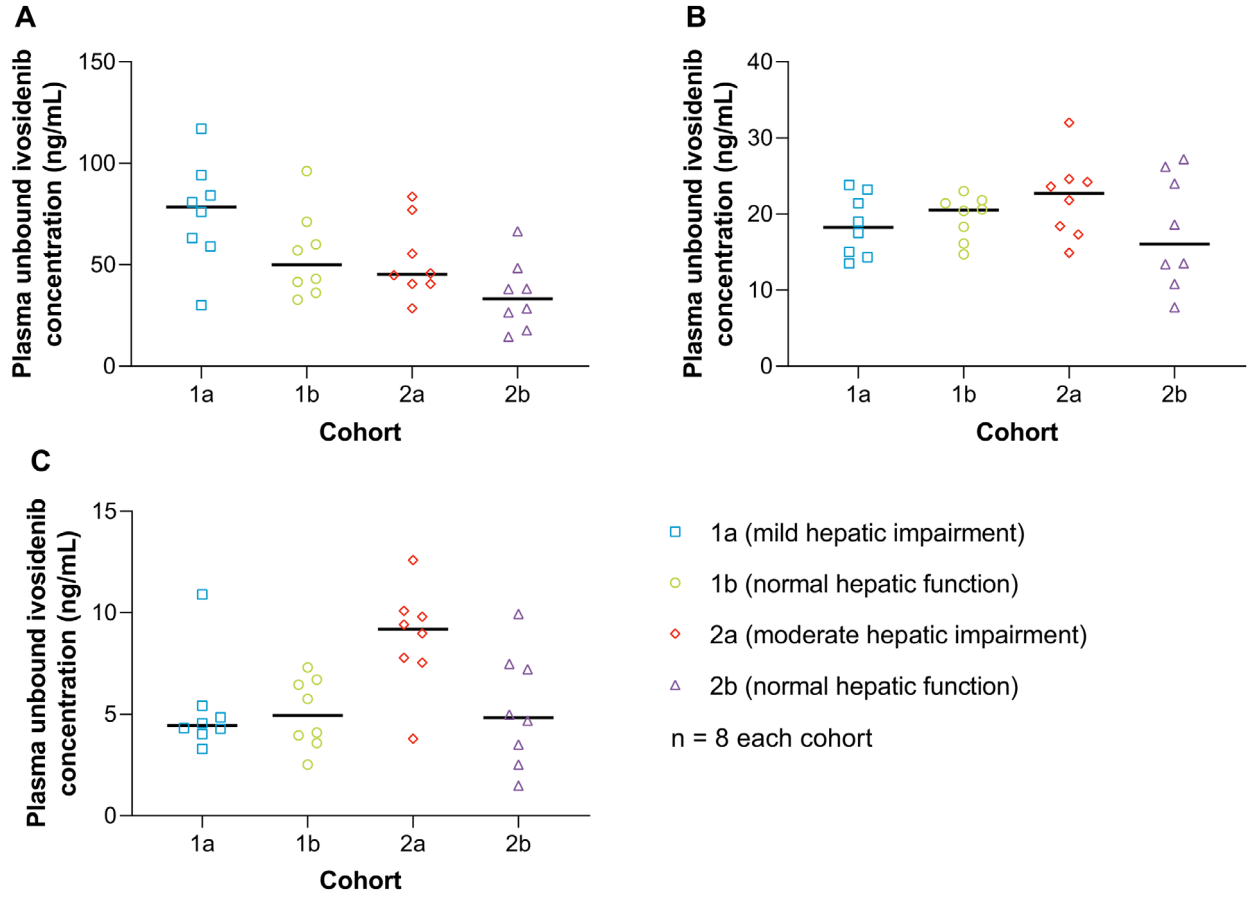

Figure 2. Unbound ivosidenib plasma concentration by cohort at (A) 3, (B) 48, and (C) 168 hours after dosing. Shapes indicate individual data and solid lines indicate median values.

participants with moderate hepatic impairment (63.6 ng/mL) and the nonmatched participants with normal hepatic function in cohort 1b (66.4 ng/mL).

Statistical Analysis for Pharmacokinetics. Statistical analyses suggest that mild hepatic impairment had a negligible effect on total ivosidenib exposure (C_{max} and AUC), with point estimates for the geometric mean ratios of 0.819 to 0.933 and 90%CIs that included 1.00 (Table 3). Moderate hepatic impairment appeared to reduce total ivosidenib exposure by approximately 28% to 44%, although the 90%CIs for $AUC_{0\text{-}inf}$ also included 1.00. Two sensitivity analyses were conducted.

Table 2. Unbound Ivosidenib Plasma Pharmacokinetic Parameters

Parameter	Cohort 1a Mild Hepatic Impairment (n = 8)	Cohort 1b Normal Hepatic Function (n = 8)	Cohort 2a Moderate Hepatic Impairment (n = 8)	Cohort 2b Normal Hepatic Function (n = 8)
$C_{max\_unbound}$[a], ng/mL	93.1 (32.3)	66.4 (21.1)	63.6 (19.7)	48.7 (12.7)
$F_{u\text{-}3}$, %	3.78 (1.19)	2.48 (0.63)	3.93 (0.97)	1.75 (0.54)
$F_{u\text{-}48}$, %	2.48 (0.58)	1.94 (0.35)	3.19 (0.91)	1.33 (0.39)
$F_{u\text{-}168}$, %	1.87 (0.38)	1.48 (0.34)	2.68 (0.90)	1.18 (0.33)
$F_{u\text{-}avg}$, %	2.71 (0.63)	1.97 (0.39)	3.27 (0.89)	1.42 (0.38)

$C_{max\_unbound}$, maximum observed plasma drug concentration for unbound ivosidenib; $F_{u\text{-}3}$, fraction unbound in plasma at 3 h after dosing; $F_{u\text{-}48}$, fraction unbound in plasma at 48 h after dosing; $F_{u\text{-}168}$, fraction unbound in plasma at 168 h after dosing; $F_{u\text{-}avg}$, fraction unbound in plasma: average of the 3 time points.

Data are expressed as arithmetic mean (standard deviation).

[a]$C_{max\_unbound}$ was calculated by multiplying total ivosidenib C_{max} by $F_{u\text{-}3}$ for each individual.

Table 3. Statistical Analysis of Ivosidenib Plasma Pharmacokinetic Parameters by Child-Pugh Classification

Comparison	Parameter	Geometric Mean Ratio, %	90% Confidence Intervals
Mild hepatic impairment (test) vs matched normal hepatic function (reference)	$AUC_{0\text{-}t}$	0.819	0.596-1.12
	$AUC_{0\text{-}inf}$	0.847	0.624-1.15
	C_{max}	0.933	0.715-1.22
	$C_{max\_unbound}$[a]	1.40	0.987-1.97
Moderate hepatic impairment (test) vs matched normal hepatic function (reference)	$AUC_{0\text{-}t}$	0.659	0.435-0.998
	$AUC_{0\text{-}inf}$	0.716	0.479-1.07
	C_{max}	0.565	0.419-0.763
	$C_{max\_unbound}$[a]	1.29	1.00-1.66

$AUC_{0\text{-}inf}$, area under the concentration-time curve extrapolated to infinity; $AUC_{0\text{-}t}$, area under the concentration-time curve from time 0 to the last measurable concentration; C_{max}, maximum observed plasma drug concentration; $C_{max\_unbound}$, maximum observed plasma drug concentration for unbound ivosidenib.

Analysis of variance was performed on ln-transformed values using cohort as a fixed effect and participant as a random effect.

[a]$C_{max\_unbound}$ was calculated by correcting individual total ivosidenib C_{max} with the value for fraction unbound in plasma at 3 h after dose.

The first assessed if there was any impact of a (high) outlier in cohort 2b on the primary analysis, and the other involved combining the 2 cohorts with normal hepatic function to see if increasing the sample size in this group had an impact on the conclusions. Both sensitivity analyses provided similar results to the primary analysis. The point estimates for $C_{max\_unbound}$ suggested a 29% to 40% increase in participants with mild or moderate hepatic impairment compared with their matched participants with normal hepatic function, but for both comparisons, the 90%CIs were wide and included 1.00. There was no apparent trend of increasing $C_{max\_unbound}$ as the severity of hepatic impairment increased.

Pearson correlation analysis was used to investigate the relationship between total ivosidenib exposure (in terms of C_{max}, $AUC_{0\text{-}t}$, $AUC_{0\text{-}inf}$, and $t_{\frac{1}{2}}$) and Child-Pugh score (Table 4). This analysis suggested a statistically significant positive correlation between $t_{\frac{1}{2}}$ and Child-Pugh score ($P < .05$), and a negative correlation between total ivosidenib C_{max} and Child-Pugh score.

Table 4. Pearson Correlation Analysis of Plasma Total Ivosidenib Pharmacokinetic Parameters and Child-Pugh Score

Parameter	R^2
C_{max}	0.434
$AUC_{0\text{-}t}$	0.306
$AUC_{0\text{-}inf}$	0.00767
$t_{\frac{1}{2}}$	0.293

$AUC_{0\text{-}inf}$, area under the concentration-time curve extrapolated to infinity; $AUC_{0\text{-}t}$, area under the concentration-time curve from time 0 to the last measurable concentration; C_{max}, maximum observed plasma drug concentration; $t_{\frac{1}{2}}$, apparent terminal elimination half-life.

N = 16.

Sixteen participants with mild or moderate hepatic impairment (8 each) based on Child-Pugh score were classified per NCI-ODWG as having normal hepatic

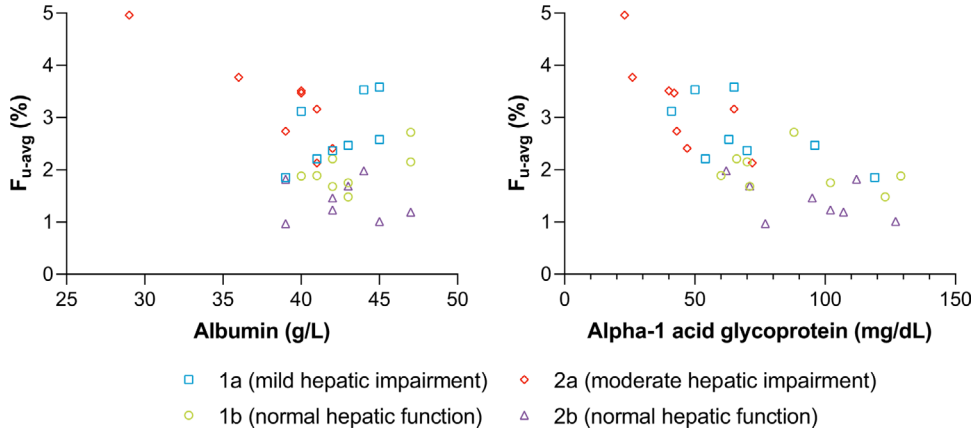

Figure 3. The relationship between the average unbound fraction of ivosidenib (F_{u_avg}) and plasma levels of albumin or alpha-1 acid glycoprotein at baseline. Shapes indicate individual data.

function (n = 9), mild hepatic dysfunction (n = 5), or moderate hepatic dysfunction (n = 2). Total ivosidenib exposure for these participants was compared with their matched controls using ANOVA, with NCI-ODWG criteria as a fixed effect (except for moderate dysfunction, for which there were insufficient data). Geometric mean ratios for participants with mild hepatic dysfunction relative to healthy matched participants were C_{max} = 0.862 (90%CI, 0.614–1.21), $AUC_{0\text{-}t}$ = 1.03 (90%CI, 0.646-1.65), and $AUC_{0\text{-}inf}$ = 1.06 (90%CI, 0.676-1.68).

Child-Pugh scores are derived with input from multiple laboratory values. Examination of total exposure ($AUC_{0\text{-}inf}$ and C_{max}) or F_u of plasma ivosidenib versus some of these components suggested that some plasma proteins influenced exposure or F_u of ivosidenib. Alpha-1-acid glycoprotein (AAG) was more closely correlated with ivosidenib F_u than albumin changes were (Figure 3). Total plasma exposure tended to increase slightly as AAG levels increased, and F_u tended to decrease as AAG levels increased, although there was no clear relationship between exposure or F_u and albumin levels; *P* values from a regression analysis were statistically significant for AAG (0.0193 and 0.00128 for $AUC_{0\text{-}inf}$ and C_{max}, respectively) but not for albumin (*P* = .954 and .276, respectively). Baseline AAG concentrations were lower in participants with moderate hepatic impairment than in participants with normal hepatic function. Total ivosidenib exposure tended to decrease as aspartate aminotransferase (AST) levels increased, although this trend was not consistently observed for alanine aminotransferase and may be of little clinical significance. There was a slight trend toward a lower total C_{max} with increasing bilirubin levels (*P* = .0334), although this was not observed for $AUC_{0\text{-}inf}$.

Safety Results

Seventeen participants had ≥1 AE, and 3 participants with mild hepatic impairment experienced treatment-related AEs (Table 5). No participants developed serious or severe (grade ≥3) AEs, and no participants were discontinued from the study owing to AEs. The most common AEs across all cohorts were upper respiratory tract infection, headache, and fatigue. No other AEs were reported by >1 participant. There was no evidence of an increased incidence of any individual AEs with increasing degree of hepatic impairment. All AEs were considered mild by the investigator, except for hernia pain (1 participant with mild hepatic impairment), upper respiratory tract infection, and hepatic encephalopathy (1 participant each with moderate hepatic impairment), which were considered moderate. The participant with hepatic encephalopathy had a history of the condition and the event was described as an exacerbation starting on day 7. The participant received treatment with lactulose from day 8 and the event was considered resolved by day 17. Of note, this participant had alanine aminotransferase and AST values within the reference range throughout the study.

There were no clinically significant findings for laboratory safety tests, vital signs, or electrocardiogram parameters, and no evidence of any trends with increasing degree of hepatic impairment. No participants had a QT interval corrected using Fridericia's method (QTcF) of >500 milliseconds or a change from baseline in QTcF >60 milliseconds. There was no evidence of an increased risk of QTcF prolongation in participants with mild or moderate hepatic impairment. The mean change from baseline QTcF was smaller in participants who had mild and moderate hepatic impairment compared with their matched participants who had normal hepatic function at 3 and 6 hours after dosing.

Table 5. Summary of Adverse Events

	Cohort 1a Mild Hepatic Impairment (n = 9)	Cohort 2a Moderate Hepatic Impairment (n = 8)	Cohort 1b/2b Normal Hepatic Function (n = 16)
Number of participants with any adverse event, n (%)	6 (66.7)	5 (62.5)	6 (37.5)
Number of participants with any treatment-related adverse event, n (%)	3 (33.3)	0	0
Adverse event, n (%)			
Headache	1 (11.1)[a]	2 (25.0)	1 (6.3)
Upper respiratory tract infection	0	2 (25.0)	2 (12.5)
Fatigue	0	0	2 (12.5)
Dysgeusia	1 (11.1)[a]	0	0
Ecchymosis	1 (11.1)	0	0
Flatulence	1 (11.1)[a]	0	0
Hepatic encephalopathy	0	1 (12.5)	0
Hernia pain	1 (11.1)	0	0
Inguinal hernia	1 (11.1)	0	0
Nausea	1 (11.1)	0	0
Pain in extremity	1 (11.1)	0	0
Rash	1 (11.1)	0	0
Viral infection	0	0	1 (6.3)
Vision blurred	0	0	1 (6.3)

[a]Adverse events considered causally related to treatment.

Discussion

This study evaluated the pharmacokinetics and safety of a single dose of ivosidenib in participants with mild or moderate hepatic impairment and in matched participants with normal hepatic function. Total ivosidenib exposure was similar in participants with mild hepatic impairment and their matched participants with normal hepatic function. Total ivosidenib exposure in participants with moderate hepatic impairment was slightly lower (by 28%-44%) relative to healthy controls; however, the 90%CIs for $AUC_{0\text{-inf}}$ included 1.00, and no statistically significant positive correlation (Pearson) was observed between AUC and Child-Pugh score ($P > .05$). Sensitivity analyses provided similar results to the primary analysis and hence supported the overall findings of the study.

Although effects on total ivosidenib exposure were limited in participants with hepatic impairment, $t_{\frac{1}{2}}$ increased with hepatic impairment from approximately 74 to 76 hours in participants with normal hepatic function to 80 and 120 hours in participants with mild and moderate hepatic impairment, respectively. However, in participants with mild and moderate hepatic impairment, CL/F estimates were higher (approximately 20%-40%) than in participants with normal hepatic function. Since the full pharmacokinetic profiles were based on total (free + bound) plasma concentrations, any impairment of free drug clearance in participants with hepatic insufficiency could be masked by the increase in F_u.[8] However, the increased $C_{max\_unbound}$ observed in participants with hepatic impairment indicated that the clearance of free ivosidenib was decreased, in contrast to the increased total clearance in participants with hepatic impairment.

A statistically significant positive correlation (Pearson) was observed between $t_{\frac{1}{2}}$ and Child-Pugh score ($P < .05$). A statistically significant negative correlation (Pearson) was observed between total ivosidenib C_{max} and Child-Pugh score ($P < .01$), likely attributable to changes in plasma protein levels, allowing for higher levels of unbound drug and increased tissue distribution. This result may have been influenced by variability between participants, most notably 1 participant with a relatively high Child-Pugh score of 9. Overall, ivosidenib was shown to have low hepatic extraction (Agios, data on file) and be highly protein bound (>95%). Thus, pharmacokinetic parameters for unbound drug were compared in order to characterize the impact of hepatic impairment on unbound ivosidenib exposure.

Although there was an apparent increase in F_u in participants with hepatic impairment relative to participants with normal hepatic function, the concentration-dependent effect appeared similar in all cohorts, and the absolute unbound ivosidenib concentrations measured at 3, 48, and 168 hours after dosing also

overlapped between the cohorts. Because F_u changed with total ivosidenib concentration within each cohort, it was decided to use the value determined at 3 hours after dosing to generate unbound ivosidenib concentrations from the total ivosidenib concentrations for the calculation of $C_{max\_unbound}$. This approach seems reasonable given the limitations of the data, but we accept that it is an approximation and does not account for the slight differences in t_{max} between participants. Nevertheless, the analysis for unbound C_{max} supports a limited impact of mild and moderate hepatic impairment. Notably, we did not observe an increase in $C_{max\_unbound}$ as the severity of hepatic impairment increased from mild to moderate, suggesting that the impact of either mild or moderate hepatic impairment on $C_{max\_unbound}$ may be within the observed between-patient variability (approximately 40%).

It was originally planned to use an average F_u value to calculate unbound AUC values. However, this calculation is limited owing to the dependence of F_u on total ivosidenib concentration (exhibited within cohorts), which was not taken into consideration, and the limited time points at which F_u was measured (3) compared with the number of plasma samples contributing to the total AUC. Thus, the unbound AUC parameters were not considered to be robust and are not reported. Based on the concentration dependent protein binding data, F_u was maximum at C_{max}, and decreased over time from 3 to 168 hours after dosing as ivosidenib concentration decreased. Hence, $C_{max\_unbound}$ represents the maximal scenario of approximately 30% to 40% increases in unbound concentration for participants with mild or moderate hepatic impairment compared with matched participants with normal hepatic function. That said, with respect to unbound ivosidenib pharmacokinetic parameters, it is considered unlikely that the small magnitude of difference in exposure would result in any clinically relevant impact on D-2-hydroxyglutarate inhibition or the efficacy of ivosidenib in patients with moderate hepatic impairment.

The underlying reasons for the lower total AUC, and more notably for total C_{max}, are not clear but are likely multifactorial. The magnitude of reduction in C_{max} in participants with moderate hepatic impairment appears to be greater than the reduction in AUC. There are a number of possible factors that may contribute to altered ivosidenib pharmacokinetics in participants with hepatic impairment: reduced gastrointestinal absorption; decreased protein binding due to reduced AAG levels in participants with moderate hepatic impairment; altered tissue distribution; and competing protein binding components such as bilirubin (bilirubin was higher in participants with mild and moderate hepatic impairment than in participants with normal hepatic function).

Ivosidenib has a low turnover rate in human liver microsomes, and the projected hepatic clearance based on liver microsomal data correlates well with data from the study of radio-labeled ivosidenib in healthy participants.[6] This study also reported renal clearance of 0.537 L/h, less than the typical glomerular filtration rate, indicating negligible extrahepatic clearance. Together, the low total clearance and low hepatic extraction ratio suggest that hepatic first pass metabolism is very low.

Ivosidenib has a moderate food effect on C_{max}, which is attributed to its solubility-limited absorption.[3] Participants with hepatic impairment may have changes in gastrointestinal environment, such as bile salt content and phospholipids, which influence the solubility of the drug and thus reduce ivosidenib absorption. The lower C_{max} in participants with hepatic impairment may be explained by reduced absorption of ivosidenib and has been observed with other drugs.[9-11] Protein binding is another important factor. In an in vitro ultracentrifugation protein-binding assay, the human plasma protein binding of ivosidenib was 95.8%, 95.4%, and 91.6% at 0.2, 1, and 10 μM, respectively. Although AAG and albumin are known plasma protein-binding partners, in vitro studies to evaluate exact binding affinities have not been done. The results presented here suggest that changes in ivosidenib pharmacokinetics in participants with moderate hepatic impairment may be due to changes in F_u. Higher unbound ivosidenib may contribute to higher elimination, which may lead to lower total AUC. Additional observations from comparisons between pharmacokinetic and laboratory values included a negative correlation between total ivosidenib exposure and bilirubin (C_{max} only) and AST ($AUC_{0\text{-}inf}$ and C_{max}). As most participants with moderate hepatic impairment had elevated bilirubin, it is plausible that elevated bilirubin competes with ivosidenib at the binding site, thus leading to higher unbound ivosidenib concentrations.

The association between total ivosidenib exposure (C_{max} and AUC parameters) and hepatic dysfunction according to NCI-ODWG criteria was also explored. Seven of 8 participants with mild hepatic impairment using Child-Pugh criteria—and 2 participants with moderate hepatic impairment using Child-Pugh criteria—were classified as having normal hepatic function using NCI-ODWG criteria. The NCI-ODWG classification is less conservative than Child-Pugh, such that "normal" captures individuals with diagnosed hepatic disease by Child-Pugh. To assess the effect of moderate hepatic dysfunction based on NCI-ODWG criteria, individuals with more severe hepatic impairment would be needed. In this study, ANOVA indicated similar results in participants with mild hepatic impairment based on either Child-Pugh or NCI-ODWG criteria.

Of the available comparisons (insufficient data for moderate hepatic impairment), total ivosidenib exposure was generally the same in participants with mild hepatic impairment and their healthy matched participants. These data should be treated with caution because of the small sample size; nonetheless, the findings are supported by data from 2 other studies in patients with solid tumors[4] or advanced hematologic malignancies[1,12] who were being treated continuously with 500-mg ivosidenib once daily. In neither study was there an apparent effect of mild hepatic dysfunction (according to NCI-ODWG criteria) compared with patients with normal hepatic function. Neither of these studies had sufficient data to adequately assess the effect of moderate hepatic dysfunction (by NCI-ODWG) on ivosidenib pharmacokinetics.

Safety was assessed throughout the current study, and there were no severe or serious AEs or discontinuations owing to AEs. The mean change from baseline QTcF was smaller in participants with mild and moderate hepatic impairment than in matched participants with normal hepatic function at times consistent with peak ivosidenib concentrations. Therefore, C_{max} achieved in mild or moderate hepatic impairment groups is not expected to lead to increased changes in QTcF compared with participants with normal hepatic function.

The authors acknowledge the limitations of this single-dose study in extrapolating to chronic dosing in patients, given the increased $t_{\frac{1}{2}}$ of ivosidenib with increasing severity of hepatic impairment and hence the potential for accumulation and interactions with concomitant medications in the target population. A study is planned to address this in patients with hematologic malignancies dosed with ivosidenib to steady state and experiencing moderate and severe hepatic impairment.

Conclusion

Overall, these data suggest that mild and moderate hepatic impairment in otherwise healthy participants do not lead to clinically relevant changes in total or unbound ivosidenib concentrations following a single oral dose of 500 mg. A single dose of 500-mg ivosidenib was well tolerated, and there was no evidence of an increased risk associated with ivosidenib in participants with mild or moderate hepatic impairment than in matched participants with normal hepatic function.

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Conflicts of Interest

F.Y., R.N., M.M., C.A., and H.Y. are Agios employees and stockholders. B.F., H.X., and F.G.B. were Agios employees and stockholders at the time of the study. M.C. is the owner of MBC Pharma Solutions and an Agios consultant.

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