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PHARMACOKINETICS AND DISPOSITION

Effect of itraconazole, food, and ethnic origin on the pharmacokinetics of ivosidenib in healthy subjects

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Abstract

Purpose To assess the effect of ethnicity, food, and itraconazole (strong CYP3A4 inhibitor) on the pharmacokinetics of ivosidenib after single oral doses in healthy subjects.

Methods Three phase 1 open-label studies were performed. Study 1: Japanese and Caucasian subjects received single doses of 250, 500, or 1000 mg ivosidenib (NCT03071770). Part 1 of study 2 (a two-period crossover study): subjects received 500 mg ivosidenib after either an overnight fast or a high-fat meal. Subjects received 1000 mg ivosidenib after an overnight fast in the single period of part 2 (NCT02579707). Study 3: in period 1, subjects received 250 mg ivosidenib; then, in period 2, subjects received oral itraconazole (200 mg once daily) on days 1–18, plus 250 mg ivosidenib on day 5 (NCT02831972).

Results Ivosidenib was well tolerated in all three studies. Study 1: pharmacokinetic profiles were generally comparable, although AUC and C_{max} were slightly lower in Japanese subjects than in Caucasian subjects, by ~ 30 and 17%, respectively. Study 2: AUC increased by ~ 25% and C_{max} by ~ 98%, when ivosidenib was administered with a high-fat meal compared with a fasted state. Study 3: co-administration of itraconazole increased ivosidenib AUC by 169% (90% CI 145–195) but had no effect on ivosidenib C_{max}.

Conclusions No ivosidenib dose adjustment is deemed necessary for Japanese subjects. High-fat meals should be avoided when ivosidenib is taken with food. When co-administered with strong CYP3A4 inhibitors, monitoring for QT interval prolongation (a previously defined adverse event of interest) is recommended and an ivosidenib dose interruption or reduction may be considered. ClinicalTrials.gov NCT03071770, NCT02579707, and NCT02831972.

Keywords Ivosidenib · Isocitrate dehydrogenase 1 inhibitor · Pharmacokinetics · Drug interaction · Food effect · CYP3A4 inhibitors

Introduction

Somatic mutations in isocitrate dehydrogenase (IDH) 1 and 2 confer a gain of function, modifying the activity of the enzyme so that it catalyzes the reduction of alpha-ketoglutarate (α-KG) to the oncometabolite D(-)2-hydroxyglutarate (2-HG) [1, 2]. 2-HG exerts its oncogenic effects via several pathways, including the competitive inhibition of α-KG-dependent dioxygenases that modulate gene expression [3, 4], blocking normal cellular differentiation [5]. Direct inhibition of mutant IDH1 (mIDH1) suppresses the production of 2-HG, restoring cellular differentiation [6]. Cancer-associated mutations in IDH1 and IDH2 have been identified in a range of hematologic malignancies and solid tumors [7].

It is estimated that 6–10% of patients with acute myeloid leukemia (AML) carry IDH1 mutations [2, 8–10]. Meta-analyses evaluating the prognostic impact of mIDH1 in patients with AML suggest that mIDH1 is associated with worse outcomes compared with wild-type IDH1 [11–13]. The prognosis of patients with relapsed/refractory (R/R) AML is especially poor and treatment options are inadequate [14].

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Ivosidenib (TIBSOVO®) is a first-in-class, potent, targeted, oral, small-molecule inhibitor of mIDH1, with no significant off-target activity (structure described in [6]). It has an acceptable safety profile and has demonstrated clinical activity in a phase 1 study of patients with R/R AML [15]. In July 2018, ivosidenib became the first approved targeted therapy for adult patients with R/R AML with a susceptible IDH1 mutation (as detected by an FDA-approved test) in the USA, and development is ongoing worldwide [16]. Ongoing studies are investigating the effects of ivosidenib in several additional patient populations, including patients with mIDH1-positive cholangiocarcinoma, glioma, and newly diagnosed AML.

Here, we report the results of three clinical trials conducted in healthy subjects to inform the continued clinical development of ivosidenib. These studies assessed the effect of selected intrinsic (i.e., ethnicity) and extrinsic (i.e., food and CYP3A4 inhibition) factors on the pharmacokinetics (PK) of single oral doses of ivosidenib. Knowledge of factors that may increase ivosidenib exposure could contribute to patient safety, for example, electrocardiogram (ECG) QT prolongation has previously been identified as a potential adverse event (AE) of special interest [15]. Study 1 compared the single-dose PK and safety of ivosidenib in healthy Japanese versus Caucasian subjects to determine if dose adjustments are required for Japanese subjects in clinical trials with ivosidenib. Study 2 investigated the effect of a high-fat meal on the single-dose PK of ivosidenib. Prior modeling work indicated that food may have a positive effect on ivosidenib absorption, although no food effect was seen in animal studies (data on file, Agios Pharmaceuticals, Inc.). Furthermore, owing to its low solubility and high permeability, ivosidenib has been categorized as a class 2 drug according to the Food and Drug Administration Biopharmaceutics Classification System [17]. Consequently, understanding the effect of food on the bioavailability of ivosidenib after oral administration in tablet form is essential for optimizing dosing in future clinical trials. Study 3 evaluated the effect of itraconazole, a strong inhibitor of CYP3A4 and P-glycoprotein (P-gp), on the PK of ivosidenib, for the following reasons. (1) In a human absorption, metabolism, and excretion study, ivosidenib was slowly metabolized, and parent drug was the only component circulating in plasma. Elimination of absorbed ivosidenib occurred largely by oxidative metabolism with minor contributions from N-dealkylation and hydrolytic metabolism. In vitro studies have shown that ivosidenib is predominantly metabolized by CYP3A4 [16, 18]. These findings indicate that co-administration of CYP3A4 inhibitors therefore has the potential to increase ivosidenib exposure and thereby increase the risk of toxicity. Ivosidenib is also a substrate of P-gp. (2) Patients with AML are considered at risk of developing invasive fungal infections and are often prescribed triazole antifungal medications, [19] many of which are either moderate or strong CYP3A4 inhibitors. Therefore, co-administration of CYP3A4 inhibitors and ivosidenib is likely to occur. The overall objective of the three studies was to determine if the selected factors impact ivosidenib exposure and to mitigate potential clinical risks to patients by providing quantitative data with minimal confounding factors.

Methods

Study design

Study 1 was a phase 1, open-label study in healthy adult male Japanese and Caucasian subjects. The primary objective was to compare the PK of single oral doses of ivosidenib in each population to investigate the effect of ethnicity. Subjects were screened up to 21 days prior to dosing to assess eligibility. Eligible subjects were enrolled into one of three cohorts (10 Japanese and 10 Caucasian subjects each) and received 250 mg (cohort A), 500 mg (cohort B), or 1000 mg (cohort C) ivosidenib after an overnight (minimum 10 h) fast. Subjects were resident in the study center from the day prior to dosing (day 1) until completion of the 72-h post-dose assessments and returned as outpatients for the remaining assessments.

Study 2 was a phase 1, open-label study consisting of two parts. Part 1 was a randomized, two-period crossover study that investigated the effect of a high-fat meal on the PK of a single oral dose of 500 mg ivosidenib in healthy subjects. Part 2 was a single-period study that investigated the safety and PK of a single oral dose of 1000 mg ivosidenib in healthy subjects. Subjects were screened up to 27 days prior to dosing to assess eligibility. In part 1, eligible subjects received a single oral dose of 500 mg ivosidenib after an overnight (minimum 10 h) fast in one period and after a high-fat meal in the other period. The order of high-fat meal or fasted states was randomized. There was a washout period of at least 25 days between ivosidenib doses in periods 1 and 2. The timing and content of the high-fat, high-calorie breakfast was in accordance with the US Food and Drug Administration guideline for food-effect studies, containing a total of 1000 cal and 58 g of fat and typically consisting of two eggs fried in butter, two strips of bacon, two slices of toast with butter, 4 oz of hash brown potatoes, and 8 oz of whole milk [20]. In part 2, all subjects received a single oral dose of 1000 mg ivosidenib whilst in a fasted state. In both parts, subjects were resident in the study center from the day prior to dosing (day 1) until completion of the 72-h post-dose assessments and returned as outpatients for the remaining assessments.

Study 3 was a phase 1, open-label, two-period, fixed-sequence study that investigated the effect of multiple oral doses of itraconazole on the PK of a single oral dose of 250 mg ivosidenib in healthy subjects (Supplementary Fig. 1). Eligible subjects received a single oral dose of

ivosidenib on day 1 of period 1 after an overnight fast. In period 2, subjects received 200 mg once daily (QD) itraconazole on days 1 to 18, plus a single dose of ivosidenib on day 5, 30 min after itraconazole administration and after an overnight fast. Itraconazole was administered after a standard breakfast on all days except day 5. There was a washout period of 21 days between ivosidenib dosing in period 1 and the first dose of itraconazole in period 2. Subjects were resident in the study center from the day prior to dosing in both periods until completion of the 72-h post-ivosidenib dose assessments in each period and returned as outpatients for the remaining assessments.

Ivosidenib was administered in the formulation intended for marketing in all three studies. All three studies were conducted in accordance with the International Conference on Harmonization guideline for Good Clinical Practice and the ethical principles of the Declaration of Helsinki. All three studies were registered on ClinicalTrials.gov (study 1: NCT03071770, study 2: NCT02579707, and study 3: NCT02831972). The studies were conducted between March and May 2017 (study 1), September and December 2015 (study 2), and July and September 2016 (study 3). All three studies were conducted at single clinical pharmacology study sites in the USA and were approved by local investigational review boards (Supplementary Table 1).

Subjects

In all three studies, subjects provided written informed consent prior to participation and were willing to comply with study requirements. All subjects were aged 18–55 years and were in good health. In study 1, all subjects were male and either Caucasian or Japanese. Japanese subjects must have been born in Japan, had both parents and grandparents of Japanese origin, and not have lived outside of Japan for more than 5 years. In studies 2 and 3, both male and female subjects were eligible and there were no restrictions for race or ethnicity. Female subjects had to either be of non-childbearing potential or comply with contraceptive requirements.

Exclusion criteria varied slightly between studies but typically included any current or recent clinically significant medical or psychiatric condition, laboratory abnormalities, drug hypersensitivity, or risk factors for torsades de pointes. Use of other medications (prescribed or over-the-counter), exposure to other investigational drugs, and consumption of alcohol were restricted.

Pharmacokinetic assessments

In all three studies, blood samples for assessment of ivosidenib concentration in plasma were collected at intervals from pre-dose through 504 h after each ivosidenib dose. In study 3, blood samples were collected for assessment of the concentration of itraconazole and its metabolite hydroxy-itraconazole in plasma.

Plasma ivosidenib, itraconazole, and hydroxy-itraconazole were all measured using validated liquid chromatography-tandem mass spectrometry methods [21]. Details are given in Supplementary Material.

Ivosidenib plasma PK parameters were calculated using non-compartmental methods (Phoenix WinNonlin version 6.2.1 or 6.3). PK parameters included area under the plasma concentration-time curve from time zero to the last measurable concentration (AUC_{0-t}), area under the plasma concentration-time curve extrapolated to infinity ($AUC_{0-\infty}$), maximum plasma concentration (C_{max}), time to maximum plasma concentration (T_{max}), and terminal elimination half-life ($t_{1/2}$). Apparent oral clearance (CL/F) was also calculated in studies 1 and 3.

Safety assessments

Safety was assessed in all studies by the monitoring of AEs, vital signs, 12-lead electrocardiograms (ECGs), clinical laboratory tests (hematology, clinical chemistry, and urinalysis), and physical examinations.

Statistical assessments and sample size

In study 1, a total of 60 were chosen as the suitable number of eligible subjects (30 Japanese and 30 Caucasian), based on empirical considerations, literature, and past experience. The analyses were descriptive, and no formal hypothesis testing was conducted. Dose proportionality was explored graphically by plotting C_{max}, AUC_{0-t}, and $AUC_{0-\infty}$ against the dose for each ethnic group. To compare ivosidenib PK in Japanese and Caucasian subjects, an analysis of variance (ANOVA) was performed on natural log-transformed C_{max}, AUC_{0-t}, and $AUC_{0-\infty}$. The ethnicity-specific geometric means, geometric mean ratio (GMR) between Japanese and Caucasian subjects, and corresponding 90% confidence intervals (CI) were presented for each dose cohort. The overall comparison between ethnic groups was conducted by treating the dose as a blocking factor.

In study 2, the sample size for part 1 was based on the expected two-sided 90% CI for the AUC ratio. Assuming that the AUC ratio of high-fat meal to fasted was 1, with a sample size of 24, the 95% CI for the AUC ratio was expected to be (0.771, 1.297) based on the preliminary human PK data from previous studies. To account for dropouts, 30 subjects were enrolled. ANOVA was performed on log-transformed PK variables with treatment, period, and sequence (when applicable) as fixed effects and the subject as random effect.

In study 3, itraconazole was anticipated to alter the PK profile of ivosidenib. Data from 16 subjects was expected to provide at least 90% confidence that the GMR for AUC and

C_{max} for the comparison between ivosidenib alone and ivosidenib co-administered with itraconazole will be within 20% of the true ratio, using variability obtained from study 2. Twenty-two subjects were enrolled to allow for potential dropouts.

Results

Patient disposition and demographics

Participant flow in all studies is shown in Supplementary Fig. 2. In study 1, a total of 60 male subjects (30 Japanese and 30 Caucasian) were enrolled and received ivosidenib. All subjects completed the study and were included in the PK and safety analyses. Demographic characteristics were similar between the two populations, with mean (SD) age and body mass index of 34 (8.2) years and 23 (2.5) kg/m^2, respectively, for Japanese subjects, and 39 (9.8) years and 25 (2.8) kg/m^2, respectively, for Caucasian subjects.

In study 2, a total of 30 subjects were enrolled in part 1, 6 subjects were enrolled in part 2, and all 36 subjects received ivosidenib. Three subjects in part 1 discontinued owing to AEs. All 36 subjects were included in the PK and safety analyses. The majority of subjects were male (53%) and white (58%).

In study 3, a total of 22 subjects were enrolled and received ivosidenib, and all subjects completed the study and were included in the safety analyses. One subject discontinued itraconazole on day 12 of period 2 (owing to an AE) but completed the remaining procedures; however, this subject's data was excluded from the PK analyses. The majority of subjects were male (68%) and white (100%).

Pharmacokinetics

In study 1, Japanese and Caucasian subjects showed similar PK profiles following administration of ivosidenib (Fig. 1, Supplementary Fig. 3). Japanese subjects generally had slightly lower values for AUC_{0-t}, $AUC_{0-\infty}$, and C_{max} and slightly higher values for CL/F (Table 1). Following administration of ivosidenib in the fasted state, ivosidenib was steadily absorbed, with median T_{max} of 3.00–4.00 h in both Japanese and Caucasian subjects. After reaching C_{max}, plasma concentrations declined slowly, with mean $t_{1/2}$ values ranging from 40.9 to 46.0 h in Japanese subjects and from 45.8 to 64.0 h in Caucasian subjects. Following administration of single oral doses of 250–1000 mg ivosidenib, the between-subject variability was moderate, with the %CV for C_{max} and AUC parameters ranging from 21 to 46% in Japanese subjects and from 16 to 46% in Caucasian subjects.

In study 2, following administration of 500 mg ivosidenib in the high-fat meal and fasted states, ivosidenib was readily absorbed, with similar median T_{max} values of 3.00 and 3.03 h post dose, respectively (Fig. 2, Table 2). After reaching C_{max}, plasma concentrations slowly declined generally in a multiphasic manner, with similar mean $t_{1/2}$ values of 53.2 h in the high-fat meal state and 55.4 h in the fasted state. Following administration of 1000 mg ivosidenib in the fasted state, ivosidenib was steadily absorbed, with a median T_{max} of 6 h, which was approximately 3 h later than the median T_{max} following a single dose of 500 mg ivosidenib. After reaching C_{max}, plasma concentrations declined slowly in a multiphasic manner after both doses, although the mean $t_{1/2}$ was longer after an ivosidenib dose of 1000 mg (76.8 h) than after a dose of 500 mg in the fasted state. Following administration of single oral doses of 500 mg and 1000 mg ivosidenib, the between-subject variability was moderate, with the %CV for C_{max} and AUC parameters ranging from 19 to 47%.

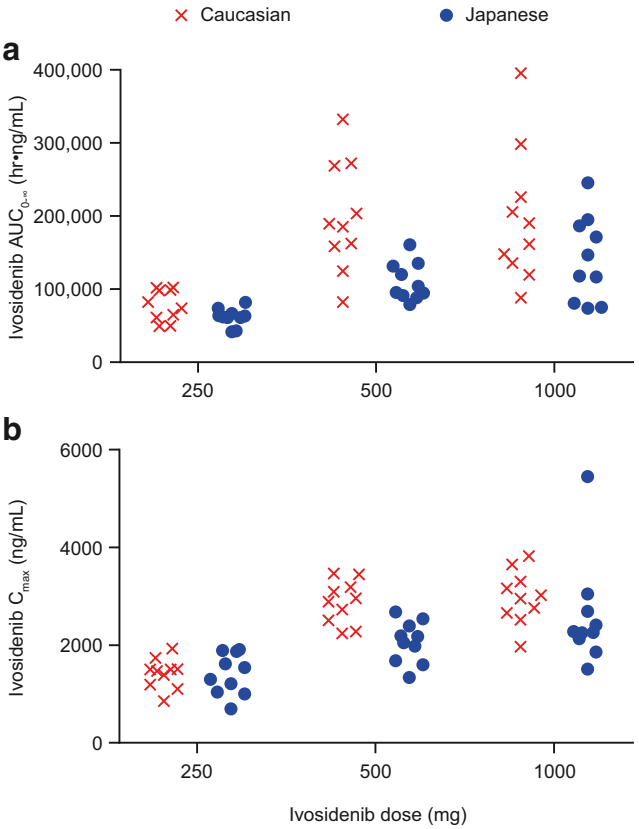

Fig. 1 Distribution of ivosidenib **a** $AUC_{0-\infty}$ and **b** C_{max} by dose level and ethnicity

In study 3, mean ivosidenib concentrations peaked at 5 h post dose in both periods and slowly declined in a multiexponential manner (Fig. 3). Ivosidenib AUC parameters were higher, and CL/F was lower following co-administration of ivosidenib and itraconazole when compared with administration of ivosidenib alone (Table 3). Mean ivosidenib $t_{1/2}$ was higher when ivosidenib was co-administered with itraconazole compared with ivosidenib administered alone. Ivosidenib C_{max} and T_{max} were similar in the

Table 1 Pharmacokinetics of ivosidenib in Japanese and Caucasian subjects (study 1)

PK parameter[a]	250 mg ivosidenib		500 mg ivosidenib		1000 mg ivosidenib	
	Japanese $n = 10$	Caucasian $n = 10$	Japanese $n = 10$	Caucasian $n = 10$	Japanese $n = 10$	Caucasian $n = 10$
C_{max} (μg/mL)	1.34 (34)	1.39 (24)	2.02 (22)	2.85 (16)	2.44 (35)	2.93 (19)
T_{max} (h)	3.50 (3.00, 18.10)	3.00 (2.00, 12.00)	3.00 (2.00, 6.00)	3.02 (1.00, 9.00)	3.00 (2.00, 9.00)	4.00 (2.00, 24.18)
AUC_{0-t} (μg h/mL)	55.1 (24)	69.3 (32)	102 (24)	176 (43)	125 (46)	174 (46)
$AUC_{0-\infty}$ (μg h/mL)	60.8 (21)	75.5 (29)	108 (23)	185 (42)	130 (45)	180 (46)
$t_{1/2}$ (h)	40.9 (11.6)	45.8 (7.02)	46.0 (15.9)	64.0 (22.5)	41.7 (15.2)	48.3 (26.2)
CL/F (L/h)	4.12 (21)	3.31 (29)	4.65 (23)	2.71 (42)	7.68 (45)	5.55 (46)

[a] Values are presented as geometric mean (geometric coefficient of variation %) for C_{max}, AUC parameters, and CL/F; as median (minimum, maximum) for T_{max}; and as arithmetic mean (standard deviation) for $t_{1/2}$

$AUC_{0-\infty}$ area under the concentration-time curve extrapolated to infinity, *AUC_{0-t}* area under the concentration-time curve from time zero to the last measurable concentration, *CL/F* oral clearance, *C_{max}* maximum plasma concentration, *PK* pharmacokinetics, *$t_{1/2}$* terminal elimination half-life, *T_{max}* time to maximum plasma concentration

presence and absence of itraconazole. Steady-state concentrations of itraconazole and hydroxyl-itraconazole were achieved 5 days following the start of itraconazole QD dosing (corresponding to day 5 in period 2, Supplementary Table 2). Arithmetic mean (SD) pharmacokinetic parameters are presented in Supplementary Tables 3–5 for studies 1–3, respectively.

Dose proportionality

Ivosidenib exposure (C_{max} and AUC parameters) appeared to increase less than proportionally to the dose in both Japanese and Caucasian subjects in study 1 (Table 1); when the dose quadrupled from 250 to 1000 mg, the $AUC_{0-\infty}$ slightly more than doubled in each subject group. Ivosidenib exposure also appeared to increase less than proportionally to the dose over the 500–1000 mg dose range in study 2, where mean C_{max}, AUC_{0-t}, and $AUC_{0-\infty}$ values at 1000 mg were approximately 36, 71, and 81% greater, respectively, than those observed at 500 mg (Table 2).

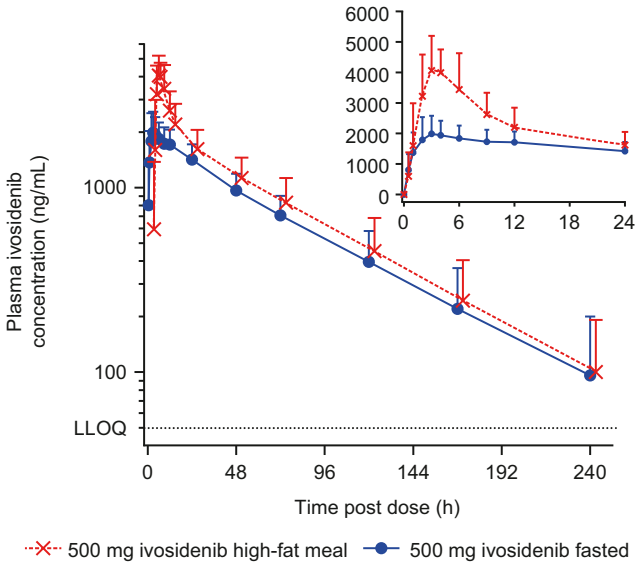

Fig. 2 Mean (+ SD) plasma ivosidenib concentration-time profiles following administration of ivosidenib under high-fat meal and fasted states (study 2). Post-dose below the level of quantification values were set as "missing," and one series was shifted to the right to enhance visualization. *LLOQ* lower limit of quantification

Effect of ethnic origin, food, and itraconazole on ivosidenib pharmacokinetics

The geometric mean ratios (90% CI) of ivosidenib PK parameters for the comparison between Japanese and Caucasian subjects were comparable across all the doses in study 1 (Table 4). The point estimates for the geometric mean ratios overall for AUC_{0-t}, $AUC_{0-\infty}$, and C_{max} were 0.69, 0.70, and 0.83, respectively, and the 90% CIs excluded 1.00. This reflects an average exposure that was lower overall in the Japanese subjects compared with the Caucasian subjects by 30–31% (AUC parameters) and 17% (C_{max}). The observed difference was largely driven by the 500-mg and 1000-mg cohorts with GMRs of 0.58 and 0.72 for AUC parameters, respectively. For the 250-mg cohort, the GMR 90% CIs contain 1.0, indicating comparable PK exposure between two ethnic groups. Given the small sample size, the distribution of AUC and C_{max} values for Japanese subjects generally fell within the range of values for Caucasian subjects (Fig. 1).

In study 2, there was an approximate 25% increase in AUC_{0-t} and $AUC_{0-\infty}$ and an approximate 98% increase in C_{max} when ivosidenib was administered under the high-fat meal state compared with the fasted state. The median T_{max} and the mean $t_{1/2}$ of ivosidenib were not affected by the consumption of food (Table 4).

Table 2 Pharmacokinetics of ivosidenib under high-fat meal and fasted states (study 2)

PK parameter[a]	500 mg ivosidenib fasted $n = 29$	500 mg ivosidenib high-fat meal $n = 27$	1000 mg ivosidenib fasted $n = 6$
C_{max} (μg/mL)	2.27 (21)	4.49 (24)	3.08 (19)
T_{max} (h)	3.03 (1.00, 24.0)	3.00 (1.00, 6.00)	6.00 (3.00, 12.0)
AUC_{0-t} (μg h/mL)	136 (32)	166 (31)	232 (47)
$AUC_{0-\infty}$ (μg h/mL)	143 (31)	174 (31)	259 (47)[b]
$t_{1/2}$ (h)	55.4 (20.5)	53.2 (18.3)	76.8 (36.7)[b]

[a] Values are presented as geometric mean (geometric coefficient of variation %) for C_{max} and AUC parameters, as median (minimum, maximum) for T_{max}, and as arithmetic mean (standard deviation) for $t_{1/2}$

[b] $n = 5$

$AUC_{0-\infty}$ area under the concentration-time curve extrapolated to infinity, *AUC_{0-t}* area under the concentration-time curve from time zero to the last measurable concentration, *C_{max}* maximum plasma concentration, *PK* pharmacokinetics, *$t_{1/2}$* terminal elimination half-life, *T_{max}* time to maximum plasma concentration

In study 3, the GMRs for AUC_{0-t} and $AUC_{0-\infty}$ suggest that ivosidenib exposure was increased by approximately 169% ($AUC_{0-\infty}$ GMR of 2.69) in the presence of itraconazole (Table 4); however, there was no apparent effect of itraconazole on ivosidenib C_{max} (90% CIs were within the 0.80–1.25 interval).

Safety

Across the three studies, the majority of AEs were grade 1 or 2 in severity, and ivosidenib administered alone or co-administered with food or itraconazole was generally safe and well tolerated by the subjects.

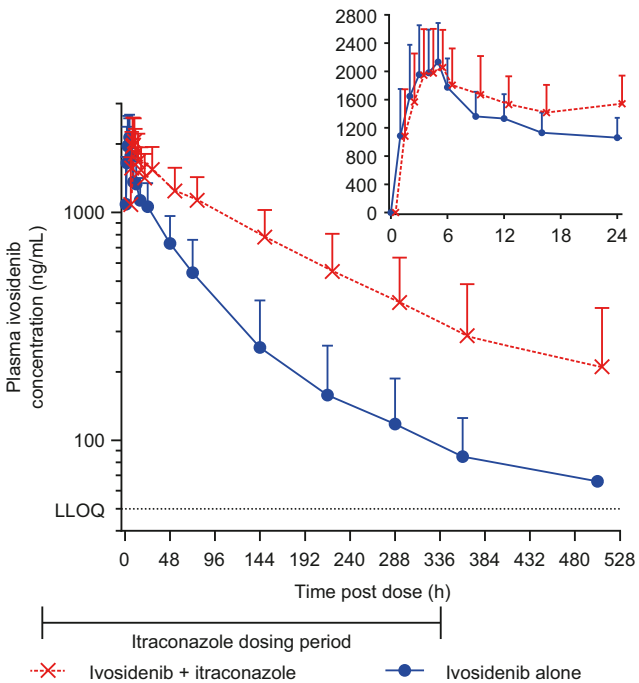

Fig. 3 Mean (+ SD) plasma ivosidenib concentration-time profiles following administration of ivosidenib in the presence and absence of itraconazole (study 3). Post-dose below the level of quantification values were set as "missing", and one series was shifted to the right to enhance visualization. *LLOQ* lower limit of quantification

In study 1, of the 60 subjects who received ivosidenib, two reported AEs (Supplementary Table 6); one Japanese subject in the 250-mg ivosidenib cohort reported a grade 2 upper respiratory tract infection, but the subject recovered and completed the study. One Caucasian subject in the 1000-mg ivosidenib cohort reported a grade 1 migraine headache. Both AEs were assessed by the investigator as not related to ivosidenib. There were no deaths, serious AEs (SAEs), or grade ≥ 3 (severe) AEs during the study.

Single oral doses of 500 mg ivosidenib administered in the high-fat meal and fasted states and single oral doses of 1000 mg ivosidenib administered in the fasted state appeared to be reasonably safe and well tolerated in healthy male and female subjects in study 2 (Supplementary Table 7). There were no deaths, SAEs, or grade ≥ 3 AEs during the study. Three subjects in part 1 discontinued because of AEs following fasted administration. Of these AEs, left bundle branch block and renal impairment were grade 1 in severity and considered by the investigator to be unrelated to the study drug, and vomiting was grade 2 in severity and considered by the investigator to be related to the study drug. Consistent with plasma concentration levels, the incidence of AEs was slightly higher following high-fat meal treatment (14 (46.7%) subjects) than following fasted treatment (11 (36.7%) subjects).

In study 3, one subject had itraconazole treatment withdrawn owing to laboratory events of increased aspartate aminotransferase (AST) and increased creatine kinase (CK). The event of increased CK was considered a grade 4 medically important event and was recorded as an SAE. Overall, a total of nine AEs were experienced by four subjects in this study (Supplementary Table 8). Each event occurrence was reported once during the study. The majority of events were reported following administration of ivosidenib and itraconazole, and there were no events reported following ivosidenib alone. The events of increased

Table 3 Pharmacokinetics of ivosidenib in the presence and absence of itraconazole (study 3)

PK parameter[a]	250 mg ivosidenib alone $n = 22$	250 mg ivosidenib + 200 mg QD itraconazole $n = 21$
C_{max} (μg/mL)	2.24 (25)	2.27 (25)
T_{max} (h)	3.99 (1.00, 5.02)	4.00 (1.00, 16.00)
AUC_{0-t} (μg h/mL)	107.5 (41)	282.0 (34)
$AUC_{0-\infty}$ (μg h/mL)	115.0 (39)	302.3 (31)[b]
$t_{1/2}$ (h)	60.7 (22.5)	140.2 (65.2)
CL/F (L/h)	2.31 (0.778)	0.863 (0.247)[b]

[a] Values are presented as geometric mean (geometric coefficient of variation %) for C_{max} and AUC parameters, as median (minimum, maximum) for T_{max}, and as arithmetic mean (standard deviation) for CL/F and $t_{1/2}$

[b] $n = 20$

$AUC_{0-\infty}$ area under the concentration-time curve extrapolated to infinity, *AUC_{0-t}* area under the concentration-time curve from time zero to the last measurable concentration, *CL/F* oral clearance, *C_{max}* maximum plasma concentration, *PK* pharmacokinetics, *QD* once daily, *$t_{1/2}$* terminal elimination half-life, *T_{max}* time to maximum plasma concentration

AST and increased CK were considered by the investigator to be related to itraconazole alone, and the remaining seven AEs were considered unrelated to either ivosidenib or itraconazole. All events, including the SAE of increased CK, resolved without sequelae. Overall, triplicate 12-lead ECG assessments were within normal limits. There were no additional clinically meaningful findings in the safety events for clinical laboratory tests, vital signs, ECGs (single and triplicate assessments), and physical examinations.

Discussion

These three studies were conducted to investigate if an intrinsic factor (ethnicity) and extrinsic factors (a high-fat meal or a strong CYP3A4 inhibitor (itraconazole)) have an effect, in healthy subjects, on the PK of ivosidenib administered in the formulation intended for marketing.

A non-proportional dose-exposure relationship was observed for ivosidenib in study 1 and study 2 from 250 to

Table 4 Summary statistics for effect of intrinsic and extrinsic factors on the pharmacokinetics of ivosidenib (studies 1, 2, and 3)

Comparison	Parameter	Ivosidenib dose	Geometric mean ratio (90% CI)
Japanese vs. Caucasian	C_{max}	250 mg	0.97 (0.80–1.17)
		500 mg	0.71 (0.59–0.86)
		1000 mg	0.83 (0.69–1.01)
		Overall	0.83 (0.74–0.93)
	AUC_{0-t}	250 mg	0.80 (0.61–1.04)
		500 mg	0.58 (0.44–0.75)
		1000 mg	0.72 (0.55–0.94)
		Overall	0.69 (0.59–0.81)
	$AUC_{0-\infty}$	250 mg	0.80 (0.62–1.04)
		500 mg	0.58 (0.45–0.75)
		1000 mg	0.72 (0.56–0.94)
		Overall	0.70 (0.60–0.81)
High-fat meal vs. fasted	C_{max}	500 mg	1.978 (1.787–2.189)
	AUC_{0-t}		1.256 (1.172–1.346)
	$AUC_{0-\infty}$		1.243 (1.163–1.329)
Ivosidenib + itraconazole vs. ivosidenib alone	C_{max}	250 mg	1.024 (0.927–1.131)
	AUC_{0-t}		2.563 (2.348–2.798)
	$AUC_{0-\infty}$		2.687 (2.449–2.948)

$AUC_{0-\infty}$ area under the concentration-time curve extrapolated to infinity, *AUC_{0-t}* area under the concentration-time curve from time zero to the last measurable concentration, *CI* confidence interval, *C_{max}* maximum plasma concentration

1000 mg. Plasma ivosidenib exposure increases that were less than proportional to increasing doses were also observed in patients with R/R AML, who received single doses from 100 to 1200 mg or multiple doses ranging from 100 twice daily (BID) to 1200 mg QD [15, 22]. In both aqueous and biorelevant media, ivosidenib exhibits low solubility (< 50 μg/mL), but the permeability is high. The solubility-limited absorption of ivosidenib may contribute to the non-proportionality observed after single and multiple dosing.

Study 1 investigated the impact of ethnicity on ivosidenib exposure and was intended to support the ivosidenib global development program in Japan. Ivosidenib was equally well tolerated in both the Japanese and Caucasian subjects. Study 1 showed a small but not clinically significant decrease in ivosidenib exposure in Japanese subjects (~30% for AUC) compared with Caucasian subjects. Ivosidenib is primarily metabolized by CYP3A4, and drugs that are metabolized by CYP3A4/5 are thought to be largely unaffected by ethnicity and known genotypes [23]. Therefore, the observed 30% lower AUC in Japanese subjects is unlikely to be caused by underlying ethnic differences in ivosidenib metabolic activity or elimination pathways. Furthermore, ivosidenib doses < 500 mg (100 mg BID and 300 mg QD) have been shown to be clinically active in subjects with mIDH1-advanced hematologic malignancies, and these doses were associated with significant reductions (> 90%) in plasma and bone marrow 2-HG concentration [15, 22]. This broad relationship between ivosidenib exposure and 2-HG reduction suggests that the slight reduction in exposure seen in Japanese subjects is unlikely to affect the magnitude of 2-HG inhibition by ivosidenib. Based on the maximum 2-HG inhibition data across a wide exposure range, the observed small difference in PK between Japanese and Caucasian subjects, and the assessment of ethnic differences according to ICH E5 guidance [24], ivosidenib is unlikely to be sensitive to ethnic factors, and no clinically relevant differences in therapeutic dose or tolerability across ethnic groups are expected. Therefore, no dosage adjustment is deemed necessary in Japanese subjects with hematologic or solid malignancies harboring an IDH1 mutation.

Study 2 demonstrated that when administered in tablet form, ivosidenib $AUC_{0-\infty}$ and C_{max} were approximately 25 and 98% higher, respectively, after subject consumption of high-fat food compared with overnight fasting. Because ivosidenib is a low-clearance drug and CYP3A4-mediated first pass metabolism may be low, it is possible that the increased bile salt content and gastric emptying time expected under high-fat meal conditions allow for a longer duration of ivosidenib dissolution in the upper intestine; therefore, the observed food effect is likely caused by enhanced drug absorption. Initially, there were no food restrictions in all ongoing phase 1 clinical studies of ivosidenib. However, in light of the findings from study 2, the current food administration instructions in ivosidenib clinical studies advise patients to avoid a high-fat meal. This advice is considered appropriate in order to minimize the potential QT prolongation risk, based on the approximate 98% increase in C_{max}. Therefore, the proposed administration instructions with regard to food are as follows in the US prescribing label. Patients may take ivosidenib tablets with or without food. Patients should be advised that, if ivosidenib tablets are taken with food, they should avoid consuming a high-fat meal.

The dedicated clinical study of the co-administration of ivosidenib with a strong CYP3A4 inhibitor (itraconazole, study 3) confirmed the anticipated clinical drug interaction based on the estimated ivosidenib clearance pathways. Among triazole antifungal agents commonly used in patients with AML, itraconazole was chosen for study 3, rather than voriconazole or posaconazole, because it potently inhibits both CYP3A4 and P-gp and represents a real-world co-administration scenario likely to be encountered in clinical practice. Study 3 demonstrates that itraconazole administered at 200 mg QD increased ivosidenib AUC by 169% (i.e., geometric mean ratio of 2.69) but had no effect on C_{max}. It is worth noting that ivosidenib C_{max} was not affected by itraconazole, suggesting CYP3A4-mediated intestinal and/or hepatic first pass metabolism is likely to be minimal. Consequently, drug interactions with triazole antifungal agents or other moderate/strong CYP3A4 inhibitors (e.g., certain antibiotics) are anticipated. Therefore, wherever possible during treatment with ivosidenib, co-administration of ivosidenib with strong or moderate CYP3A4 inhibitors (such as the antifungals voriconazole, posaconazole, itraconazole, isavuconazole, and fluconazole) should be avoided, as this can increase ivosidenib plasma concentrations, which may increase the risk of QT interval prolongation. However, when co-administration of ivosidenib with a moderate or strong CYP3A4 inhibitor is unavoidable, patients should be monitored for QT interval prolongation by periodic ECG assessments, and electrolyte repletion and ivosidenib dose interruption or reduction may be considered.

Conclusion

The results from these three clinical pharmacology studies provide key information regarding administration of ivosidenib with high-fat food or strong CYP3A4 inhibitors, and to different ethnic groups, e.g., Japanese subjects, in whom no dosage adjustment is deemed necessary. Owing to the 98% increase in C_{max} observed if administered with a high-fat meal, it is recommended that ivosidenib be taken with or without food, but that high-fat meals should be avoided. When co-administration of ivosidenib with a strong CYP3A4 inhibitor is unavoidable, monitoring for QT interval prolongation is recommended and ivosidenib dose interruption or reduction may be considered.

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Authors' contributions DD and BF drafted the manuscript; DD, HY, and BF designed the studies; SN, DH, GL, and BF performed the research; DD and BF analyzed the data; DD, HL, HY, CP, SA, CB, and BF contributed to the interpretation of results. JZ and AV were the study principal investigators. All authors critically reviewed the manuscript and approved the final version.

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Data availability The datasets generated during and/or analysedanalyzed during the current studies are not publicly available but we encourage investigators interested in data sharing and collaboration to contact the corresponding author.

Compliance with ethical standards

Conflict of interest HY, SN, DH, GL, CP, CB, and BF are employees of Agios Pharmaceuticals, Inc. JZ is an employee of Celerion. AV is an employee of WCCT Global. DD and SA were employees of Agios Pharmaceuticals, Inc. at the time of the studies.

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. This article does not contain any studies with animals performed by any of the authors.

Informed consent Informed consent was obtained from all individual participants included in the studies.

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