ARTICLE

Population pharmacokinetic and exposure-response analyses of ivosidenib in patients with *IDH1*-mutant advanced hematologic malignancies

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Abstract

Ivosidenib is a once daily (q.d.), orally available, potent mutant isocitrate dehydrogenase 1 (mIDH1) inhibitor approved for treatment of patients with relapsed or refractory (R/R) acute myeloid leukemia (AML) and intensive chemotherapy ineligible AML with a susceptible *IDH1* mutation. Population pharmacokinetics (PKs; $N = 253$), exposure-response (efficacy [$n = 201$] and safety [$n = 253$]), and concentration-corrected electrocardiogram QT interval (QTc; $n = 171$) analyses were performed using phase I data (100 mg twice daily and 300–1200 mg q.d.). Ivosidenib disposition was well-described by a two-compartment PK model with first-order absorption and elimination. Between-subject variability was moderate for PK parameters. Intrinsic factors did not affect ivosidenib PKs. Moderate/strong CYP3A4 inhibitors increased the area under the plasma ivosidenib concentration-time curve at steady state (AUC_{ss}) by 60%. Efficacy responders and nonresponders had similar ivosidenib exposures. Based on AUC_{ss}, there was no apparent relationship between ivosidenib exposure and efficacy or adverse events. The plasma ivosidenib concentration-QT analysis showed a mean change in QTc using Fridericia's method ($\Delta QTcF$) of 17.2 msec at the approved 500 mg q.d. dose. Because of the direct association between ivosidenib exposure and QTcF, patients should have their electrocardiograms and electrolytes monitored, and comedications that increase ivosidenib exposure or prolong the QT interval should be avoided. These model-based analyses quantitatively provide a framework to describe the relationship among ivosidenib dose, exposure, and clinical end points. With precautions for QTc prolongation, the exposure-response analyses support the 500 mg q.d. dose in patients with AML with a susceptible *IDH1* mutation.

Study Highlights

WHAT IS THE CURRENT KNOWLEDGE ON THE TOPIC?

Ivosidenib (AG-120), a first-in-class, oral, potent mutant isocitrate dehydrogenase 1 (mIDH1) inhibitor, induces durable remissions in patients with m*IDH1* advanced

hematologic malignancies, including relapsed/refractory (R/R) acute myeloid leukemia (AML), with few grade ≥3 treatment-related adverse events.

WHAT QUESTION DID THIS STUDY ADDRESS?

In determining the effect of ivosidenib exposure on clinically relevant safety/efficacy end points, are the pharmacokinetics (PKs) of ivosidenib affected by baseline covariates, including demographics, disease characteristics, renal or hepatic impairment, and concomitant medication that would require dose adjustments?

WHAT DOES THIS STUDY ADD TO OUR KNOWLEDGE?

Concomitant use of moderate/strong CYP3A4 inhibitors increased ivosidenib exposure, whereas other concomitant medications and covariates had no influence. The apparent lack of exposure-efficacy relationship over the exposure range suggests a wide therapeutic index and supports the approved ivosidenib dose of 500 mg once daily.

HOW MIGHT THIS CHANGE CLINICAL PHARMACOLOGY OR TRANSLATIONAL SCIENCE?

Population PKs and exposure-response analyses can be used to provide valuable information on covariates that influence PK and exposure-response profiles, and, consequently, requirements for dose adjustments in clinical use.

INTRODUCTION

Somatic point mutations in the active site of the key metabolic enzyme isocitrate dehydrogenase 1 (IDH1) have been shown to occur in 6–10% of patients with acute myeloid leukemia (AML).[1-4] Mutant IDH1 (mIDH1) proteins have novel enzymatic activity, catalyzing the reduction of alpha-ketoglutarate (α-KG) to produce the oncometabolite D-2-hydroxyglutarate (2-HG).[5] The 2-HG accumulation results in the inhibition of α-KG–dependent enzymes, which drives multiple oncogenic processes, including impaired cellular differentiation.[6,7]

Ivosidenib (TIBSOVO; AG-120; Agios Pharmaceuticals, Cambridge, MA) is a first-in-class, oral, potent, reversible, targeted inhibitor of the mIDH1 protein.[8] The efficacy, safety, and pharmacokinetic (PK) profiles of ivosidenib were evaluated in a phase I study of mIDH1 advanced hematologic malignancies, including relapsed or refractory (R/R) AML (study AG120-C-001, ClinicalTrials.gov NCT02074839).[9] The dose escalation phase included ivosidenib doses of 100 mg twice daily (b.i.d.) and 300 to 1200 mg once daily (q.d.); the dose expansion phase included the recommended dose of 500 mg q.d. At the recommended dose, the rate of complete remission (CR) plus CR with partial hematologic recovery (CRh) in 174 patients with mIDH1 R/R AML was 32.8% (95% confidence interval [CI], 25.8–40.3), the median duration of CR/CRh was 8.2 months (95% CI, 5.6–12.0), and median time to CR/CRh response was 2 (range, 0.9–5.6) months.[10] Ivosidenib was not associated with dose-limiting toxic effects at the approved dose of 500 mg q.d.; the observed adverse events (AEs) were those expected for a population of immunosuppressed patients with advanced disease.[9]

The PK profile of ivosidenib was determined following both single and multiple dosing. Median time to maximal concentration range was 2.4–5.5 h for single dose administration, and 1.9–4.0 h for multiple dosing, across the dose range studied.[11] After peaking, ivosidenib mean concentrations declined in a biexponential manner, with a half-life of 72–138 h after a single dose, a finding that supports a daily dose regimen. Steady-state oral clearance (CL/F) increased with increasing single and multiple doses, ranging from 2.68 to 6.09 L/h, with steady state being achieved within 14 days of dosing. Ivosidenib exposure increased less than proportionally to dose after both single and multiple doses. CYP3A4 is a major metabolism pathway of ivosidenib, with minor contributions from CYP2B6 and CYP2C8.[10,12]

Based on the phase I study data, ivosidenib received US Food and Drug Administration (FDA) approval for the treatment of AML with a susceptible IDH1 mutation as detected by an FDA-approved test in adults with newly diagnosed disease ≥75 years old or with comorbidities precluding use of intensive induction chemotherapy, and in adults with R/R AML.[10] The recommended dose of ivosidenib is 500 mg q.d. orally for a minimum of 6 months to allow time for clinical response, or until disease progression or unacceptable toxicity.[10]

The present study objective was to develop a population PK model for ivosidenib using a subset of available phase I study data.[9,11] The disposition of ivosidenib in the target population, identification of intrinsic and extrinsic factors influencing ivosidenib PK variability (including concomitant medications), and assessments of ivosidenib systemic exposure and response (efficacy and safety) relationships were evaluated.

METHODS

Patients and study design

PK samples from patients with m*IDH1* advanced hematologic malignancies enrolled in the phase I study were used for analysis. The study design has been previously described.[9] In brief, single-agent ivosidenib was administered orally in continuous 28-day cycles. During the dose escalation phase, the first 3 patients enrolled in each dose cohort (100 mg b.i.d. and 300, 500, 800, and 1200 mg q.d.) also received a single dose of ivosidenib on day −3 (3 days prior to start of continuous daily dosing on cycle 1 day 1). PK sampling was conducted as detailed in the Supplementary Material. During the expansion phase (ivosidenib 500 mg q.d.), triplicate electrocardiograms (ECGs) were collected along with time-matched PK samples.

The phase I study was conducted in accordance with the principles of the Declaration of Helsinki and Good Clinical Practice guidelines, and the protocol was approved by human investigation committees at participating centers. Written informed consent was provided by all patients before screening and enrollment.

Plasma ivosidenib quantification

Ivosidenib concentrations were determined using validated liquid chromatography-tandem mass spectrometry (LC-MS/MS)–based methods.[9,13] Two LC-MS/MS assays with different dynamic ranges (1–1000 ng/ml and 50–50,000 ng/ml) were used, with lower limits of quantitation of 1 and 50 ng/ml, respectively. The lower curve range assay (1–1000 ng/ml) was revalidated at a higher curve range (50–50,000 ng/ml) to better fit the study sample concentrations. The two assays were successfully bridged with study samples. Missing concentrations were not included (or imputed) in the population PK analysis.

Population PK model development and evaluation

Nonlinear mixed-effects models were fitted to the concentration-time data. Alternate linear compartmental models (e.g., one-, two-, and three-compartments) and absorption models (e.g., first-order, zero-order, and mixed-order) were considered. Any identified PK nonlinearities were included as part of the structural model. Proportional and additive random residual error terms were normal, independent, identically distributed, random variables. Between-subject variability (BSV) was modeled using exponential random effects. Random between-subject effects were multivariate normally distributed. Between-subject and within-subject error terms, as well as between-subject

error terms associated with different patients, were independent. Population PK modeling was conducted with the first-order conditional estimation method with interaction (FOCE-I) in NONMEM (version 7.3; ICON, GloboMax; Hanover, MD). Perl-speaks-NONMEM (version 4.2.0) was used to facilitate evaluation of the PK model, and the results were further analyzed by R (version 3.2.3; The R Foundation for Statistical Computing).

Covariates assessed included patient demographics, disease characteristics, concomitant CYP3A4 inhibitors/inducers, and concomitant gastric acid reducers, which were dosed on the same days as the ivosidenib PK days (see Tables S1, S2). The three most commonly used concomitant medications in each category were selected for covariate analysis. Model covariates were selected using a forward addition and backward elimination method based on significance levels of $p < 0.01$ and $p < 0.001$, respectively.

The performance of the final model was assessed by visual inspection of diagnostic plots, successful convergence, changes in objective function values, precision of parameter estimates, and plausibility of parameter estimates. The final model was also evaluated using the visual predictive check to allow visual comparison between the distributions of simulated and observed ivosidenib concentrations. Based on the estimates from the model, concentration-time profiles were simulated using 1000 replicates. A graphical comparison of the simulated and observed percentiles of ivosidenib concentrations was generated (95% CIs for the simulated median; 5th and 95th percentiles were compared with corresponding observed percentiles).

Exposure-response analysis

The individual empirical Bayes estimates of PK parameters from the final population PK model were used to predict the individual exposure of ivosidenib in patients. Steady-state maximum plasma concentration (C_{max}), minimum plasma concentration (C_{min}), or area under the plasma concentration-time curve over a dosing interval (AUC_{ss}), based on the nominal dose, were calculated for each individual and used as a predictor of the safety and efficacy variables. A secondary independent variable for the exposure-safety analysis used exposure estimates calculated from the average dose based on the actual dosing history. Exploratory plots investigated the correlation among predicted individual exposure parameters (AUC, C_{min}, and C_{max}) that showed a strong correlation between post hoc exposure estimates for AUC-C_{min} and AUC-C_{max}. AUC was the most robust estimator of total systemic exposure and was used for exposure-safety and exposure-efficacy analyses.

Clinically relevant safety end points investigated included: any grade and grade ≥3 rash, leukocytosis, isocitrate dehydrogenase (IDH) differentiation syndrome, and polyneuropathy; grade ≥2 gastrointestinal events (nausea/vomiting);

liver dysfunction (alanine aminotransferase [ALT] or aspartate aminotransferase [AST] ≥3 × upper limit of the normal range, and associated with an increase in bilirubin ≥2 × upper limit of the normal range [±10 days]); hepatic enzyme elevation (newly occurring or worsening laboratory abnormalities all grade and grade ≥2 for ALT and AST); acute renal failure (all grade); and tumor lysis syndrome (grade ≥3). Clinically relevant efficacy end points were CR, CR/CRh, overall response (OR), and non-CR/CRh response. Exploratory analyses of exposure-safety and exposure-efficacy relationships included logistic regression and Kaplan-Meier plots. When clear relationships were observed, quantitative exposure-response models with covariates were considered.

Concentration-corrected QT analysis

To maximize model precision, data from two additional phase I studies were included in the concentration-QTc analysis: a study of similar design in patients with m*IDH1* advanced solid tumors (AG120-C-002) and a healthy volunteer study (AG120-C-004). A linear mixed-effects model based on the methods described by Darpo et al. was used.[14]

The intercept and slope were modeled as population mean values with additive BSVs drawn from a bivariate normal distribution. A study effect on slope was tested. Covariates were tested as additions to the intercept term in a standard stepwise forward selection-backward elimination search strategy. Covariates included baseline demographic variables, baseline QTc interval using Fridericia's method (QTcF), electrolytes (as continuous variables and as binary flags indicating values greater than the mean), study effects, effects in healthy participants versus patients, tumor type, flags for medications with risk of QT interval prolongation and torsades de pointes, and a flag for cardiac disorder at baseline. Relative performances of the models were evaluated using the likelihood ratio test at the 0.05 significance level, and by the precision of the parameter estimates. The final model was used to predict the expected QTc prolongation and associated 90% CI at the geometric mean C_{max} values for various q.d. doses. The Fridericia and Bazett correction methods were compared for removal of heart rate effect on the QT interval. Baseline QTcF (Fridericia) and QTcB (Bazett) values were plotted against the ECG RR interval, and the correction method that resulted in the estimated linear regression slope closest to 0 was selected.

RESULTS

Baseline patient characteristics and PK sampling

Patients included in this analysis received oral ivosidenib 100 mg b.i.d. (*n* = 4), 300 mg (*n* = 4), 500 mg (*n* = 48),

800 mg (*n* = 15), or 1200 mg q.d. (*n* = 7) in the dose escalation phase (*n* = 78 overall) and 500 mg q.d. in the dose expansion phase (*n* = 180). Samples for PK analysis were available from 255 of 258 patients who received at least one dose of ivosidenib (225 patients received the approved 500 mg q.d. dosage). Overall, 4.7% of postdose concentrations were below the limit of quantification. Two patients were excluded from the analysis because of missing administration times. In total, 4656 samples from 253 patients were analyzed. Baseline covariates and concomitant medications of patient populations are summarized in Tables S1 and S2. The majority of patients were men (*n* = 137, 54%), had R/R AML (*n* = 203, 80%), and had an Eastern Cooperative Oncology Group (ECOG) performance status (PS) of 0 or 1 (*n* = 198, 78%).

Covariate analysis was performed for voriconazole, fluconazole, and posaconazole, the most frequently used individual strong or moderate CYP3A4 inhibitors in this study. Other CYP3A4 inhibitors were combined into a separate "other strong or moderate CYP3A4 inhibitors" group to ensure accurate estimation of covariate effect to the absence of CYP3A4 inhibitors. Of CYP3A4 inducers, dexamethasone and prednisone were used most frequently in this study, but as weak inducers, were not selected for covariate analysis. Pantoprazole and famotidine were the most frequently used proton-pump inhibitor and H_2-receptor antagonist in this study, respectively, and were selected for covariate analysis.

Base population PK model

Ivosidenib exposure was found to be slightly less than dose proportional (Figure S1a). The plasma concentration-time profiles observed over 72 h after a single 500 mg dose indicated two-compartment behavior (Figure S1b). Plasma concentrations accumulated to a stable level by day 15 of cycle 1 (Figure S1b).

The base model was a two-compartment model with sequential zero-order release (lag time) and first-order oral absorption. To account for the long terminal half-life after a single dose without the expected accumulation, a fold-increase in CL was required; thus, the model was augmented with a single-dose to steady-state factor for CL, and also for relative bioavailability (Figure S1c). The initial CL was difficult to estimate due to limited washout data; therefore, the model was reparameterized to reflect steady-state PK parameters for ivosidenib 500 mg q.d. (Table S3). Shrinkage was small, ranging from 5% for CL/F to 36% for the absorption rate constant. Goodness-of-fit plots for the base model indicated a good match (data not shown).

Final population PK model

In the final model, ivosidenib oral PKs were described by a two-compartment model with first-order absorption and
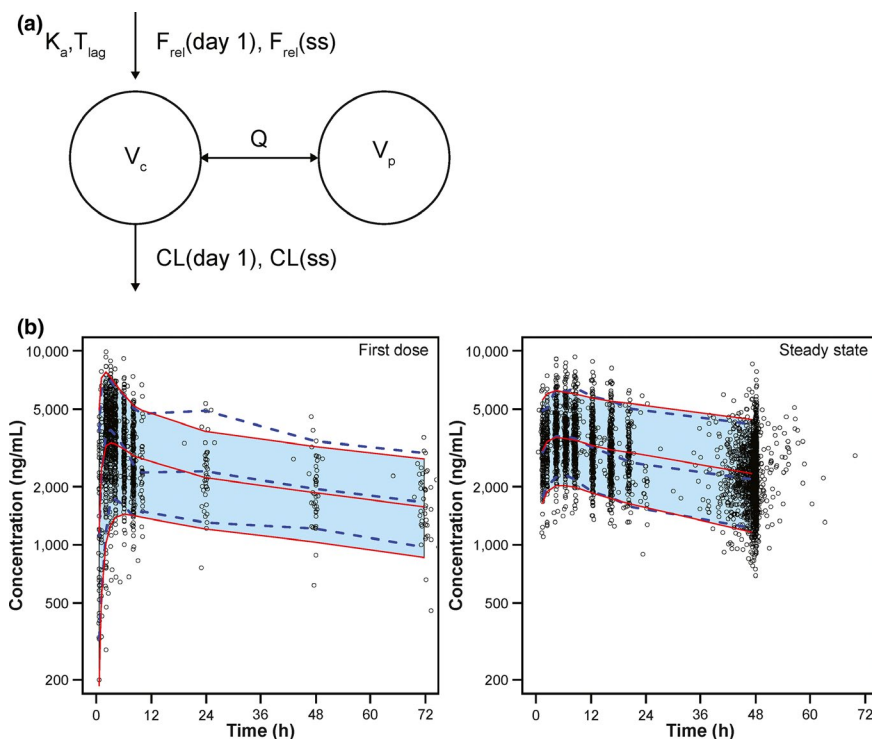
FIGURE 1 (a) Schematic of final population pharmacokinetic model and (b) visual predictive check. In (b), the blue shaded regions represent 90% prediction intervals on the range of prediction-corrected data. The red solid lines represent the simulated 5th, 50th, and 95th percentiles for 1000 simulations, and the blue dashed lines represent corresponding statistics for the prediction-corrected observed data. The right panel includes all samples after day –3 in patients in the dose escalation phase and cycle 1 day 1 in patients in the dose expansion phase. The x-axis represents time after dose, and predose samples are plotted at ~ 24 h. CL, clearance; F_{rel}, relative bioavailability on day 1; Ka, first-order absorption rate constant; Q, between-compartment clearance; T_{lag}, zero-order release duration (lag-time); $_{SS}$, steady state; V_c, volume of distribution for central compartment; V_p, volume of distribution for the peripheral compartment

elimination (Figure 1a). The model PK parameters are shown in Table 1. At steady state, CL/F (% coefficient of variation) was 5.39 L/h (35%) and apparent central volume of distribution (V_c/F) was 234 L (47%). The apparent CL was estimated to be 1.63 L/h after a single dose and 5.39 L/h at steady state. The change from single dose to multiple doses at steady state was modeled as a 2-fold decrease in relative bioavailability and a 1.66-fold increase in CL/F, such that the net change in apparent CL was 3.3-fold. The increase in CL/F at steady state may be related to auto-induction of CYP3A4. The dose-nonlinearity exponent on relative bioavailability was −0.49, suggesting less-than-dose-proportional exposure, with a doubling of dose translating into an ~ 40% increase in exposure. Visual predictive check plots (Figure 1b) indicate that the final model accurately describes the range of data observed in the population.

Covariate analysis suggested that age, body weight, body mass index, sex, race, disease type, and ECOG PS were uncorrelated to ivosidenib CL/F. Renal function indicators, including creatinine clearance and renal impairment category, also had no effect on CL/F. This conclusion should be interpreted with caution as there were only two patients with severe renal impairment (creatinine clearance <30 ml/min). There was no correlation between CL/F and hepatic function indicators, including

ALT, AST, bilirubin, and hepatic impairment category (based on National Cancer Institute Organ Dysfunction Working Group criteria) in patients with mild hepatic impairment. Low albumin at baseline and during treatment correlated with decreased CL/F and V_c/F. Baseline body weight had a significant impact on V_c/F. The moderate or strong CYP3A4 inhibitors voriconazole, fluconazole, and posaconazole were associated with 36%, 41%, and 35% reductions in ivosidenib CL/F, and 57%, 69%, and 53% increases in the ivosidenib AUC_{ss}, respectively (Figure 2). Other strong or moderate CYP3A4 inhibitors and mild CYP3A4 inhibitors were grouped and modeled to more accurately assess the individual drug (i.e., voriconazole, fluconazole, and posaconazole) effect. The impact of mild CYP3A4 inhibitors was minimal. In addition, concomitant use of pantoprazole or famotidine did not affect ivosidenib CL/F.

Exposure-response analyses

Exposure-safety analysis

Among 253 patients in the exposure-safety dataset, 424 events were reported across 16 selected safety end points. Of

TABLE 1 Parameter estimates for the final population PK model

PK parameter	Fixed effect		Between-patient variability		Shrinkage (%)
	Estimate	RSE (%)	CV%	RSE (%)	
Steady-state CL/F, L/h	5.39	4	35	6	5
Steady-state V_c/F, L	234	7	47	6	11
Steady-state Q/F, L/h	15.8	19	–	–	–
Steady-state V_p/F, L	151	22	–	–	–
First-dose CL/F, L/h	1.63	–	–	–	–
First-dose V_c/F, L	71	–	–	–	–
First-dose Q/F, L/h	4.8	–	–	–	–
First-dose V_p/F, L	46	–	–	–	–
k_a, 1/h	1.38	10	108	7	32
T_{lag}, h	0.27	11	–	–	–
Steady-state fold change in F_{rel}	0.50	7	–	–	–
Steady-state fold change in CL	1.66	11	–	–	–
Dose-F_{rel} exponent	–0.49	19	–	–	–
W_t-V_c/F exponent	0.92	13	–	–	–
Baseline albumin-CL/F exponent	0.82	20	–	–	–
Albumin ratio-CL/F exponent	0.99	19	–	–	–
Baseline albumin-V_c/F exponent	0.73	28	–	–	–
Albumin ratio-V_c/F exponent	1.1	38	–	–	–
Fold change in CL with voriconazole	0.64	6	–	–	–
Fold change in CL with fluconazole	0.59	6	–	–	–
Fold change in CL with posaconazole	0.65	12	–	–	–
Fold change in CL with other moderate/strong CYP3A inhibitors	0.92	17	–	–	–
Fold change in CL with mild CYP3A inhibitors	1.04	6	–	–	–
Log-additive CV%	26	3	–	–	6

First-dose parameters do not have standard errors as they are derived from steady-state parameters and fold changes in F_{rel} and/or CL/F. Albumin ratio calculated as albumin at a given time divided by baseline albumin (reflects within-patient variability)
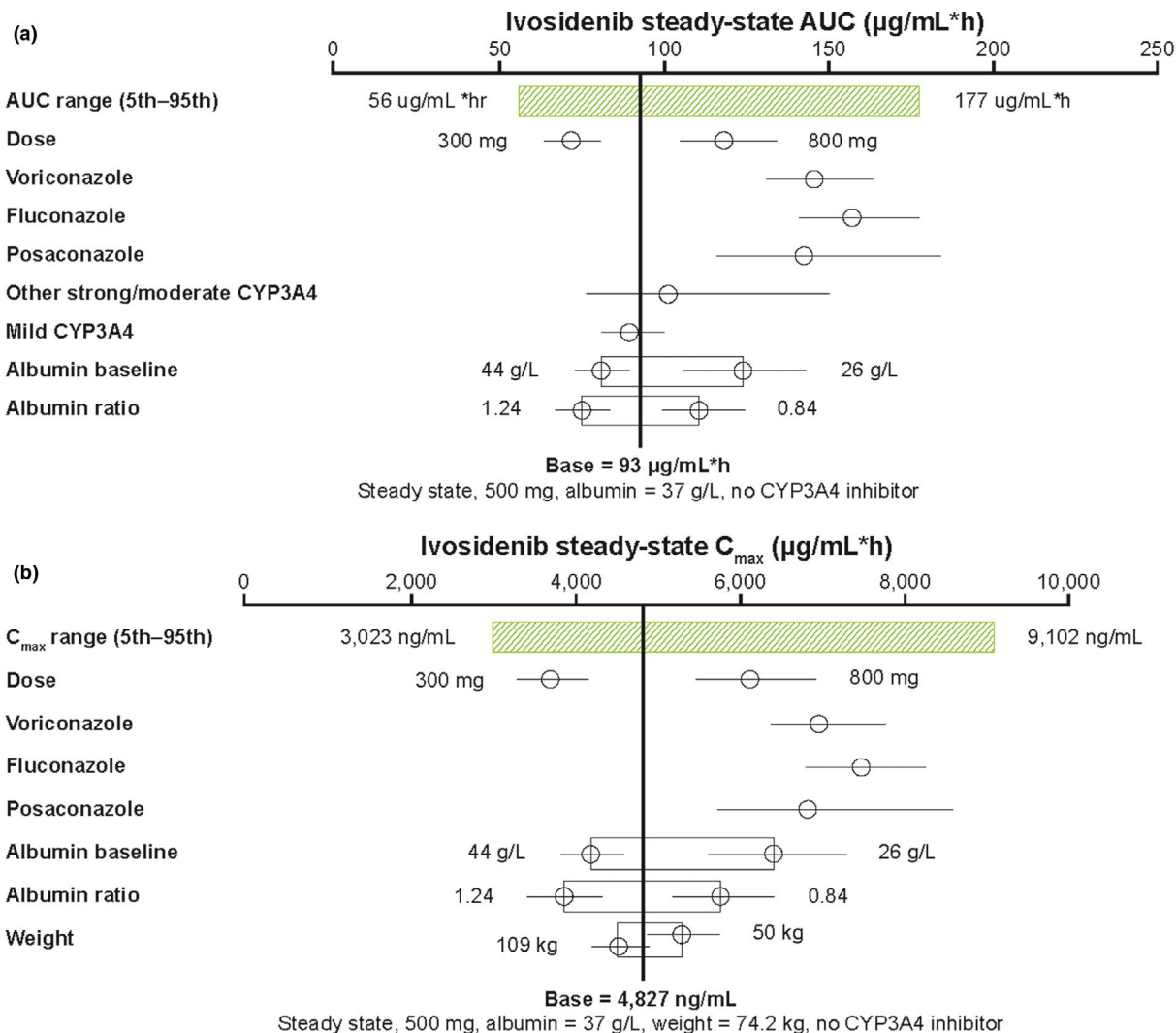
Abbreviations: CL, clearance; CL/F, apparent clearance; CV, coefficient of variation (square root of variance/mean × 100%); F_{rel}, relative bioavailability; k_a, first-order absorption rate constant; PK, pharmacokinetic; Q/F, apparent distribution clearance; RSE, relative standard error (standard error/estimate × 100%, RSE on standard deviation terms = RSE of variance/2); T_{lag}, zero-order release duration (lag-time); V_c/F, apparent central volume of distribution; V_p/F, apparent peripheral volume of distribution; W_t, baseline body weight.

these, the following events occurred in ≥15% of patients: all grade leukocytosis ($n = 93$, 37%), new or worsening all grade AST ($n = 68$, 27%), all grade rash ($n = 58$, 23%), and new or worsening all grade ALT ($n = 37$, 15%). Liver dysfunction and grade ≥3 polyneuropathy were reported in one patient each. Generally, for each safety end point, the exposure distributions were similar and overlapping for patients with or without an event (Figure 3a). The event incidence by nominal AUC_{ss} quartile showed no clear relationships for most safety end points. For new and worsening all grade ALT and AST AEs, the first quartile incidence was lower than the other quartiles, but there were no differences among the second, third, and fourth quartiles (Figure 4). The relationship between ivosidenib exposure and AEs was predominantly driven by mild grade 1 ALT and AST AEs, as indicated by

the absence of an exposure effect for grade ≥2 ALT and AST AEs. Logistic regression indicated no association between the incidence of events for all safety end points and AUC_{ss}. Similar findings were observed when using average AUC as the independent variable.

Exposure-efficacy analysis

The exposure-efficacy analysis dataset consisted of 201 patients with R/R AML (59 from the dose escalation phase and 142 from the expansion phase). There were 75, 43, 59, and 16 patients with OR, CR, CR/CRh, and non-CR/CRh responses, respectively. Nominal AUC_{ss} ranges were similar for all efficacy end points analyzed including CR versus non-CR,

(a)

Ivosidenib steady-state AUC (µg/mL*h)

Base = 93 µg/mL*h
Steady state, 500 mg, albumin = 37 g/L, no CYP3A4 inhibitor

(b)

Ivosidenib steady-state C$_{max}$ (µg/mL*h)

Base = 4,827 ng/mL
Steady state, 500 mg, albumin = 37 g/L, weight = 74.2 kg, no CYP3A4 inhibitor

(c)

Covariate value		AUC estimate (µg/mL*h)	Covariate effect (% of typical value)
Typical participant receiving 500 mg QD with no concomitant CYP3A4 inhibitors and albumin of 37 g/L		93	–
Clearance	5th percentile (2.82 L/h)	177	+91%
	95th percentile (8.86 L/h)	56	−39%
Dose	300 mg	71	−23%
	800 mg	118	+27%
CYP3A4 inhibitor	Voriconazole	145	+57%
	Fluconazole	157	+69%
	Posaconazole	142	+53%
Albumin baseline	5th percentile (26 g/L)	124	+34%
	95th percentile (44 g/L)	80	−13%
Albumin ratio	5th percentile (0.84)	111	+19%
	95th percentile (1.24)	75	−19%

FIGURE 2 Forest plot of covariates and dose for (a) area under the plasma ivosidenib concentration-time curve at steady state (AUC$_{ss}$) and (b) maximal plasma ivosidenib concentration (C$_{max}$); and (c) factors explaining variability in AUC$_{ss}$ estimates. In (a) and (b), the vertical lines represent the predicted AUC$_{ss}$ (93 µg·h/ml) and C$_{max}$ (4827 ng/ml) in the typical patient receiving ivosidenib 500 mg once daily (q.d.). This patient has albumin levels of 37 g/L and is not taking a strong or moderate concomitant CYP3A4 inhibitor. The top hatched bar shows the 5th to 95th percentiles of modeled AUC$_{ss}$ and C$_{max}$, across the patient population. The points show the variation in modeled AUC and C$_{max}$ as covariates are changed one at a time to indicated values. For continuous variables, the extreme values are 5th and 95th percentiles of the population. Horizontal lines represent 95th percentile confidence intervals of the estimate. Albumin ratio calculated as albumin at a given time divided by baseline albumin (reflects within-patient variability)

FIGURE 3 (a) Exposure versus adverse event (AE) occurrence, with vertical boxplots showing area under the plasma ivosidenib concentration-time curve at steady state (AUC_{ss}) distributions for each AE and (b) post hoc AUC_{ss} distributions in responders and nonresponders for efficacy end points overall response, complete remission, complete remission or complete remission with partial hematologic recovery (CR/CRh), and non-CR/CRh response. Dots represent the median; hinges represent the 25th and 75th percentiles; and whiskers represent extended hinges to 1.5 × interquartile range. Not shown: ≥grade 3 polyneuropathy and liver dysfunction, both $n = 1$. ARF, acute renal failure; ALT, alanine aminotransferase; AST, aspartate aminotransferase; IDH, isocitrate dehydrogenase

CR/CRh versus non-CR/CRh, OR versus non-OR, and CR/CRh versus non-CR/CRh responders (Figure 3b). Efficacy responses across nominal AUC_{ss} quartiles appeared similar and this was confirmed by logistic regression analysis. Association between the nominal AUC_{ss} and the probability of achieving a clinical response, or the incidence of response for each of the efficacy end points, was minimal (Table 2).

QTc analysis

The QTc analysis dataset comprised samples from 171 patients, totaling 1203 triplicate ECG measurements and time-matched plasma concentrations. The Fridericia correction succeeded in removing heart rate effects on QTcF, with a nonsignificant slope of QTcF versus RR. There was no evidence of hysteresis
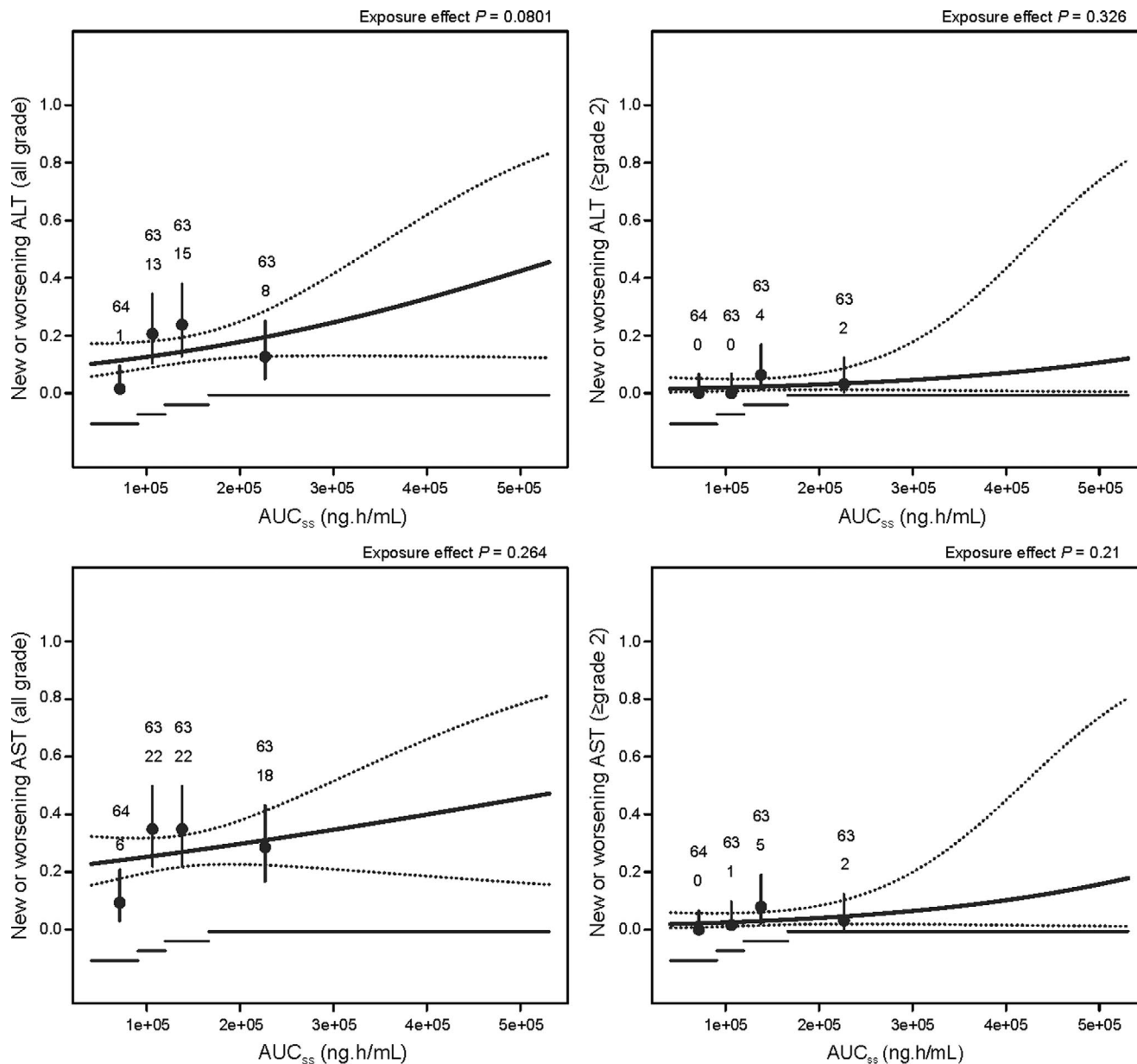
FIGURE 4 Adverse event (AE) incidence versus area under the plasma ivosidenib concentration-time curve at steady state (AUC_{ss}) with incidence grouped by AUC_{ss} quartile and a linear logistic regression fit for alanine aminotransferase (ALT) or aspartate aminotransferase (AST) AEs. Numbers represent total number of subjects (upper row) and number of subjects with an event (lower row) within corresponding quartile; solid dot and vertical line represent incidence and 95% confidence interval (CI) of observation within quartile; bold solid line is the logistic regression fit of the form: Response ~AUCss * slope + intercept; dashed lines are the 95% CI; horizontal solid lines are the width of exposure quartiles. ALT, alanine aminotransferase; AST, aspartate aminotransferase

(delay) between changes in concentration and changes in QTcF. A significant direct relationship between ΔQTcF and ivosidenib concentration was found (Figure 5). In this study population, ΔQTcF was predicted to increase with plasma ivosidenib concentration at 0.00258 msec/(ng/ml). At a concentration of 6551 ng/ml, the geometric mean C_{max} for the 500 mg q.d. dose, ΔQTcF was predicted to be 17.2 msec (90% CI, 14.7–19.7).

Increasing age, lower levels of electrolytes (calcium and magnesium), lower baseline QTcF, and lower use of medications with known QT interval prolongation risk were associated with increased ΔQTcF. Including these covariates in the analysis slightly reduced unexplained variability, but varying them over values for all participants in the dataset had much less effect on ΔQTcF than varying C_{max} likewise.

DISCUSSION

In the present analysis, a population PK model satisfactorily described ivosidenib disposition and variability by a

TABLE 2 Incidence of clinical response by AUC_{ss} quartile for all patients included in the exposure-efficacy analysis

AUC_{ss} quartile	AUC_{ss}, ng·h/ml	No. of patients	Incidence, *n*		
			OR	CR	CR/CRh
1	40,900–93,079	51	20 (39%)	11 (22%)	17 (33%)
2	93,393–121,715	50	18 (36%)	12 (24%)	15 (30%)
3	123,526–169,509	50	18 (36%)	9 (18%)	12 (24%)
4	170,758–360,780	50	19 (38%)	11 (22%)	15 (30%)

Abbreviations: AUC_{ss}, area under the plasma ivosidenib concentration-time profile at steady state; CR, complete remission; CR/CRh, complete remission or complete remission with partial hematologic recovery; OR, overall response.

FIGURE 5 Relationship between mean change in corrected QT interval using Fridericia's method (ΔQTcF) and ivosidenib concentration. CI, confidence interval
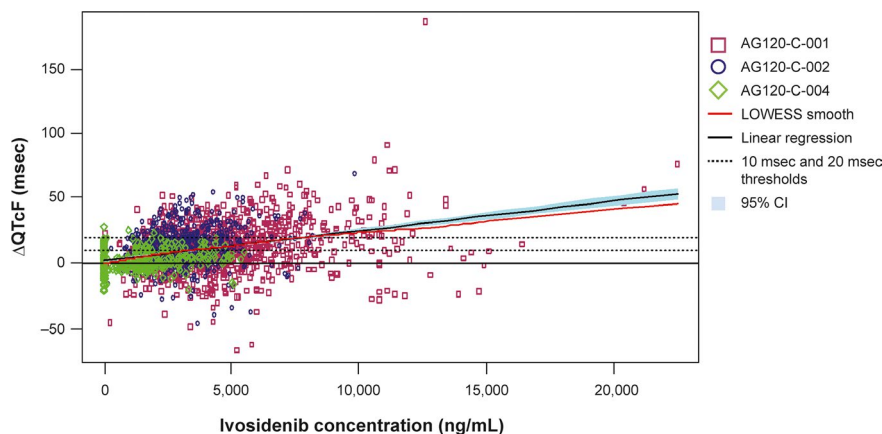
two-compartment model with first-order absorption and elimination. BSV was moderate for the PK parameters. Ivosidenib was characterized by less than dose-proportional bioavailability, with a doubling of dose translating to an ~ 40% increase in exposure. Furthermore, ivosidenib showed a 0.5-fold change in relative bioavailability and a 1.66-fold change in CL from a single dose to steady state. The CL, in this population of patients with advanced hematologic malignancies, was estimated to be 1.63 L/h after a single dose and 5.39 L/h after multiple doses. The increase in CL at steady state may be related to auto-induction. The magnitude of auto-induction, however, was deemed not clinically relevant. Although CL increased by 1.66-fold from day 1 to steady state, no drop in plasma exposure over time was observed and there was no apparent exposure-efficacy relationship. After 2 weeks, auto-induction reached steady state and no further changes were observed in CL over time. Using data from in vitro studies and a phase I clinical trial (study AG120-C-001), a physiologically based PK model for ivosidenib in patients with AML was developed that reasonably predicted the observed steady-state exposures of ivosidenib as well as the auto-induction effect across all dose levels.[12] In vitro, it was found that ivosidenib is a substrate for, and an inducer of, human CYP3A4, and may also be an inducer of CYP2B6, CYP2C8, and CYP2C9.[10]

The covariate effects of moderate and strong CYP3A4 inhibition with concomitant voriconazole, fluconazole, and posaconazole had a moderate effect on ivosidenib exposure

based on AUC. Although the detailed dose, regimen, and compliance for these concomitant medications were unknown in this study, the magnitude of strong CYP3A4 inhibition predicted from this analysis was broadly similar to the results from a dedicated clinical pharmacology study of the effect of the strong CYP3A4 inhibitor itraconazole on ivosidenib exposure (1.69-fold change in plasma AUC in healthy participants after multiple doses of ivosidenib)[15] and a physiologically based PK model prediction (1.44-fold change in plasma AUC in patients with AML after multiple doses of ivosidenib in the presence of itraconazole).[12] Thus, co-administration of strong CYP3A4 inhibitors with ivosidenib requires an ivosidenib dose reduction.[10] The effect of mild CYP3A4 inhibitors was predicted to be minimal. The effect of CYP3A4 inducers could not be evaluated in this population as the most frequently used were weak inducers and not included in the covariate analysis. Regardless, CYP3A4 inducers should be avoided when using ivosidenib.[10]

All other covariate effects on ivosidenib exposure assessed were not deemed clinically relevant. Albumin levels are a common covariate in population PK models, especially in oncology studies.[16,17] In the current study, reduced baseline albumin levels were associated with increased exposure; low albumin levels of 26 g/L were associated with a 34% increase in AUC relative to an albumin level of 37 g/L. However, ivosidenib is not highly protein bound (~ 90% in human plasma), and albumin binding is not expected to alter

ivosidenib CL. The effect of time-varying albumin changes on plasma exposure was less than 20% and was not considered clinically relevant. As there was no clinically meaningful effect of mild hepatic or renal impairment on ivosidenib exposure, no dose adjustments are currently recommended for these target patient populations; however, these findings should be interpreted with caution as patients with severe renal impairment and moderate and severe hepatic impairment were under-represented in this dataset. A study dedicated to evaluating the single-dose PKs of ivosidenib 500 mg in patients with mild or moderate hepatic impairment (ClinicalTrials.gov NCT03282513) has been reported elsewhere, and showed that mild/moderate hepatic impairment did not lead to clinically relevant changes in ivosidenib exposure.[18] A substudy to evaluate the single-dose PKs of ivosidenib in patients with renal impairment was added to the phase I study (ClinicalTrials.gov NCT02074839).

Based on the totality of the data in the exposure-response analyses, the incidence of AEs was not associated with model-predicted ivosidenib AUC_{ss}. Median onset times of the investigated safety end points ranged between 15 and 115 days after start of ivosidenib treatment, which supported the use of total systemic exposure at steady state as the appropriate parameter for this analysis. Although 34 of 253 patients took less than 90% of the nominal dose (due to dose modification or doses missed), on average, patients took 97.5% of the nominal dose. Thus, results from analyses using average AUC as a predictor were similar to those using AUC_{ss}. In general, the baseline demographic covariates of disease type, *IDH1* mutation status, number of prior anticancer regimens, prior transplantation, cytogenetic risk, and history of myelodysplastic syndrome, race, sex, weight, and age were evenly distributed across the exposure quartiles except for a small imbalance in baseline ECOG PS. Covariate effects were not evaluated in the exposure-safety analyses because there was no apparent exposure-response relationship. Linear logistic regression revealed no significant correlations between ivosidenib exposure and selected AEs. For new or worsening ALT (all grades) and new or worsening AST (all grades), the AE rate was less in the lowest exposure quartile relative to the other exposure quartiles, a trend likely driven by transitioning to grade 1 ALT or AST AEs indicated by the limited number or absence of grade 2 ALT or AST AEs.

Determination of the recommended 500 mg dose of ivosidenib was based on pharmacodynamic (2-HG inhibition), PK, safety, and efficacy data from the dose escalation portion of the phase I study.[11] Furthermore, this dose was associated with encouraging remission rates and an acceptable toxicity profile.[9] Exposure-efficacy analysis revealed no relationship between exposure and selected efficacy end points or probability of achieving clinical response. The lack of exposure-efficacy relationship over the observed exposure range suggests a wide therapeutic index. Taken together, these data support the approved ivosidenib dose of 500 mg q.d.

Concentration-QTc modeling provided a robust assessment of the effect of therapeutic and supratherapeutic doses of ivosidenib on QT interval prolongation. QTcF interval prolongation is regarded as present if the upper bound of the 90% two-sided confidence limit of the change in QTcF at the mean C_{max} exceeds 10 msec.[19] An ivosidenib C_{max} of 6551 ng/ml was predicted to result in a 17.2 msec increase from baseline in QTcF. Thus, ivosidenib 500 mg q.d. is associated with a risk of prolonging the QTc interval in patients with advanced hematologic malignancies. Risk mitigation includes monitoring ECGs and electrolytes. If a QTcF interval of greater than 480–500 msec does occur, then the ivosidenib dose should be withheld until the interval returns to ≤480 msec. If the QTcF interval is greater than 500 msec, ivosidenib dosing should be held until the interval returns to within 30 msec of baseline or ≤480 msec, and dosing resumed at a reduced dose of 250 mg. If QT prolongation is accompanied by signs/symptoms of life-threatening arrhythmia, ivosidenib should be permanently discontinued.[10] Increased age increased QTcF, in line with a previous study.[20] Three factors tended to decrease QTcF. Low electrolytes (calcium and magnesium) were an expected factor because low levels of calcium, potassium, and magnesium have been associated with QT interval prolongation.[21,22] Baseline QTcF as an inverse effect could arise from natural regulation of the QT interval as well as regression to the mean. The inverse effect of use of medications with known QT interval prolongation risk could be due to baseline differences in the subpopulations taking these medications, such as an overall higher baseline QTcF.

In conclusion, ivosidenib oral PKs were well described by a two-compartment model with first-order absorption and elimination. No effects of age, body weight, body mass index, sex, race, disease type, and ECOG PS were detected on CL/F. Mild and moderate renal impairment and mild hepatic impairment did not alter the PKs of ivosidenib. Concomitant strong/moderate CYP3A4 inhibitors, but not mild CYP3A4 inhibitors, proton-pump inhibitors, or H_2-receptor antagonists, increased ivosidenib AUC_{ss} to a clinically significant extent. No significant relationship was found between ivosidenib total systemic exposure and efficacy or safety end points. However, a clinically significant direct relationship between ΔQTcF and plasma ivosidenib concentration was observed. Overall, the PK properties of ivosidenib determined in this study support 500 mg q.d. as the regimen that achieves maximum efficacy with acceptable tolerability.

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AUTHOR CONTRIBUTIONS

X.J., R.W., B.P., H.J.K., B.F., G.L., H.L., S.K., H.Y., and K.L. wrote the manuscript. K.L. and R.W. designed the research. R.W., B.P., and H.J.K. and performed the research. R.W., B.P., and H.J.K. analyzed the data.

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