Population pharmacokinetics of ivosidenib (AG-120) in patients with IDH1-mutant advanced hematologic malignancies

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BACKGROUND

- Isocitrate dehydrogenase (IDH) is a critical metabolic enzyme that catalyzes the oxidative decarboxylation of isocitrate to produce alpha-ketoglutarate (α-KG).
- Somatic *IDH1* mutations 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 α-KG to produce the oncometabolite D-2-hydroxyglutarate (2-HG).[5]
- 2-HG accumulation results in the inhibition of α-KG–dependent enzymes, which drives multiple oncogenic processes, including impaired cellular differentiation.[6,7]
- Ivosidenib is a first-in-class, oral, potent, reversible, targeted inhibitor of the mIDH1 protein.[8]
- Ivosidenib is currently being assessed in a phase 1 study of mIDH1 advanced hematologic malignancies, including relapsed or refractory (R/R) AML.[9]
  - On the basis of data from this study, ivosidenib received US FDA approval on July 20, 2018 for the treatment of adult patients with R/R AML with a susceptible IDH1 mutation, as detected by an FDA-approved test.

OBJECTIVES

- To characterize the pharmacokinetics (PK) of ivosidenib in patients with hematologic malignancies, and the effects of patient and disease characteristics and concomitant medications on ivosidenib PK.

METHODS

- The ivosidenib phase 1, open-label, dose escalation and expansion study included evaluations of safety, tolerability, maximum tolerated dose, PK, pharmacodynamics, and clinical activity in patients with advanced hematologic malignancies (NCT02074839).
- Single-agent ivosidenib was administered orally, once daily (QD) or twice daily (BID), in continuous 28-day cycles.
  - During the dose escalation phase, the first three patients enrolled in each cohort received a single dose on Day −3 (prior to start of daily dosing on Cycle 1 Day 1), and samples for PK and pharmacodynamic analysis were collected for up to 72 hr.
- Enrollment is complete, and patients included in this analysis received doses of 100 mg BID, 300 mg, 500 mg, 800 mg, or 1200 mg QD in dose escalation (n=78) and 500 mg QD (n=180) in dose expansion.
  - Samples for PK analysis were available from 253 patients, of whom 223 received ivosidenib 500 mg QD.
  - The data presented here are based on the cutoff date of May 12, 2017.
- Blood samples were collected for determination of ivosidenib concentrations using validated liquid chromatography-tandem mass spectrometry methods.
- Population PK modeling was conducted using the first-order conditional estimation method in NONMEM® Version 7.3.
- 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.
- Model quality was checked by inspection of model parameters and confidence intervals, and standard residual-based and simulation-based diagnostics.
- The sensitivity of the area under the curve (AUC) to covariates was examined by varying covariates one by one to extreme values, and comparing values with the overall range in the study population.
  - Covariates were deemed to be potentially clinically relevant if changes in AUC were >20%.
- The covariates assessed in this population PK model are summarized in **Table 1**, and included demographics, disease characteristics, concomitant cytochrome P450 3A4 (CYP3A4) inhibitors/inducers, and concomitant gastric acid reducers.
  - Voriconazole, fluconazole, and posaconazole were selected as covariates because they had been taken most frequently and are moderate or strong CYP3A4 inhibitors.
  - Pantoprazole and famotidine were selected as the most frequently taken proton-pump inhibitor (PPI) and H2 antagonist, respectively.

Table 1. Baseline covariates included in the model

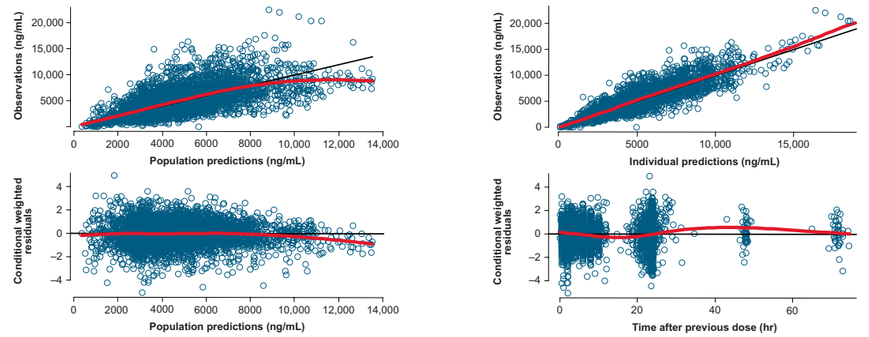
Baseline continuous covariates	Baseline categorical covariates	Concomitant medication	
		Drug	% of samples
Age, years	Sex	Voriconazole	21
Weight, kg	Race	Fluconazole	18
BSA, m^2	NCI hepatic impairment category	Posaconazole	6
CrCl, mL/min	• Normal	Other moderate/strong CYP3A4 inhibitors	6
Albumin, g/L	• Mild	Other mild CYP3A4 inhibitors	24
ALT, U/L	• Moderate	Any CYP3A4 inhibitor	61
AST, U/L	• Severe	Pantoprazole	7
Total bilirubin, μmol/L	• Missing	Other PPI	9
	Cancer type	Any PPI	15
	• R/R AML	Famotidine	4
	• Untreated AML	Other H2 antagonist	1
	• Other	Any H2 antagonist	5
	ECOG performance status		
	• 0		
	• 1		
	• 2		
	• 3		

CYP3A4 inducers were also included as covariates in the analysis plan. However, the CYP3A4 inducers that were used most frequently (dexamethasone and prednisone) are weak inducers and were therefore not selected for covariate analysis
ALT = alanine aminotransferase; AST = aspartate aminotransferase; BSA = body surface area; CrCl = creatinine clearance; ECOG = Eastern Cooperative Oncology Group; NCI = National Cancer Institute

RESULTS

- Ivosidenib PK were best described by a two-compartment model with first-order absorption, dose-dependent bioavailability, and a time-dependent change in relative bioavailability and clearance between Day 1 and steady state.
- Diagnostic plots and parameter estimates for the final population PK model are shown in **Figure 1** and **Table 2**, respectively.
  - Mean steady-state apparent clearance (CL/F) was 5.39 L/hr (between-patient variability ~35%).
  - Mean central volume of distribution (V_c/F) was 234 L (~47%).
- No effects of demographics, disease characteristics, renal function (CrCl), or measures of liver function (ALT, AST, bilirubin, within the range studied) on ivosidenib CL/F were detected.
  - Renal and hepatic conclusions should be interpreted with caution owing to low numbers of patients in the categories of: 1) severe renal impairment and 2) moderate or severe hepatic impairment.
- Baseline body weight had a significant impact on V_c/F, and low albumin at baseline and during treatment correlated with decreased CL/F and V_c/F. However, these effects did not appear to be clinically relevant.
- Less than dose-proportional bioavailability was observed, with a dose doubling from 500 mg to 1000 mg translating to a ~40% increase in exposure.
- Visual predictive checks for the final model are shown in **Figure 2**.
- The effects of all covariates included in the final model on AUC and maximum plasma concentration (C_{max}), varied one by one, are shown in **Figure 3**.
- The effect of patient covariates on steady-state AUC are shown in **Table 3**.
  - Varying the dose from 300 to 800 mg is expected to translate to a change in exposure of –23% and 27%, respectively, compared with the 500 mg QD exposure.
  - The moderate/strong CYP3A4 inhibitors voriconazole, fluconazole, and posaconazole were associated with 36%, 41%, and 35% reductions in CL/F, and hence 57%, 69%, and 53% increases in AUC, respectively.
  - There are insufficient samples to conclusively determine the magnitude of effect of other strong/moderate CYP3A4 inhibitors. The impact of mild CYP3A4 inhibitors is minimal. PPIs and H2 antagonists did not have an effect on exposure.
  - An increase in baseline albumin from 26 to 44 g/L is expected to translate to a decrease in AUC from 34 to –13% of the typical value. Within-patient variation in albumin from baseline (albumin ratio 0.84–1.24) translates to a <20% change in AUC.

Figure 1. Goodness-of-fit plots for the final population PK model



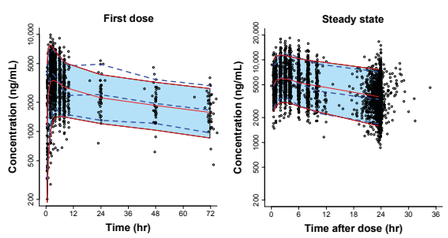
Black lines represent reference lines (line of identity for observations vs predictions plots, y = 0 for conditional weighted residual plots); red lines represent locally weighted smoothing of the data

Table 2. Parameter estimates for the final population PK model

PK parameters	Fixed effect		Between-patient variability		Shrinkage (%)
	Estimate	RSE (%)	CV%	RSE (%)	
Steady-state CL/F, L/hr	5.39	4	35	6	5
Steady-state V_c/F, L	234	7	47	6	11
Steady-state Q/F, L/hr	15.8	19	–	–	–
Steady-state V_p/F, L	151	22	–	–	–
First-dose CL/F, L/hr	1.63	–	–	–	–
First-dose V_c/F, L	71	–	–	–	–
First-dose Q/F, L/hr	4.8	–	–	–	–
First-dose V_p/F, L	46	–	–	–	–
k_a, 1/hr	1.38	10	108	7	32
T_{lag}, hr	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	–	–	–
Wt-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

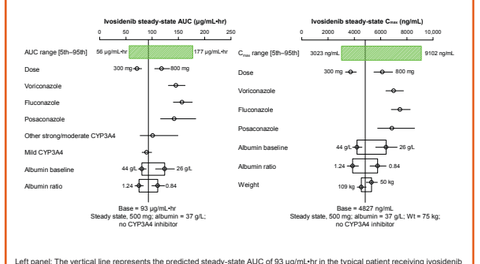
First-dose parameters do not have standard errors as they are derived from steady-state parameters and fold-changes in F_{rel} and/or CL
CL = clearance; CL/F = apparent clearance; CV = coefficient of variation (square root of variance/mean × 100%); F_{rel} = relative bioavailability; k_a = first-order absorption rate constant; 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; Wt = baseline body weight

Figure 2. Prediction-corrected visual predictive check for final model



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 escalation patients and Cycle 1 Day 1 in expansion patients, and because the x-axis represents time after dose, predose samples are plotted at approximately 24 hr

Figure 3. Sensitivity of AUC and C_{max} to covariates and dose



Left panel: The vertical line represents the predicted steady-state AUC of 93 μg/mL•hr in the typical patient receiving ivosidenib 500 mg QD. This patient has albumin levels of 37 g/L, and is not taking a strong/moderate concomitant CYP3A4 inhibitor
Right panel: The vertical line represents the predicted steady-state C_{max} of 4827 ng/mL in the typical patient receiving ivosidenib 500 mg QD. This patient has an albumin level of 37 g/L and weighs 75 kg
Both panels: The green hatched bar shows the 5th to 95th percentile of modelled AUC or C_{max} values across the patient population. The points show the variation in modelled AUC or C_{max} when covariates are changed one at a time to the 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 estimates. Albumin ratio calculated as albumin at a given time divided by baseline albumin (reflects within-patient variability)

Table 3. Factors explaining variability in steady-state AUC

Covariate	AUC estimate (μg/mL•hr)	Covariate effect (% of typical value)
Typical patient receiving 500 mg QD with no concomitant CYP3A4 inhibitors and albumin of 37 g/L	93	–
Clearance		
5th percentile (2.82 L/hr)	177	+91
95th percentile (8.86 L/hr)	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

Albumin ratio calculated as albumin at a given time divided by baseline albumin (reflects within-patient variability)

CONCLUSIONS

- Ivosidenib PK were described by a two-compartment model with first-order absorption.
- Ivosidenib was characterized by less than dose-proportional bioavailability, with a doubling of dose translating to a ~40% increase in exposure.
- Ivosidenib showed a 0.5-fold change in relative bioavailability and a 1.66-fold change in clearance from Day 1 to steady state. The increase in clearance at steady state may be related to autoinduction.
- Concomitant use of moderate and strong CYP3A4 inhibitors was associated with increases in ivosidenib exposure, as measured by AUC.
  - However, the magnitude of CYP3A4 inhibition should be interpreted cautiously given that the dose, regimen, and compliance for these concomitant medications were unknown.
- Decreased baseline albumin was also associated with increased ivosidenib 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. Ivosidenib is not highly protein bound (~90% in human plasma), so albumin binding is not expected to alter ivosidenib clearance. Albumin, however, is a common covariate in population PK models, especially in oncology.[10,11]
- This population PK model of ivosidenib suggests that no dose adjustments are needed on the basis of the range of patient and disease characteristics analyzed.

Acknowledgments

We would like to thank the patients taking part in this study.

Disclosures

This study was funded by Agios Pharmaceuticals, Inc.

KL: Agios – employment and equity ownership; Millennium – patents and royalties. RW: Certara – employment; Agios – consultancy. DD, BF, GL, HL, ECA, SVA, and HY: Agios – employment and equity ownership.

Writing assistance was provided by Helen Varley, PhD, CMMP, Excel Medical Affairs, Horsham, UK, and supported by Agios.

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Presented at the 60th American Society of Hematology (ASH) Annual Meeting, December 1–4, 2018, San Diego, CA, USA