Isocitrate dehydrogenase (IDH) is a critical metabolic enzyme that catalyzes the competitive deamination of isocitrate to produce α-ketoglutarate (α-KG) and NADH. Mutant IDH1 (H39Q) produces highly abundant wild-type isocitrate dehydrogenase (IDH1) and exhibits increased sensitivity to reactive oxygen species.

**BACKGROUND**
- Isocitrate dehydrogenase (IDH) is a critical metabolic enzyme that catalyzes the competitive deamination of isocitrate to produce α-ketoglutarate (α-KG) and NADH.
- Mutant IDH1 (H39Q) produces highly abundant wild-type isocitrate dehydrogenase (IDH1) and exhibits increased sensitivity to reactive oxygen species.

**METHODS**
- The investigators performed a population pharmacokinetic (PK) analysis of ivosidenib (AG-120) in patients with IDH1-mutant hematologic malignancies.
- PK evaluations of safety, tolerability, maximum tolerated dose, PK, pharmacodynamics, and clinical activity in patients with advanced hematologic malignancies.
- A 1-4 compartment model was selected as the PK model for ivosidenib (AG-120).
- The mean ± standard deviation values for the area under the curve (AUC) and maximum plasma concentration (Cmax) were 374 ± 123 ng·h·mL−1 and 96 ± 28 ng·mL−1, respectively.
- Disposition kinetic parameters for ivosidenib (AG-120).

**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.
- Model predictions were compared to the original data.
- AUC and Cmax values for ivosidenib (AG-120) were 374 ± 123 ng·h·mL−1 and 96 ± 28 ng·mL−1, respectively.

**CONCLUSIONS**
- ivosidenib was characterized by a low dose-proportional biocavailability, with a doubling of dose translating to a ~40% increase in exposure.
- ivosidenib showed a 5-fold increase 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.
- The model predictions for steady-state AUC of ivosidenib (AG-120) were 374 ± 123 ng·h·mL−1 and 96 ± 28 ng·mL−1, respectively.

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**References**