Somatic mutations in the metabolic enzyme isocitrate dehydrogenase 1 (IDH1) result in gain-of-function activity, catalyzing the reduction of α-ketoglutarate (α-KG) to the oncometabolite D-2-hydroxyglutarate (2-HG). 2-HG accumulation results in inhibition of α-KG-dependent enzymes, which drives multiple oncogenic processes, including impaired cellular differentiation.10 Mutant IDH1 (miIDH) has been identified in multiple types of solid tumors and hematologic malignancies.11 Ivosidenib (AG-120) is an oral, potent, targeted, small-molecule miIDH inhibitor that has the potential to be the foundation of treatment for miIDH-driven cancers, and is under evaluation in multiple clinical studies of miIDH malignancies.12 Ivosidenib has been well tolerated in all patient populations studied.13 In a phase 1 study, ivosidenib treatment resulted in an overall response rate of 42%, a complete remission (CR) rate of 24%, and a CR+PR with partial hematologic recovery rate of 32% in patients with miIDH1 relapsed or refractory acute myeloid leukemia. – See presentation S1560 Polyea DA et al., Sunday, 17 June, 08:00–08:15. Ivosidenib has also shown activity in patients with solid tumors, including advanced cholangiocarcinoma,14 chondrosarcoma,15 and glioma.16 As ivosidenib is orally administered, it is important to understand the effect on food of the pharmacokinetic (PK) characteristics of ivosidenib and to determine the relative bioavailability of ivosidenib in relation to meal consumption; this is essential for optimal dosing in future clinical trials.

**OBJECTIVE**

To investigate the effect of a high-fat, high-calorie meal on the PK of ivosidenib in healthy subjects.

**METHODS**

**Design**

This was a phase 1, open-label, randomized, two-period crossover study to evaluate the effect of food on ivosidenib PK following administration of a single oral dose of 500 mg in healthy subjects aged 18–55 years (ClinicalTrials.gov NCT02579707).

The study was conducted according to the United States Food and Drug Administration (FDA) 2002 Guidance for Industry “Food Effect Bioavailability and Fed Bioequivalence Studies.”

**Treatment**

Treatments A and B, each comprising a single oral dose of 500 mg ivosidenib, were administered as shown in Table 1. A (fasted): two 250 mg tablets administered after an overnight fast (~10 hr), B (fed): two 250 mg tablets administered after a standardized high-fat breakfast, consumed within 30 min prior to ivosidenib dosing.

The standardized FDA high-fat content meal contains the equivalent of 150 protein calories, ~2500 carbohydrate calories, and ~500–600 fat calories, and comprises two eggs fried in butter, two strips of bacon, two slices of toast with butter, and eight ounces (240 mL) of whole milk.

Of the 30 subjects enrolled, 15 were randomized to sequence AB and 15 were randomized to sequence BA.

**RESULTS**

**Follow-up administration in the high-fat fed and fasted conditions.** 500 mg ivosidenib was readily absorbed, with similar median time to Cmax (Tmax) values of 3.00 and 3.33 hr post dose, respectively (Figure 1).

After reaching Cmax, plasma concentrations slowly declined in a multiphasic manner, with similar mean apparent terminal elimination half-life (t1/2) values of 53.2 hr in the fed condition and 55.4 hr in the fasted condition. A large increase in Cmax was observed in the fed compared with the fasted condition, while the extent of exposure (assessed by mean AUC), and AUCmax was higher following dosing in the fed versus the fasted condition (Table 2).

**Assessments**

- Blood samples for the analysis of ivosidenib concentrations were collected pre-dose and 0.5, 1, 2, 3, 4, 6, 9, 12, 24, 48, 72, 120, 168, 240, 336, and 504 hr post dose.
- Plasma concentrations of ivosidenib were determined using a validated liquid chromatography with tandem mass spectrometry method.
- PK parameters were calculated using WinNonlin (Pharsight Corporation, Version 6.2.1).
- Linear mixed model analysis was performed on natural logarithm-transformed maximum plasma concentrations (Cmax) and area under the plasma concentration-time curve extrapolated to infinity (AUCinf). The analyses were performed using the SAS® MIXED® procedure.
- The geometric mean ratio (fasted vs fed) and their associated 90% CIs for Cmax and AUCinf were calculated to determine whether food had an effect on the PK of ivosidenib.
- Inter-subject variability was determined using the geometric coefficient of variation percent (CV%).
- Incidence of adverse events and serious adverse events was assessed.

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**Figure 1. Mean (±SD) plasma concentrations of ivosidenib over time following a single 500 mg oral dose under fasted and fed conditions**

**Table 1. Treatment sequence**

<table>
<thead>
<tr>
<th>Sequence</th>
<th>Period 1</th>
<th>Washout period</th>
<th>Period 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>AB</td>
<td>500 mg ivosidenib (fasted)</td>
<td>225 days</td>
<td>500 mg ivosidenib (fasted)</td>
</tr>
<tr>
<td>BA</td>
<td>500 mg ivosidenib (fed)</td>
<td>225 days</td>
<td>500 mg ivosidenib (fasted)</td>
</tr>
</tbody>
</table>

**Table 2. Plasma PK parameters of ivosidenib following a single oral dose of 500 mg ivosidenib under fasted and fed conditions**

<table>
<thead>
<tr>
<th>PK parameter</th>
<th>500 mg ivosidenib, fasted n=29</th>
<th>500 mg ivosidenib, fed n=27</th>
</tr>
</thead>
<tbody>
<tr>
<td>AUCinf (hr ng/mL)</td>
<td>136,000 (31.6)</td>
<td>166,000 (31.2)</td>
</tr>
<tr>
<td>Cmax (ng/mL)</td>
<td>143,000 (31.1)</td>
<td>174,000 (31.2)</td>
</tr>
<tr>
<td>Tmax (hr)</td>
<td>2970 (21.3)</td>
<td>4400 (24.3)</td>
</tr>
<tr>
<td>t1/2 (hr)</td>
<td>3.03 (1.00–24.00)</td>
<td>3.00 (1.00–6.00)</td>
</tr>
<tr>
<td>C0 (ng/mL)</td>
<td>55.4 (20.5)</td>
<td>53.2 (18.3)</td>
</tr>
</tbody>
</table>

**Table 3. Statistical summary of the effect of food on ivosidenib PK (n=27)**

<table>
<thead>
<tr>
<th>Comparison</th>
<th>Parameter</th>
<th>Geometric mean ratio (%)</th>
<th>90% CI (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ivosidenib administered in the fed condition (test) versus the fasted condition (reference)</td>
<td>Cmax</td>
<td>197.8</td>
<td>178.7, 218.9</td>
</tr>
<tr>
<td>Ivosidenib administered in the fasted condition</td>
<td>AUCinf</td>
<td>125.6</td>
<td>117.2, 134.6</td>
</tr>
<tr>
<td>Ivosidenib administered in the fed condition (test) versus the fasted condition (reference)</td>
<td>AUCmax</td>
<td>124.3</td>
<td>116.3, 132.9</td>
</tr>
</tbody>
</table>

**CONCLUSIONS**

- Consumption of a high-fat meal prior to dosing had an effect on ivosidenib exposure, with a ~2-fold increase in Cmax and a ~25% increase in AUC. It is recommended that ivosidenib be administered with or without food, however, high-fat meals at time of dosing should be avoided.

**Disclosures**

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**References**