Clinical pharmacokinetics/pharmacodynamics (PK/PD) of ivosidenib in patients with IDH1-mutant advanced hematologic malignancies from a phase 1 study

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BACKGROUND

- Isocitrate dehydrogenase 1 (IDH1) is a critical metabolic enzyme, which catalyzes the conversion of α-KG to produce the oncometabolite D-2-hydroxyglutarate (2-HG).
- IDH1 mutations occur in 6–10% of patients with acute myeloid leukemia (AML).

OBJECTIVES

- Evaluate ivosidenib PK/PD relationships in patients with IDH1-mutant hematologic malignancies.
- Evaluate ivosidenib safety.

METHODS

- This is a phase 1b clinical trial investigating ivosidenib in patients with AML, myelodysplastic syndrome (MDS), and other hematologic malignancies with IDH1/2 mutations.
- Dose escalation to determine the maximum tolerated dose (MTD).
- The recommended phase 2 dose (RP2D) is 500 mg QD.
- Safety assessments, including adverse events, laboratory test results, and vital signs, were evaluated.

RESULTS

- Ivosidenib was rapidly absorbed, with a half-life suitable for QD dosing. Moderate accumulation was observed after multiple dosing, and steady state was achieved within 14 days.
- Data from dose escalation phase, all hematologic malignancies.

CONCLUSIONS

- Ivosidenib was rapidly absorbed, with a half-life suitable for QD dosing. Moderate accumulation was observed after multiple dosing, and steady state was achieved within 14 days.
- Ivosidenib was well tolerated and displayed a favorable safety profile.
- These findings support further development of ivosidenib in patients with IDH1-mutant hematologic malignancies.

Figure 1. Plasma concentrations of ivosidenib over time after a single dose on Day 1 and on Cycle 2 Day 1 after multiple doses.

Figure 2. Nonlinear dose-exposure relationship of ivosidenib after multiple oral doses on Cycle 2 Day 1.

Figure 3. Plasma ivosidenib clearance in the setting of renal and hepatic insufficiency.

Figure 4. Plasma and bone marrow 2-HG inhibition by ivosidenib after lower doses of 80 mg QD.

Figure 5. Plasma 2-HG concentration by visit after oral administration of ivosidenib, by dose category.

Table 1. Ivosidenib plasma PK parameters on Cycle 2 Day 1 after multiple doses of 80 mg QD.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Arm 1</th>
<th>Arm 2</th>
<th>Arm 3</th>
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<tbody>
<tr>
<td>AUC0-tau (ng•hr/mL)</td>
<td>10,400 (40.6)</td>
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</tr>
<tr>
<td>Cmax (ng/mL)</td>
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<td>T1/2 (hours)</td>
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Table 2. Summary statistics for dose expansion by arm and overall.

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Figure 6. Percentage inhibition of 2-HG in plasma and bone marrow versus plasma half-life.