Long-term efficacy and safety of the oral pyruvate kinase activator mitapivat in adults with non–transfusion-dependent alpha- or beta-thalassemia

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OBJECTIVE

To determine the long-term efficacy and safety of mitapivat in adults with non–transfusion-dependent alpha- or beta-thalassemia.

RESULTS

We conducted a phase 2, open-label, randomized, parallel-group, 24-week core period and 10-year extension period study. Patients (N=79) were randomized to mitapivat (N=39) or placebo (N=40). Mitapivat was generally well tolerated, and the safety profile was consistent with that of previously published mitapivat studies. Mean hemoglobin (Hb) increase from baseline during the core period was 1.5 g/dL (95% CI, 0.7 to 2.3 g/dL). Mean Hb change from baseline to Week 60 was 2.0 (SD, 1.5) g/dL.

Table 1. Patient demographics and baseline characteristics for patients who entered the long-term extension period

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Mitapivat (N=11)</th>
<th>Placebo (N=10)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, median (range), years</td>
<td>43 (22–67)</td>
<td>42 (27–69)</td>
</tr>
<tr>
<td>Hb baseline, median (range), g/dL</td>
<td>8.5 (5.6, 9.8)</td>
<td>7.5 (6.0, 8.9)</td>
</tr>
</tbody>
</table>

Figure 1. Proposed mitapivat mechanism of action in thalassemia

A. Glucose

B. Pyruvate

C. Enolase

D. Fumarate

E. Mitapivat

F. ATP

G. PKR

H. RBC-specific form of pyruvate kinase

I. PK

J. RBC, red blood cell

K. 1,3-DPG

L. 2,3-DPG

M. FBP

N. G6P

O. ADP

P. ATP

Q. AMP

R. ADP

S. ADP

T. ADP

U. ADP

V. ADP

W. ADP

X. ADP

Y. ADP

Z. ADP

Table 2. Safety summary for the core and extension periods

<table>
<thead>
<tr>
<th>Event</th>
<th>Mitapivat (N=11)</th>
<th>Placebo (N=10)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Grade  ≥ 3 TEAEs</td>
<td>2 (18.2)</td>
<td>0</td>
</tr>
<tr>
<td>Grade  ≥ 3 TEAEs leading to study drug</td>
<td>1 (9.1)</td>
<td>0</td>
</tr>
<tr>
<td>Grade  ≥ 3 TEAEs leading to discontinuation</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

Figure 2. Mean Hb change from baseline over time

Figure 3. Markers of hematopoiesis and ineffective erythropoiesis

Figure 4. Plot of individual patient BMD by worst DXA T-scores over time

CONCLUSIONS

Mitapivat was generally well tolerated, and the safety profile was consistent with that of previously published mitapivat studies. The long-term results confirm that mitapivat improved markers of Hb response, increased Hb, and reduced reticulocytes in adults with thalassemia. Therefore, mitapivat may be a disease-modifying therapy for thalassemia patients with symptomatic anemia.