A Phase 2a, Open-Label, Dose-Finding Study to Determine the Safety and Tolerability of Sotatercept (ACE-011) in Adults With Beta (β)-Thalassemia: Interim Results

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BACKGROUND

β-thalassemia is characterized by ineffective erythropoiesis leading to anemia, bone marrow enlargement, hypertension, liver and spleen enlargement, and organ failure.

Sotatercept (ACE-011) is a novel and first-in-class type IIA receptor agonist that binds to and activates the activin receptor type II A (ActRIIA) fusion protein that acts on late-stage erythropoiesis to increase the production of mature red blood cells (RBCs) into circulation.

Clinical data in healthy volunteers have shown that treatment with sotatercept results in increased hemoglobin (Hb) level, hematocrit, and red blood cell (RBC) count.

Increased Hb levels have also been reported in patients with multiple myeloma.

A randomization of sotatercept, RAP-011, has shown to be effective in a mouse model of β-thalassemia and further decreases in anemia and increasing levels of Hb, thereby supporting the clinical development of sotatercept in patients with β-thalassemia.

OBJECTIVE

To determine a safe and active dose level of sotatercept in adult patients with β-thalassemia major who are transfusion dependent (TD) defined as any transfusion requirement of ≥ 2 RBCs per 30 days for ≥ 6 months, or patients with non-transfusion dependent (NTD) defined as ≤ 4 RBC units in the 6 months preceding enrollment.

METHODS

Study Design and Treatment

This is an ongoing phase 1a, multicenter, open-label, dose-finding study; interim data are presented.

Patients with either β-thalassemia major or TD or NTD β-thalassemia intermedia were eligible for inclusion in this study.

- 125 ± 15 years of age
- 0.1 mg/kg (n = 5)
- 0.3 mg/kg (n = 5)
- 0.5 mg/kg (n = 5)

Safety

- 0.1 mg/kg
- 0.3 mg/kg
- 0.5 mg/kg

Hb Levels

- Mean increase in Hb levels from baseline for NTD patients increased with increasing dose levels for the 0.1, 0.3, and 0.5 mg/kg cohorts (Figure 3).
- Changes in Hb levels from baseline for individual TD patients treated with sotatercept are presented in Figure 3, demonstrating sustained increases above baseline in the 0.3 and 0.5 mg/kg dose cohorts.
- A greater number of NTD patients achieved an increase in Hb levels of ≥ 1 g/dL (4 patients) and ≥ 2 g/dL (3 patients) at the 0.5 mg/kg dose level, compared with those in the 0.1 mg/kg cohort during the first 3 treatment cycles (Figure 3).

Pharmacokinetics

- Pharmacokinetic parameters for sotatercept are presented in Table 4.
- Pharmacokinetic parameters are characterized by a dose-dependent increase in the area under the curve (AUC) and peak concentration (Cmax).

CONCLUSIONS

Sotatercept was generally well tolerated and was associated with a dose-dependent increase in Hb levels.

DISCUSSION

Based on these preliminary data, sotatercept may be a safe and beneficial option for the treatment of anemia in patients with β-thalassemia.

Figure 4. Mean Change from Baseline in Hb Levels by dose cohort in NTD β-thalassemia Patients Treated With Sotatercept 0.1 mg/kg (A), 0.3 mg/kg (B), and 0.5 mg/kg (C).

Table 4. Pharmacokinetic Parameters of Sotatercept in Patients With β-thalassemia by Days 64 to 84

<table>
<thead>
<tr>
<th>Parameter</th>
<th>0.1 mg/kg</th>
<th>0.3 mg/kg</th>
<th>0.5 mg/kg</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cmax (µg/mL)</td>
<td>1.6 (0.7)</td>
<td>2.8 (1.2)</td>
<td>3.0 (1.0)</td>
</tr>
<tr>
<td>Tmax (days)</td>
<td>6 (3–9)</td>
<td>6 (3–9)</td>
<td>6 (3–9)</td>
</tr>
<tr>
<td>CL/F (L/day)</td>
<td>0.79 (0.4)</td>
<td>1.3 (0.6)</td>
<td>1.5 (0.6)</td>
</tr>
<tr>
<td>V/F (L)</td>
<td>6.94 (45.3)</td>
<td>7.11 (29.5)</td>
<td>7.76 (36.4)</td>
</tr>
<tr>
<td>AUC (µg*days/mL)</td>
<td>1.1 (0.5)</td>
<td>1.5 (0.6)</td>
<td>1.6 (0.9)</td>
</tr>
</tbody>
</table>

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