Longitudinal effect of luspatercept treatment on iron overload and iron chelation therapy in adult patients with β-thalassemia in the BELIEVE trial

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Introduction

- RBC transfusions are the main supportive treatment for chronic anemia due to β-thalassemia
  - Transfusion-dependent patients require ICT to prevent iron overload from RBC transfusions and associated complications
- Thus, there is a clinical need to reduce transfusions and iron burden in patients with anemia due to β-thalassemia
- Luspatercept, a first-in-class erythroid maturation agent, is approved by the US Food and Drug Administration for the treatment of anemia in adult patients with β-thalassemia requiring regular RBC transfusions
- This analysis assessed the effect of long-term luspatercept use on iron loading and ICT use in the phase 3 BELIEVE trial (NCT02604433)

Figure 1. BELIEVE study trial design

Patients with β-thalassemia ≥ 18 years of age, requiring regular RBC transfusions (defined as: 6–20 RBC units in the 24 weeks prior to randomization with no > 35-day transfusion-free period during that time) (N = 336)

Randomized 2:1
- Luspaterceptb 1 mg/kg s.c. every 21 days + BSC (n = 224)
- Placebob s.c. every 21 days + BSC (n = 112)

Double-blind period (48 weeks)

Study unblinding

Open-label (up to 5 years)

Post-treatment follow-up (3 years)

Crossover from placebo to luspatercept permitted (n = 92)

Current study status

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aβ-thalassemia or Hb E / β-thalassemia (compound β-thalassemia with mutation and/or multiplication of α-globin genes was allowed). bPatients could receive RBC transfusions to maintain their baseline Hb level and ICT. cThe trial is fully enrolled and patients continue to receive treatment or follow-up.

Results

Table. Patient baseline characteristics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Luspatercept (N = 224)</th>
<th>Placebo (N = 112)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, median (range), years</td>
<td>30 (18-66)</td>
<td>30 (18-59)</td>
</tr>
<tr>
<td>Female, n (%)</td>
<td>132 (58.9)</td>
<td>63 (56.3)</td>
</tr>
<tr>
<td>Hb (24 weeks), a median (range), g/dL</td>
<td>9.31 (4.5-11.4)</td>
<td>9.15 (5.8-11.7)</td>
</tr>
<tr>
<td>RBC transfusion burden, median (range), units/12 weeks</td>
<td>6.1 (3-14)</td>
<td>6.3 (3-12)</td>
</tr>
<tr>
<td>RBC transfusion burden, median (range), units/24 weeks</td>
<td>14 (6-24)</td>
<td>15 (6-26)</td>
</tr>
<tr>
<td>Splenectomy, n (%)</td>
<td>129 (57.6)</td>
<td>65 (58.0)</td>
</tr>
<tr>
<td>SF, mean (SD), μg/L</td>
<td>2,097 (1,757)</td>
<td>1,845 (1,669)</td>
</tr>
<tr>
<td>LIC, mean (SD), mg/g dw &gt; 3 mg/g dw, n (%)</td>
<td>12.0 (14.8)</td>
<td>10.1 (11.5)</td>
</tr>
<tr>
<td></td>
<td>154 (68.8)</td>
<td>75 (67.0)</td>
</tr>
<tr>
<td>Myocardial iron by T2* MRI, mean (SD), ms</td>
<td>33.5 (16.2)</td>
<td>34.8 (10.7)</td>
</tr>
<tr>
<td>ICT useb,c, n (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Deferasirox</td>
<td>139 (62.3)</td>
<td>63 (57.8)</td>
</tr>
<tr>
<td>Deferiprone</td>
<td>92 (41.3)</td>
<td>40 (36.7)</td>
</tr>
<tr>
<td>Deferoxamine mesylate / deferoxamine</td>
<td>83 (37.2)</td>
<td>39 (35.8)</td>
</tr>
</tbody>
</table>

aDefined as the mean of all documented pre-transfusion Hb values during the 24 weeks prior to first dose for each patient. bDefined as started before the start of study treatment and either ended before the start of the study treatment or continued after study treatment. cAnalyzed using the safety population (luspatercept n = 223, placebo n = 109). dw, dry weight; LIC, liver iron concentration; SD, standard deviation; SF, serum ferritin; T2* MRI, T2-weighted magnetic resonance imaging.
Results (cont.)

Figure 2. Decrease in SF categories baseline ≥ 1,000 μg/L to post-baseline < 1,000 μg/L (A) and baseline ≥ 2,500 μg/L to post-baseline < 2,500 μg/L (B)

Data cutoff: July 1, 2019.

*P* values are estimated from Cochran-Mantel-Haenszel test. SF levels ≥ 1,000 μg/L and ≥ 2,500 μg/L indicate iron overload and increased risk of cardiac-related mortality, respectively.

*Placebo patients evaluated up to Week 48.*
Results (cont.)

Figure 3. Decrease in LIC (A) and myocardial iron T2* categories (B)

Data cutoff: July 1, 2019.

*Placebo patients evaluated up to Week 48.

P values are estimated from Cochran-Mantel-Haenszel test. Patients with LIC ≥ 3 mg/g dw are considered to have iron overload. Myocardial iron T2* < 20 ms indicates increased cardiac risk.

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A  
LIC  
Baseline > 3 mg/g dw to post-baseline ≤ 3 mg/g dw

<table>
<thead>
<tr>
<th></th>
<th>Week 24</th>
<th>Week 48</th>
<th>Week 96</th>
</tr>
</thead>
<tbody>
<tr>
<td>Luspatercept</td>
<td>4.2 (5/120)</td>
<td>6.6 (4/61)</td>
<td>14.3 (15/105)</td>
</tr>
<tr>
<td>Placebo</td>
<td>9.7 (13/134)</td>
<td>5.9 (4/68)</td>
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B  
Myocardial iron T2*  
Baseline ≤ 20 ms to post-baseline > 20 ms

<table>
<thead>
<tr>
<th></th>
<th>Week 48</th>
<th>Week 96</th>
</tr>
</thead>
<tbody>
<tr>
<td>Luspatercept</td>
<td>20.0 (6/30)</td>
<td>25.0 (6/24)</td>
</tr>
<tr>
<td>Placebo</td>
<td>9.1 (1/11)</td>
<td></td>
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</tbody>
</table>
The mean (SD) daily dose of deferasirox in all luspatercept-treated patients at baseline was 1,332.37 mg (1,087.0).

During Weeks 85-96, the mean change (SD) in daily dose of deferasirox from baseline in the luspatercept arm overall (n = 118), responders (n = 32), and non-responders (n = 86) was −189.8 mg (768.5), −201.1 mg (740.2), and −185.6 mg (783.0), respectively.

The mean change (SD) in the luspatercept arm overall at Week 144 (n = 25) was −810.1 mg (1,614.8).

Data cutoff: July 1, 2019.

Only a small number of patients could be evaluated at the later time points due to poor tracking and ICT adherence.

aIncludes only patients initially randomized to receive luspatercept. bResponders are defined as patients achieving ≥ 33% reduction in transfusion burden during Weeks 13-24, with a reduction of ≥ 2 RBC units, versus baseline.
Summary

• A significant number of luspatercept-treated patients with baseline SF ≥ 1,000 μg/L shifted to SF < 1,000 μg/L during the first 48 weeks
• The proportion of patients receiving ≥ 1 ICT gradually declined in both luspatercept responders and non-responders over time up to Week 144
• Both luspatercept responders and non-responders experienced decreases in mean daily dose of deferasirox over time
Acknowledgments

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