Luspatercept Increases Hemoglobin, Reduces Liver Iron Concentration and Improves Quality of Life in Non-Transfusion Dependent Adults with Beta-Thalassemia

Introduction

- β-thalassemia is an inherited anemia due to defective synthesis of β-globin
- Excess unpaired α-globin chains lead to ineffective erythropoiesis characterized by apoptosis of maturing erythroblasts in the bone marrow
- Excess GDF11 and other TGF-β superfamily ligands increase Smad 2/3 signaling and block RBC maturation, resulting in erythroid hyperplasia in the bone marrow

Non-Clincial Studies

- RAP-S36 (murine luspatercept) reduces ineffective erythropoiesis and disease burden in mouse model of β-thalassemia
- RBC Epo-E, CFU-E, Pro-E, Baso E, Poly E, Ortho E, Retic E, RBC
- BFU-E, CFU-E, Pro-E
- Increased EPO levels drive proliferation
- Increased GDF signaling inhibits RBC maturation
- Luspatercept is an investigational drug that is a recombinant fusion protein containing a modified extracellular domain (ECD) of the activin receptor type IB (ActRIB)
- Luspatercept binds to GDF11 and other ligands, inhibits Smad 2/3 signaling, and promotes late-stage erythroid differentiation
- Luspatercept increased hemoglobin levels in healthy volunteers and patients with myelodysplastic syndromes

Methods

- This is an ongoing, Phase 2, multicenter, open-label study in adults with β-thalassemia (data as of 11/16/2016)
- Non-transfusion dependent (NTD): < 4 units/wk, Hb < 10 g/dL
- Transfusion dependent (TD): ≥ 4 units/wk
- Primary efficacy endpoints (over 8 or 12 wk):
  - NTD: Hemoglobin increase ≥ 1.0 or 1.5 g/dL
  - TD: Transfusion burden decrease ≥ 20% or ≥ 50%
- Secondary endpoints include:
  - Safety, liver iron concentration (LIC), health-related quality of life (FACT-An), biomarkers
- Data for TD patients are presented separately (abstract S836)

Study Design

- Dose levels (SC q3 weeks):
  - Base study dose escalation phase (n=35): 0.2, 0.4, 0.6, 0.8, 1.0, and 1.25 mg/kg and expansion cohort (n=29): starting dose 0.8 mg/kg, titration up to 1.25 mg/kg (total n=64)
  - Extension study (n=51): 0.8-1.25 mg/kg
- Follow-up
  - All patients are followed for 2 months post treatment completion or early discontinuation

NTD Patients: Baseline Characteristics

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Base Study N=34</th>
<th>Extension Study N=27</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, yr, median (range)</td>
<td>38.5 (20-62)</td>
<td>37 (23-62)</td>
</tr>
<tr>
<td>Sex, male, n (%)</td>
<td>21 (62%)</td>
<td>17 (63%)</td>
</tr>
<tr>
<td>Splenectomy, n (%)</td>
<td>23 (68%)</td>
<td>18 (67%)</td>
</tr>
<tr>
<td>Hemoglobin, g/dL, median (range)</td>
<td>8.5 (6.5-9.8)</td>
<td>8.7 (7.6-9.8)</td>
</tr>
<tr>
<td>LIC, mg/g dry wt, mean ± SD</td>
<td>5.5 ± 3.8</td>
<td>4.9 ± 3.4</td>
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</tbody>
</table>

NTD Patients: Quality of Life Assessments

- FACT-F is a 13-question patient-reported outcome (PRO) questionnaire (subscore of FACT-An) used to assess anemia related symptoms (e.g., fatigue)
- 9/13 (69%) patients with baseline deficit (<44) improved by ≥ 3 points (proposed minimal clinically important difference) at 24 weeks (last observation carried forward)
- Increase in mean hemoglobin over a 12-wk period correlated with increase in FACT-F (r=0.67, p<0.001)

NTD Patients: Hemoglobin Change

<table>
<thead>
<tr>
<th>Hemoglobin response over a 12 wk period vs 12 wk pre-treatment</th>
<th>Base Study N=22</th>
<th>Extension Study N=27</th>
</tr>
</thead>
<tbody>
<tr>
<td>Increase in mean Hb ≥ 1.0 g/dL</td>
<td>14 (64%)</td>
<td>21 (78%)</td>
</tr>
<tr>
<td>Increase in mean Hb ≥ 1.5 g/dL</td>
<td>8 (36%)</td>
<td>15 (56%)</td>
</tr>
</tbody>
</table>
- Sustained increase in hemoglobin with long term treatment
- Median time to response was 8 days
- Duration of response (change in Hb ≥ 1.0 g/dL) ranged from 113 to 505+ days

Safety Results

- No related serious adverse events in either study
- One grade 3 related adverse event of headache (n=1, extension)
- Reasons for discontinuation in NTD patients included non-compliance (n=2) and prohibited medication, headache, bone pain, lost to follow-up, and patient request (n=1 each)

Summary/Conclusions

- Luspatercept was generally safe and well-tolerated
- Sustained hemoglobin increase was observed in the majority of NTD patients in the higher dose groups and correlated with an improvement in Quality of Life
- Reductions in liver iron concentration were also observed
- These results support further investigation of luspatercept in patients with non-transfusion dependent β-thalassemia
- A Phase 3 study of luspatercept in regularly transfused patients with β-thalassemia is currently enrolling patients (The BELIEVE Study; NCT02604433)

References

3. Platet-Benon et al., EHA 2010 abstract S131
5. MartinPep et al., EHA 2016 abstract S136