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

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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 GDF-11 and other TGF-β superfamily ligands increase Smad 2/3 signaling and block RBC maturation, resulting in erythroid hyperplasia in the bone marrow

Non-Clinical Studies

- Luspatercept is an investigational drug that is a recombinant fusion protein containing a modified extracellular domain of the activin receptor type IIB (ActRIIB)
- Luspatercept binds to GDF-11 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 11Mar2016)
- 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, by MRI), health-related quality of life (FACT-An), biomarkers
- Data for TD patients are presented separately

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, stratified 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>Spleenecotomy, 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>
</tr>
</tbody>
</table>

Baseline (n=64) 3 Months NCT01749540 2 years (ongoing) NCT02268409

NTD Patients: Hemoglobin Change

<table>
<thead>
<tr>
<th>Hemoglobin response over a 12 week period vs baseline</th>
<th>Patients Treated with ≥ 0.6 mg/kg with HB Response, n (%)</th>
</tr>
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<tbody>
<tr>
<td>Base Study N=22</td>
<td>Extension Study N=27</td>
</tr>
<tr>
<td>Increase in mean HB ≥ 1.0 g/dL</td>
<td>Increase in mean HB ≥ 1.5 g/dL</td>
</tr>
<tr>
<td>14 (64%)</td>
<td>8 (36%)</td>
</tr>
<tr>
<td>21 (78%)</td>
<td>15 (56%)</td>
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</table>

NTD Patients: Quality of Life Assessments

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

NTD Patients: Liver Iron Concentration (MRI)

- 60% (3/5) of patients treated for ≥ 6 months with baseline LIC ≥ 5 had decrease in LIC ≥ 2 mg/g dw
- 89% (8/9) patients with baseline LIC < 5 maintained LIC < 5 mg/g dw

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; NCT025604433)

References

1 Suranga R et al., Nature Med 2014
2 Attie, K et al., Am J Hematol 2014
3 Plattebecker U et al., EHA 2010 abstract S131
4 Suranga R et al., Blood, 2014
5 Martinez P et al., EHA 2016 abstract L536