Luspatercept (ACE-536) Increases Hemoglobin and Decreases Transfusion Burden and Serum Ferritin in Adults with Beta-Thalassemia: Preliminary Results from a Phase 2 Study

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**β-Thalassemia**

- β-thalassemia is an inherited anemia due to defective synthesis of the β-globin chains
  - α-globin inclusion bodies contribute to **ineffective erythropoiesis**

  ![Diagram](image)

- Most severe forms require regular RBC transfusions to manage complications
- Iron overload can result in major organ damage, including heart and liver, and death
- Life-long daily iron chelation therapy is often inadequate in preventing iron toxicity
- There are currently no safe and effective alternatives to RBC transfusion

Rund D, Rachmilewitz E, NEJM 2005
• **Ineffective erythropoiesis** is characterized by elevated TGF-β superfamily ligands and Smad 2/3 signaling

• Luspatercept is a recombinant fusion protein containing a modified extracellular domain (ECD) of the activin receptor type IIB (ActRIIB)

• Luspatercept binds to GDF11 and other ligands, inhibits Smad 2/3 signaling, and promotes late-stage erythroid differentiation

Suragani R et al., Nature Med 2014
**RAP-536* Corrects Ineffective Erythropoiesis in β-Thalassemia Mouse Model (Hbb^-/-)**

**Increased RBC**

![Graph showing increased RBC levels with RAP-536 compared to control and TBS groups](image)

<table>
<thead>
<tr>
<th></th>
<th>wt</th>
<th>bthal+TBS</th>
<th>bthal+RAP-536</th>
</tr>
</thead>
<tbody>
<tr>
<td>Erythrocytes (10^6 cells)</td>
<td>9</td>
<td>7</td>
<td><strong>6</strong></td>
</tr>
</tbody>
</table>

### P-values

- **p< 0.001** vs wt
- **p< 0.01** vs bthal + TBS

**Reduced Spleen Size**

![Spleen size comparison](image)

**Improved RBC Morphology**

![RBC morphology images](image)

**Decreased Liver Iron**

![Liver iron images](image)

**Improved Bone Mineral Density**

![Bone mineral density images](image)

*RAP-536 is the murine analog of luspatercept

Suragani R et al., Blood 2014
Study Overview
*Luspatercept β-Thalassemia Phase 2 Clinical Trial*

- A phase 2, multicenter, open-label, dose escalation study in adults with β-thalassemia
- Primary efficacy endpoints:
  - Non-transfusion dependent (NTD)* → Hb increase of ≥ 1.5 g/dL for ≥ 2 weeks
  - Transfusion dependent (TD)** → Transfusion burden decrease ≥ 20% over 12 weeks
- Secondary endpoints:
  - Safety and tolerability
  - PK
  - PD such as liver iron concentration, serum ferritin, and biomarkers of erythropoiesis

Treatment: Luspatercept administered subcutaneously every 3 weeks for 3 months:

- **Screening Period**: Study Week -4
- **BL (Baseline)**: Study Week 0
- **Luspatercept Treatment Period**: Study Weeks 3, 6, 9, 12
- **Follow-up Period**: Study Weeks 16, 20

* NTD = <4 U/8 weeks, hemoglobin < 10 g/dL
** TD = ≥4 U/8 weeks confirmed over 6 months

NCT01749540, EudraCT 2012-002499-15
Study Design
Luspatercept β-Thalassemia Phase 2 Clinical Trial

3 Months Treatment

- Cohort 1: 0.2 mg/kg (N=6)
- Cohort 2: 0.4 mg/kg (N=6)
- Cohort 3: 0.6 mg/kg (N=6)
- Cohort 4: 0.8 mg/kg (N=6)
- Cohort 5: 1.0 mg/kg (N=6)
- Cohort 6: 1.25 mg/kg (N=6)

Expansion Cohort: Individually titrated dose (N=30)

Data from completed cohorts presented
- Completed
- Active

Patients completing base study can enroll into a 12-month extension study

As of 1 Dec 2014
### Baseline Characteristics

**Luspatercept β-Thalassemia Phase 2 Clinical Trial**

<table>
<thead>
<tr>
<th></th>
<th>N=30</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>All Patients</strong></td>
<td></td>
</tr>
<tr>
<td>Age, yr, median (range)</td>
<td>34.5 (20-57)</td>
</tr>
<tr>
<td>Sex, male (%)</td>
<td>16 (53%)</td>
</tr>
<tr>
<td>Splenectomy (%)</td>
<td>25 (83%)</td>
</tr>
<tr>
<td><strong>Non-Transfusion Dependent (NTD)</strong></td>
<td>N= 23 (77%)</td>
</tr>
<tr>
<td>Hemoglobin, g/dL, mean ± SD</td>
<td>8.3 ± 0.9</td>
</tr>
<tr>
<td><strong>Transfusion Dependent (TD)</strong></td>
<td>N=7 (23%)</td>
</tr>
<tr>
<td>RBC Units/12 weeks, mean ± SD</td>
<td>7.3 ± 1.0</td>
</tr>
</tbody>
</table>

Data as of 10 Oct 2014
Safety Summary
Luspatercept β-Thalassemia Phase 2 Clinical Trial

• No related serious adverse events
  – 1 grade 3 dose-limiting toxicity (worsening lumbar spine bone pain)
• 3 patients discontinued early associated with an AE
  – 1 each with occipital headache, ankle pain, and back pain

### Related Adverse Events in ≥5% Patients

<table>
<thead>
<tr>
<th>Preferred Term</th>
<th>0.2 mg/kg (N = 6)</th>
<th>0.4 mg/kg (N = 6)</th>
<th>0.6 mg/kg (N = 6)</th>
<th>0.8 mg/kg (N = 6)</th>
<th>1.0 mg/kg (N = 6)</th>
<th>Overall (N = 30) n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bone pain</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>3</td>
<td>2</td>
<td>6 (20.0%)</td>
</tr>
<tr>
<td>Headache</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>2</td>
<td>5 (16.7%)</td>
</tr>
<tr>
<td>Myalgia</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>1</td>
<td>0</td>
<td>4 (13.3%)</td>
</tr>
<tr>
<td>Asthenia</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3 (10.0%)</td>
</tr>
<tr>
<td>Influenza</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>2</td>
<td>2 (6.7%)</td>
</tr>
<tr>
<td>Macule</td>
<td>2</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>2 (6.7%)</td>
</tr>
<tr>
<td>Pain in Extremity</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>2</td>
<td>0</td>
<td>2 (6.7%)</td>
</tr>
</tbody>
</table>

• No development of antidrug antibodies on treatment

Data as of 10 Oct 2014
Non-Transfusion Dependent Patients
Maximum Hemoglobin Increase in NTD Patients

Luspatercept β-Thalassemia Phase 2 Clinical Trial

Data as of 10 Oct 2014

Proportion of Patients (%)

<table>
<thead>
<tr>
<th>Dose (mg/kg)</th>
<th>≥ 1.5 g/dL</th>
<th>≥ 2.0 g/dL</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.2</td>
<td>17%</td>
<td>0%</td>
</tr>
<tr>
<td>0.4</td>
<td>0%</td>
<td>0%</td>
</tr>
<tr>
<td>0.6</td>
<td>67%</td>
<td>0%</td>
</tr>
<tr>
<td>0.8</td>
<td>67%</td>
<td>20%</td>
</tr>
<tr>
<td>1.0</td>
<td>67%</td>
<td>33%</td>
</tr>
</tbody>
</table>

NTD, Non-transfusion dependent
• Higher doses (0.8-1.0 mg/kg) produced sustained increases in hemoglobin levels

<table>
<thead>
<tr>
<th></th>
<th>0.2-0.6 mg/kg (N=17) n (%)</th>
<th>0.8-1.0 mg/kg (N=6) n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hb increase ≥ 1.5 g/dL for ≥2 weeks (1° endpoint)</td>
<td>0 (0%)</td>
<td>3 (50%)</td>
</tr>
<tr>
<td>Mean Hb increase ≥ 1.5 g/dL for ≥ 9 weeks</td>
<td>0 (0%)</td>
<td>2 (33%)</td>
</tr>
</tbody>
</table>

NTD, Non-transfusion dependent

Data as of 10 Oct 2014
NTD Responder Hemoglobin
Luspatercept β-Thalassemia Phase 2 Clinical Trial

Data as of 10 Oct 2014

NTD, Non-transfusion dependent
Liver Iron Concentration (LIC by MRI) in NTD Patients
Luspatercept β-Thalassemia Phase 2 Clinical Trial

Baseline LIC ≥ 5 mg/g dry weight (dw) (n=12)
• 8/12 patients had a decrease of ≥1 mg/g dw

![Graph showing change in LIC from baseline at 16 weeks for different doses with and without iron chelator.]

NTD, Non-transfusion dependent  Data as of 10 Oct 2014
Transfusion Dependent Patients
Reduced Transfusion Burden in TD Patients

Luspatercept β-Thalassemia Phase 2 Clinical Trial

• 7/7 (100%) patients had >60% reduction in transfusion burden over 12 weeks
• Includes 2 patients with β0β0 genotype (79%, 75% reduction)

*Based on 8 weeks data

TD, Transfusion dependent

Data as of 10 Oct 2014
TD Responder Hemoglobin
Luspatercept β-Thalassemia Phase 2 Clinical Trial

Data as of 10 Oct 2014
Reduced Liver Iron Concentration (MRI) in TD Patients
Luspatercept β-Thalassemia Phase 2 Clinical Trial

Baseline LIC ≥ 5 mg/g dw (n=5)

<table>
<thead>
<tr>
<th>Baseline LIC</th>
<th>Max. % Decr. Ferritin</th>
<th>Change from Baseline at 16 weeks in LIC (mg/g dw)</th>
</tr>
</thead>
<tbody>
<tr>
<td>6.8</td>
<td>-39.7</td>
<td>-2</td>
</tr>
<tr>
<td>7.3</td>
<td>-27.5</td>
<td>-4</td>
</tr>
<tr>
<td>6.5</td>
<td>-59.5</td>
<td>-2</td>
</tr>
<tr>
<td>21.4</td>
<td>-26.5</td>
<td>0</td>
</tr>
<tr>
<td>12.2</td>
<td>-12.3</td>
<td>2</td>
</tr>
</tbody>
</table>

Iron chelation therapy

Data as of 10 Oct 2014
Healing of Leg Ulcers in 2 of 2 Patients

Luspatercept β-Thalassemia Phase 2 Clinical Trial

NTD patient treated at 0.4 mg/kg

TD patient treated at 1.0 mg/kg

Data as of 10 Oct 2014
Conclusions
Luspatercept β-Thalassemia Phase 2 Clinical Trial

- Luspatercept treatment of β-thalassemia patients for 3 months at dose levels of 0.8-1.0 mg/kg demonstrated 75% of patients met the primary efficacy endpoint
  - Increase in hemoglobin ≥ 1.5 g/dL for ≥ 2 weeks in 50% of NTD patients
  - Decrease in RBC transfusion burden > 60% in 100% of TD patients
- Liver iron concentration and serum ferritin decreased in TD and NTD patients
- Rapid healing of leg ulcers was observed in 2 of 2 patients
- The safety profile was favorable with no related serious adverse events
- These data strongly support further evaluation of luspatercept in patients with β-thalassemia
Acknowledgments
Luspatercept β-Thalassemia Phase 2 Clinical Trial

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• **Independent Safety Reviewer:** E Neufeld

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