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

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Background: 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 of Erythroblast and Inclusion Bodies](image)

  - Mutations and deletions, chromosomes 11 (β-thal) and 16 (α-thal)
  - Excess α-globin chain synthesis with reduced β-globin synthesis
  - Inclusion bodies
  - Apoptosis
  - Unpaired α-globin chains form hemichromes

- Transfusion-dependent patients require regular RBC transfusions and iron chelation
- Non-transfusion dependent patients have chronic anemia and long-term complications
- In both, iron overload may result in major organ damage and increased mortality
- Life-long daily iron chelation therapy is often inadequate in preventing iron toxicity
- There are currently no safe and effective alternatives to RBC transfusions for anemia

Rund D, Rachmilewitz E, NEJM 2005
Background: Luspatercept (ACE-536)

Luspatercept
 Modified ECD of ActRIIB receptor
 Fc domain of human IgG1 antibody

- **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)
  - Binds to GDF11 and other ligands, inhibits Smad 2/3 signaling, and promotes late-stage erythroid differentiation\(^1\)
  - Increased hemoglobin levels in healthy volunteer study\(^2\)

\(^1\)Suragani R et al., Nature Med 2014
\(^2\)Attie, K et al.. Am J Hematol 2014
RAP-536 (Murine Analog of Luspatercept) Corrects Ineffective Erythropoiesis in β-Thalassemia Mouse Model (Hbb\(^{-/-}\))

**Increased RBC**

![Graph showing increased RBC levels with significant differences](image)

- wt
- bthal+TBS
- bthal+RAP-536

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

**Reduced Spleen Size**

![Image showing reduced spleen size](image)

**Improved RBC Morphology**

![Images comparing RBC morphology](image)

**Decreased Liver Iron**

![Images showing decreased liver iron](image)

**Improved Bone Mineral Density**

![Images showing improved bone density](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 efficacy endpoints:**
  - Liver iron concentration (MRI), serum ferritin, and biomarkers of erythropoiesis
- **Treatment:**
  - Luspatercept administered subcutaneously every 3 weeks for 3 months
  - Extension study ongoing for additional 12 months treatment

NTD = <4 U/8 weeks, hemoglobin < 10 g/dL
TD = ≥4 U/8 weeks confirmed over 6 months
NCT01749540, EudraCT 2012-002499-15
• **Dose escalation cohorts**: n=35, completed
  - n=3-6/cohort, 0.2 to 1.25 mg/kg
• **Expansion cohort**: as of 8 Jun 2015, 20 of 30 patients enrolled
  - Starting dose 0.8 mg/kg, individual dose titration up to 1.25 mg/kg

• **Preliminary results**: n=39 (dose escalation cohorts n=35, expansion n=4)

<table>
<thead>
<tr>
<th>Dose Level (mg/kg)</th>
<th>Dose Escalation</th>
<th>Expansion</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>0.2</td>
<td>0.4</td>
</tr>
<tr>
<td>No. of patients</td>
<td>6</td>
<td>6</td>
</tr>
</tbody>
</table>

* Starting dose level; dose level increased to 1.0 mg/kg in 2 patients
## Baseline Characteristics

<table>
<thead>
<tr>
<th>All Patients</th>
<th>N=39</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, yr, median (range)</td>
<td>40 (20-57)</td>
</tr>
<tr>
<td>Sex, male, n (%)</td>
<td>19 (49%)</td>
</tr>
<tr>
<td>Splenectomy, n (%)</td>
<td>32 (82%)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Non-Transfusion Dependent (NTD)</th>
<th>N=25 (64%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hemoglobin, g/dL, median (range)</td>
<td>8.4 (6.5-9.6)</td>
</tr>
<tr>
<td>LIC, mg/g dw, mean ± SD</td>
<td>5.8 ± 3.8</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Transfusion Dependent (TD)</th>
<th>N=14 (36%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>RBC Units/12 weeks, median (range)</td>
<td>7.5 (4-12)</td>
</tr>
<tr>
<td>LIC, mg/g dw, mean ± SD</td>
<td>5.2 ± 5.7</td>
</tr>
</tbody>
</table>

LIC = liver iron concentration (by MRI); dw = dry weight
Non-Transfusion Dependent (NTD) Patients
Patients treated with 0.8-1.25 mg/kg experienced sustained increases in hemoglobin levels.

<table>
<thead>
<tr>
<th></th>
<th>0.2-0.6 mg/kg</th>
<th>0.8-1.25 mg/kg</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N=17 n (%)</td>
<td>N=8 n (%)</td>
</tr>
<tr>
<td>Hb increase ≥ 1.5 g/dL for ≥2 weeks</td>
<td>0 (0%)</td>
<td>4 (50%)</td>
</tr>
<tr>
<td>Mean Hb increase ≥ 1.5 g/dL for ≥9 weeks</td>
<td>0 (0%)</td>
<td>3 (38%)</td>
</tr>
</tbody>
</table>

Data as of 10 Apr 2015
Mean Hemoglobin Change in NTD Patients

- Patients treated with 0.8-1.25 mg/kg had greater increase in hemoglobin
Reduction in Liver Iron Concentration (LIC) in NTD Patients with Baseline LIC ≥ 5 mg/g dw

- 8/12 patients with baseline LIC ≥ 5 mg/g dw had decrease ≥ 1 mg/g dw at Month 4

- 10/10 patients with baseline LIC < 5 mg/g dw maintained LIC < 5 mg/g dw

Data as of 10 Apr 2015
Increase in Hemoglobin Correlated with Reduction in Liver Iron Concentration (LIC) in NTD Patients

NTD Patients with Baseline LIC ≥ 5

![Graph showing the relationship between maximum change in hemoglobin and liver iron concentration (LIC). The graph includes a line of best fit with an R² value of 0.3048.]

R² = 0.3048

Data as of 10 Apr 2015
Transfusion Dependent (TD) Patients
Reduction in Transfusion Burden in TD Patients

- 10/14 patients were treated for ≥12 weeks and were evaluable for change in transfusion burden
- All 10 evaluable patients had >40% reduction in transfusion burden over 12 weeks

**Individual Patient Data**

- Baseline transfusion burden: 6-8 units/12 weeks
- Dose levels: 0.6 to 1.25 mg/kg

- - - Protocol-defined reduction for response

Data as of 10 Apr 2015
Reduction in Liver Iron Concentration (LIC) in TD Patients with Baseline LIC ≥ 7 mg/g dw

- 2/3 patients with baseline LIC ≥ 7 mg/g dw had decrease ≥ 1 mg/g dw at Month 4

- 7/7 patients with baseline LIC < 7 mg/g dw maintained LIC < 7 mg/g dw

Data as of 10 Apr 2015
3 of 3 patients with long-term, persistent leg ulcers experienced rapid healing with luspatercept treatment:

- 1 NTD patient at 0.4 mg/kg, experienced complete healing after 6 weeks
- 1 TD patient at 1.0 mg/kg experienced complete healing after 18 weeks

Data as of 10 Apr 2015
Healing of Leg Ulcers in 3 of 3 Patients (2 of 2)

- 1 NTD patient (shown below) at 1.25 mg/kg experienced healing after 5 weeks
Safety Summary

- No related serious adverse events
- 2 patients had related grade 3 adverse events: bone pain (n=2), asthenia (n=1)
- 6/39 (15%) patients discontinued early, associated with an adverse event: headache, ankle pain, back pain, spider nevi, superficial thrombosis, and bone pain

### Related Adverse Events (all grades) in ≥ 5% Patients, n (%)

<table>
<thead>
<tr>
<th>Preferred Term</th>
<th>NTD N=25</th>
<th>TD N=14</th>
<th>Overall N=39</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bone pain</td>
<td>3 (12%)</td>
<td>6 (43%)</td>
<td>9 (23%)</td>
</tr>
<tr>
<td>Myalgia</td>
<td>3 (12%)</td>
<td>4 (29%)</td>
<td>7 (18%)</td>
</tr>
<tr>
<td>Headache</td>
<td>2 (8%)</td>
<td>4 (29%)</td>
<td>6 (15%)</td>
</tr>
<tr>
<td>Asthenia</td>
<td>1 (4%)</td>
<td>3 (21%)</td>
<td>4 (10%)</td>
</tr>
<tr>
<td>Pain in extremity</td>
<td>1 (4%)</td>
<td>2 (14%)</td>
<td>3 (8%)</td>
</tr>
<tr>
<td>Influenza</td>
<td>1 (4%)</td>
<td>1 (7%)</td>
<td>2 (5%)</td>
</tr>
<tr>
<td>Macule</td>
<td>2 (8%)</td>
<td>0</td>
<td>2 (5%)</td>
</tr>
<tr>
<td>Musculoskeletal pain</td>
<td>1 (4%)</td>
<td>1 (7%)</td>
<td>2 (5%)</td>
</tr>
</tbody>
</table>

Data as of 10 Apr 2015
Sustained Response in NTD Patient in Extension Study

Data as of 10 Apr 2015
Conclusions

• 38% of non-transfusion dependent (NTD) patients treated with \( \geq 0.8 \) mg/kg of luspatercept experienced sustained increases in total hemoglobin in this 16-week study.

• The 10 transfusion dependent (TD) patients treated for \( \geq 12 \) weeks each experienced > 40% reduction in transfusion burden.

• A trend for reduction in liver iron concentration (LIC) was observed in the majority of NTD and TD patients, with and without iron chelation therapy.

• Rapid healing of leg ulcers was observed in 3 of 3 patients.

• Luspatercept demonstrated a favorable safety profile with no related serious adverse events.

• Pivotal, controlled, Phase 3 studies of luspatercept in patients with \( \beta \)-thalassemia and myelodysplastic syndromes are planned.
Acknowledgments

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- **Central Labs**: CRL, ICON
- **Independent Safety Reviewer**: E Neufeld
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