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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**β-Thalassemia**

- β-thalassemia is an inherited anemia due to defective synthesis of β-globin
  - Excess unpaired α-globin chains lead to **ineffective erythropoiesis**
- Ineffective erythropoiesis is characterized by expanded RBC proliferation and elevated GDF11 and other TGF-β superfamily ligands and Smad 2/3 signaling

![Erythroid Precursors in Bone Marrow](image)
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![Diagram showing RBC maturation](image-url)
Ineffective Erythropoiesis Drives β-Thalassemia Complications

No approved drug therapy for anemia due to β-thalassemia

- **Luspatercept** is an experimental drug that 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
  - Increased hemoglobin levels in a Phase 1 healthy volunteer study

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**Modified ECD of ActRIIB receptor**

- Fc domain of human IgG1 antibody

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2. Attie, K et al.. Am J Hematol 2014
RAP-536 (Murine Luspatercept) Reduces Ineffective Erythropoiesis and Disease Burden in Mouse Model of β-thalassemia

Luspatercept → Ineffective Erythropoiesis

Anemia/Hemolysis → RBC Transfusions → Iron Overload

- Splenomegaly, EMH Masses, Bone Deformities, Osteoporosis
- Pulmonary Hypertension, Thrombotic events, Leg Ulcers
- Endocrinopathies, Liver disease, Heart Disease

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

- A phase 2, multicenter, open-label, dose escalation study in adults with β-thalassemia
- **Primary efficacy objectives:**
  - Non-transfusion dependent (NTD): Hemoglobin increase ≥ 1.5 g/dL
  - Transfusion dependent (TD): Transfusion burden decrease over 12 wk
- **Secondary objectives:**
  - Safety
  - Liver iron concentration (by MRI)
  - Health-related Quality of Life (SF-36, FACT-An, NTD-PRO)
  - Biomarkers of erythropoiesis

**NTD:** Non-transfusion dependent patients (< 4 Units/8 wk, Hb < 10 g/dL)
**TD:** Transfusion dependent patients (≥ 4 Units/8 wk)
Luspatercept β-Thalassemia Phase 2 Study - Overview

- **Base study (n=64):** Up to 5 doses SC q 3 weeks for 3 months
  - Dose escalation phase (n=35): 0.2, 0.4, 0.6, 0.8, 1.0, 1.25 mg/kg
  - Expansion cohort (n=29): starting dose 0.8, titration up to 1.25 mg/kg
  - 59 patients were efficacy evaluable (5 patients ongoing with <12 weeks treatment)

- **Extension study (n=51):** additional 24 months of treatment

Data as of 25 Sept 2015
Baseline Characteristics

<table>
<thead>
<tr>
<th>Evaluable Patients</th>
<th>N=59</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, yr, median (range)</td>
<td>37 (20-61)</td>
</tr>
<tr>
<td>Sex, male, n (%)</td>
<td>29 (49%)</td>
</tr>
<tr>
<td>Splenectomy, n (%)</td>
<td>41 (70%)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Non-Transfusion Dependent (NTD)</th>
<th>N=31 (53%)</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>5.6 ± 3.8</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Transfusion Dependent (TD)</th>
<th>N=28 (47%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>RBC Units/12 weeks, median (range)</td>
<td>8 (4-18)</td>
</tr>
<tr>
<td>LIC, mg/g dw, mean ± SD</td>
<td>4.5 ± 4.6</td>
</tr>
</tbody>
</table>

**LIC**: liver iron concentration (by MRI); dw: = dry weight

**NTD**: Non-transfusion dependent patients (< 4 Units/8 wk, Hb <10 g/dL)

**TD**: Transfusion dependent patients (≥ 4 Units/8 wk)
EFFICACY: Hemoglobin in NTD Patients with 3 Months Treatment Dose-Dependent Increase

- Mean hemoglobin increased steadily during 3 months of luspatercept treatment and returned to baseline in the absence of treatment during (n=24)
EFFICACY: Hemoglobin in NTD Patients with > 3 Mo Treatment Sustained Improvement

- Increase in mean hemoglobin over a 12-week period in NTD patients treated in the long-term extension study (n=17)
  - 65% (11/17) increased Hb ≥ 1.0 g/dL
  - 47% (8/17) increased Hb ≥ 1.5 g/dL
Efficacy: Reduction in Transfusion Burden, LIC in TD Patients

- Transfusion reduction from 12 weeks pre-treatment to a 12-week period on treatment:
  - 79% (22/28) had ≥ 20% reduction (study primary endpoint)
  - 75% (21/28) had ≥ 33% reduction; 57% (16/28) had ≥ 50% reduction

Data as of 25 Sept 2015

- 5 subjects discontinued before completing 12 weeks

Liver Iron Concentration (LIC): All TD patients received iron chelation therapy
  - 50% (4/8) with baseline LIC ≥ 5 mg/g dw had decrease in LIC ≥ 2 mg/g dw
  - 100% (14/14) with baseline LIC < 5 mg/g dw maintained LIC < 5

* 5 subjects discontinued before completing 12 weeks
Change in Liver Iron Concentration (MRI) at Wk 16 in NTD Patients

- 36% (5/14) with baseline LIC ≥ 5 mg/g dw had decrease in LIC ≥ 2 mg/g dw
- 100% (14/14) patients with baseline LIC < 5 mg/g dw maintained LIC < 5

Data as of 25 Sept 2015
EFFICACY: Quality of Life (SF-36, FACT-An) in NTD Patients Improvement Correlated with Increase in Hemoglobin

- **SF-36** (Short Form 36-item health survey)
  - Patient-Reported Outcome (PRO) survey of health status
  - Physical Component Summary (PCS) sub-score increase correlated with hemoglobin increase at Week 12 and Week 24 (p<0.05)

- **FACT-An** (Functional Assessment of Cancer Therapy – Anemia)
  - PRO assesses fatigue and anemia-related symptoms
  - Anemia subscale (20 items) increase correlated with hemoglobin increase:

  ![Graph showing correlation between hemoglobin change and FACT-An Anemia Score](image)

- **NTD**: Non-transfusion dependent patients (< 4 Units/8 wk, Hb < 10 g/dL)
- Data as of 25 Sept 2015
EFFICACY: Leg Ulcers \(\rightarrow\) Persistent Healing

- 3 patients with long-term, persistent leg ulcers experienced rapid healing with luspatercept treatment
  - 2 additional patients have had partial response
- Sustained healing in a patient treated over 2 years

Pre-Treatment

After 6 Weeks

After 2 Years

Data as of 25 Sept 2015
SAFETY: Summary

- No related serious adverse events
- Related grade 3 adverse events included: headache (n=1), bone pain (n=3), asthenia (n=2), myalgia (n=1)
- 6/59 (10%) patients discontinued early associated with an AE: bone pain (n=2), arthralgia, asthenia, cerebrovascular accident, headache (n=1 each)

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

<table>
<thead>
<tr>
<th>Preferred Term</th>
<th>NTD N=31</th>
<th>TD N=28</th>
<th>Overall N=59</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bone pain</td>
<td>8 (26%)</td>
<td>13 (46%)</td>
<td>21 (36%)</td>
</tr>
<tr>
<td>Myalgia</td>
<td>3 (10%)</td>
<td>8 (29%)</td>
<td>11 (19%)</td>
</tr>
<tr>
<td>Headache</td>
<td>5 (16%)</td>
<td>6 (21%)</td>
<td>11 (19%)</td>
</tr>
<tr>
<td>Arthralgia</td>
<td>3 (10%)</td>
<td>7 (25%)</td>
<td>10 (17%)</td>
</tr>
<tr>
<td>Musculoskeletal pain</td>
<td>4 (13%)</td>
<td>4 (14%)</td>
<td>8 (14%)</td>
</tr>
<tr>
<td>Asthenia</td>
<td>1 (3%)</td>
<td>5 (18%)</td>
<td>6 (10%)</td>
</tr>
<tr>
<td>Injection site pain</td>
<td>1 (3%)</td>
<td>3 (11%)</td>
<td>4 (7%)</td>
</tr>
<tr>
<td>Back pain</td>
<td>1 (3%)</td>
<td>2 (7%)</td>
<td>3 (5%)</td>
</tr>
<tr>
<td>Pain in Jaw</td>
<td>1 (3%)</td>
<td>2 (7%)</td>
<td>3 (5%)</td>
</tr>
</tbody>
</table>

**NTD:** Non-transfusion dependent patients (< 4 Units/8 wk, Hb < 10 g/dL)
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Data as of 25 Sept 2015
Luspatercept β-Thalassemia Phase 2 Study: Conclusions

- Favorable safety profile with no related serious adverse events
- Sustained hemoglobin increases in NTD patients and reduced transfusion burden in TD patients were observed in the majority of patients in the higher dose groups
- Reductions in liver iron concentration (LIC), improvement in Quality of Life scores, and rapid healing of leg ulcers were also observed
- These results support Phase 3 studies of luspatercept in patients with β-thalassemia (BELIEVE)
The BELIEVE Study  
Phase 3 Study of Luspatercept in β-thalassemia

| Patient Population / Study Design | Randomized, double-blind, placebo-controlled study in adult β-thalassemia patients (including HbE/β-thal)  
300 patients, randomized 2:1; luspatercept 1 mg/kg SC every 3 weeks, titration up to 1.25 mg/kg possible |
|-----------------------------------|----------------------------------------------------------------------------------------------------------|
| Key Inclusion Criteria           | Patients who receive 6-20 units of RBCs over past 24 weeks and no transfusion-free period ≥ 35 days (regularly transfused patients)  
No ESA or hydroxyurea |
| Primary Efficacy Endpoint        | Proportion of patients with ≥ 33% reduction in transfusion burden from weeks 13-24 compared to the 12 weeks preceding treatment |

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Luspatercept β-Thalassemia Phase 2 Study: Acknowledgments

- **Investigators:** A Piga, A Melpignano, S Perrotta, C Borgna-Pignatti, MR Gamberini, V Caruso, E Voskaridou, A Filosa, A Pietrangelo

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- **Independent Safety Reviewer:** E Neufeld

*Sponsored by Acceleron Pharma and Celgene*