Luspatercept Decreases Transfusion Burden and Liver Iron Concentration in Regularly Transfused Adults with Beta-Thalassemia

Antonio G. Piga, MD\textsuperscript{1}, Silverio Perrotta, MD\textsuperscript{2}, Angela Melpignano, MD\textsuperscript{3}, Caterina Borgna-Pignatti, MD\textsuperscript{4}, M. Rita Gamberini, MD\textsuperscript{4}, Ersi Voskaridou, MD\textsuperscript{5}, Vincenzo Caruso, MD\textsuperscript{6}, Paolo Ricchi, MD\textsuperscript{7}, Antonello Pietrangelo, MD\textsuperscript{8}, Xiaosha Zhang\textsuperscript{9}, Dawn M. Wilson\textsuperscript{9}, Ashley Bellevue\textsuperscript{9}, Abderrahmane Laadem, MD\textsuperscript{10}, Matthew L. Sherman, MD\textsuperscript{9} and Kenneth M. Attie, MD\textsuperscript{9}

\textsuperscript{1}Turin University, Turin, \textsuperscript{2}Second University of Naples, Naples, \textsuperscript{3}Ospedale "A. Perrino", Brindisi, \textsuperscript{4}Arcispedale S.Anna, Cona, Ferrara, Italy; \textsuperscript{5}Laiko General Hospital, Athens, Greece; \textsuperscript{6}ARNAS Garibaldi, Catania, \textsuperscript{7}AORN "A. Cardarelli“, Naples, Italy; \textsuperscript{8}CEMEF, Medicina 2, Modena, Italy; \textsuperscript{9}Acceleron Pharma, Cambridge, MA, USA; \textsuperscript{10}Celgene Corporation, Summit, NJ, USA.
β-Thalassemia

- 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

*Image of erythroid precursors in bone marrow with unpaired α-globin chains forming hemichromes and inclusion bodies, leading to apoptosis.*

*Source: Rund D, Rachmilewitz E, NEJM 2005*
β-Thalassemia

- 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

---

**Increased EPO levels** drive proliferation

**Increased GDF signaling** inhibits RBC maturation
Ineffective Erythropoiesis Drives β-Thalassemia Complications

Ineffective Erythropoiesis

Anemia/Hemolysis
- Splenomegaly, EMH Masses, Bone Deformities, Osteoporosis

RBC Transfusions
- Pulmonary Hypertension, Thrombotic events, Leg Ulcers

Iron Overload
- Endocrinopathies, Liver disease, Heart Disease

Iron chelation

No approved drug therapy for anemia due to β-thalassemia
Luspatercept Reduces Promotes Late-Stage Erythropoiesis and Reduces Disease Burden in Mouse Model of β-Thalassemia

- Luspatercept is an investigational 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 erythropoiesis
  - RAP-536 (murine luspatercept) reduced disease burden in mouse model of β-thalassemia
  - Increased hemoglobin levels in healthy volunteers and patients with myelodysplastic syndromes

Suragani R et al., Blood, 2014
Attie, K et al., Am J Hematol, 2014
Platzbecker U et al., EHA 2016, S131
Luspatercept β-Thalassemia Phase 2 Clinical Trials – Overview

- A phase 2, multicenter, open-label, study in adults with β-thalassemia
  - Non-transfusion dependent (NTD): < 4 units/8 wk and Hb < 10 g/dL
  - Transfusion dependent (TD): ≥ 4 units/8 wk

- Primary efficacy endpoints (over 8 or 12 wk)
  - TD: Transfusion burden decrease ≥ 20% or ≥ 50%
  - NTD: Hemoglobin increase ≥ 1.0 or ≥1.5 g/dL

- Secondary endpoints include:
  - Safety
  - Liver iron concentration (by MRI)
  - Health-related Quality of Life (FACT-An)
  - Biomarkers of erythropoiesis
Luspatercept Phase 2 Clinical Trials: Design

Dose-finding (Base) Study (n=64) 3 Months
NCT01749540

- TD: n=30
- NTD: n=34

Extension Study (n=51) → 2 years (ongoing)
NCT02268409

- TD: n=24
- NTD: n=27

Dose levels (administered 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
## Baseline Characteristics of Transfusion Dependent Patients

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Base Study</th>
<th>Extension Study</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Parameter</strong></td>
<td>N=30</td>
<td>N=24</td>
</tr>
<tr>
<td>Age, yr, median (range)</td>
<td>37.5 (21-54)</td>
<td>37.5 (22-55)</td>
</tr>
<tr>
<td>Sex, male, n (%)</td>
<td>12 (40%)</td>
<td>12 (50%)</td>
</tr>
<tr>
<td>Splenectomy, n (%)</td>
<td>20 (67%)</td>
<td>16 (67%)</td>
</tr>
<tr>
<td>RBC Units/12 weeks, median (range)</td>
<td>8 (4-18)</td>
<td>8 (4-15)</td>
</tr>
<tr>
<td>Liver iron concentration (LIC), mg/g dry wt, mean ± SD (n=29)</td>
<td>4.9 ± 5.4</td>
<td>5.1 ± 5.3</td>
</tr>
<tr>
<td>Duration of treatment, weeks (range)</td>
<td>--</td>
<td>6-71 (ongoing)</td>
</tr>
</tbody>
</table>
Reduction in Transfusion Burden

- Transfusion reduction from 12 weeks pre-treatment to any 12-wk period on treatment

<table>
<thead>
<tr>
<th>% Reduction in RBC Units Transfused</th>
<th>Patients with Reduction in Transfusion Burden, n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Base Study N=30</td>
</tr>
<tr>
<td>20% reduction</td>
<td>24 (80%)</td>
</tr>
<tr>
<td>33% reduction</td>
<td>20 (67%)</td>
</tr>
<tr>
<td>50% reduction</td>
<td>16 (53%)</td>
</tr>
</tbody>
</table>
Reduction in Transfusion Burden in Patients in Extension Study

- Transfusion reduction from 12 weeks pre-treatment to any 12-wk period on treatment
- Duration of ≥ 33% reduction ranged from 12 to 48+ weeks

Baseline Units/12 Wks:

<table>
<thead>
<tr>
<th>Units/12 Wks</th>
<th>Baseline</th>
<th>14</th>
<th>15</th>
<th>12</th>
<th>12</th>
<th>8</th>
<th>7</th>
<th>7</th>
<th>8</th>
<th>9</th>
<th>7</th>
<th>5</th>
<th>6</th>
<th>6</th>
<th>7</th>
<th>8</th>
<th>8</th>
<th>8</th>
<th>8</th>
<th>8</th>
<th>8</th>
<th>6</th>
<th>8</th>
<th>8</th>
<th>6</th>
<th>4</th>
</tr>
</thead>
<tbody>
<tr>
<td>% Change in RBC Units Transfused</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>0</td>
<td>-10</td>
<td>-20</td>
<td>-30</td>
<td>-40</td>
<td>-50</td>
<td>-60</td>
<td>-70</td>
<td>-80</td>
<td>-90</td>
<td>-100</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* 1 subject discontinued before completing 12 weeks, not shown
Change in Liver Iron Concentration (MRI) in TD Patients

- ~50% patients with baseline LIC ≥ 5 mg/g dw achieved ≥ 2mg/g dw
Safety Summary – Adverse Events in TD Patients

- No related serious adverse events
- Related grade 3 adverse events included: bone pain (n=2 base, n=1 extension), asthenia (n=2 base) and myalgia (n=1 extension)
- Favorable safety profile for luspatercept in patients with β-thalassemia was maintained in long-term extension study

<table>
<thead>
<tr>
<th>Preferred Term</th>
<th>Related AEs (all grades) in &gt;10% TD Patients, n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Base Study N=30</td>
</tr>
<tr>
<td>Bone pain</td>
<td>15 (50%)</td>
</tr>
<tr>
<td>Myalgia</td>
<td>8 (27%)</td>
</tr>
<tr>
<td>Arthralgia</td>
<td>6 (20%)</td>
</tr>
<tr>
<td>Headache</td>
<td>6 (20%)</td>
</tr>
<tr>
<td>Asthenia</td>
<td>5 (17%)</td>
</tr>
<tr>
<td>Musculoskeletal pain</td>
<td>4 (13%)</td>
</tr>
</tbody>
</table>

TD: Transfusion dependent patients (≥ 4 Units/8 wk)
Luspatercept in Transfusion-Dependent β-Thalassemia

- Luspatercept was generally safe and well-tolerated with no related serious adverse events
- Reduced transfusion burden was observed in the majority of TD patients
- Reductions in liver iron concentration (LIC) were also observed in patients on iron chelators with elevated LIC at baseline
- These results supported the initiation of a Phase 3 study of luspatercept in TD patients with β-thalassemia (The BELIEVE Study, NCT02604433)
The BELIEVE Study
Phase 3 Study of Luspatercept in β-thalassemia: NOW ENROLLING

| 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 Eligibility 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 |

Sponsored by Celgene in collaboration with Acceleron
NCT02604433
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, P Ricci, A Pietrangelo
- **Sub-investigators:** I Alasia, M Limone, E Longoni, F Della Rocca, U Pugliese, I Tartaglione, L Manfredini, A Quarta, G Abbate, S Anastasi, R Lisi, M Casale, P Cinque, S Costantini, M Marsella, P Ricchi, A Spasiano
- **Acceleron:** K Attie, M Sherman, D Wilson, A Bellevue, C Rovaldi, B O’Hare, T Akers, X Zhang, J Desiderio, S Ertel, T Sacco
- **Celgene:** A Laadem, S Ritland, J Zou, N Chen
- **Chiltern:** C Lanza, F Van der Schueren, M Belfiore
- **Central Labs:** CRL, ICON, ILS
- **Independent Safety Reviewer:** E Neufeld

*Sponsored by Acceleron Pharma and Celgene*