Improvements in Hemoglobin, Quality of Life, and Six-Minute-Walk Distance in Adults with β-Thalassemia Treated with Luspatercept: Long-Term Phase 2 Study

Antonio Piga, MD¹, Immacolata Tartaglione, MD², Rita Gamberini, MD³, Ersi Voskaridou, MD⁴, Angela Melpignano, MD⁵, Paolo Ricchi, MD⁶, Vincenzo Caruso, MD⁷, Antonello Pietrangelo, MD⁸, Joseph Reynolds⁹, Carolyn Barron⁹, Xiaosha Zhang⁹, Abderrahmane Laadem, MD¹⁰, Peter G. Linde, MD⁹, and Matthew L. Sherman, MD⁹

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

- β-thalassemia is an inherited anemia characterized by an erythroid maturation defect (EMD) and impaired synthesis of β-globin
  - An excess of unpaired α-globin chains leads to **ineffective erythropoiesis**, due to increased apoptosis of maturing erythroblasts in the bone marrow

Rund D, Rachmilewitz E, NEJM 2005
An Erythroid Maturation Defect Drives β-Thalassemia Complications

An Erythroid Maturation Defect Drives β-Thalassemia Complications

Luspatercept

Ineffective erythropoiesis/EMD

EMH masses, bone deformities, osteoporosis

EMH: erythroid maturation defect; EMH: extramedullary hematopoiesis; RBC: red blood cell

Anemia/hemolysis

Splenomegaly, pulmonary hypertension, thrombotic events, leg ulcers, fatigue

Iron overload

Endocrinopathies, liver disease, heart disease

RBC transfusions

Iron chelation

Iron overload

EMD: erythroid maturation defect; EMH: extramedullary hematopoiesis; RBC: red blood cell
Luspatercept Promotes Late-Stage Erythropoiesis

Luspatercept enhances RBC precursor differentiation

EPO-dependent

Luspatercept-responsive

Hemoglobin (Hb)

BFU-E  CFU-E  Pro-E  Baso-E  Poly-E  Ortho-E  Reticulocyte  Red blood cells (RBCs)

Luspatercept enhances RBC precursor differentiation

EPO: erythropoietin
Luspatercept Structure and Activity in β-Thalassemia

- Modified activin receptor type IIB (ActRIIB) fusion protein
- Ligand trap for TGF-β superfamily ligands (e.g., GDF11) to reduce aberrant Smad2/3 signaling; increased hemoglobin in healthy volunteers.\(^1\)
- The murine analog RAP-536 promoted late-stage erythropoiesis, increased hemoglobin, and reduced disease burden, in a murine model of β-thalassemia.\(^2\)

GDF: growth and differentiation factor; TGF: transforming growth factor

\(^1\)Attie K et al., Am J Hematol 2014
\(^2\)Suragani R et al., Nature Med 2014
Luspatercept Clinical Trials in Thalassemia
Luspatercept β-Thalassemia Phase 2 Clinical Trials: Overview

A Phase 2, multicenter, open-label, 3-month dose-escalation study in adults with β-thalassemia, followed by a 5-year extension study

<table>
<thead>
<tr>
<th>Base Study (N=64)</th>
<th>Extension Study (N=51)</th>
</tr>
</thead>
<tbody>
<tr>
<td>3 months (completed)</td>
<td>5 years (ongoing)</td>
</tr>
<tr>
<td>NCT01749540</td>
<td>NCT02268409</td>
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</table>

**Eligibility**
- Non-transfusion-dependent (NTD): < 4 units RBCs/8 weeks and Hb < 10 g/dL
- Transfusion dependent (TD): ≥ 4 units RBCs/8 weeks

**Efficacy Endpoints**
- NTD: Hemoglobin increase ≥ 1.0 g/dL; ≥ 1.5 g/dL
- TD: Transfusion burden reduction ≥ 20%; ≥ 50%

**Treatment**
- Luspatercept 0.2 – 1.25 mg/kg (base study); 0.8 – 1.25 mg/kg (extension) SC q3 weeks
- All patients followed up for 3 years post last dose or early discontinuation

**Other Endpoints**
- Safety
- Liver iron concentration
- Health-related quality of life
## Demographics and Baseline Characteristics

<table>
<thead>
<tr>
<th>Parameter</th>
<th>N=63</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, yr, median (range)</td>
<td>38 (20-62)</td>
</tr>
<tr>
<td>Sex, male, n (%)</td>
<td>33 (52)</td>
</tr>
<tr>
<td>Splenectomy, n (%)</td>
<td>42 (67)</td>
</tr>
<tr>
<td><strong>NTD patients</strong></td>
<td></td>
</tr>
<tr>
<td>Hemoglobin, g/dL, median (range)</td>
<td>8.5 (6.5-9.8)</td>
</tr>
<tr>
<td>Liver iron conc., mg/g dry wt, mean ± SD</td>
<td>5.1 ± 3.6</td>
</tr>
<tr>
<td><strong>TD patients</strong></td>
<td></td>
</tr>
<tr>
<td>RBC units/12 weeks, median (range)</td>
<td>8 (4-18)</td>
</tr>
<tr>
<td>Liver iron conc., mg/g dry wt, mean ± SD</td>
<td>4.7 ± 4.7</td>
</tr>
</tbody>
</table>

Patients treated at dose levels ≥ 0.6 mg/kg

NTD = non-transfusion dependent; TD = transfusion dependent; SD = standard deviation
Efficacy in Non-Transfusion-Dependent (NTD) Patients
## Increase in Hemoglobin in NTD Patients

<table>
<thead>
<tr>
<th>Hemoglobin ≥ 1.0 g/dL</th>
<th>Any 12-week Interval n/N (%)</th>
<th>Fixed Interval 13-24 Weeks n/N (%)</th>
<th>Fixed Interval 37-48 Weeks n/N (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>22/31 (71%)</td>
<td>16/30 (53%)</td>
<td>16/30 (53%)</td>
<td></td>
</tr>
<tr>
<td>Hemoglobin ≥ 1.5 g/dL</td>
<td>17/31 (55%)</td>
<td>12/30 (40%)</td>
<td>8/30 (27%)</td>
</tr>
</tbody>
</table>

Patients treated at dose levels ≥ 0.6 mg/kg

Hemoglobin response over a 12-week interval on treatment vs baseline Baseline: average of at least 2 values within 7-28 days prior to first dose

Data as of 06 Apr 2018
Sustained Increase in Hemoglobin in NTD Patients

- Median duration of treatment (N=31): 29.4 months (range 1.3-41.2 months; ongoing)
Improvement in Quality of Life in Symptomatic NTD Patients
Treated at Dose Levels ≥ 0.6 mg/kg

FACIT-F is a validated 13-question patient-reported outcome (PRO) questionnaire used to assess anemia-related symptoms such as fatigue and weakness.¹

- 6/7 (86%) patients had an increase in mean hemoglobin over a 12-week period of ≥ 1.0 g/dL and had an increase in FACIT-F score ≥ 3 points
- 7/12 (58%) patients with baseline FACIT-F deficit (<44 points) improved by ≥ 3 points at 48 weeks

¹Cella D, et al, Cancer 2002
Six-Minute-Walk Test and Hemoglobin in NTD Patients Treated at Dose Levels ≥ 0.6 mg/kg

At week 48, a statistically significant improvement from baseline in 6MWD was seen in NTD pts (n=9):
- Mean (SD) baseline 408 (68) meters vs 484 (121) meters at week 48, p=0.02.
Efficacy in Transfusion-Dependent (TD) Patients
Reduction in Transfusion Burden in TD Patients – Rolling

<table>
<thead>
<tr>
<th>Reduction in RBC Units Transfused</th>
<th>Any 12-Week Interval n/N (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>≥ 20% reduction</td>
<td>25/32 (78%)</td>
</tr>
<tr>
<td>≥ 33% reduction</td>
<td>22/32 (69%)</td>
</tr>
</tbody>
</table>

Patients treated at dose levels ≥ 0.6 mg/kg

- Transfusion reduction from 12 weeks pre-treatment to any 12-week interval on treatment
Reduction in Transfusion Burden in TD Patients

- Median duration of treatment (N=32): 14.2 months (range 0.7-38.9 months; ongoing)

- Patients treated at dose levels ≥ 0.6 mg/kg

- Transfusion reduction from 12 weeks pre-treatment to any 12-week interval on treatment

*6 patients discontinued before completing 12 weeks, not shown
Reduction in Transfusion Burden in TD Patients - Fixed

<table>
<thead>
<tr>
<th>Reduction in RBC Units Transfused</th>
<th>Fixed Interval 13-24 Weeks n/N (%)</th>
<th>Fixed Interval 37-48 Weeks n/N (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>≥ 33% Reduction</td>
<td>12/29 (41%)</td>
<td>12/29 (41%)</td>
</tr>
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</table>

Treated at dose levels ≥ 0.6 mg/kg

3 patients excluded who did not participate in the long-term extension study

- Transfusion reduction from 12 weeks pre-treatment to fixed 12-week intervals on treatment
Change in Liver Iron Concentration (MRI) in TD Patients
Baseline Compared to ≥4 Months

LIC Change from Baseline (mg/g dw)

Moderate/Severe Iron Overload (Baseline LIC >3)
Mild Iron Overload (Baseline LIC <3)

Treated at dose levels ≥ 0.6 mg/kg

Iron Chelator Therapy
No Iron Chelator Therapy

Data as of 06 Apr 2018
Safety Summary – Adverse Events in All Patients

- Majority of AEs grades 1 or 2
  - Related grade 3 adverse events: bone pain (n=3 patients), asthenia (n=2 patients), bone infarction (n=1 patient), headache (n=1 patient), presyncope (n=1 patient)
  - One possibly related serious adverse event of biliary colic
- Favorable safety profile maintained with long-term treatment

<table>
<thead>
<tr>
<th>Preferred Term</th>
<th>Possibly or Probably Related AEs in ≥ 10% Patients, Any Grade, n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bone pain</td>
<td>24 (38%)</td>
</tr>
<tr>
<td>Headache</td>
<td>18 (28%)</td>
</tr>
<tr>
<td>Myalgia</td>
<td>14 (22%)</td>
</tr>
<tr>
<td>Arthralgia</td>
<td>12 (19%)</td>
</tr>
<tr>
<td>Musculoskeletal pain</td>
<td>10 (16%)</td>
</tr>
<tr>
<td>Asthenia</td>
<td>9 (14%)</td>
</tr>
<tr>
<td>Injection site pain</td>
<td>9 (14%)</td>
</tr>
<tr>
<td>Back pain</td>
<td>7 (11%)</td>
</tr>
</tbody>
</table>

N=64, all patients treated at all dose levels
Conclusions - Luspatercept in Adults with β-Thalassemia

- Luspatercept was generally safe and well-tolerated at dose levels up to 1.25 mg/kg

- Clinical improvements are consistent with hematological improvements
  - Increased hemoglobin levels in NTD patients correlated with improved quality of life and 6-minute-walk distance
  - Sustained reduction in transfusion burden in TD patients was associated with reduction in liver iron concentration (LIC) in patients with elevated baseline LIC
Luspatercept β-Thalassemia Phase 2 Study: Acknowledgments

- **Co-investigators:** S Perrotta, C Borgna-Pignatti, M Dimopoulou, F Longo, A Filosa, B Vania, M Zenone, S Mercurio, F Della Rocca, U Pugliese, L Manfredini, A Quarta, G Abbate, S Anastasi, R Lisi, M Casale, P Cinque, S Costantini, M Marsella, A Spasiano

- **Acceleron:** C Rovaldi, J Oram, T Akers, B O’Hare, S Harrison, J Desiderio

- **Celgene:** J Zou, N Chen

- **Chiltern:** C Lanza, F Van der Schueren, M Belfiore

- **Independent Safety Reviewer:** E Neufeld

*Study sponsored by Celgene in collaboration with Acceleron Pharma*
Luspatercept Clinical Trials in Thalassemia

- Phase 2 base and extension studies in NTD/TD b-thalassemia (NCT01749540/NCT02268409) - **Focus of this presentation**
- Phase 3 BELIEVE randomized double-blind study in TD b-thalassemia (NCT02604433) - **Top-line results mid 2018**
- Phase 2 BEYOND randomized double-blind study in NTD b-thalassemia (NCT03342404) - **Ongoing**