Luspatercept Increases Hemoglobin, Decreases Transfusion Burden, and Improves Patient-Reported Outcomes in Adults with Beta-Thalassemia

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β-Thalassemia

- β-thalassemia is an inherited anemia due to defective synthesis of β-globin
  - An excess of unpaired α-globin chains leads to **ineffective erythropoiesis**, characterized by apoptosis of maturing erythroblasts in the bone marrow

Rund D, Rachmilewitz E, NEJM 2005
Ineffective Erythropoiesis Drives β-Thalassemia Complications

Luspatercept?

Ineffective erythropoiesis → Anemia/hemolysis → Iron overload

- EMH masses, bone deformities, osteoporosis
- Splenomegaly, pulmonary hypertension, thrombotic events, leg ulcers, fatigue
- Endocrinopathies, liver disease, heart disease

RBC transfusions → Iron chelation
Luspatercept is a modified activin receptor type IIB (ActRIIB) fusion protein

- Acts as a ligand trap for GDF11 and other TGF-β family ligands to suppress Smad2/3 signaling; increased hemoglobin in healthy volunteers.\(^1\)
- In a murine model of β-thalassemia, murine analog RAP-536 promoted late-stage erythropoiesis, increased hemoglobin, and reduced disease burden.\(^2\)

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 Promotes Late-Stage Erythropoiesis

Ineffective erythropoiesis in β-thalassemia

Increased EPO levels drive proliferation

Increased GDF signaling inhibits RBC maturation

Luspatercept promotes late-stage erythropoiesis

Luspatercept neutralizes ligands that block RBC precursor differentiation
CLINICAL TRIALS in THALASSEMIA
Luspatercept β-Thalassemia Phase 2 Clinical Trials: Overview

- **Phase 2, multicenter, open-label studies in adults with β-thalassemia**
  - Non-transfusion dependent (NTD): <4 units/8 weeks and Hb < 10 g/dL
  - Transfusion dependent (TD): ≥4 units/8 weeks

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

- **Other endpoints**
  - Safety
  - Liver iron concentration (by MRI)
  - Health-related quality of life (FACT-An)
Luspatercept Phase 2 Clinical Trials: Design

- **Base Study (N=64)**
  - 3 Months
  - 3 Months
  - **NCT01749540**

- **Extension Study (N=51)**
  - Up to 5 years (ongoing)
  - **NCT02268409**

**Dose Levels**

- **Dose escalation cohorts:**
  - 0.2-1.25 mg/kg
  - SC every 3 weeks

- **Expansion cohort:**
  - 0.8-1.25 mg/kg
  - SC every 3 weeks

**Dose Levels**

- **Extension study:**
  - 0.8-1.25 mg/kg
  - SC every 3 weeks
# Baseline Characteristics

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Base Study N=64</th>
<th>Extension Study N=51</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, yr, median (range)</td>
<td>38.5 (20-62)</td>
<td>37.0 (22-62)</td>
</tr>
<tr>
<td>Sex, male, n (%)</td>
<td>33 (52)</td>
<td>29 (57)</td>
</tr>
<tr>
<td>Splenectomy, n (%)</td>
<td>43 (67)</td>
<td>34 (67)</td>
</tr>
<tr>
<td><strong>NTD patients (n)</strong></td>
<td>33</td>
<td>27</td>
</tr>
<tr>
<td>Hemoglobin, g/dL, median (range)</td>
<td>8.5 (6.5-9.8)</td>
<td>8.7 (7.6-9.8)</td>
</tr>
<tr>
<td>Liver iron conc., mg/g dry wt, mean ± SD</td>
<td>5.4 ± 3.8</td>
<td>5.1 ± 3.8</td>
</tr>
<tr>
<td><strong>TD patients (n)</strong></td>
<td>31</td>
<td>24</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 conc., mg/g dry wt, mean ± SD</td>
<td>5.0 ± 5.3</td>
<td>4.9 ± 5.0</td>
</tr>
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</table>

Data as of 02 Sep 2016
Efficacy in Non-Transfusion-Dependent (NTD) Patients
Increase in Hemoglobin in NTD Patients

- Hemoglobin response over a 12-week period on treatment vs baseline*

<table>
<thead>
<tr>
<th>Hemoglobin response</th>
<th>Patients treated with ≥ 0.6 mg/kg</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Base Study N=21</td>
</tr>
<tr>
<td>Increase in mean Hb ≥ 1.0 g/dL</td>
<td>13 (62%)</td>
</tr>
<tr>
<td>Increase in mean Hb ≥ 1.5 g/dL</td>
<td>7 (33%)</td>
</tr>
</tbody>
</table>

*Baseline: average of at least 2 values within prior 7-28 days
Sustained Increase in Hemoglobin in NTD Patients with Longer-Term Treatment

- Median duration of treatment: 13.8 months (N=27)
- Median duration of Hb increase ≥ 1.0 g/dL/12 wks in responders (treatment ongoing): 13.5 months (N=21)
Improvement in Quality of Life in Symptomatic NTD Patients

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

- 7/9 (78%) patients with baseline FACIT-F deficit (<44 points) improved by ≥ 3 points at 24 weeks
- 6/7 (86%) patients with an increase in FACIT-F score ≥ 3 points also improved mean hemoglobin over a 12-week period by ≥ 1.0 g/dL

FACIT-F Change from Baseline to Week 24

1 Cella D, et al, Cancer 2002
Efficacy in Transfusion-Dependent (TD) Patients
Reduction in Transfusion Burden in TD Patients

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

<table>
<thead>
<tr>
<th>Reduction in RBC Units Transfused</th>
<th>Base Study N=31</th>
<th>Extension Study N=24</th>
</tr>
</thead>
<tbody>
<tr>
<td>≥ 20% reduction</td>
<td>25 (81%)</td>
<td>23 (96%)</td>
</tr>
<tr>
<td>≥ 33% reduction</td>
<td>22 (71%)</td>
<td>20 (83%)</td>
</tr>
<tr>
<td>≥ 50% reduction</td>
<td>17 (55%)</td>
<td>17 (71%)</td>
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Data as of 02 Sep 2016
Reduction in Transfusion Burden in TD Patients in Extension Study

- Transfusion reduction from 12 wks pre-treatment to any 12-wk period on treatment
- Median treatment duration was 14.5 months (n=24)
- Median duration of ≥ 33% reduction (treatment ongoing): 6.3 months (n=20)

* 1 subject discontinued before completing 12 weeks, not shown

Data as of 02 Sep 2016
Change in Liver Iron Concentration (MRI) in TD Patients
Follow-up: 5-11 Months

Data as of 02 Sep 2016
Safety Summary – Adverse Events in Patients with β thalassemia

- No related serious adverse events with luspatercept treatment (exposure ~66 pt-yr)
- Related grade 3 adverse events: bone pain (n=2 base, n=1 extension), asthenia (n=2 base) and headache (n=1 extension)
- Favorable safety profile maintained with long-term treatment
- Majority of AEs continue to be grade 1/2

<table>
<thead>
<tr>
<th>Preferred Term</th>
<th>Possibly or Probably Related AEs (all grades) in ≥ 10% Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Base Study N=64</td>
</tr>
<tr>
<td>Bone pain</td>
<td>19 (30%)</td>
</tr>
<tr>
<td>Myalgia</td>
<td>11 (17%)</td>
</tr>
<tr>
<td>Headache</td>
<td>9 (14%)</td>
</tr>
<tr>
<td>Musculoskeletal pain</td>
<td>8 (13%)</td>
</tr>
<tr>
<td>Arthralgia</td>
<td>7 (11%)</td>
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<tr>
<td>Injection site pain</td>
<td>2 (3%)</td>
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Data as of 02 Sep 2016
Conclusions - Luspatercept in Adults with β-Thalassemia

- Luspatercept was generally safe and well-tolerated at dose levels up to 1.25 mg/kg with no related serious adverse events
- Sustained hemoglobin increase in NTD patients, associated with an improvement in quality of life
- Sustained reduction in transfusion burden in TD patients, associated with reduction in liver iron concentration (LIC)
- Results supported the initiation of a Phase 3 study of luspatercept in regularly transfused patients with β-thalassemia (NCT 02604433)
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 current 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

Study sponsored by Celgene in collaboration with Acceleron Pharma
NCT02604433
Luspatercept β-Thalassemia Phase 2 Study: Acknowledgments

- **Co-investigators:** S Perrotta, C Borgna-Pignatti, 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, P Ricchi, A Spasiano

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- **Independent Safety Reviewer:** E Neufeld

*Study sponsored by Celgene in collaboration with Acceleron Pharma*