Luspatercept Increases Hemoglobin and Decreases Transfusion Burden in Adults With Beta-Thalassemia

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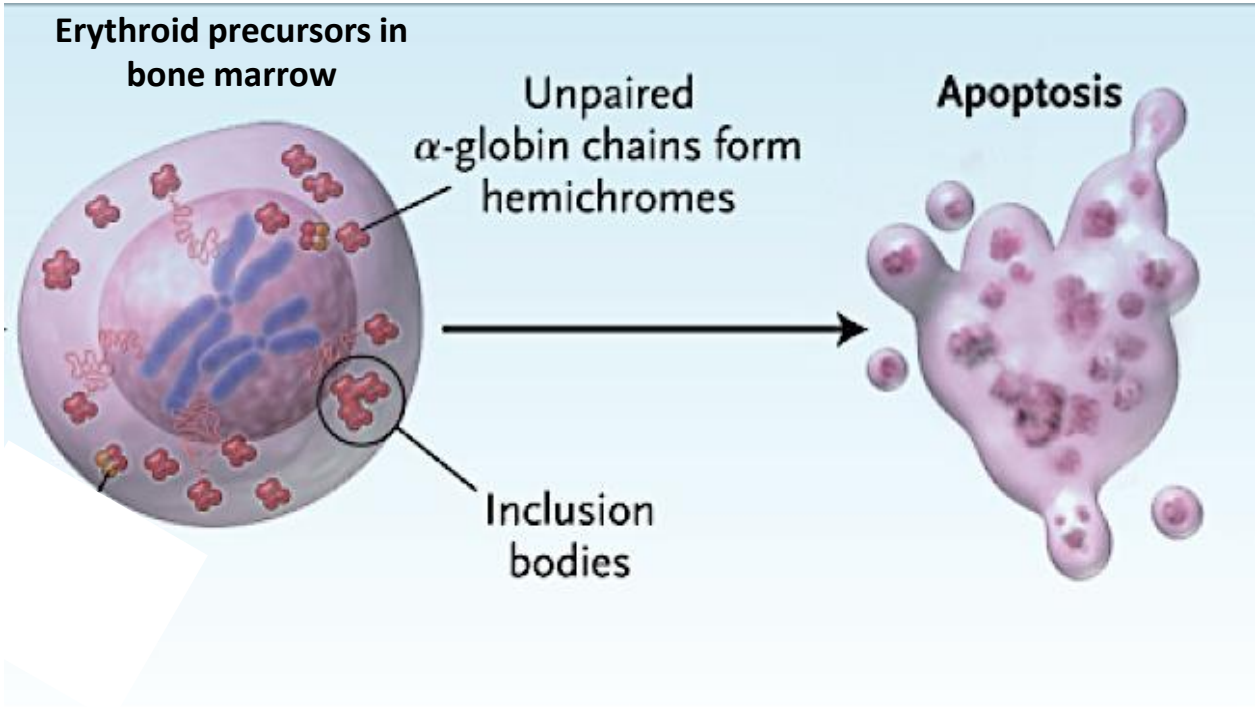
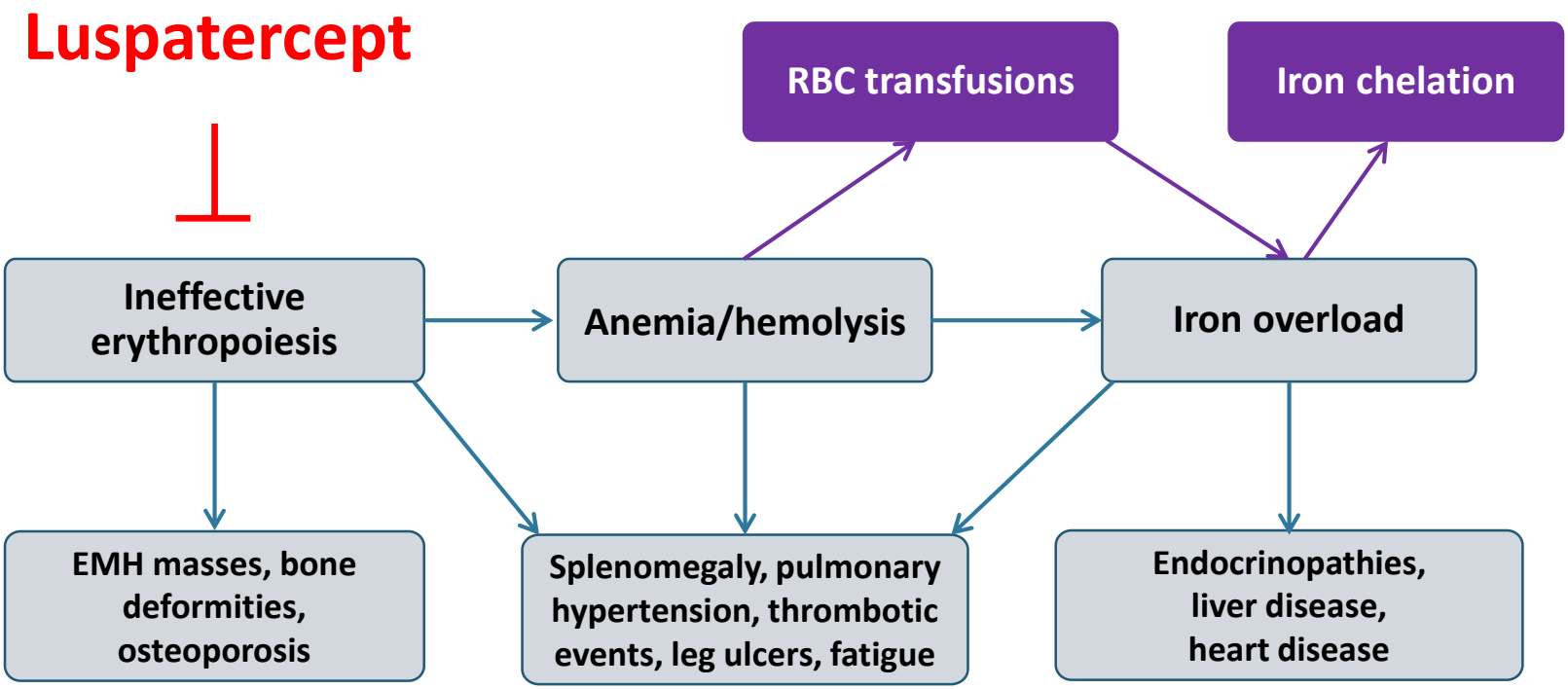
β-Thalassemia

- 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



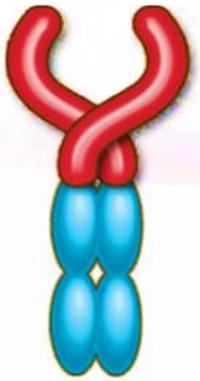
Rund D, Rachmilewitz E, NEJM 2005

Ineffective Erythropoiesis Drives β-Thalassemia Complications



EMH: extramedullary hematopoiesis; RBC: red blood cell

Luspatercept Structure and Activity in β-Thalassemia

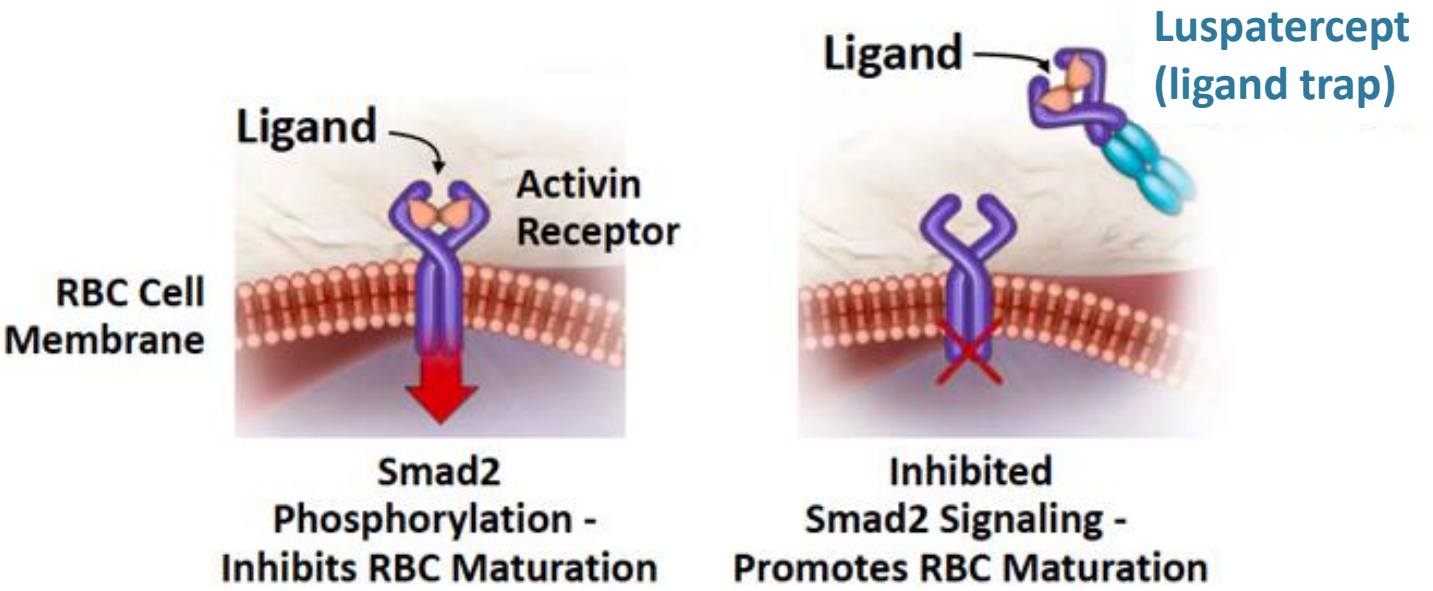


Modified ECD of ActRIIB receptor

Fc domain of human IgG1 Ab

Luspatercept

- 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]
- Its murine analog RAP-536 promoted late-stage erythropoiesis, increased hemoglobin, and reduced disease burden, in a murine model of β-thalassemia.[2]

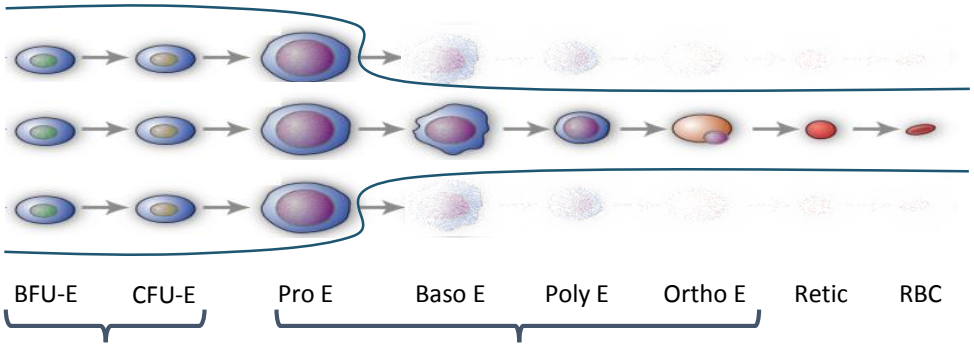


GDF: growth and differentiation factor; TGF: transforming growth factor

[1]Attie K et al., Am J Hematol 2014
[2]Suragani R et al., Nature Med 2014

Luspatercept Promotes Late-Stage Erythropoiesis

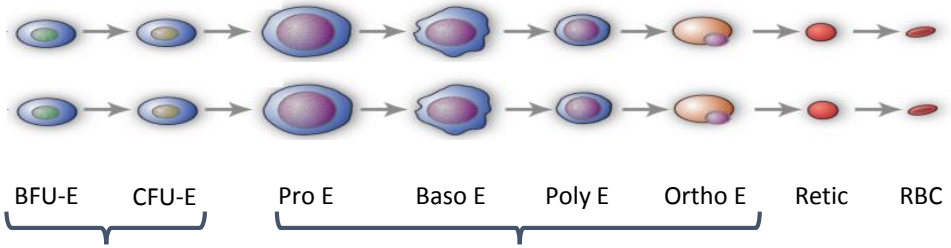
Ineffective erythropoiesis in β-thalassemia



Increased EPO levels drive proliferation

Increased GDF/activin signaling inhibits RBC maturation

Luspatercept promotes late-stage erythropoiesis



Luspatercept reduces erythroid hyperplasia

Luspatercept promotes RBC precursor differentiation

EPO: erythropoiesis; GDF: growth and differentiation factor; RBC: red blood cell

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

Base Study (N=64)
3 months (completed)
NCT01749540

→

Extension Study (N=51)
5 years (ongoing)
NCT02268409

Eligibility	Efficacy Endpoints
• Non-transfusion-dependent (NTD): < 4 units RBCs/8 weeks and Hb < 10 g/dL • Transfusion dependent (TD): ≥ 4 units RBCs/8 weeks	• NTD: Hemoglobin increase ≥ 1.0 g/dL; ≥ 1.5 g/dL • TD: Transfusion burden reduction ≥ 20%; ≥ 50%
Treatment	**Other Endpoints**
• Luspatercept 0.2 – 1.25 mg/kg (base study); 0.8 – 1.25 mg/kg (extension) SC q3 weeks • All patients followed up for 2 months post last dose or early discontinuation	• Safety • Liver iron concentration • Health-related quality of life

Data as of 13 Apr 2017

Demographics and Baseline Characteristics
Patients Treated at Dose Levels ≥ 0.6 mg/kg

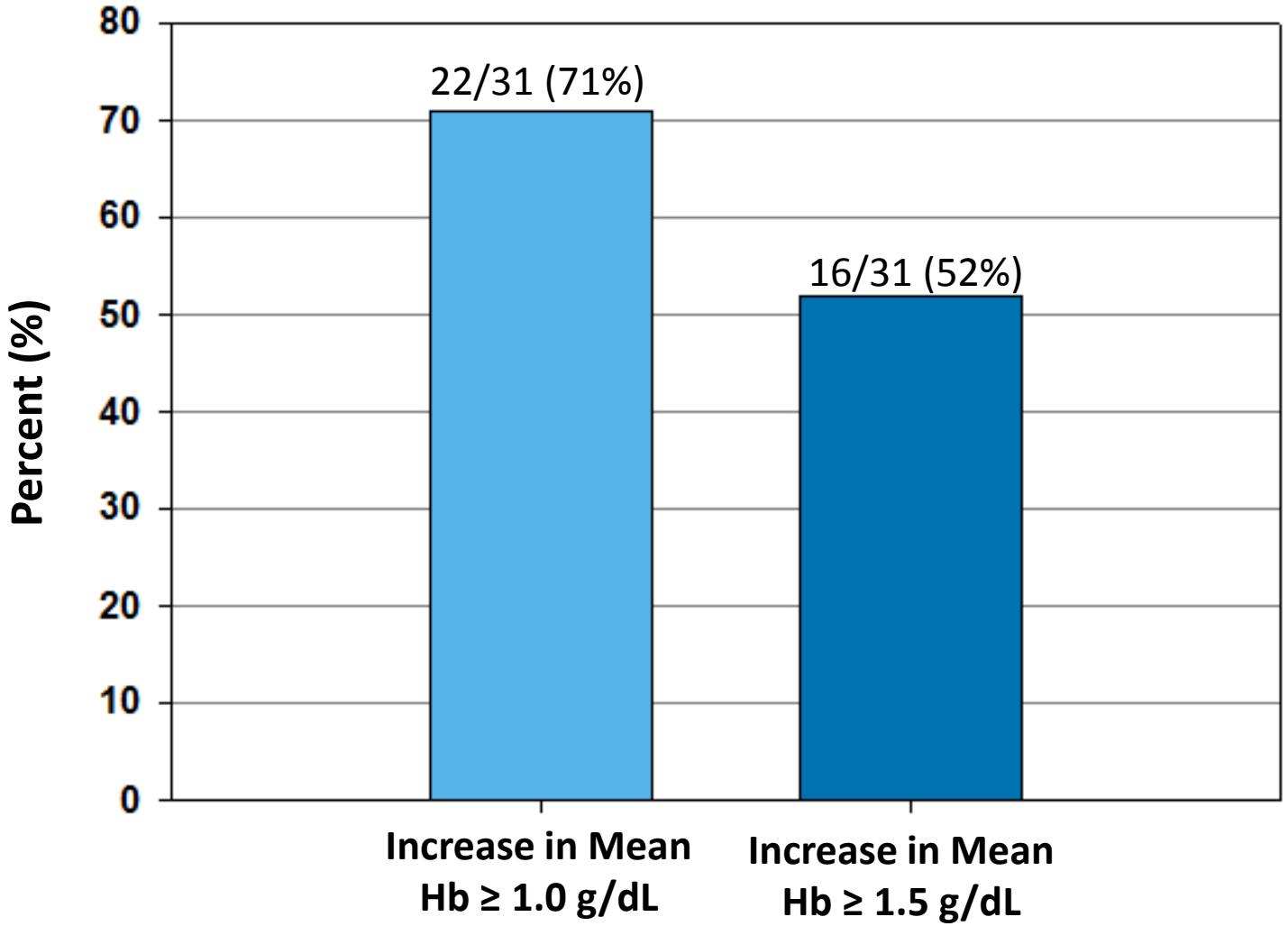
Parameter	N=63
Age, yr, median (range)	38 (20-62)
Sex, male, n (%)	33 (52)
Splenectomy, n (%)	42 (67)
NTD patients	n=31
Hemoglobin, g/dL, median (range)	8.5 (6.5-9.8)
Liver iron conc., mg/g dry wt, mean ± SD	5.1 ± 3.6
TD patients	n=32
RBC units/12 weeks, median (range)	8 (4-18)
Liver iron conc., mg/g dry wt, mean ± SD	4.7 ± 4.7

Data as of 13 Apr 2017

Efficacy in Non-Transfusion-Dependent (NTD) Patients

Increase in Hemoglobin in NTD Patients
Treated at Dose Levels ≥ 0.6 mg/kg

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

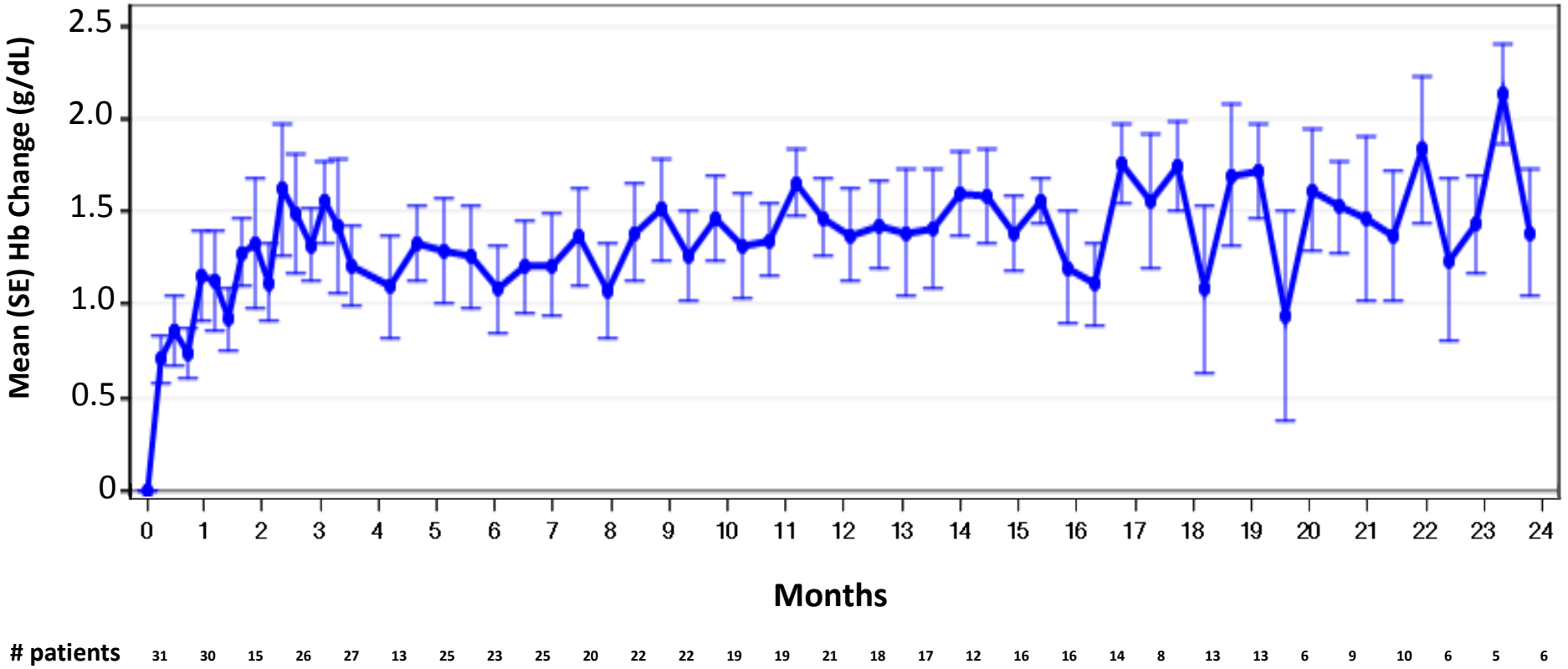


*Baseline: average of at least 2 values within 7-28 days prior to first dose

Data as of 13 Apr 2017

Sustained Increase in Hemoglobin in NTD Patients
Treated at Dose Levels ≥ 0.6 mg/kg

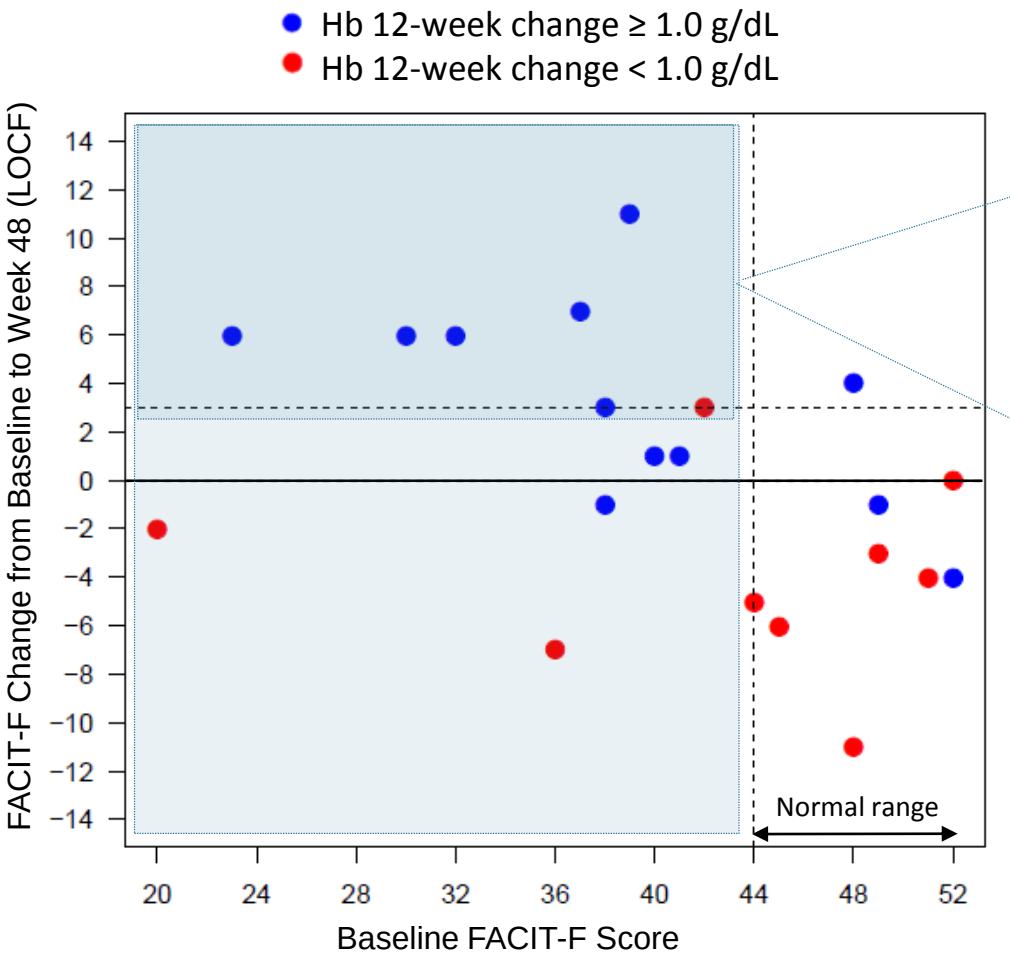
- Median duration of treatment (N=31): 18.6 months (range 1.3-29.4 months; ongoing)



Data as of 13 Apr 2017

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]



- 7/12 (58%) patients with baseline FACIT-F deficit (<44 points) improved by ≥ 3 points at 48 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

[1]*Cella D, et al, Cancer 2002*

Data as of 13 Apr 2017

Efficacy in Transfusion-Dependent (TD) Patients

Reduction in Transfusion Burden in TD Patients
Treated at Dose Levels ≥ 0.6 mg/kg

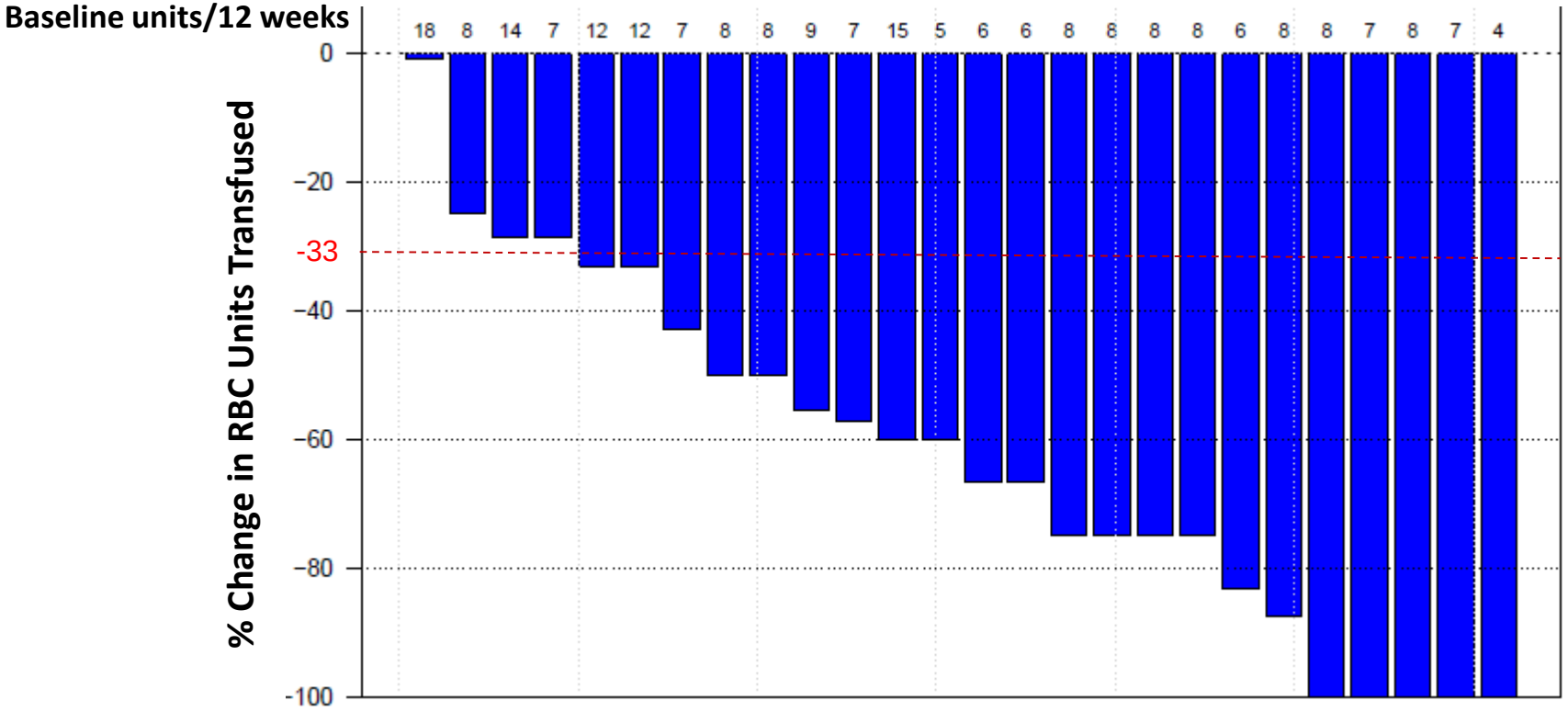
Reduction in RBC Units Transfused, n (%)	Any 12-Week Interval N=32
≥ 20% reduction	25 (78%)
≥ 33% reduction	22 (69%)

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

Data as of 13 Apr 2017

Reduction in Transfusion Burden in TD Patients
Treated at Dose Levels ≥ 0.6 mg/kg

- Median duration of treatment (N=32): 14.2 months (range 0.7-27.2 months; ongoing)



*6 patients discontinued before completing 12 weeks, not shown

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

Data as of 13 Apr 2017

Reduction in Transfusion Burden in TD Patients
Treated at Dose Levels ≥ 0.6 mg/kg

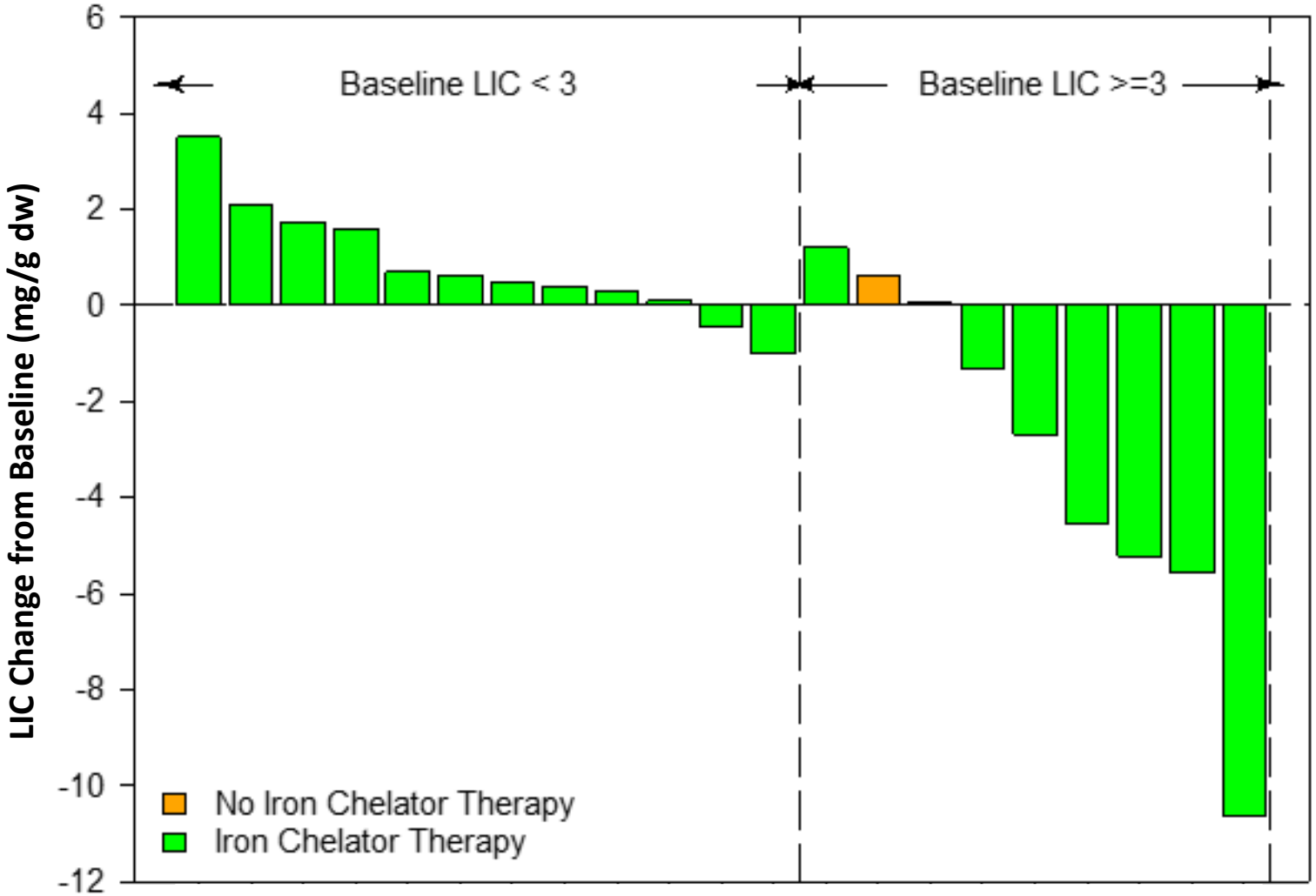
	≥ 33% Reduction in RBC Units Compared to 12 Weeks Pre-Treatment, n (%)	
	Fixed interval 13-24 weeks	**Fixed interval 37-48 weeks**
TD patients (N=29)	12 (41%)	12 (41%)
TD patients (N=24) (estimated 6-20 units/ 24 weeks)*	12 (50%)	11 (46%)

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

*Extrapolated from 12-week study data

Change in Liver Iron Concentration (MRI) in TD Patients Follow-Up: 4-18 Months

Treated at Dose Levels ≥ 0.6 mg/kg



Data as of 13 Apr2017

Safety Summary – Adverse Events in All Patients

- No related serious adverse events with luspatercept treatment
- Related grade 3 adverse events: bone pain (n=3 patients), asthenia (n=2 patients) and headache (n=1 patient)
- Favorable safety profile maintained with long-term treatment
- Majority of AEs grades 1 or 2

Preferred Term	Possibly or Probably Related AEs in ≥ 10% Patients, Any Grade, n (%)
Bone pain	24 (38%)
Headache	18 (28%)
Myalgia	14 (22%)
Arthralgia	12 (19%)
Musculoskeletal pain	11 (17%)
Asthenia	9 (14%)
Injection site pain	8 (13%)
Back pain	7 (11%)

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 with no related serious adverse events
- Sustained hemoglobin increase in NTD patients was associated with an improvement in quality of life
- Sustained reduction in transfusion burden in TD patients was associated with reduction in liver iron concentration (LIC) in patients with elevated baseline LIC
- Results continue to support an ongoing Phase 3 study of luspatercept in regularly transfused patients with β-thalassemia (NCT02604433), which has recently completed enrollment

The BELIEVE Study

Phase 3 Study of Luspatercept in β-Thalassemia: FULLY ENROLLED

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

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- **Celgene:** J Zou, N Chen
- **Chiltern:** C Lanza, F Van der Schueren, M Belfiore
- **Independent Safety Reviewer:** E Neufeld

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