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

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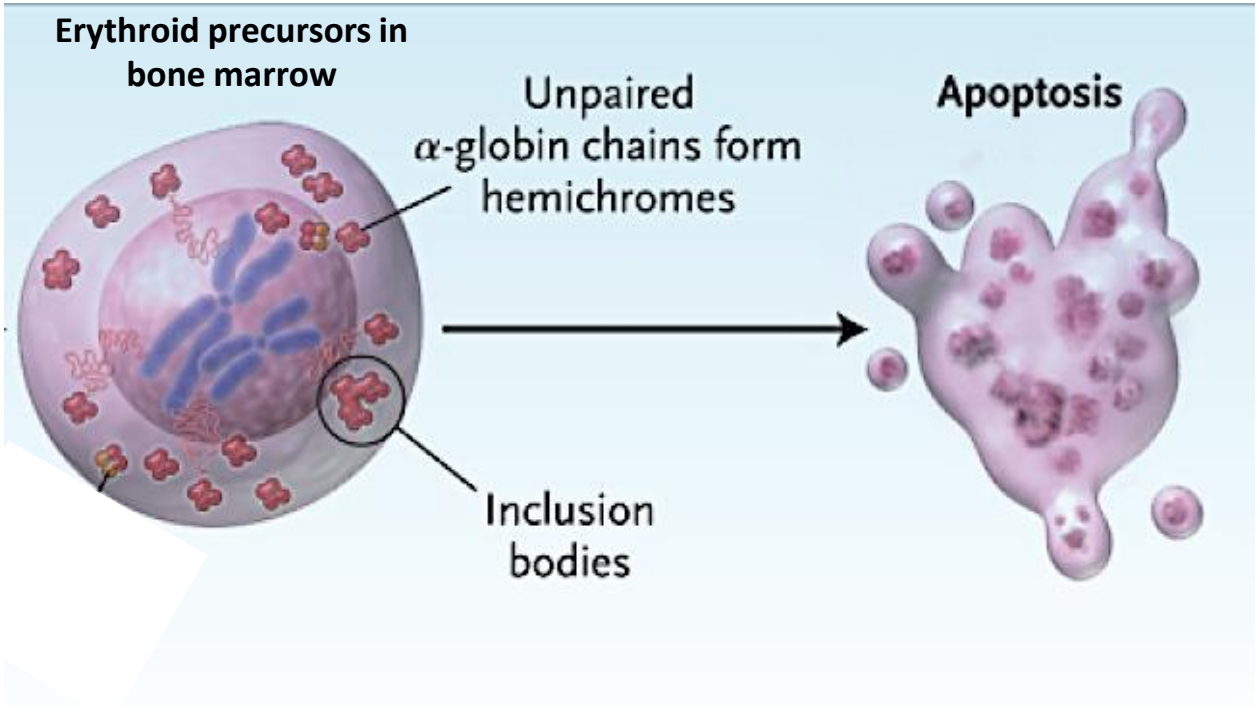
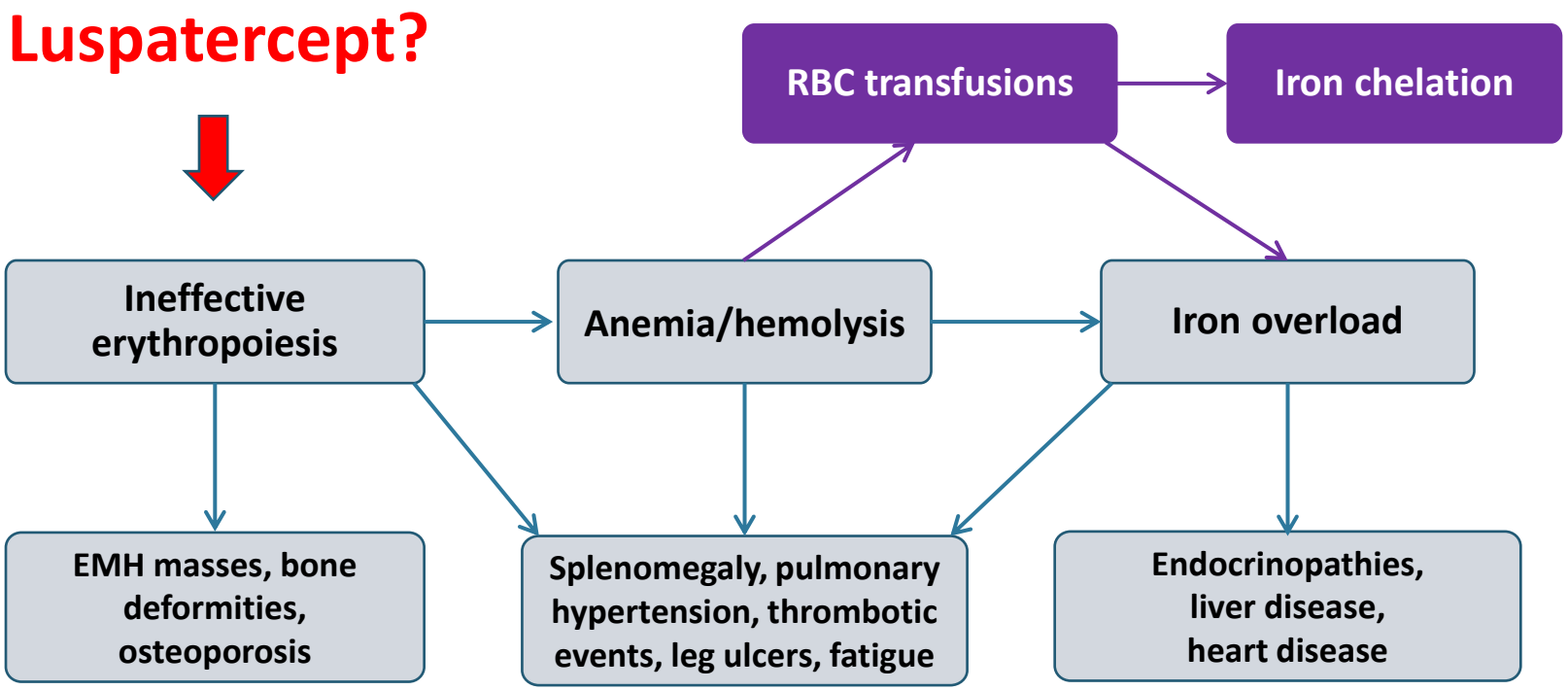
β-Thalassemia

- 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



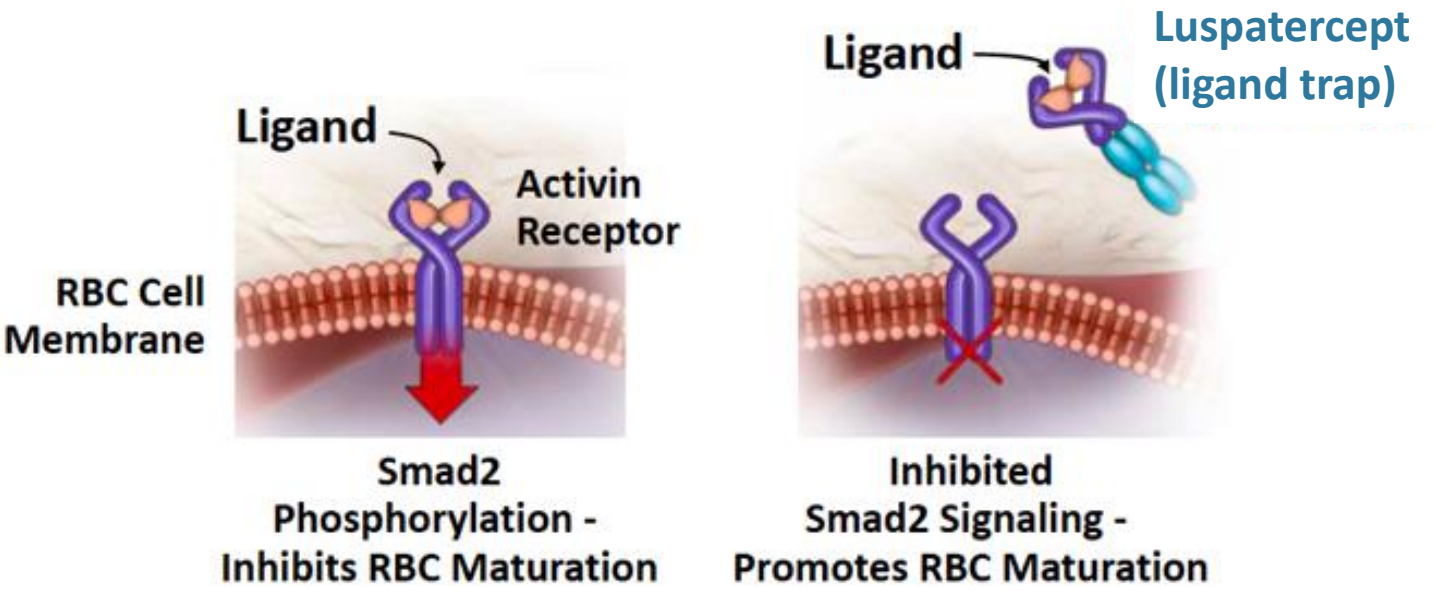
Luspatercept structure and activity in β-Thalassemia

Modified ECD of ActRIIB receptor

Fc domain of human IgG1 Ab

Luspatercept

- 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]

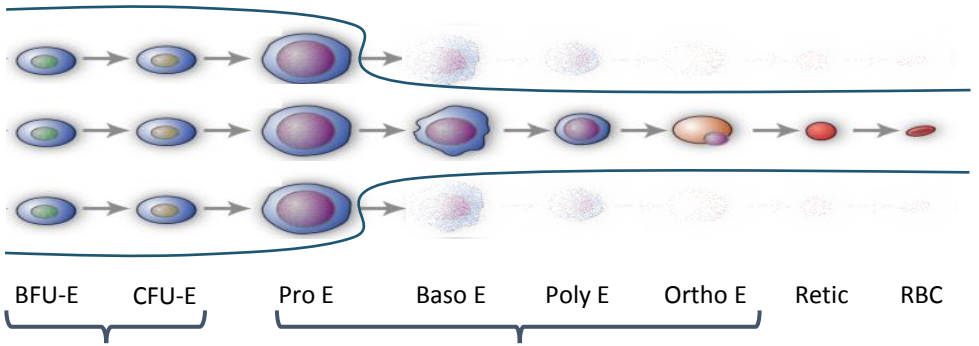


GDF: growth and differentiation factor
TGF: transforming growth factor

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

Luspatercept Promotes Late-Stage Erythropoiesis

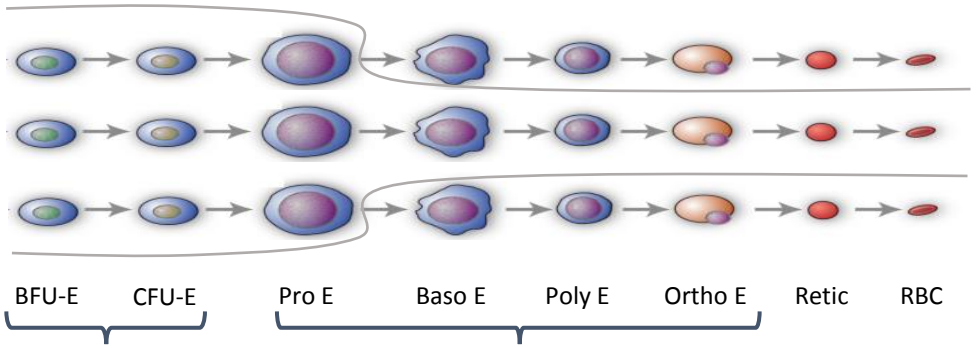
Ineffective erythropoiesis in β-thalassemia



Increased EPO levels drive proliferation

Increased GDF signaling inhibits RBC maturation

Luspatercept promotes late-stage erythropoiesis



Luspatercept neutralizes ligands that block RBC precursor differentiation

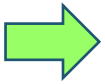
CLINICAL TRIALS in THALASSEMIA

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
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

Parameter	Base Study N=64	Extension Study N=51
Age, yr, median (range)	38.5 (20-62)	37.0 (22-62)
Sex, male, n (%)	33 (52)	29 (57)
Splenectomy, n (%)	43 (67)	34 (67)
NTD patients (n)	33	27
Hemoglobin, g/dL, median (range)	8.5 (6.5-9.8)	8.7 (7.6-9.8)
Liver iron conc., mg/g dry wt, mean ± SD	5.4 ± 3.8	5.1 ± 3.8
TD patients (n)	31	24
RBC units/12 weeks, median (range)	8 (4-18)	8 (4-15)
Liver iron conc., mg/g dry wt, mean ± SD	5.0 ± 5.3	4.9 ± 5.0

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*

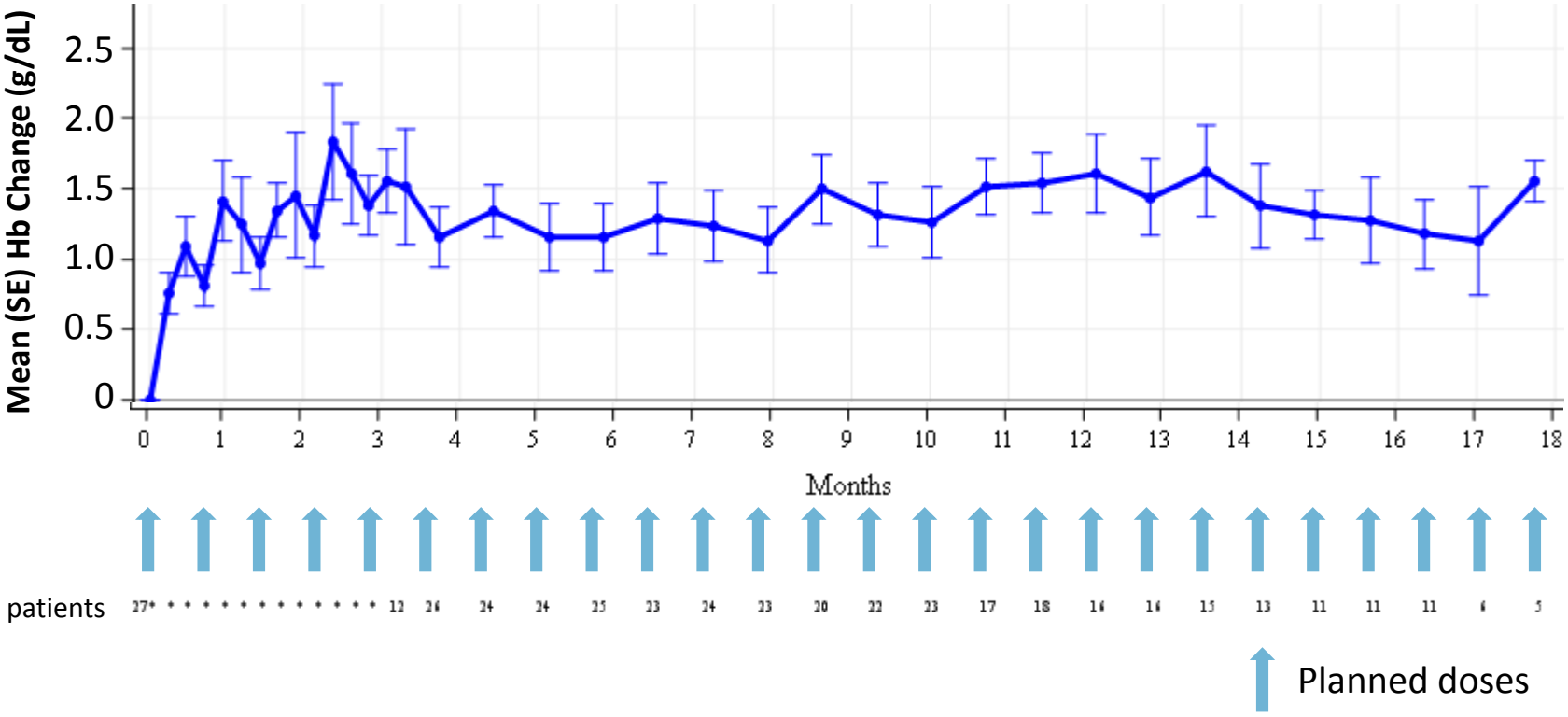
Hemoglobin response	Patients treated with ≥ 0.6 mg/kg	
	Base Study N=21	Extension Study N=27
Increase in mean Hb ≥ 1.0 g/dL	13 (62%)	21 (78%)
Increase in mean Hb ≥ 1.5 g/dL	7 (33%)	14 (52%)

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

Data as of 02 Sep 2016

Sustained Increase in Hemoglobin in NTD Patients with Longer-Term Treatment

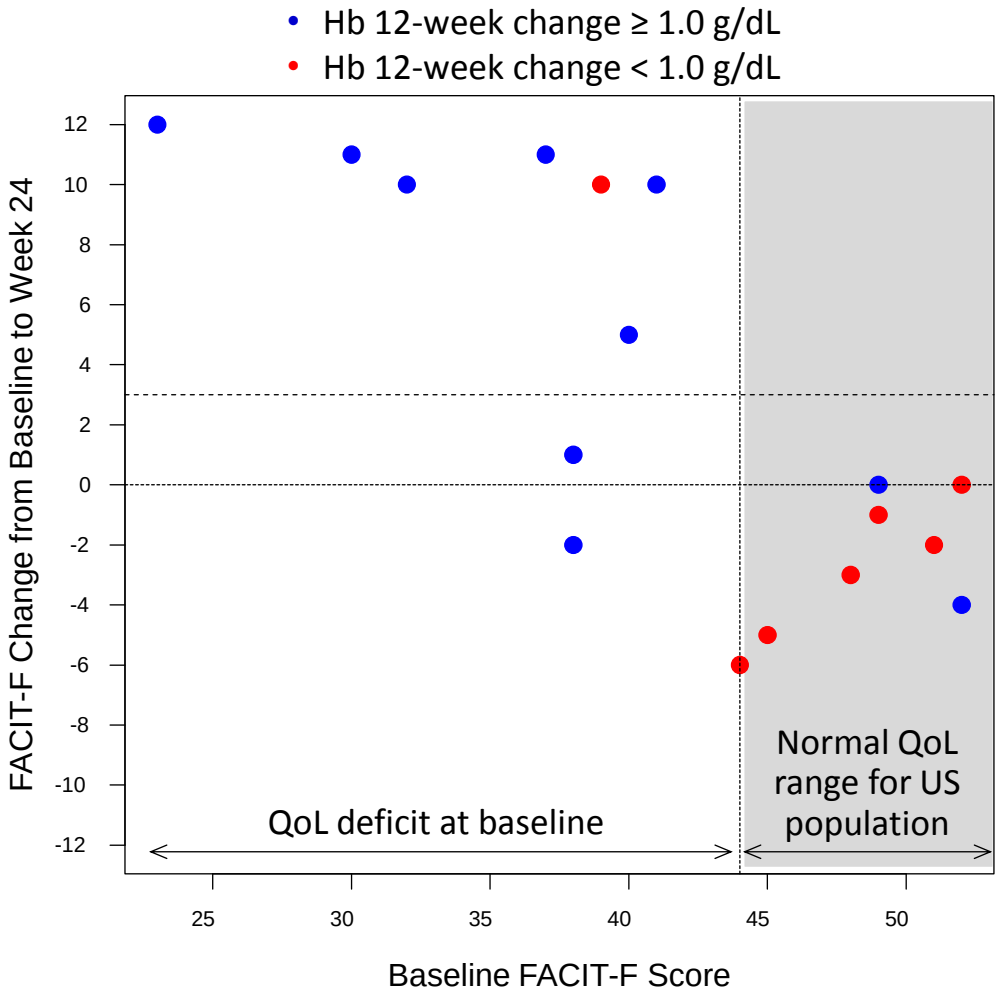
- Median duration of treatment: 13.8 months (N=27)
- Median duration of Hb increase ≥ 1.0 g/dL/12 wks in responders (treatment ongoing): 13.5 months (N=21)



Data as of 02 Sep 2016

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

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

Data as of 02 Sep 2016

Efficacy in Transfusion-Dependent (TD) Patients

Reduction in Transfusion Burden in TD Patients

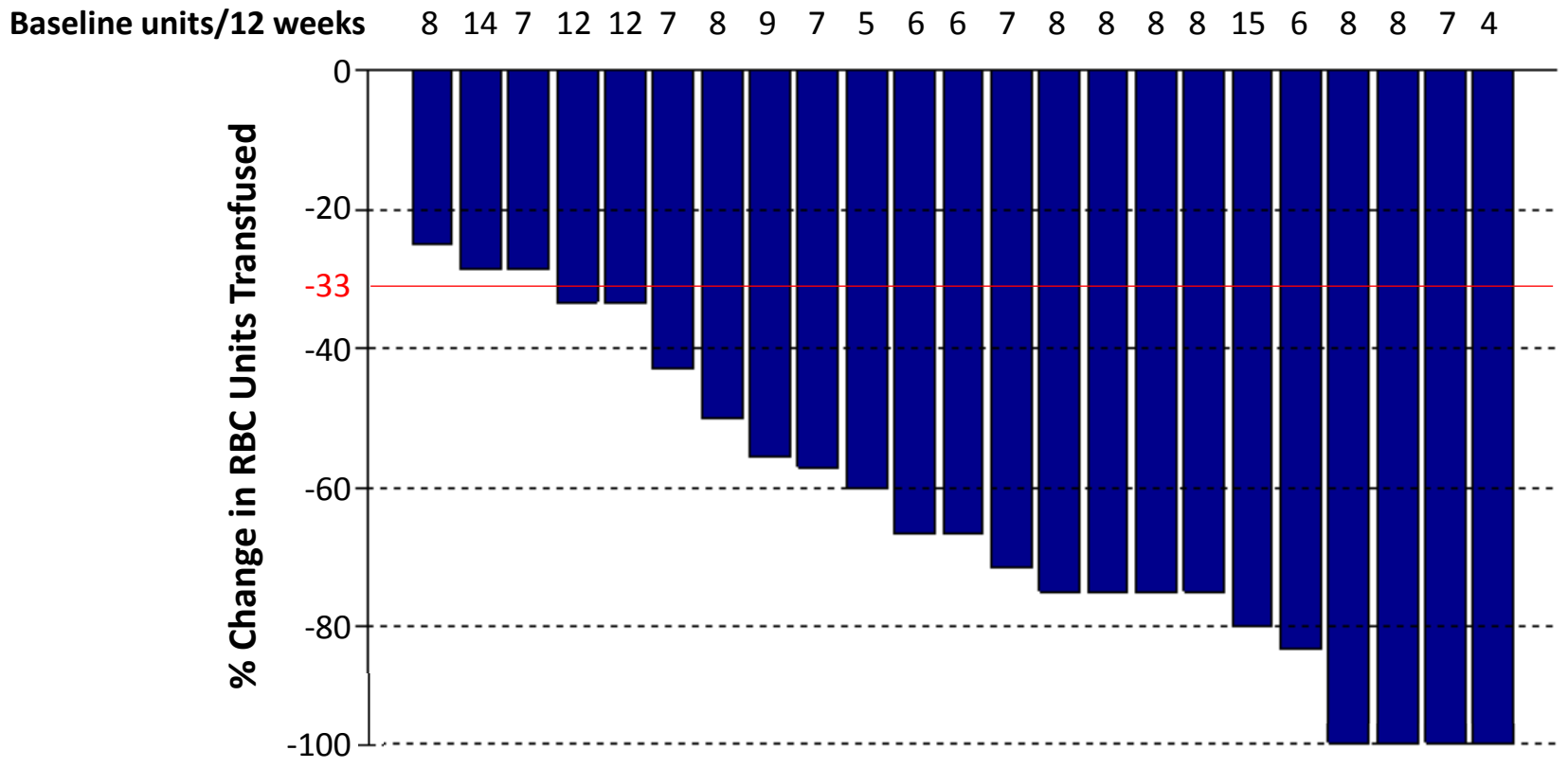
- Transfusion burden reduction from 12 weeks pre-treatment to any 12-week period on treatment

Reduction in RBC Units Transfused	Base Study N=31	Extension Study N=24
≥ 20% reduction	25 (81%)	23 (96%)
≥ 33% reduction	22 (71%)	20 (83%)
≥ 50% reduction	17 (55%)	17 (71%)

Data as of 02 Sep 2016

Reduction in Transfusion Burden in TD Patients in Extension Study

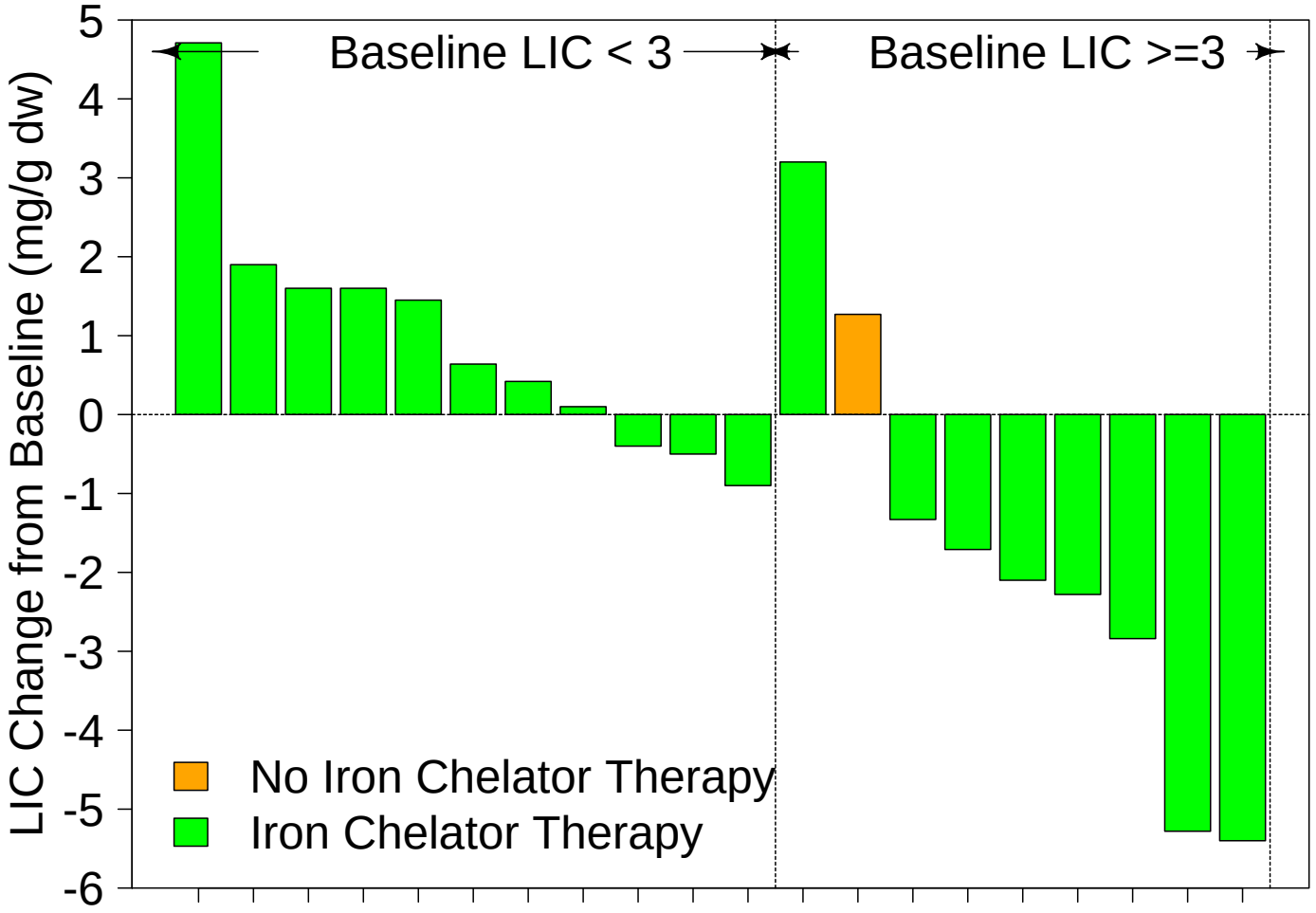
- Transfusion reduction from 12 wks pre-treatment to any 12-wk period on treatment
- Median treatment duration was 14.5 months (n=24)
- Median duration of ≥ 33% reduction (treatment ongoing): 6.3 months (n=20)



* 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

Preferred Term	Possibly or Probably Related AEs (all grades) in ≥ 10% Patients	
	Base Study N=64	Extension Study N=51
Bone pain	19 (30%)	11 (22%)
Myalgia	11 (17%)	4 (8%)
Headache	9 (14%)	8 (16%)
Musculoskeletal pain	8 (13%)	5 (10%)
Arthralgia	7 (11%)	5 (10%)
Injection site pain	2 (3%)	5 (10%)

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

BELIEVE

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:** A Laadem, 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