Luspatercept (ACE-536) Increases Hemoglobin and Decreases Transfusion Burden and Liver Iron Concentration in Adults with Beta-Thalassemia: Preliminary Results from a Phase 2 Study

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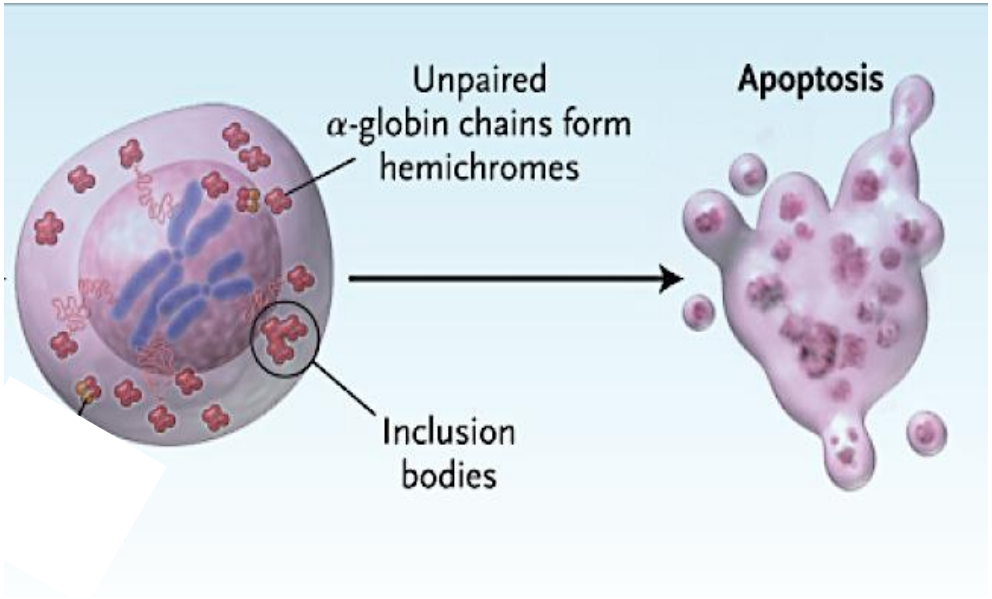
β-Thalassemia

- β-thalassemia is an inherited anemia due to defective synthesis of β-globin
  - Excess unpaired α-globin chains lead to **ineffective erythropoiesis**
- Ineffective erythropoiesis is characterized by expanded RBC proliferation and elevated GDF11 and other TGF-β superfamily ligands and Smad 2/3 signaling

Erythroid Precursors in Bone Marrow



Rund D, Rachmilewitz E, NEJM 2005

β-Thalassemia

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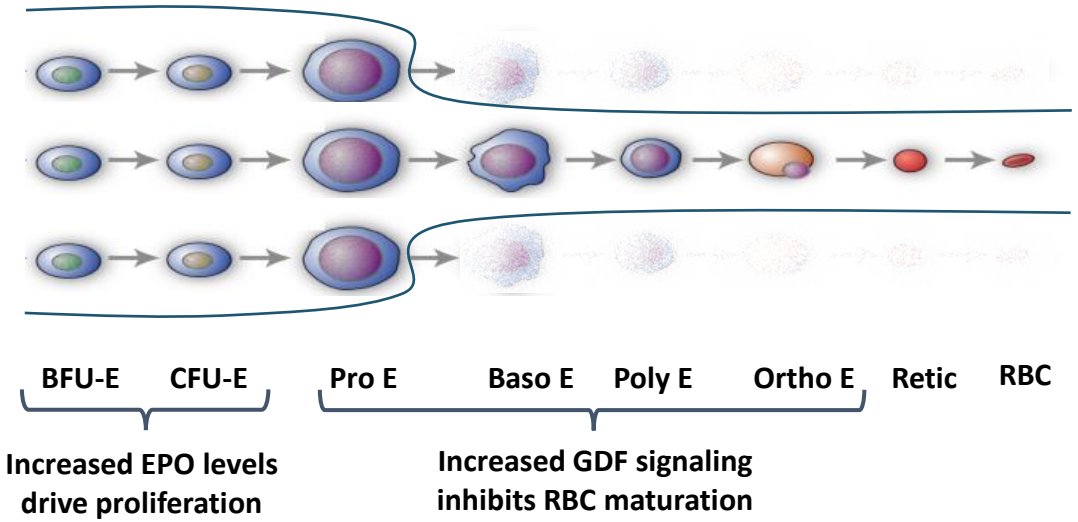
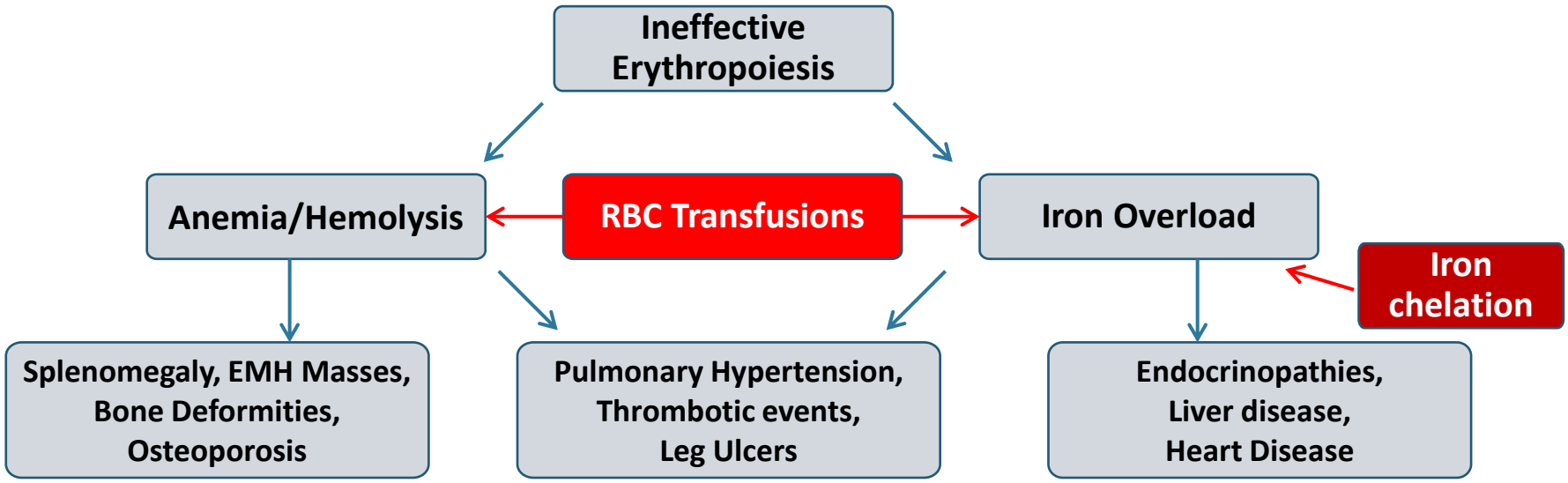
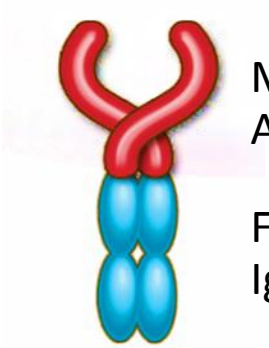


Ineffective Erythropoiesis Drives β-Thalassemia Complications



No approved drug therapy for anemia due to β-thalassemia



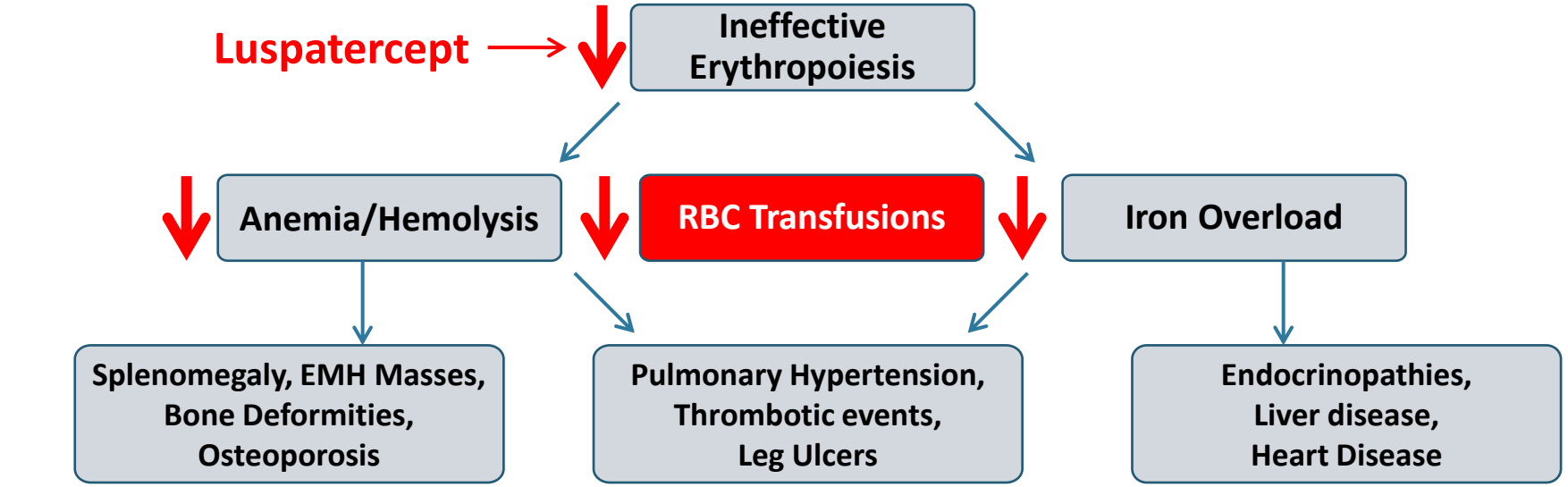
Modified ECD of ActRIIB receptor

Fc domain of human IgG_1 antibody

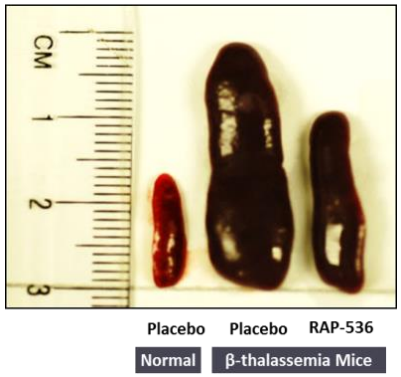
- **Luspatercept** is an experimental drug that is a recombinant fusion protein containing a modified extracellular domain (ECD) of the activin receptor type IIB (ActRIIB)
  - Binds to GDF11 and other ligands, inhibits Smad 2/3 signaling, and promotes late-stage erythroid differentiation[1]
  - Increased hemoglobin levels in a Phase 1 healthy volunteer study[2]

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

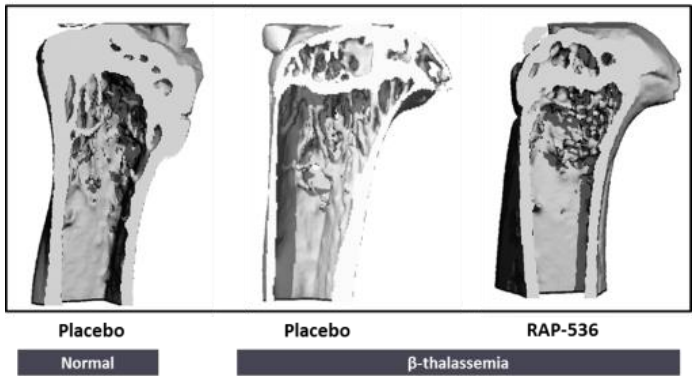
RAP-536 (Murine Luspatercept) Reduces Ineffective Erythropoiesis and Disease Burden in Mouse Model of β-thalassemia



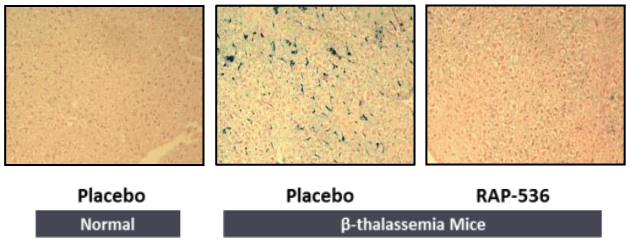
Spleen



Bone



Liver Iron



Suragani R et al., Blood, 2014

Luspatercept β-Thalassemia Phase 2 Study - Overview

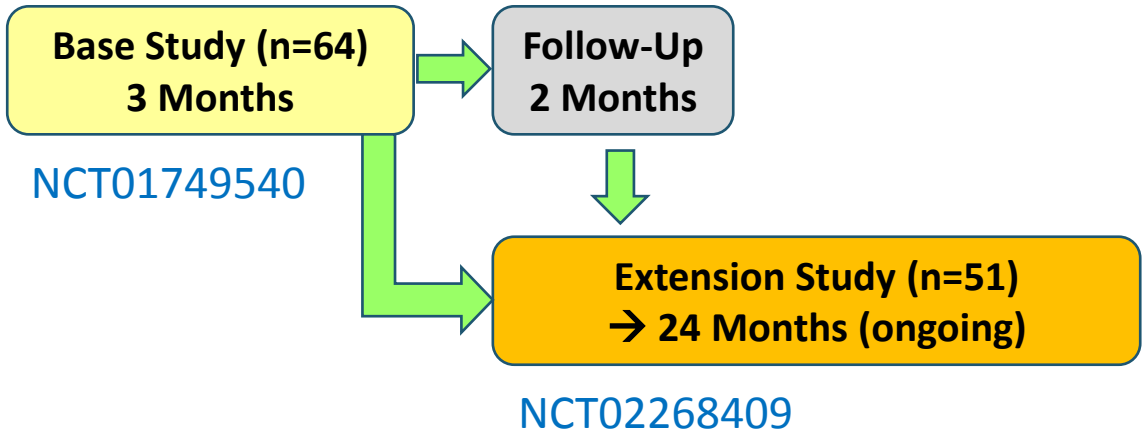
- A phase 2, multicenter, open-label, dose escalation study in adults with β-thalassemia
- **Primary efficacy objectives:**
  - Non-transfusion dependent (**NTD**): Hemoglobin increase ≥ 1.5 g/dL
  - Transfusion dependent (**TD**): Transfusion burden decrease over 12 wk
- **Secondary objectives:**
  - Safety
  - Liver iron concentration (by MRI)
  - Health-related Quality of Life (SF-36, FACT-An, *NTD-PRO*)
  - Biomarkers of erythropoiesis

NTD: Non-transfusion dependent patients (< 4 Units/8 wk, Hb <10 g/dL)

TD: Transfusion dependent patients (≥ 4 Units/8 wk)

Luspatercept β-Thalassemia Phase 2 Study - Overview

- **Base study (n=64):** Up to 5 doses SC q 3 weeks for 3 months
  - Dose escalation phase (n=35): 0.2, 0.4, 0.6, 0.8, 1.0, 1.25 mg/kg
  - Expansion cohort (n=29): starting dose 0.8, titration up to 1.25 mg/kg
  - 59 patients were efficacy evaluable (5 patients ongoing with <12 weeks treatment)
- **Extension study (n=51):** additional 24 months of treatment



Data as of 25 Sept 2015

Baseline Characteristics

Evaluable Patients	N=59
Age, yr, median (range)	37 (20-61)
Sex, male, n (%)	29 (49%)
Splenectomy, n (%)	41 (70%)
Non-Transfusion Dependent (NTD)	**N=31 (53%)**
Hemoglobin, g/dL, median (range)	8.4 (6.5-9.6)
LIC, mg/g dw, mean ± SD	5.6 ± 3.8
Transfusion Dependent (TD)	**N=28 (47%)**
RBC Units/12 weeks, median (range)	8 (4-18)
LIC, mg/g dw, mean ± SD	4.5 ± 4.6

LIC: liver iron concentration (by MRI); dw: = dry weight

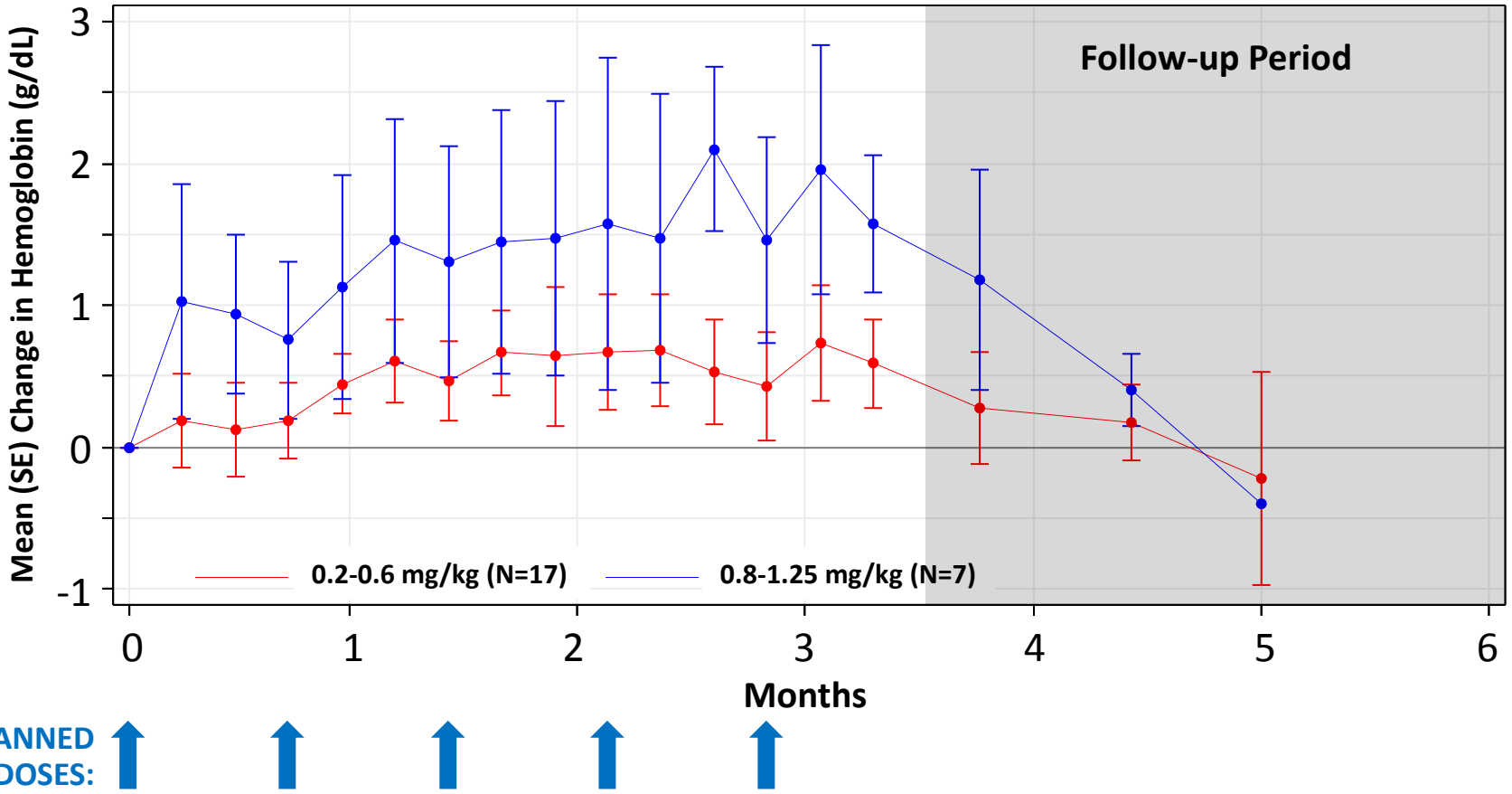
NTD: Non-transfusion dependent patients (< 4 Units/8 wk, Hb <10 g/dL)

TD: Transfusion dependent patients (≥ 4 Units/8 wk)

Data as of 25 Sept 2015

EFFICACY: Hemoglobin in NTD Patients with 3 Months Treatment Dose-Dependent Increase

- Mean hemoglobin increased steadily during 3 months of luspatercept treatment and returned to baseline in the absence of treatment during (n=24)

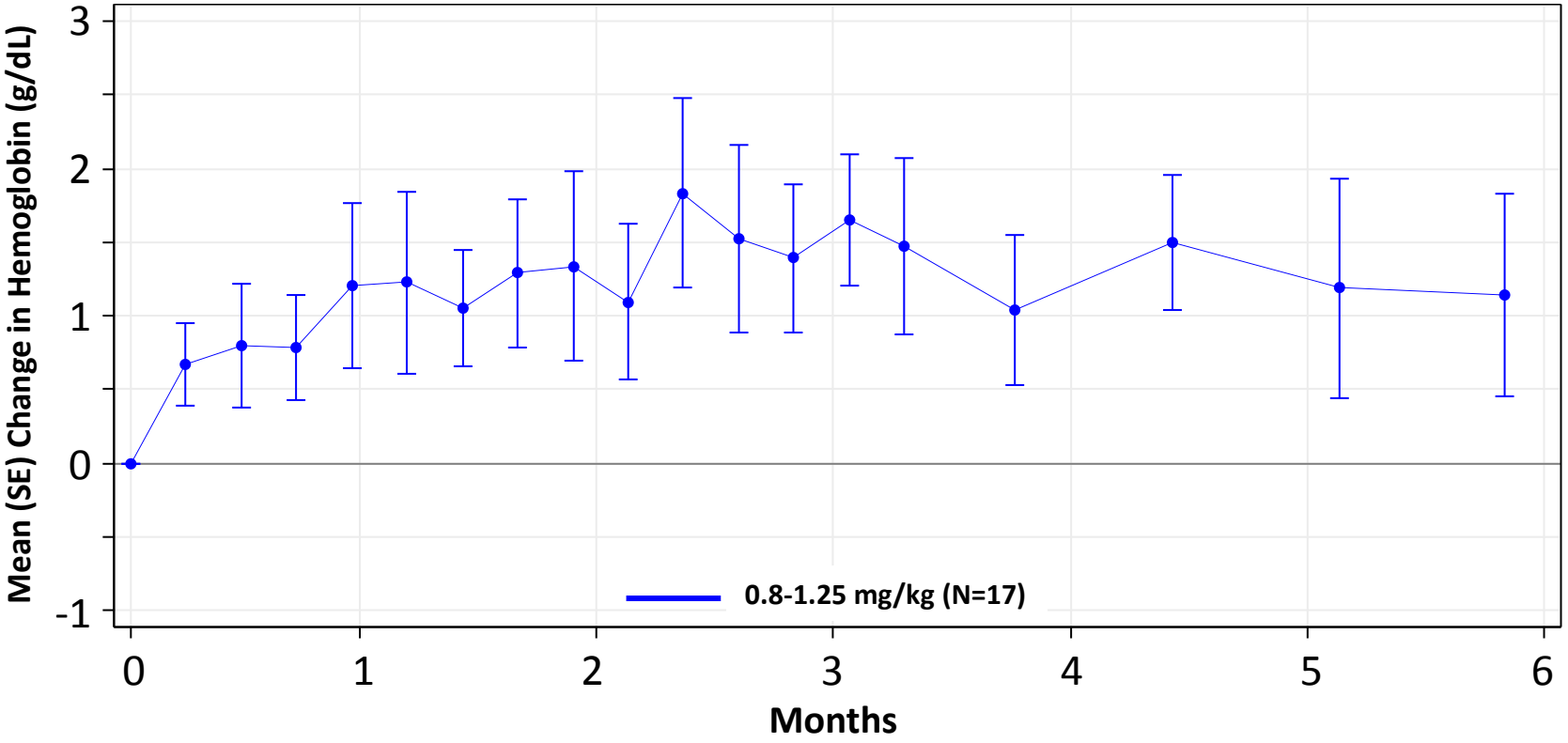


NTD: Non-transfusion dependent patients (< 4 Units/8 wk, Hb <10 g/dL)

Data as of 25 Sept 2015

EFFICACY: Hemoglobin in NTD Patients with > 3 Mo Treatment Sustained Improvement

- Increase in mean hemoglobin over a 12-week period in NTD patients treated in the long-term extension study (n=17)
  - 65% (11/17) increased Hb ≥ 1.0 g/dL
  - 47% (8/17) increased Hb ≥ 1.5 g/dL

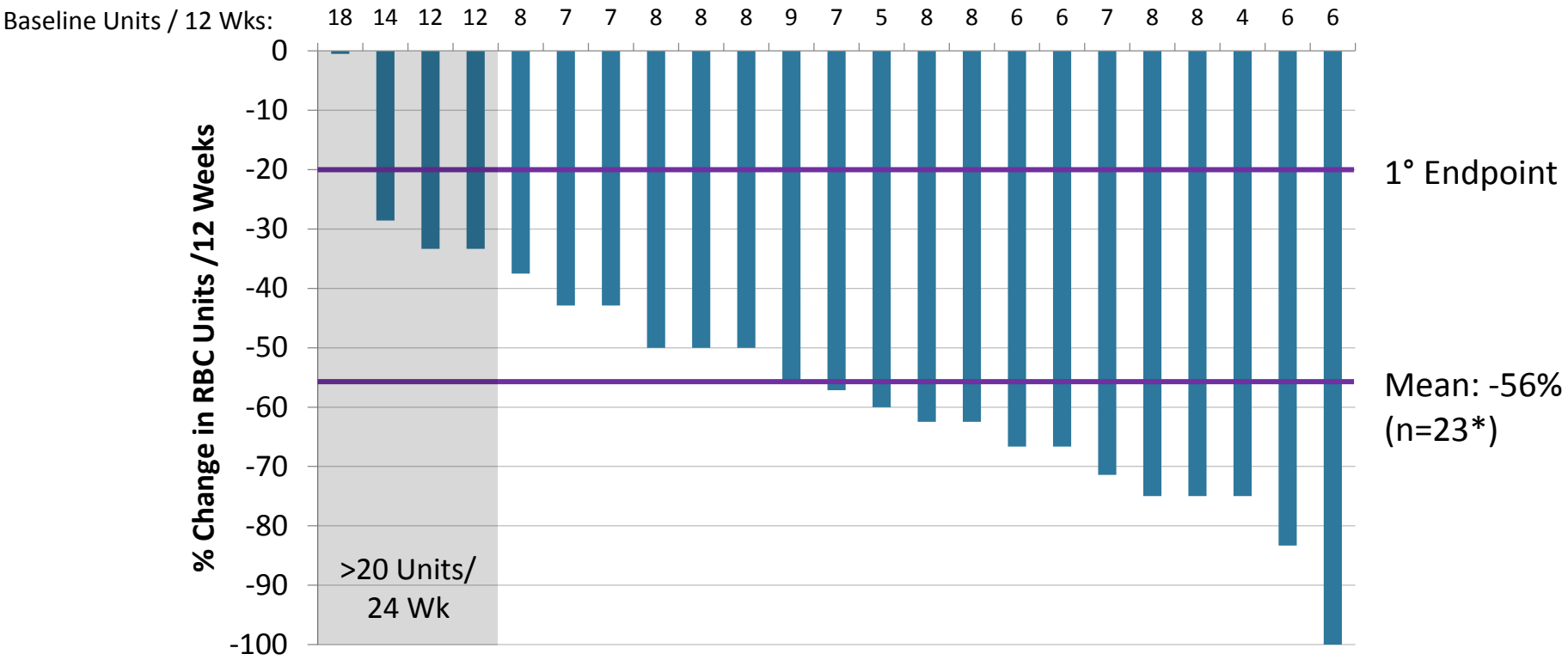


NTD: Non-transfusion dependent patients (< 4 Units/8 wk, Hb <10 g/dL)

Data as of 25 Sept 2015

EFFICACY: Reduction in Transfusion Burden, LIC in TD Patients

- Transfusion reduction from 12 weeks pre-treatment to a 12-week period on treatment:
  - 79% (22/28) had ≥ 20% reduction (study primary endpoint)
  - 75% (21/28) had ≥ 33% reduction; 57% (16/28) had ≥ 50% reduction



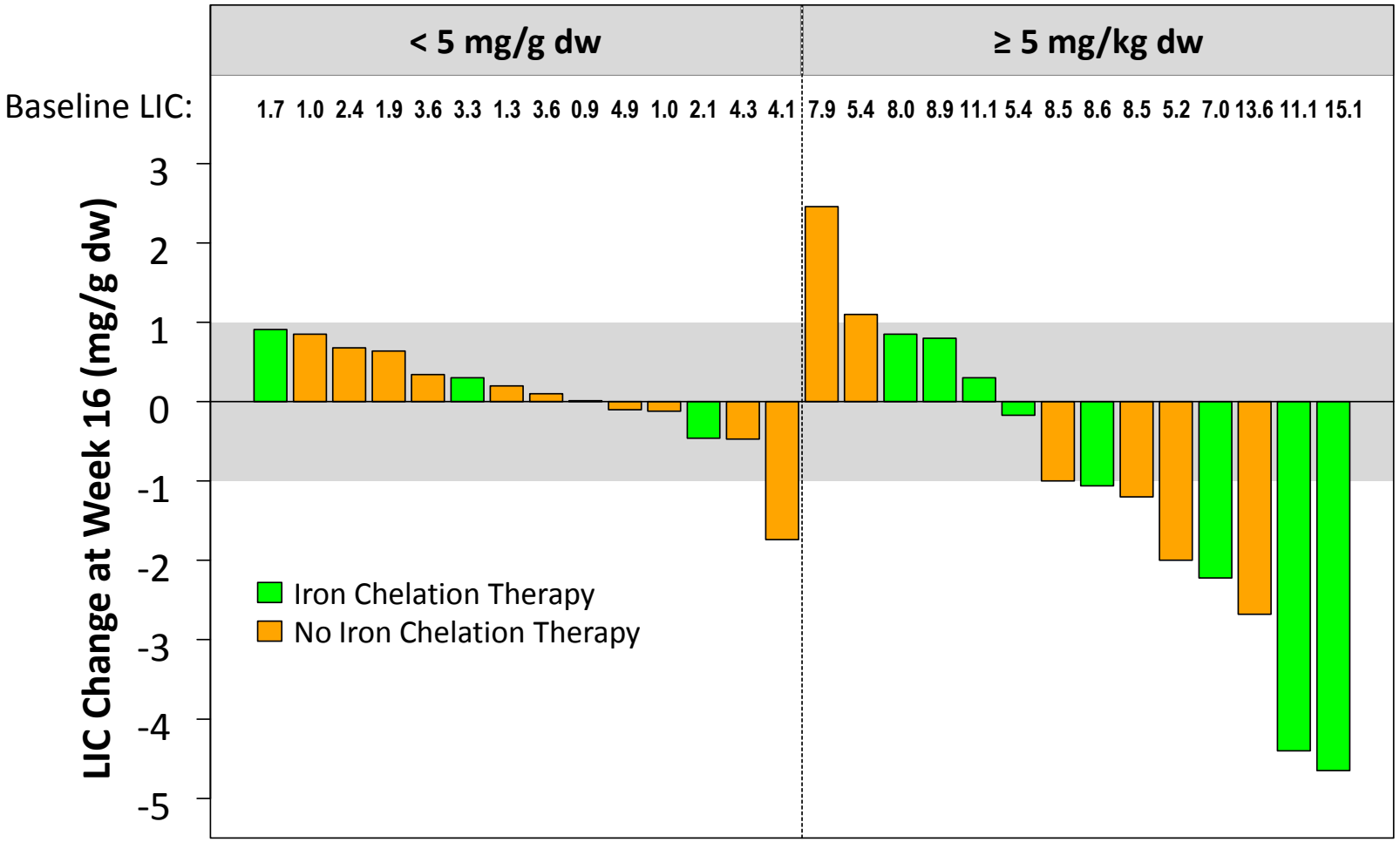
- **Liver Iron Concentration (LIC):** All TD patients received iron chelation therapy
  - 50% (4/8) with baseline LIC ≥ 5 mg/g dw had decrease in LIC ≥ 2 mg/g dw
  - 100% (14/14) with baseline LIC < 5 mg/g dw maintained LIC < 5

Data as of 25 Sept 2015

*** 5 subjects discontinued before completing 12 weeks**

Change in Liver Iron Concentration (MRI) at Wk 16 in NTD Patients

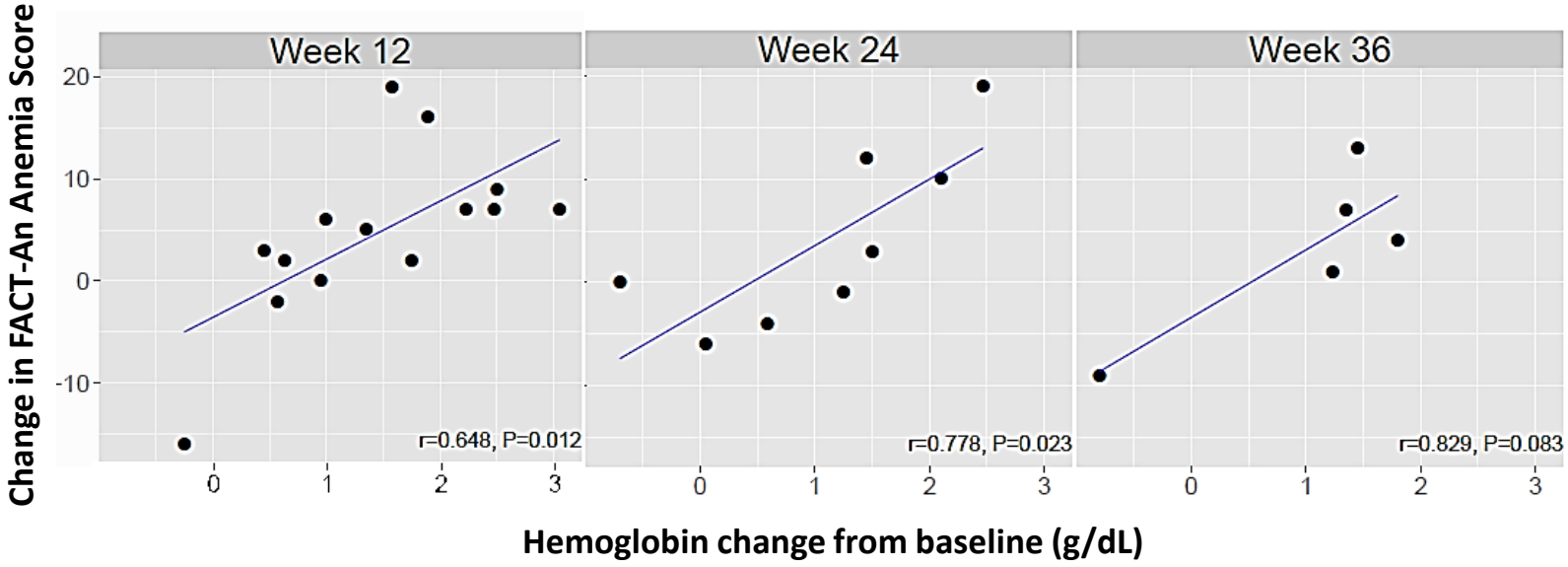
- 36% (5/14) with baseline LIC ≥ 5 mg/g dw had decrease in LIC ≥ 2 mg/g dw
- 100% (14/14) patients with baseline LIC < 5 mg/g dw maintained LIC < 5



Data as of 25 Sept 2015

EFFICACY: Quality of Life (SF-36,FACT-An) in NTD Patients Improvement Correlated with Increase in Hemoglobin

- **SF-36** (Short Form 36-item health survey)
  - Patient-Reported Outcome (PRO) survey of health status
  - Physical Component Summary (PCS) sub-score increase correlated with hemoglobin increase at Week 12 and Week 24 ($p<0.05$)
- **FACT-An** (Functional Assessment of Cancer Therapy – Anemia)
  - PRO assesses fatigue and anemia-related symptoms
  - Anemia subscale (20 items) increase correlated with hemoglobin increase:



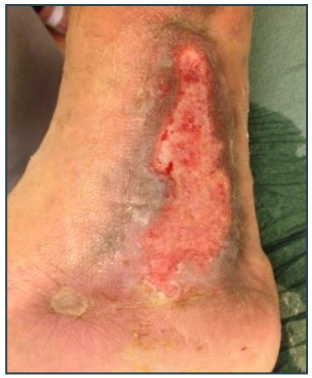
NTD: Non-transfusion dependent patients (< 4 Units/8 wk, Hb <10 g/dL)

Data as of 25 Sept 2015

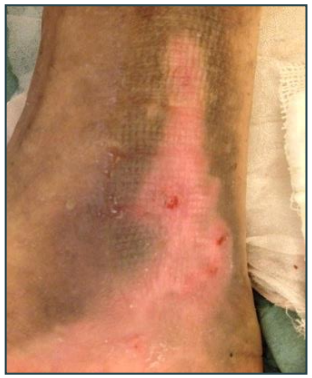
EFFICACY: Leg Ulcers → Persistent Healing

- 3 patients with long-term, persistent leg ulcers experienced rapid healing with luspatercept treatment
  - 2 additional patients have had partial response
- Sustained healing in a patient treated over 2 years

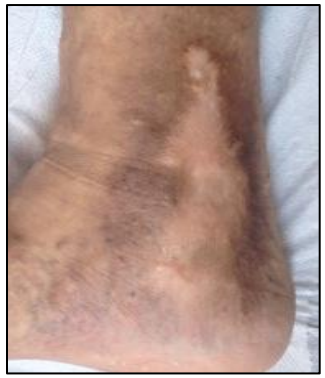
Pre-Treatment



After 6 Weeks



After 2 Years



Data as of 25 Sept 2015

SAFETY: Summary

- No related serious adverse events
- Related grade 3 adverse events included: headache (n=1), bone pain (n=3), asthenia (n=2), myalgia (n=1)
- 6/59 (10%) patients discontinued early associated with an AE: bone pain (n=2), arthralgia, asthenia, cerebrovascular accident, headache (n=1 each)

Related Adverse Events (all grades) in ≥ 5% Patients, n (%)

Preferred Term	NTD N=31	TD N=28	Overall N=59
Bone pain	8 (26%)	13 (46%)	21 (36%)
Myalgia	3 (10%)	8 (29%)	11 (19%)
Headache	5 (16%)	6 (21%)	11 (19%)
Arthralgia	3 10%)	7 (25%)	10 (17%)
Musculoskeletal pain	4 (13%)	4 (14%)	8 (14%)
Asthenia	1 (3%)	5 (18%)	6 (10%)
Injection site pain	1 (3%)	3 (11%)	4 (7%)
Back pain	1 (3%)	2 (7%)	3 (5%)
Pain in Jaw	1 (3%)	2 (7%)	3 (5%)

NTD: Non-transfusion dependent patients (< 4 Units/8 wk, Hb <10 g/dL)

TD: Transfusion dependent patients (≥ 4 Units/8 wk)

Data as of 25 Sept 2015

Luspatercept β-Thalassemia Phase 2 Study: Conclusions

- Favorable safety profile with no related serious adverse events
- Sustained hemoglobin increases in NTD patients and reduced transfusion burden in TD patients were observed in the majority of patients in the higher dose groups
- Reductions in liver iron concentration (LIC), improvement in Quality of Life scores, and rapid healing of leg ulcers were also observed
- These results support Phase 3 studies of luspatercept in patients with β-thalassemia (**BELIEVE**)

The BELIEVE Study

Phase 3 Study of Luspatercept in β-thalassemia

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 Inclusion 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

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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, A Pietrangelo
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- **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

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