San Giuseppe Moscati - Avellino
Azienda Ospedaliera di Rilievo Nazionale e di Alta Specializzazione

1ST SYMPOSIUM ON INNOVATIVE THERAPIES IN HEMATOLOGY

Luspatercet per il trattamento delle talassemie e della eritropoiesi inefficace

Maria Domenica Cappellini
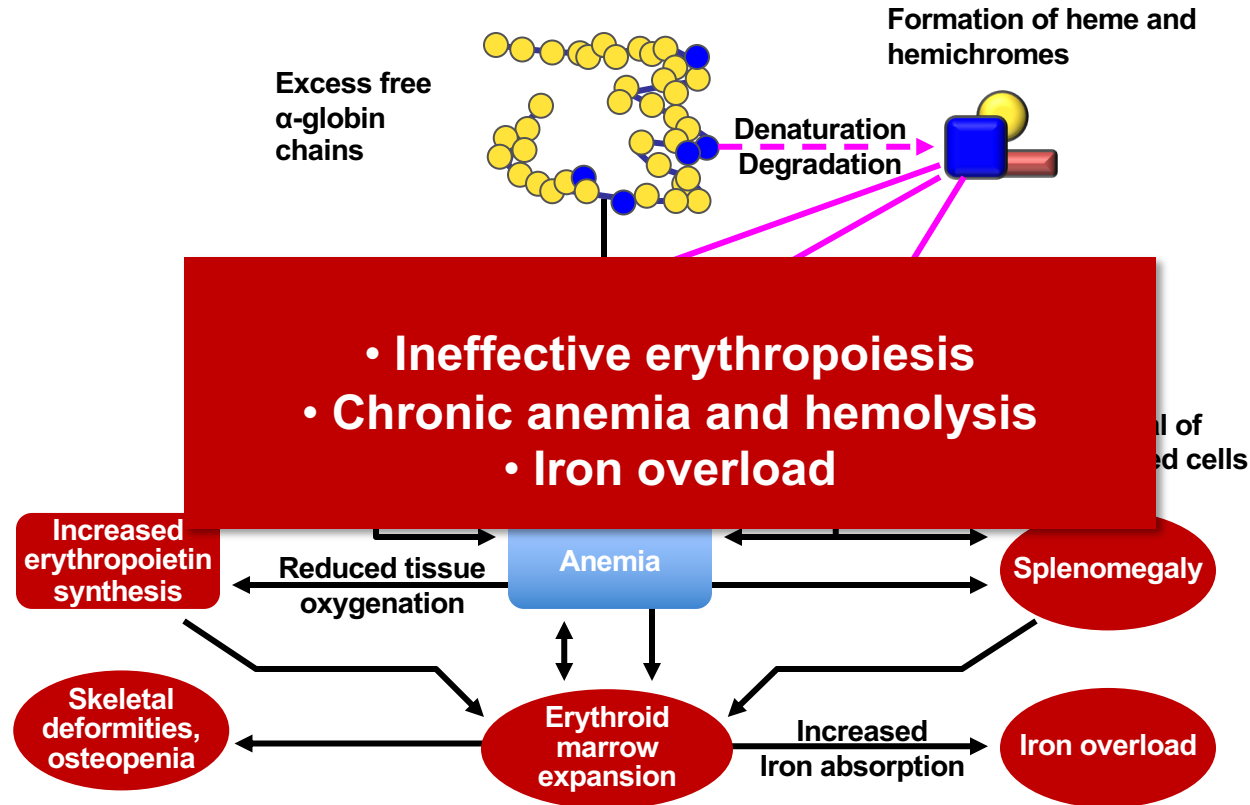*Fondazione IRCCS Ca Granda Policlinico*
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Disclosures of Name Surname

Company name	Research support	Employee	Consultant	Stockholder	Speakers bureau	Advisory board	Other
BMS						x	
Sanofi/Genzyme						x	
Vertex						x	
Silence						x	
Pharmacosmos						x	
Agios						x	

Agenda

- **Ineffective erythropoiesis and Thalassemia**
- **Luspatercept: mechanism of action**
- **Believe trial**
- **Beyond trial**
- **Future development**

Pathophysiology of Thalassemia Syndromes

Excess free
α-globin
chains

Formation of heme and
hemichromes

Denaturation
Degradation

- **Ineffective erythropoiesis**
- **Chronic anemia and hemolysis**
- **Iron overload**

al of
ed cells

Increased
erythropoietin
synthesis

Reduced tissue
oxygenation

Anemia

Splenomegaly

Skeletal
deformities,
osteopenia

Erythroid
marrow
expansion

Increased
Iron absorption

Iron overload

Olivieri NF, et al. N Engl J Med. 1999;341:99-109.

Chronic Anemia is a burden for patients with β-thalassaemia

» Chronic anemia is characterized by lower than normal: **number of circulating RBCs, hemoglobin level, and hematocrit level[1]**

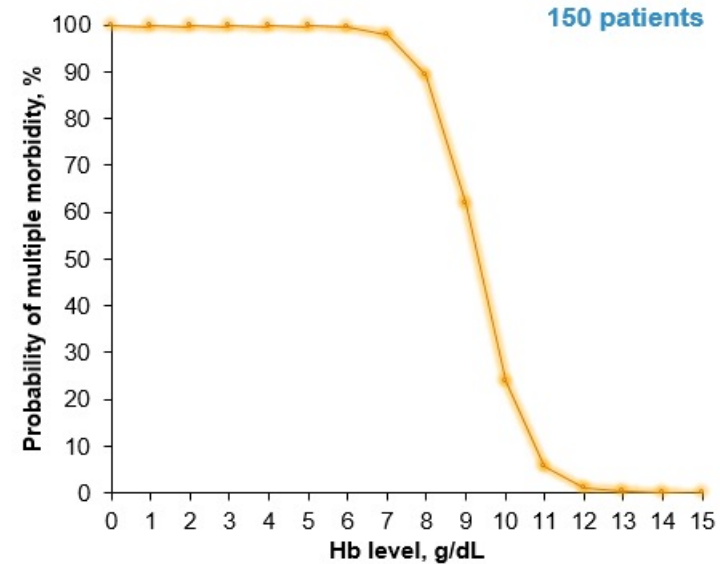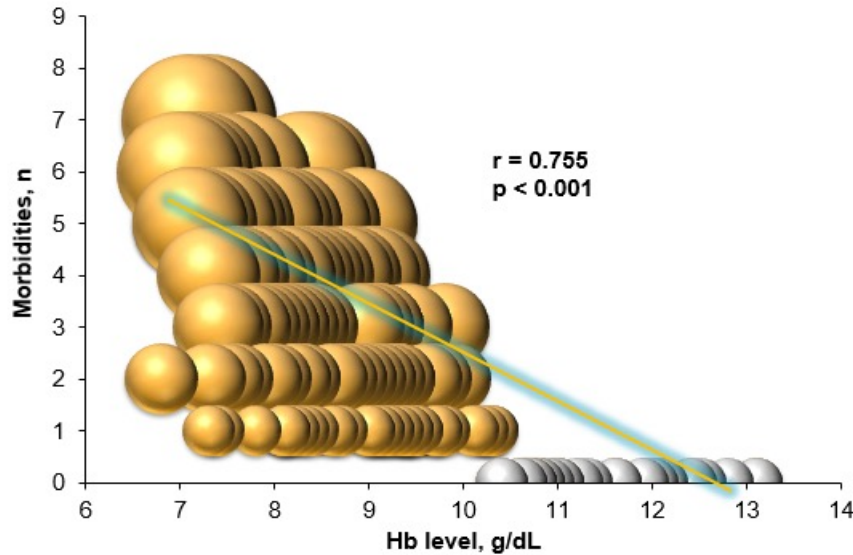» Outcomes of chronic anemia:

↓ Oxygen[2]

- Reduced delivery of oxygen to tissues
- Increased cardiac output
- Tissue hypoxia that can affect the function of major organs

Symptoms[2,3]

- Fatigue
- Weakness
- Shortness of breath
- Pallor
- ➢ Worsened health-related quality of life (QoL)

1. Smith RE. Am J Manag Care. 2010;16:S59–66; 2. Metivier F, et al. Nephrol Dial Transplant. 2000;15:14–18; 3. Balducci L. Cancer. 2006;106:2087–94;

Variations of 1 g/dL in Hb level vs morbidity in thalassemia

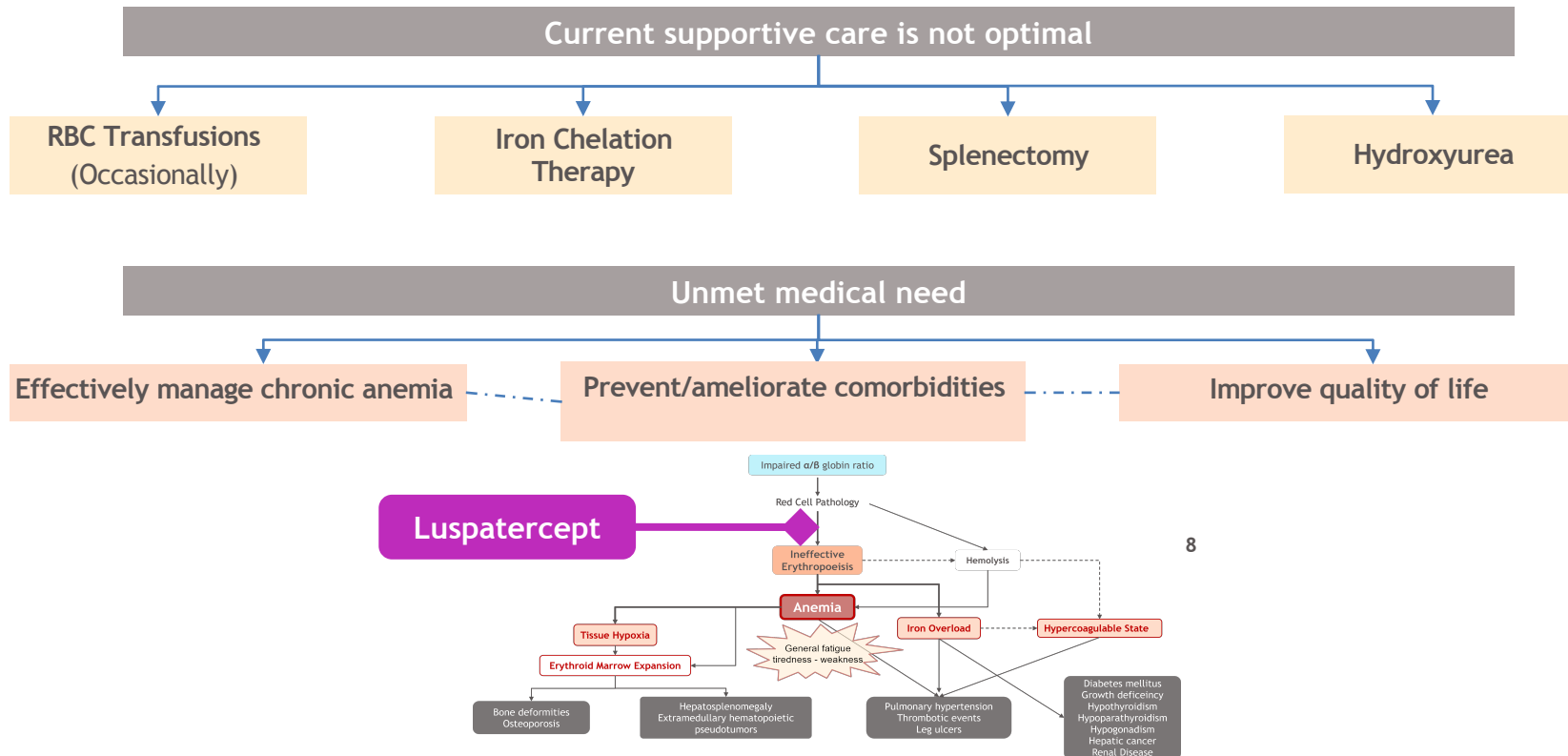

Musallam KM et al. *Ann Hematol* 2021;100:1903-1905.

Morbidity free-survival vs hemoglobin level in thalassemia
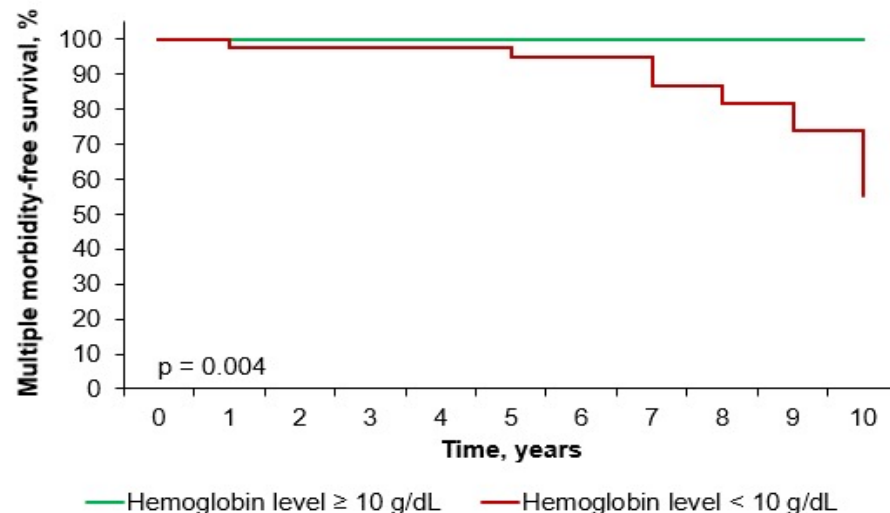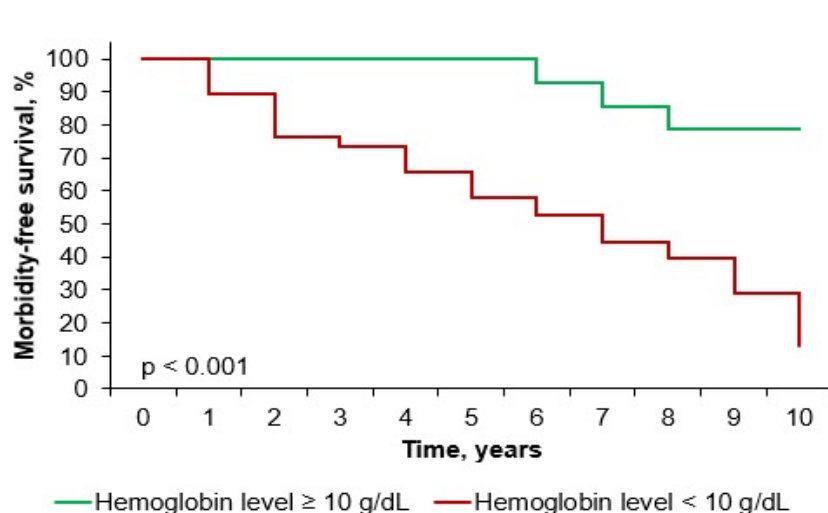
53 patients

Luspatercept brings a new mechanism of action to robustly improve ineffective erythropoiesis

Current supportive care is not optimal

RBC Transfusions (Occasionally)	Iron Chelation Therapy	Splenectomy	Hydroxyurea

Unmet medical need

Effectively manage chronic anemia	Prevent/ameliorate comorbidities	Improve quality of life

Impaired α/β globin ratio

Red Cell Pathology

Luspatercept

Ineffective Erythropoeisis

Hemolysis

Anemia

Tissue Hypoxia

Iron Overload

Hypercoagulable State

General fatigue tiredness - weakness

Erythroid Marrow Expansion

Bone deformities Osteoporosis

Hepatosplenomegaly Extramedullary hematopoietic pseudotumors

Pulmonary hypertension Thrombotic events Leg ulcers

Diabetes mellitus Growth deficeincy Hypothyroidism Hypoparathyroidism Hypogonadism Hepatic cancer Renal Disease

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Luspatercept: an erythroid maturation agent acting on late-stage erythropiesis

Luspatercept is a first-in-class erythroid maturation agent that neutralizes select TGF-β superfamily ligands to inhibit aberrant Smad2/3 signaling and enhance late-stage erythropoiesis

Luspatercept
ActRIIB / IgG1 Fc recombinant fusion protein

Modified extracellular domain of ActRIIB

Human IgG1 Fc domain

TGF-β superfamily ligand

ActRIIB

Cytoplasm

Nucleus

P

Smad2/3

Complex

Erythroid maturation

Motta I *et al. Expert Opin Investig Drugs* 2017;26:793-802; Attie *et al. Am J Hematol* 2014;89:766-770; Suragani RN et al. Nat Med 2014;20:408-414; Suragani RN et al. Blood 2014;123:3864-3872.

Luspatercept and Sotatercept (erythroid maturation agents) trials

Agent	Clinical Trials*	Design	n‡, population, age	Key efficacy measures
Erythroid maturation agents				
Luspatercept (ACE-536)	● NCT01749540 ● Completed†	● Phase 2 ● Open-label	● n = 64 ● TDT, NTDT with Hb <10 g/dL ● ≥18 yr	● TDT: Transfusion reduction (≥20%)§ ● NTDT: Hb increase ≥1.5 g/dL§, Hb ● Biomarkers of erythropoiesis, hemolysis, iron metabolism, bone metabolism
	● NCT02268409 ● Completed	● Phase 2 extension	● n = 51 ● TDT, NTDT included in phase 2	● TDT: Transfusion reduction (any, ≥20%, ≥50%), Hb ● NTDT: Hb increase ≥1.5 g/dL, Hb ● Reticulocytes, EPO, nRBC, sTfR, SF, TIBC, TSAT, NTBI ● HR-QoL
	● BELIEVE ● NCT02604433 ● Active, not recruiting†	● Phase 3 ● Randomized, placebo-controlled, double-blind	● n = 336 ● TDT ● ≥18 yr	● Transfusion reduction (≥33%§, ≥50%) ● Transfusion requirement ● Transfusion independence ● SF, LIC, MIC, ICT use ● BMD ● HR-QoL, healthcare resource utilization
	● NCT04143724 ● Not yet recruiting	● Phase 2 ● Open-label	● n = 46 ● TDT ● 6 months-18 yr	● Transfusion reduction ● Hb
	● BEYOND ● NCT03342404 ● Active, not recruiting	● Phase 2 ● Randomized, placebo-controlled, double-blind	● n = 145 ● NTDT with Hb ≤10 g/dL ● ≥18 yr	● Hb increase (any, ≥1 g/dL§, ≥1.5 g/dL) ● Transfusion requirement ● PRO, HR-QoL, 6MWT ● SF, LIC, ICT use
Sotatercept (ACE-011)	● NCT01571635 ● Active, not recruiting†	● Phase 2 ● Open-label	● n = 46 ● TDT, NTDT ● ≥18 yr	● Transfusion reduction (any, ≥20%) ● Hb

*Status per clinicaltrials.gov on 09 April 2021; †Available interim or final results; ‡Actual or estimated, per clinicaltrials.gov on 09 April 2021; §Primary endpoint.

Musallam KM et al. Am J Hematol 2021; Submitted; Piga A et al. Blood 2019;133:1279-89; Cappellini MD et al. N Engl J Med 2020;382:1219-1231; Cappellini MD et al. Haematologica 2019;104:477-484.

Luspatercept: key findings from the phase 2 trial

Piga A et al. Blood 2019;133:1279-1289.

BELIEVE: a randomized, double-blind, placebo-controlled, phase 3 study of luspatercept in adults with TDT
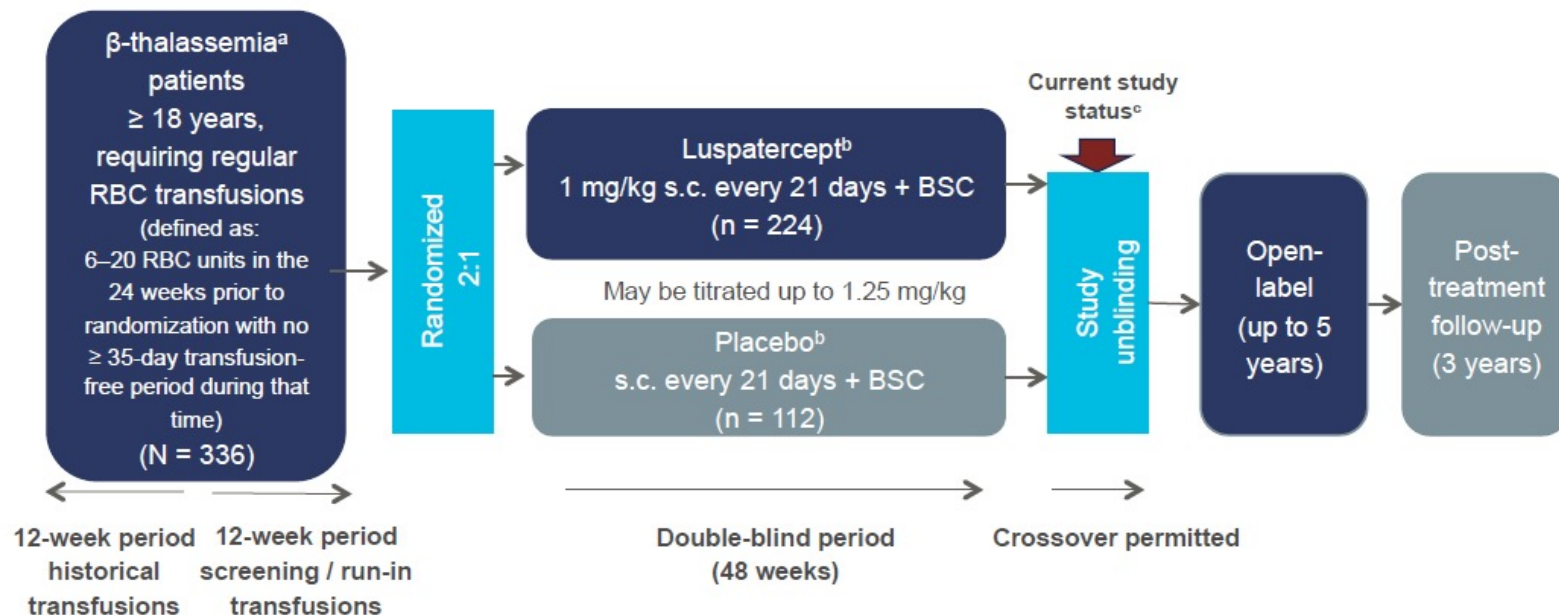
[a] β-thalassemia or hemoglobin E / β-thalassemia (β-thalassemia with mutation and / or multiplication of α-globin was allowed. [b] RBC transfusions and iron chelation therapy to maintain each patient's baseline hemoglobin level. [c] The trial is fully enrolled and patients continue to receive treatment or follow-up. BSC, best supportive care; RBC, red blood cell; s.c., subcutaneously.

Cappellini MD *et al. N Engl J Med* 2020;382:1219-1231.

Primary endpoint met: Rate of erythroid response

A significantly greater proportion of luspatercept-treated patients achieved a ≥33% reduction from baseline in transfusion burden during weeks 13 to 24

■ Luspatercept
■ Placebo

P < 0.0001
(OR 5.79, 95% CI 2.24–14.97)

Patients Achieving ≥ 33% Transfusion Burden Reduction (%)

21.4%
(n = 48)

4.5%

Luspatercept
(n = 224)

Placebo
(n = 112)

Cappellini MD *et al. N Engl J Med* 2020;382:1219-1231.
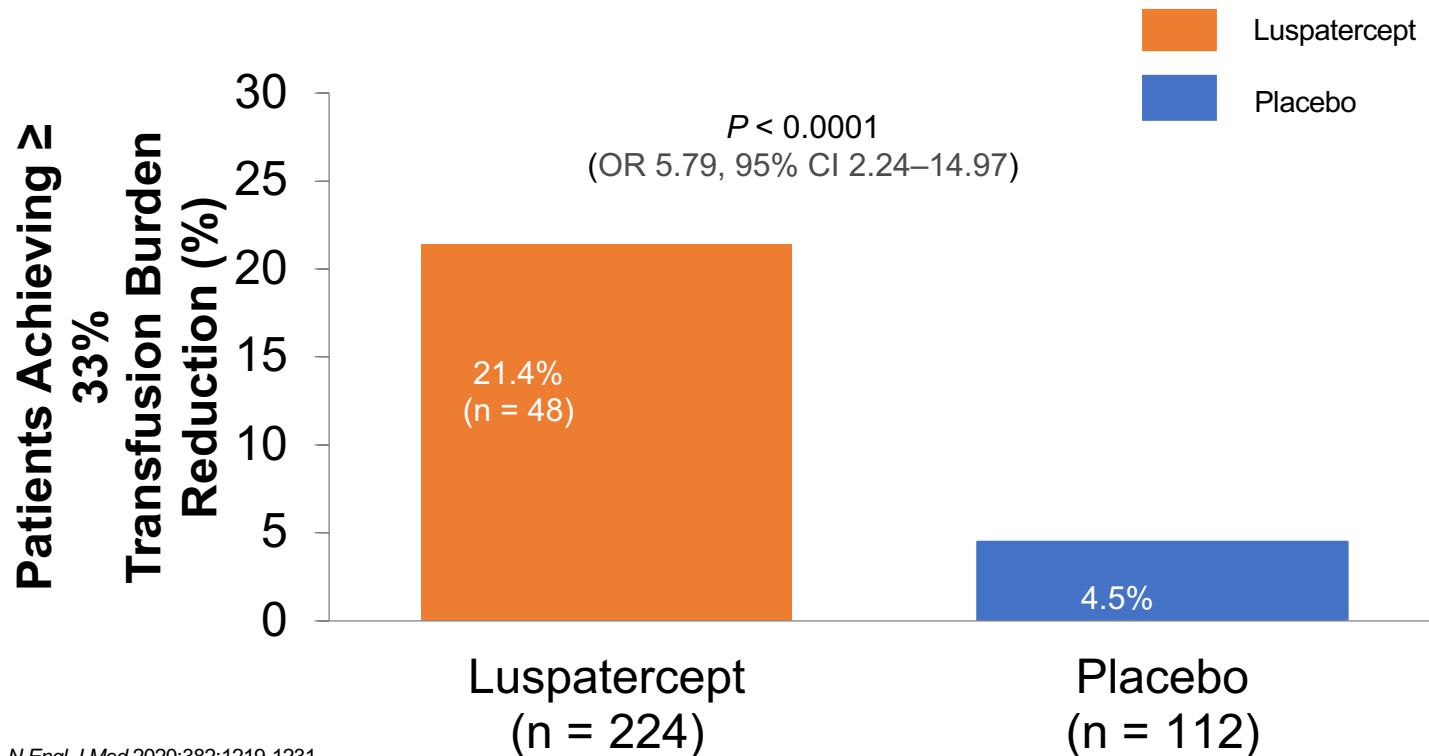
Primary endpoint: Subgroup analysis favors luspatercept

| Sub-groups		Luspatercept n/N (%)	Placebo n/N (%)	OR (95% CI)	P value
Overall		48/224 (21.4)	5/112 (4.5)	5.79 (2.24, 14.97)	< 0.0001
Region: North America & Europe		23/100 (23.0)	1/51 (2.0)	14.94 (1.95, 114.12)	0.0009
Region: Middle East & North Africa		11/52 (21.2)	2/26 (7.7)	3.22 (0.66, 15.77)	0.1351
Region: Asia–Pacific		14/72 (19.4)	2/35 (5.7)	3.98 (0.85, 18.62)	0.0629
Age: ≤ 32 years		22/129 (17.1)	4/63 (6.3)	3.00 (0.98, 9.20)	0.0476
Age: > 32 years		26/95 (27.4)	1/49 (2.0)	17.50 (2.27, 134.98)	0.0004
Splenectomy: Yes		31/129 (24.0)	2/65 (3.1)	9.72 (2.22, 42.53)	0.0003
Splenectomy: No		17/95 (17.9)	3/47 (6.4)	2.94 (0.81, 10.69)	0.0918
Sex: Female		35/132 (26.5)	4/63 (6.3)	5.33 (1.80, 15.80)	0.0011
Sex: Male		13/92 (14.1)	1/49 (2.0)	8.05 (1.01, 64.16)	0.0218
β-thalassemia Gene: β^0/β^0		9/68 (13.2)	2/35 (5.7)	2.54 (0.48, 13.51)	0.2708
β-thalassemia Gene: Non-β^0/β^0		39/155 (25.2)	3/77 (3.9)	8.35 (2.47, 28.23)	< 0.0001
Baseline Transfusion Burden: ≤ 6 units/12 weeks		27/112 (24.1)	3/56 (5.4)	5.61 (1.60, 19.65)	0.0033
Baseline Transfusion Burden: > 6 units/12 weeks		21/112 (18.8)	2/56 (3.6)	6.16 (1.38, 27.44)	0.0082
Baseline Hemoglobin: < 9 g/dL		22/87 (25.3)	4/51 (7.8)	3.78 (1.25, 11.42)	0.0128
Baseline Hemoglobin: ≥ 9 g/dL		26/137 (19.0)	1/61 (1.6)	14.17 (1.85, 108.79)	0.0012
Baseline Liver Iron: ≤ 3 mg/g dry weight		12/70 (17.1)	1/37 (2.7)	7.18 (0.88, 58.63)	0.0335
Baseline Liver Iron: > 3 to ≤ 7 mg/g dry weight		13/51 (25.5)	0/30 (0)	Infinity	0.0053
Baseline Liver Iron: > 7 to ≤ 15 mg/g dry weight		10/38 (26.3)	1/19 (5.3)	5.41 (0.67, 43.34)	0.0741
Baseline Liver Iron: > 15 mg/g dry weight		13/65 (20.0)	3/26 (11.5)	1.79 (0.47, 6.78)	0.3831

0.1 1 10 100

← Favors placebo   Favors luspatercept →

Cappellini MD et al. N Engl J Med 2020;382:1219-1231.
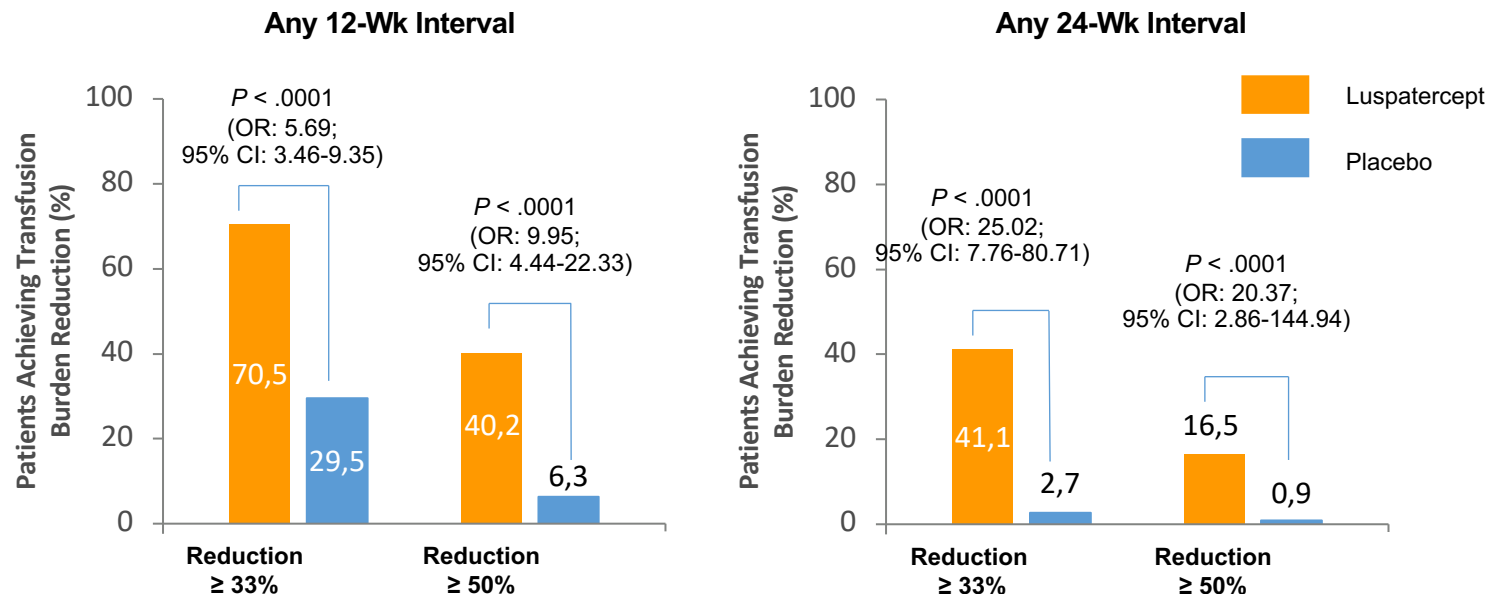
All key secondary endpoints met: Rates of erythroid response

A significantly greater proportion of luspatercept-treated patients achieved clinically meaningful reductions in transfusion burden of ≥ 33% and ≥ 50%
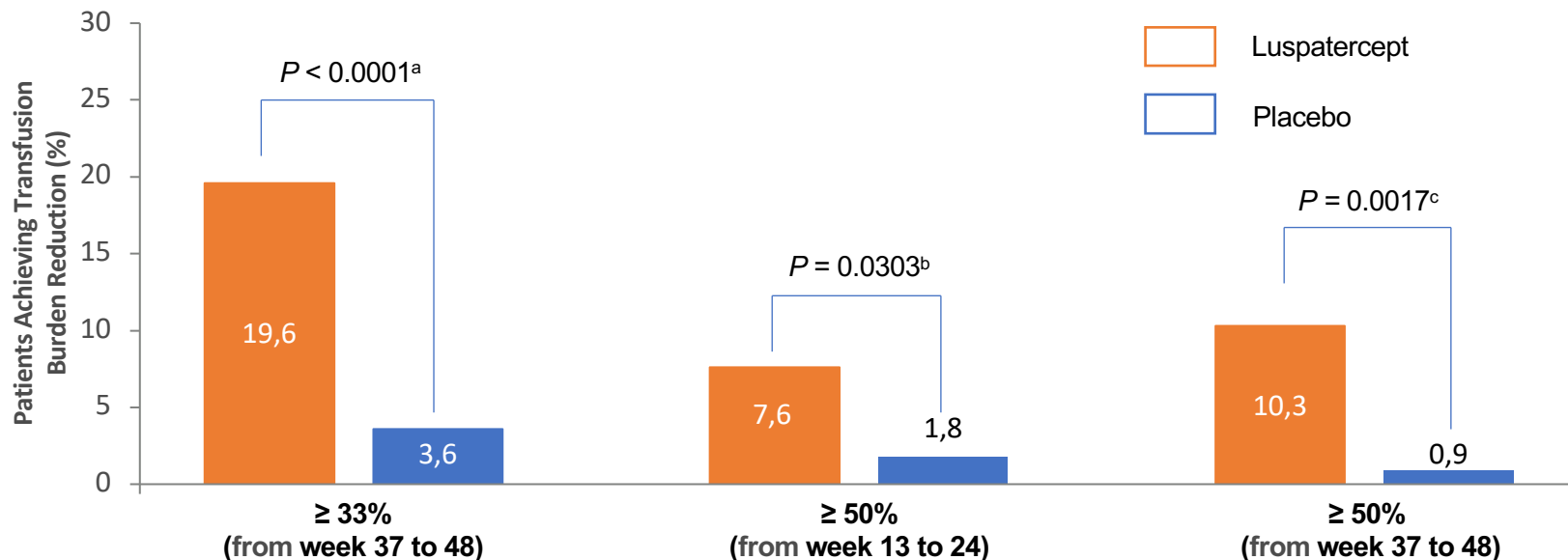
- The least squares mean change in transfusion burden from baseline to weeks 13–24 (luspatercept versus placebo) was −1.35 RBC units/12 weeks (95% CI −1.77 to −0.93; $P < 0.0001$)

[a]OR 6.44, 95% CI 2.27–18.26. [b] OR 4.55, 95% CI 1.03–20.11. [c] OR 11.92, 95% CI 1.65–86.29.

Cappellini MD *et al. N Engl J Med* 2020;382:1219-1231.

Reduction in RBC transfusion burden during any 12-Wk and 24-Wk interval

Any 12-Wk Interval

P < .0001
(OR: 5.69;
95% CI: 3.46-9.35)

P < .0001
(OR: 9.95;
95% CI: 4.44-22.33)

Patients Achieving Transfusion Burden Reduction (%)

70,5   29,5   40,2   6,3

Reduction ≥ 33%   Reduction ≥ 50%

Any 24-Wk Interval

Luspatercept
Placebo

P < .0001
(OR: 25.02;
95% CI: 7.76-80.71)

P < .0001
(OR: 20.37;
95% CI: 2.86-144.94)

Patients Achieving Transfusion Burden Reduction (%)

41,1   2,7   16,5   0,9

Reduction ≥ 33%   Reduction ≥ 50%

Significantly more patients treated with luspatercept vs placebo achieved reductions in RBC transfusion burden of ≥ 33% and ≥ 50% during any 12-wk or 24-wk interval

Cappellini MD *et al. N Engl J Med* 2020;382:1219-1231.

The BELIEVE study

The BELIEVE study, a phase 3, double-blind, randomized trial, showed the efficacy and safety of luspatercept in adult patients with TDT[1]

- Patients treated with luspatercept were significantly more likely to achieve a ≥ 33% reduction in RBC transfusion burden (primary endpoint) compared with placebo[1]

- Subsequent analysis has shown that patients in the ITT population continue to benefit from longer-term luspatercept treatment[2]

Patients experiencing ≥ 33% reduction in RBC transfusion burden during weeks 1-24 (primary endpoint)

Patients experiencing ≥ 33% reduction in RBC transfusion burden (any 12-week interval)
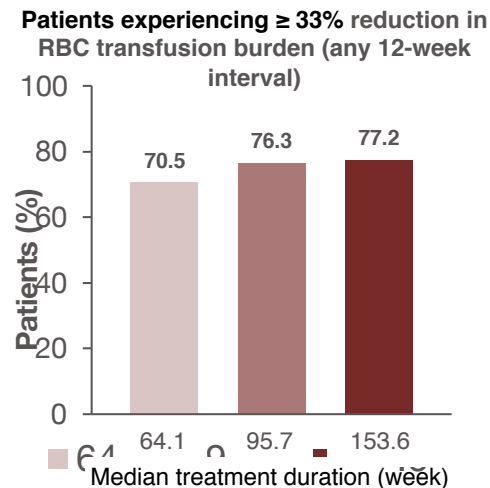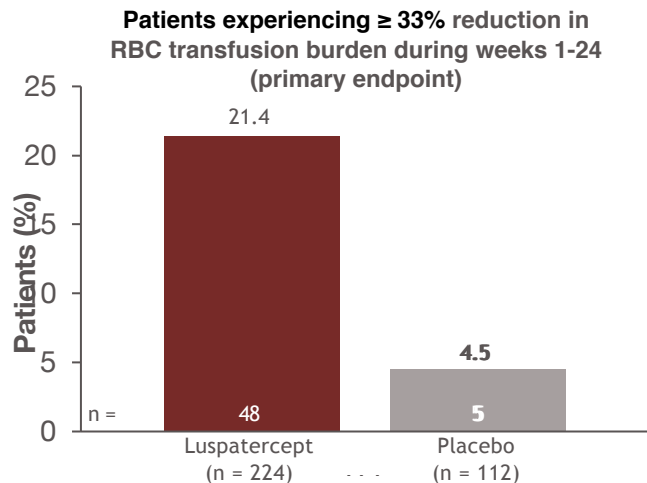
TDT, transfusion-dependent thalassemia. [1]Cappellini MD, et al. *N Engl J Med* 2020;382:1219-1231. Primary database lock, data cut: May 11, 2018.; [2]Cappellini MD, et al. *HemaSphere* 2022;6 [Suppl 3]. Abstract 270.

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TEAE with >10% frequency

n (%)	Luspatercept (n = 223[a])	Placebo (n = 109[a])
Back pain	61 (27.4)	32 (29.4)
Upper respiratory tract infection	59 (26.5)	36 (33.0)
Headache	58 (26.0)	26 (23.9)
Bone pain	**44 (19.7)**	**9 (8.3)**
Arthralgia	**43 (19.3)**	**13 (11.9)**
Pyrexia	36 (16.1)	23 (21.1)
Cough	32 (14.3)	12 (11.0)
Fatigue	30 (13.5)	14 (12.8)
Oropharyngeal pain	28 (12.6)	12 (11.0)
Diarrhea	27 (12.1)	11 (10.1)
Dizziness	**25 (11.2)**	**5 (4.6)**
Asthenia	22 (9.9)	11 (10.1)
Myalgia	22 (9.9)	11 (10.1)
Pharyngitis	20 (9.0)	13 (11.9)

[a] Safety population.

Cappellini MD *et al. N Engl J Med* 2020;382:1219-1231.

Luspatercept approval

Luspatercept has been approved by the US Food and Drug Administration (FDA) in 2019 and by the European Medicines Agency (EMA) in 2020 to treat anemia in adult patients with beta-thalassemia who require regular red blood cell transfusions

Effect of luspatercept in β-thalassemia patients with β⁰/β⁰ genotype: a subgroup analysis of the BELIEVE study

Sujit Sheth,[1] Olivier Hermine,[2,3] Ali T. Taher,[4] Kevin H. M. Kuo,[5] John B. Porter,[6]

Antonio G. Piga,[7] Thomas D. Coates,[8,9] Antonis Kattamis,[10] Loyse Felber Medlin,[11]

Wen-Ling Kuo,[12] Natalia Holot,[12] Maria Domenica Cappellini[13]

Objective

To investigate the long-term efficacy
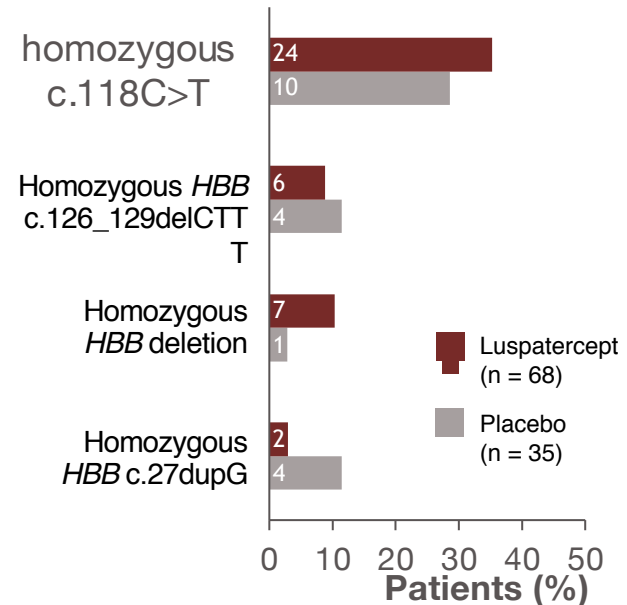of luspatercept in patients with
β^0/β^0 genotypes from the BELIEVE trial

Sheth S, et al. ASH 2022 [Abstract #804]

Patients with β0/β0 genotypes

The BELIEVE study enrolled 336 patients

103 patients had a β⁰/β⁰ genotype[a]…
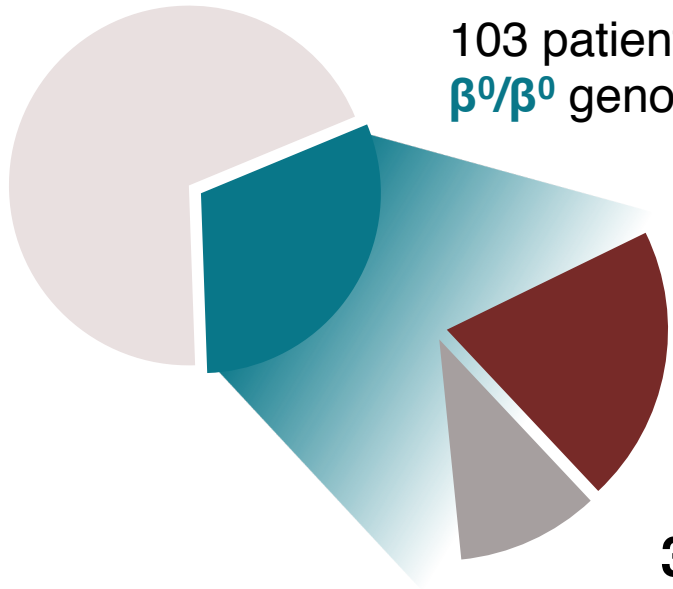
The most common **β⁰/β⁰** genotypes in each group were:

68 of whom received **luspatercept**

35 of whom received **placebo**

homozygous c.118C>T — 24 (Luspatercept), 10 (Placebo)

Homozygous *HBB* c.126_129delCTTT — 6 (Luspatercept), 4 (Placebo)

Homozygous *HBB* deletion — 7 (Luspatercept), 1 (Placebo)

Homozygous *HBB* c.27dupG — 2 (Luspatercept), 4 (Placebo)

Luspatercept (n = 68)

Placebo (n = 35)

0 10 20 30 40 50

Patients (%)

[a]Genotyping was performed if genotype information was not included in the patient's medical history.

Sheth S, et al. ASH 2022 [Abstract #804]

Response to luspatercept

ITT patients (n = 224)   Patients with β^0/β^0 genotype (n = 68)

Patients(%)

Response	ITT	β^0/β^0
≥ 33% reduction in RBC transfusion burden during weeks 1-24 (primary endpoint)	21.4	13.2
≥ 33% reduction in RBC transfusion burden during any 12 weeks[a]	77.2	76.5
≥ 50% reduction in RBC transfusion burden during any 12 weeks[a]	50.0	52.9
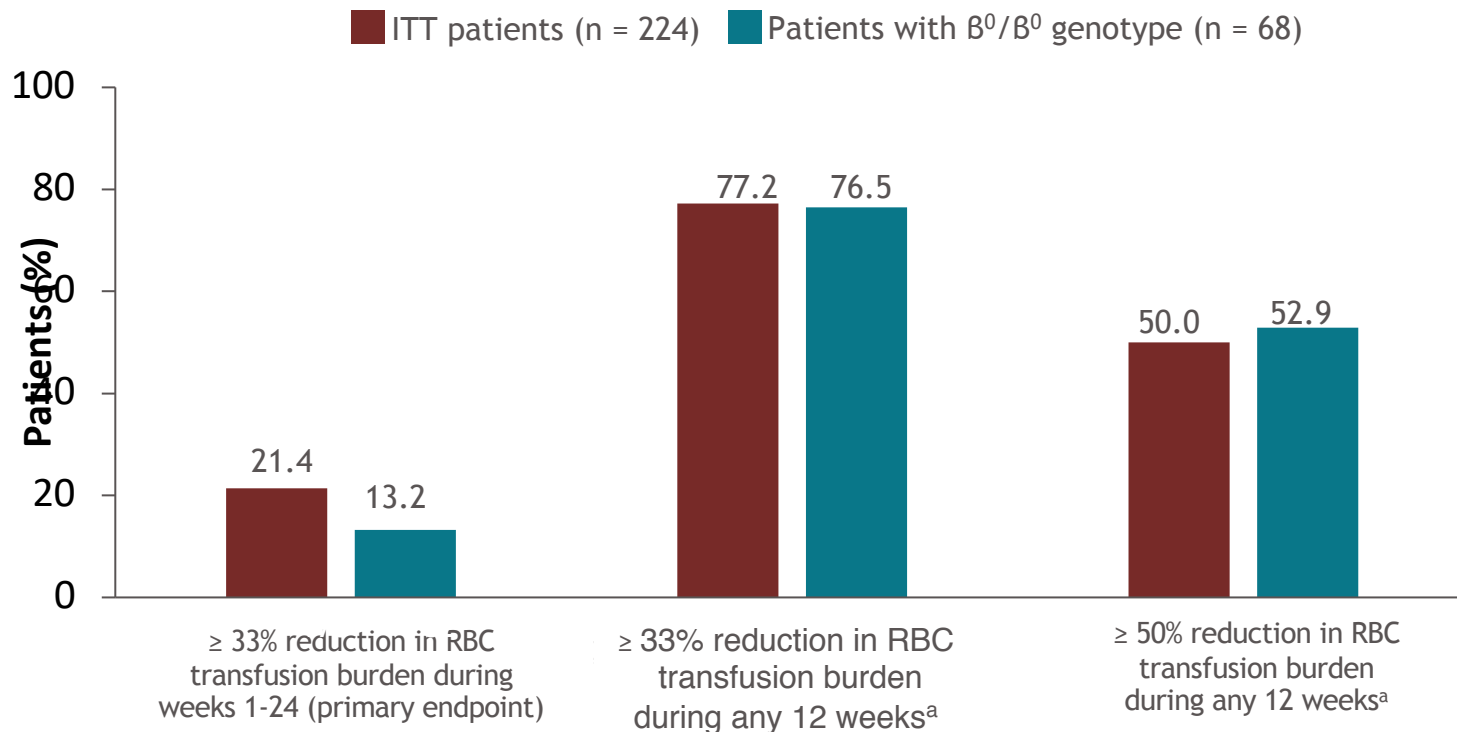
[a]During any 12-week interval over entire treatment period. ITT, intent-to-treat; RBC, red blood cell.

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Median total duration of response

Legend: ITT patients (n = 224) — Patients with β^0/β^0 genotype (n = 68)

≥ 33% reduction in RBC transfusion burden[a]
- n = 173: 586.0 (84–1300)
- n = 52: 516.5 (84–1243)

≥ 50% reduction in RBC transfusion burden[a]
- n = 112: 357.5 (84–1267)
- n = 36: 276.5 (84–1165)

X-axis: Time (days) — 0, 100, 200, 300, 400, 500, 600, 700
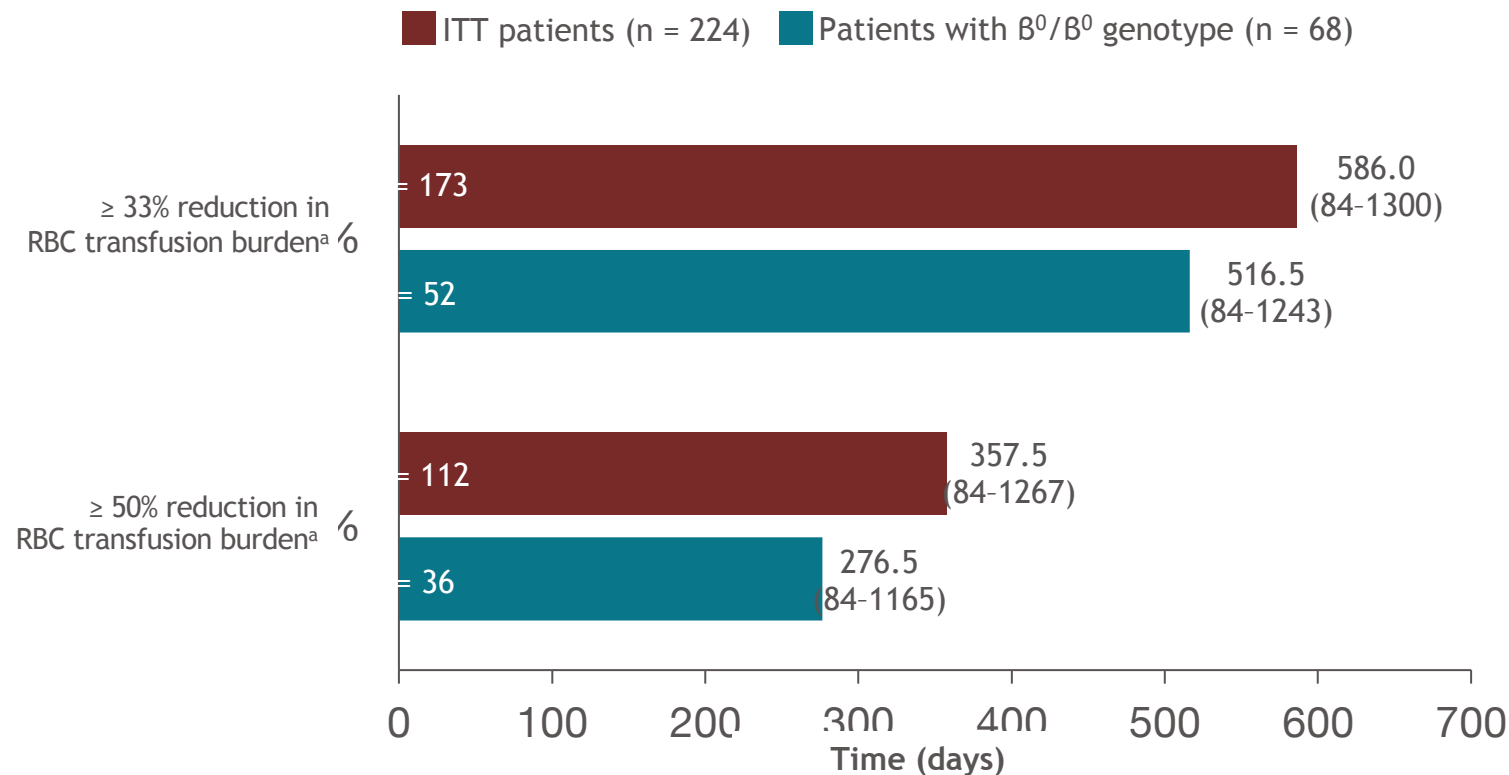
[a]During any 12-week interval. ITT, intent-to-treat; RBC, red blood cell.

Sheth S, et al. ASH 2022 [Abstract #804]

RBC transfusion independence

Legend: ITT patients (n = 224); Patients with β^0/β^0 genotype (n = 68)

Y-axis: Patients (%) — 0, 5, 10, 15, 20, 25, 30

Interval	ITT patients	β^0/β^0 genotype
Any 6-week interval	25.4	25.0
Any 8-week interval	12.1	10.3
Any 12-week interval	4.9	2.9

ITT, intent-to-treat.

Sheth S, et al. ASH 2022 [Abstract #804]

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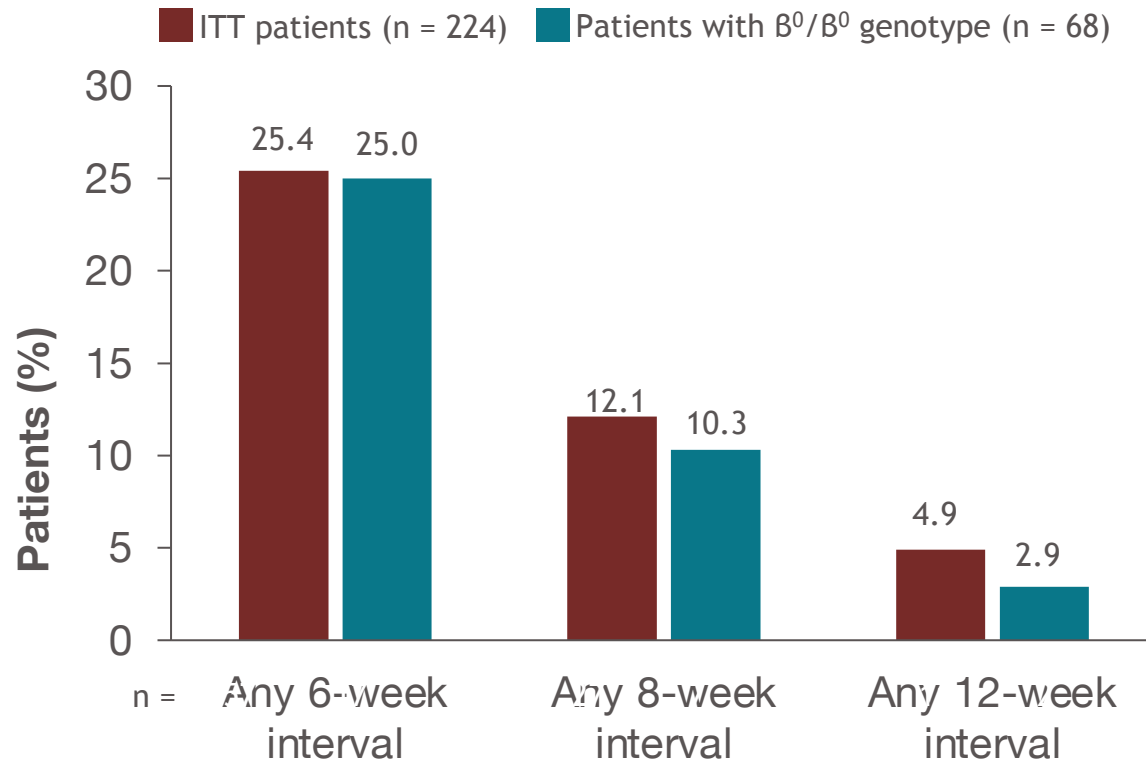
Response to luspatercept by β^0/β^0 genotype and splenectomy status
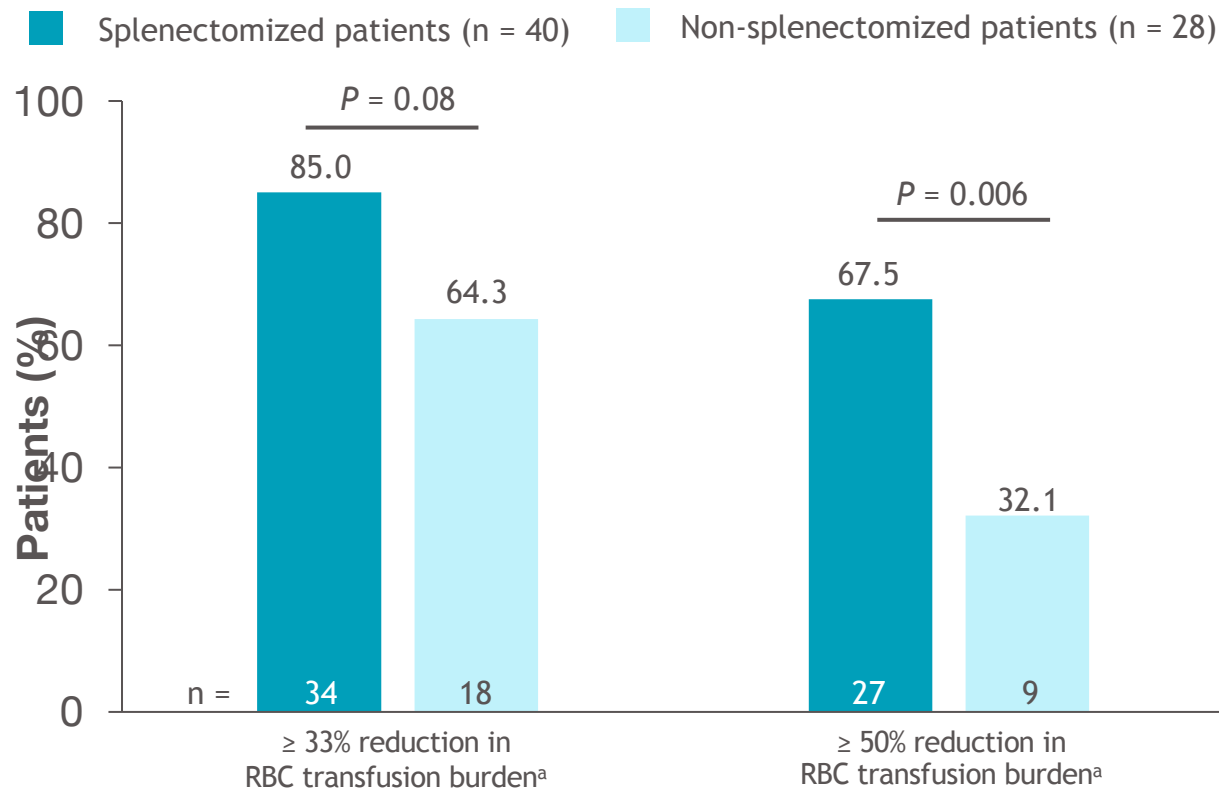
Median (range) luspatercept treatment duration: 153.43 (6.0-203.1) weeks for splenectomized vs 153.71 (5.1–180.1) weeks for non-splenectomized patients.
[a]During any 12-week interval. RBC, red blood cell.

Sheth S, et al. ASH 2022 [Abstract #804]

Summary

- Patients with a β^0/β^0 genotype have the most severe disease and transfusion burden of all patients with β-thalassemia

- In the BELIEVE trial, patients with a β^0/β^0 genotype treated with luspatercept experienced similar RBC transfusion reductions compared with the ITT population

- More splenectomized patients with a β^0/β^0 genotype achieved reductions in RBC transfusion burden compared with β^0/β^0 patients who were not splenectomized

  — Further research is required to determine why a higher proportion of splenectomized patients with a β^0/β^0 genotype achieved response

- The benefit of luspatercept has the potential to be extended to other patient populations who rely on limited sources of blood for RBC transfusions

These longer-term data demonstrate the efficacy of luspatercept in a patient population with severe disease representation

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Sheth S, et al. ASH 2022 [Abstract #804]

Effect of luspatercept on red blood cell transfusion burden, iron chelation therapy, and iron overload in adults with transfusion-dependent β-thalassemia from the BELIEVE trial: a long-term analysis

Olivier Hermine, Maria Domenica Cappellini, Ali T Taher, Thomas D Coates, Vip Viprakasit, Antonis Kattamis, Jeevan K Shetty, Marija Bosilkovska Weisskopf, Natalia Holot, Sadanand Vodala, Wen-Ling Kuo, John B Porter
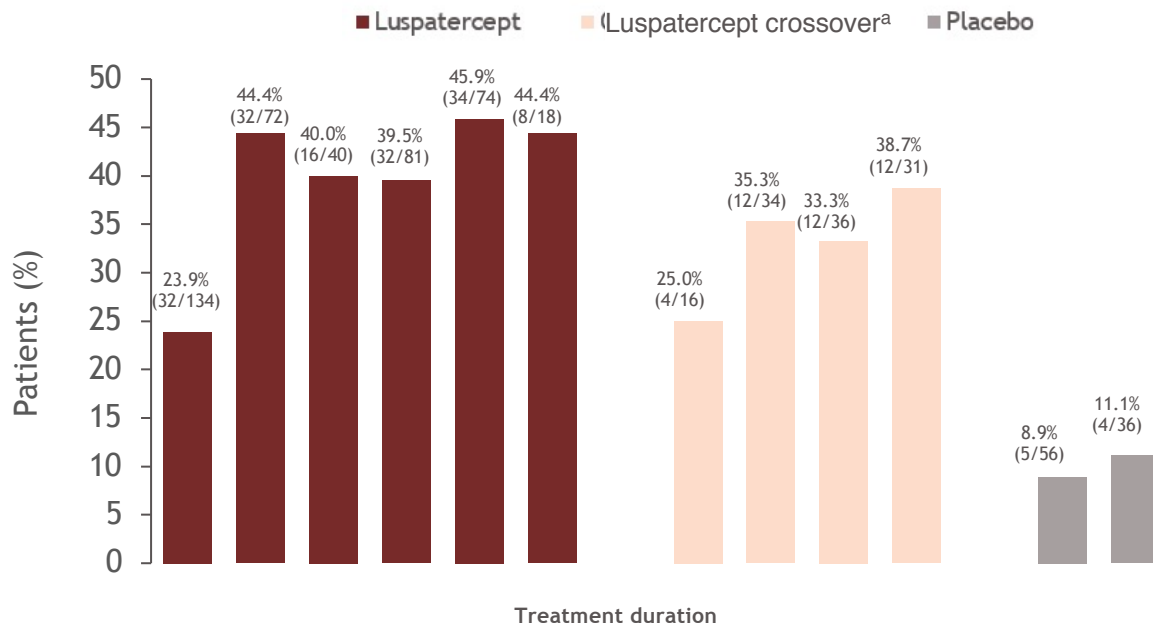
Presentation Number 3671   ASH 2022

Results

Figure 1. Mean change from baseline in mean RBC transfusion burden
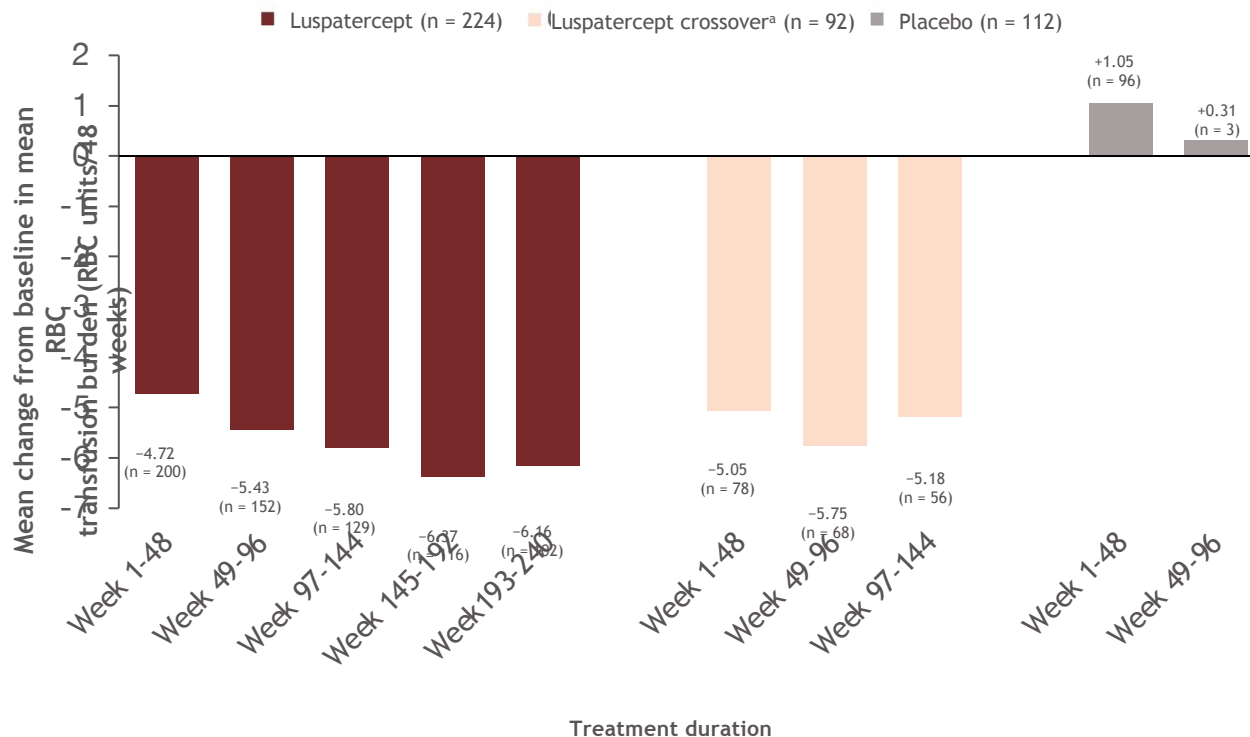
Footnote: [a]Luspatercept crossover patients were first randomized to receive placebo for ≤ 96 weeks prior to crossing over to begin luspatercept treatment.

Results (cont.)

Figure 4. Proportion of patients who shifted from baseline SF levels ≥ 1,000 μg/L to < 1,000 μg/L

Legend: ■ Luspatercept   (Luspatercept crossover[a]   ■ Placebo

Bar values:
- 23.9% (32/134)
- 44.4% (32/72)
- 40.0% (16/40)
- 39.5% (32/81)
- 45.9% (34/74)
- 44.4% (8/18)
- 25.0% (4/16)
- 35.3% (12/34)
- 33.3% (12/36)
- 38.7% (12/31)
- 8.9% (5/56)
- 11.1% (4/36)

Y-axis: Patients (%)
X-axis: Treatment duration

[a]Luspatercept crossover patients were first randomized to receive placebo for ≤ 96 weeks prior to crossing over to begin luspatercept treatment.

Luspatercept dose modifications in β-thalassemia

Prior to each luspatercept administration, assess the patient's (pre-transfusion) Hb level[1,2]

In patients who do not achieve a response* at 1.00 mg/kg, increase dose to

1.25 mg/kg[†]

Starting dose

1.00 mg/kg

Weeks   3   6   9   12   15
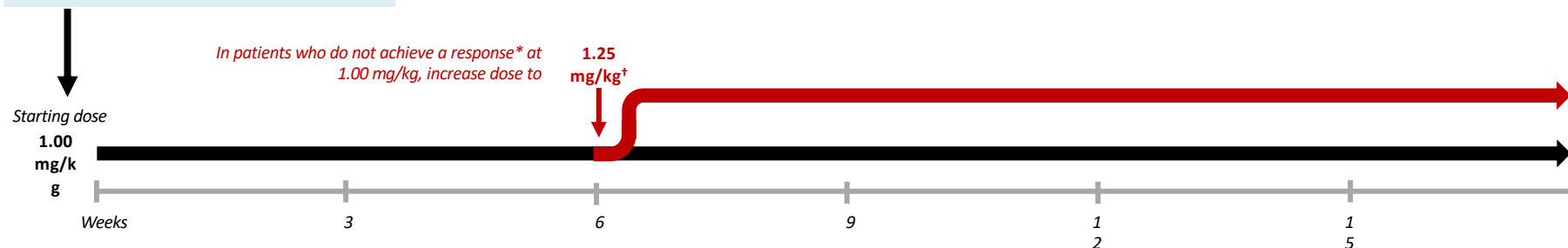
- If no response (after ≥2 consecutive doses) or patient loses response, increase to 1.25 mg/kg[1,2]

» If in 3 weeks, Hb 10.5–11.5, give luspatercept but reduce transfusion volume (1 unit instead of 2)[‡]

» If the Hb level is ≥11.5 g/dL in the absence of transfusion for at least 3 weeks, the dose should be delayed until the Hb is ≤11.0 g/dL[2]

» Monitor for response; if no response after 9 weeks of treatment, discontinue luspatercept

*Defined as a reduction in RBC transfusion burden of at least a third after ≥2 consecutive doses (6 weeks). [†]The dose should not be increased beyond the maximum dose of 1.25 mg/kg every 3 weeks[1,2].
[‡]Presenter's conclusions.
1. Reblozyl® US Prescribing Information. FDA. 10/2021. https://packageinserts.bms.com/pi/pi_reblozyl.pdf Accessed May 2022. 2. Reblozyl® Summary of Product Characteristics. EMA. 07/2021.
https://www.ema.europa.eu/en/documents/product-information/reblozyl-epar-product-information_en.pdf Accessed May 2022.

Transfusion requirement is now used to distinguish two major clinical phenotypes: NTDT and TDT

- This allowed standardization of research and clinical management based on transfusion-requirement, a key driver in pathophysiology
- It also recognized that severe morbidity can be observed across both intermedia and major patients
- International management guidelines have been developed for NTDT and TDT separately

Non-transfusion-dependent thalassemia (NTDT)
- β-thalassaemia intermedia
- Mild/moderate HbE/β-thalassemia
- HbH disease (α-thalassemia intermedia)

Transfusions seldom required

Occasional transfusions required (e.g. surgery, pregnancy, infection)

Intermittent transfusions required (e.g. poor growth and development, specific morbidities)

Regular, lifelong transfusions required for survival

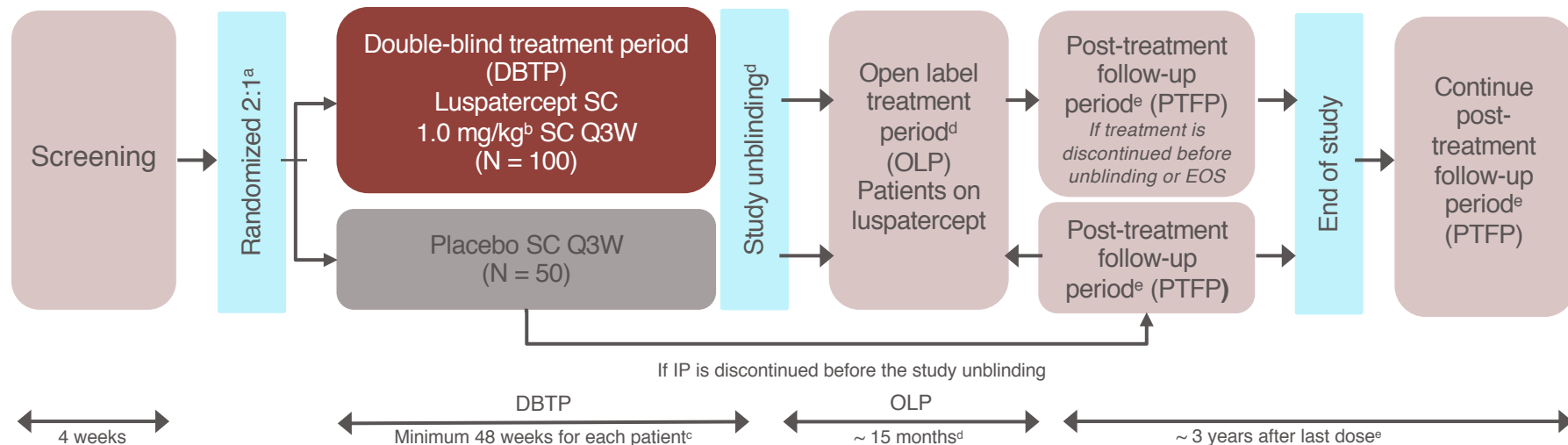Transfusions not required
- α-thalassemia trait
- β-thalassemia minor

Transfusion-dependent thalassemia (TDT)
- β-thalassaemia major
- Severe HbE/β-thalassemia
- Hb Barts hydrops (α-thalassemia major)

GUIDELINES FOR THE MANAGEMENT OF TRANSFUSION DEPENDENT THALASSAEMIA (TDT)

3RD EDITION

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GUIDELINES FOR THE MANAGEMENT OF NON TRANSFUSION DEPENDENT THALASSAEMIA (NTDT) 2ND EDITION

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Musallam KM *et al. Haematologica* 2013;98:833-844.

Phase II RCT trial of luspatercept in adults with NTDT: The BEYOND trial
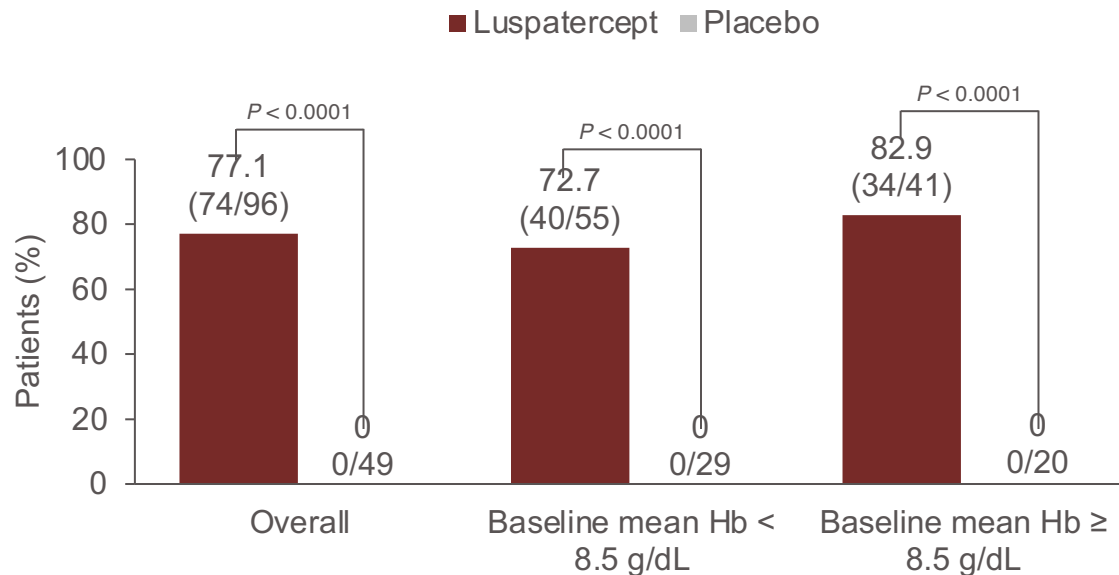

» **Primary endpoint**

— Achievement of ≥ 1.0 g/dL mean Hb increase from baseline over a continuous 12-week interval during weeks 13–24 in the absence of RBC transfusions

» **Key secondary endpoint**

— Mean change from baseline in NTDT-PRO T/W domain score over a continuous 12-week interval during weeks 13–24

Taher AT *et al*. EHA 2021; Presentation Number S101.

BEYOND results: primary endpoint

- **The study met its primary endpoint**

  - 74 (77.1%) of patients in the luspatercept arm vs 0 placebo patients achieved a mean Hb increase of ≥ 1.0 g/dL from baseline[a] over a continuous 12-week interval during weeks 13–24 in the absence of RBC transfusions
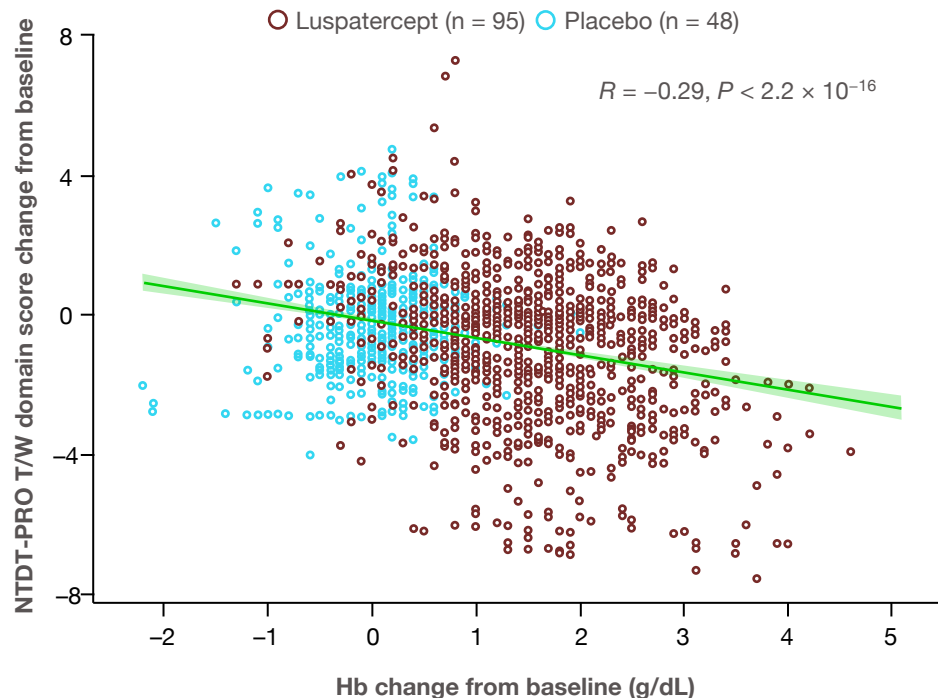
Key secondary endpoint

Mean change in NTDT-PRO T/W scores from baseline
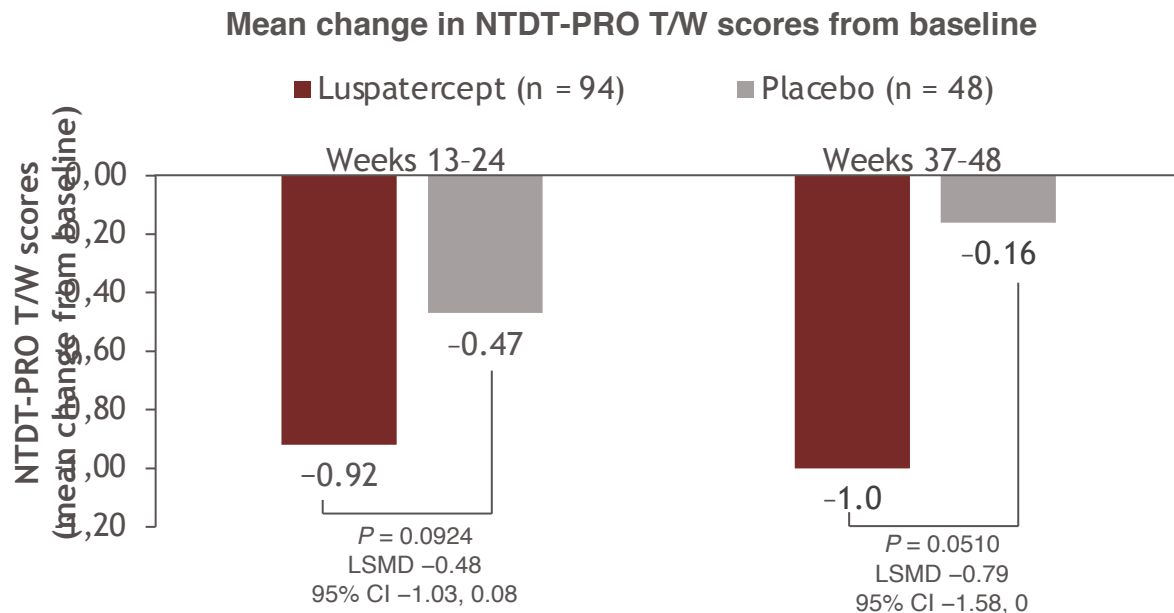
- Improvement in NTDT-PRO T/W scores from baseline occurred more frequently in patients receiving luspatercept compared with placebo during weeks 13–24 and 37–48

## NTDT-PRO T/W domain score improvement and Hb increase

$R = -0.29, P < 2.2 \times 10^{-16}$

Legend: Luspatercept (n = 95)　Placebo (n = 48)

Y-axis: NTDT-PRO T/W domain score change from baseline

X-axis: Hb change from baseline (g/dL)

- Improvement in NTDT-PRO T/W domain scores was correlated with Hb increase

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A closer look at changes in hemoglobin levels in patients with non-transfusion dependent β-thalassemia treated with luspatercept: post hoc analysis of the phase 2 BEYOND trial

Khaled M. Musallam,[1] Ali T. Taher,[2] John B. Porter,[3] Antonis Kattamis,[4] Mrudula Glassberg,[5] Luciana Bueno,[6] Jeevan Shetty,[6] Frederik Lersch,[6] Barbara Rosettani,[6] Maria Domenica Cappellini[7]
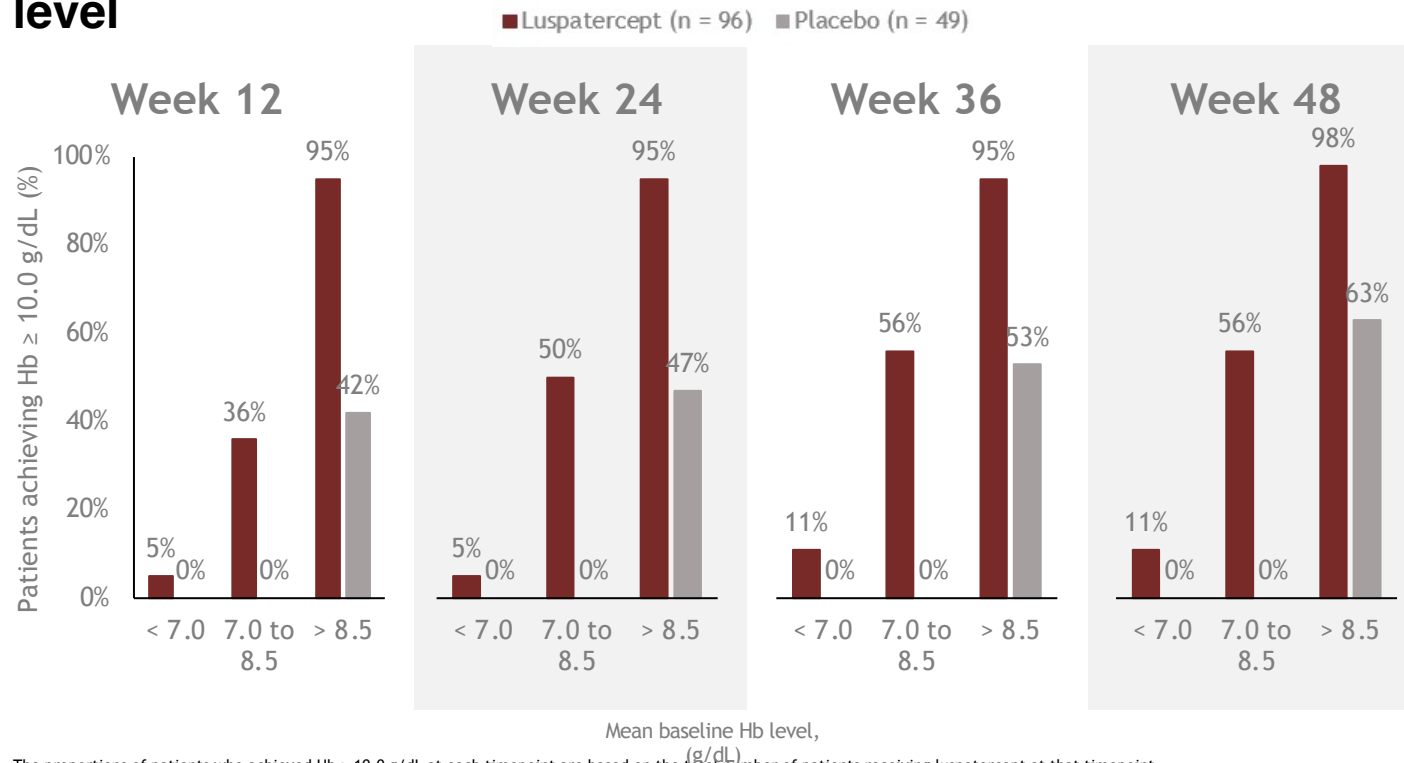
ASH 2022Presentation Number 2349

Results

Figure 2. Patients receiving luspatercept achieving Hb > 10 g/dL by timepoint
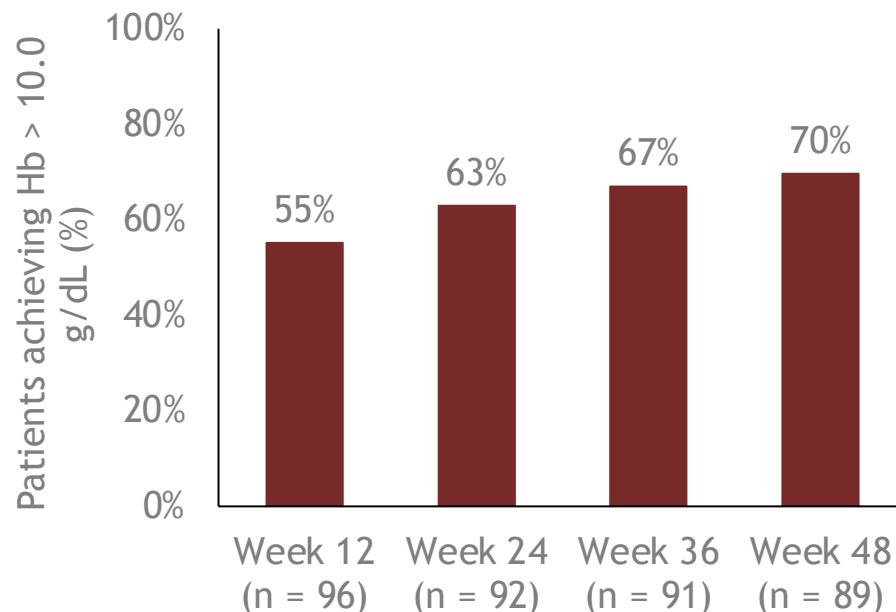
The proportions of patients who achieved Hb > 10.0 g/dL at each timepoint are based on the total number of patients receiving luspatercept at that timepoint. Hb, hemoglobin.

Results

Figure 3. Patients achieving Hb ≥ 10 g/dL by baseline Hb level

The proportions of patients who achieved Hb ≥ 10.0 g/dL at each timepoint are based on the total number of patients receiving luspatercept at that timepoint.
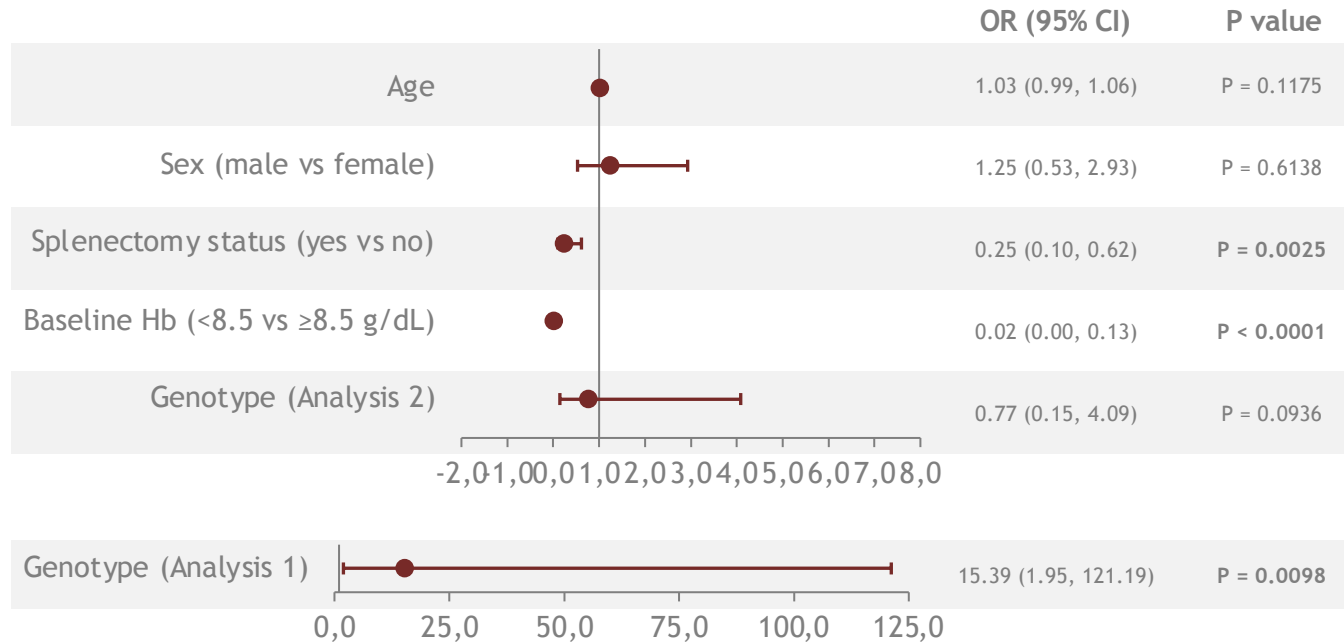Hb, hemoglobin.

Results

Figure 4. Predictors of achieving Hb > 10.0 g/dL at Week 48

	OR (95% CI)	P value
Age	1.03 (0.99, 1.06)	P = 0.1175
Sex (male vs female)	1.25 (0.53, 2.93)	P = 0.6138
Splenectomy status (yes vs no)	0.25 (0.10, 0.62)	**P = 0.0025**
Baseline Hb (<8.5 vs ≥8.5 g/dL)	0.02 (0.00, 0.13)	**P < 0.0001**
Genotype (Analysis 2)	0.77 (0.15, 4.09)	P = 0.0936
Genotype (Analysis 1)	15.39 (1.95, 121.19)	**P = 0.0098**

Genotype Analysis 1: B0/B, B+/B with Alpha gene duplication vs B0/B0, B+/B+, B+/B0 without alpha-thalassemia
Genotype analysis 2: B0/B0, B+/B+, B+/B0 with alpha-thalassemia vs B0/B0, B+/B+, B+/B0 without alpha-thalassemia

Results

Achievement of ≥ 1 g/dL Hb increase by baseline Hb level

- The ORs (95% CI) for achievement of ≥ 1 g/dL increase during any rolling 24-week period were compared to the reference group of those with baseline Hb < 7.0 g/dL:
  - Baseline Hb 7.0 to 8.5 g/dL: 3.69 (0.89, 15.27)
  - Baseline Hb > 8.5 g/dL: 3.23 (0.87, 12.76)

Results

Figure 5. Patients achieving a ≥ 1.0 g/dL increase from baseline in mean Hb level during any rolling 24-week period
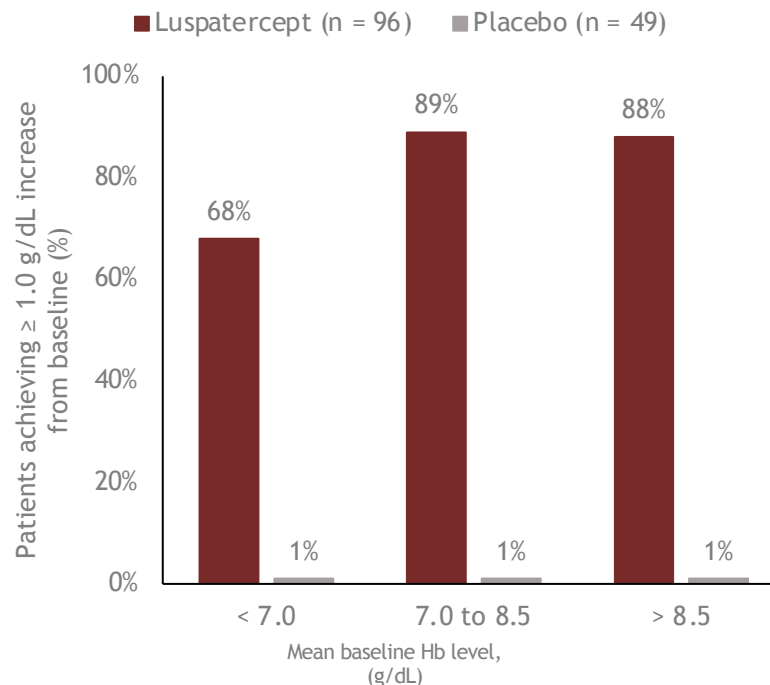
Baseline Hb < 7.0 g/dL: Luspatercept, n = 13/19; placebo, n = x/X.
Baseline Hb ≥ 7.0 and ≤ 8.5 g/dL: Luspatercept, n = 32/36; placebo, n = x/X.
Baseline Hb > 8.5 g/dL: Luspatercept, n = 36/41; placebo, n = x/X.

Conclusions

- This analysis of the BEYOND clinical trial showed the majority of patients with NTDT receiving luspatercept achieved Hb > 10.0 g/dL over time, a-threshold associated with reduced morbidity and mortality

- Clinically relevant Hb level increases of ≥ 1.0 g/dL were observed across all baseline Hb level subgroups

- These findings further support the ability of luspatercept to achieve clinically meaningful increases in Hb levels for patients with NTDT, irrespective of baseline severity of anemia

Acknowledgements

My collaborators in Milan

I thank all the patients, their families, and the investigators who participated in the Luspatercept studies