EUROPEAN HEMATOLOGY ASSOCIATION

Assessment of response to luspatercept by β-globin genotype in adult patients with β-thalassemia in the BELIEVE trial

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Disclosures

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- Leadership/membership on an entity's board of directors or advisory committee
  - CRISPR Therapeutics, Genzyme/Sanofi, Novartis, Vifor Pharma

Introduction

- ß-thalassemia is a genetic blood disorder caused by mutations that downregulate ($ß^+$) or silence ($ß^0$) expression of the *HBB* gene, which encodes the ß-globin chain

- Reduced expression of normal ß-globin leads to ineffective erythropoiesis, anemia, increased iron absorption, and, in TD patients, frequent and lifelong RBC transfusions[1–3]

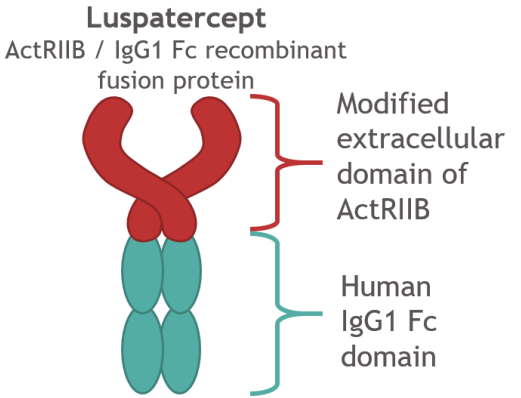
- The majority of patients experience multiple comorbidities due to iron toxicity from frequent RBC transfusions, which may contribute to increased mortality; thus there is a need for treatment options to decrease dependence on transfusions[4]

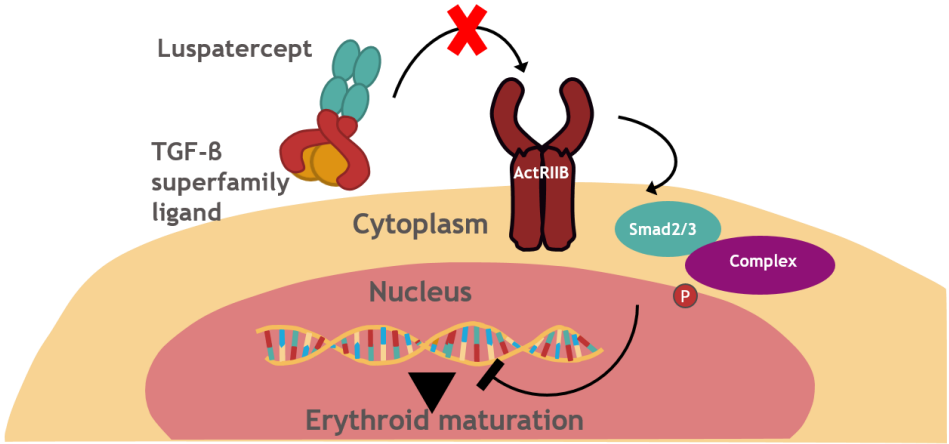
HBB, hemoglobin subunit beta; RBC, red blood cell; TD, transfusion dependent.

1. Higgs DR, et al. *Lancet* 2012;379:373-383. 2. Camaschella C, Nai A. *Br J Haematol* 2016;172:512-523. 3. Taher AT, et al. *Lancet* 2018;391:155-167. 4. Taher AT, et al. *Blood* 2018;132:1781-1791.

Introduction (cont.)

- Luspatercept is a first-in-class erythroid maturation agent that binds to select TGF-β superfamily ligands to diminish Smad2/3 signaling and enhance late-stage erythropoiesis[1]
- Luspatercept was approved by the US FDA for treatment of anemia due to β-thalassemia in adult patients who require regular RBC transfusions,[2] and received positive feedback from CHMP



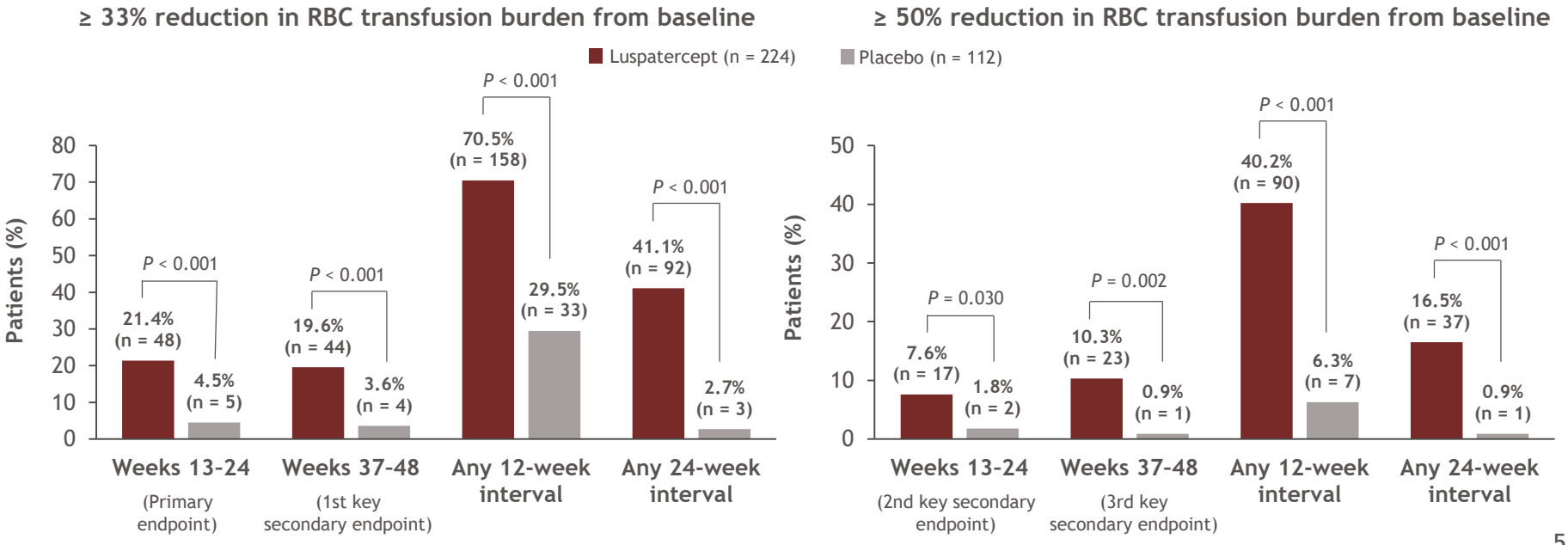


ActRIIB, human activin receptor type IIB; CHMP, Committee for Medicinal Products for Human Use; IgG1 Fc, immunoglobulin G1 fragment crystallizable; TGF-β, transforming growth factor beta; US FDA, United States Food and Drug Administration.

1. Suragani RN, et al. *Nat Med* 2014;20:408-414. 2. Reblozyl® (luspatercept-aamt) [prescribing information]. Summit, NJ: Celgene Corporation; April 2020.

Introduction (cont.)

- The primary results of the BELIEVE study (NCT02604433), a phase 3, double-blind, randomized, placebo-controlled trial evaluating the efficacy and safety of luspatercept in regularly transfused adult patients with β-thalassemia, achieved primary and key secondary endpoints with statistical significance



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

Objective

- To explore the association between β-globin genotype and response to luspatercept in adult patients with β–thalassemia in the BELIEVE trial, as of May 11, 2018

Demographics and baseline characteristics

Characteristic[a]	Luspatercept (n = 224)	Placebo (n = 112)
Age, median (range), years	30 (18–66)	30 (18–59)
Female, n (%)	132 (58.9)	63 (56.3)
Hb (24 weeks), median (range), g/dL[b]	9.31 (4.5–11.4)	9.15 (5.8–11.7)
RBC transfusion burden, median (range), units/12 weeks	6.1 (3–14)	6.3 (3–12)
RBC transfusion burden, median (range), units/24 weeks[c]	14 (6–24)	15 (6–26)
Splenectomy, n (%)	129 (57.6)	65 (58.0)
Serum ferritin, mean (SD), µg/L	2,096.9 (1,756.6)	1,845.1 (1,669.1)
LIC, mean (SD), mg/g dw	12.0 (14.8)	10.1 (11.5)
> 7 mg/g dw, n (%)	103 (46.0)	45 (40.2)
Myocardial iron by T2* MRI, mean (SD), ms	33.5 (16.2)	34.8 (10.7)

[a]Data on endocrine function were not collected; [b]Defined as the mean of all documented pre-transfusion Hb values during the 24 weeks prior to first dose for each patient; [c]Transfusions that occurred on study Day 1 (Dose 1 Day 1) were counted as part of the baseline RBC transfusion burden.
dw, dry weight; Hb, hemoglobin; LIC, liver iron concentration; SD, standard deviation; T2* MRI, T2-weighted magnetic resonance imaging.

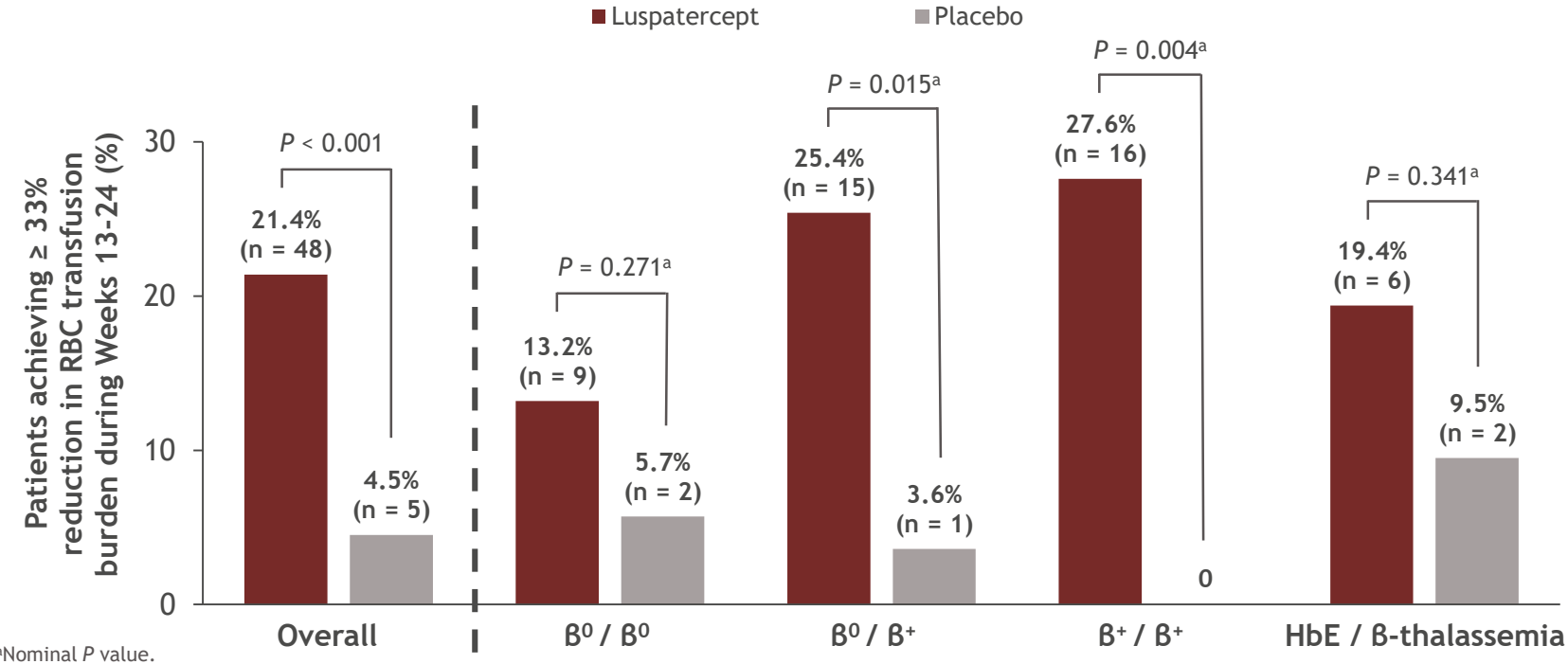
ß-globin genotypes in the intent-to-treat population

Parameter	Luspatercept[a] (n = 224)	Placebo[b] (n = 112)
$ß^0$ / $ß^0$, n (%)	68 (30.4)	35 (31.3)
Baseline RBC transfusion burden, median (range), units/12 weeks	6.3 (3–14)	7.0 (3–11)
$ß^0$ / $ß^+$, n (%)	59 (26.3)	28 (25.0)
Baseline RBC transfusion burden, median (range), units/12 weeks	6.5 (3–11)	7.5 (3–12)
$ß^+$ / $ß^+$, n (%)	58 (25.9)	26 (23.2)
Baseline RBC transfusion burden, median (range), units/12 weeks	6.6 (3–12)	6.0 (4–12)
HbE / ß-thalassemia, n (%)	31 (13.8)	21 (18.8)
Baseline RBC transfusion burden, median (range), units/12 weeks	6.0 (4–12)	7.0 (3–12)

[a]Includes 7 patients with ≥ 1 unmutated ß (including $ß^+$/ß or $ß^0$/ß) and 1 patient who, after randomization, was determined to have α-thalassemia only and was disenrolled.
[b]Includes 2 patients with ≥ 1 unmutated ß.
Data cutoff: May 11, 2018.
HbE, hemoglobin E.

Achievement of ≥ 33% reduction in RBC transfusion burden during Weeks 13-24 (primary endpoint)

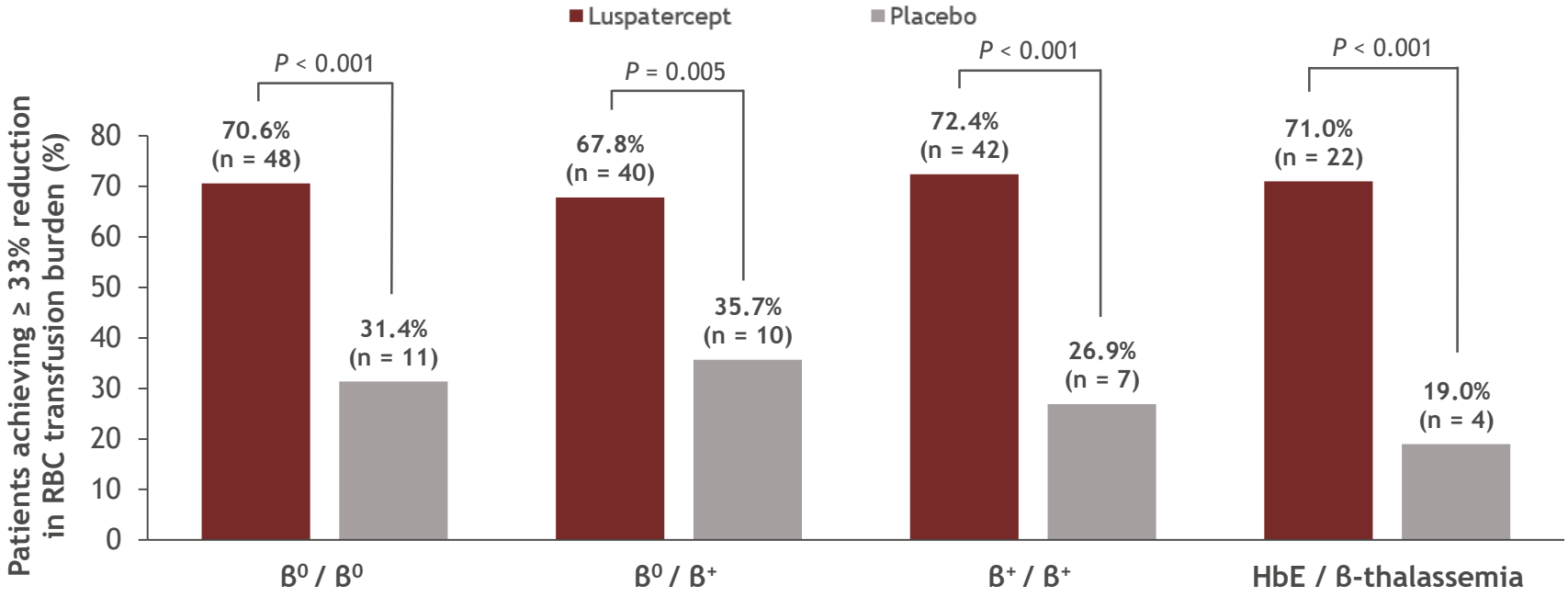
- A greater proportion of luspatercept-treated patients achieved ≥ 33% reduction from baseline in RBC transfusion burden during Weeks 13-24 versus placebo, regardless of β-globin genotype



aNominal *P* value.
Data cutoff: May 11, 2018.

Achievement of ≥ 33% reduction in RBC transfusion burden during any 12 weeks

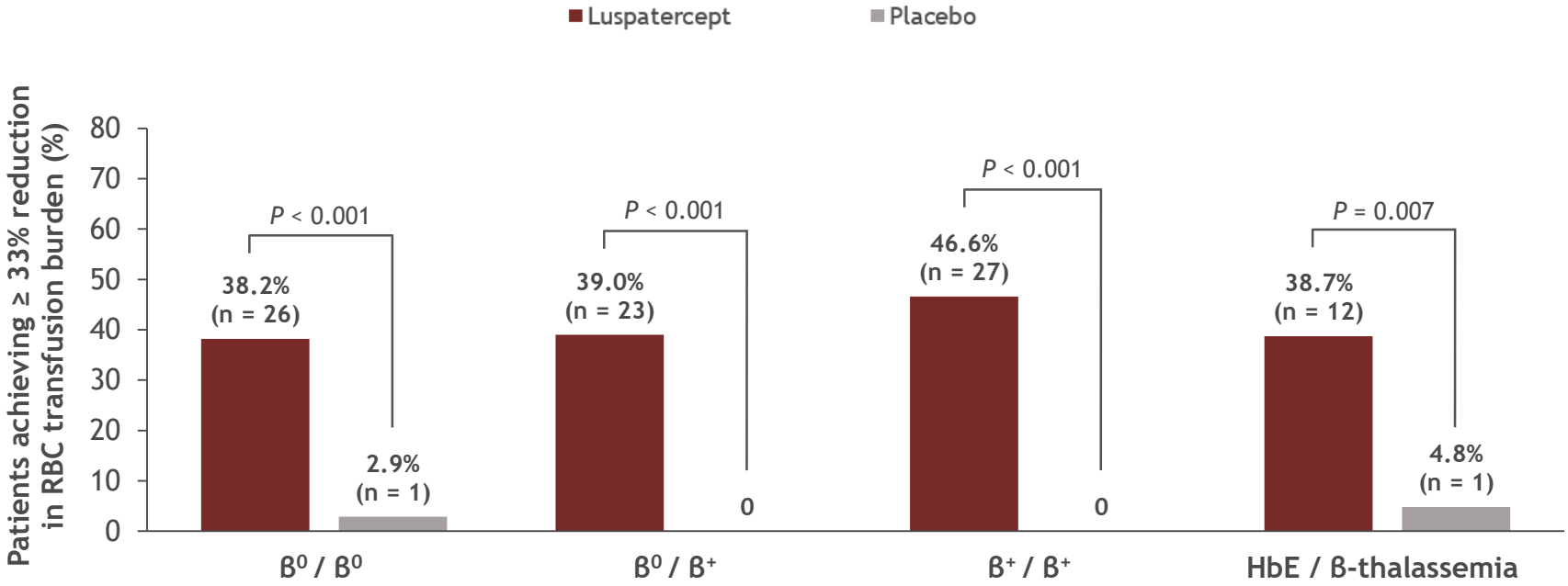
- A significantly greater proportion of luspatercept-treated patients achieved clinically meaningful reductions in RBC transfusion burden of ≥ 33% during any 12 weeks versus placebo, regardless of β-globin genotype



Data cutoff: May 11, 2018.

Achievement of ≥ 33% reduction in RBC transfusion burden during any 24 weeks

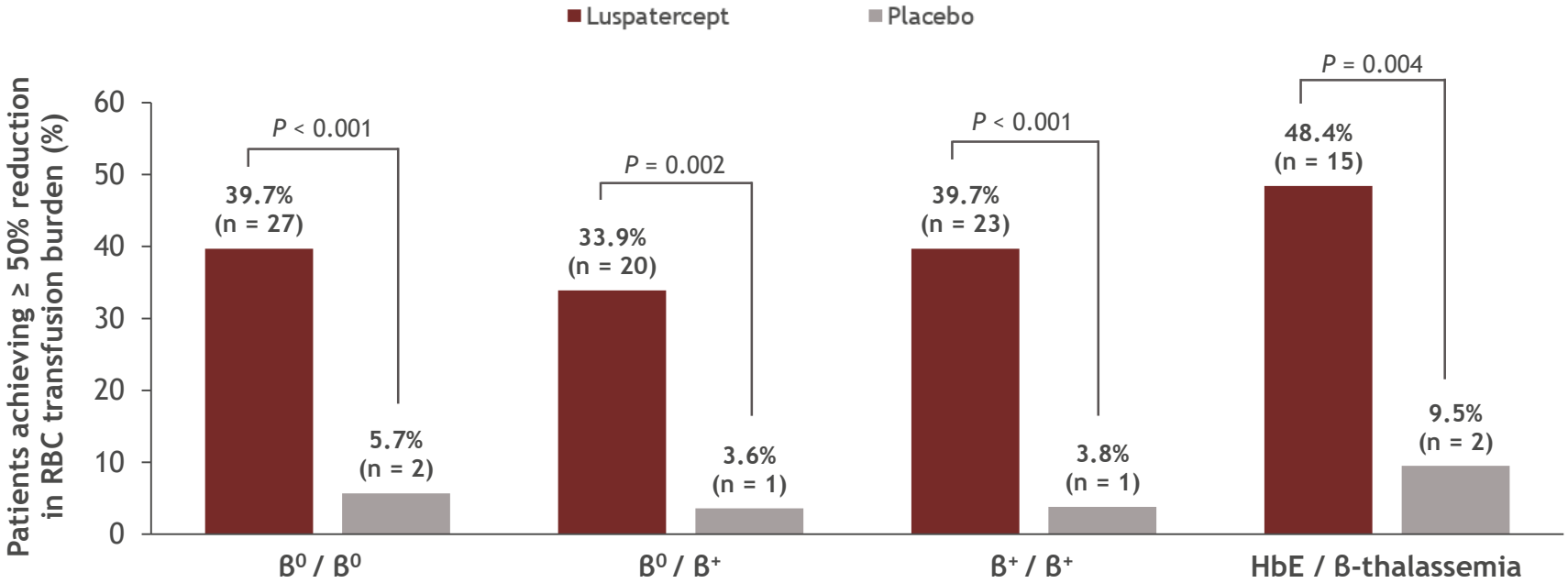
- A significantly greater proportion of luspatercept-treated patients achieved clinically meaningful reductions in RBC transfusion burden of ≥ 33% during any 24 weeks versus placebo, regardless of ß-globin genotype



Data cutoff: May 11, 2018.

Achievement of ≥ 50% reduction in RBC transfusion burden during any 12 weeks

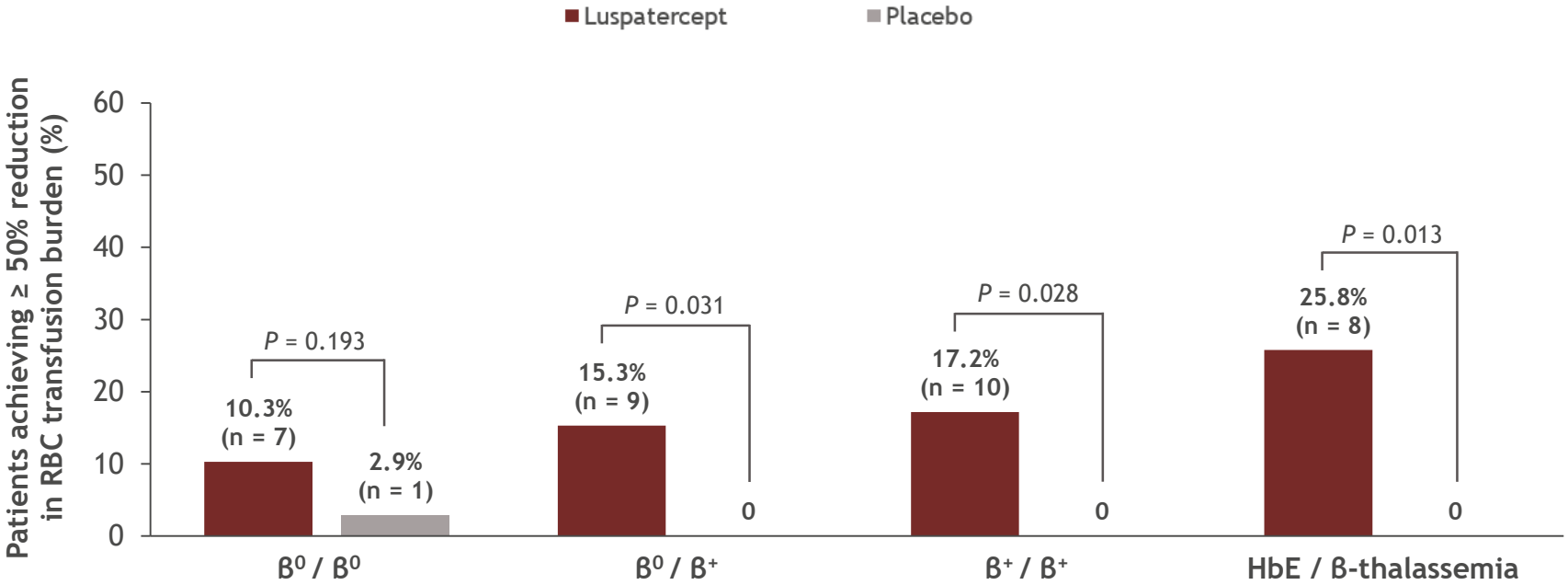
- A greater proportion of luspatercept-treated patients achieved meaningful reductions in RBC transfusion burden of ≥ 50% during any 12-week interval versus placebo, regardless of ß-globin genotype



Data cutoff: May 11, 2018.

Achievement of ≥ 50% reduction in RBC transfusion burden during any 24 weeks

- A greater proportion of luspatercept-treated patients achieved meaningful reductions in RBC transfusion burden of ≥ 50% during any 24-week interval versus placebo, regardless of ß-globin genotype



Data cutoff: May 11, 2018.

Safety summary

	Overall[a]		β^0/β^0		β^0/β^+		β^+/β^+		HbE / β-thalassemia	
AE, n (%)	Luspatercept (N = 223)	Placebo (N = 109)	Luspatercept (n = 68)	Placebo (n = 35)	Luspatercept (n = 58)	Placebo (n = 28)	Luspatercept (n = 58)	Placebo (n = 23)	Luspatercept (n = 31)	Placebo (n = 21)
Patients with ≥ 1 TEAE (grade ≥ 3)	65 (29.1)	17 (15.6)	18 (26.5)	7 (20.0)	17 (29.3)	4 (14.3)	14 (24.1)	2 (8.7)	14 (45.2)	4 (19.0)
Patients with ≥ 1 serious AE	34 (15.2)	6 (5.5)	13 (19.1)	1 (2.9)	9 (15.5)	2 (7.1)	7 (12.1)	2 (8.7)	4 (12.9)	1 (4.8)

- The incidence of specific AEs within each subgroup was consistent with the overall population

[a]The safety population includes all randomized patients who received ≥ 1 dose of study drug.
Data cutoff: May 11, 2018.
AE, adverse event; TEAE, treatment-emergent adverse event

Summary

- Clinically meaningful reductions in RBC transfusion burdens were sustained over longer periods of time (24 weeks) across all β-globin genotypes, including more severe β-thalassemia subgroups
- Luspatercept was well tolerated across β-globin genotypes
- Luspatercept is being expanded in adult patients with non-transfusion-dependent β-thalassemia (BEYOND trial; NCT03342404) and pediatric patients with transfusion-dependent β-thalassemia (NCT04143724)

- See also Taher et al. “Assessment of longer-term efficacy and safety in the phase 3 BELIEVE trial of luspatercept to treat anemia in patients with β-thalassemia” (Abstract: EP1548)

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