

# Health-related quality of life outcomes for patients with transfusion-dependent beta-thalassemia treated with luspatercept in the BELIEVE trial

Maria Domenica Cappellini,<sup>1</sup> Ali T. Taher,<sup>2</sup> Antonio Piga,<sup>3</sup> Farrukh Shah,<sup>4</sup> Ersi Voskaridou,<sup>5</sup> Vip Viprakasit,<sup>6</sup> John B. Porter,<sup>7</sup> Olivier Hermine,<sup>8,9</sup> Ellis J. Neufeld,<sup>10</sup> Alexis A. Thompson,<sup>11</sup> Derek Tang,<sup>12</sup> Peiwen Yu,<sup>13</sup> Shien Guo,<sup>13</sup> Jeevan K. Shetty,<sup>12</sup> Dimana Miteva,<sup>12</sup> Tatiana Zinger,<sup>12</sup> Jay T. Backstrom,<sup>14</sup> Esther Natalie Oliva<sup>15</sup>

<sup>1</sup>Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico, University of Milan, Milan, Italy; <sup>2</sup>Department of Internal Medicine, American University of Beirut Medical Center, Beirut, Lebanon; <sup>3</sup>Department of Clinical and Biological Sciences, University of Turin, Turin, Italy; <sup>4</sup>Department of Haematology, Whittington Health NHS Trust, London, UK; <sup>5</sup>Thalassemia and Sickle Cell Center of Laiko General Hospital, Athens, Greece; <sup>6</sup>Siriraj Hospital, Mahidol University, Bangkok, Thailand; <sup>7</sup>University College London Hospitals NHS Foundation Trust, London, UK; <sup>8</sup>Necker Hospital, Assistance Publique-Hôpitaux de Paris, Paris, France; <sup>9</sup>Imagine Institute, INSERM Unité 1163, University of Paris, Paris, France; <sup>10</sup>St. Jude Children's Research Hospital, Memphis, TN, USA; <sup>11</sup>Ann & Robert H. Lurie Children's Hospital of Chicago, Chicago, IL, USA; <sup>12</sup>Bristol Myers Squibb, Princeton, NJ, USA; <sup>13</sup>Evidera, Waltham, MA, USA; <sup>14</sup>Acceleron Pharma, Cambridge, MA, USA; <sup>15</sup>Grande Ospedale Metropolitano Bianchi Melacrina Morelli, Reggio Calabria, Italy

# Presenting author disclosures

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- Honoraria
  - Bristol Myers Squibb, Genzyme/Sanofi
- Membership on an entity's board of directors
  - CRISPR Therapeutics, Genzyme/Sanofi, Novartis, Vifor Pharma

# Introduction

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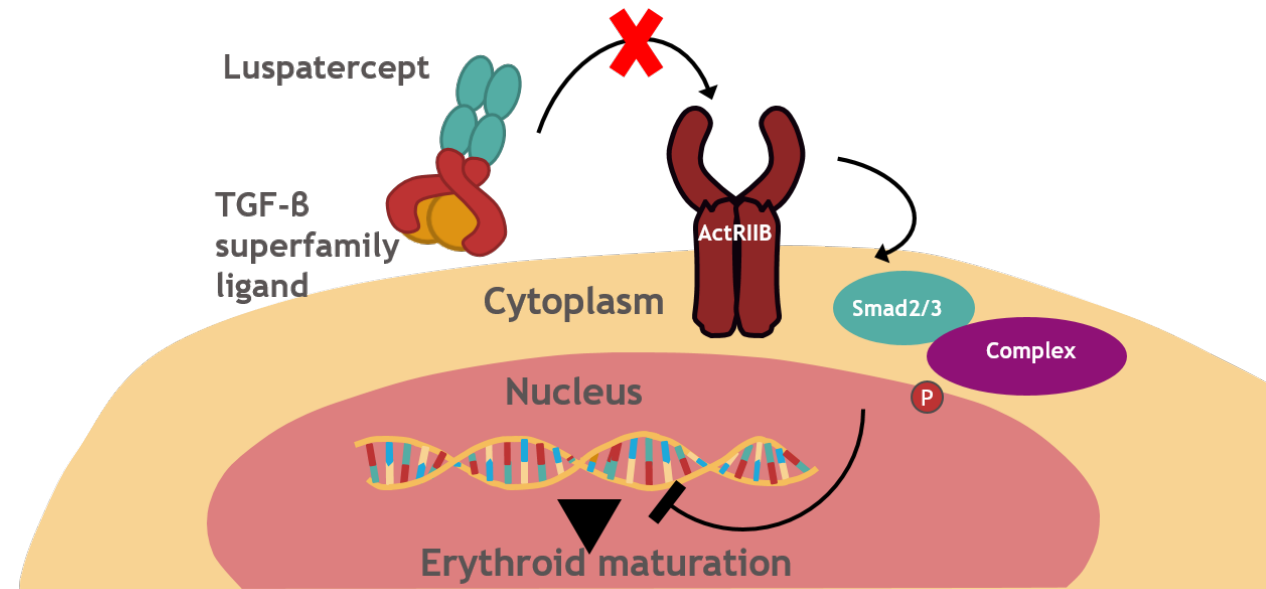
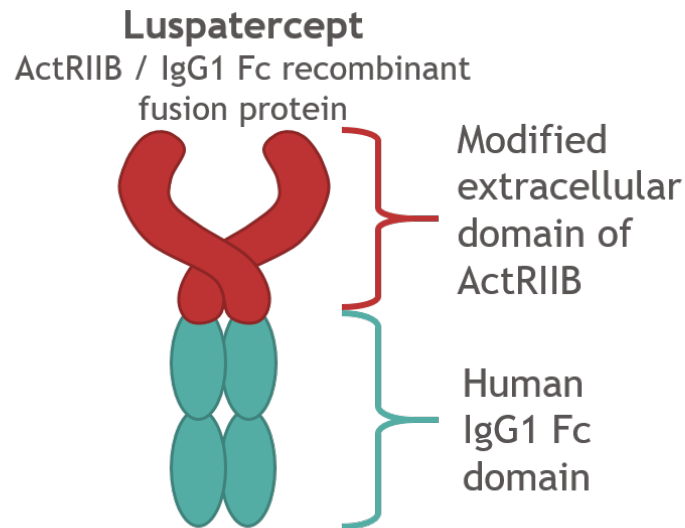
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- Patients with TD  $\beta$ -thalassemia may require long-term RBCT that can lead to iron overload and associated complications, which impact negatively on HRQoL<sup>1</sup>
- A reduction in the number or frequency of RBCT, without other treatment modification, may increase anemia-related symptoms and thereby worsen HRQoL<sup>1</sup>
- The international phase 3 BELIEVE study (NCT02604433) showed that the first-in-class erythroid maturation agent luspatercept provided clinically meaningful reduction in RBCT burden, but the impact of luspatercept on HRQoL is not yet understood<sup>2</sup>

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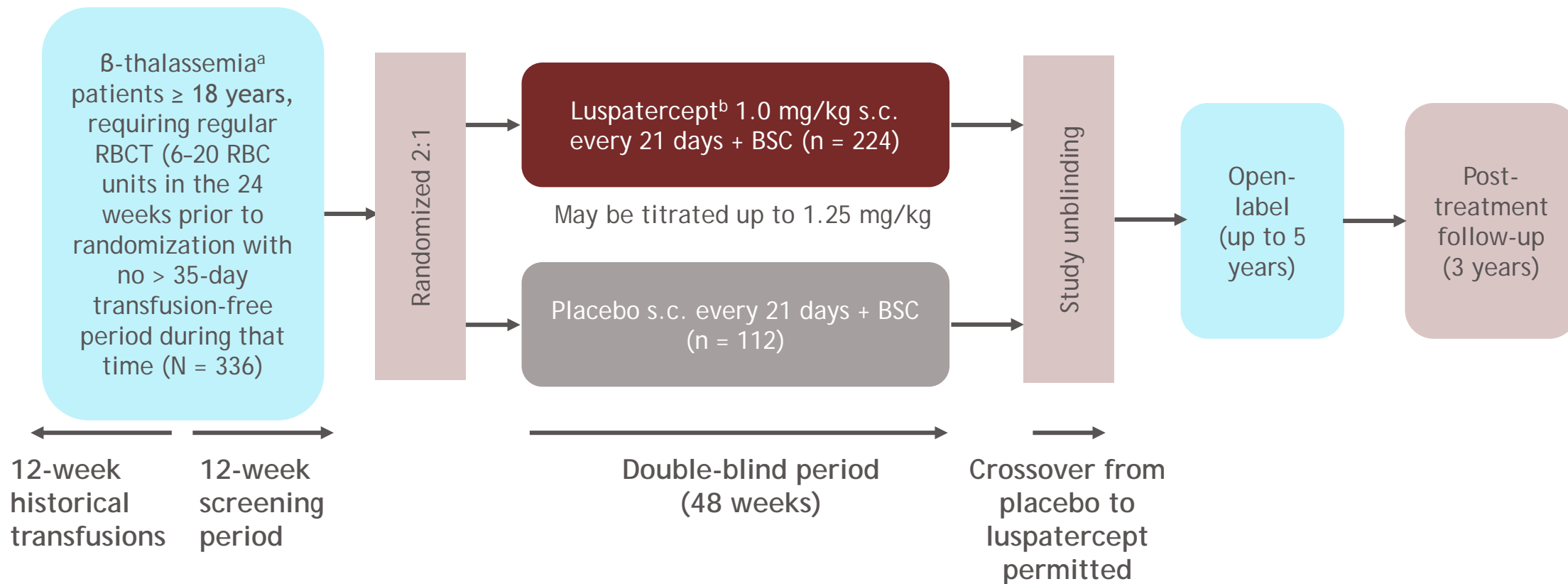
- Luspatercept is a first-in-class erythroid maturation agent that binds to select TGF- $\beta$  superfamily ligands to diminish Smad2/3 signaling and enhance late-stage erythropoiesis<sup>1</sup>
  - Luspatercept was approved by the US Food and Drug<sup>2</sup> and European Medicines Agency<sup>3</sup> for treatment of anemia due to  $\beta$ -thalassemia in adult patients who require regular RBC transfusions



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## BELIEVE study design<sup>1</sup>



<sup>a</sup> $\beta$ -thalassemia of Hb E/ $\beta$ -thalassemia (compound  $\beta$ -thalassemia with mutation and/or multiplication of  $\alpha$ -globin genes was allowed); <sup>b</sup>Patients could receive RBCT and ICT to maintain their baseline Hb level; <sup>c</sup>The trial is fully enrolled and patients continue to receive treatment or follow-up. BSC, best supportive care; Hb, hemoglobin; ICT, iron chelation therapy; RBC, red blood cell; s.c., subcutaneous. 1. Cappellini MD, et al. *N Engl J Med* 2020;382:1219-1231.

# Objective

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- To assess the effect of luspatercept plus BSC (including RBCT and ICT) versus placebo plus BSC on HRQoL in patients with TD  $\beta$ -thalassemia in the phase 3 BELIEVE study

- HRQoL was assessed at screening ( $\leq 4$  weeks prior to first study dose) and every 12 weeks up to 48 weeks of treatment using:
  - The generic 36-item Short Form Health Survey (SF-36)<sup>a</sup>
  - The thalassemia-specific Transfusion-dependent Quality of Life questionnaire (TranQoL) which includes the domains Physical, Emotional, Sexual, Family, and School/Career Health<sup>b,1,2</sup>
- The HRQoL evaluable population included all patients who completed the HRQoL assessment at screening and  $\geq 1$  post-screening assessment visit
- Domains of the TranQoL and SF-36 were considered complete if  $\geq 75\%$  and  $\geq 50\%$  of items, respectively, were answered at a given time point

<sup>a</sup>SF-36 consists of 8 domains and 2 component summary scales: Physical Component Summary (Physical Functioning, Role Physical, Bodily Pain, and General Health domains), Mental Component Summary (Vitality, Mental Health, Role Emotional and Social Functioning).

<sup>b</sup>The TranQoL has a total of 36 items across the 5 domains (Physical, 10 items; Emotional, 14 items; Sexual, 1 item; Family, 5 items; School/Career Health, 6 items). Possible scores for each domain and Total Score range from 0-100 with higher scores denoting better HRQoL.

1. Klaasen RJ, et al. *Br J Haematol* 2014;164:431-437. 2. Klonizakis P, et al. *Ann Hematol* 2017;96:1937-1944.

# Primary HRQoL endpoints

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- The primary endpoint was change from baseline between groups up to Week 48 in:
  - SF-36 Physical Component Summary, Physical Functioning, and General Health
  - TranQoL Total Score and Physical Health
  - Other domains were considered exploratory domains
- Changes from baseline were compared using ANCOVA models adjusting for baseline domain scores and geographic region



# Exploratory HRQoL endpoints

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- Exploratory analyses included comparison of clinically meaningful improvement in domain scores between patients on luspatercept achieving a clinical response and patients on placebo
- Clinical response to luspatercept was defined as:
  - $\geq 50\%$  reduction in RBCT burden over any 12 weeks at Weeks 24 and 48
  - $\geq 33\%$  reduction in RBCT burden over any 12 weeks at Weeks 24 and 48
  - Transfusion independence over any 8 or 12 weeks at Weeks 24 and 48

# Patient demographics

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- The HRQoL evaluable population was 211 patients (94.2%) in the luspatercept arm and 103 patients (92.0%) in the placebo arm

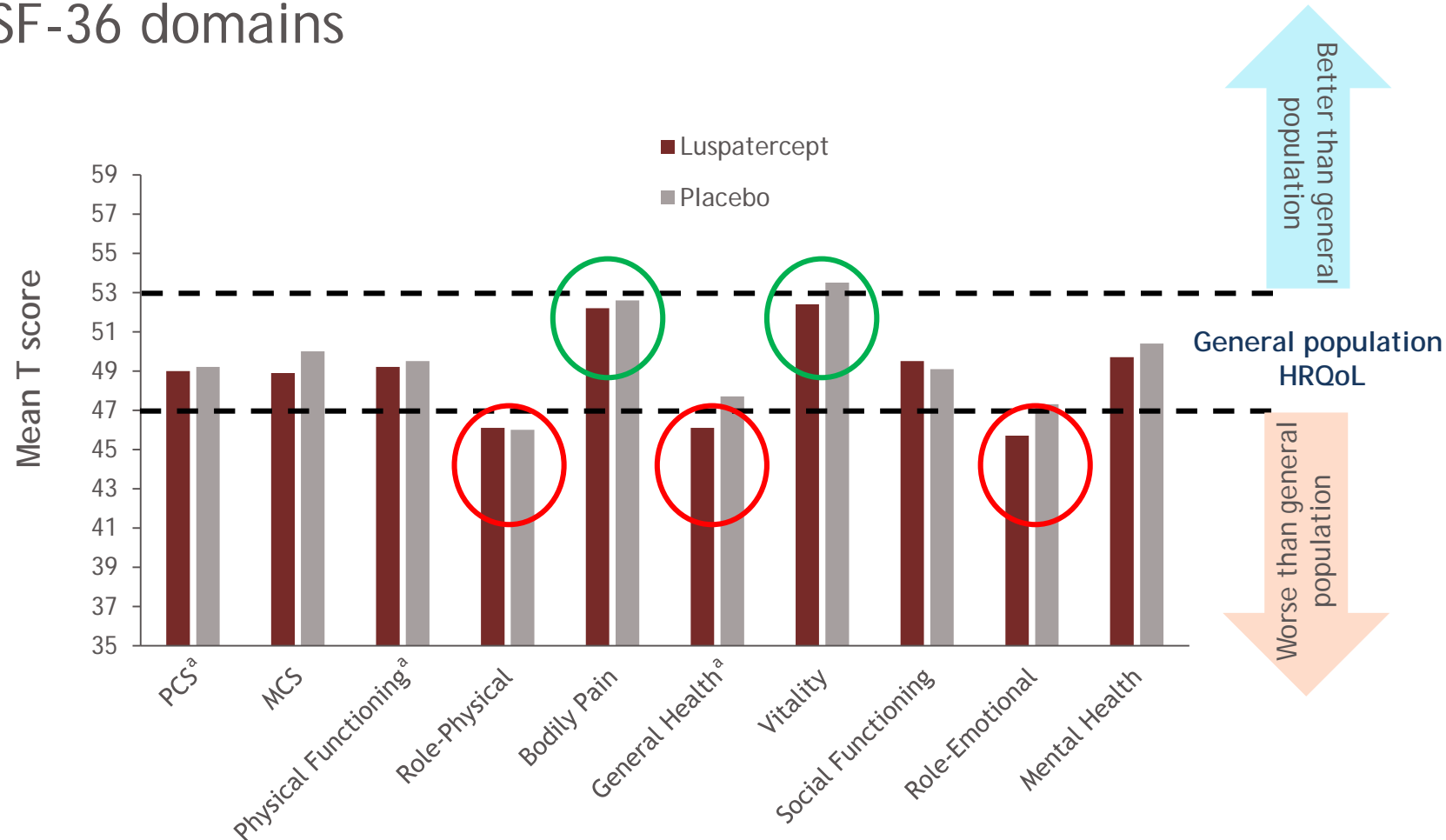
	Luspatercept (n = 211)	Placebo (n = 103)
Age, mean (SD), years	32.1 (10.8)	31.6 (9.9)
Sex, n (%)		
Male	87 (41.2)	46 (44.7)
Region, n (%)		
North America and Europe	89 (42.2)	46 (44.7)
Middle East and North Africa	51 (24.2)	25 (24.3)
Asia-Pacific	71 (33.6)	32 (31.1)
Baseline transfusion rate		
≤ 6 units/12 weeks	107 (50.7)	52 (50.5)
> 6 units/12 weeks	104 (49.3)	51 (49.5)

- HRQoL questionnaire compliance rates among patients still on treatment were > 87.5% for both questionnaires at Week 48

# Baseline HRQoL scores for SF-36 domains

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- Baseline HRQoL scores were similar to the US general population for most SF-36 domains



- Green circles denote highest-scoring domain scores compared with the general population
- Red circles denote domain scores which were impaired in the BELIEVE population

<sup>a</sup>Primary HRQoL endpoints.  
MCS, Mental Component Summary; PCS, Physical Component Summary.

# Changes in HRQoL primary endpoints up to Week 48

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## SF-36 scores

- There was no clinically meaningful change from baseline nor difference between treatment groups up to Week 48 in:
  - General Health
  - Physical Functioning
  - PCS

## TranQoI scores

- There was no clinically meaningful change from baseline nor difference between treatment groups up to Week 48 in:
  - Total Score
  - Physical Health

# Correlation between RBCT and changes in HRQoL

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## SF-36 scores

- There was no significant correlation ( $r$ ,  $P$  value) between the number of RBC units transfused and change in SF-36 Physical Functioning, Global Health, and PCS at Week 24 (0.02,  $P = 0.821$ ; -0.09,  $P = 0.194$ ; 0.01,  $P = 0.891$ ; respectively) or Week 48 (0.08,  $P = 0.453$ ; -0.18,  $P = 0.080$ ; 0.06,  $P = 0.594$ ; respectively)

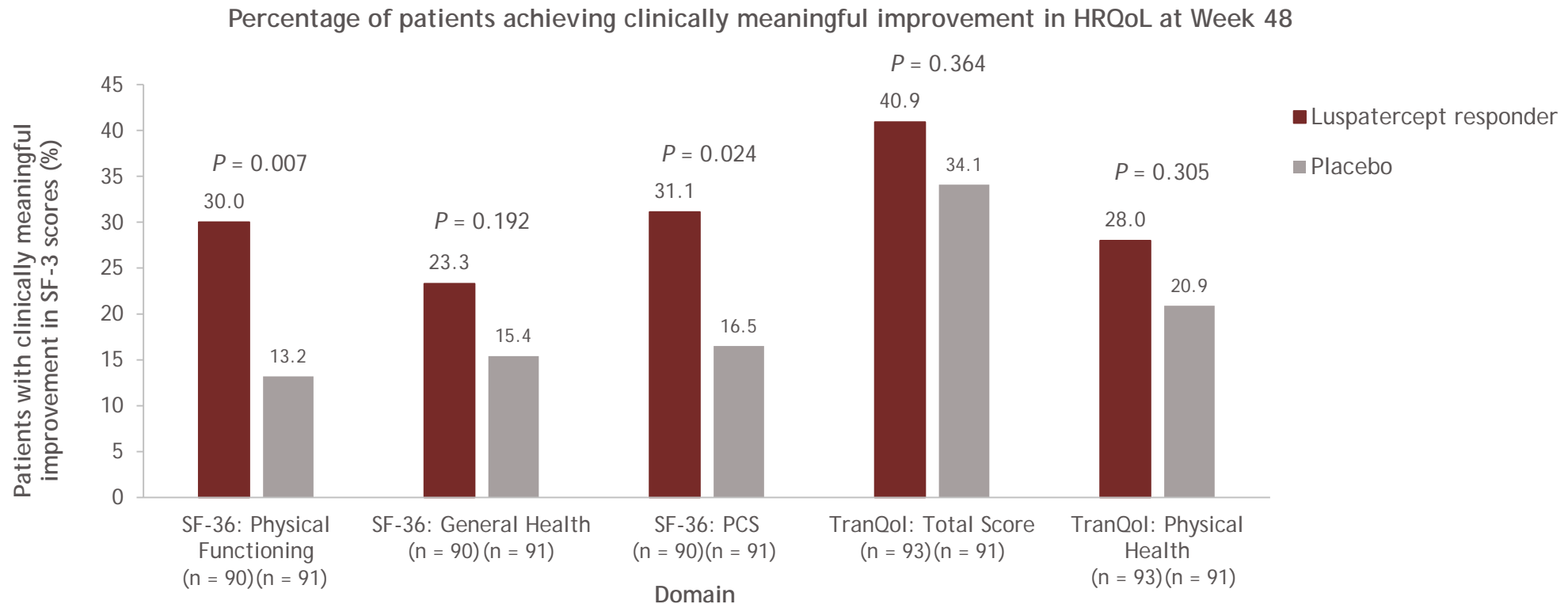
## TranQoI scores

- There was no significant correlation ( $r$ ,  $P$  value) between the number of RBC units transfused and change in TranQoI Total Score and Physical Health at Week 24 (-0.09,  $P = 0.217$ ; 0.02,  $P = 0.814$ ; respectively) or Week 48 (0.05,  $P = 0.606$ ; 0.04,  $P = 0.703$ ; respectively)

# Changes in HRQoL at Week 48 in luspatercept responders achieving reduction in RBCT

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- Patients receiving luspatercept and achieving a  $\geq 50\%$  reduction in RBCT burden over any 12 weeks were significantly more likely than patients receiving placebo to have a clinically meaningful improvement in SF-36 PCS and Physical Functioning at Week 48

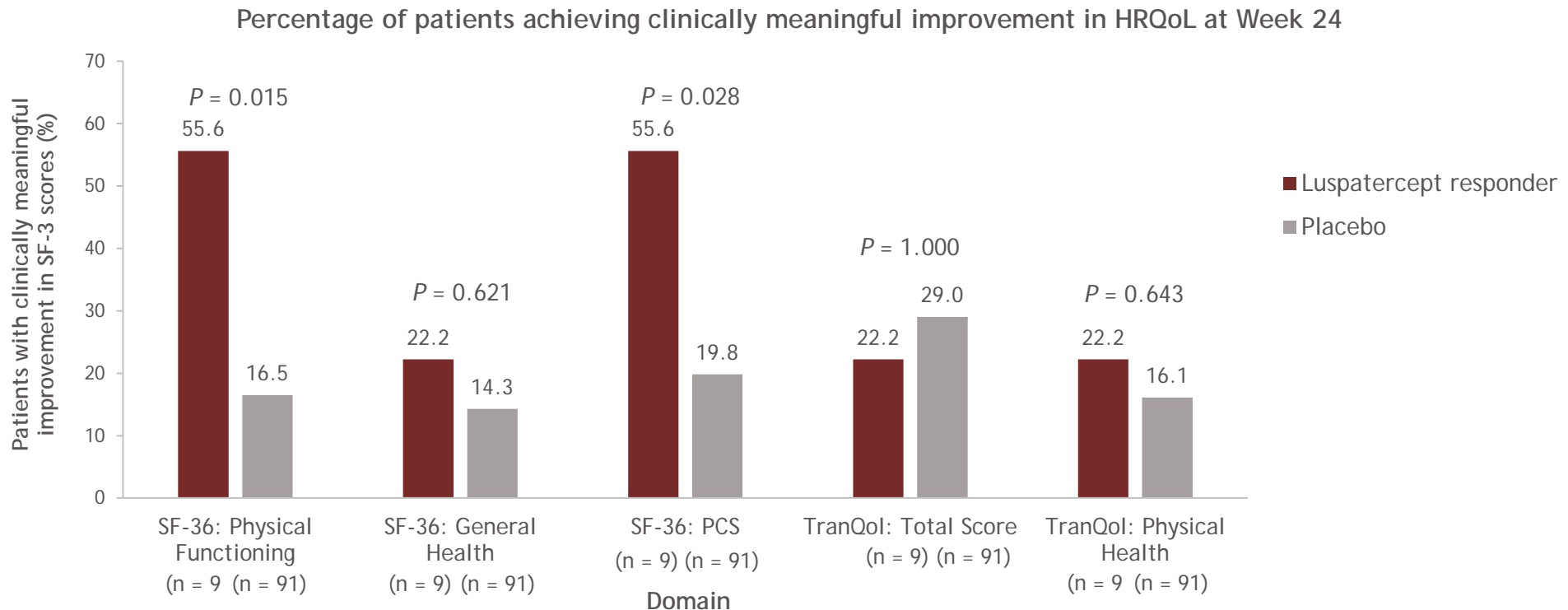


<sup>a</sup>Within-patient clinically meaningful change from baseline was defined as 3.8-7.0-point improvement, based on the prespecified domain-specific cutoff values for the domains of the SF-36 questionnaire; <sup>b</sup>Within-patient clinically meaningful change from baseline was defined as a  $\geq 4$ -point change for the TranQoL total score and  $\geq 0.5^*$  SDs of the pooled domain score for other domains of the TranQoL.

# Changes in HRQoL at Week 24 in luspatercept responders achieving TI

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- Patients receiving luspatercept and achieving TI for any 12 weeks were significantly more likely than patients receiving placebo to have a clinically meaningful improvement in SF-36 Physical Functioning and PCS at Week 24



<sup>a</sup>Within-patient clinically meaningful change from baseline was defined as 3.8-7.0-point improvement, based on the prespecified domain-specific cutoff values for the domains of the SF-36 questionnaire; <sup>b</sup>Within-patient clinically meaningful change from baseline was defined as a  $\geq 4$ -point change for the TranQoL total score and  $\geq 0.5^*$  SDs of the pooled domain score for other domains of the TranQoL.

# Limitations

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- Some key benefits of luspatercept treatment, such as the impact of reducing RBC transfusions on HRQoL, are not covered by the SF-36 and TranQoL instruments
- Per study protocol, patients were still required to attend the clinic; therefore, any reduction in visits to receive RBC transfusions may not have been observed by the patient
- HRQoL was assessed at prespecified time points; however, patients were allowed to receive transfusions as needed at any time during the study, which could impact HRQoL assessments, particularly in key domains related to anemia (e.g. Physical Functioning, Physical Health)



# Summary

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- Luspatercept with BSC reduced RBCT burden while maintaining TranQoL and SF-36 HRQoL scores through Week 48 compared with placebo
- HRQoL at baseline was similar to the general population
- Patients responding to luspatercept were more likely to achieve a clinically meaningful improvement in HRQoL than patients receiving placebo
- A higher proportion of luspatercept responders achieved clinically meaningful improvements in Physical Functioning and PCS compared with placebo

# Acknowledgments

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