EUROPEAN HEMATOLOGY ASSOCIATION

The BEYOND study: results of a phase 2, double-blind, randomized, placebo-controlled multicenter study of luspatercept in adult patients with non-transfusion-dependent β-thalassemia

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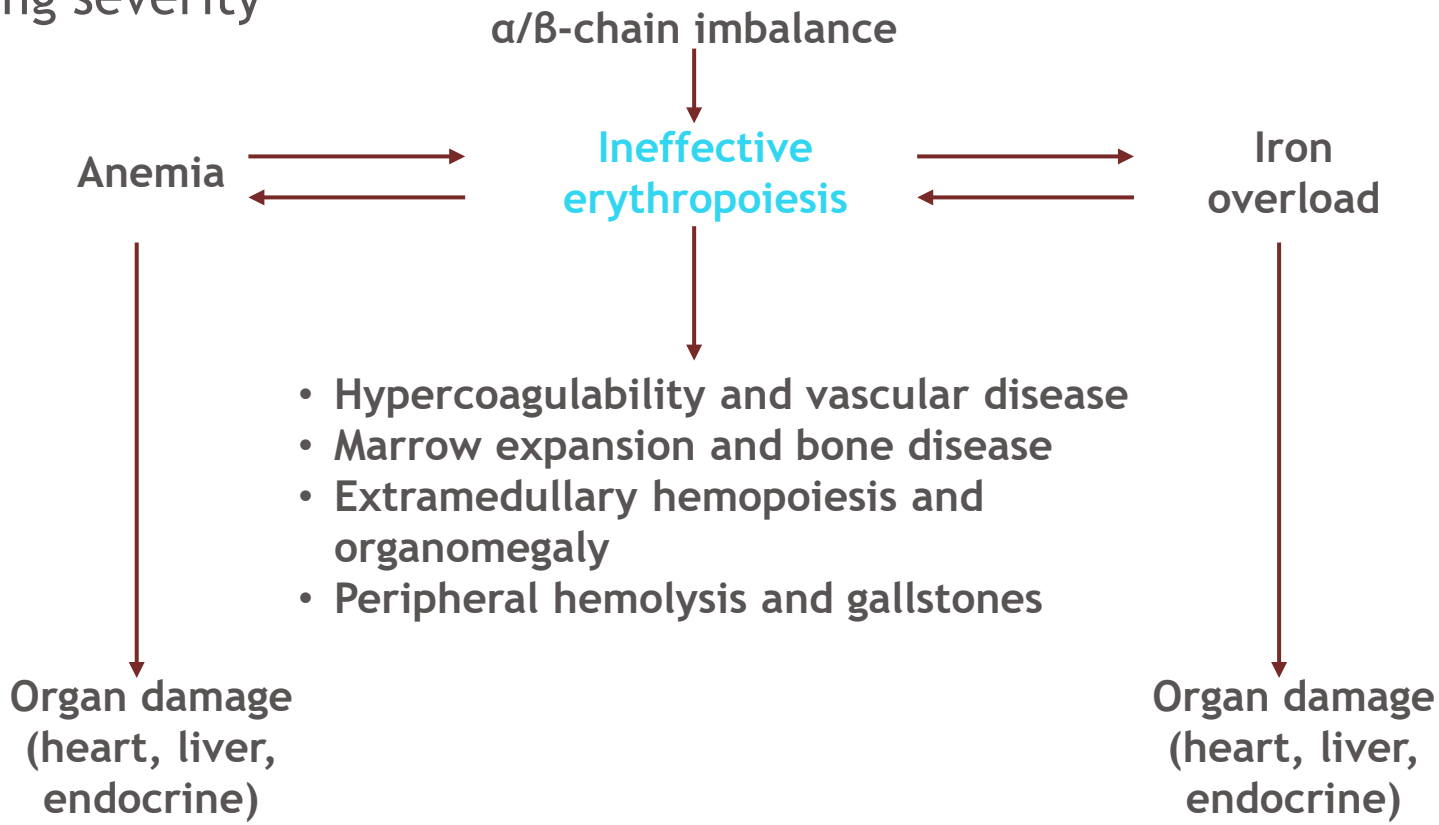
Presentation Number S101

Disclosures

- Consultancy fees
  - Agios, Celgene (BMS), Ionis Pharmaceuticals, Novartis Pharmaceuticals, Vifor Pharma
- Grants for research
  - Celgene (BMS), Ionis Pharmaceuticals, Novartis Pharmaceuticals, Vifor Pharma

Pathophysiology of β-thalassemia

- β-thalassemia is a hereditary blood disorder characterized by impaired Hb production and chronic anemia of varying severity[1]



Tailored RBC transfusions, ICT, and novel therapies target key pathophysiologic mechanisms in TDT and NTDT

Figure adapted from Taher AT, et al. *Lancet* 2018;391(10116):155-167.
Hb, hemoglobin; ICT, iron chelation therapy; NTDT, non-transfusion-dependent thalassemia; RBC, red blood cell; TDT, transfusion-dependent-thalassemia.
1. Taher AT, et al. *N Engl J Med* 2021;384:727-743.

Non-transfusion-dependent β-thalassemia

- Patients with NTDT do not require lifelong regular RBC transfusions for survival, however, they may require occasional RBC transfusions during surgeries or infections

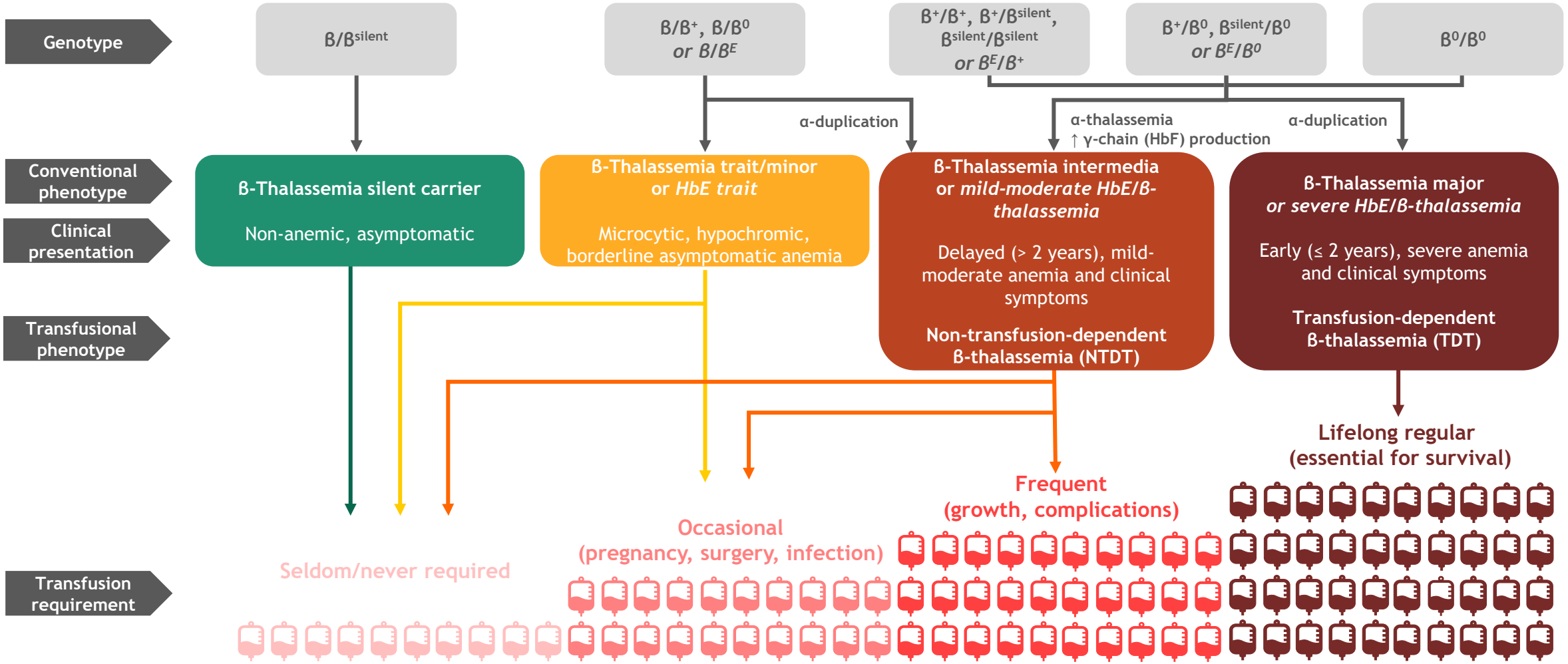
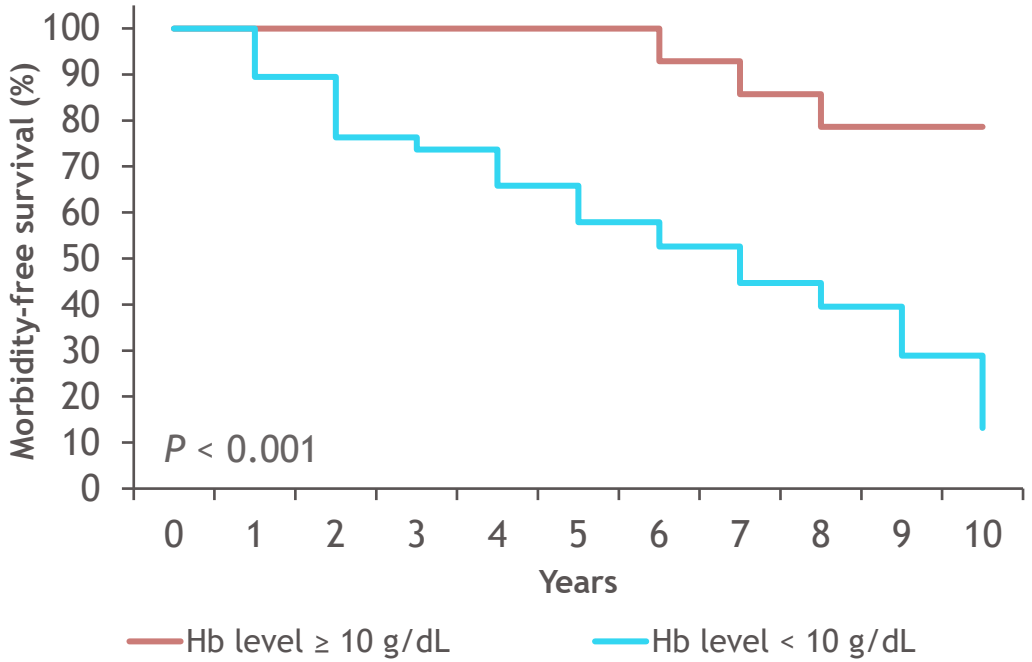
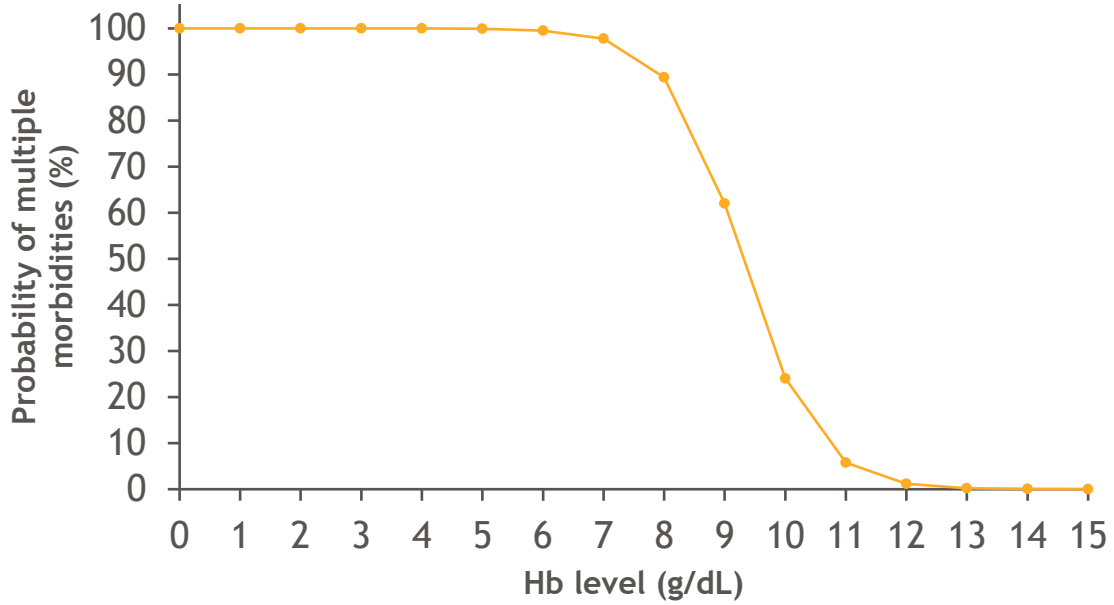


Figure adapted from Taher AT, et al. *N Engl J Med* 2021;384:727–743. Copyrights permission requested.
HbE, hemoglobin E; HbF, fetal hemoglobin.

Morbidity-free survival vs Hb level in NTDT

- Patients with NTDT with baseline Hb ≥ 10 g/dL have significantly longer morbidity-free survival than patients with < 10 g/dL ($P < 0.001$)[1,2]
- A significant correlation between improvement in Hb levels by 1 g/dL and decreased odds of developing morbidities was also shown in patients with NTDT and baseline Hb < 10 g/dL[1,2]
- Improvement of anemia and disease complications are unmet needs in patients with NTDT





Figures adapted from Musallam KM, et al. *Ann Hematol* 2021 Feb 11 [Epub ahead of print] and Musallam KM, et al. *Ann Hematol* 2021 Jan 20 [Epub ahead of print].

1. Musallam KM, et al. *Ann Hematol* 2021 Feb 11 [Epub ahead of print]; 2. Musallam KM, et al. *Ann Hematol* 2021 Jan 20 [Epub ahead of print].

Need for management options for anemia in NTDT

- There are currently no effective management options for anemia in patients with NTDT

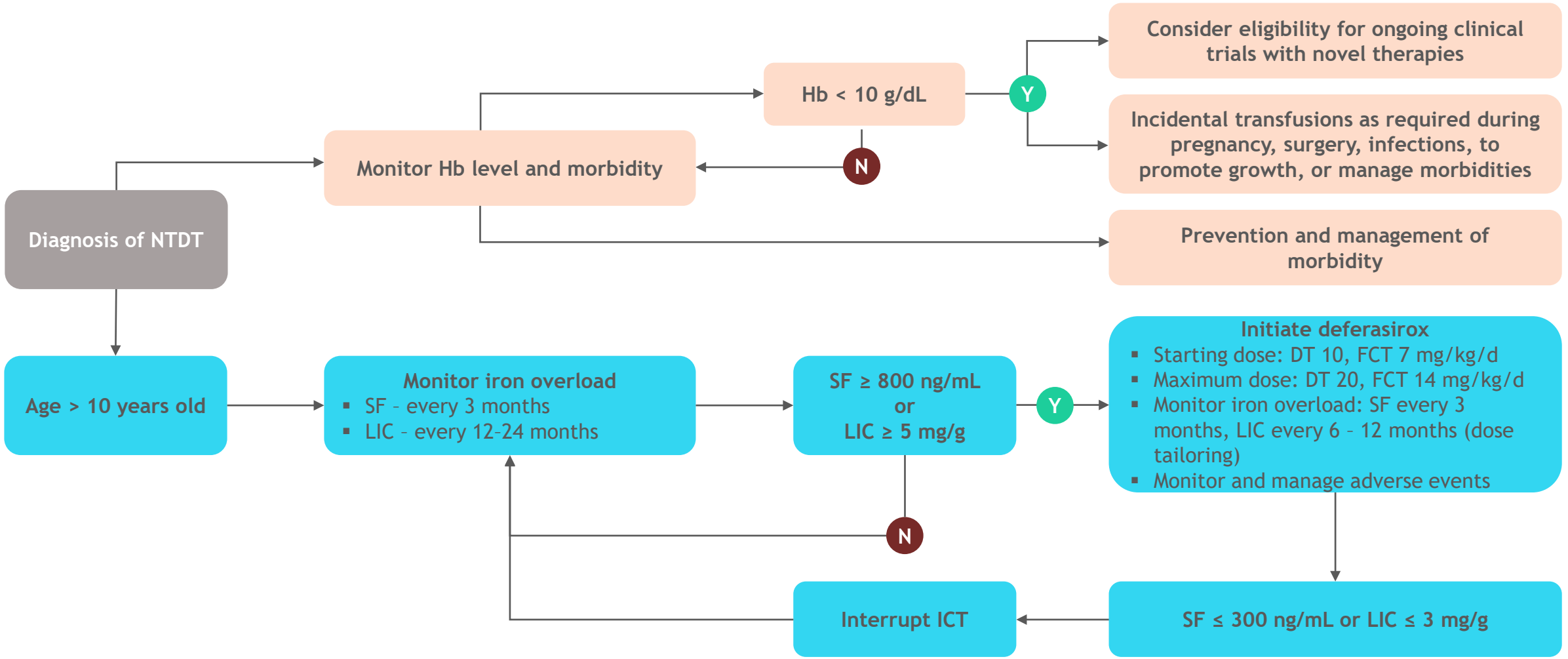
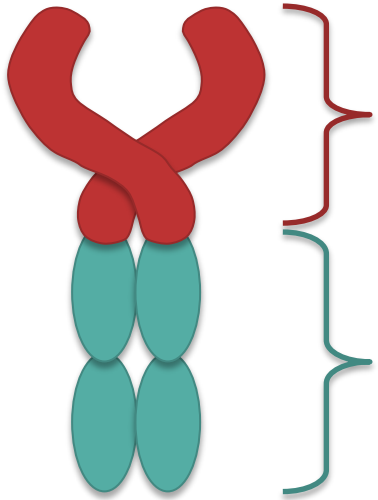


Figure adapted from Taher AT, et al. *N Engl J Med* 2021;384:727-743. Copyrights permission requested.
DT, dispersible tablet; FCT, film-coated tablet; LIC, liver iron content; SF, serum ferritin.

Luspatercept, a first-in-class erythroid maturation agent

- Luspatercept binds select TGF-β superfamily ligands to diminish Smad2/3 signaling and enhance late-stage erythropoiesis[1,2]

Luspatercept
ActRIIB / IgG1 Fc recombinant fusion protein



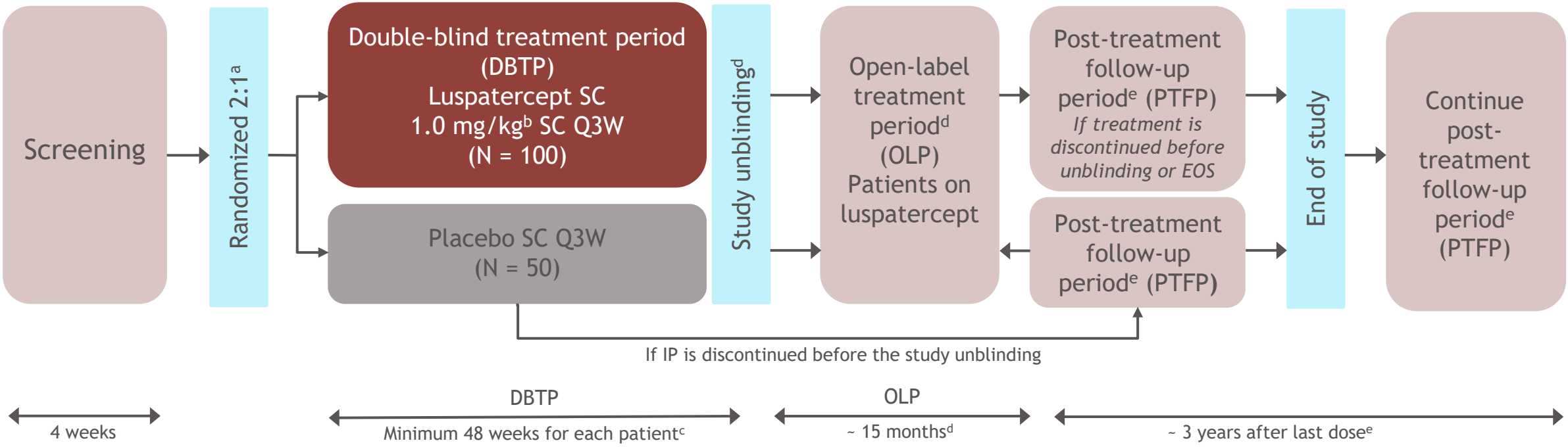
Modified extracellular domain of ActRIIB

Human IgG1 Fc domain

- Luspatercept was approved by the EMA (in 2020) and US FDA (in 2019) for treatment of anemia in adult patients with transfusion-dependent thalassemia (TDT)[3,4]
- In the phase 3 BELIEVE study, 21.4% of TDT patients receiving luspatercept vs 4.5% of patients receiving placebo achieved ≥ 33% RBC transfusion burden reduction during weeks 13–24, compared with baseline[2]
- Luspatercept may have potential clinical benefit for treatment of anemia and its complications, and for improvement of outcomes, in patients with NTDT
- The aim of the BEYOND study was to determine safety and efficacy of luspatercept vs placebo in adult patients with NTDT

ActRIIB, human activin receptor type IIB; EMA, European Medicines Agency; Fc, fragment crystallizable; IgG1, immunoglobulin G1; TGF-β, transforming growth factor beta; US FDA, US Food and Drug Administration. 1. Suragani RN, et al. *Nat Med* 2014;20:408-414; 2. Cappellini MD, et al. *N Engl J Med* 2020;382:1219-1231; 3. Reblozyl-EPAR – Product Information 04/02/2021 Reblozyl-EMEA/H/C/004444-T/0003; 4. REBLOZYL® (luspatercept-aamt) [package insert]. Princeton, NJ: Bristol Myers Squibb; April 2020.

Study design



- The multicenter, double-blind, placebo-controlled BEYOND trial is registered at ClinicalTrials.gov (NCT03342404) and EudraCT (2015-003225-33)

Data cutoff: September 14, 2020.

[a]Patients will be stratified based on baseline Hb levels (≥ 8.5 g/dL or < 8.5 g/dL) and baseline NTDT-PRO T/W domain score ≥ 3 or < 3. [b]Dose may be titrated up to a maximum of 1.25 mg/kg. [c]DBTP will end after last patient enrolled has completed 48 weeks of treatment or discontinued earlier, or when study is unblinded. [d]Study will be unblinded 48 weeks after last patient has received first dose of IP. At that time, patients still benefitting from luspatercept treatment as well as patients who received placebo and have been assessed as per protocol up to 48 weeks after the first dose of IP (even if they have discontinued the IP before completing 48 weeks of treatment), may access the OLP to receive luspatercept for maximum 15 months on the basis of DMC recommendation after unblinded data review, and can continue treatment in the rollover protocol after end of treatment up to 5 years of dose 1, or treatment discontinuation, whichever occurs later. [e]Patients in the DBTP who have discontinued luspatercept before the unblinding will continue the PTFP until the end of study and may continue the PTFP in the rollover study up to 5 years from first dose of IP, or 3 years from last dose (whichever occurs later), may complete the PTFP under the rollover protocol. Patients in the DBTP who have discontinued placebo before unblinding will continue the PTFP until unblinding and may access the OLP, after DMC's recommendation. DMC, data monitoring committee; EOS, end of study; IP, investigational product; NTDT-PRO T/W; non-transfusion-dependent β-thalassemia patient reported outcome tiredness and weakness; Q3W, every 3 weeks; SC, subcutaneous.

Study endpoints

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

Secondary endpoints

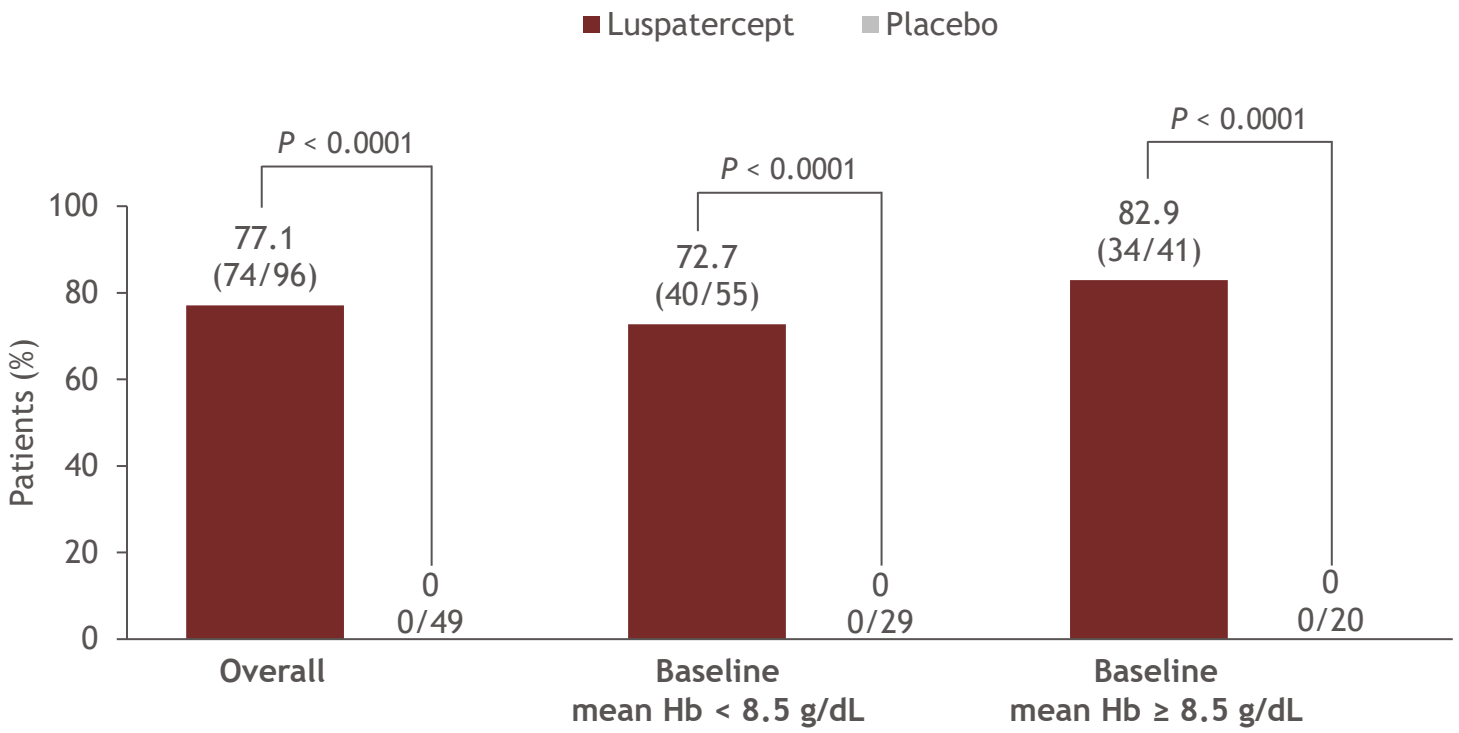
- Achievement of ≥ 1.5 g/dL mean Hb increase from baseline over a continuous 12-week interval during weeks 13–24 in the absence of RBC transfusions
- Proportion of patients who remained RBC transfusion-free over 24 weeks
- Mean change in NTDT-PRO T/W domain score by visit
- Achievement of ≥ 1.0 g/dL mean Hb increase from baseline over a continuous 12-week interval during weeks 37–48 in the absence of RBC transfusions
- Duration of the mean Hb increase from baseline ≥ 1.0 g/dL during any 12-week interval
- Safety and tolerability of luspatercept

Demographics and baseline characteristics

Characteristic	Luspatercept (N = 96)	Placebo (N = 49)	Total (N = 145)
Age, median (range), years	39.5 (18.0–71.0)	41.0 (19.0–66.0)	40.0 (18.0–71.0)
Male, n (%)	40 (41.7)	23 (46.9)	63 (43.4)
Diagnosis, n (%)			
ß-thalassemia	63 (65.6)	34 (69.4)	97 (66.9)
Hb E/ß-thalassemia	28 (29.2)	11 (22.4)	39 (26.9)
Baseline Hb, median (range), g/dL[a]	8.2 (5.3–10.1)	8.1 (5.7–10.1)	8.2 (5.3–10.1)
Baseline Hb category, n (%)			
≥ 8.5 g/dL	41 (42.7)	20 (40.8)	61 (42.1)
< 8.5 g/dL	55 (57.3)	29 (59.2)	84 (57.9)
Baseline NTDT-PRO T/W score, median (range)	4.3 (0–9.5)	4.1 (0.4–9.5)	4.3 (0–9.5)
Baseline NTDT-PRO T/W score category, n (%)			
≥ 3	66 (68.8)	35 (71.4)	101 (69.7)
< 3	30 (31.3)	14 (28.6)	44 (30.3)
Baseline RBC transfusion burden, median (range), U/24 weeks[b,c]	0 (0–4)	0 (0–4)	0 (0–4)
0 U/24 weeks, n (%)	83 (86.5)	42 (85.7)	125 (86.2)
Serum ferritin level, mean (SD), µg/L	567.8 (523.2)	528.8 (444.9)	554.6 (496.9)
LIC, mean (SD), mg/g dw	6.1 (6.2)	5.9 (5.8)	6.0 (6.0)

[a]Baseline Hb value was defined as the average of 2 or more Hb measurements, at least 1 week apart, within 4 weeks before randomization. [b]Baseline transfusion burden was defined as the number of RBC units transfused in the 24 weeks before the first dose of luspatercept or placebo; RBC units transfused on the day of the first dose of study treatment were considered part of the baseline transfusion burden. [c]20 patients (13.8%) received RBC transfusions (maximum 5 RBC units) in the 24 weeks prior to randomization.
dw, dry weight; ITT, intention-to-treat; SD, standard deviation; U, unit.

Primary endpoint

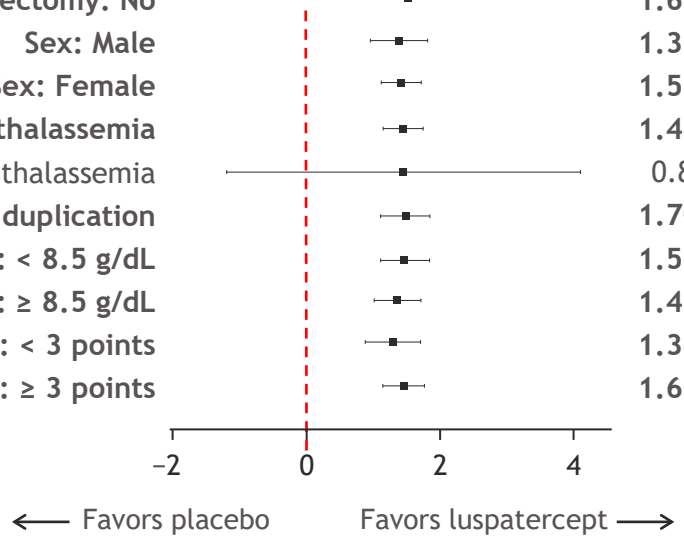


- The study met its primary endpoint
  - 74 (77.1%) of patients in the luspatercept arm vs 0 placebo patients achieved a mean Hb increase of ≥ 1.0 g/dL from baseline[a] over a continuous 12-week interval during weeks 13–24 in the absence of RBC transfusions

Data cutoff: September 14, 2020.
[a]Baseline Hb is defined as the average of 2 or more Hb measurements ≥ 1 week apart within 4 weeks prior to randomization. Primary endpoint was defined as a ≥ 1.0 g/dL mean increase in Hb from baseline over a continuous 12-week interval from weeks 13 to 24, in the absence of RBC transfusions.

Mean change in Hb from baseline to weeks 13-24: subgroup analysis

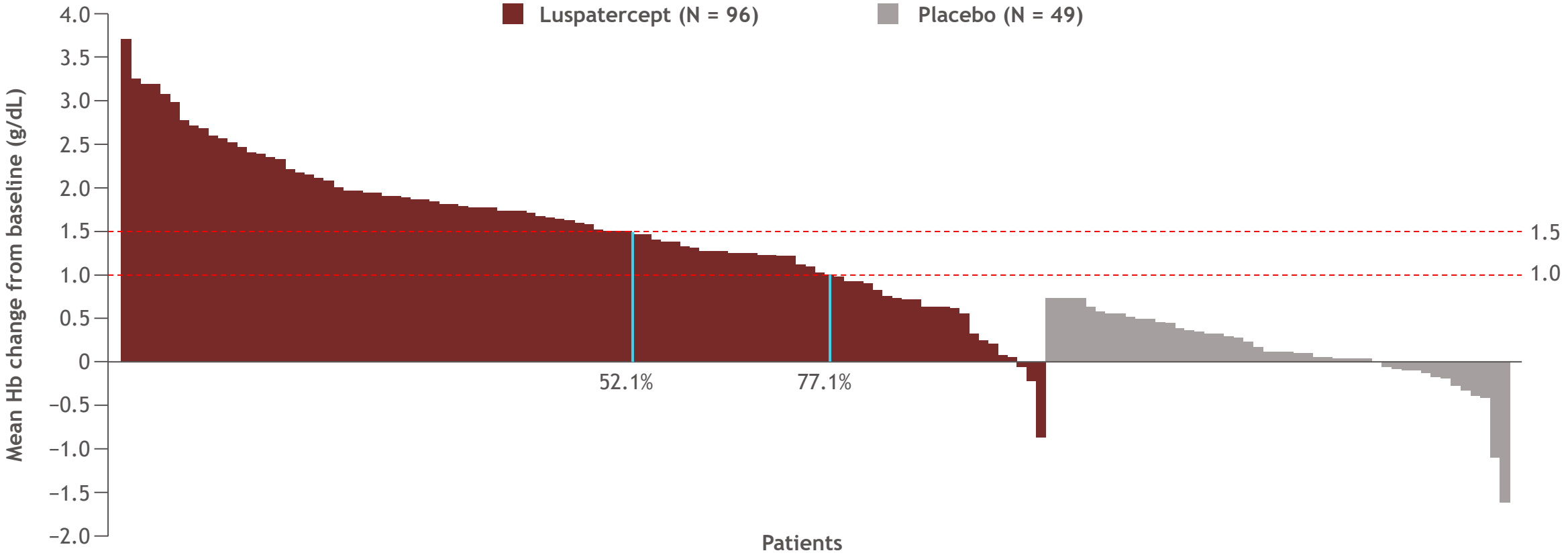
Subgroups	Luspatercept (N = 96) LS mean (± SE)	Placebo (N = 49) LS mean (± SE)	LS mean Difference (95% CI)	*P* value
Splenectomy: Yes	1.17 (0.125)	0.09 (0.151)	1.09 (0.72, 1.45)	< 0.0001
Splenectomy: No	1.63 (0.093)	0.10 (0.143)	1.53 (1.20, 1.86)	< 0.0001
Sex: Male	1.36 (0.141)	−0.03 (0.190)	1.39 (0.96, 1.81)	< 0.0001
Sex: Female	1.57 (0.089)	0.15 (0.128)	1.42 (1.12, 1.72)	< 0.0001
[Β0/Β0, Β+/Β+, Β+/Β0] without α-thalassemia	1.44 (0.094)	−0.01 (0.134)	1.45 (1.15, 1.75)	< 0.0001
[Β0/Β0, Β+/Β+, Β+/Β0] with α-thalassemia	0.82 (0.632)	−0.63 (1.053)	1.46 (−1.20, 4.11)	0.2174
[Β0/Β, Β+/Β] with α gene duplication	1.70 (0.123)	0.22 (0.160)	1.48 (1.12, 1.85)	< 0.0001
Baseline Hb: < 8.5 g/dL	1.52 (0.105)	0.06 (0.150)	1.46 (1.10, 1.82)	< 0.0001
Baseline Hb: ≥ 8.5 g/dL	1.46 (0.118)	0.10 (0.156)	1.36 (1.01, 1.70)	< 0.0001
Baseline NTDT-PRO T/W score: < 3 points	1.31 (0.125)	0.01 (0.174)	1.30 (0.89, 1.71)	< 0.0001
Baseline NTDT-PRO T/W score: ≥ 3 points	1.65 (0.092)	0.19 (0.131)	1.47 (1.15, 1.78)	< 0.0001



- Regardless of patients' splenectomy status, sex, baseline Hb level, baseline NTDT-PRO T/W domain score, and Β-thalassemia genotype, achievement of mean Hb increase from baseline to weeks 13–24 in the absence of RBC transfusions was in favor of luspatercept

Data cutoff: September 14, 2020.
CI, confidence interval; LS, least squares; SE, standard error.

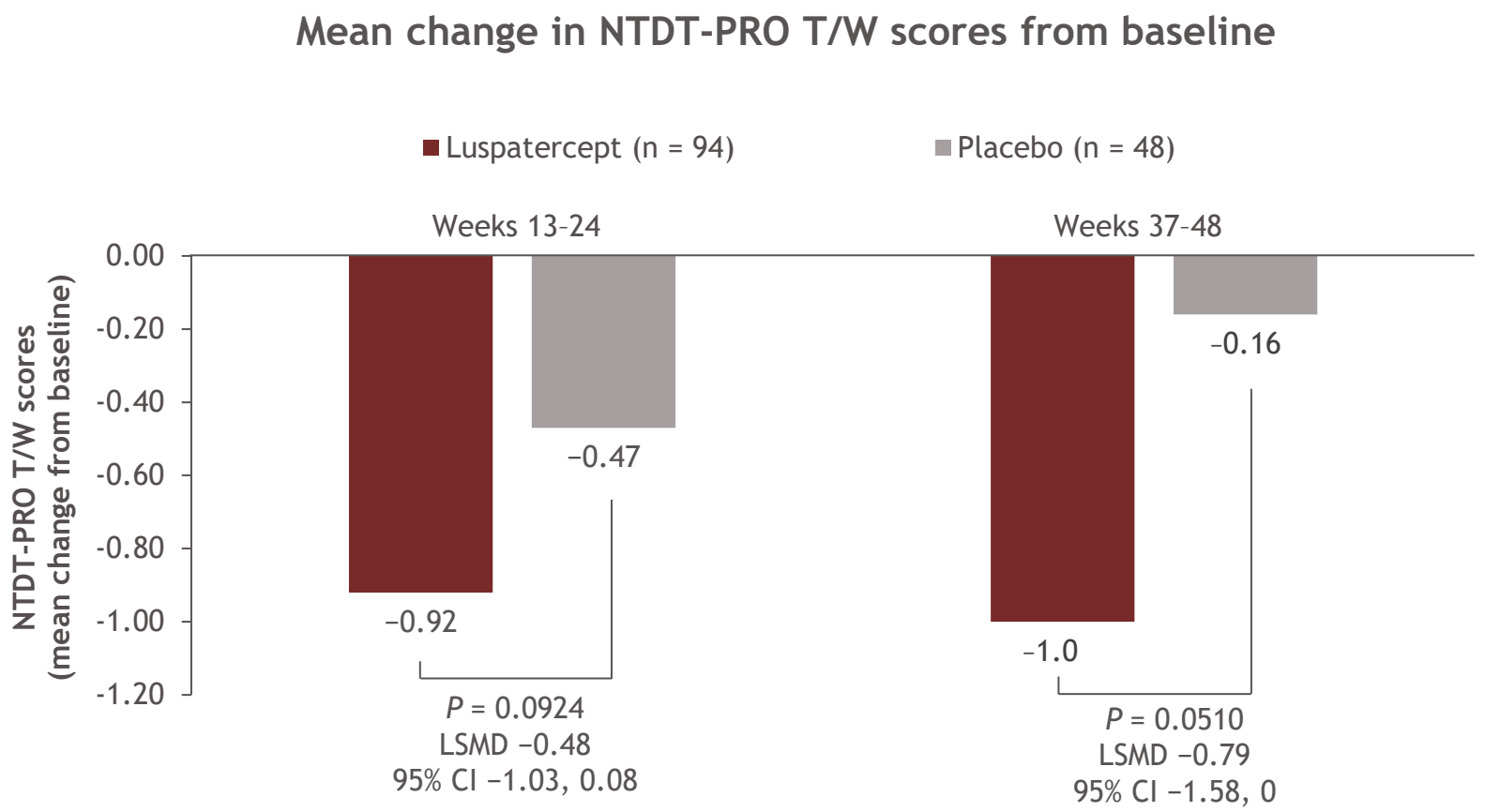
Mean Hb change from baseline during weeks 13–24



- During weeks 13–24, 50 (52.1%) patients in the luspatercept arm achieved a mean Hb increase of ≥ 1.5 g/dL from baseline

Data cutoff: September 14, 2020.

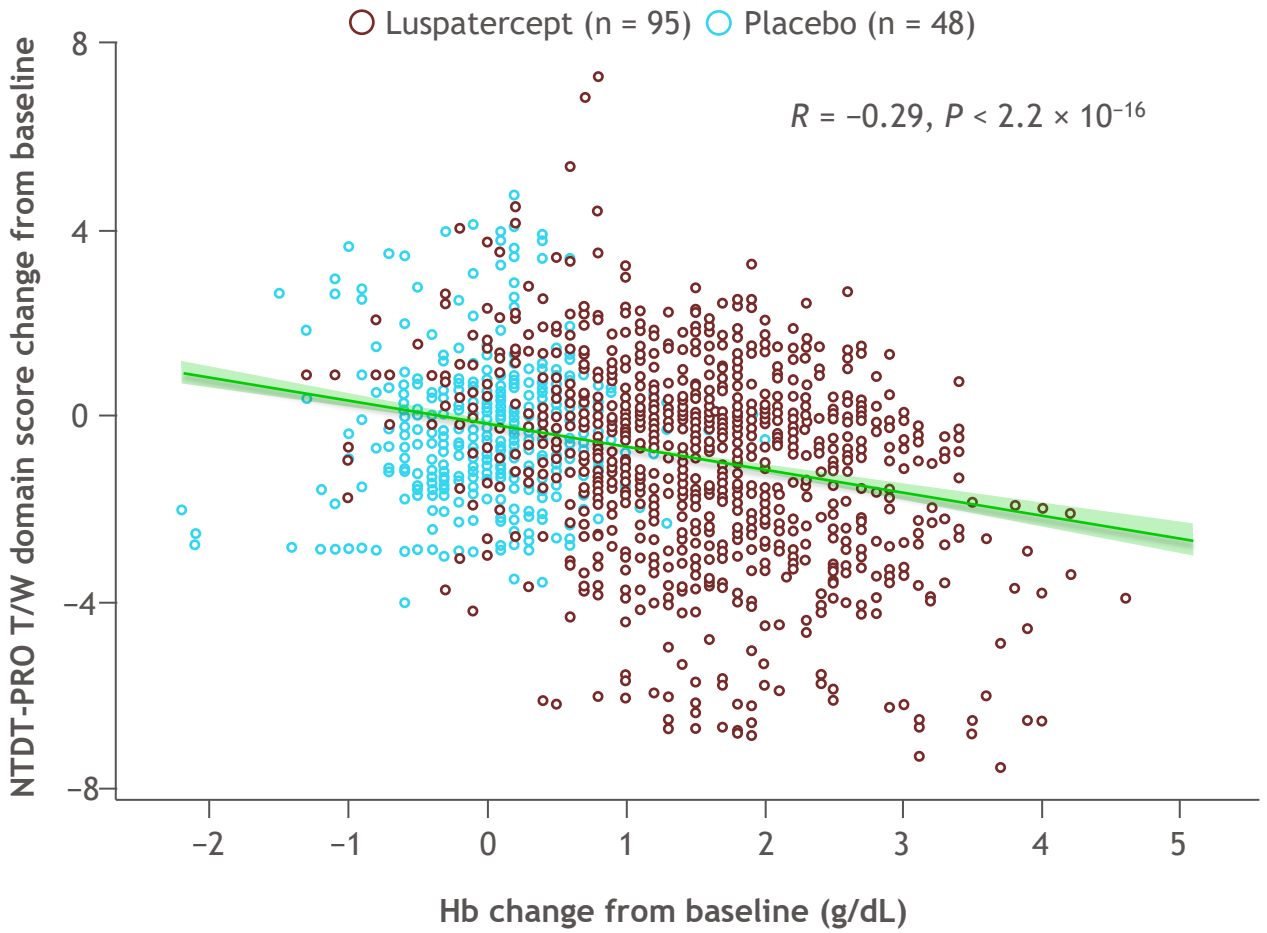
Key secondary endpoint



- 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

Data cutoff: September 14, 2020.
LSMD, least squares mean difference.

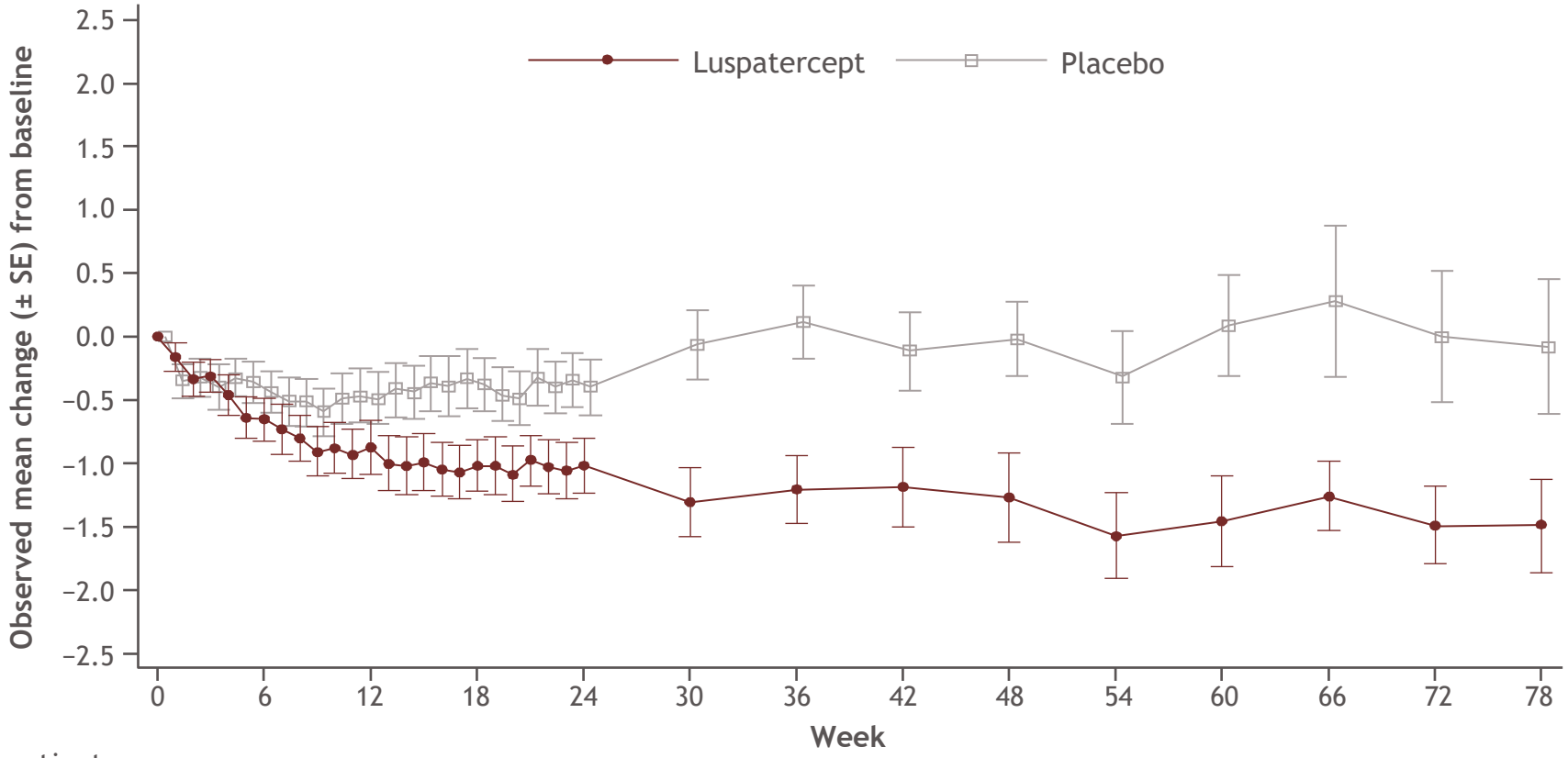
NTDT-PRO T/W domain score improvement and Hb increase



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

Data cutoff: September 14, 2020.

Change from baseline in NTDT-PRO T/W score by visit



No. of patients														
Luspatercept	93	90	85	85	77	59	58	53	48	38	39	39	41	35
Placebo	49	45	41	43	36	31	27	23	21	16	14	9	13	10

- Mean change from baseline in NTDT-PRO T/W score by visit showed a gradual and consistent improvement in the luspatercept group, which was maintained through week 78

Data cutoff: September 14, 2020.

Secondary endpoints

Secondary endpoints	Luspatercept (N = 96)	Placebo (N = 49)	*P* value
Proportion of patients who remained RBC transfusion-free over 24 weeks, n (%)	86 (89.6)	33 (67.3)	0.0013
Achievement of ≥ 1.0 g/dL mean Hb increase from baseline over a continuous 12-week interval during weeks 37–48 in the absence of RBC transfusions	68 (70.8)	1 (2.0)	< 0.0001[a]
Total duration of the mean Hb increase from baseline ≥ 1.0 g/dL during any 12-week interval, mean, (SD), days[b]	611.7 (243.3)	176.5 (132.9)	N/A

Data cutoff: September 14, 2020.
[a]*P* values nominal only; as key secondary endpoint was not met, this secondary endpoint cannot be statistically claimed [b]Only patients who have a mean Hb increase are included.
N/A, not applicable.

Safety

AE, n (%)	Luspatercept (N = 96)	Placebo (N = 49)	Total (N = 145)
≥ 1 treatment-related TEAE	73 (76.0)	18 (36.7)	91 (62.8)
≥ 1 TEAE grade ≥ 3	27 (28.1)	12 (24.5)	39 (26.9)
≥ 1 serious TEAE	11 (11.5)	12 (24.5)	23 (15.9)
Thromboembolic event	0 (0)	0 (0)	0 (0)
Any malignant event	0 (0)	2 (4.1)	2 (1.4)
Diffuse large B-cell lymphoma	0 (0)	1 (2.0)	1 (0.7)
Hepatocellular carcinoma	0 (0)	1 (2.0)	1 (0.7)

- The most common treatment-emergent AEs (any grade) occurring in ≥ 5% of patients were bone pain (36.5% luspatercept vs 6.1% placebo), headache (30.2% vs 20.4%), and arthralgia (29.2% vs 14.3%)
- No deaths were reported
- No malignancies or thromboembolic events were reported in patients treated with luspatercept

Data cutoff: September 14, 2020.
AE, adverse event; TEAE, treatment-emergent AE.

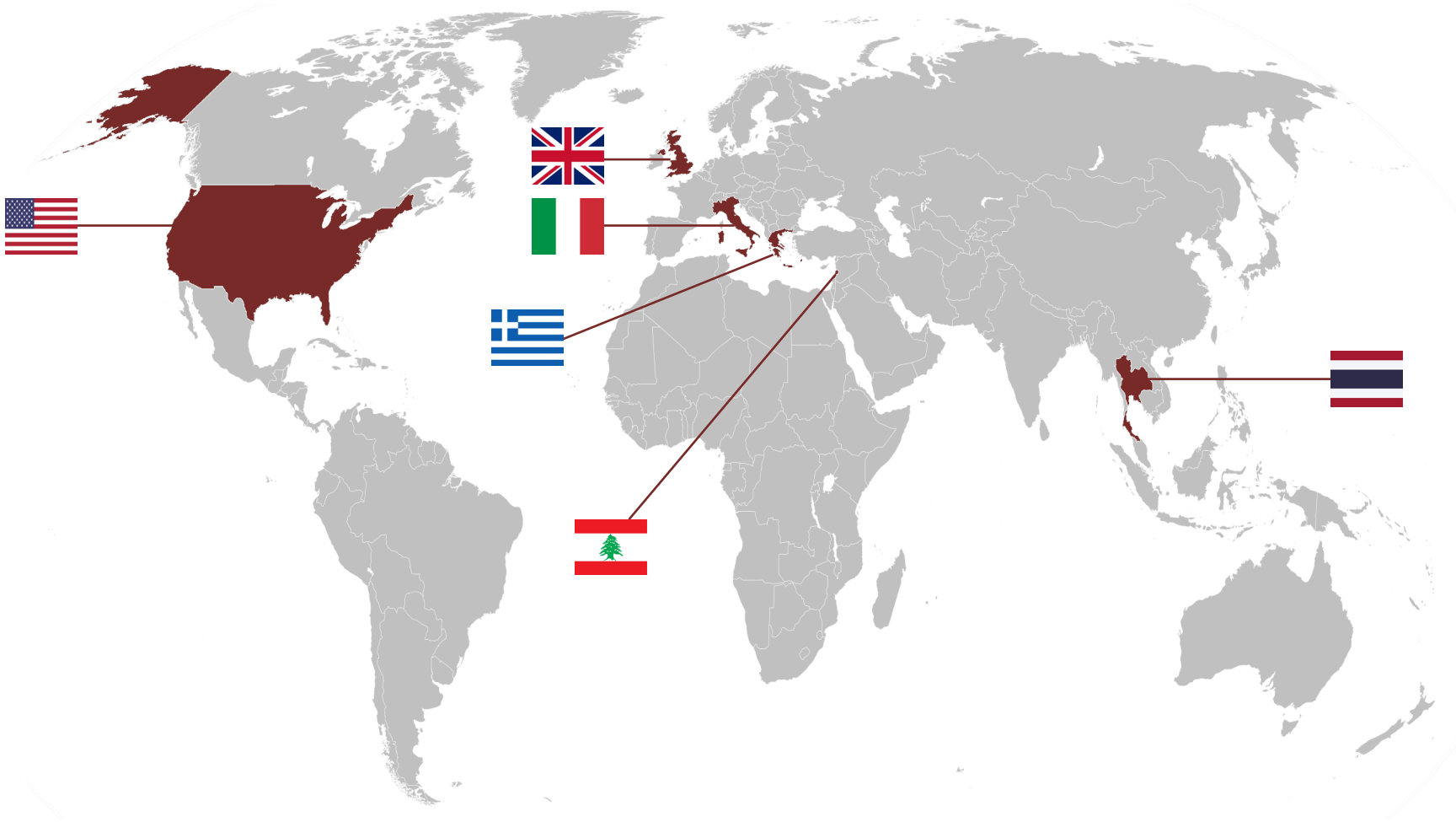
Conclusions

- The BEYOND study met its primary endpoint of mean Hb increase of ≥ 1.0 g/dL from baseline over a continuous 12-week interval during weeks 13–24 in the absence of RBC transfusions with a statistically significant difference in favor of luspatercept
- Treatment with luspatercept resulted in clinically significant and sustained improvements of anemia in adults with NTDT, as measured by Hb levels, with > 50% of patients receiving luspatercept achieving and maintaining a mean Hb increase of ≥ 1.5 g/dL
- Improvement in quality of life, as measured by the NTDT-PRO T/W domain score, favored luspatercept and was correlated with increases in Hb levels
- Luspatercept was well tolerated over a prolonged period of time
- Clinical benefit of luspatercept treatment, previously observed in patients with TDT through significant reduction in RBC transfusion burden, has now also been observed in patients with NTDT, as measured by meaningful improvement of anemia

Acknowledgments

- The patients and families who made this study possible
- The study was supported by Celgene, a Bristol-Myers Squibb Company
- All authors contributed to and approved the presentation; writing and editorial assistance were provided by Karolina Lech, PhD and Jacqueline Moy, PhD, of Excerpta Medica, funded by Bristol Myers Squibb

BEYOND study sites



UNITED STATES:
- Children's Hospital of Los Angeles, Los Angeles, California
- Children's Hospital and Research Center at Oakland, Oakland, California
- Ann & Robert H Lurie Children's Hospital of Chicago, Chicago, Illinois

GREECE:
- Laiko General Hospital of Athens, Athens
- Aghia Sofia Children's Hospital, Athens

ITALY:
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- Ente Ospedaliero Ospedali Galliera - Centro della Microcitemia e delle Anemie Congenite, Genoa
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