# AGGIORNAMENTO SU DIAGNOSI E TERAPIA DELLE EMOGLOBINOPATIE

Napoli, 7 novembre 2025 | Starhotels Terminus

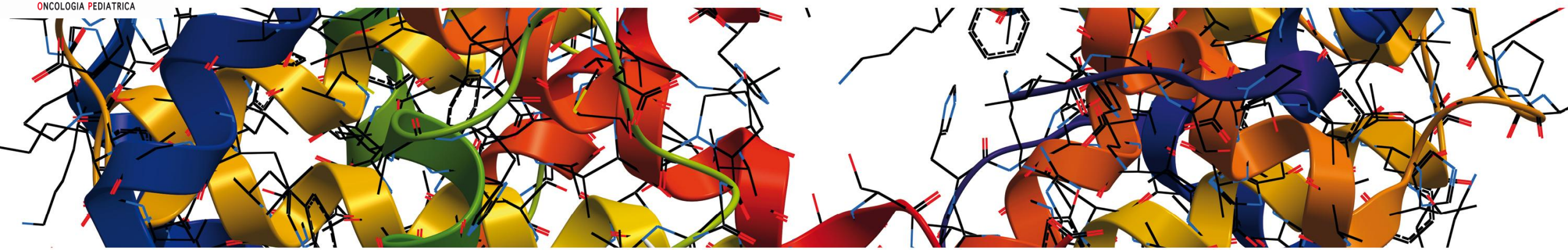
## Nuove prospettive terapeutiche nella talassemia


**Perrotta Silverio**

*Ematologia ed Oncologia pediatrica*
*Centro ERN-EuroBloodNet*
*Università della Campania "L. Vanvitelli"*

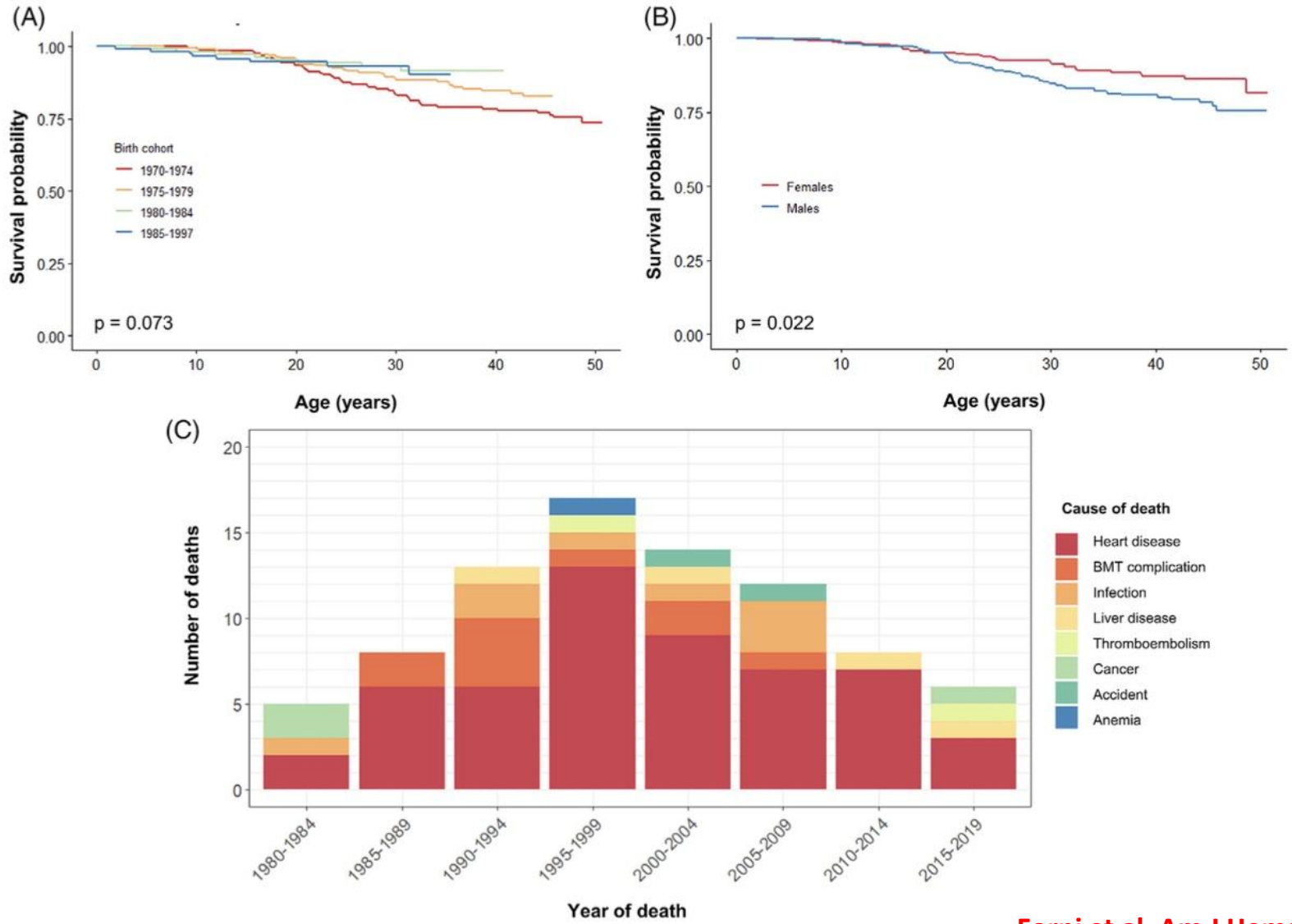

AIEOP
ASSOCIAZIONE ITALIANA EMATOLOGIA ONCOLOGIA PEDIATRICA

AOV: Azienda Ospedaliera Universitaria Luigi Vanvitelli



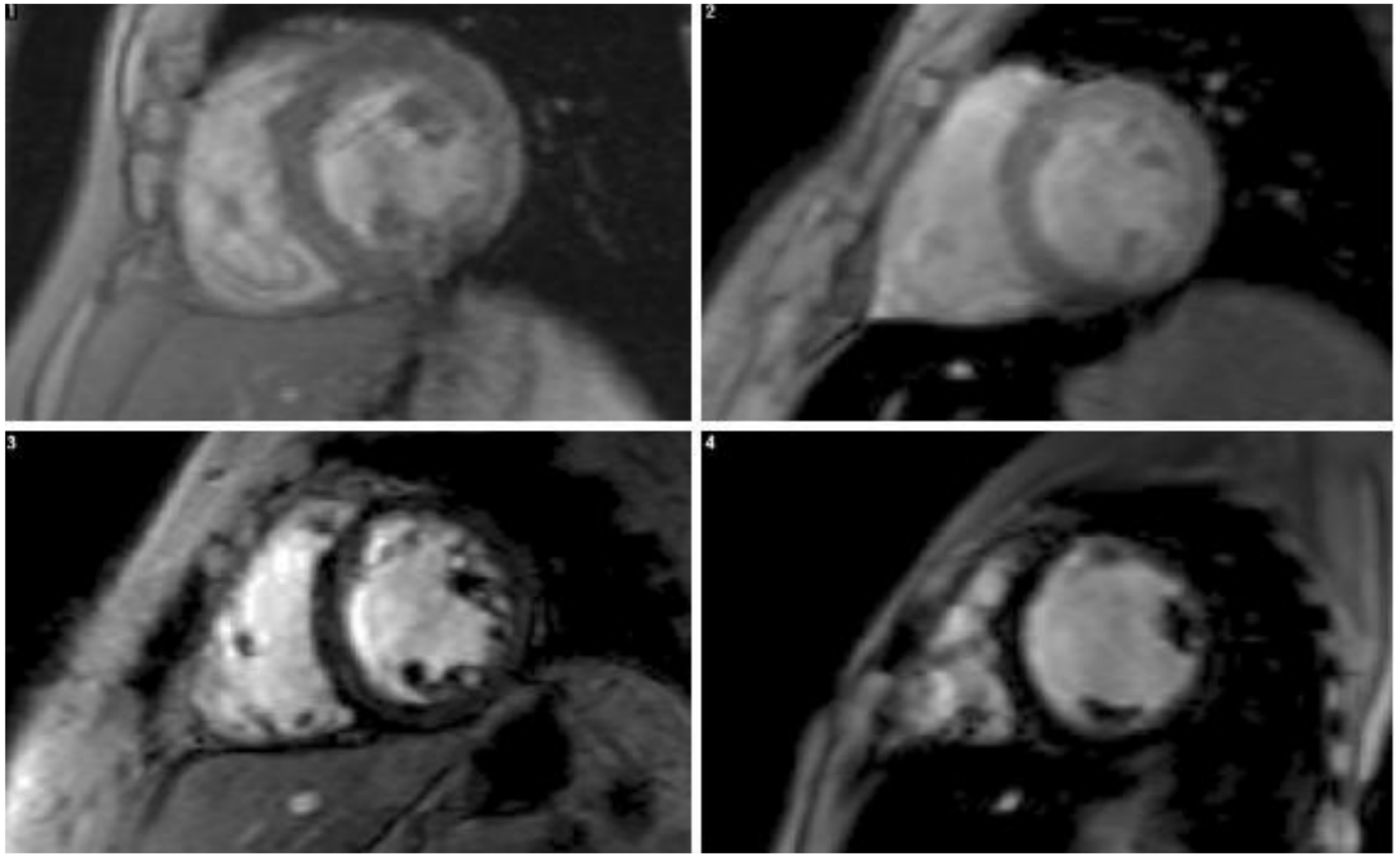
# Disclosures of Silverio Perrotta

| Company name | Research support | Employee | Consultant | Stockholder | Speakers bureau | Advisory board | Other |
|---|---|---|---|---|---|---|---|
| NOVARTIS | YES | | | | | YES | |
| CELGENE/BMS | YES | | | | | YES | |
| Acceleron | YES | | | | | YES | |
| BlueBird bio | | | YES | | | YES | |
| Biovalley Investments Partner | | | YES | | | | |
| AGIOS | | | YES | | | YES | |
| Novo Nordisk | | | YES | | | YES | |
| Pfizer | | | YES | | | YES | |
| Astrazeneca | | | YES | | | YES | |




Forni et al. Am J Hematol. 2023;98:381–387.

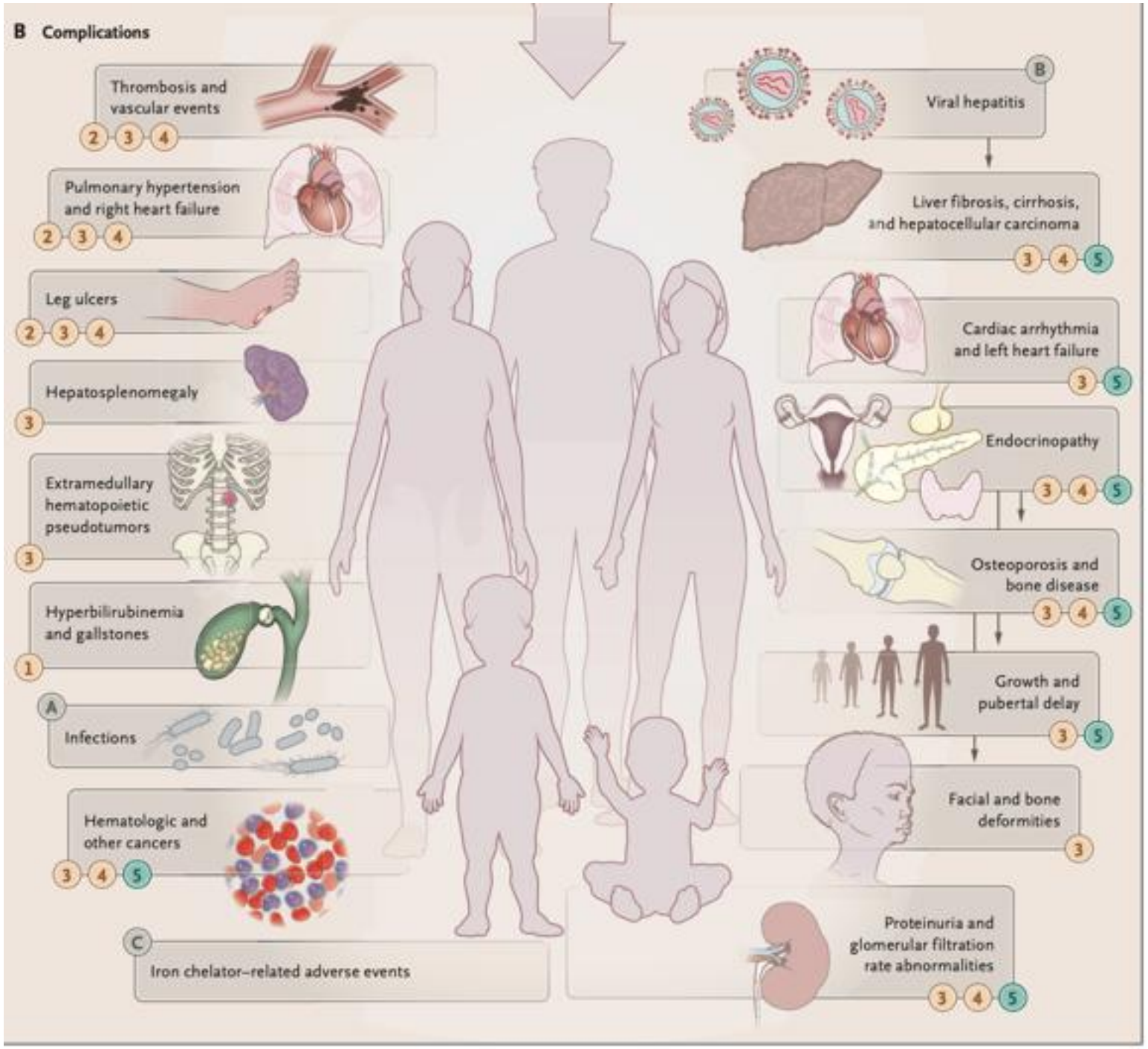
# Gradi diversi di sovraccarico marziale



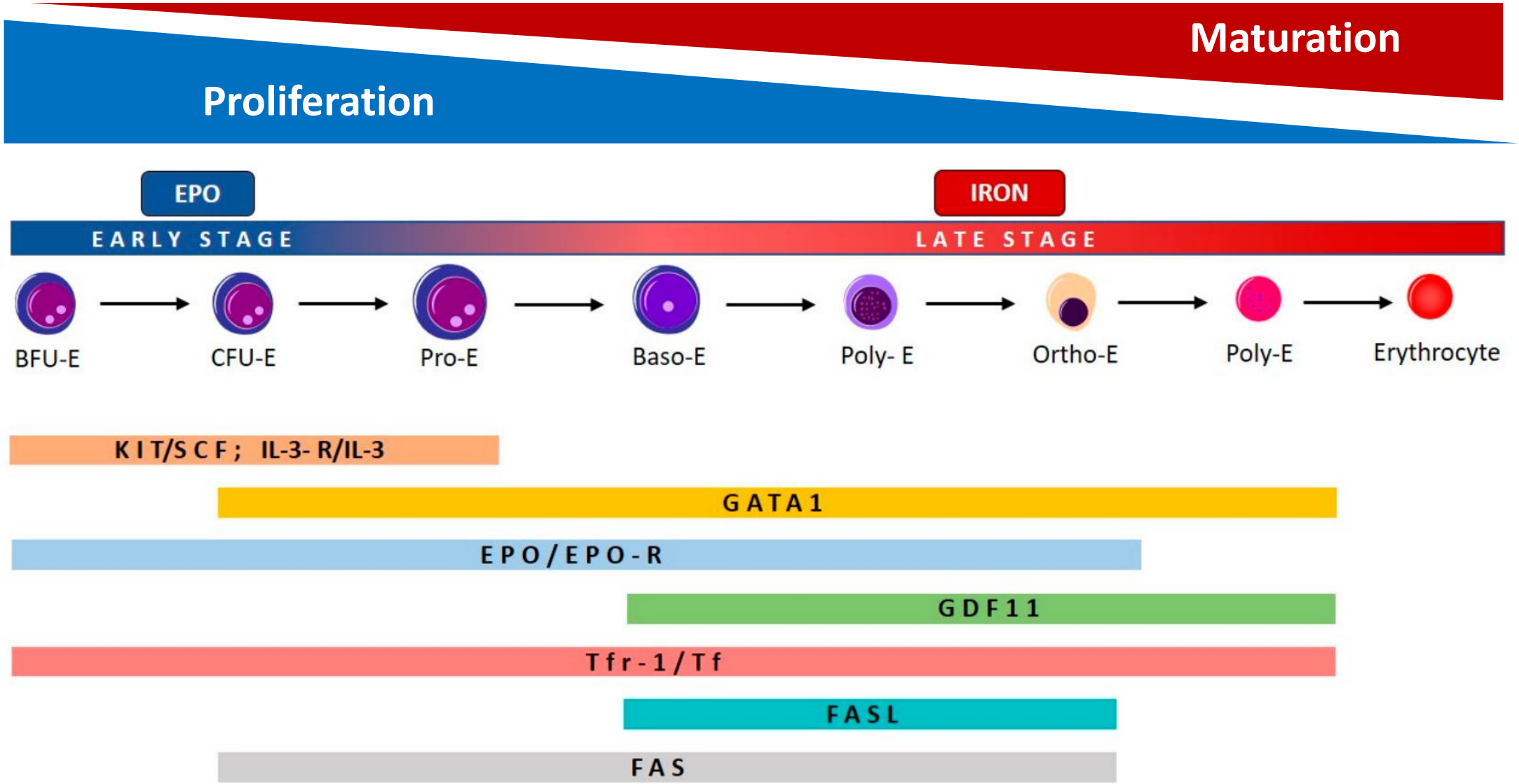
# Characteristics and evidence on iron chelators for the management of iron overload in thalassaemia

| | Deferoxamine | Deferiprone | Deferasirox |
|---|---|---|---|
| Administration[33] | | | |
| Method | Subcutaneous or intravenous | Oral | Oral |
| Frequency | 8–12 h, 5–7 days per week | 3 times daily | Once daily |
| Half-life of iron-free drug[33] | 20–30 min | 3–4 h | 12–16 h |
| Lipid solubility[33] | Low | Intermediate | High |
| Route of iron excretion[33] | Urinary and faecal | Urinary | Faecal |
| Recommended dose[23,33] | 30–60 mg/kg per day | 75–100 mg/kg per day | TDT: 20–40 mg/kg per day; NTDT: 5–20 mg/kg per day |
| TIF guidelines indication | | | |
| TDT[33] | >2 years: first-line | 2–6 years: no sufficient data; >6 years: second-line† | 2–6 years: first-line (USA), second-line (EU); >6 years: first-line |
| NTDT[23] | No sufficient data | No sufficient data | >10 years: first-line |
| Most relevant clinical data | | | |
| TDT[33] | Reduction in serum ferritin and liver iron concentration;[108] improvement in cardiac T2*;[108] improvement in cardiac dysfunction with continuous infusion[109] | Improvement of cardiac T2* in monotherapy or in combination with deferoxamine (higher doses than commonly used in clinical practice)‡;[110,111] improvement in cardiac dysfunction in combination with deferoxamine†‡;[112] improvement in endocrine dysfunction in combination with deferoxamine or deferasirox[113,114] | Reduction in serum ferritin and liver iron concentration after up to 5 years, and cardiac T2* after up to 3 years of therapy, even in patients with severe iron overload;[115–118] not inferior to deferoxamine for improving cardiac T2*;[108] improvements in hepatic fibrosis and inflammation;[119] stabilisation of heart function;[108,115] stabilisation of endocrine function[120] |
| NTDT[23] | Data restricted to case series and small studies | Data restricted to case series and small studies | Significant reduction in serum ferritin and liver iron concentration after up to 2 years of therapy[121] |
| Main adverse events[33] | Ocular and auditory symptoms, bone-growth retardation, local reactions, allergy | Gastrointestinal symptoms, arthralgia, agranulocytosis or neutropenia | Gastrointestinal symptoms, increased creatinine, increased hepatic enzymes |
| Pregnancy[33] | Contraindicated (but has been used in third trimester) | Contraindicated | Contraindicated |

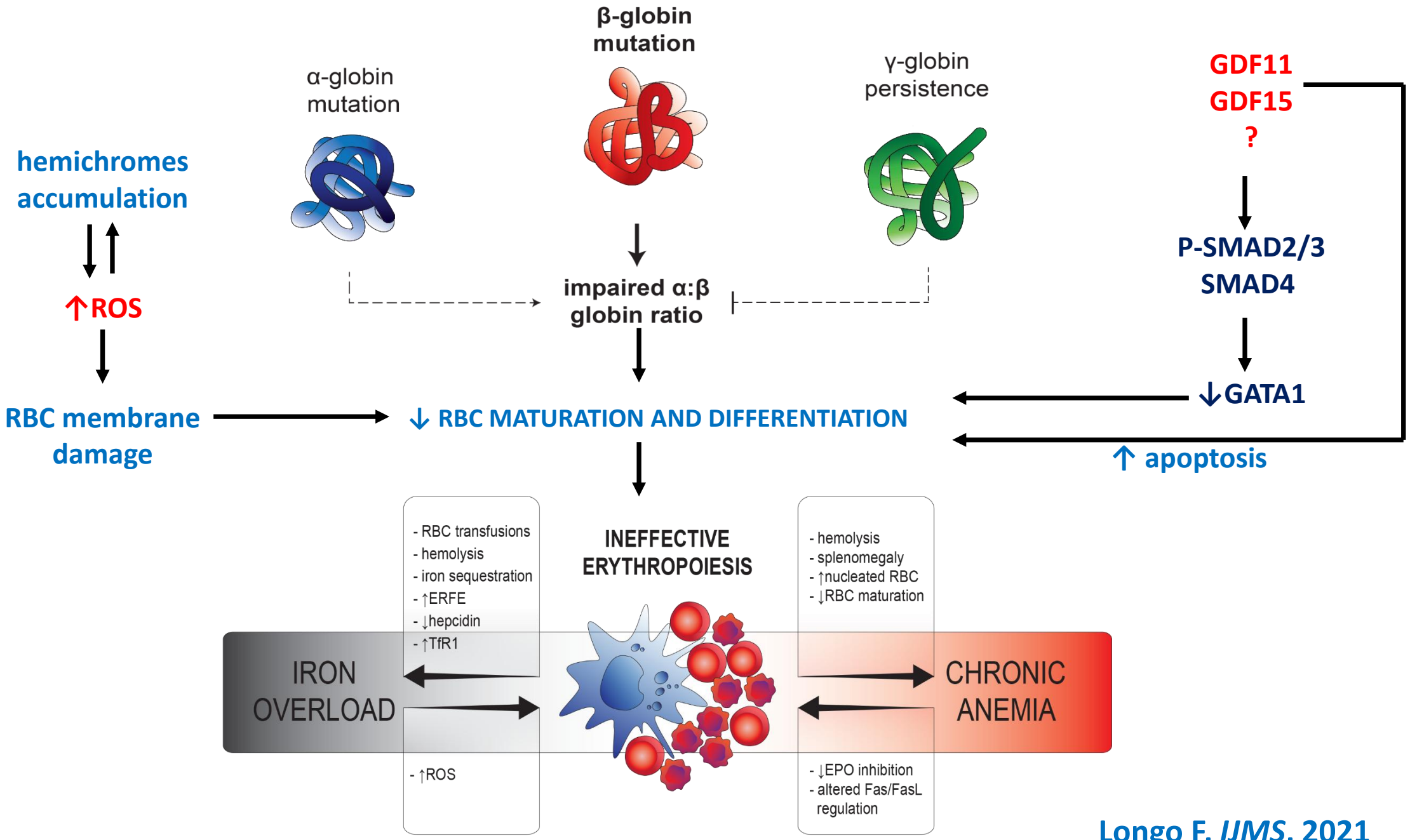
*Ali T Taher, David J Weatherall, Maria Domenica Cappellini* Lancet 2017



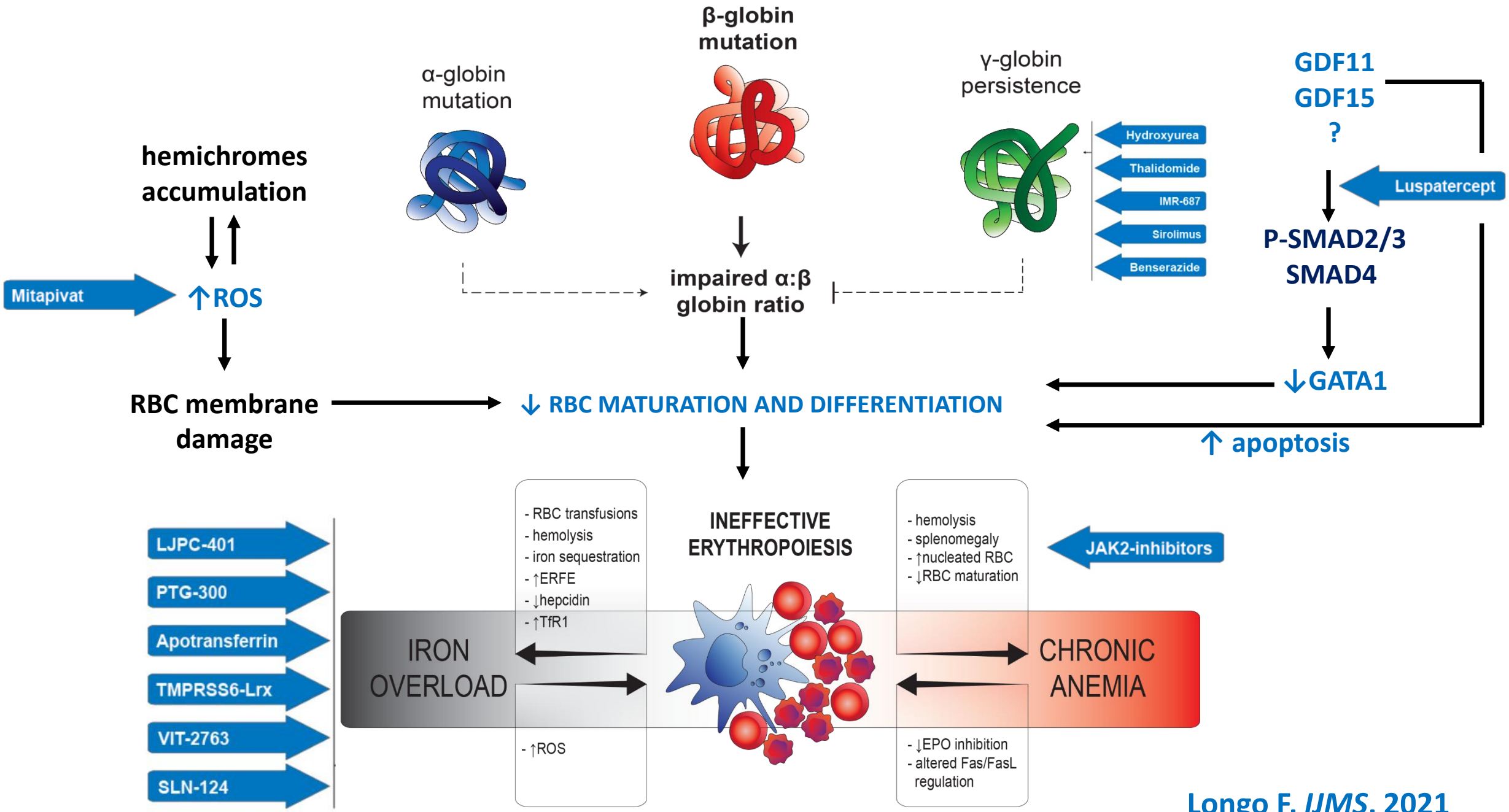

Taher et al NEJM2021;384:727-43



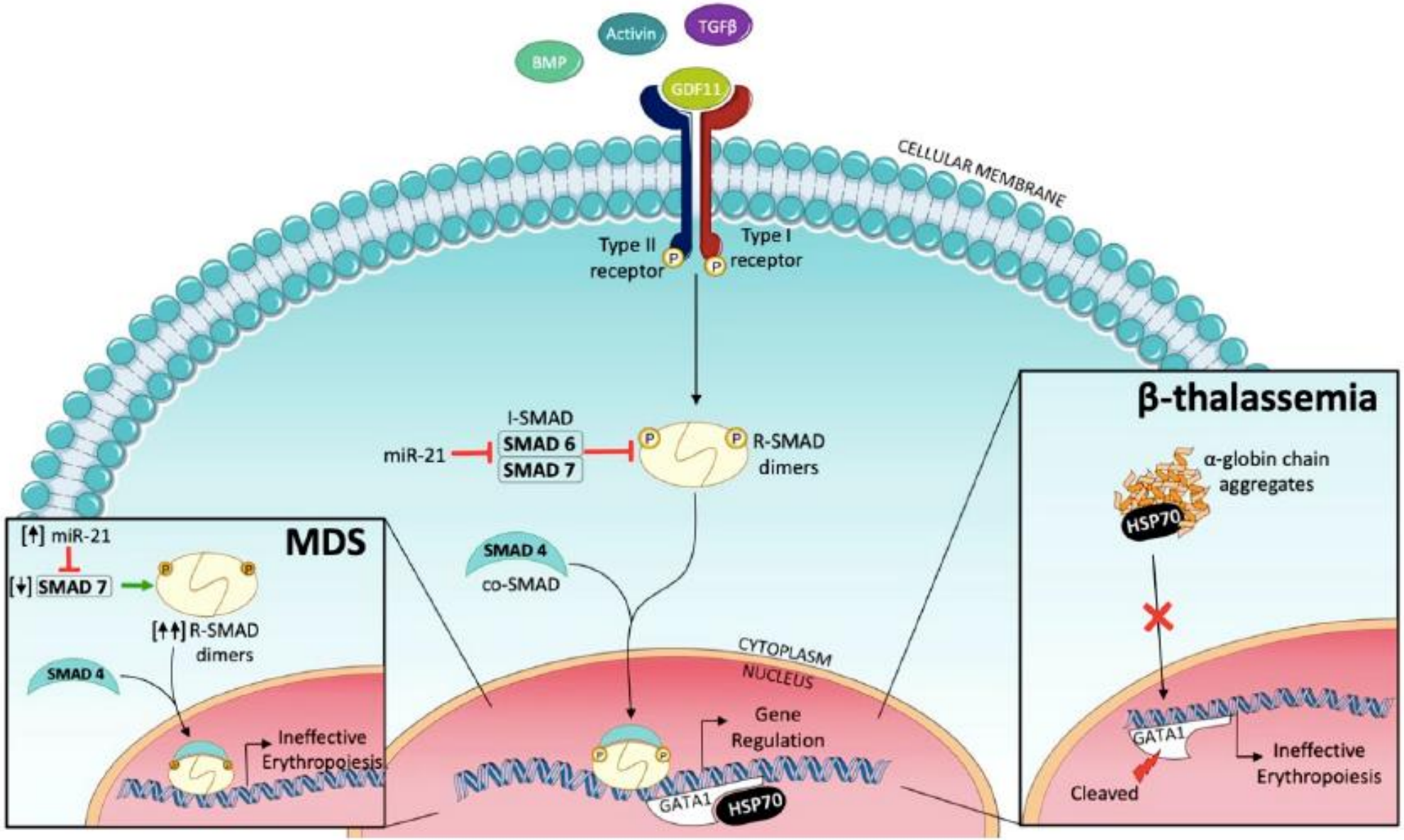

Adapted from Parisi S, *IJMS*, 2021




Longo F, *IJMS*, 2021




Longo F, *IJMS*, 2021




Adapted from Parisi S, *IJMS*, 2021

# Luspatercept decreases Smad2/3 signaling

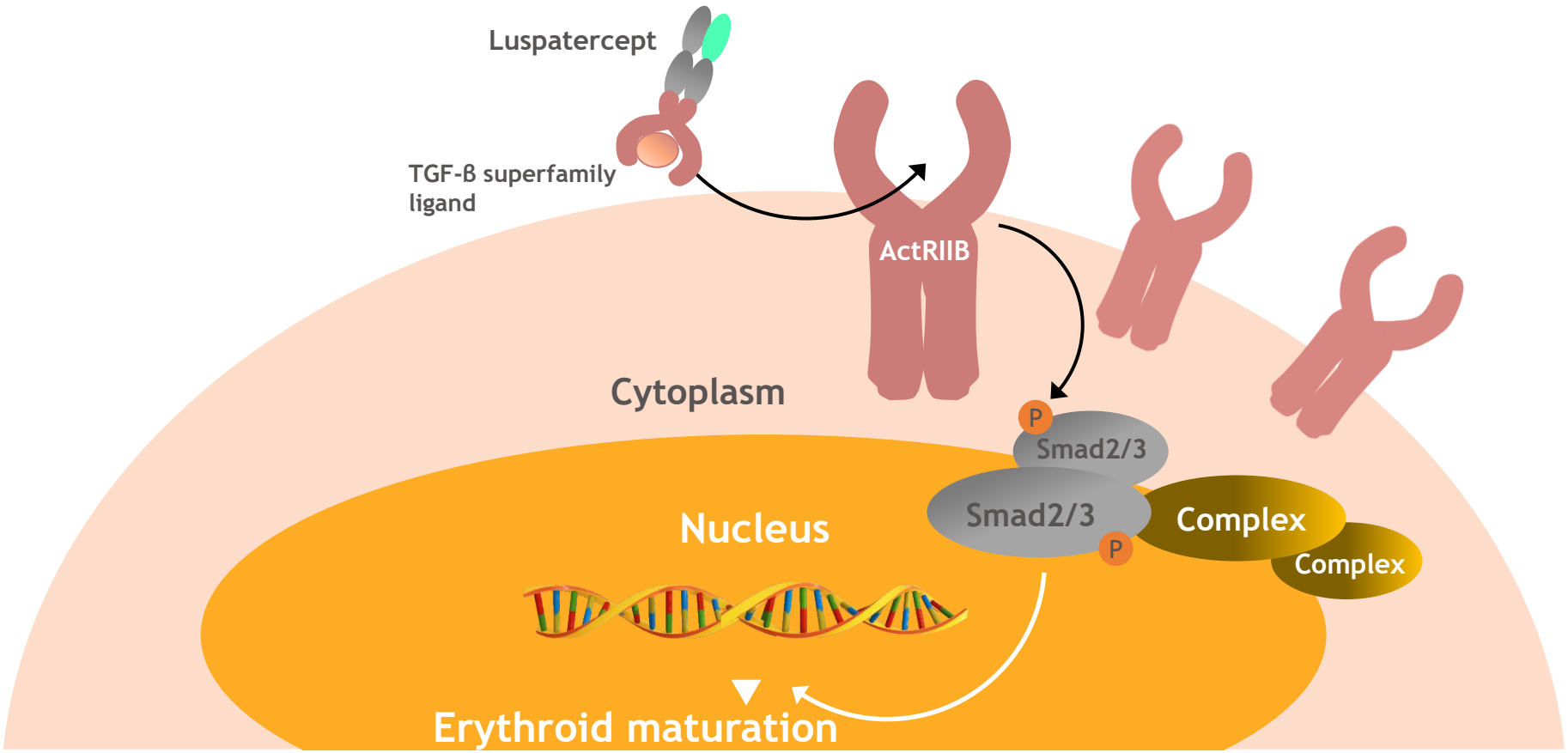
Luspatercept is a first-in-classe erythroid maturation agent: a recombinant fusion protein consisting of a modified form of the extracellular domain of the human ActRIIB linked to the human IgG1 Fc domain[1]

Luspatercept binds to select TGF-β superfamily ligands[2-4]…

… inhibiting ActRIIB activation and decreasing Smad2/3 signaling[2]

Decreasing Smad2/3 signaling enhances erythroid maturation in late-stage erythropoiesis[3]

Increased aberrant TGF-β superfamily signaling via the Smad2/3 pathway is a component of ineffective erythropoiesis and impaired erythroid maturation[2,3]




ActRIIB, activin receptor type IIB; IgG1 Fc, immunoglobulin G1 fragment crystallizable; P, phosphorylation; Smad, small mothers against decapentaplegic; TGF-β, transforming growth factor β.

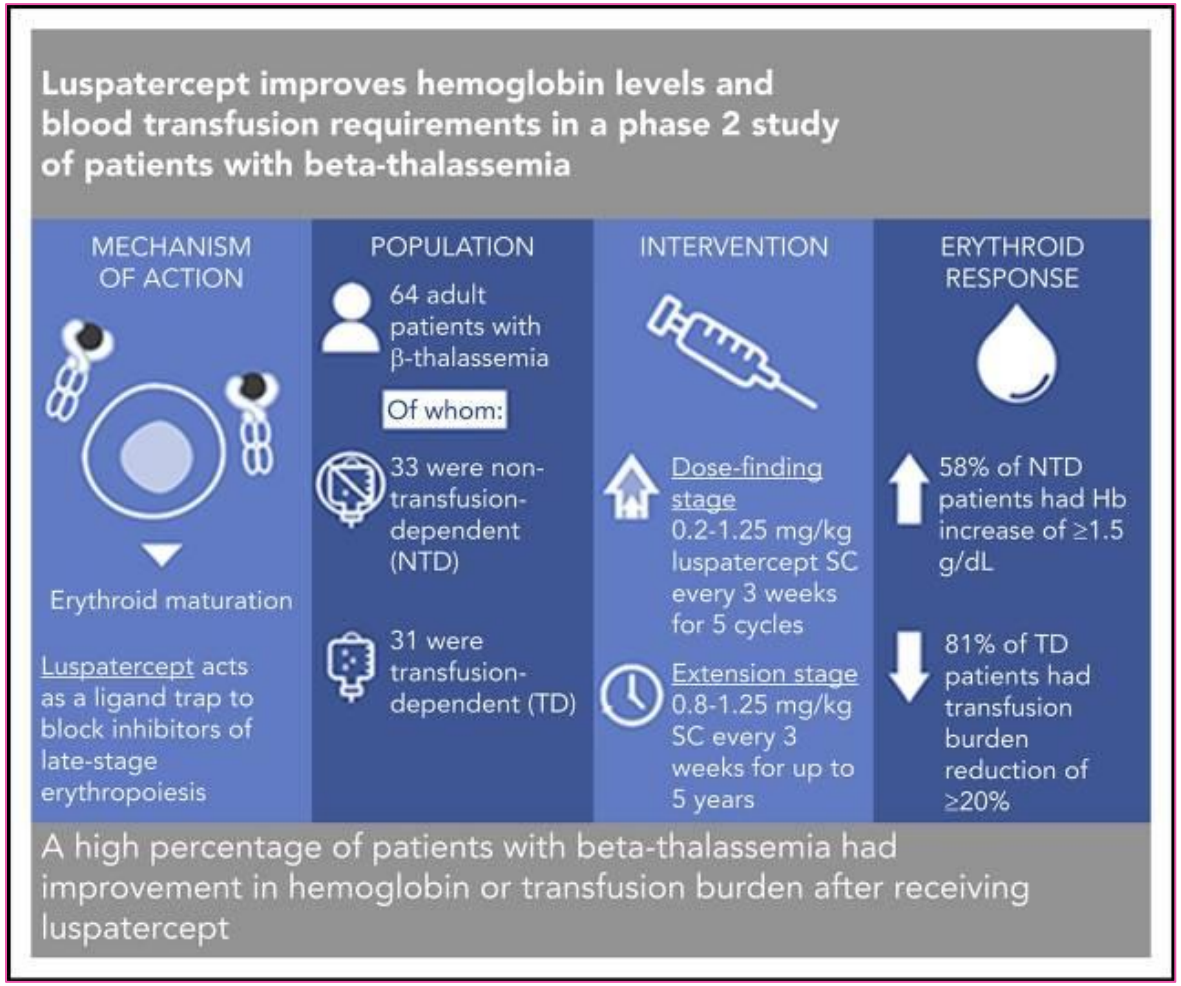

1. Attie KM et al. *Am J Hematol* 2014;89:766–770. 2. Suragani RN et al. *Nat Med* 2014;20:408–414. 3. Suragani RN et al. *Blood* 2014;123:3864–3872. 4. Cappellini MD et al. *Blood* 2018;132:163.

CLINICAL TRIALS AND OBSERVATIONS

# Luspatercept improves hemoglobin levels and blood transfusion requirements in a study of patients with β-thalassemia

Antonio Piga,[1] Silverio Perrotta,[2] Maria Rita Gamberini,[3] Ersi Voskaridou,[4] Angela Melpignano,[5] Aldo Filosa,[6] Vincenzo Caruso,[7] Antonello Pietrangelo,[8] Filomena Longo,[1] Immacolata Tartaglione,[2] Caterina Borgna-Pignatti,[9] Xiaosha Zhang,[10] Abderrahmane Laadem,[11] Matthew L. Sherman,[10] and Kenneth M. Attie[10]

blood® 21 MARCH 2019 | VOLUME 133, NUMBER 12

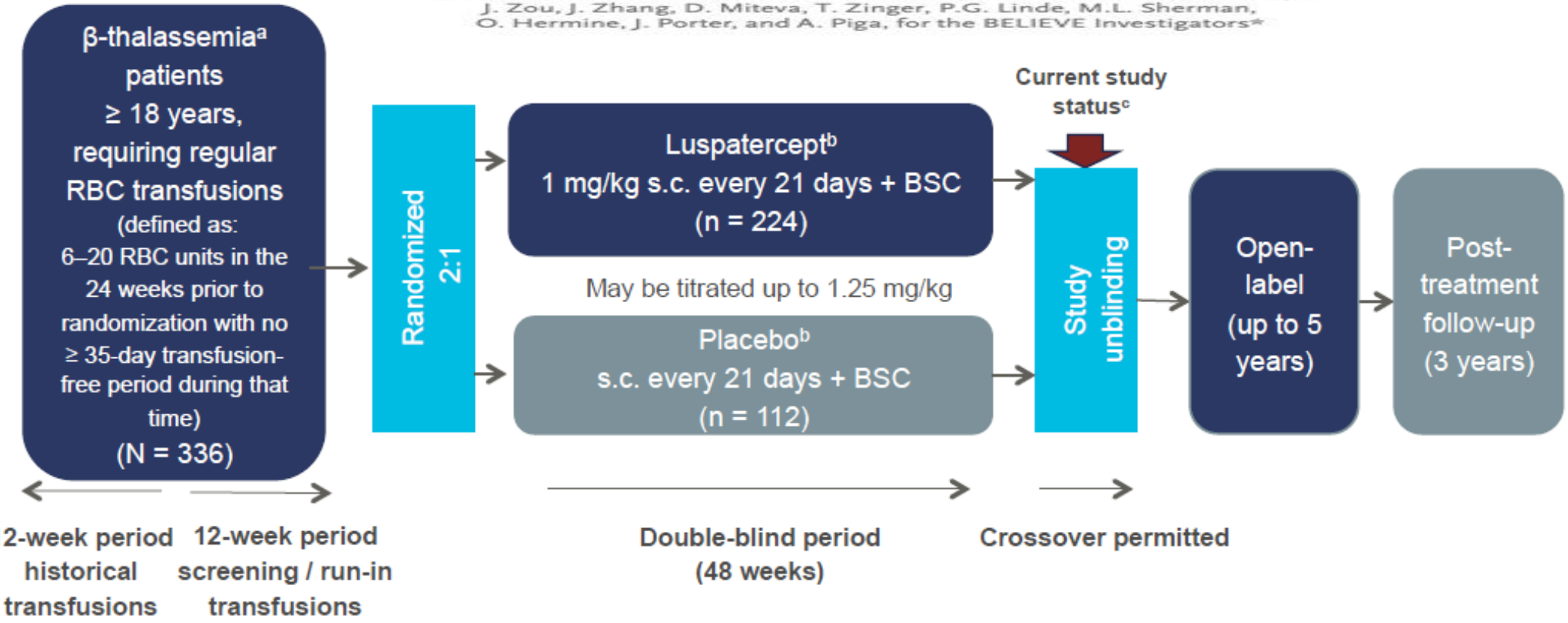


The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

# A Phase 3 Trial of Luspatercept in Patients with Transfusion-Dependent β-Thalassemia

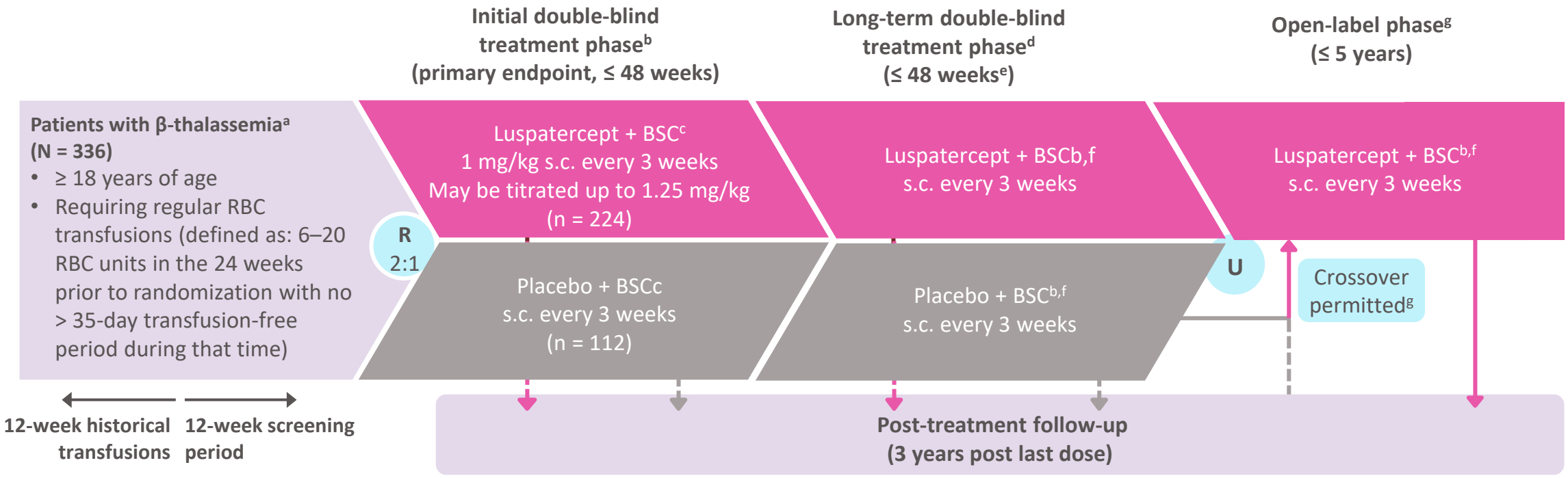
M.D. Cappellini, V. Viprakasit, A.T. Taher, P. Georgiev, K.H.M. Kuo, T. Coates, E. Voskaridou, H.-K. Liew, I. Pazgal-Kobrowski, G.L. Forni, S. Perrotta, A. Khelif, A. Lal, A. Kattamis, E. Vlachaki, R. Origa, Y. Aydinok, M. Bejaoui, P.J. Ho, L.-P. Chew, P.-C. Bee, S.-M. Lim, M.-Y. Lu, A. Tantiworawit, P. Ganeva, L. Gercheva, F. Shah, E.J. Neufeld, A. Thompson, A. Laadem, J.K. Shetty, J. Zou, J. Zhang, D. Miteva, T. Zinger, P.G. Linde, M.L. Sherman, O. Hermine, J. Porter, and A. Piga, for the BELIEVE Investigators*




[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.

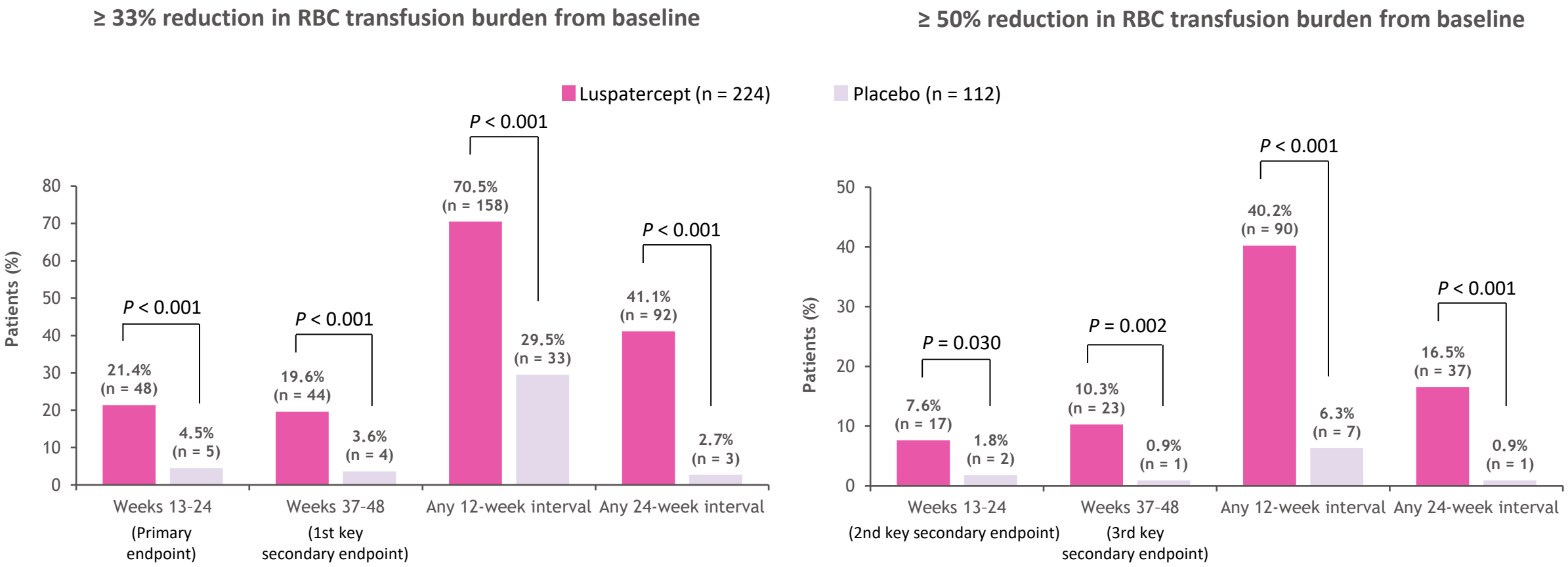
# BELIEVE: a randomized, double blind, placebo-controlled, phase 3 study of luspatercept in adults with TDT




BSC: Best Supportive Care

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

# Efficacy: reduction in RBC transfusion burden from baseline




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

# BELIEVE Trial

TEAEs by frequency ≥ 10% in Either Arm (all grades)

| 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.

The BELIEVE Trial studied adult patients.

# BELIEVE Trial

## Grade 3–4 TEAEs by frequency ≥ 1% in Either Arm

| n (%) | Luspatercept (n = 223[a]) | Placebo (n = 109[a]) |
|---|---|---|
| **Anemia** | 7 (3.1) | 0 |
| **Increased LIC** | 6 (2.7) | 1 (0.9) |
| **Hyperuricemia** | 6 (2.7) | 0 |
| Hypertension | 4 (1.8) | 0 |
| Syncope | 4 (1.8) | 0 |
| Back pain | 3 (1.3) | 1 (0.9) |
| Bone pain | 3 (1.3) | 0 |
| Blood uric acid increased | 3 (1.3) | 0 |
| Increased AST | 3 (1.3) | 0 |
| Increased ALT | 2 (0.9) | 3 (2.8) |
| Thromboembolic events[b] | 2 (0.9) | 0 |

In total, thromboembolic events (all grades) were reported in **8/223 (3.6%)** luspatercept-treated patients (deep venous thrombosis, pulmonary embolism, portal vein thrombosis, ischemic stroke, thrombophlebitis, superficial phlebitis) and 1/109 (0.9%) placebo-treated patients (phlebitis). In all cases, patients had multiple risk factors for thromboembolic events

[a] Safety population. [b] Thromboembolic events included as a TEAE of interest; other events occurring in < 1% of patients are not shown.
ALT, alanine aminotransferase; AST, aspartate aminotransferase.
The BELIEVE Trial studied adult patients.

# Luspatercept approval in TDT patients

Luspatercept has been approved by the US Food and Drug Administration (FDA) in 2019 and by the European Medicines Agency (EMA) in 2020 and by the **AIFA in December 2021** to treat anemia in adult patients with beta-thalassemia who require regular red blood cell transfusions

Collana Scientifica SITE

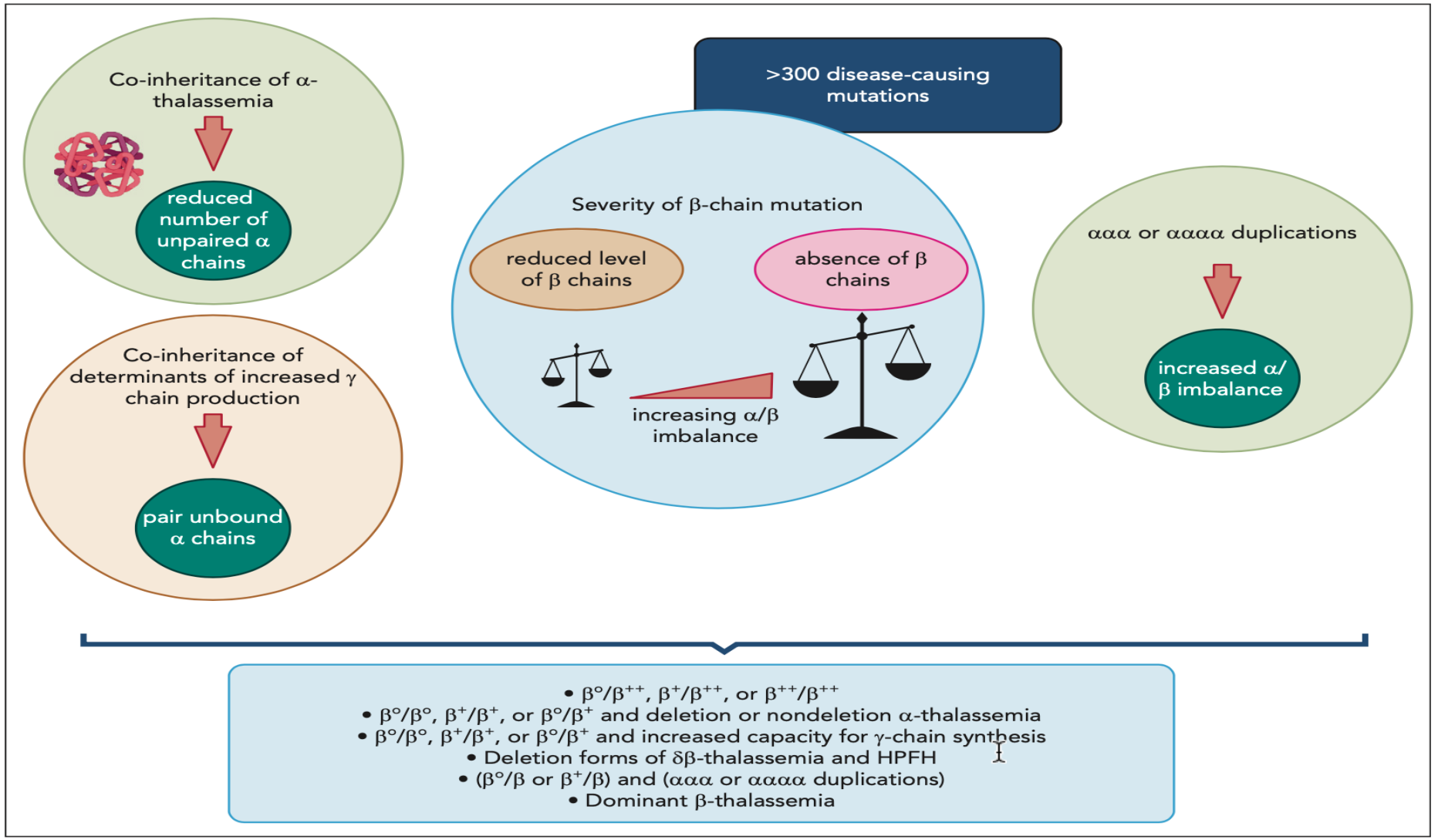
# IDENTIFICAZIONE E GESTIONE DEL PAZIENTE CON INDICAZIONE AL TRATTAMENTO CON LUSPATERCEPT

## Buone Pratiche SITE

SOCIETA' ITALIANA TALASSEMIE
ED EMOGLOBINOPATIE

REV Giugno 2024

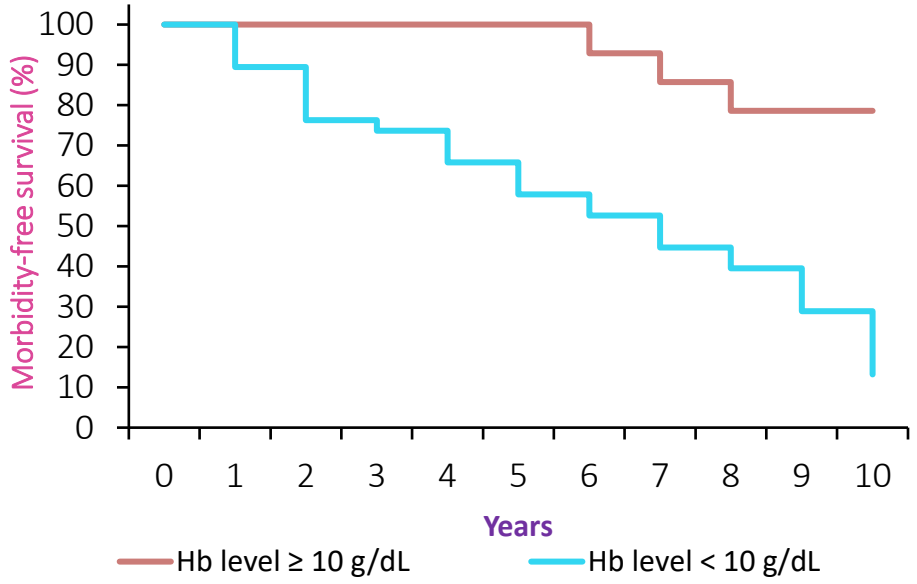
# Who are the NTD β-thalassemia patients?

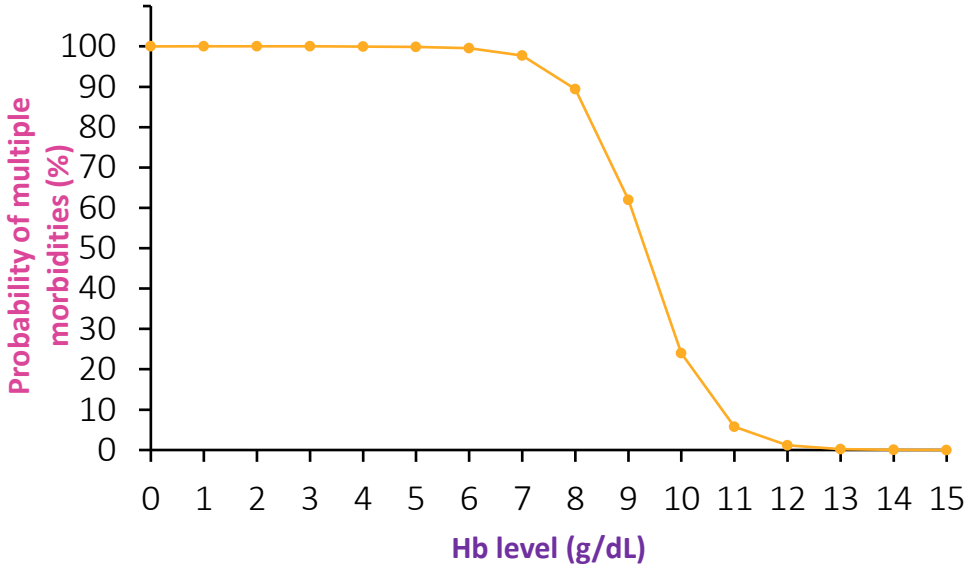



Saliba A, Musallam K, Taher A. Blood 2023;142,11

# 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 ($P < 0.001$)
- 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
- Improvement of anemia and disease complications are unmet needs in patients with NTDT





1. Taher AT et al. EHA 2021; Oral S101.
2. Musallam KM, et al. Annals of Hematology (2022) 101:203–204
3. Musallam Ann Hematol (2021) 100:1903–1905

HemaSphere

EHA EUROPEAN HEMATOLOGY ASSOCIATION

Perspective
Open Access

# Untreated Anemia in Nontransfusion-dependent β-thalassemia: Time to Sound the Alarm

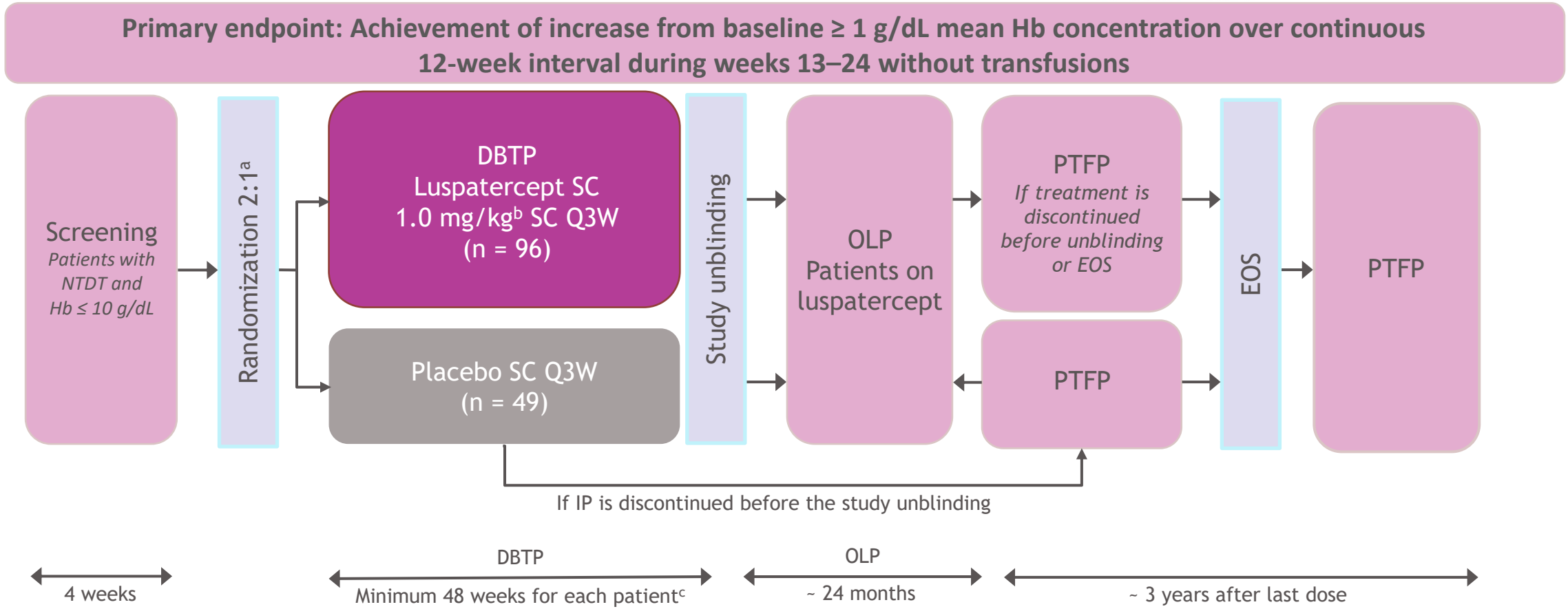
Khaled M. Musallam[1], Ali T. Taher[2], Maria Domenica Cappellini[3], Olivier Hermine[4], Kevin H. M. Kuo[5], Sujit Sheth[6], Vip Viprakasit[7], John B. Porter[8]

Musallam K et al. HemaSphere (2022) 6:12(e806).

# BEYOND study design

**Luspatercept for the treatment of anaemia in non-transfusion-dependent β-thalassaemia (BEYOND): a phase 2, randomised, double-blind, multicentre, placebo-controlled trial**

*Ali T Taher*, Maria Domenica Cappellini*, Antonis Kattamis, Ersi Voskaridou, Silverio Perrotta, Antonio G Piga, Aldo Filosa, John B Porter, Thomas D Coates, Gian Luca Forni, Alexis A Thompson, Immacolata Tartaglione, Khaled M Musallam, Jay T Backstrom, Oriana Esposito, Ana Carolina Giuseppi, Wen-Ling Kuo, Dimana Miteva, Jennifer Lord-Bessen, Aylin Yucel, Tatiana Zinger, Jeevan K Shetty, Vip Viprakasit, on behalf of the BEYOND Investigators†*




**Primary data cut was September 14, 2020 and current data cut was September 22, 2021**.

[a]Patients were stratified by baseline Hb level (< 8.5 or ≥ 8.5 g/dL) and NTDT-PRO T/W domain score (≥ 3 or < 3); [b]Dose could be titrated to a maximum of 1.25 mg/kg; [c]DBTP ended after last patient enrolled had completed 48 weeks of treatment or discontinued earlier, or when study was unblinded.

DBTP, double-blind treatment period; EOS, end of study; IP, investigational product; NTDT-PRO T/W, Non-Transfusion-Dependent β-Thalassemia Patient-Reported Outcomes Tiredness/Weakness domain; OLP, open-label period; PTFP, post-treatment follow-up period; Q3W, every 3 weeks; SC, subcutaneously.

1. Taher AT, et al. Lancet Haematol 2022;9:e733–e744.

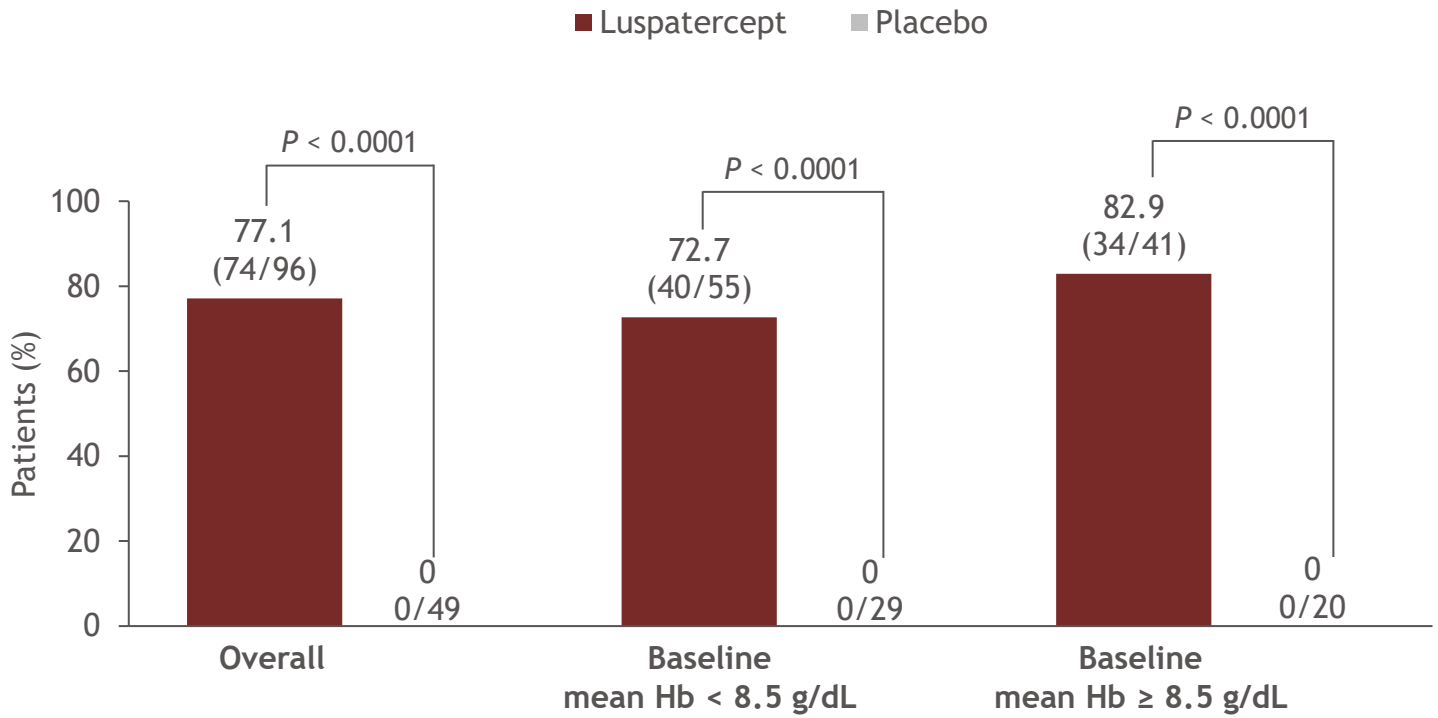
Taher AT, et al. EHA 2023 [Abstract #S273]

# NTDT-PRO instrument

- NTDT-PRO is the first PRO instrument developed specifically for assessment of quality-of-life (QoL) in patients with NTDT
- It contains six items assessing the severity of tiredness, weakness, and shortness of breath with or without physical activity
- The Tiredness/Weakness domain is the weekly scores average from four tiredness and weakness items
- The tool employs a 24-h recall method, with scores ranging from 0 (absent) to 10 (extreme)
  - - A decrease in NTDT-PRO T/W domain score is considered an improvement
  - - Scores of 3 or higher are indicative of symptomatic NTDT

Taher AT, et al. *Lancet Haematol 2022*

# 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.

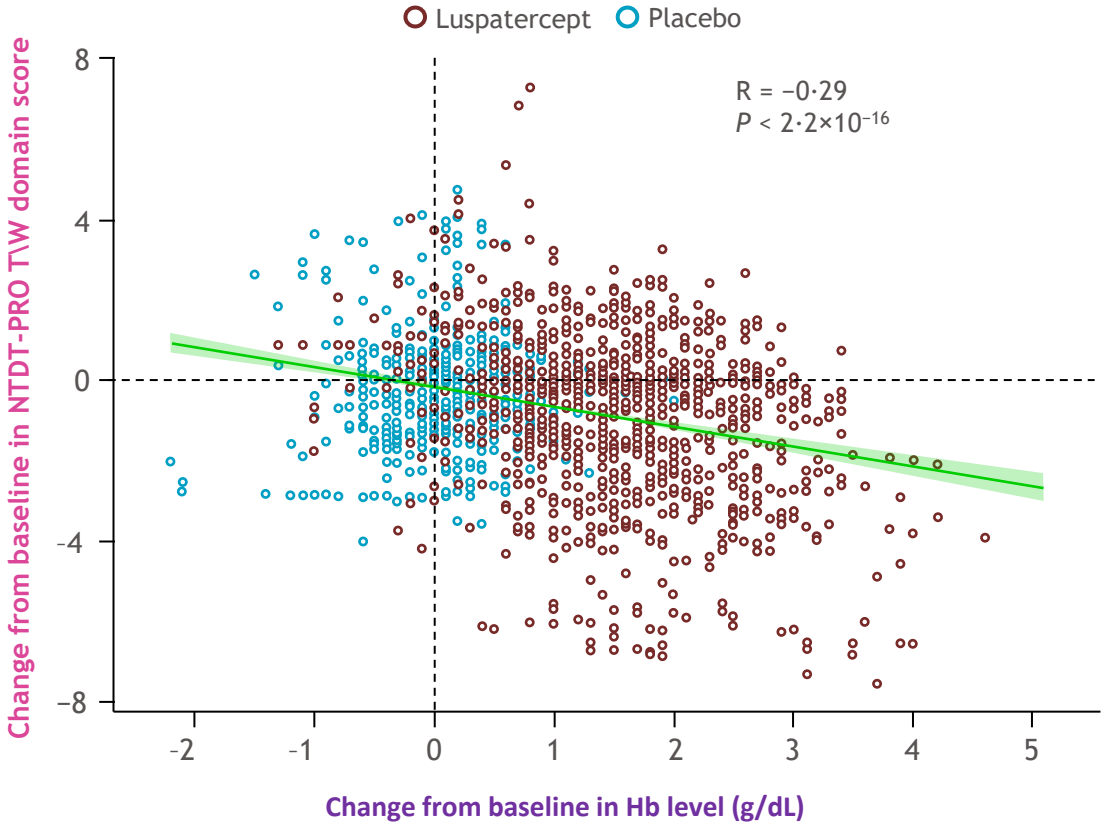
[a]Baseline Hb is defined as the average of 2 or more Hb measurements ≥ 1 week apart within 4 weeks prior to randomization. Primary endpoint was defined as a ≥ 1.0 g/dL mean increase in Hb from baseline over a continuous 12-week interval from weeks 13 to 24, in the absence of RBC transfusions.

Hb, hemoglobin; RBC, red blood cell.

Taher AT et al. EHA 2021; Oral S101.

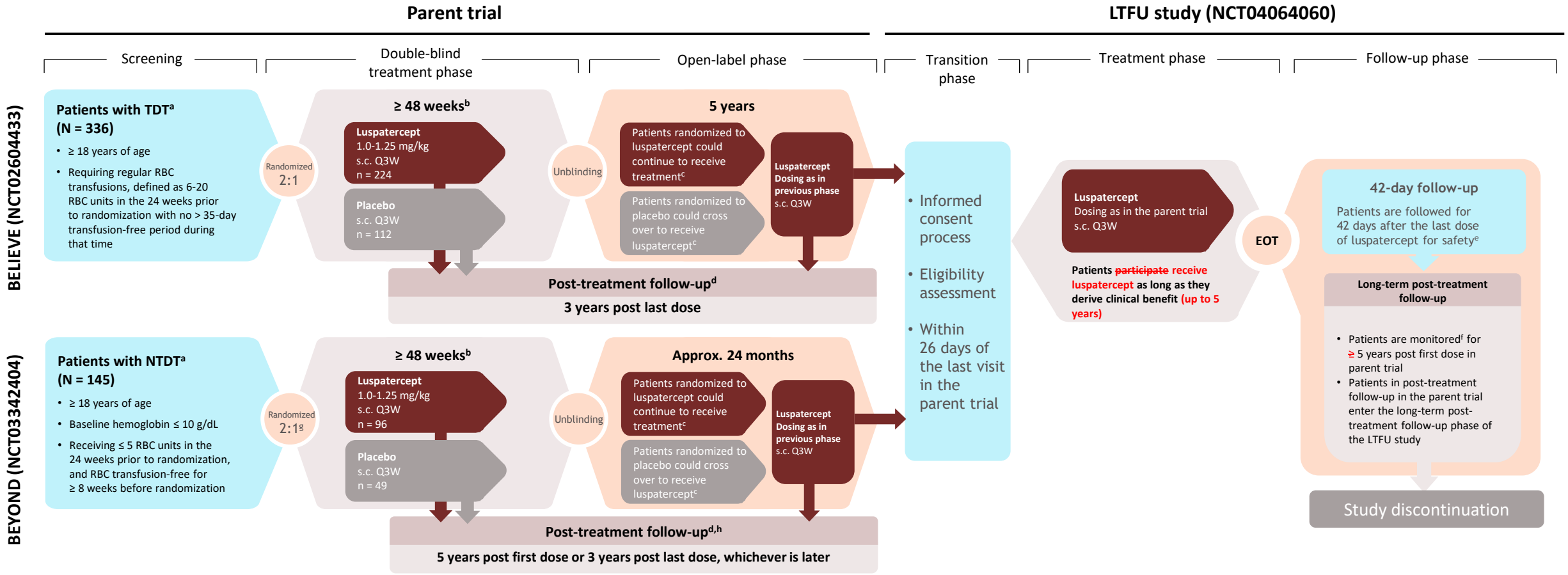
# Post hoc analyses-NTDT-PRO T/W domain score improvement and Hb increase

- The correlation analysis showed that as hemoglobin levels increased, NTDT-PRO T/W domain scores decreased, suggesting improvement in patient-reported tiredness and weakness (R = −0.29; *P* < 0.0001)




Taher AT, et al. *Lancet Haematol 2022*

# BELIEVE, BEYOND, and LTFU study designs



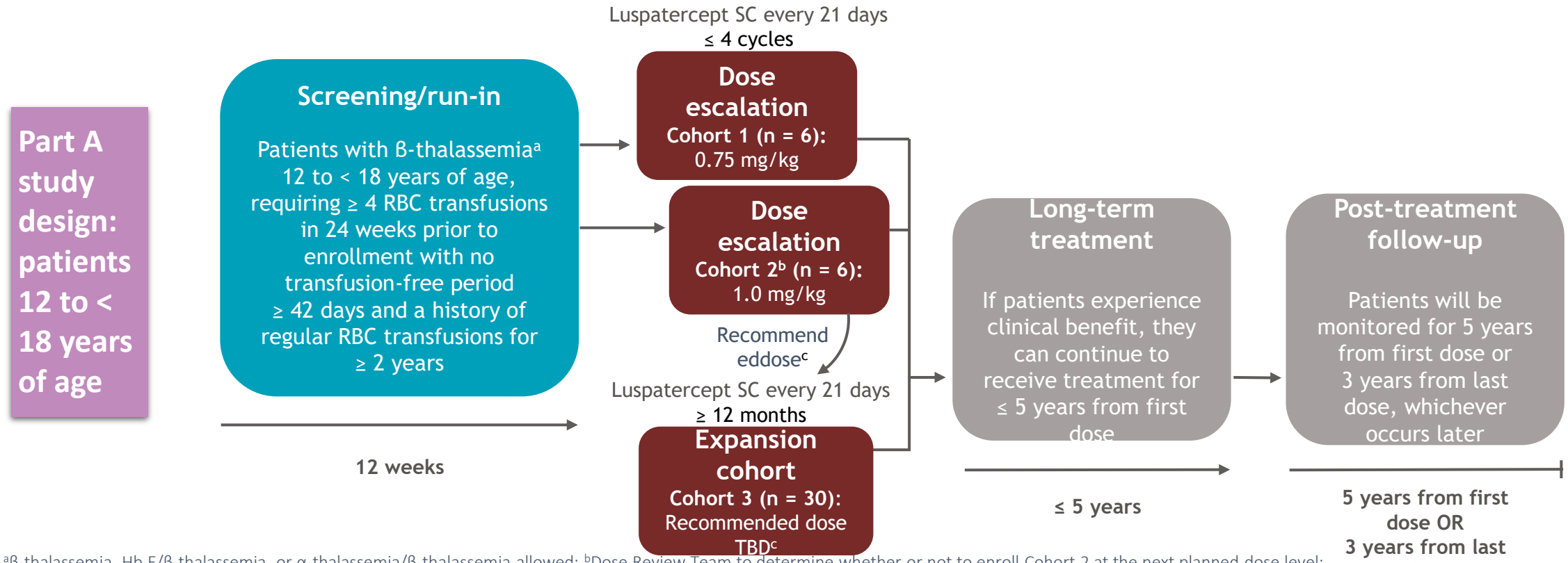

[a]β-thalassemia or HbE/β-thalassemia (compound β-thalassemia with mutation and/or multiplication of α-globin genes allowed); [b]The double-blind treatment phase ended after the last patient enrolled completed 48 weeks of treatment or discontinued earlier, or when the study was unblinded. Patients who completed 48 weeks of double-blind treatment could continue treatment until study unblinding; patients who did not continue treatment or discontinued early entered post-treatment follow-up; [c]Patients who were compliant with the protocol 48 weeks post dose 1 day 1, including patients in post-treatment follow-up who continued compliant participation until study unblinding, could enroll in the open-label phase; [d]Patients who discontinued treatment continued to be followed at weeks 9, 24, 48, 72, 96, 120, 144, and 156 (3 years) after their last dose; [e]Safety-related parameters, AEs, and serious AEs were monitored; [f]Patients are followed for overall survival every 6 months and monitored for any malignancies/pre-malignancies; [g]Patients were stratified based on baseline Hb level (< 8.5 or ≥ 8.5 g/dL) and NTDT-PRO T/W domain score (≥ 3 or < 3); [h]Patients could continue or complete post-treatment follow-up in the LTFU study. AE, adverse event; EOT, end of treatment; HbE, hemoglobin E; NTDT-PRO T/W, Non-Transfusion-Dependent β-Thalassemia Patient-Reported Outcomes Tiredness/Weakness domain; Q3W, every 3 weeks; s.c., subcutaneously.

# Luspatercept approval in NTD patients

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

*The European Commission has granted a full marketing authorization to luspatercept-aamt for use in adult patients with anemia associated with non–transfusion-dependent (NTD) β-thalassemia on February 27th 2023*

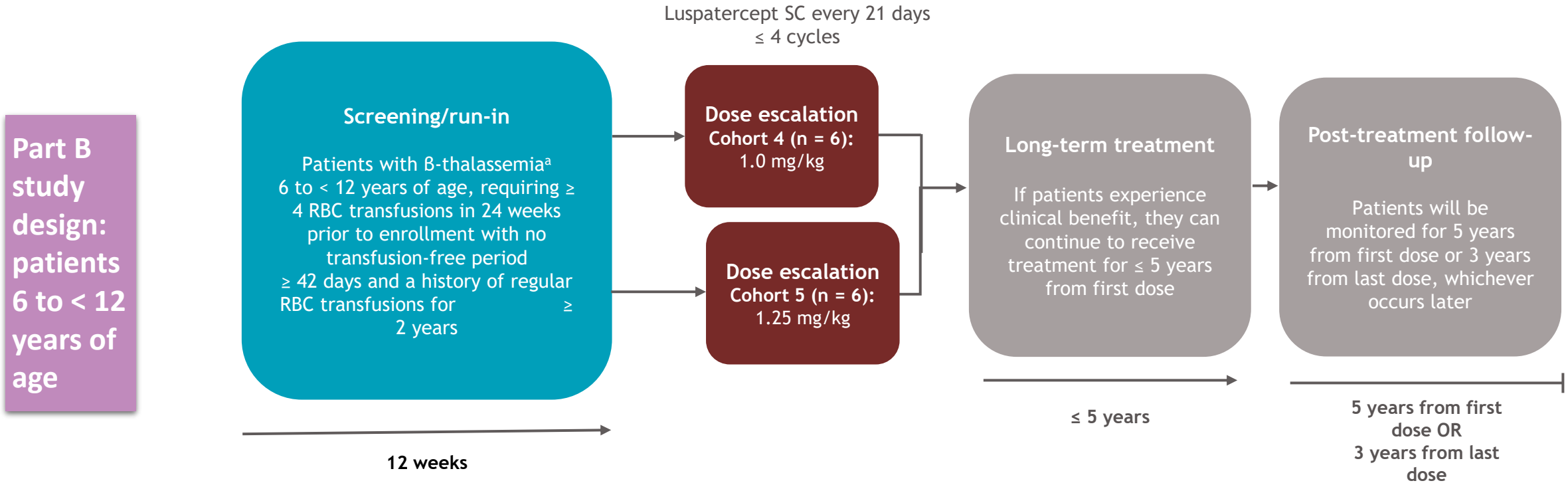
# Luspatercept in pediatric patients with transfusion-dependent β-thalassemia: a phase 2a study evaluating safety and pharmacokinetics of luspatercept in children (NCT04143724)




[a]β-thalassemia, Hb E/β-thalassemia, or α-thalassemia/β-thalassemia allowed; [b]Dose Review Team to determine whether or not to enroll Cohort 2 at the next planned dose level; [c]Recommended dose based on tolerability and safety data from Cohorts 1 and 2; if the RD is 1.0 mg/kg, titration up to 1.25 mg/kg is allowed based on erythroid response during the previous 2 dose cycles.
TBD, to be determined.

Viprakasit V, et al. Blood 2021;138(suppl 1). Abstract 4161.

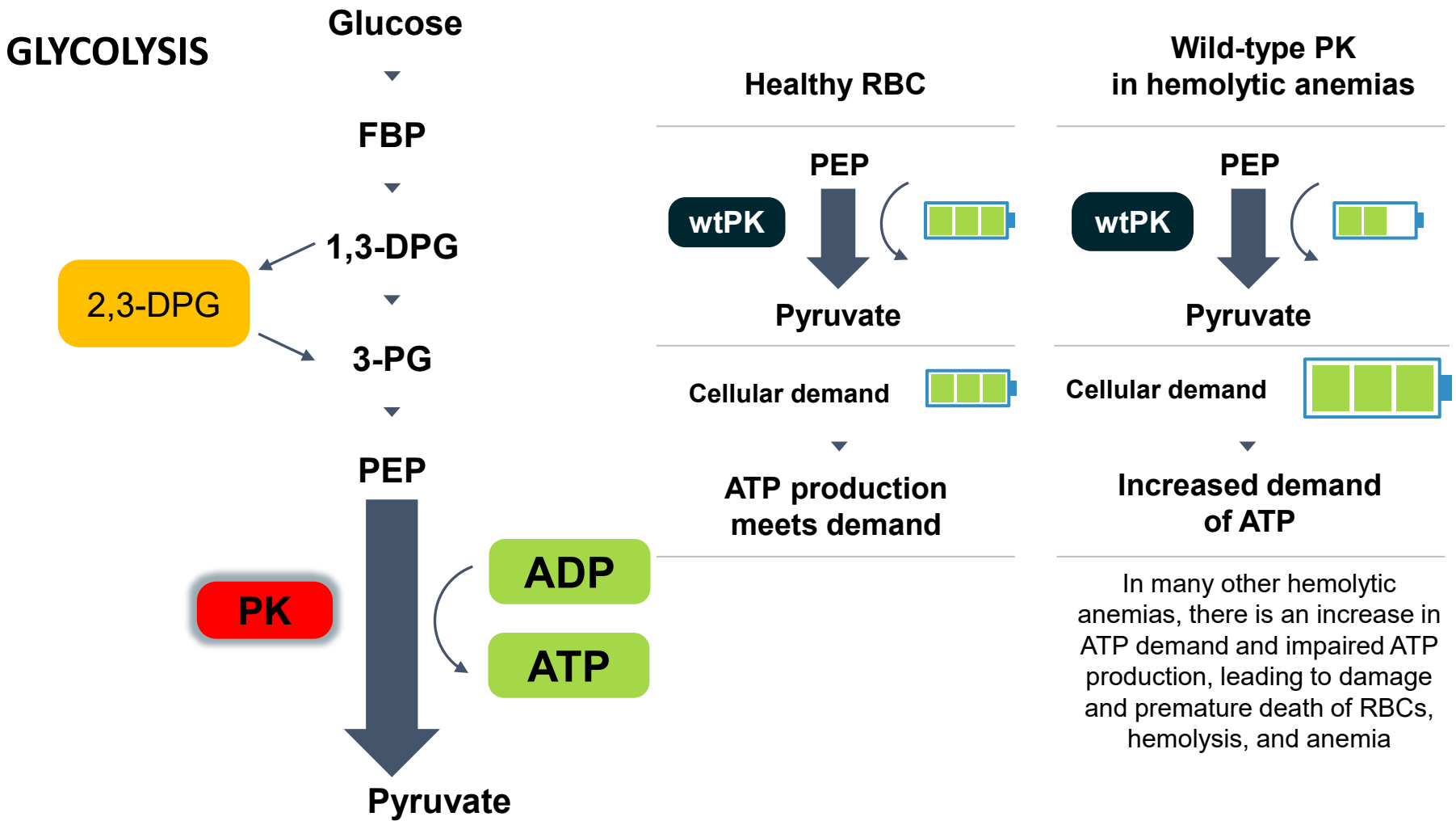
# Luspatercept in pediatric patients with transfusion-dependent β-thalassemia: a phase 2a study evaluating safety and pharmacokinetics of luspatercept in children (NCT04143724)




aβ-thalassemia, Hb E/β-thalassemia, or α-thalassemia/β-thalassemia allowed

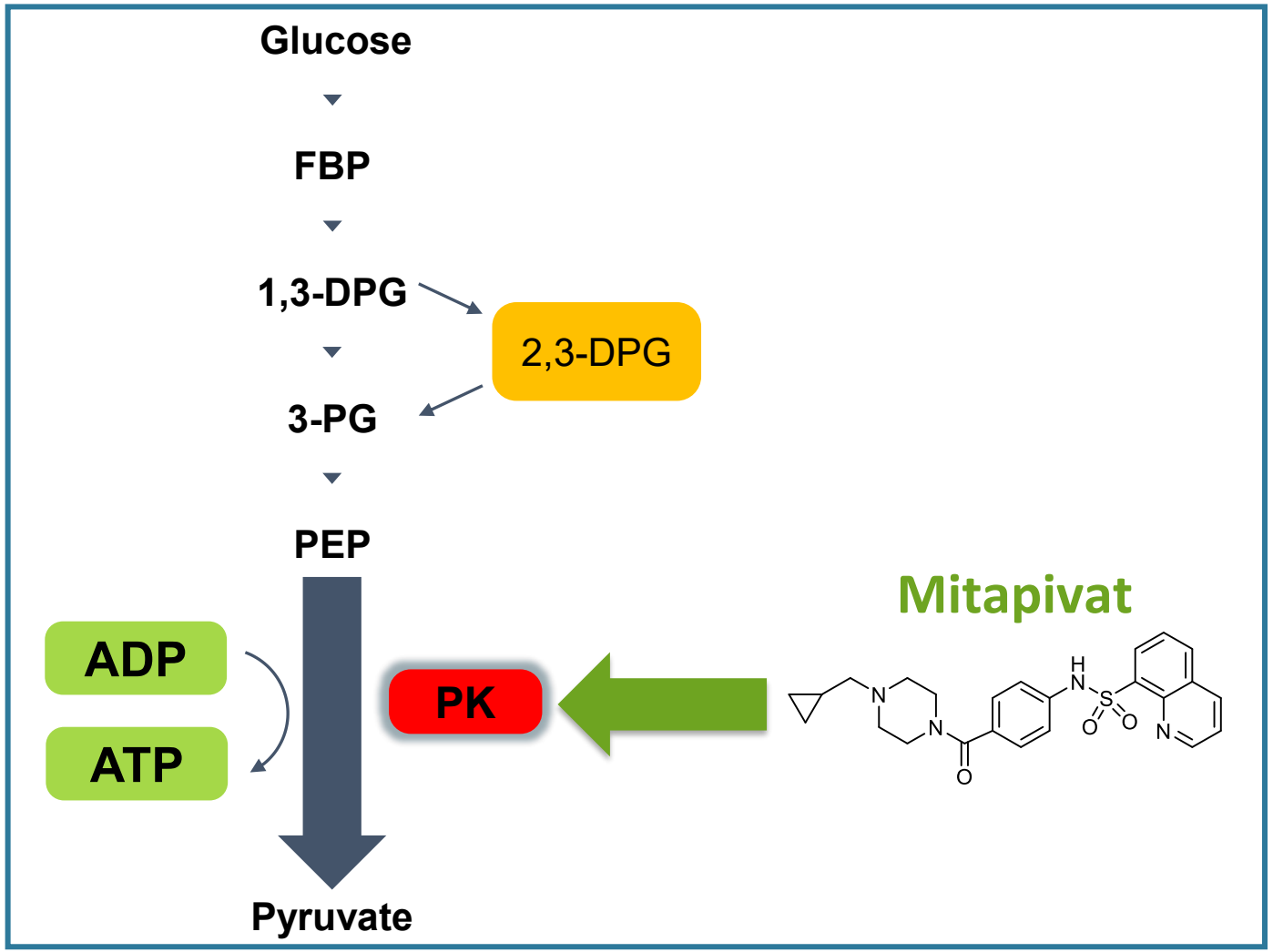
Viprakasit V, et al. Blood 2021;138(suppl 1). Abstract 4161.

# Pyruvate kinase activation represents a unique mechanism of action with the potential to address a broad range of hemolytic anemias




ADP, adenosine diphosphate; ATP, adenosine triphosphate; DPG, diphosphoglycerate; FBP, fructose bisphosphate; m, mutant; PEP, phosphoenolpyruvate; PG, phosphoglycerate; PK, pyruvate kinase; RBC, red blood cell; wt, wild-type.

# Mitapivat is an oral, small-molecule allosteric activator of pyruvate kinase




- ATP generation is essential for RBC function and stability[1,2]
- 2,3-DPG is an important regulator of the oxygen affinity of Hb[3]
- Mitapivat activates wild-type and mutant PK enzymes, which act at the final step of glycolysis to generate energy in the form of ATP in RBCs[1,4]

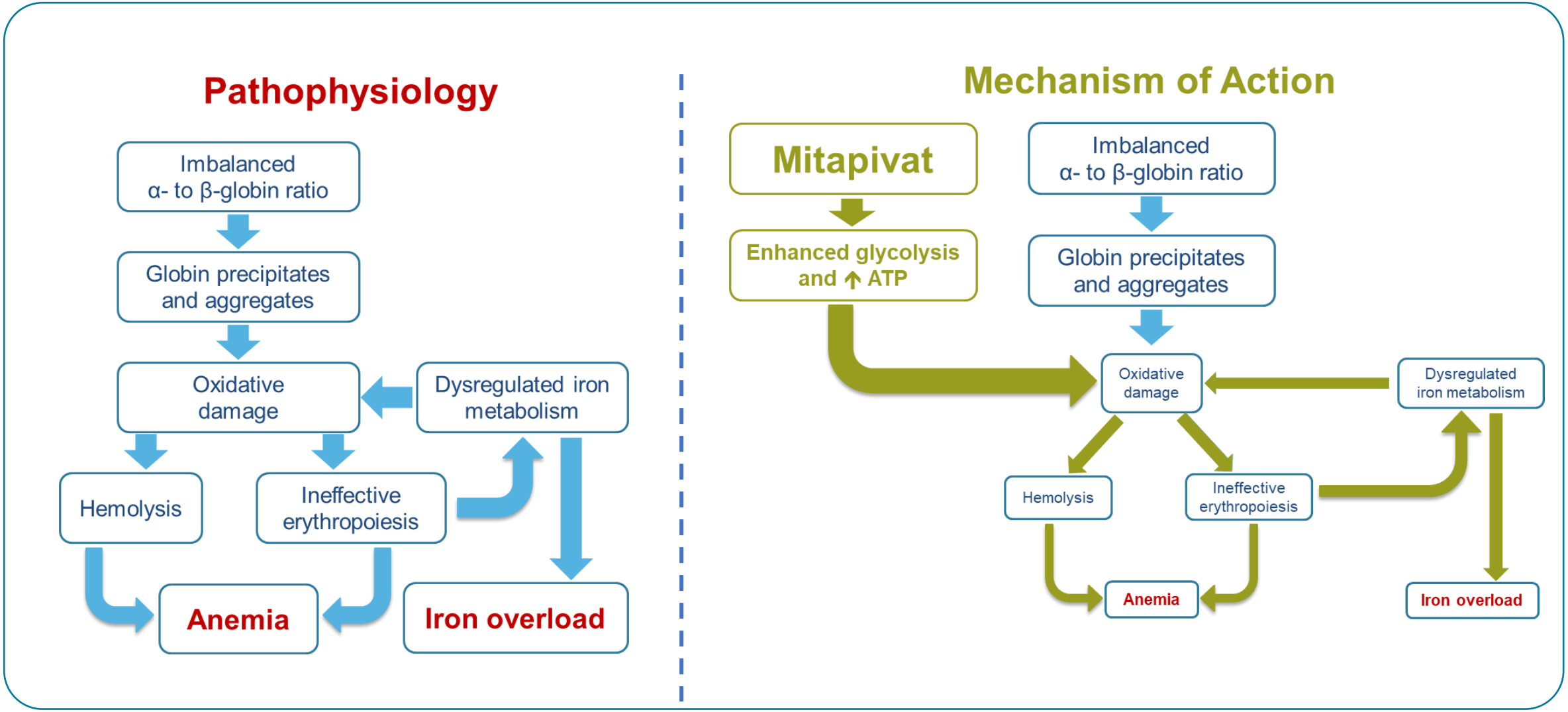
ADP, adenosine diphosphate; ATP, adenosine triphosphate; DPG, diphosphoglyceric acid; FBP, fructose bisphosphate; Hb, hemoglobin; PEP, phosphoenolpyruvate; PG, phosphoglycerate; PK, pyruvate kinase; RBC, red blood cell; SCD, sickle cell disease.

**1.** Kung C et al. Blood 2017;130:1347; **2.** Valentini G et al. J Biol Chem 2002;277:23807; **3.** Rab MAE et al. Blood 2021;137:2997–3001; **4.** Yang H et al. Clin Pharmacol Drug Dev 2019;8:246.

# Mitapivat approval

Mitapivat has been approved by the US Food and Drug Administration (FDA) in Feb 2022 and by the European Medicines Agency (EMA) in Nov 2022 to treat anemia in adult patients with PK deficiency

# Pathophysiology and proposed mitapivat mechanism of action in thalassemia




ATP, adenosine triphosphate.

THE LANCET

# Safety and efficacy of mitapivat, an oral pyruvate kinase activator, in adults with non-transfusion dependent α-thalassaemia or β-thalassaemia: an open-label, multicentre, phase 2 study

*Kevin H M Kuo, D Mark Layton, Ashutosh Lal, Hanny Al-Samkari, Joy Bhatia, Penelope A Kosinski, Bo Tong, Megan Lynch, Katrin Uhlig, Elliott P Vichinsky*

## Summary

**Background** Patients with non-transfusion-dependent thalassaemia (NTDT), although they do not require regular blood transfusions for survival, can still accrue a heavy burden of comorbidities. No approved disease-modifying therapies exist for these patients. We aimed to investigate the safety and efficacy of mitapivat (Agios Pharmaceuticals, Cambridge, MA, USA), a pyruvate kinase activator, in adults with non-transfusion-dependent (NTD) α-thalassaemia or NTD β-thalassaemia.

**Methods** In this open-label, multicentre, phase 2 study, patients were recruited from four academic clinical study sites in Oakland, CA, and Boston, MA, USA; Toronto, ON, Canada; and London, UK. Patients were eligible if they were aged 18 years or older, with NTDT (including β-thalassaemia with or without α-globin gene mutations, haemoglobin E β-thalassaemia, or α-thalassaemia), and a baseline haemoglobin concentration of 10·0 g/dL or lower. During a 24-week core period, mitapivat was administered orally at 50 mg twice daily for the first 6 weeks followed by an escalation to 100 mg twice daily for 18 weeks thereafter. The primary endpoint was haemoglobin response (a ≥1·0 g/dL increase in haemoglobin concentration from baseline at one or more assessments between weeks 4 and 12). Efficacy and safety were assessed in the full analysis set (ie, all patients who received at least one dose of study drug). This study is registered with ClinicalTrials.gov, NCT03692052, and is closed to accrual.

**Findings** Between Dec 28, 2018, and Feb 6, 2020, 27 patients were screened, of whom 20 were enrolled (15 [75%] with β-thalassaemia and five [25%] with α-thalassaemia) and received mitapivat. The median age of patients was 44 years (IQR 35–56), 15 (75%) of 20 patients were female, five (25%) were male, and ten (50%) identified as Asian. 16 (80% [90% CI 60–93]) of 20 patients had a haemoglobin response (p<0·0001), five (100%) of five with α-thalassaemia and 11 (73%) of 15 with β-thalassaemia. 17 (85%) patients had a treatment-emergent adverse event, and 13 had a treatment-emergent event that was considered to be treatment related. One serious treatment-emergent adverse event occurred (grade 3 renal impairment), which was considered unrelated to study drug, resulting in discontinuation of treatment. The most commonly reported treatment-emergent adverse events were initial insomnia (ten [50%] patients), dizziness (six [30%]), and headache (five [25%]). No patients died during the 24-week core period.

**Interpretation** These efficacy and safety results support the continued investigation of mitapivat for the treatment of both α-thalassaemia and β-thalassaemia.

*Lancet* 2022; 400: 493–501

See **Comment** page 470

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**Objectives:**

*Primary Objective:*

The primary objective of this study is to evaluate the efficacy of treatment with AG-348 in increasing hemoglobin (Hb) concentrations in subjects with non-transfusion-dependent thalassemia (NTDT).

*Secondary Objectives:*

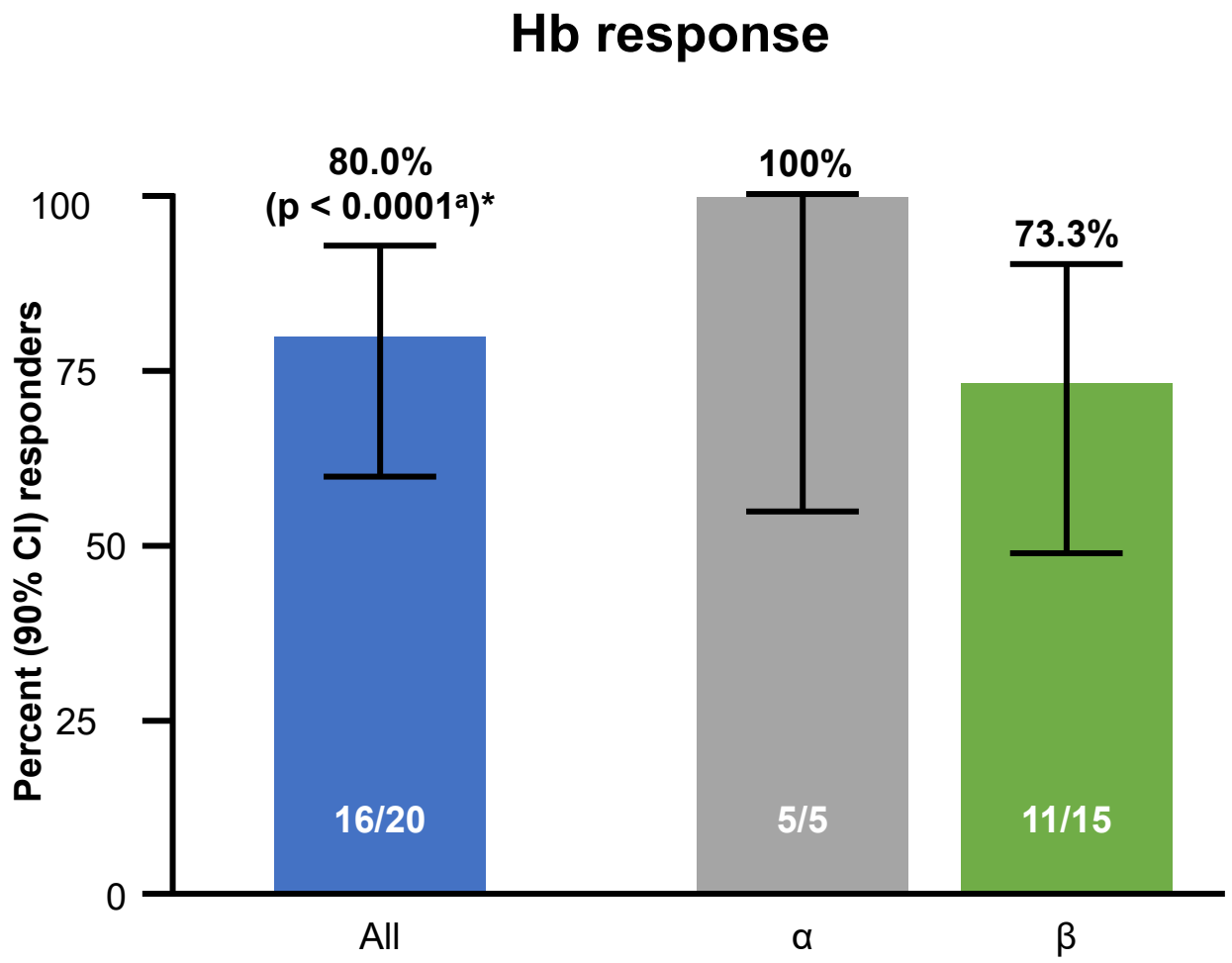
The following secondary objectives will be assessed in subjects with NTDT:

- To evaluate the safety of AG-348
- To determine the effect of AG-348 on markers of hemolysis and erythropoietic activity
- To evaluate the pharmacokinetics of AG-348

*Exploratory Objectives:*

- To determine the effect of AG-348 in subjects with NTDT on the following:
  - Pharmacodynamic (PD) markers of thalassemia
  - Other markers of erythropoietic activity
  - Markers of iron metabolism and indicators of iron overload
  - Markers of oxidative stress and other related markers
  - Transfusion burden
  - Spleen size
- To evaluate the relationship between AG-348 pharmacokinetics and indicators of clinical activity in subjects with NTDT
- To evaluate the relationship between the dose of AG-348 and change in Hb concentrations in subjects with NTDT

# Mitapivat met the primary endpoint with an observed Hb response rate of 80%




## Primary endpoint

**Hb response:**
≥ 1.0 g/dL increase in Hb concentration from BL at ≥ 1 assessments between Weeks 4–12 (inclusive)

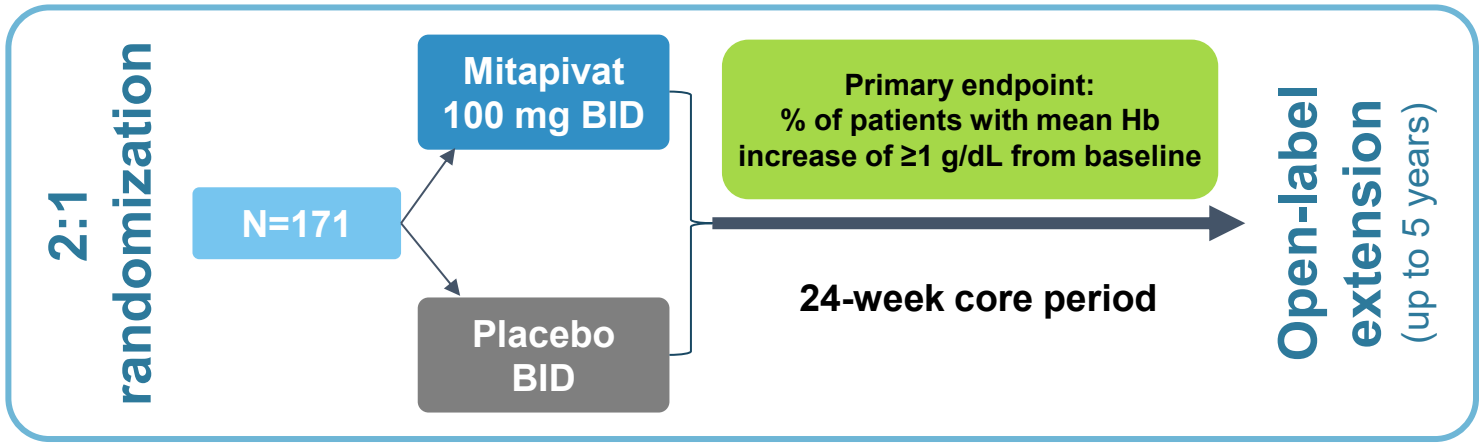
## Secondary endpoints

**Hemolysis and Erythopoesis:**

- Reductions in bilirubin, LDH, and EPO, **correlates** with Hb increase
- Indirect bilirubin and LDH showed declines in both alpha and beta-thalassemia patient
- Erythropoietin approached the ULN in both groups by Wk 6

# Two Phase 3, global, randomized, controlled trials of mitapivat in adults with α- or β-thalassemia are active, not recruiting[a]

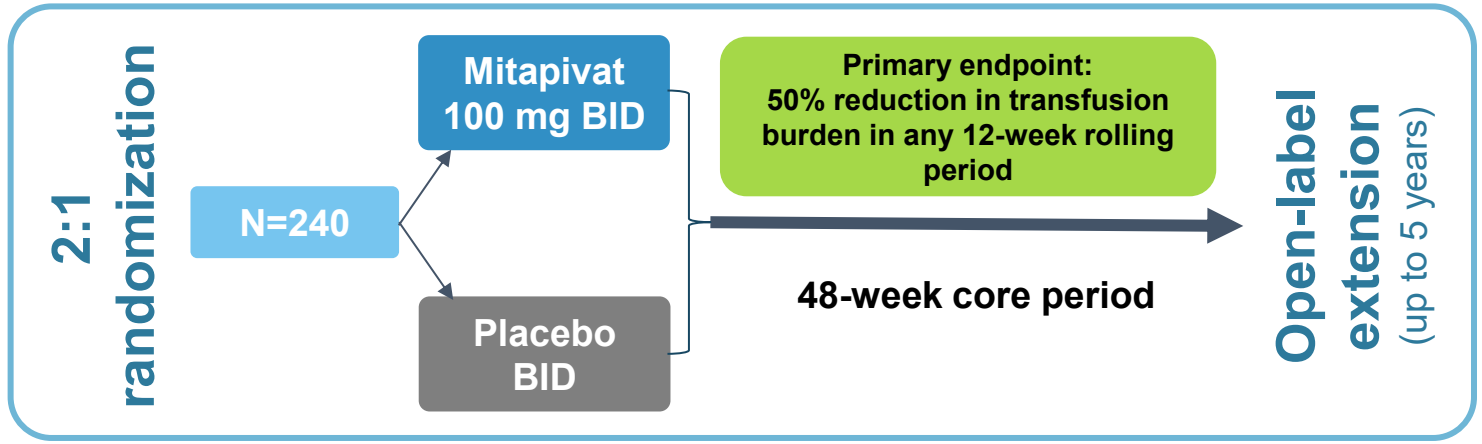
## ENERGIZE




**Key inclusion criteria**

- ≥18 years
- β-thalassemia ± α-globin mutations, HbE β-thalassemia, or α-thalassemia (HbH disease)
- Non-transfusion-dependent (≤ 5 RBC units during the 24-week period before randomization and no RBC transfusions ≤8 weeks prior)
- Hb ≤10.0 g/dL

## ENERGIZE-T

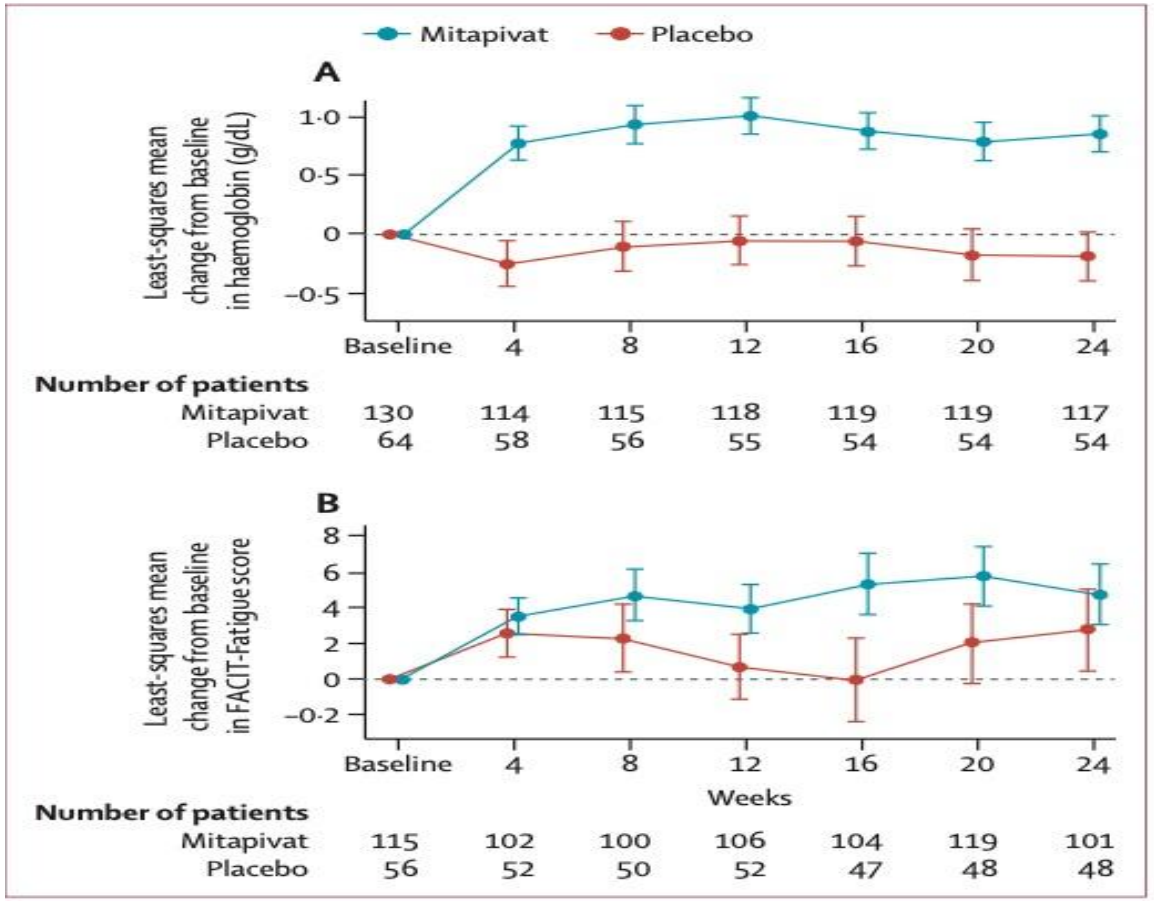



**Key inclusion criteria**

- ≥18 years
- β-thalassemia ± α-globin mutations, HbE β-thalassemia, or α-thalassemia (HbH disease)
- Transfusion-dependent (6–20 RBC units transfused and ≤6-week transfusion-free period during the 24-week period before randomization)

[a]Status as of June 30 2023.
BID, twice daily; Hb, hemoglobin; HbE, hemoglobin E; HbH, hemoglobin H; RBC, red blood cell.
ClinicalTrials.gov: ENERGIZE (NCT04770753); ClinicalTrials.gov: ENERGIZE-T (NCT04770779).

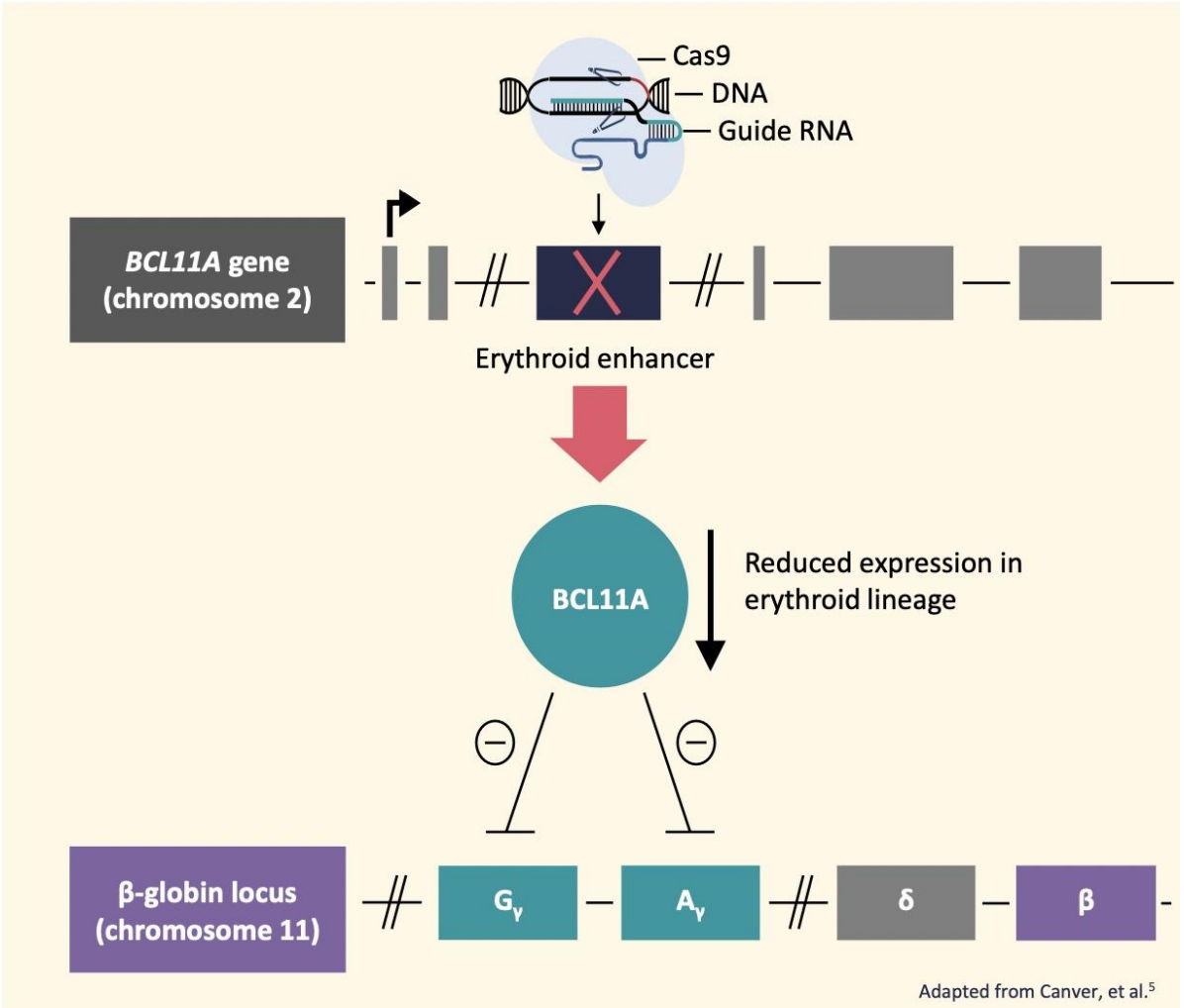
# Mitapivat in adults with non-transfusion-dependent α-thalassaemia or β-thalassaemia (ENERGIZE): a phase 3, international, randomised, double-blind, placebo-controlled trial




Lancet 2025; 406: 33–42

# Exa-cel Is a Cell Product Consisting of Autologous CD34⁺ HSPCs Modified Using Non-viral, *Ex Vivo* CRISPR-Cas9

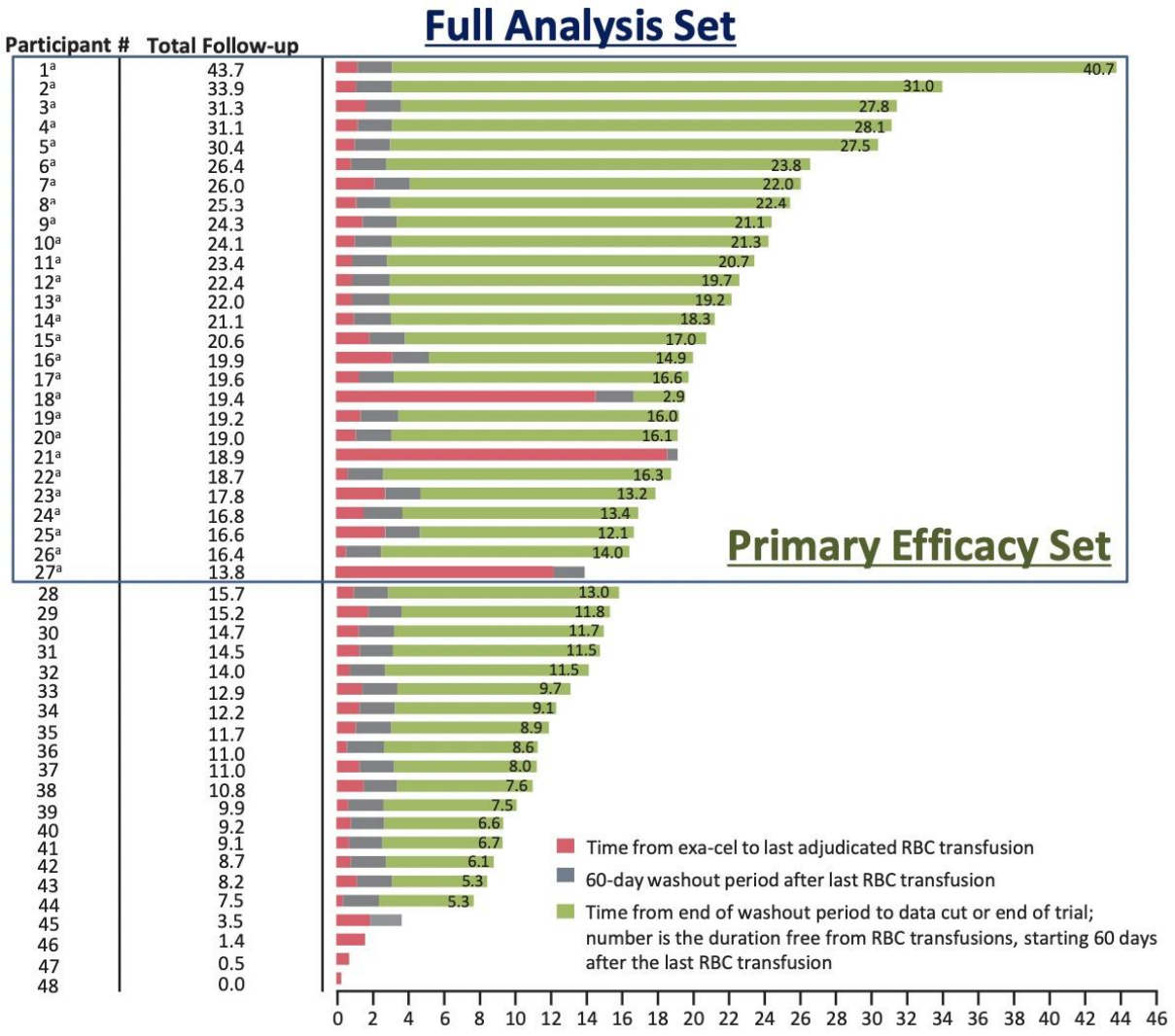
- **Elevated levels of HbF**, such as in hereditary persistence of fetal hemoglobin, are associated with **reduced morbidity and mortality** in patients with **TDT[1] and SCD[1]**
- HbF production is developmentally regulated, with **BCL11A suppressing HbF** after the first months of life[2,3]
- **Exa-cel** is produced using non-viral, *ex vivo* editing of the erythroid-specific enhancer region of *BCL11A* in CD34⁺ HSPCs **to reduce erythroid-specific expression of *BCL11A***
- **Infusion of exa-cel increases HbF** to levels similar to hereditary persistence of fetal hemoglobin, eliminating the need for **RBC transfusions** and **eliminating VOCs**[4]




***BCL11A*,** B-cell lymphoma/leukemia 11A; **Cas9,** CRISPR-associated 9 nuclease; **CRISPR,** clustered regularly interspaced short palindromic repeats; **DNA,** deoxyribonucleic acid; **exa-cel,** exagamglogene autotemcel; **HbF,** fetal hemoglobin; **HSPC,** hematopoietic stem and progenitor cell; **RBC,** red blood cells; **RNA,** ribonucleic acid; **SCD,** sickle cell disease; **TDT,** transfusion-dependent β-thalassemia, **VOC,** vaso-occlusive crisis.

**1**. Steinberg MH, et al. *Blood*. 2020;136(21):2392-2400. **2**. Sankaran VG, Orkin SH. *Cold Spring Harb Perspect Med*. 2013;3(1):a011643. **3**. Bauer DE, et al. *Curr Opin Gene Dev*. 2015;33:62-70. **4**. Frangoul H, et al. *N Engl J Med.* 2021; 384(3):252-260; 5. Canver MC, et al. *Blood*. 2016;127(21):2536-2545.

# TDT: Participants Who Achieved Transfusion Independence (TI12) Had Normal Hemoglobin and Maintained Transfusion Independence From 12.1 to 40.7 Months




Each row in the figure represents an individual participant.

[a]Participants evaluable for the primary endpoint.

## Participants Who Achieved TI12 had Durable Transfusion Independence with Normal Mean Hemoglobin

- Duration of **transfusion independence** of 12.1 to 40.7 months **(mean of 20.5 months)**
  - Participants **stopped transfusions** after a mean of 37 days
  - Once T12 achieved, all participants **remained transfusion independent through follow-up**
- **Maintained normal mean hemoglobin** of 12.9 g/dL (SD 1.6)

## Participants Who did Not Achieve TI12 had Substantial Benefit

- **Three participants** did not achieve TI12
  - 1 participant **stopped transfusions** 14.5 months after exa-cel infusion and was **transfusion free** for 2.9 months
  - 2 participants had **significant reductions in transfusion volume** (80% and 96%)

## Majority of Trial Participants Stopped RBC Transfusions

- **Excluding participants with <3.5 months of follow-up (N=4),** 42 of 44 (95.5%) participants stopped RBC transfusions (duration 2.9 to 40.7 months)
- **Efficacy was consistent** across genotype, age, and sex subgroup

**exa-cel,** exagamglogene autotemcel; **RBC,** red blood cell; **SD,** standard deviation; **TDT,** transfusion dependent β-thalassemia; **TI6,** maintained weighted average Hb ≥9 g/dL without RBC transfusions for at least 6 consecutive months any time after exa-cel infusion; **TI12,** maintained weighted average Hb ≥9 g/dL without RBC transfusions for at least 12 consecutive months any time after exa-cel infusion.

nature medicine

LETTERS

https://doi.org/10.1038/s41591-018-0301-6

# Intrabone hematopoietic stem cell gene therapy for adult and pediatric patients affected by transfusion-dependent ß-thalassemia

Sarah Marktel[1,2,14], Samantha Scaramuzza[1,14], Maria Pia Cicalese[1,3], Fabio Giglio[2], Stefania Galimberti[4], Maria Rosa Lidonnici[1], Valeria Calbi[1,3], Andrea Assanelli[2], Maria Ester Bernardo[1,3], Claudia Rossi[1], Andrea Calabria[1], Raffaella Milani[5], Salvatore Gattillo[5], Fabrizio Benedicenti[1], Giulio Spinozzi[1], Annamaria Aprile[1], Alessandra Bergami[1], Miriam Casiraghi[1,3], Giulia Consiglieri[1,3], Nicoletta Masera[6], Emanuela D'Angelo[7], Nadia Mirra[7], Raffaella Origa[8], Immacolata Tartaglione[9], Silverio Perrotta[9], Robert Winter[10], Milena Coppola[5], Gianluca Viarengo[11], Luca Santoleri[5], Giovanna Graziadei[12], Michela Gabaldo[1], Maria Grazia Valsecchi[4], Eugenio Montini[1], Luigi Naldini[1,13], Maria Domenica Cappellini[12], Fabio Ciceri[1,2,13,14], Alessandro Aiuti[1,3,13,14] and Giuliana Ferrari[1,13,14]*

# Ringraziamenti

**Ematologia ed Oncologia Pediatrica, Università della Campania "L. Vanvitelli"**

Francesca Rossi
Maddalena Casale
Sofia Maria Rosaria Matarese
Martina di Martino
Daniela Di Pinto
Elvira Pota
Imma Tartaglione
Angelo Perrotta
Gelsomina Simeone
Domenico Roberti
Claudia Santoro
Velia D'Angelo
Saverio Scianguetta