19th Annual Sickle Cell & Thalassaemia Conference

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Achieving Equitable Progress:
A Call for Collaborative Action
in a World of Growing Disparities

ENERGIZE: A global, phase 3 study of mitapivat demonstrating efficacy and safety in adults with alpha- or beta-non–transfusion-dependent thalassemia

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**Former employee of Agios Pharmaceuticals, Inc.*

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Conflict of interest disclosures

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    - Pharmacosmos (consultancy, research funding);
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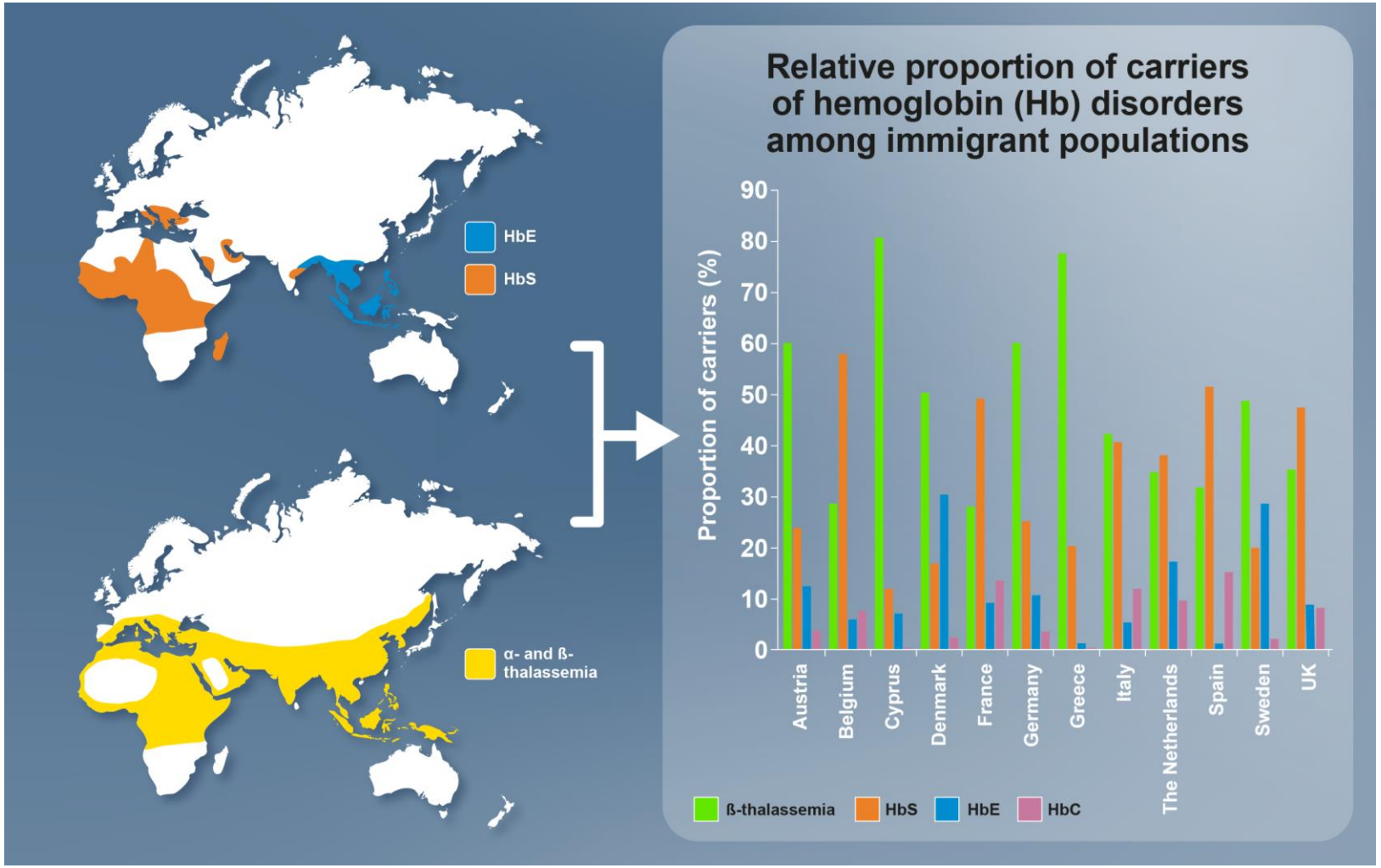
Changing epidemiology of thalassemia[1,2]

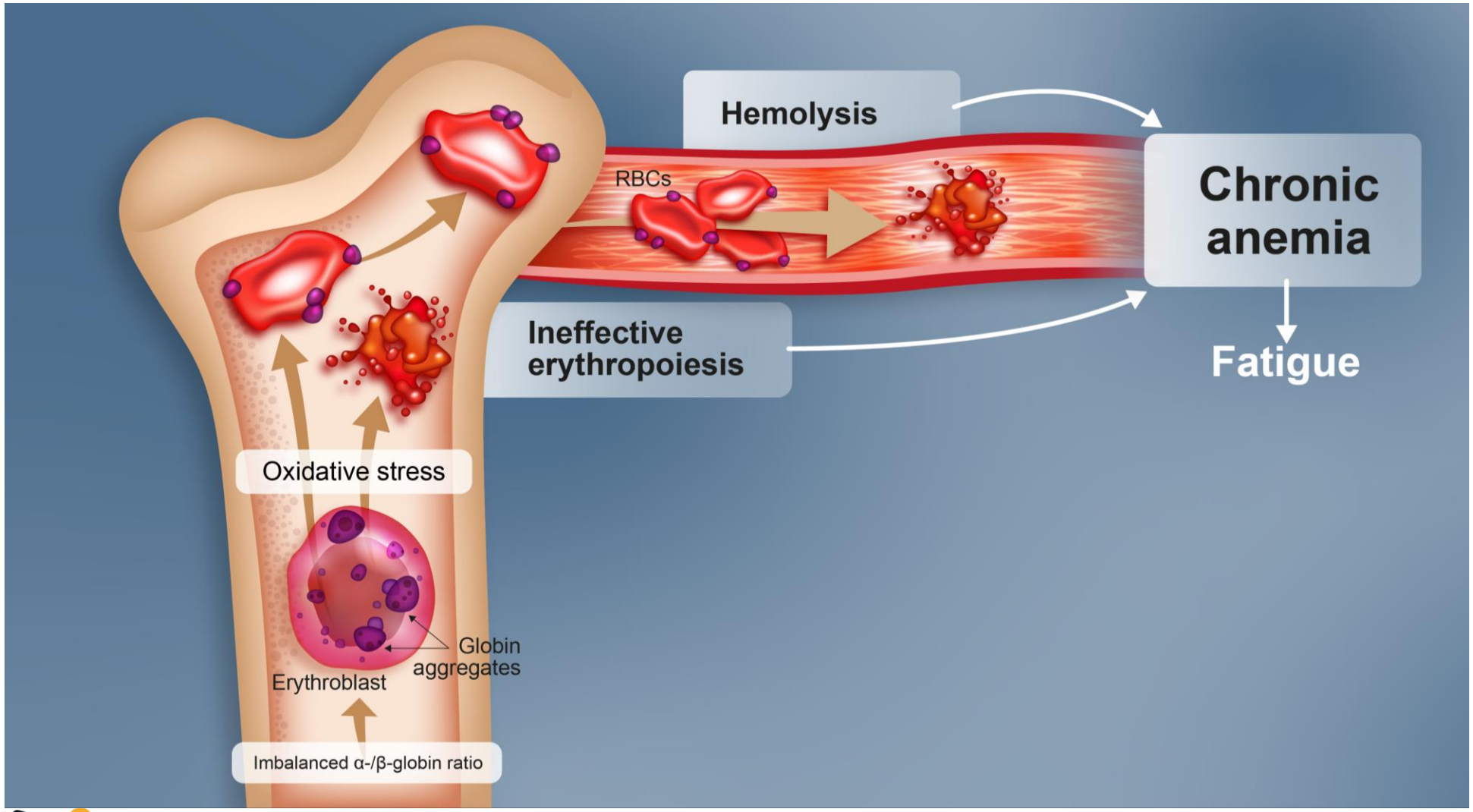


- The evolutionary association between the thalassemia carrier state and resistance to *malaria* explains its high prevalence in the area extending from sub-Saharan Africa, the Middle East, and the Mediterranean basin to Southeast Asia[1]
- Population *migrations* have also introduced thalassemia to Europe and the Americas, where the disease was previously relatively rare[2–4]

HbC, hemoglobin C; HbE, hemoglobin E; HbS, hemoglobin S

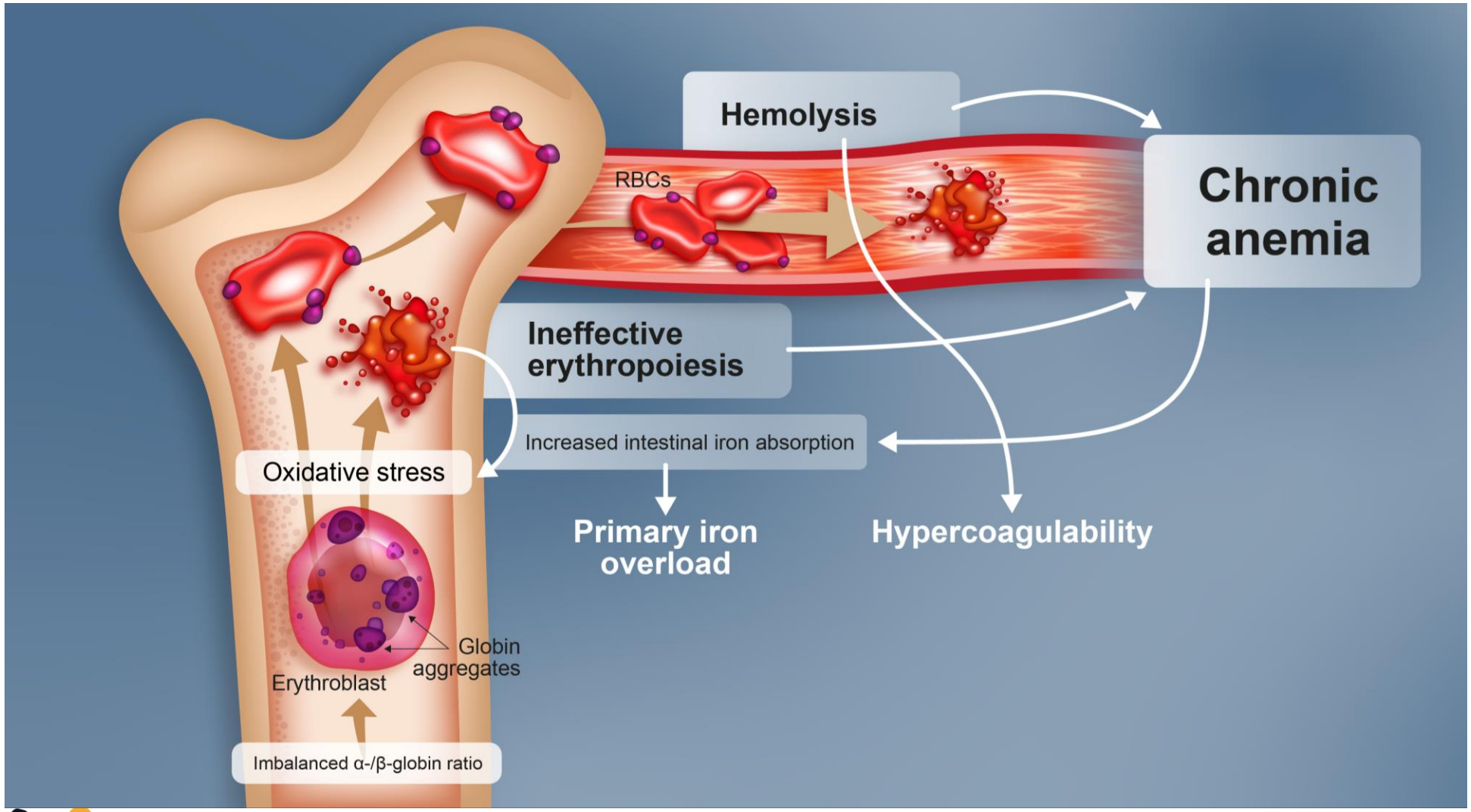
1. Weatherall DJ. *Blood Rev* 2012;26:S3–S6; 2. Angastiniotis M et al. *Sci World J* 2013;2013:727905; 3. Kattamis A et al. *Eur J Haematol* 2020;105:692–703; 4. Musallam KM et al. *Am J Hematol.* 2023;98:1436–51. Figure (left) reprinted from Weatherall DJ. *Blood Rev* 2012;26:S3–S6, Copyright (2012) with permission from Elsevier. Figure (right) reprinted from Angastiniotis M et al. *Sci World J* 2013;2013:727905 (https://onlinelibrary.wiley.com/doi/10.1155/2013/727905), per CC BY 3.0 (https://creativecommons.org/licenses/by/3.0/).

Pathophysiology of thalassemia



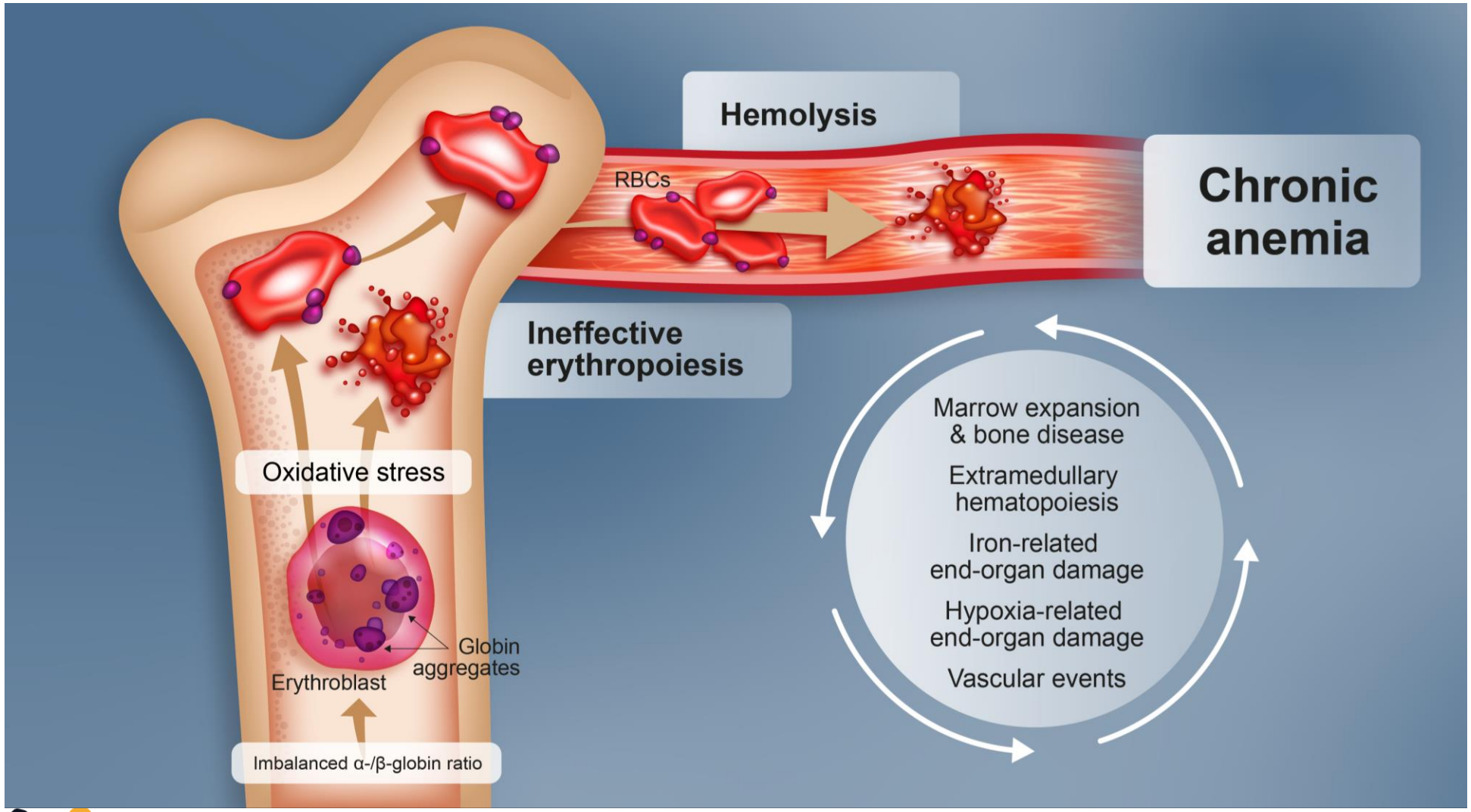
RBC, red blood cell

Pathophysiology of thalassemia



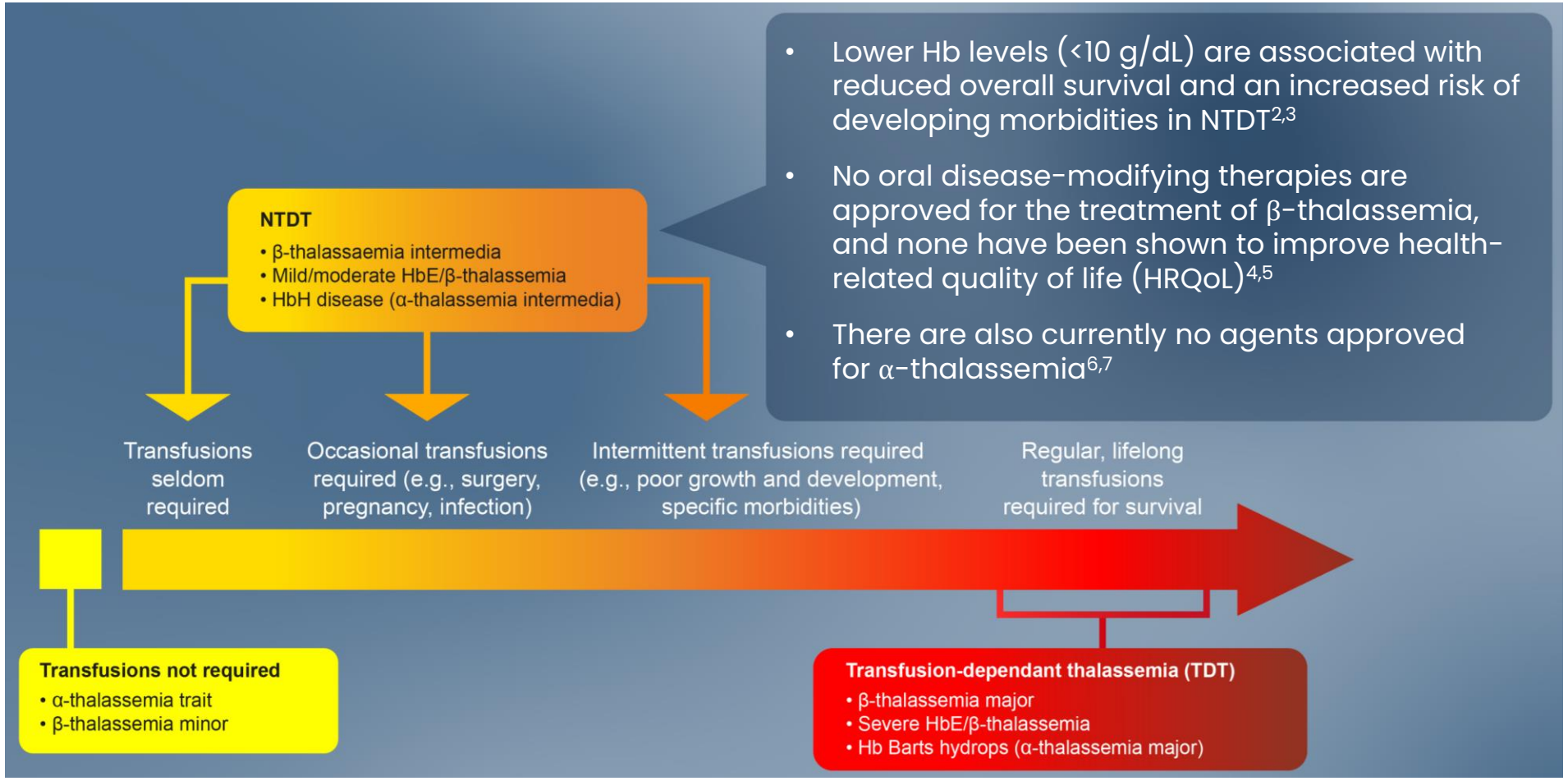
RBC, red blood cell

Pathophysiology of thalassemia



RBC, red blood cell

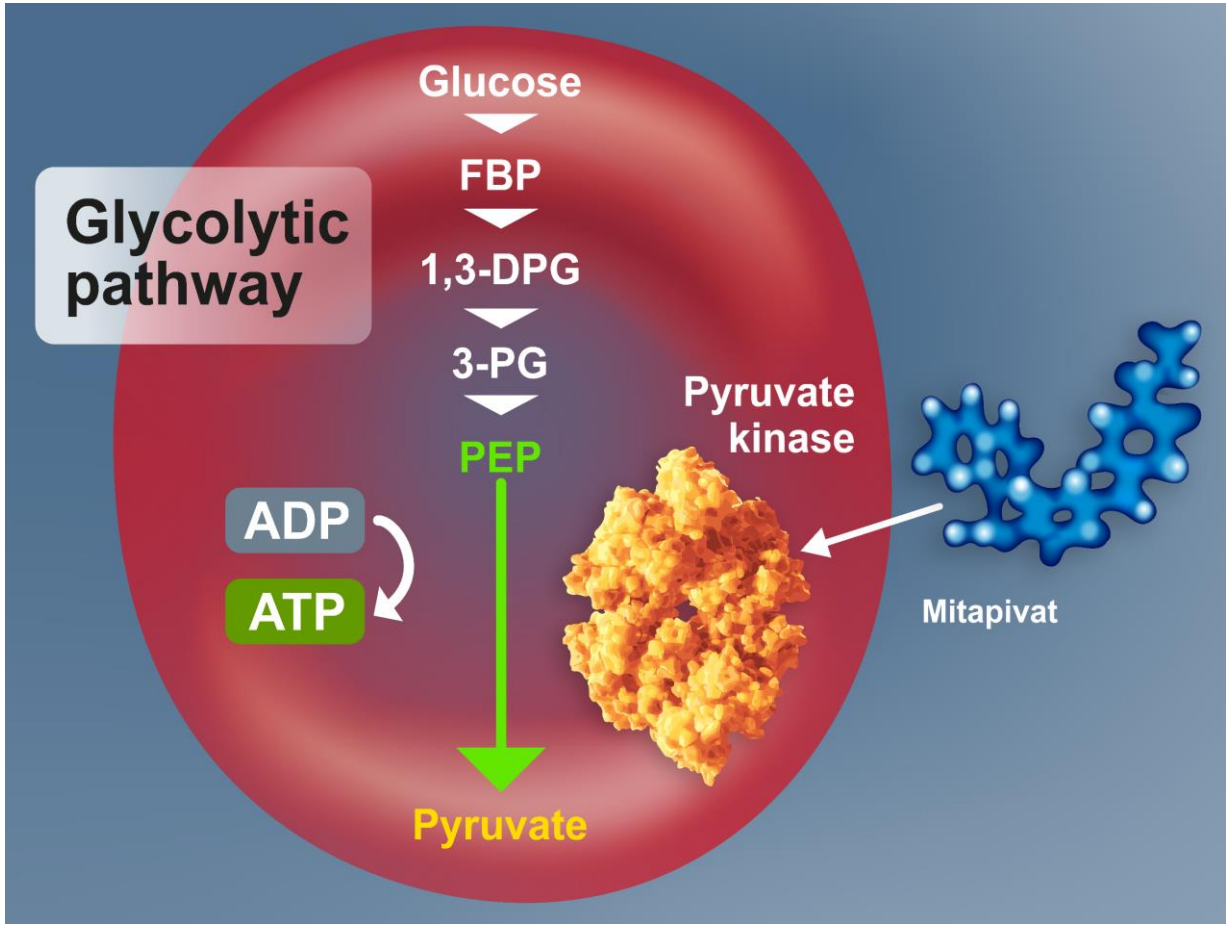
Non–transfusion-dependent thalassemia (NTDT) and unmet needs[1]



Hb, hemoglobin; HbE, hemoglobin E; HbH, hemoglobin H

1. Musallam KM et al. *Haematologica* 2013;98:833–44; 2. Musallam KM et al. *Am J Hematol* 2022;97:E78–80; 3. Musallam KM et al. *Ann Hematol* 2020;101(1):203–4; 4. Langer AL, Esrick EB. *Hematology Am Soc Hematol Educ Program* 2021:600–06; 5. Taher AT et al. *Expert Rev Hematol* 2021;14:897–909; 6. Amid A et al. Nicosia (Cyprus): Thalassaemia International Federation; 2023. https://thalassaemia.org.cy/publications/tif-publications/guidelines-for-the-management-of-%ce%b1-thalassaemia/. Accessed 22May2024; 7. Harewood J, Azevedo AM. In: StatPearls [Internet]. Treasure Island (FL); 2022. Figure adapted from Musallam KM et al. *Haematologica* 2013;98:833–44, Copyright (2013), with permission from Ferrata Storti Foundation.

Mitapivat enhances cellular energy supply to support increased metabolic demands of thalassemic red cells

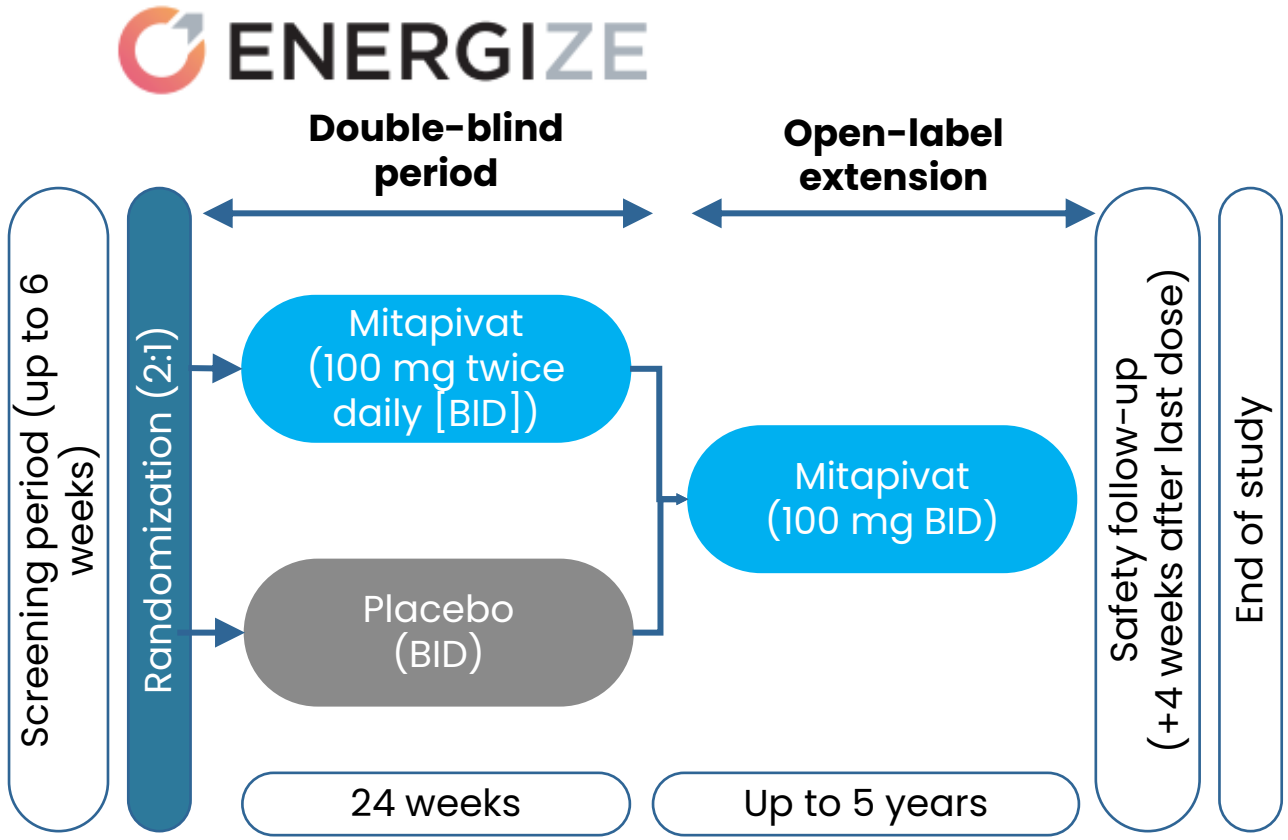


- In thalassemia, there is increased energy demand to maintain RBC health[1–4]
- Mitapivat is an activator of the red cell–specific (PKR) and M2 (PKM2) isoforms of pyruvate kinase (PK), which act in glycolysis to generate adenosine triphosphate (ATP)[5,6]
- In preclinical thalassemia models, mitapivat reduced oxidative stress, and improved erythropoiesis, hemolysis, and anemia[7–9]
- A phase 2 study of mitapivat in α- or β-NTDT demonstrated improvements in Hb and markers of erythropoiesis and hemolysis[10]

ADP, adenosine diphosphate; DPG, diphosphoglyceric acid; FBP, fructose biphosphate; Hb, hemoglobin; NTDT, non–transfusion-dependent thalassemia; PEP, phosphoenolpyruvate; PG, phosphoglycerate; RBC, red blood cell

1. Chakraborty I et al. *Arch Med Res* 2012;43:112–6; 2. Ting YL et al. *Br J Haematol* 1994;88:547–54; 3. Shaeffer JR. *J Biol Chem* 1983;258:13172–7; 4. Khandros E, Weiss MJ. *Hematol Oncol Clin North Am* 2010;24:1071–88; 5. Kung C et al. *Blood* 2017;130:1347; 6. Yang H et al. *Clin Pharmacol Drug Dev* 2019;8:246; 7. Matte A et al. *J Clin Invest* 2021;131:e144206; 8. Rab MAE et al. *Blood* 2019;134:3506; 9. Matte A et al. *Blood* 2023;142:3850; 10. Kuo KHM et al. *Lancet* 2022;400:493–501.

ENERGIZE: A phase 3 study of mitapivat in adults with α- or β-NTDT



Key inclusion criteria
- ≥18 years of age at time of informed consent
- β-thalassemia ± α-globin mutations, HbE/β-thalassemia, or α-thalassemia (HbH disease)
- Non–transfusion-dependent (≤5 RBC units transfused during the 24-week period before randomization and no RBC transfusions ≤8 weeks before informed consent and during screening)
- Hb ≤10.0 g/dL

Key exclusion criteria
- Prior exposure to gene therapy or hematopoietic stem cell transplant
- Homozygous or heterozygous for HbS or HbC
- Receiving treatment with luspatercept or a hematopoietic stimulating agent (last dose must be received ≥18 weeks before randomization)

Randomization stratification factors
- Baseline Hb (≤9.0 g/dL or 9.1–10.0 g/dL)
- Thalassemia genotype (α-thalassemia/HbH or β-thalassemia)

Hb, hemoglobin; HbC, hemoglobin C; HbE, hemoglobin E; HbH, hemoglobin H; HbS, hemoglobin S; NTDT, non–transfusion-dependent thalassemia; RBC, red blood cell

Kuo KHM et al. *Hemasphere* 2022;6:23–4.

Endpoints

Primary endpoint

- Hb response, defined as an increase of ≥1.0 g/dL in average Hb concentration from Week 12 through Week 24, compared with baseline

Key secondary endpoints

- Change from baseline in average Functional Assessment of Chronic Illness Therapy–Fatigue Scale (FACIT-Fatigue) score from Week 12 through Week 24
- Change from baseline in average Hb concentration from Week 12 through Week 24

Secondary efficacy endpoints associated with hemolysis and erythropoietic activity

- Change from baseline in indirect bilirubin, lactate dehydrogenase (LDH), and haptoglobin at Week 24
- Change from baseline in reticulocytes and erythropoietin at Week 24

Safety endpoints

- Type, severity, and relationship of adverse events and serious adverse events

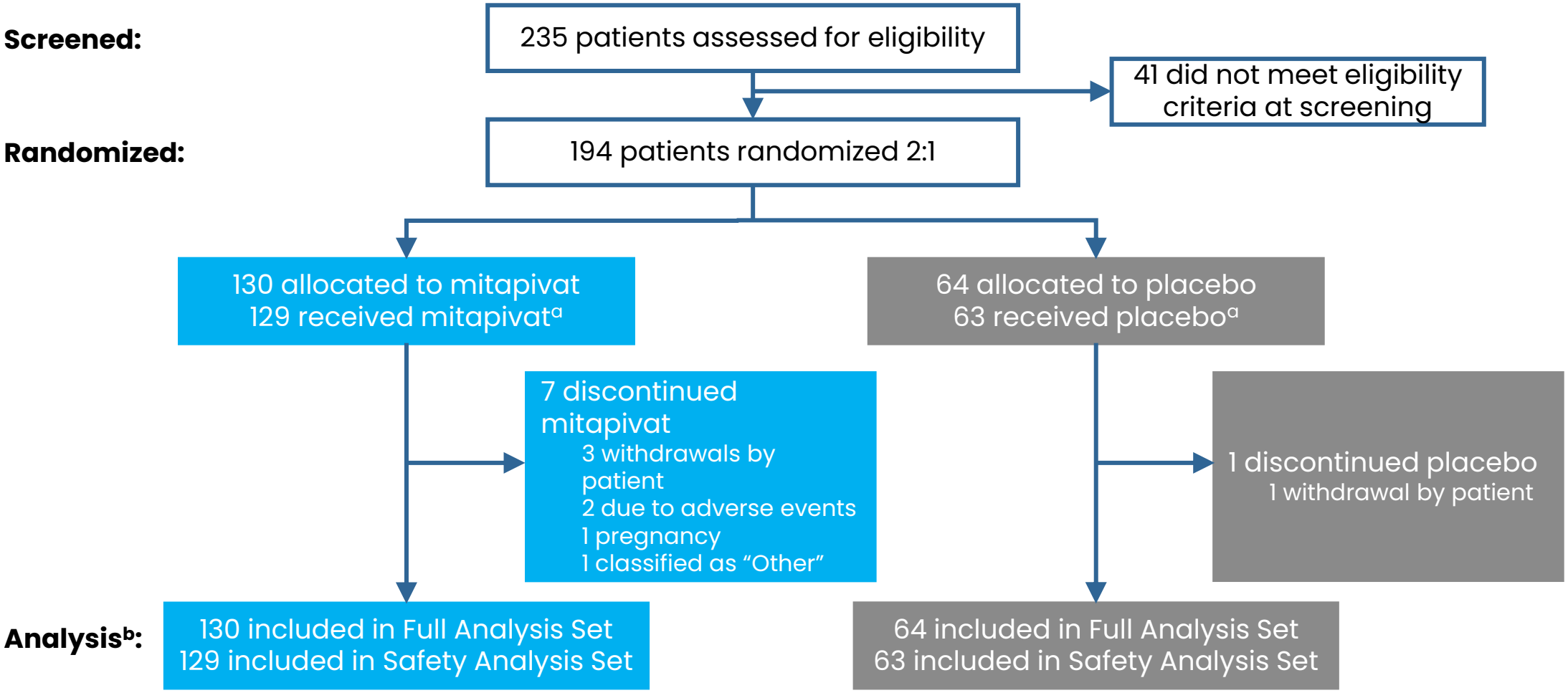
Hb, hemoglobin

Statistical methods

- The primary endpoint of Hb response was tested using the Mantel–Haenszel stratum weighted method, after adjusting for randomization stratification factors
- The key secondary endpoints were compared between the mitapivat and placebo arms using an analysis of covariance model
    - The secondary endpoints of change from baseline in indirect bilirubin, LDH, and haptoglobin at Week 24 and change from baseline in reticulocytes and erythropoietin at Week 24 were compared between the mitapivat and placebo arms using this method
- The primary and key secondary endpoints were tested using a fixed-sequence statistical testing procedure and were also assessed in prespecified subgroups
- Descriptive statistics were reported for the safety endpoint

Hb, hemoglobin; LDH, lactate dehydrogenase

Patient flowchart: 194 patients were randomized in the study



[a]1 patient in each treatment arm was randomized but not dosed.
[b]Full Analysis Set: All patients randomized. Patients are classified according to the randomized treatment group.
Safety Analysis Set: All patients who received ≥1 dose of study treatment. If a patient randomized to placebo received ≥1 dose of mitapivat in the double-blind period, then the patient was classified to the mitapivat arm.

Baseline demographics and disease characteristics were generally balanced between treatment arms

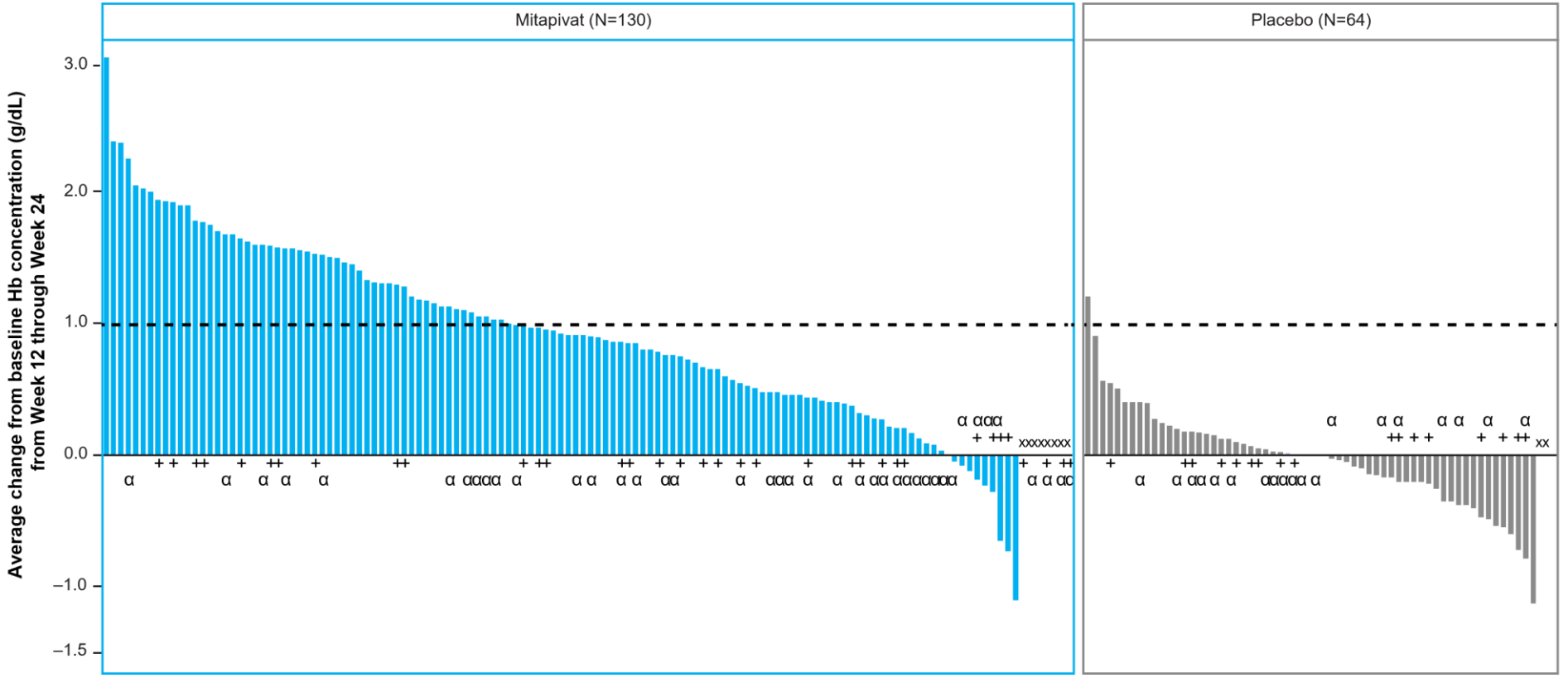
Demographics and disease characteristics	Mitapivat (N=130)	Placebo (N=64)
Age, mean (±SD), years	42.4 (13.0)	38.9 (13.0)
Female, n (%)	84 (64.6)	39 (60.9)
Thalassemia type, n (%) α-thalassemia/HbH disease β-thalassemia	 42 (32.3) 88 (67.7)	 20 (31.3) 44 (68.8)
Transfusion burden,[a] n (%) 0 1–2 3–5 >5	 114 (87.7) 10 (7.7) 6 (4.6) 0 (0.0)	 54 (84.4) 7 (10.9) 3 (4.7) 0 (0.0)
Prior splenectomy,[b] n (%)	47 (36.2)	25 (39.1)
Prior cholecystectomy,[b] n (%)	45 (34.6)	16 (25.0)
Received iron chelation in prior year,[c] n (%)	46 (35.4)	22 (34.4)
Hb, median (range), g/dL	8.4 (5.3–10.4)	8.4 (5.9–10.7)
Indirect bilirubin, median (range), µmol/L	23.4 (2.2–155.8)	22.6 (2.7–81.6)
LDH, median (range), U/L	264 (108–1208)	267 (110–1009)
Haptoglobin,[d] median (range), g/L	0.1 (0.1–1.7)	0.1 (0.1–2.8)
Reticulocyte percentage, median (range), %	4.6 (0.3–29.8)	4.4 (0.0–21.9)
Erythropoietin, median (range), IU/L	65.1 (8.3–1587.0)	64.1 (15.7–4710.0)

[a]Total number of RBC units transfused in the 24-week period before randomization. [b]As recorded in medical/surgical history electronic case report form (eCRF). [c]As recorded in disease characteristics eCRF. "Yes" if a patient received chelation therapy within 1 year (365 days) before randomization. [d]For cases reported as "<0.1," a haptoglobin value of 0.099 was used for the summary.
Hb, hemoglobin; HbH, hemoglobin H; LDH, lactate dehydrogenase; RBC, red blood cell

Mitapivat demonstrated a statistically significant improvement in Hb response vs placebo

Primary endpoint

	Mitapivat N=130	Placebo N=64	2-sided p-value
Hb response,[a] n (%)	55 (42.3)	1 (1.6)	p<0.0001



α = α-thalassemia/HbH disease
\+ = Baseline Hb category: 9.1–10 g/dL

x = Patient with missing baseline or with no assessments from Week 12 through Week 24

Analysis conducted on Full Analysis Set.
[a]A Hb response was defined as an increase of ≥1.0 g/dL in average Hb concentration from Week 12 through Week 24, compared with baseline.
Hb, hemoglobin; HbH, hemoglobin H

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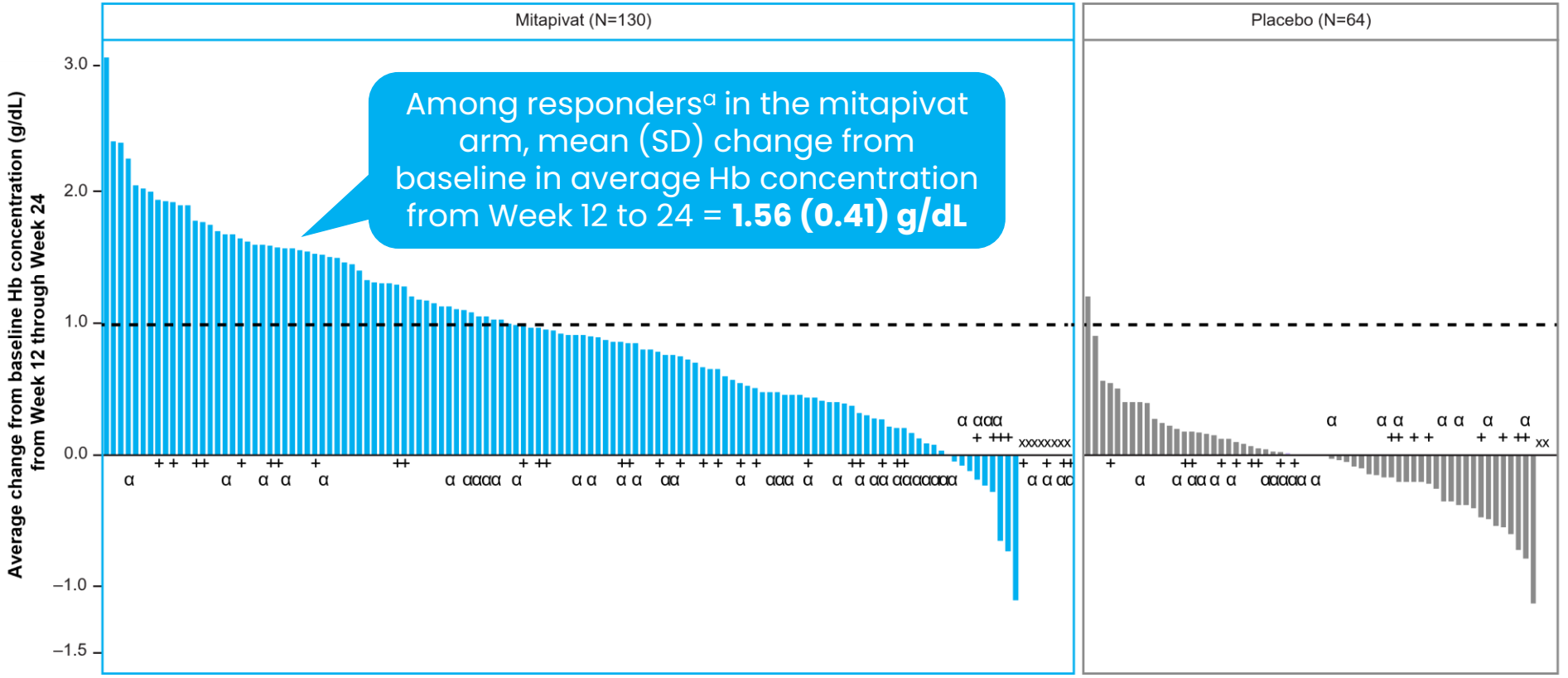

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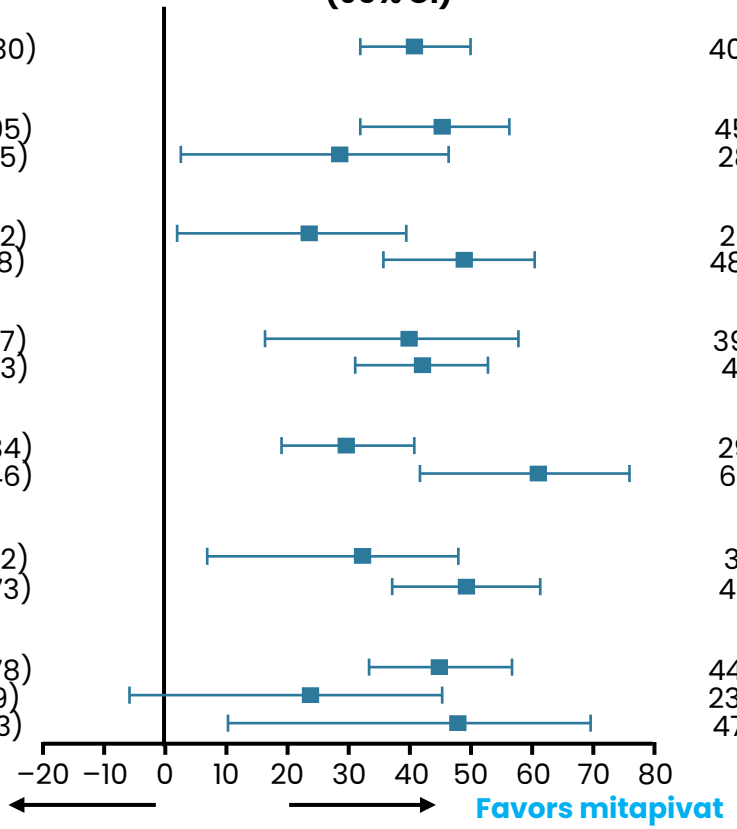
Analysis conducted on Full Analysis Set.
[a]A Hb response was defined as an increase of ≥1.0 g/dL in average Hb concentration from Week 12 through Week 24, compared with baseline.
Hb, hemoglobin; HbH, hemoglobin H

Subgroup analyses showed that the effects were robust and not driven by any individual subgroup

Subgroup analysis of primary endpoint

Subgroup	Hb response rate, % (n/N) Placebo	Hb response rate, % (n/N) Mitapivat	Difference (95% CI)[b]
All patients (stratified)[a] (N=64 vs 130)	1.6 (1/64)	42.3 (55/130)	40.9 (32.0, 49.8)
Baseline Hb concentration			
≤9.0 g/dL (≤90 g/L)	2.1 (1/47)	47.4 (45/95)	45.2 (32.1, 56.2)
9.1–10.0 g/dL (91–100 g/L)	0 (0/17)	28.6 (10/35)	28.6 (2.6, 46.3)
Thalassemia genotype			
α-thalassemia/HbH disease	0 (0/20)	23.8 (10/42)	23.8 (2.2, 39.5)
β-thalassemia	2.3 (1/44)	51.1 (45/88)	48.9 (35.7, 60.2)
Age at screening (years)			
<35	3.7 (1/27)	43.2 (16/37)	39.5 (16.5, 57.6)
≥35	0 (0/37)	41.9 (39/93)	41.9 (31.1, 52.6)
Sex			
Female	0 (0/39)	29.8 (25/84)	29.8 (19.1, 40.7)
Male	4.0 (1/25)	65.2 (30/46)	61.2 (41.6, 75.7)
Race			
Asian	4.2 (1/24)	36.5 (19/52)	32.4 (7.1, 47.9)
White	0 (0/36)	49.3 (36/73)	49.3 (37.1, 61.3)
Geographic region			
North America and Europe	0 (0/39)	44.9 (35/78)	44.9 (33.4, 56.6)
Asia-Pacific	7.1 (1/14)	31.0 (9/29)	23.9 (−5.6, 45.3)
Rest of the world	0 (0/11)	47.8 (11/23)	47.8 (10.4, 69.4)

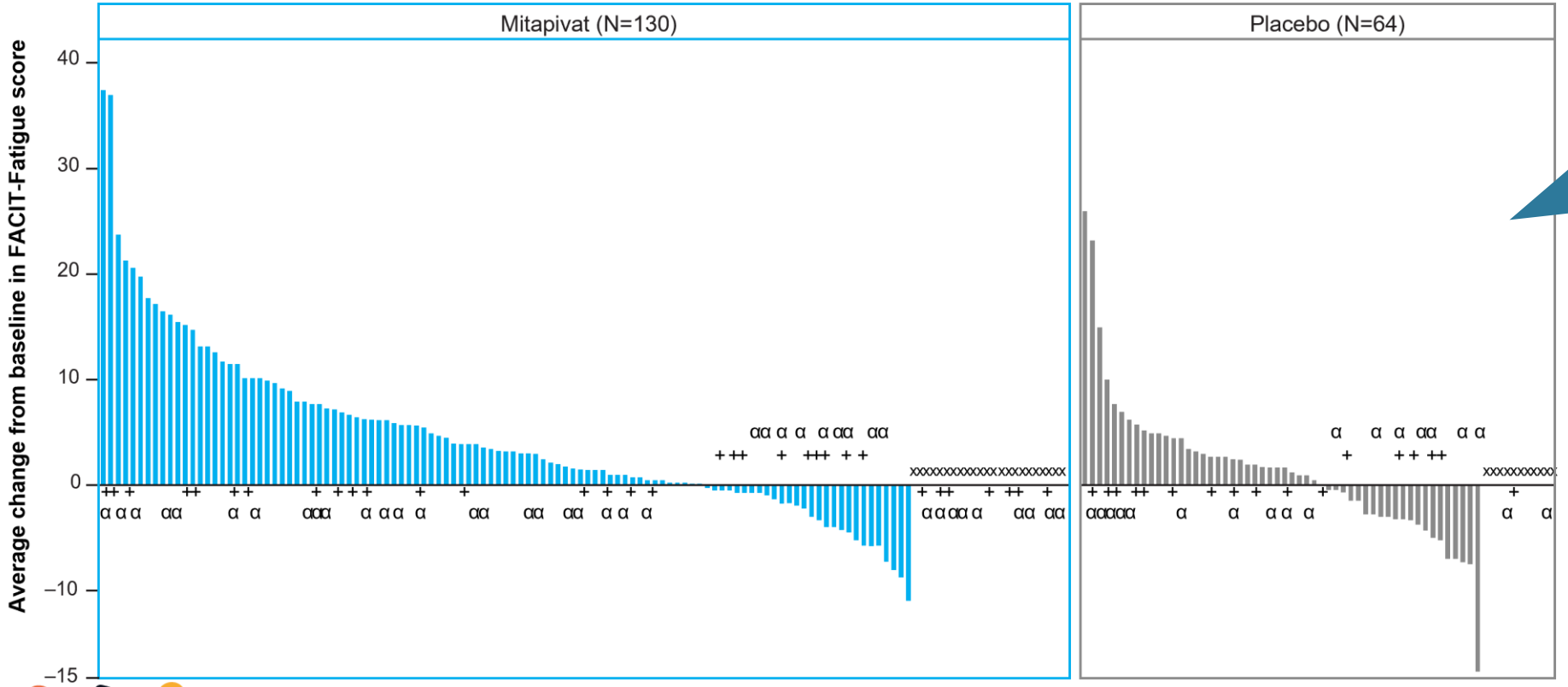


Analysis conducted on Full Analysis Set. aStratified by baseline Hb concentration (≤9.0 g/dL or 9.1–10.0 g/dL) and thalassemia genotype (α-thalassemia/HbH disease or β-thalassemia). [b]For "All patients," the estimates for the difference and the 95% CIs are based on the Mantel–Haenszel stratum weighted method adjusting for the randomization stratification factors. For subgroups, the estimates for the difference and the 95% CIs are based on unstratified analyses.
Hb, hemoglobin; HbH, hemoglobin H

Mitapivat demonstrated a statistically significant improvement from baseline in average FACIT-Fatigue score from Weeks 12–24 vs placebo

Key secondary endpoint

	Mitapivat N=130	Placebo N=64	LSM difference	2-sided p-value
FACIT-Fatigue score, least-squares mean (LSM) (95% CI) change from baseline in average of Weeks 12–24	4.85 (3.41, 6.30)	1.46 (−0.43, 3.34)	3.40 (1.21, 5.59)	p=0.0026



See **poster 6422479** for further details on HRQoL-related data

α = α-thalassemia/HbH disease

\+ = Baseline Hb category: 9.1–10 g/dL

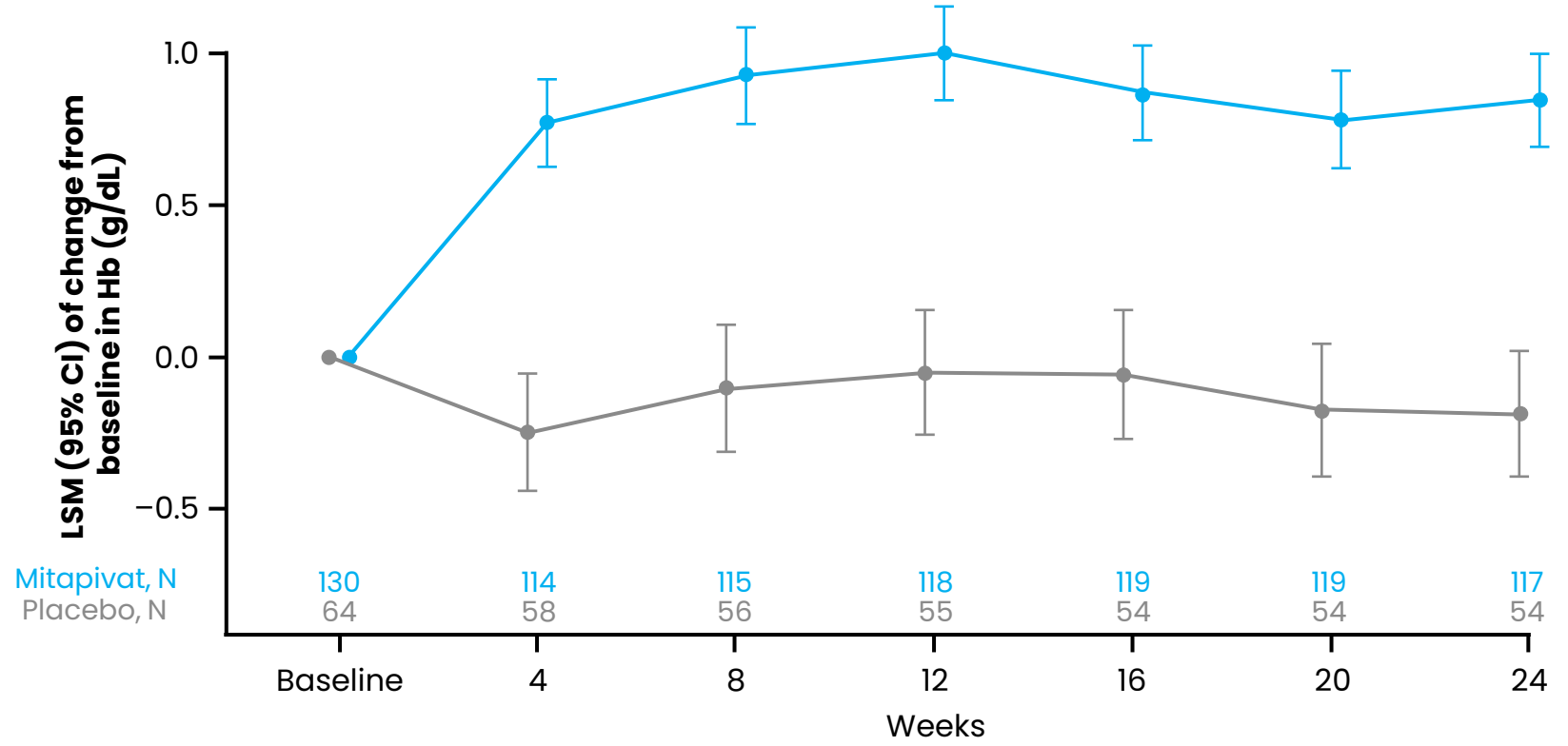
x = Patient with missing baseline or with no assessments from Week 12 through Week 24

Analysis conducted on Full Analysis Set.
FACIT-Fatigue, Functional Assessment of Chronic Illness Therapy–Fatigue Scale; Hb, hemoglobin; HbH, hemoglobin H; HRQoL, health-related quality of life

Mitapivat demonstrated a statistically significant improvement in change from baseline in average Hb concentration from Weeks 12–24 vs placebo

Key secondary endpoint

	Mitapivat N=130	Placebo N=64	LSM difference	2-sided p-value
Hb, LSM (95% CI) change from baseline in average of Weeks 12–24, g/dL	0.86 (0.73, 0.99)	−0.11 (−0.28, 0.07)	0.96 (0.78, 1.15)	p<0.0001



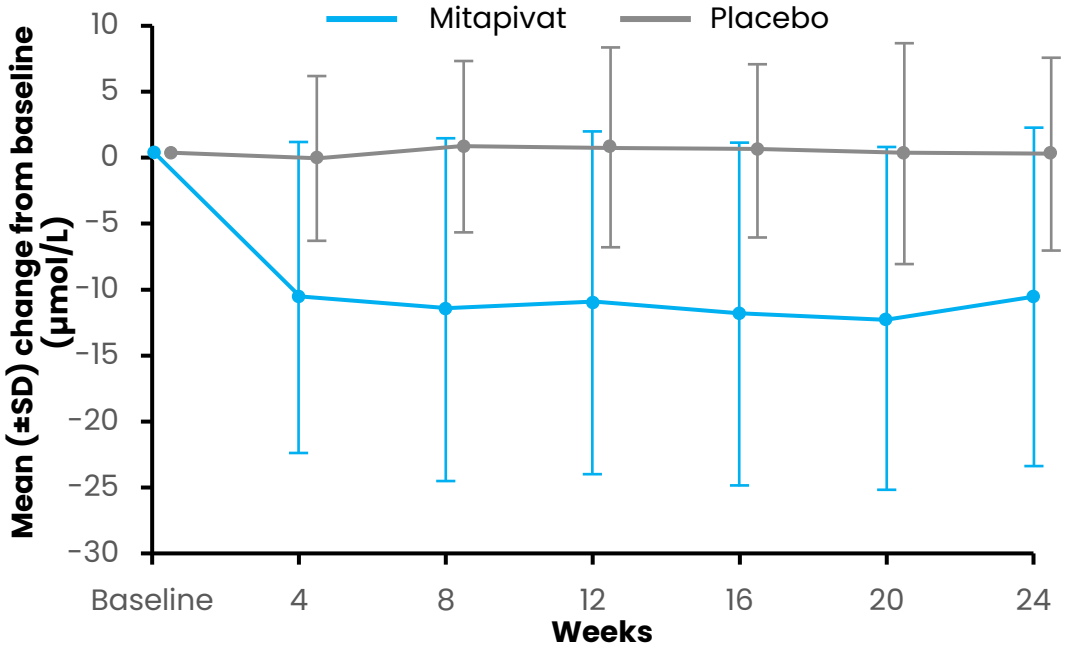
Analysis conducted on Full Analysis Set.
Hb, hemoglobin; LSM, least-squares mean

Improvements in markers of hemolysis were observed in the mitapivat arm vs placebo

Secondary endpoints

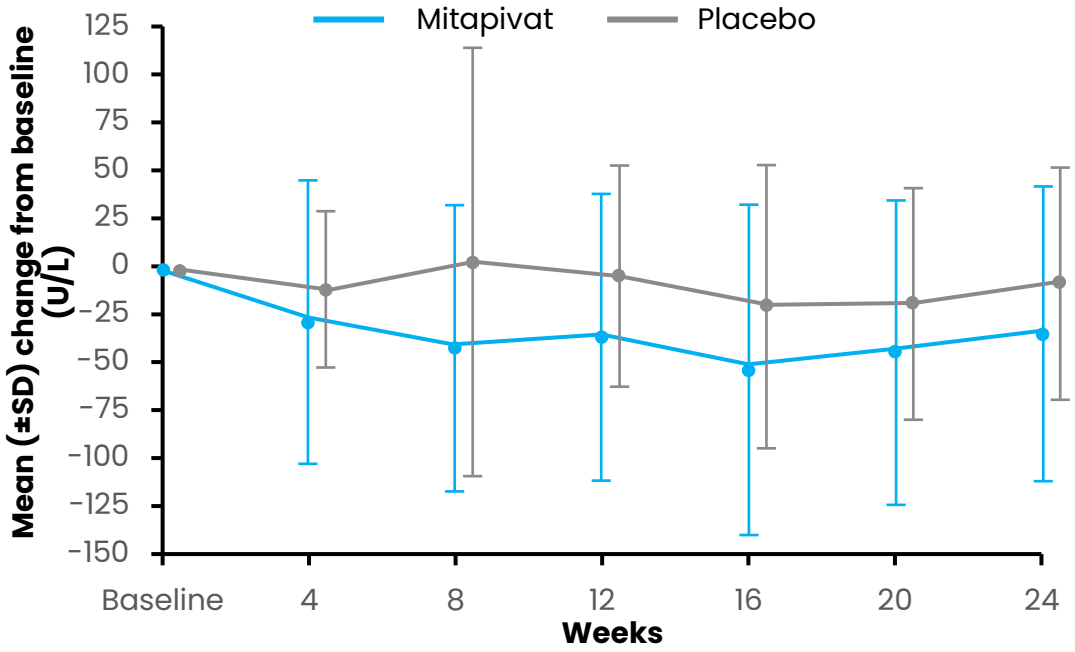
Indirect bilirubin

	Mitapivat N=116	Placebo N=54	LSM difference
Indirect bilirubin, LSM (95% CI) change from baseline at Week 24, µmol/L	−10.65 (−12.72, −8.58)	−0.03 (−2.80, 2.74)	−10.62 (−13.74, −7.50)



LDH

	Mitapivat N=116	Placebo N=54	LSM difference
LDH, LSM (95% CI) change from baseline at Week 24, U/L	−30.07 (−44.15, −15.99)	−5.79 (−24.43, 12.85)	−24.28 (−45.40, −3.15)



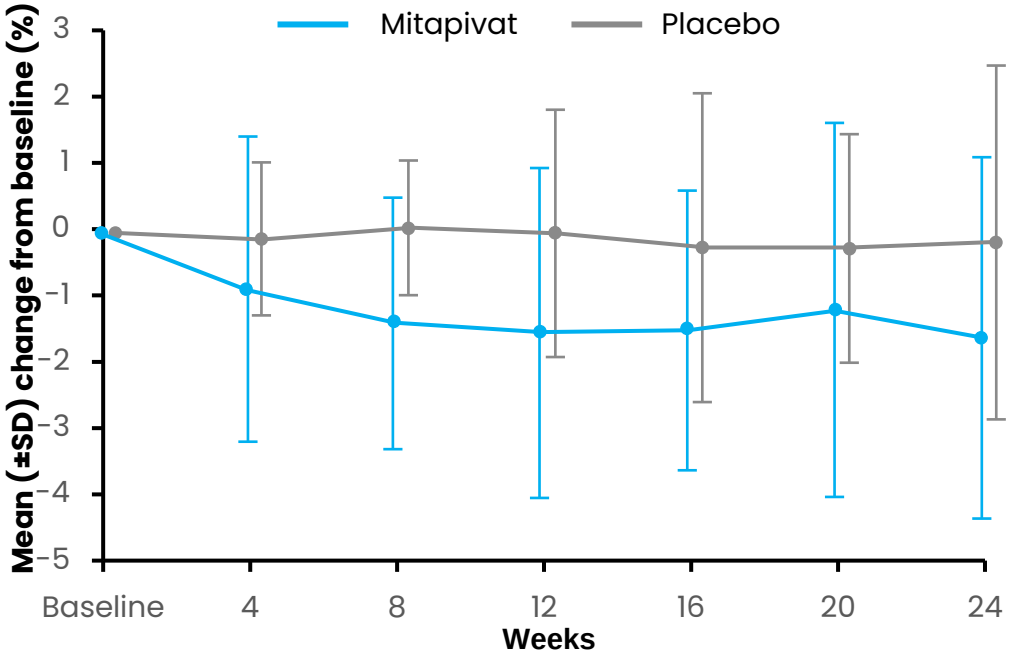
Note: numeric data are reported as LSM (95% CI) and figures are plotted with mean (±SD)
Analysis conducted on Full Analysis Set.
LDH, lactate dehydrogenase; LSM, least-squares mean

Improvement in reticulocyte percentage was observed in the mitapivat arm vs placebo

Secondary endpoints

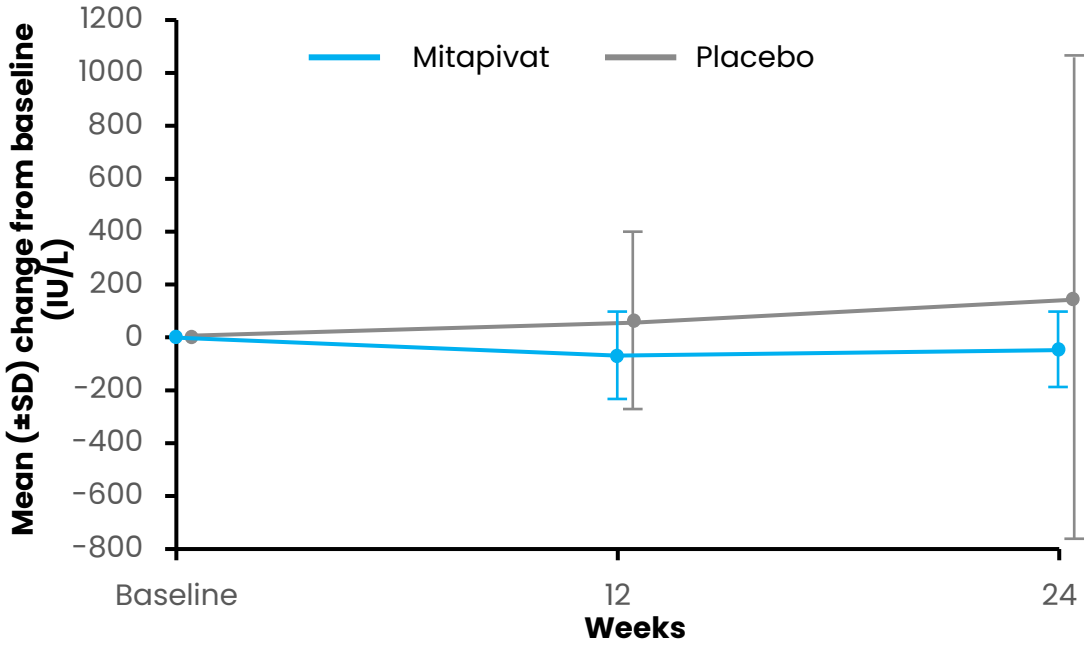
Reticulocyte percentage

	Mitapivat N=87	Placebo N=40	LSM difference
Reticulocyte percentage, LSM (95% CI) change from baseline at Week 24, %	−1.59 (−2.12, −1.07)	−0.25 (−0.97, 0.48)	−1.35 (−2.17, −0.53)



Erythropoietin

	Mitapivat N=103	Placebo N=47	LSM difference
Erythropoietin, LSM (95% CI) change from baseline at Week 24, IU/L	19.21 (−55.45, 93.86)	115.71 (18.04, 213.37)	−96.50 (−209.59, 16.60)



Note: numeric data are reported as LSM (95% CI) and figures are plotted with mean (±SD).
Analysis conducted on Full Analysis Set.
LDH, lactate dehydrogenase; LSM, least-squares mean

Summary of safety

Secondary endpoint

Patients, n (%)	Mitapivat (N=129)	Placebo (N=63)
Any treatment-emergent adverse events (TEAEs)	107 (82.9)	50 (79.4)
Grade ≥3 TEAEs	18 (14.0)	2 (3.2)
Treatment-related TEAEs	56 (43.4)	13 (20.6)
Grade ≥3 treatment-related TEAEs	5 (3.9)	0 (0.0)
Serious TEAEs	8 (6.2)	0 (0.0)
Serious treatment-related TEAEs	0 (0.0)	0 (0.0)
TEAEs leading to discontinuation of study drug	4 (3.1)	0 (0.0)
TEAEs leading to dose reduction	7 (5.4)	2 (3.2)
TEAEs leading to interruption of study drug	2 (1.6)	1 (1.6)
TEAEs leading to death	0 (0.0)	0 (0.0)

Analysis conducted on Safety Analysis Set. The denominator used to calculate percentages is N, the number of patients in the Safety Analysis Set within each treatment arm. The severity of all TEAEs, including clinically significant laboratory abnormalities, was graded by the Investigator according to Version 4.03 of the National Cancer Institute Common Terminology Criteria for Adverse Event on a 5-point severity scale (Grade 1–5). Adverse events that led to discontinuation of study drug with mitapivat were thrombocytopenia, arthralgia, abdominal distension, and 5 concurrent laboratory adverse events (alanine aminotransferase increase, aspartate aminotransferase increase, blood bilirubin increase, blood LDH increase, and international normalized ratio increase) (all in 1 patient each).

Most frequently reported (≥10%) TEAEs

Secondary endpoint

Preferred Term, n (%)	Mitapivat (N=129)	Placebo (N=63)
Headache		
Any grade	29 (22.5)	6 (9.5)
Grade ≥3	0 (0.0)	0 (0.0)
Initial insomnia		
Any grade	18 (14.0)	3 (4.8)
Grade ≥3	1 (0.8)	0 (0.0)
Nausea		
Any grade	15 (11.6)	5 (7.9)
Grade ≥3	0 (0.0)	0 (0.0)
Upper respiratory tract infection		
Any grade	14 (10.9)	4 (6.3)
Grade ≥3	0 (0.0)	0 (0.0)

Analysis conducted on Safety Analysis Set. Summarized in order of decreasing frequency of patients with events based on the frequencies observed in any grade for the mitapivat arm. The denominator used to calculate percentages is N, the number of patients in the Safety Analysis Set within each treatment arm. The severity of all TEAEs, including clinically significant laboratory abnormalities, was graded by the Investigator according to Version 4.03 of the National Cancer Institute Common Terminology Criteria for Adverse Event on a 5-point severity scale (Grade 1–5).
TEAE, treatment-emergent adverse event

Summary

- This global study was the first to enroll patients with α-thalassemia in addition to β-thalassemia
- The primary and key secondary endpoints were met, with statistically significant improvements in Hb and fatigue with mitapivat vs placebo
  - Subgroup analyses showed that the effects were robust and not driven by any individual subgroup
- Improvements in indirect bilirubin, LDH, and reticulocyte percentage were observed, consistent with the mechanism of mitapivat[1–3]
- Mitapivat was generally safe and well tolerated, with a low treatment discontinuation rate

ENERGIZE demonstrated efficacy of mitapivat, a disease-modifying therapy, with significant improvements in both Hb and fatigue across the full range of NTDT, including both α- and β-thalassemia

Hb, hemoglobin; NTDT, non–transfusion-dependent thalassemia

1. Kung C et al. *Blood* 2017;130:1347–56; 2. Matte A et al. *J Clin Invest* 2021;131:e144206; 3. Kuo KHM et al. *Lancet* 2022;400:493–501.

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Supplemental data are available via the QR code