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ENERGIZE-T: A global, phase 3, double-blind, randomized, placebo-controlled study of mitapivat in adults with transfusion-dependent alpha- or beta-thalassemia

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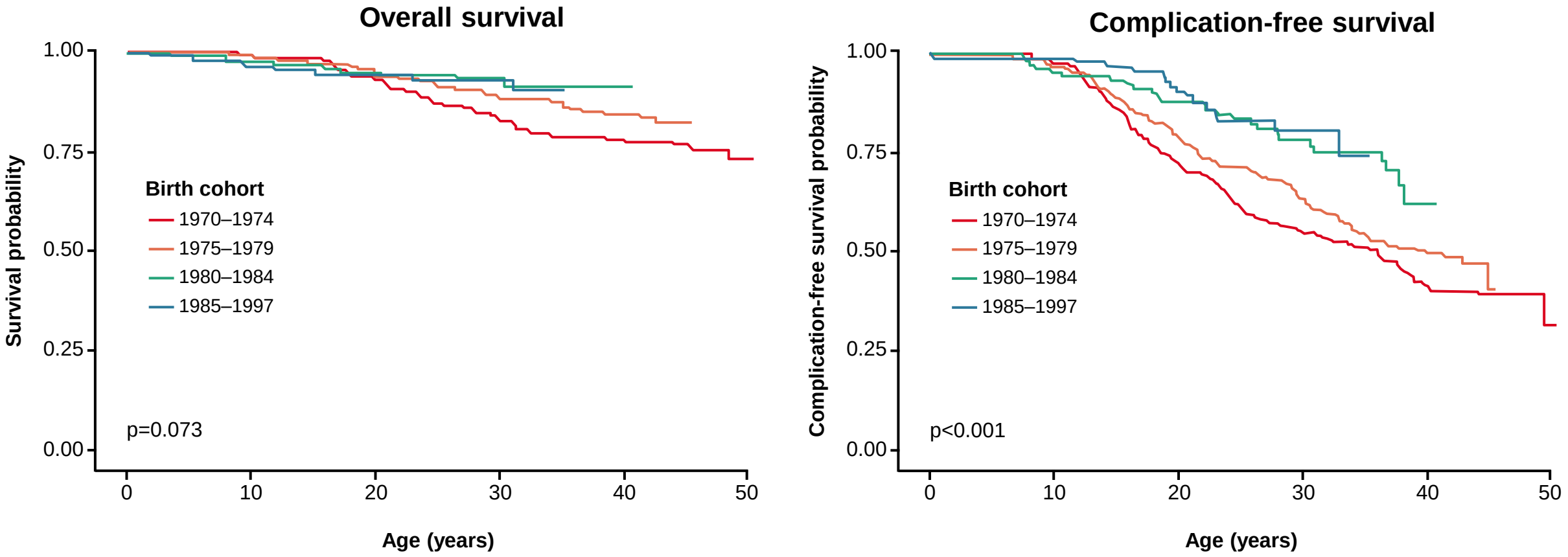
Although survival and clinical outcomes in patients with transfusion-dependent thalassemia (TDT) have improved over past decades, there remains an unmet need

Survival and complications in patients with TDT by birth cohort (N=709)



- The introduction of transfusion and iron chelation therapy in the management of TDT contributed to these improved outcomes

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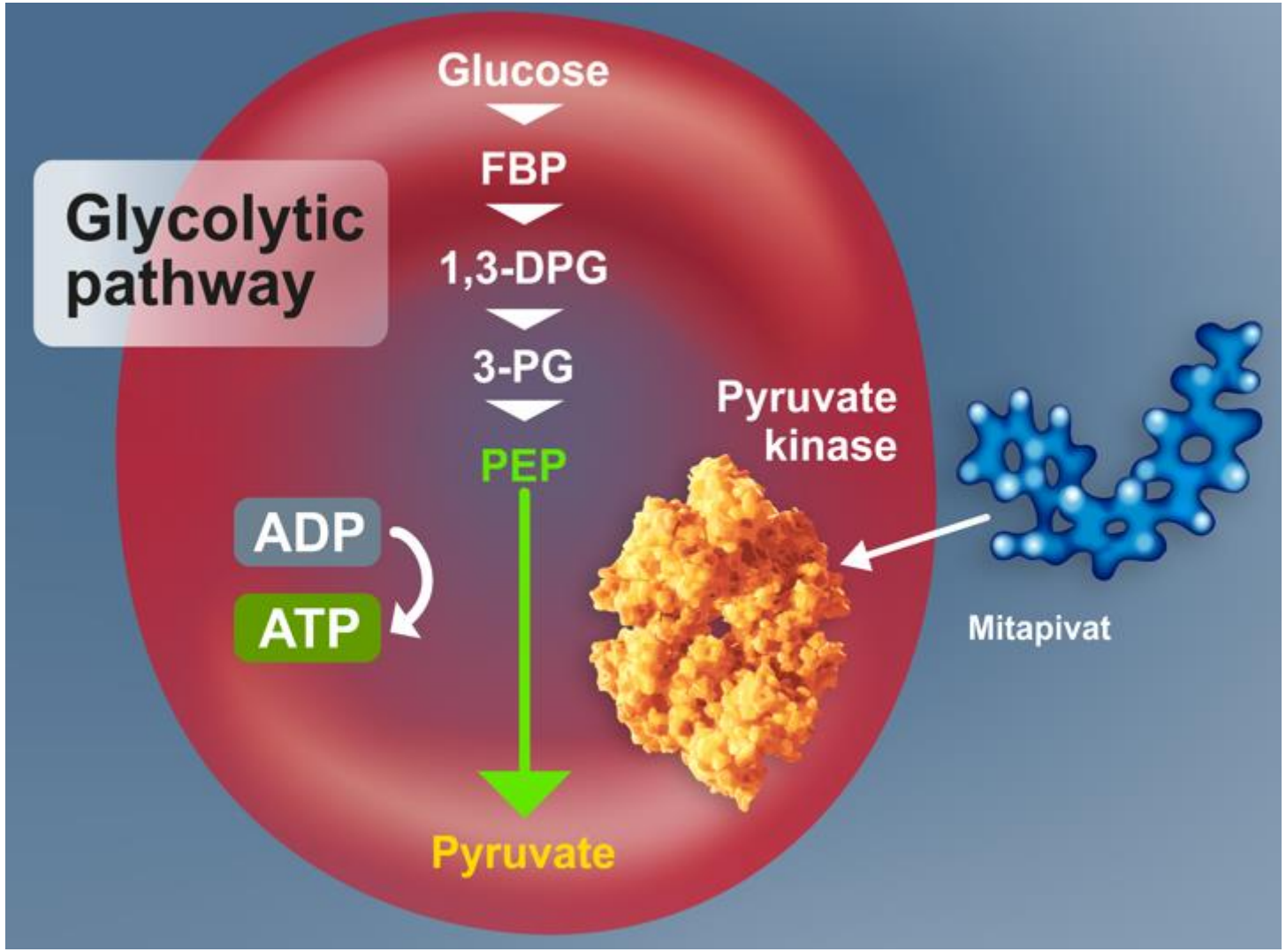
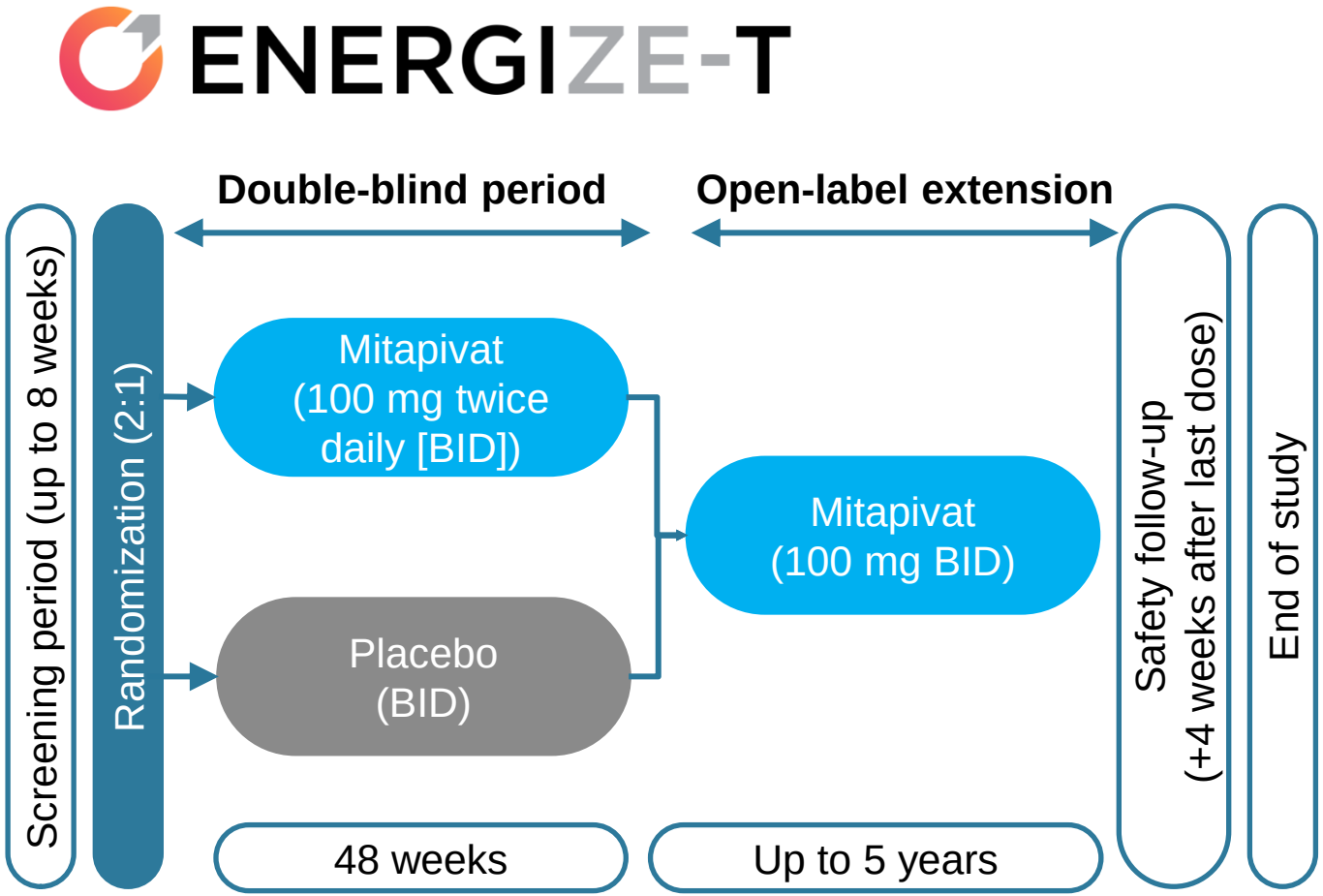
Mitapivat enhances cellular energy supply to support increased metabolic demands of thalassemic red cells



- In thalassemia, there is increased energy demand to maintain RBC health[1–4]
- Mitapivat is an activator of pyruvate kinase (PK), including the red cell-specific (PKR) and M2 (PKM2) isoforms, which act in glycolysis to generate ATP[5,6]
- In the phase 3 ENERGIZE study of patients with non–transfusion-dependent α- or β-thalassemia (NCT04770753), mitapivat increased Hb and improved fatigue vs placebo[7]

ADP, adenosine diphosphate; ATP, adenosine triphosphate; DPG, diphosphoglyceric acid; FBP, fructose biphosphate; Hb, hemoglobin; 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. Taher AT et al. 2024. EHA 2024, Madrid, Spain: Abstract S102.

ENERGIZE-T: A phase 3 study of mitapivat in adults with transfusion-dependent α- or β-thalassemia



Key inclusion criteria

- ≥18 years of age at time of informed consent
- Documented diagnosis of thalassemia (β-thalassemia ± α-globin mutations, HbE/β-thalassemia, or α-thalassemia/HbH disease)
- Transfusion-dependent (6–20 RBC units transfused and a ≤6-week transfusion-free period during the 24-week period before randomization)
- If taking hydroxyurea, a stable hydroxyurea dose for ≥16 weeks before randomization

Key exclusion criteria

- Prior exposure to gene therapy or hematopoietic stem cell transplantation
- Homozygous or heterozygous for HbS or HbC
- Receiving treatment with luspatercept or hematopoietic stimulating agents (last doses must have been administered ≥36 weeks before randomization)

Randomization stratification factors

- Thalassemia genotype (patients who do not have a β^0 mutation at both alleles of the β-globin gene [non-β^0/β^0], including patients with HbE/β thalassemia and α thalassemia/HbH disease; or patients who have a β^0 mutation at both alleles of the β-globin gene [β^0/β^0])
- Geographic region (North America and Europe, Asia-Pacific, and Rest of World)

Hb, hemoglobin; HbC, hemoglobin C; HbE, hemoglobin E; HbH, hemoglobin H; HbS, hemoglobin S; RBC, red blood cell. Clinicaltrials.gov. https://clinicaltrials.gov/study/NCT04770779. Accessed November 2024.

Endpoints

Primary endpoint

- Transfusion reduction response (TRR), defined as a ≥50% reduction in transfused RBC units and a reduction of ≥2 units of transfused RBCs in any consecutive 12-week period through Week 48 compared with baseline

Key secondary endpoints

- TRR2, defined as a ≥50% reduction in transfused RBC units in any consecutive 24-week period through Week 48 compared with baseline
- TRR3, defined as a ≥33% reduction in transfused RBC units from Week 13 through Week 48 (fixed 36-week period) compared with baseline
- TRR4, defined as a ≥50% reduction in transfused RBC units from Week 13 through Week 48 (fixed 36-week period) compared with baseline

Other secondary efficacy endpoints included

- Transfusion independence, defined as transfusion-free for ≥8 consecutive weeks through Week 48

Safety endpoints

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

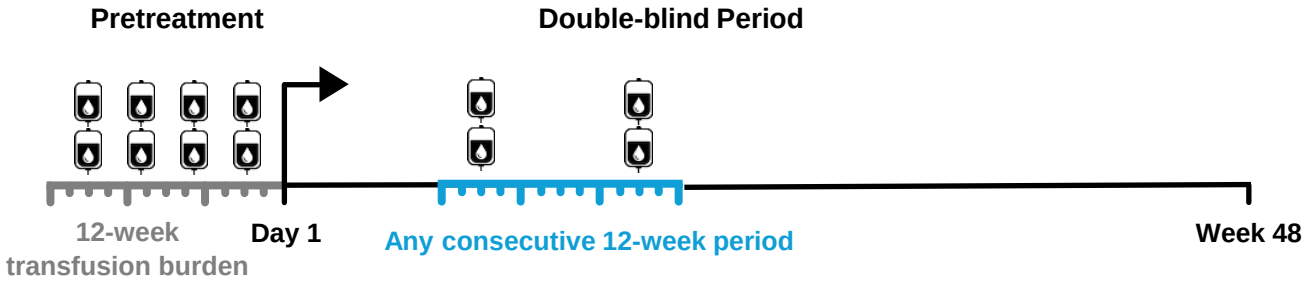
RBC, red blood cell.

Depiction of endpoint concept[a]

KEY	
	= Units of RBCs transfused
	= Start of treatment

Primary endpoint:

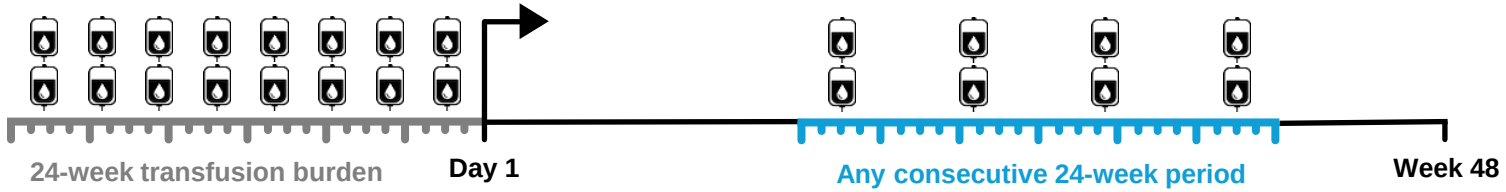
Transfusion reduction response (TRR)



≥50% reduction
+ ≥2 units reduction

Key secondary endpoints:

TRR2

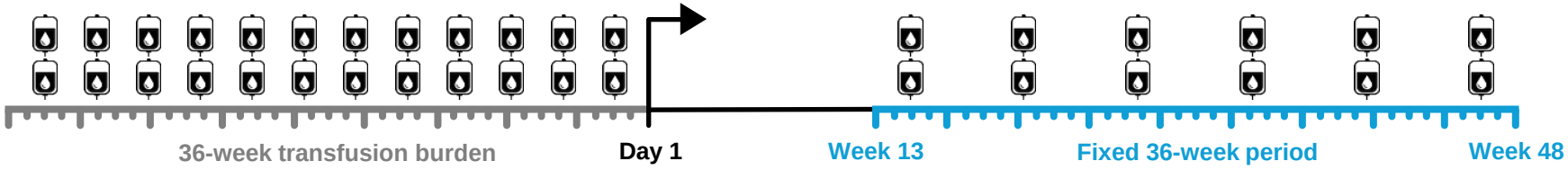


≥50% reduction

TRR3

≥33% reduction

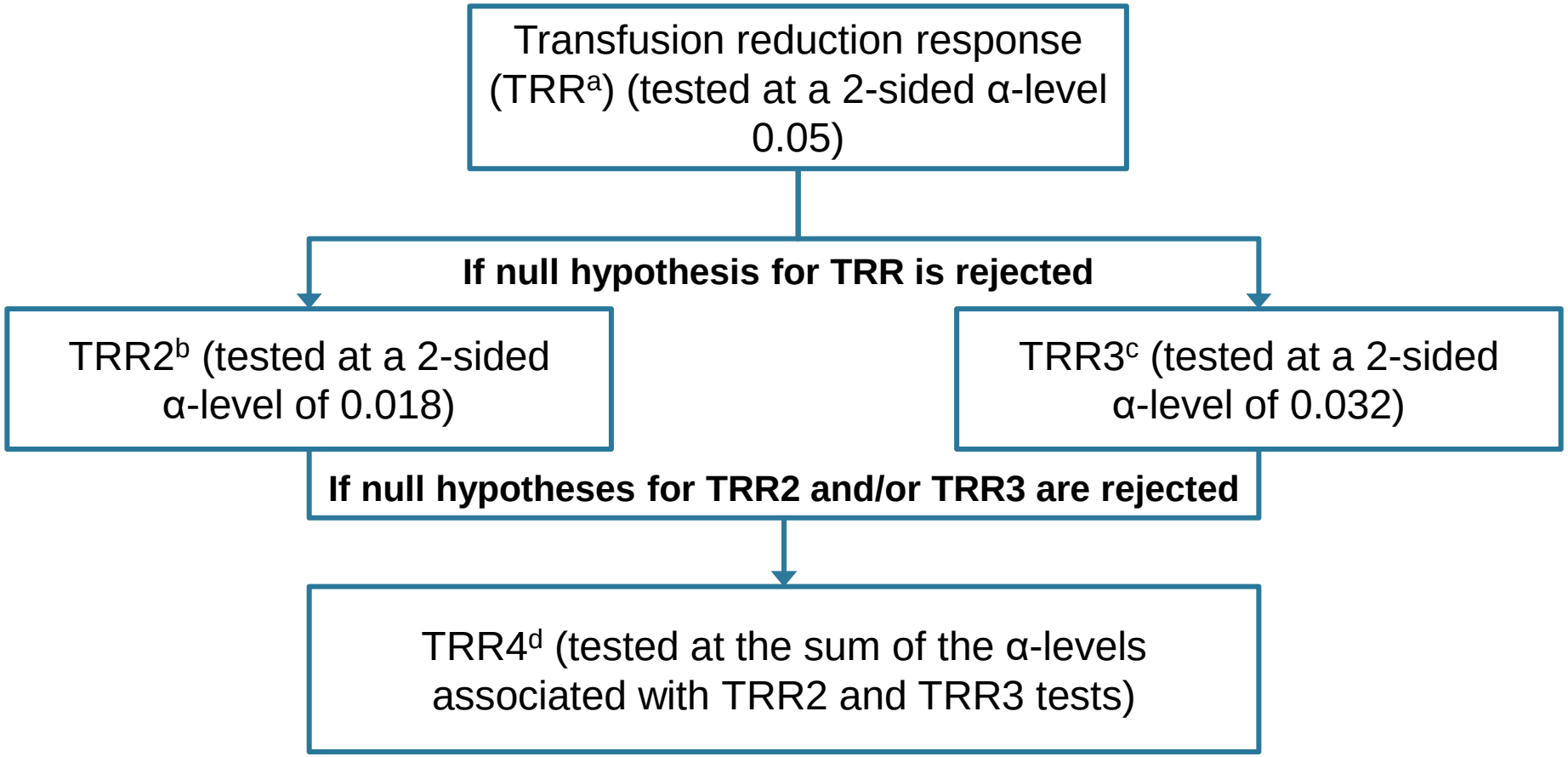
TRR4



≥50% reduction

[a]Visuals shown on this slide do not depict actual data and are shown for illustrative purposes only. RBC, red blood cell; TRR, transfusion reduction response.

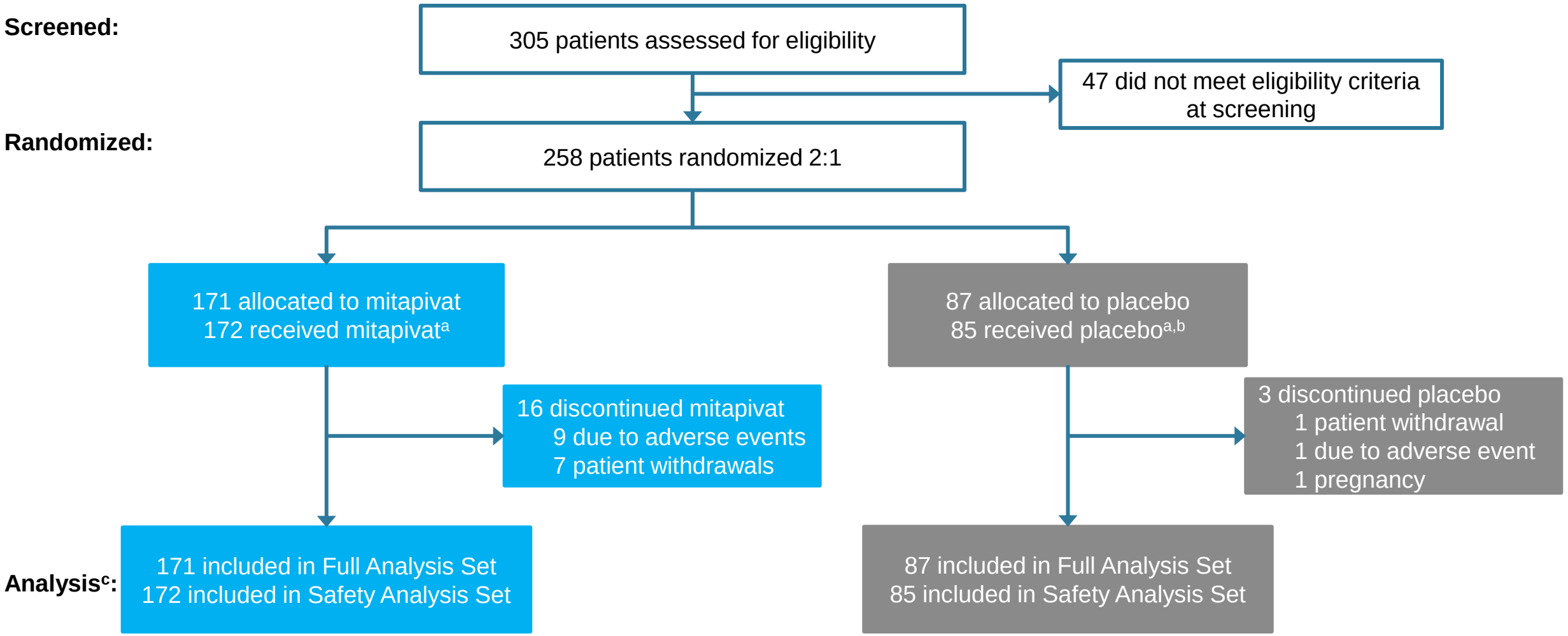
Statistical testing strategy



Primary and key secondary endpoints were tested using the Mantel–Haenszel stratum weighted method adjusting for randomization stratification factors[e]

[a]TRR was defined as a ≥50% reduction in transfused RBC units and a reduction of ≥2 units of transfused RBCs in any consecutive 12-week period through Week 48 compared with baseline. [b]TRR2 was defined as a ≥50% reduction in transfused RBC units in any consecutive 24-week period through Week 48 compared with baseline. [c]TRR3 was defined as a ≥33% reduction in transfused RBC units from Week 13 through Week 48 compared with baseline. [d]TRR4 was defined as a ≥50% reduction in transfused RBC units from Week 13 through Week 48 compared with baseline. [e]Additional information on the statistical methodology is included in the Supplemental Materials.

Patient disposition: 258 patients were randomized in the study



[a]One patient, randomized to placebo, received mitapivat and was classified in the mitapivat group in the Safety Analysis Set. [b]One patient was randomized but not dosed. [c]Full Analysis Set: All patients randomized. Patients were 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 group.

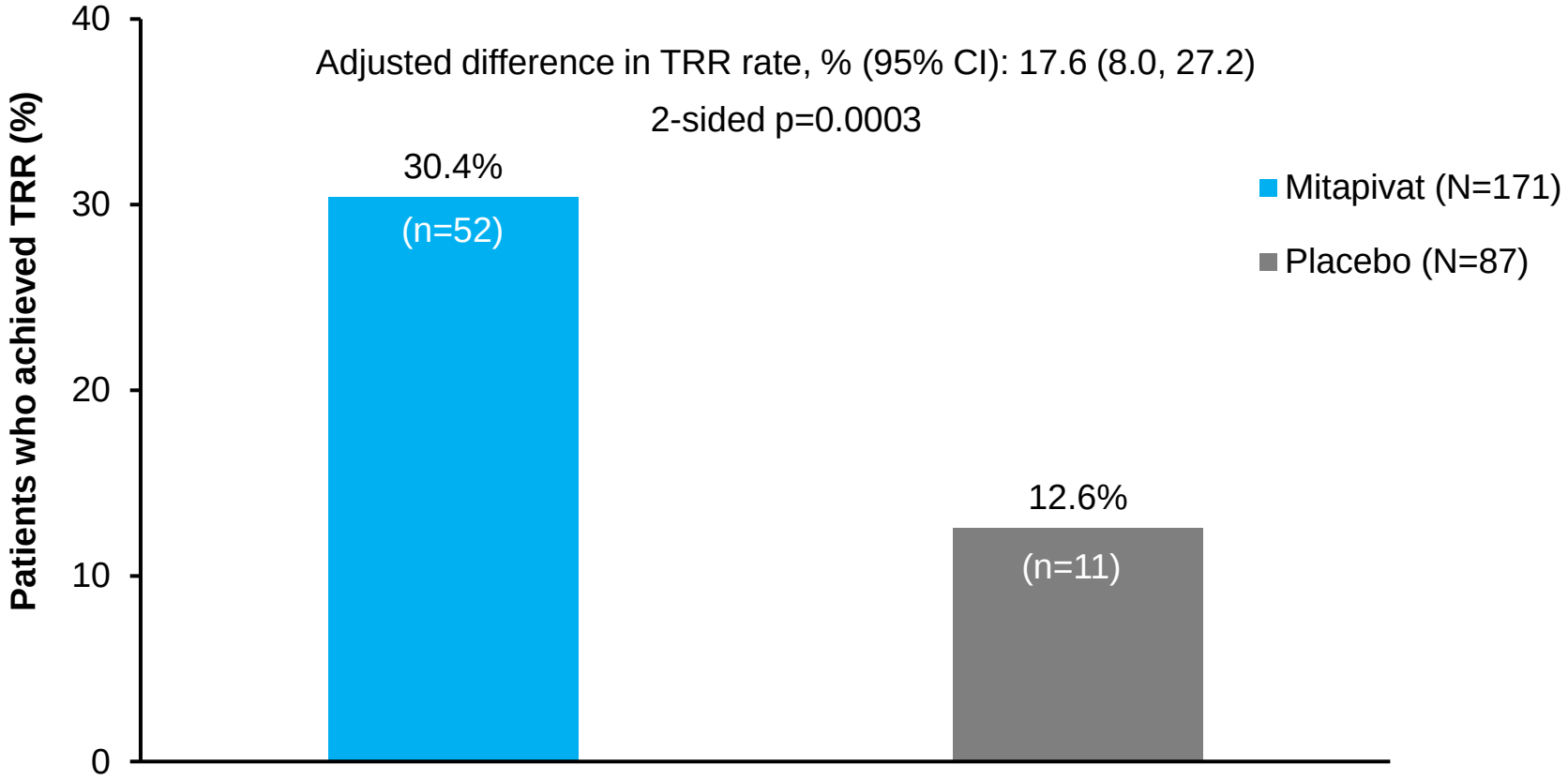
Baseline demographics and disease characteristics

Demographics and disease characteristics	Mitapivat (N=171)	Placebo (N=87)
Age, mean (SD), years	35.8 (11.6)	34.7 (9.8)
Female, n (%)	93 (54.4)	43 (49.4)
Race, n (%)		
White	99 (57.9)	56 (64.4)
Asian	56 (32.7)	22 (25.3)
Black or African American	1 (0.6)	1 (1.1)
Multiracial	2 (1.2)	0 (0.0)
Unknown	7 (4.1)	3 (3.4)
Not reported	6 (3.5)	5 (5.7)
Thalassemia genotype, n (%)		
Non-β^0/β^0 [a]	96 (56.1)	48 (55.2)
β^0/β^0 [b]	75 (43.9)	39 (44.8)
24-week transfusion burden,[c] n (%)		
≤12 RBC units	54 (31.6)	21 (24.1)
>12 RBC units	117 (68.4)	66 (75.9)
Pretransfusion Hb threshold,[d] median (range), g/dL	9.0 (5.1–11.8)	8.9 (5.1–10.9)
Prior splenectomy,[e] n (%)	92 (53.8)	49 (56.3)
Received iron chelation in prior year,[f] n (%)	165 (96.5)	87 (100.0)
Geographic region, n (%)		
North America and Europe	106 (62.0)	54 (62.1)
Asia-Pacific	31 (18.1)	16 (18.4)
Rest of world[g]	34 (19.9)	17 (19.5)

No statistical comparisons were made between treatment groups for baseline demographics and disease characteristics. [a]Patients who do not have a β^0 mutation at both alleles of the β-globin gene including patients with HbE/β thalassemia and α thalassemia/HbH disease. [b]Patients who have a β^0 mutation at both alleles of the β-globin gene. [c]Total number of RBC units transfused in the 24-week period before randomization. [d]Pretransfusion Hb threshold was defined as the mean of all documented pretransfusion Hb concentration values recorded for the RBC transfusions administered during the 24-week period before randomization. [e]As recorded in medical/surgical history electronic case report form (eCRF). [f]As recorded in disease characteristics eCRF. "Yes" if a patient received chelation therapy within 1 year (365 days) before randomization. [g]Rest of world included Latin America and the Middle East. Hb, hemoglobin; RBC, red blood cell; SD, standard deviation.

Mitapivat demonstrated a statistically significant reduction in transfusion burden vs placebo

Primary endpoint



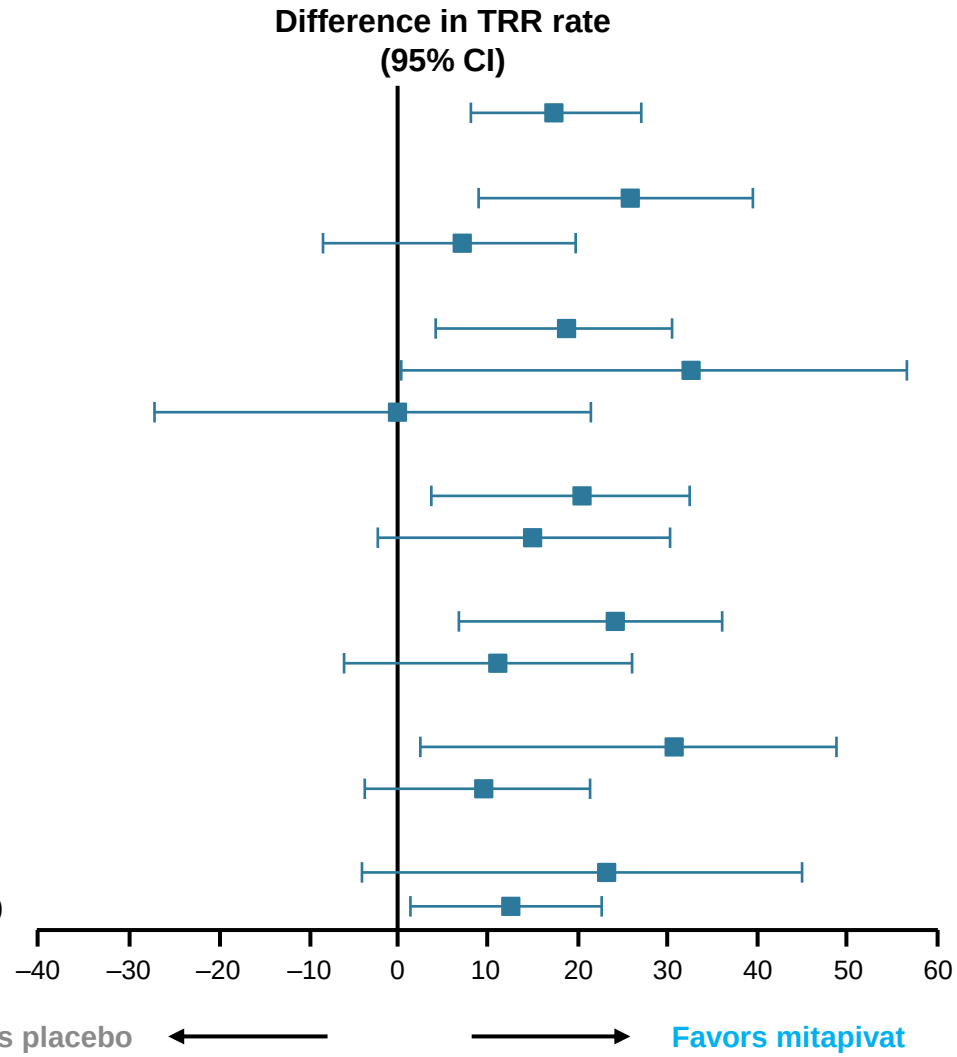
Transfusion reduction response (TRR) was defined as a ≥50% reduction in transfused RBC units and a reduction of ≥2 units of transfused RBCs in any consecutive 12-week period through Week 48 compared with baseline

Analysis conducted on Full Analysis Set. Baseline transfusion burden standardized to 12 weeks=total number of RBC units transfused during the 24-week period (168 days) before "reference date"×12/24, where "reference date" is the randomization date for subjects randomized and not dosed or the start of study treatment for subjects randomized and dosed. Subjects withdrawn from the study before Week 12 (Day 85) are considered non-responders. CI, confidence interval; RBC, red blood cell; TRR, transfusion reduction response.

Reduction in transfusion burden by prespecified subgroups

Subgroup analysis of primary endpoint

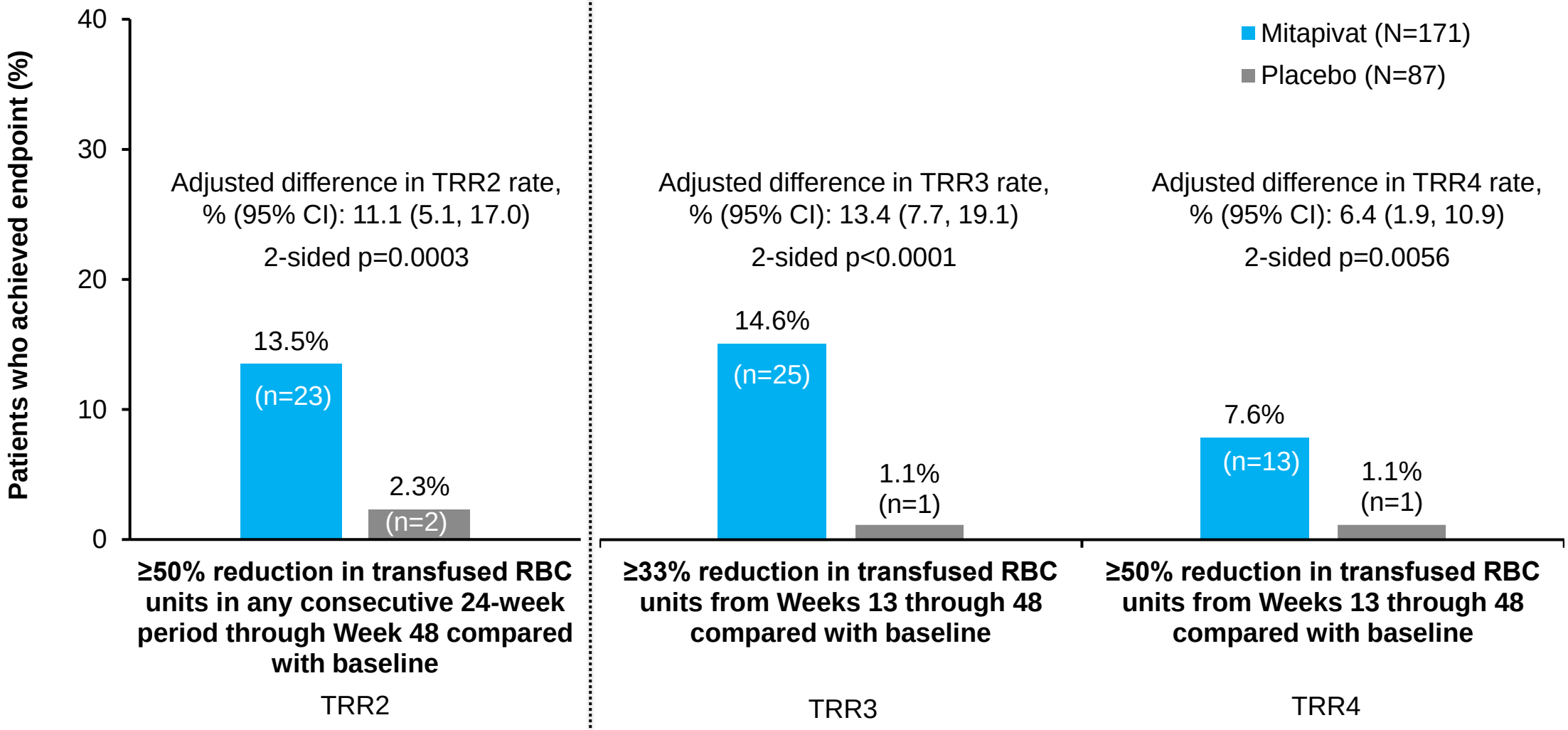
Subgroup	TRR response rate, % (n/N) Placebo	Mitapivat	Difference (95% CI)[b]
All patients (stratified)[a]	12.6 (11/87)	30.4 (52/171)	17.6 (8.0, 27.2)
Thalassemia genotype			
Non-β^0/β^0	14.6 (7/48)	40.6 (39/96)	26.0 (8.9, 39.6)
β^0/β^0	10.3 (4/39)	17.3 (13/75)	7.1 (–8.3, 19.7)
Geographic region, n (%)			
North America and Europe	9.3 (5/54)	28.3 (30/106)	19.0 (4.2, 30.5)
Asia-Pacific	18.8 (3/16)	51.6 (16/31)	32.9 (0.3, 56.6)
Rest of world	17.6 (3/17)	17.6 (6/34)	0.0 (–27.1, 21.5)
Age at screening (year)			
<35	6.8 (3/44)	27.5 (25/91)	20.7 (3.8, 32.4)
≥35	18.6 (8/43)	33.8 (27/80)	15.1 (–2.3, 30.3)
Sex			
Female	7.0 (3/43)	31.2 (29/93)	24.2 (6.8, 36.1)
Male	18.2 (8/44)	29.5 (23/78)	11.3 (–6.0, 26.0)
Race			
Asian	13.6 (3/22)	44.6 (25/56)	31.0 (2.5, 48.8)
White	12.5 (7/56)	22.2 (22/99)	9.7 (–3.7, 21.4)
24-week baseline transfusion burden			
≤12 RBC units	28.6 (6/21)	51.9 (28/54)	23.3 (–4.0, 45.0)
>12 RBC units	7.6 (5/66)	20.5 (24/177)	12.9 (1.4, 22.7)



Analysis conducted on Full Analysis Set. TRR was defined as a ≥50% reduction in transfused RBC units and a reduction of ≥2 units of transfused RBCs in any consecutive 12-week period through Week 48 compared with baseline. [a]Stratified by thalassemia genotype and geographic region. [b]For "All patients," the estimates for the difference and the 95% CI 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. CI, confidence interval; RBC, red blood cell; TRR, transfusion reduction response.

Mitapivat also demonstrated statistically significant reductions in transfusion burden vs placebo as measured by all 3 key secondary endpoints

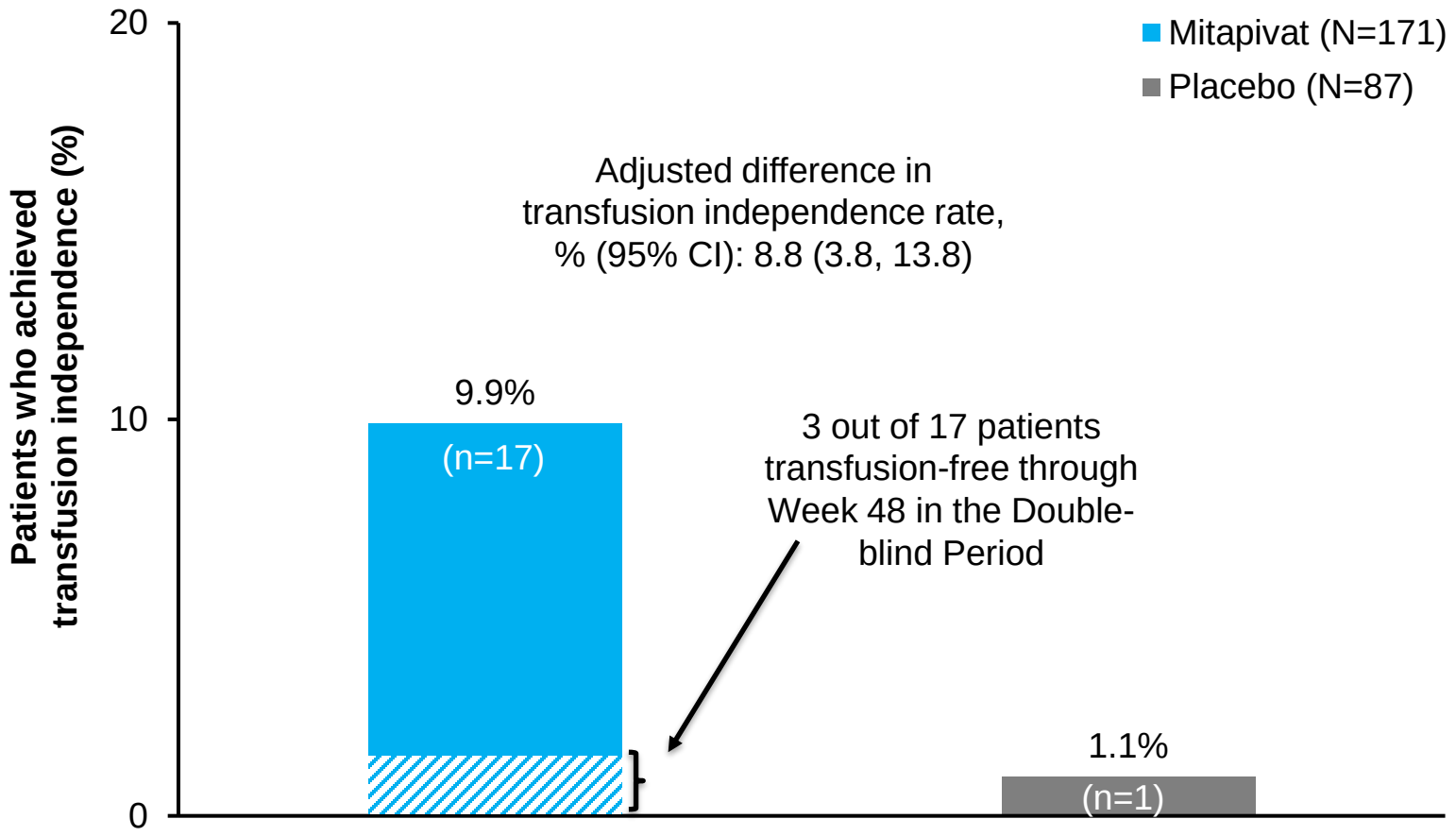
Key secondary endpoints



Analysis conducted on Full Analysis Set. 24-week baseline transfusion burden=total number of RBC units transfused during the 24-week period before "reference date," where "reference date" is the randomization date for patients randomized and not dosed or the start of study treatment for patients randomized and dosed. Patients withdrawn from the study before Week 24/Week 48 were considered non-responders for TRR2, TRR3, and TRR4, respectively (per protocol). CI, confidence interval; RBC, red blood cell; TRR, transfusion reduction response.

A higher proportion of patients in the mitapivat group achieved transfusion independence vs placebo

Secondary endpoint



Transfusion independence was defined as transfusion-free for ≥8 consecutive weeks through Week 48 in the Double-blind Period

Analysis conducted on Full Analysis Set. CI, confidence interval.

Summary of safety

Patients, n (%)	Mitapivat (N=172)	Placebo (N=85)
Any treatment-emergent adverse events (TEAEs)	155 (90.1)	71 (83.5)
Grade ≥3 TEAEs	32 (18.6)	12 (14.1)
Treatment-related TEAEs	65 (37.8)	16 (18.8)
Grade ≥3 treatment-related TEAEs	13 (7.6)	1 (1.2)
Serious TEAEs	19 (11.0)[a]	13 (15.3)[b]
Serious treatment-related TEAEs	4 (2.3)	1 (1.2)
TEAEs leading to discontinuation of study drug	10 (5.8)[c]	1 (1.2)[d]
TEAEs leading to dose reduction	20 (11.6)	2 (2.4)
TEAEs leading to interruption of study drug	13 (7.6)	5 (5.9)
TEAEs leading to death	0	0

Analysis conducted on Safety Analysis Set. CTCAE v4.03 used. [a]Serious TEAEs with mitapivat were gastroenteritis (in 2 patients), pneumonia, COVID-19 pneumonia, cellulitis, dengue fever, influenza, lower respiratory tract infection, hypersplenism, mesenteric lymphadenitis, pancytopenia, cholecystitis, acute cholecystitis, supraventricular arrythmia, supraventricular tachycardia, radius fracture, proctitis, asthenia, hepatic cancer, dizziness, renal mass, and ruptured ovarian cyst (all in 1 patient each). [b]Serious TEAEs with placebo were pneumonia (in 2 patients), viral infection, splenic hematoma, cholecystitis, acute cholecystitis, acute cholangitis, arrhythmia, left ventricular dysfunction, infusion-related reaction, cataract, increased blood creatine phosphokinase, limb deformity, spontaneous abortion, and pulmonary hypertension (all in 1 patient each). [c]The TEAEs leading to discontinuation of mitapivat, each of which occurred in one patient, were diarrhea, paresthesia oral, concurrent anxiety and insomnia, initial insomnia, supraventricular tachycardia, fatigue, hypertransaminasemia, hepatitis C, hepatic cancer, and renal mass. [d]The TEAE that led to discontinuation of the one patient on placebo was blood creatine phosphokinase increased. CTCAE, Common Terminology Criteria for Adverse Events.

Most frequently reported (≥10%) TEAEs

	Mitapivat (N=172)		Placebo (N=85)	
Preferred Term, n (%)	Any grade	Grade ≥3	Any grade	Grade ≥3
Headache	46 (26.7)	0	10 (11.8)	0
Upper respiratory tract infection	27 (15.7)	0	14 (16.5)	0
Initial insomnia	24 (14.0)	3 (1.7)	4 (4.7)	0
Diarrhea	19 (11.0)	0	7 (8.2)	0
Fatigue	18 (10.5)	0	2 (2.4)	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 group. CTCAE v4.03 used. CTCAE, Common Terminology Criteria for Adverse Events; TEAE, treatment-emergent adverse event.

Summary

- The primary and all key secondary endpoints of the study were met; mitapivat led to significant reductions in transfusion burden, with durability of response up to 36 weeks during the 48-week Double-blind Period
  - Efficacy was not driven by any prespecified subgroups
- A higher proportion of patients in the mitapivat group achieved transfusion independence compared with the placebo group; 3 patients in the mitapivat group were transfusion-free through Week 48 of the Double-blind Period
- Mitapivat was generally well tolerated in this study, with a low treatment discontinuation rate

In ENERGIZE-T, treatment with mitapivat, a disease-modifying therapy, was effective and resulted in significant reductions in transfusion burden in a globally representative population of patients with TDT, including both α- and β-thalassemia

TDT, transfusion-dependent thalassemia.

Acknowledgments

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Supplemental materials are available via the QR code