Efficacy and safety of mitapivat in pediatric patients with pyruvate kinase deficiency who are regularly transfused: Results from the phase 3 randomized global placebo-controlled ACTIVATE-KidsT trial

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Conflict of interest disclosures

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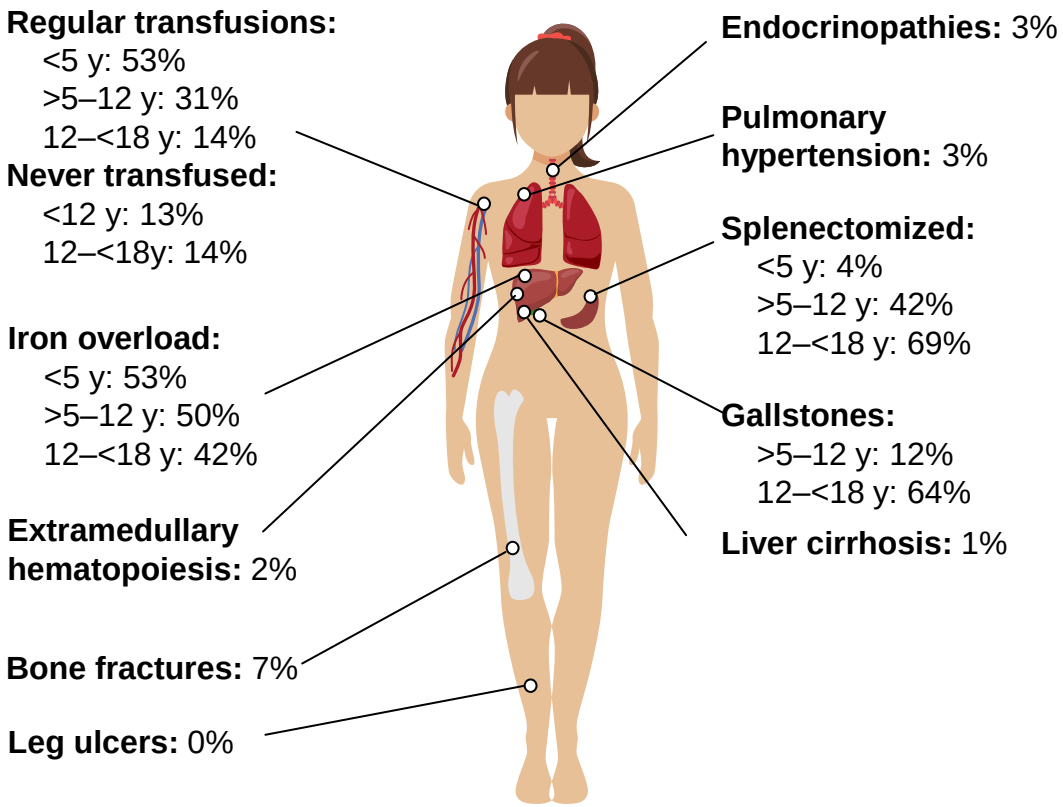
    - Sobi (consultancy, research funding)

Children with PK deficiency have considerable disease burden

- Pyruvate kinase (PK) deficiency is a rare, inherited disorder caused by mutations in the *PKLR* gene resulting in defects in the red blood cell (RBC) PK enzyme (PKR)[1,2]
- PK deficiency in children is primarily managed with RBC transfusions and splenectomy[3,4]
- Complications of disease and treatment are associated with significant morbidity and effect on quality of life[5]
- No pharmacotherapies are approved for the treatment of PK deficiency in children, and therapies targeting the underlying cause of hemolysis are needed[3]
- Mitapivat is a first-in-class oral allosteric activator of PKR and PK muscle isoenzyme 2 (PKM2), approved in the US for the treatment of hemolytic anemia in adults with PK deficiency, and in the EU and UK for the treatment of PK deficiency in adult patients[6–8]

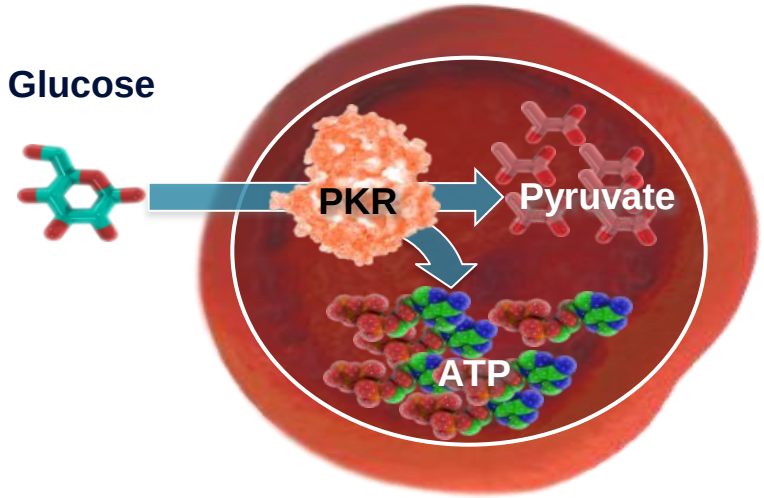
PK deficiency in children and adolescents[3]



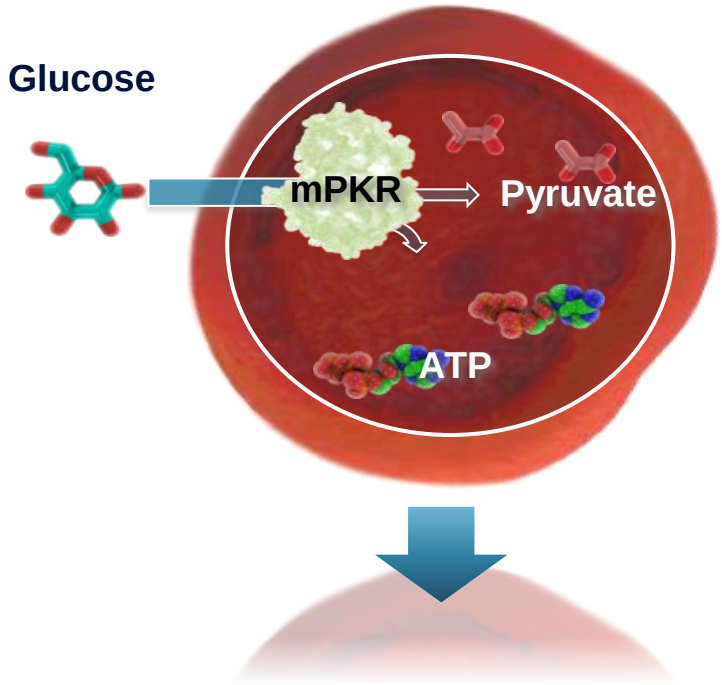
EU, European Union; MHRA, Medications and Healthcare products Regulatory Agency; PK, pyruvate kinase; PKM2, pyruvate kinase muscle isoenzyme 2; PKR, pyruvate kinase R; RBC, red blood cell; UK, United Kingdom; US, United States; y, year. 1. Grace RF, et al. *Am J Hematol* 2015;90:825–30; 2. Zanella A, et al. *Br J Haematol* 2005;130:11–25; 3. Grace RF, et al. *Blood* 2020;136:1241–49; 4. Chonat S, et al. *Pediatr Blood Cancer* 2021;68:e29148; 5. Al-Samkari H, et al. *Blood Adv* 2022;6:1844–53; 6. Agios Pharmaceuticals Inc. Pyrukynd (mitapivat). Prescribing information; 2025; https://www.agios.com/prescribinginfo.pdf; 7. EMA. Pyrukynd (mitapivat). Prescribing information; 2022; https://www.ema.europa.eu/en/documents/product-information/pyrukynd-epar-product-information_en.pdf; 8. MHRA. Pyrukynd (mitapivat). Prescribing information; 2022; https://mhraproducts4853.blob.core.windows.net/docs/3d274209928160e9f785bbc9cf857a8b6dd33e1d. All websites accessed May 2025.

Mitapivat is an oral, allosteric activator of PKR and PKM2 with the potential to correct RBC metabolism

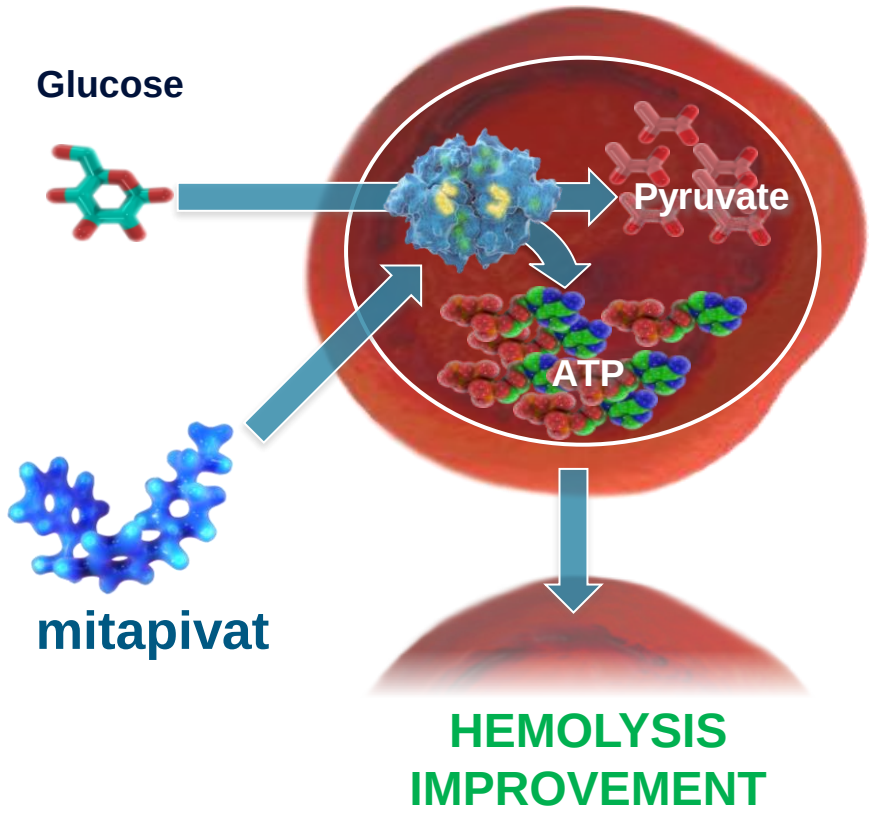
Healthy RBC, wild-type



PK-deficient RBC, mPKR



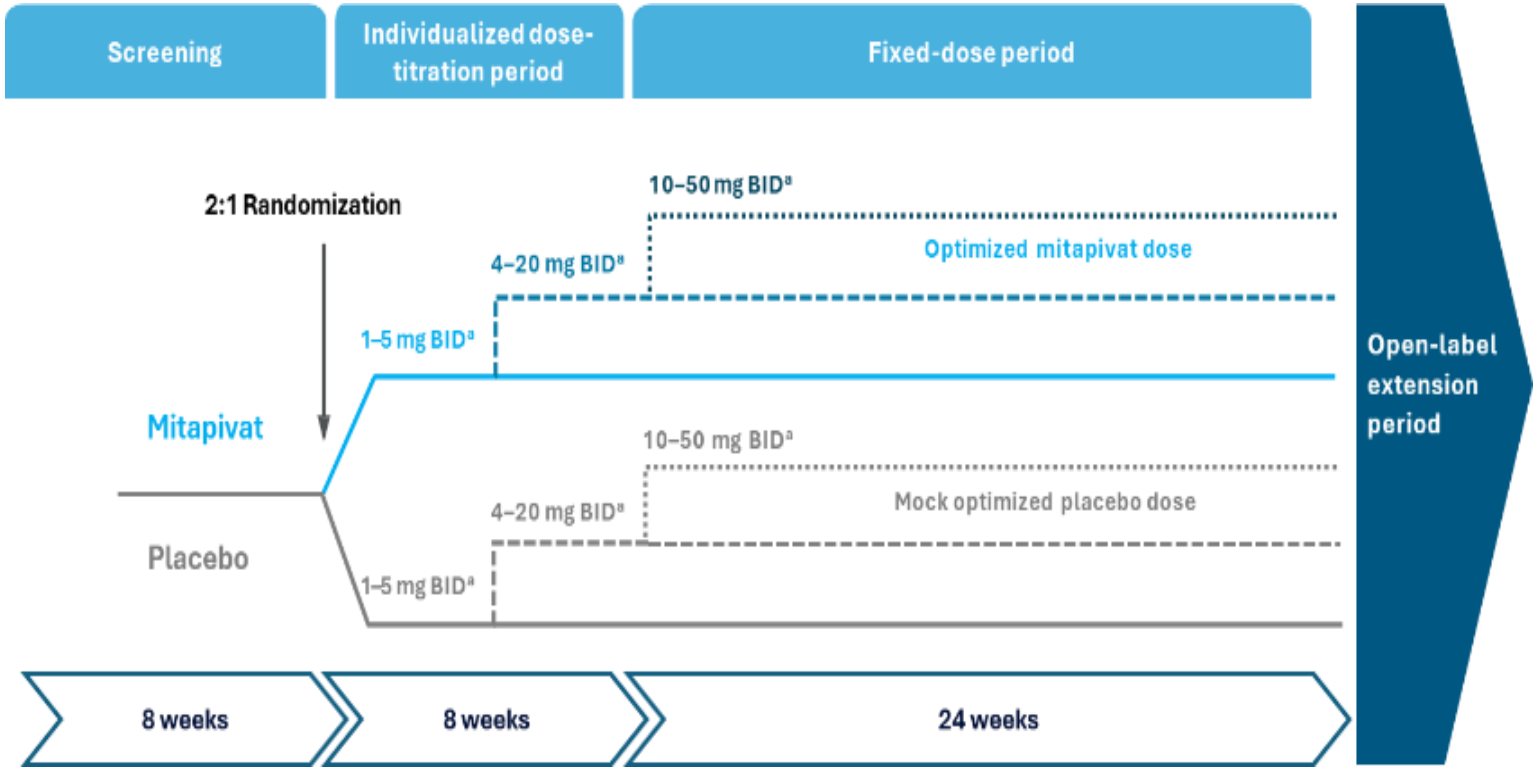
RBC post mitapivat treatment



ATP, adenosine triphosphate; mPKR, mutant PKR; PK, pyruvate kinase; PKM2, pyruvate kinase muscle isoenzyme 2; PKR, pyruvate kinase R; RBC, red blood cell.

ACTIVATE-KidsT is a phase 3, global, multicenter, randomized, double-blind, placebo-controlled study

ACTIVATE-KidsT™



Mitapivat was administered orally (as granules taken with food or tablets swallowed whole) at a dose of 1-50 mg twice daily, depending on age and weight

Key inclusion criteria

- 1 to <18 years of age with central laboratory confirmation of PK deficiency (presence of ≥2 mutant alleles in the *PKLR* gene, of which ≥1 is a missense mutation)
- 6–26 transfusion episodes in the 52-week period before providing informed consent/assent

Key exclusion criteria

- Homozygous for the R479H mutation or have 2 non-missense mutations, without presence of another missense mutation, in the *PKLR* gene

Randomization stratification factors

- Age (1 to <6 years, 6 to <12 years, and 12 to <18 years)
- Splenectomy status (yes, no)

[a]Dose of mitapivat or matched placebo, based on patient's age and weight.
BID, twice daily; PK, pyruvate kinase.

Endpoints

Primary endpoint

- Transfusion reduction response (TRR), defined as a ≥33% reduction in the total RBC transfusion volume from Week 9 through Week 32 normalized by weight and actual study drug duration, compared with the historical transfusion volume standardized by weight and to 24 weeks

Secondary endpoints

- Change from historical transfusion volume, defined as percentage change in weight-normalized and study treatment duration-normalized total transfusion volume during Week 9 through Week 32
- Transfusion-free response, defined as 0 RBC transfusions from Week 9 through Week 32
- Normal Hb response, defined as Hb concentrations in the normal range at least once, 8 weeks or more after a transfusion, during Week 9 through Week 32

Safety endpoints

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

Hb, hemoglobin; RBC, red blood cell.

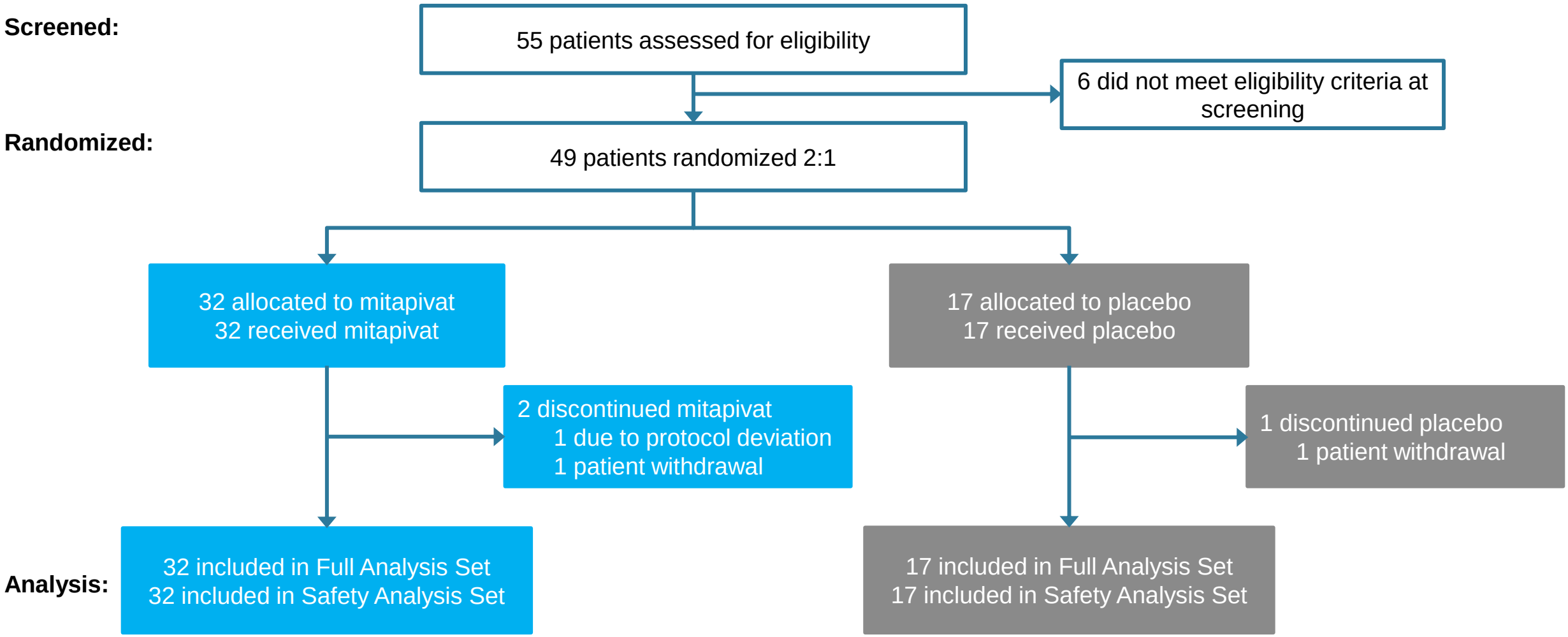
Methods: Bayesian statistical methodology

- The primary endpoint was analyzed using Bayesian methodology that incorporated TRR data from the adult ACTIVATE-T study

- The study would meet the primary endpoint if the lower bound of the 95% credible interval for the odds ratio of TRR rate (mitapivat vs placebo) was >1 for a borrowing weight deemed to be clinically reasonable

TRR, transfusion reduction response.

Patient disposition: 49 patients were randomized in the study



All screened patients: patients who signed informed consent/assent; Full Analysis Set: all patients randomized; patients are classified according to the randomized treatment group; Safety Analysis Set: all patients who received at least 1 dose of study treatment. If a patient randomized to placebo received at least 1 dose of mitapivat in the double-blind period, the patient was classified to the mitapivat arm.

Baseline demographics

Demographics	Mitapivat (N=32)	Placebo (N=17)
Age (years), n (%)		
1 to <6	11 (34.4)	6 (35.3)
6 to <12	13 (40.6)	7 (41.2)
12 to <18	8 (25.0)	4 (23.5)
Female, n (%)	21 (65.6)	9 (52.9)
Childbearing potential, n (%)[a]	7 (33.3)	1 (11.1)
Race, n (%)		
White	28 (87.5)	15 (88.2)
American Indian or Alaska Native	1 (3.1)	1 (5.9)
Multiracial	1 (3.1)	0
Unknown	0	1 (5.9)
Not reported	2 (6.3)	0
Region, n (%)		
Middle East	10 (31.3)	8 (47.1)
North America	12 (37.5)	5 (29.4)
Western Europe	9 (28.1)	3 (17.6)
Eastern Europe	1 (3.1)	1 (5.9)

[a]The childbearing potential % is calculated based on the number of female subjects in the full analysis set within each treatment group.
No statistical comparisons were made between treatment groups for baseline demographics and disease characteristics.

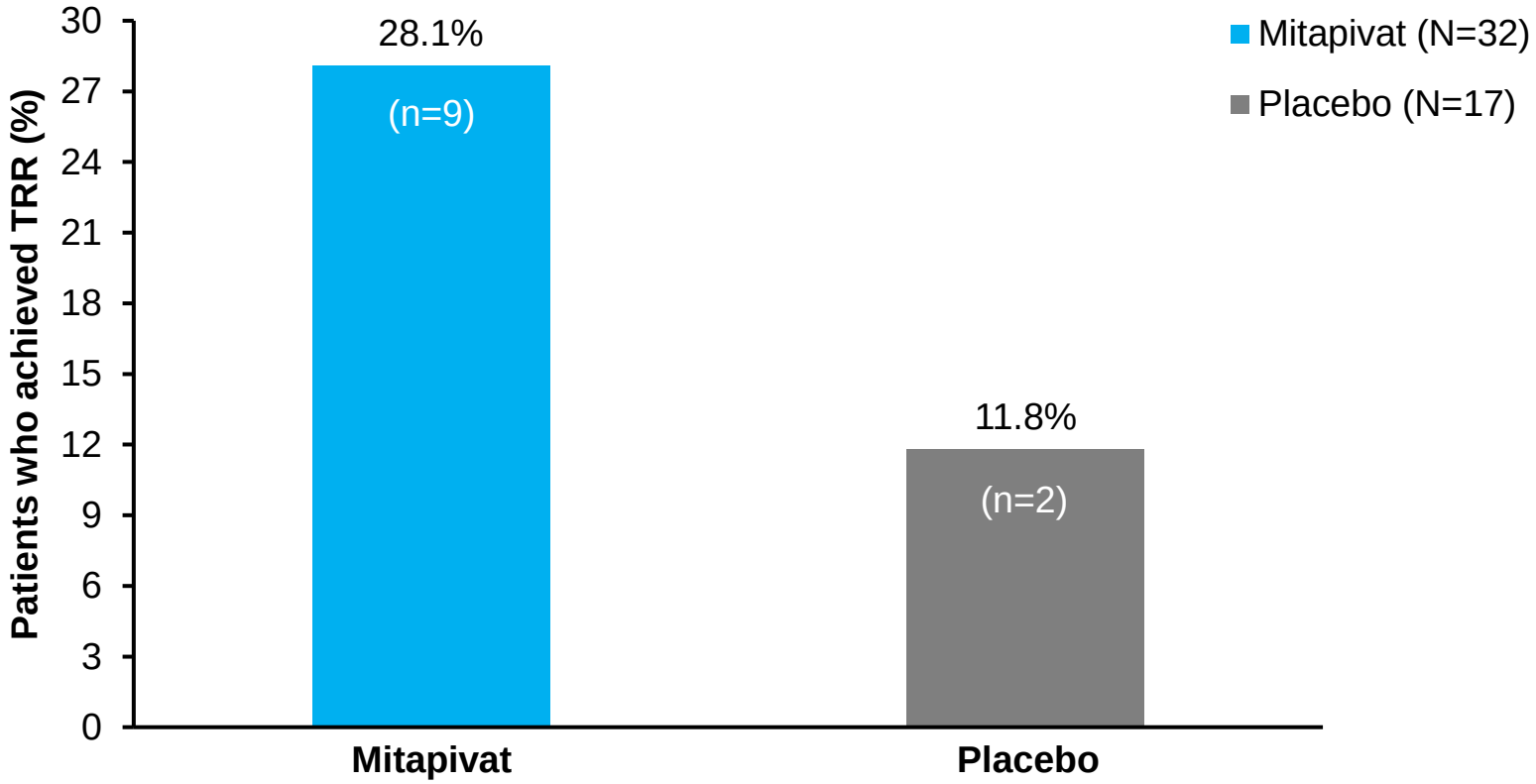
Baseline disease characteristics and transfusion history

Disease characteristics	Mitapivat (N=32)	Placebo (N=17)
Mutation category, n (%)		
Missense/missense	21 (65.6)	9 (52.9)
Missense/non-missense	11 (34.4)	8 (47.1)
Splenectomy status,[a] n (%)		
No	28 (87.5)	16 (94.1)
Yes	4 (12.5)	1 (5.9)
Prior cholecystectomy status,[a] n (%)		
No	29 (90.6)	15 (88.2)
Yes	3 (9.4)	2 (11.8)
Prior iron chelation status,[a,b] n (%)		
No	5 (15.6)	3 (17.6)
Yes	27 (84.4)	14 (82.4)
Pretransfusion Hb threshold, mean (SD),[c] (g/dL)	8.11 (1.081)	8.19 (0.649)
Pretransfusion Hb threshold category,[c] n (%)		
<8.5 g/dL	19 (59.4)	8 (47.1)
≥8.5 g/dL	13 (40.6)	9 (52.9)
Transfusion history during the 52-week period before informed consent/assent		
Number of transfusion episodes,[d] mean (SD)	11.5 (4.22)	13.3 (3.51)
Number of transfusion episodes standardized to 24 weeks,[d] mean (SD)	5.32 (1.948)	6.14 (1.622)
Number of transfusion episodes standardized to 24 weeks categories,[d] n (%)		
≤6	22 (68.8)	6 (35.3)
>6	10 (31.3)	11 (64.7)
Volume of RBC transfused standardized by weight and to 24 weeks (mL/kg), mean (SD)	74.79 (32.958)	85.67 (23.439)

[a]As recorded in prior and concomitant procedures eCRF; [b]'Yes' if a patient received chelation therapy within 365 days before randomization for patients randomized and not dosed or before start of study treatment for patients randomized and dosed; [c]A pretransfusion Hb threshold is determined for each patient based on transfusion history and is defined as the mean of all documented pretransfusion Hb concentration values recorded for the RBC transfusions administered during the 52-week period before informed consent/assent; [d]Transfusions received over up to 3 consecutive days are counted as one episode. eCRF, electronic case report form; Hb, hemoglobin; RBC, red blood cell; SD, standard deviation.

A greater number of patients achieved a transfusion reduction response in the mitapivat arm than in the placebo arm

Primary endpoint



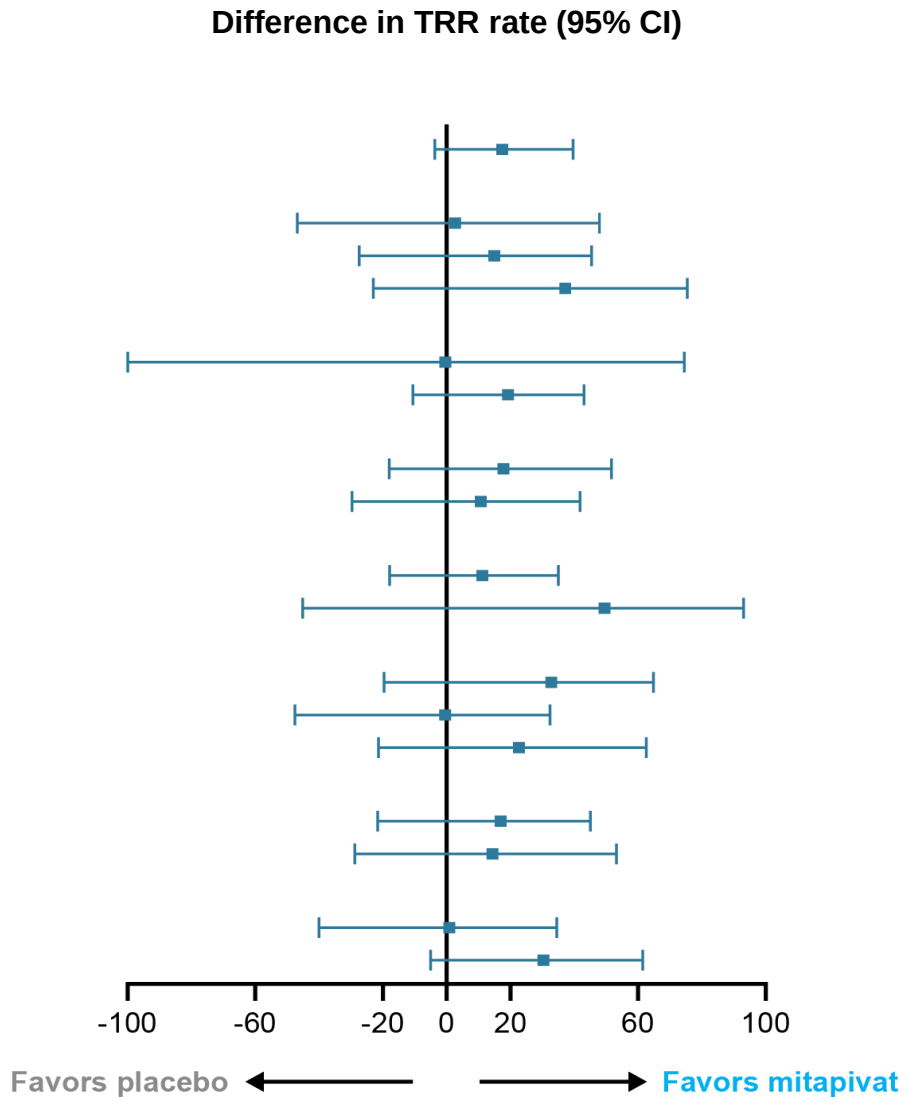
The prespecified statistical criterion for the primary endpoint (TRR) was not met with low or moderate borrowed information from the adult ACTIVATE-T study

Analysis conducted on Full Analysis Set. TRR is defined as a a ≥33% reduction in the total RBC transfusion volume from Week 9 through Week 32 normalized by weight and actual study drug duration, compared with the historical transfusion volume standardized by weight and to 24 weeks. TRR, transfusion reduction response; RBC, red blood cell.

Reduction in transfusion burden was not driven by prespecified subgroups

Subgroup analysis of primary endpoint

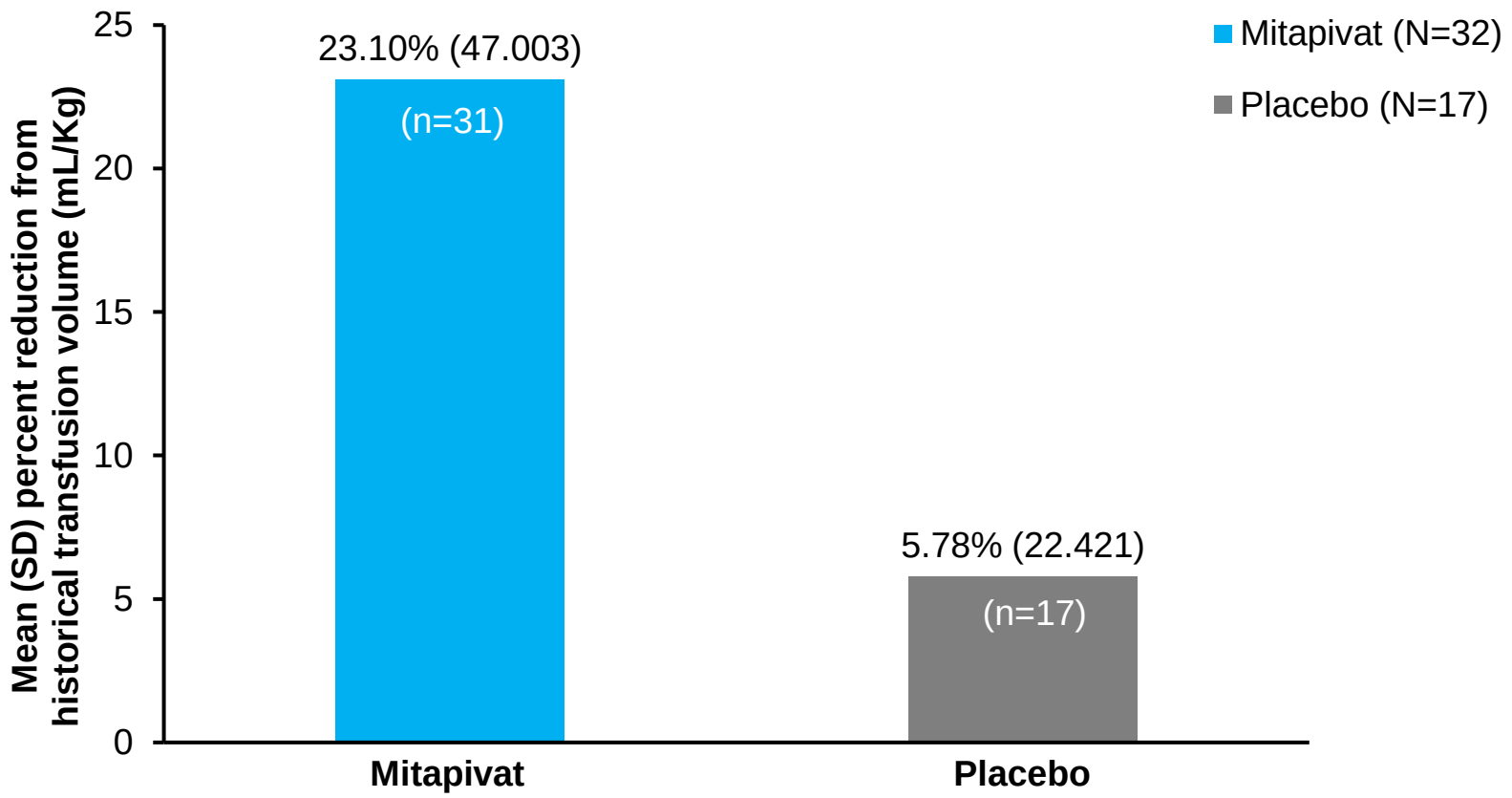
Subgroup	TRR response rate, % (n/N) Placebo	Mitapivat	Difference (95% CI)[b]
All patients (stratified)[a]	11.8 (2/17)	28.1 (9/32)	18.1 (–3.6, 39.8)
Age category			
1 to <6 years	33.3 (2/6)	36.4 (4/11)	3.0 (–46.7, 48.1)
6 to <12 years	0 (0/7)	15.4 (2/13)	15.4 (–27.4, 45.5)
12 to <18 years	0 (0/4)	37.5 (3/8)	37.5 (–23.1, 75.5)
Splenectomy status			
Yes	0 (0/1)	0 (0/4)	0.0 (–100, 74.8)
No	12.5 (2/16)	32.1 (9/28)	19.6 (–10.5, 43.1)
Sex			
Male	0 (0/8)	18.2 (2/11)	18.2 (–18.0, 51.8)
Female	22.2 (2/9)	33.3 (7/21)	11.1 (–29.6, 42.1)
Race			
White	13.3 (2/15)	25.0 (7/28)	11.7 (–17.9, 35.0)
Other	0 (0/2)	50.0 (2/4)	50.0 (–45.2, 93.2)
Geographic region			
North America	0 (0/5)	33.3 (4/12)	33.3 (–19.6, 65.1)
Western Europe	0 (0/3)	0 (0/9)	0.0 (–47.5, 32.5)
Rest of world	22.2 (2/9)	45.5 (5/11)	23.2 (–21.3, 62.6)
Mutation category			
Missense/missense	11.1 (1/9)	28.6 (6/21)	17.5 (–21.7, 45.1)
Missense/non-missense	12.5 (1/8)	27.3 (3/11)	14.8 (–28.8, 53.4)
Pretransfusion Hb threshold			
<8.5 g/dL	25.0 (2/8)	26.3 (5/19)	1.3 (–40.2, 34.7)
≥8.5 g/dL	0 (0/9)	30.8 (4/13)	30.8 (–5.0, 61.6)



Analysis conducted on Full Analysis Set. TRR is defined as a a ≥33% reduction in the total RBC transfusion volume from Week 9 through Week 32 normalized by weight and actual study drug duration, compared with the historical transfusion volume standardized by weight and to 24 weeks. [a]Stratified by age group and splenectomy status; [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; Hb, hemoglobin; TRR, transfusion reduction response.

Percent reduction from historical transfusion volume was greater in the mitapivat arm compared to the placebo arm

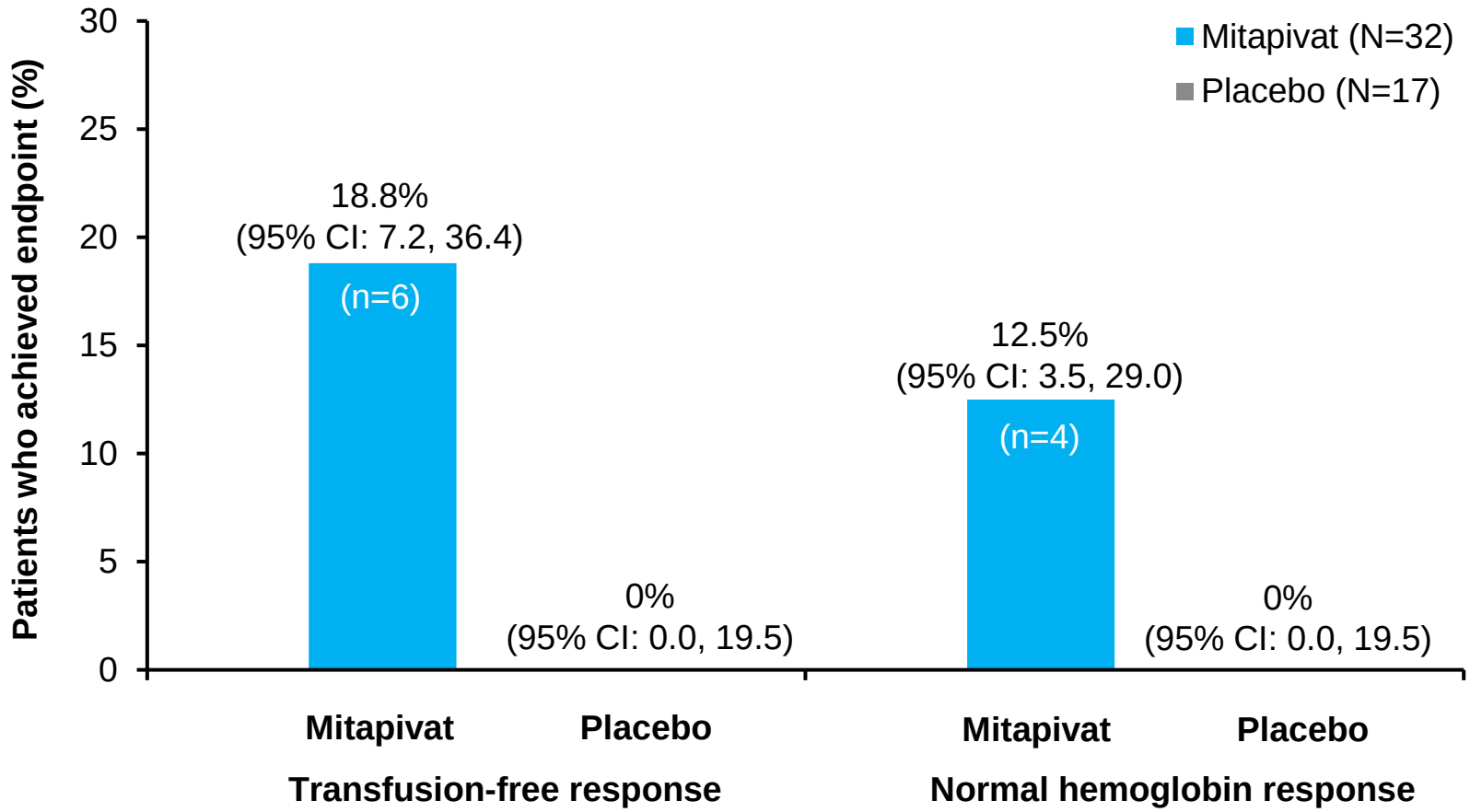
Secondary endpoint



n is the number of patients in the Full Analysis Set for baseline or the number of patients in the Full Analysis Set who did not discontinue the study before Week 9 of the double-blind period for post-baseline change from baseline summaries.Percent reduction is calculated based on the total transfusion volume standardized by weight and up to 24 weeks. For patients who discontinued before completing at least 12 weeks of study treatment starting from Week 8, the percentage change in weight-normalized and study treatment-duration normalized total transfusion volume is reported based on the data as collected. SD, standard deviation.

Transfusion-free and normal Hb responses were only observed in the mitapivat arm

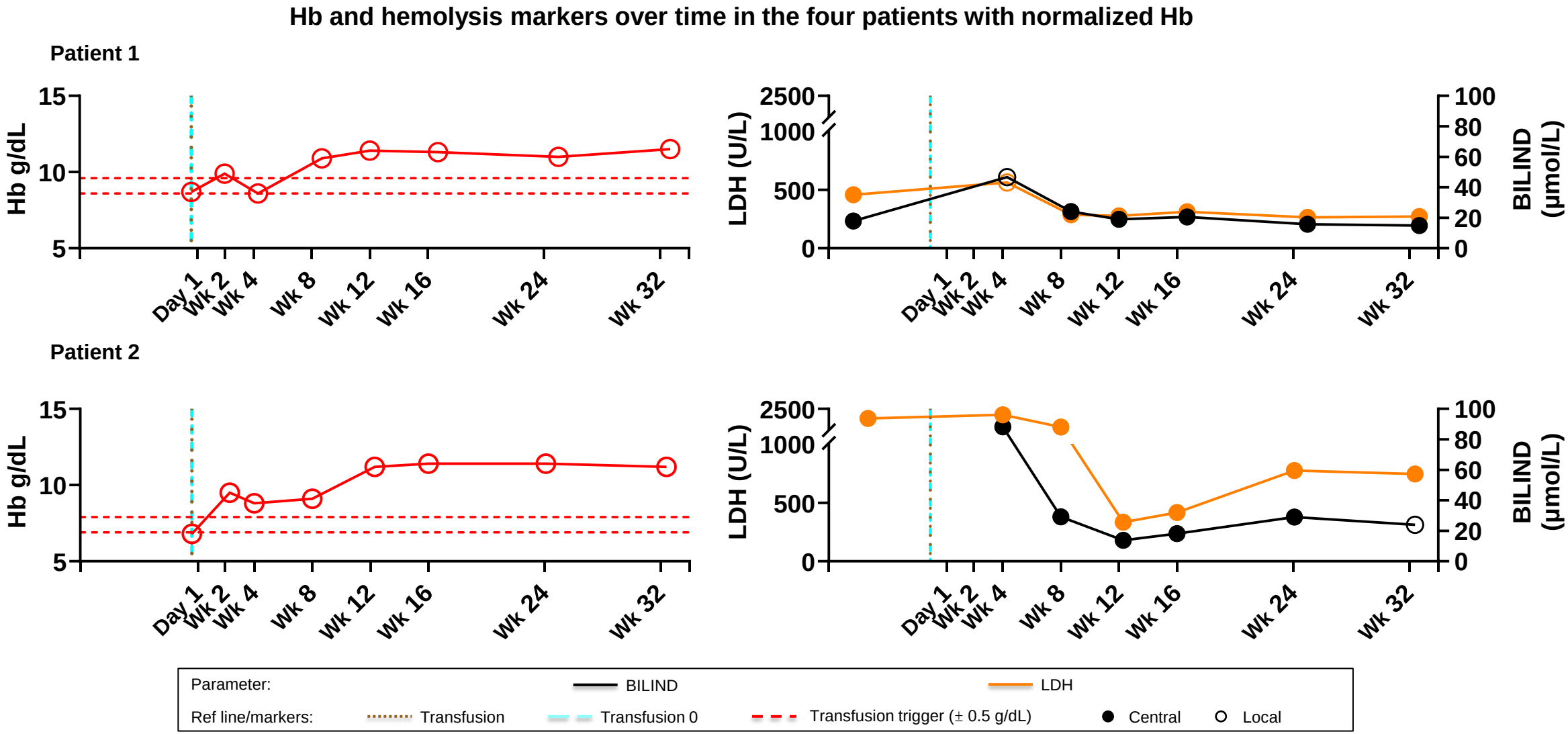
Secondary endpoints



A higher proportion of children in the mitapivat group achieved transfusion-free response (18.8%) and normal Hb response (12.5%) than no children in the placebo group through Week 32 of the double-blind period

Analysis conducted on Full Analysis Set. Transfusion-free response is defined as 0 RBC transfusions from Week 9 through Week 32. Normal Hb response, defined as achievement of Hb concentrations in the normal range at least once, 8 weeks or more after a transfusion, during Week 9 through Week 32 of the double-blind period.
CI, confidence interval; Hb, hemoglobin; RBC, red blood cell.

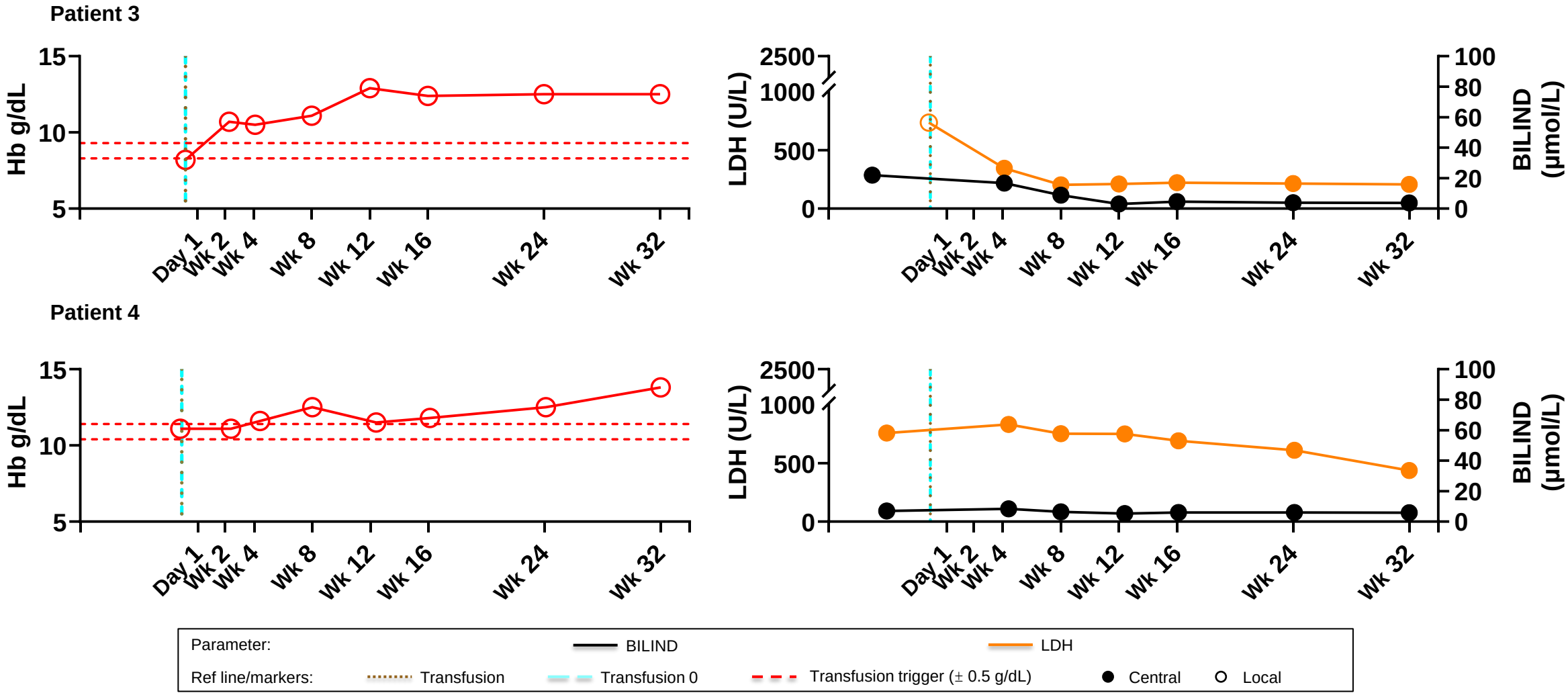
Mitapivat has the potential to normalize Hb levels and improve markers of hemolysis in transfusion-free responders[a]



[a]Defined as a patient who was transfusion free between Week 9 through Week 32 of the double-blind period. Transfusion-free response is defined as 0 RBC transfusions from Week 9 through Week 32. Normal Hb response, defined as achievement of Hb concentrations in the normal range at least once, 8 weeks or more after a transfusion, during Week 9 through Week 32 of the double-blind period.
BILIND, indirect bilirubin; Hb, hemoglobin; LDH, lactate dehydrogenase; Wk, week.

Mitapivat has the potential to normalize Hb levels and improve markers of hemolysis in transfusion-free responders[a]

Hb and hemolysis markers over time in the four patients with normalized Hb



[a]Defined as a patient who was transfusion free between Week 9 through Week 32 of the double-blind period. Transfusion-free response is defined as 0 RBC transfusions from Week 9 through Week 32. Normal Hb response, defined as achievement of Hb concentrations in the normal range at least once, 8 weeks or more after a transfusion, during Week 9 through Week 32 of the double-blind period.
BILIND, indirect bilirubin; Hb, hemoglobin; LDH, lactate dehydrogenase; Wk, week.

Summary of safety

Safety endpoint

Patients, n (%)	Mitapivat (N=32)	Placebo (N=17)
Any treatment-emergent adverse events (TEAEs)	28 (87.5)	14 (82.4)
Grade ≥3 TEAEs	8 (25.0)	2 (11.8)
Treatment-related TEAEs	8 (25.0)	4 (23.5)
Grade ≥3 treatment-related TEAEs	2 (6.3)	0
Serious TEAEs	5 (15.6)[a]	2 (11.8)[b]
Serious treatment-related TEAEs	1 (3.1)	0
TEAEs leading to discontinuation of study drug	0	0
TEAEs leading to dose reduction	1 (3.1)	0
TEAEs leading to interruption of study drug	1 (3.1)	0
TEAEs leading to death	0	0

Analysis conducted on Safety Analysis Set. [a]Serious TEAEs with mitapivat were cholelithiasis, bile duct stone, appendicitis, large intestine infection, anemia, hemolysis, and procedural pain. [b]Serious TEAEs with placebo were cholelithiasis and gastroenteritis. Patients with multiple serious TEAEs within an organ system class are counted only once in the overall number of serious TEAEs.

Most frequently reported TEAEs (any Grade in ≥10% patients or Grade ≥3 in ≥5% patients in the mitapivat treatment group)

Safety endpoint

	Mitapivat (N=32)		Placebo (N=17)	
Preferred Term, n (%)	Any grade	Grade ≥3	Any grade	Grade ≥3
Patients with events	28 (87.5)	8 (25.0)	14 (82.4)	2 (11.8)
Cough	6 (18.8)	0	4 (23.5)	0
Pyrexia	6 (18.8)	0	1 (5.9)	0
Upper respiratory tract infection	5 (15.6)	0	4 (23.5)	0
Headache	4 (12.5)	0	7 (41.2)	0
Gastroenteritis	4 (12.5)	0	2 (11.8)	0
Alanine aminotransferase increased	4 (12.5)	0	1 (5.9)	1 (5.9)
Otitis media	4 (12.5)	0	1 (5.9)	0
Pain in extremity	4 (12.5)	0	1 (5.9)	0
Anemia	2 (6.3)	2 (6.3)	0	0
Blood bilirubin increased	2 (6.3)	2 (6.3)	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 group. CTCAE v4.03 used. CTCAE, Common Terminology Criteria for Adverse Event; TEAE, treatment-emergent adverse event.

Summary

- The observed response rates were higher for children (1 to <18 years of age) in the mitapivat treatment arm than in the placebo arm for transfusion reduction response; however, the prespecified statistical criterion for the primary endpoint was not met
- A higher proportion of children in the mitapivat group achieved transfusion-free response (18.8%) and normal Hb response (12.5%) compared to 0% in the placebo group through Week 32 of the double-blind period
- Mitapivat, in tablet and pediatric granule formulation, was generally well tolerated in children, with a low treatment discontinuation rate and no new safety signals reported

In ACTIVATE-KidsT, treatment with mitapivat resulted in clinically meaningful improvements in transfusion burden, offering the potential to provide therapeutic benefit in pediatric patients with PK deficiency

Hb, hemoglobin; PK, pyruvate kinase.

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Supplemental materials are available via the QR code