ACTIVATE-T: A Phase 3, Open-label, Multicenter Study Of Mitapivat In Adults With Pyruvate Kinase Deficiency Who Are Regularly Transfused

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  - **Andreas Glenthøj**: Agios, bluebird bio, Celgene, Novartis – consultancy and advisory board member; Alexion – research grant; Novo Nordisk – honoraria
  - **Eduard J. van Beers**: Agios – advisory board member; Agios, Novartis, Pfizer, RR Mechatronics – research funding
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  - **Kevin H. M. Kuo**: Agios, Alexion, Apellis, bluebird bio, Celgene, Pfizer, Novartis – consultancy; Alexion, Novartis – honoraria; Bioverativ – membership on an entity's Board of Directors or advisory committees; Pfizer – research funding
  - **Frédéric Galactéros**: Addmedica – board membership or advisory committee
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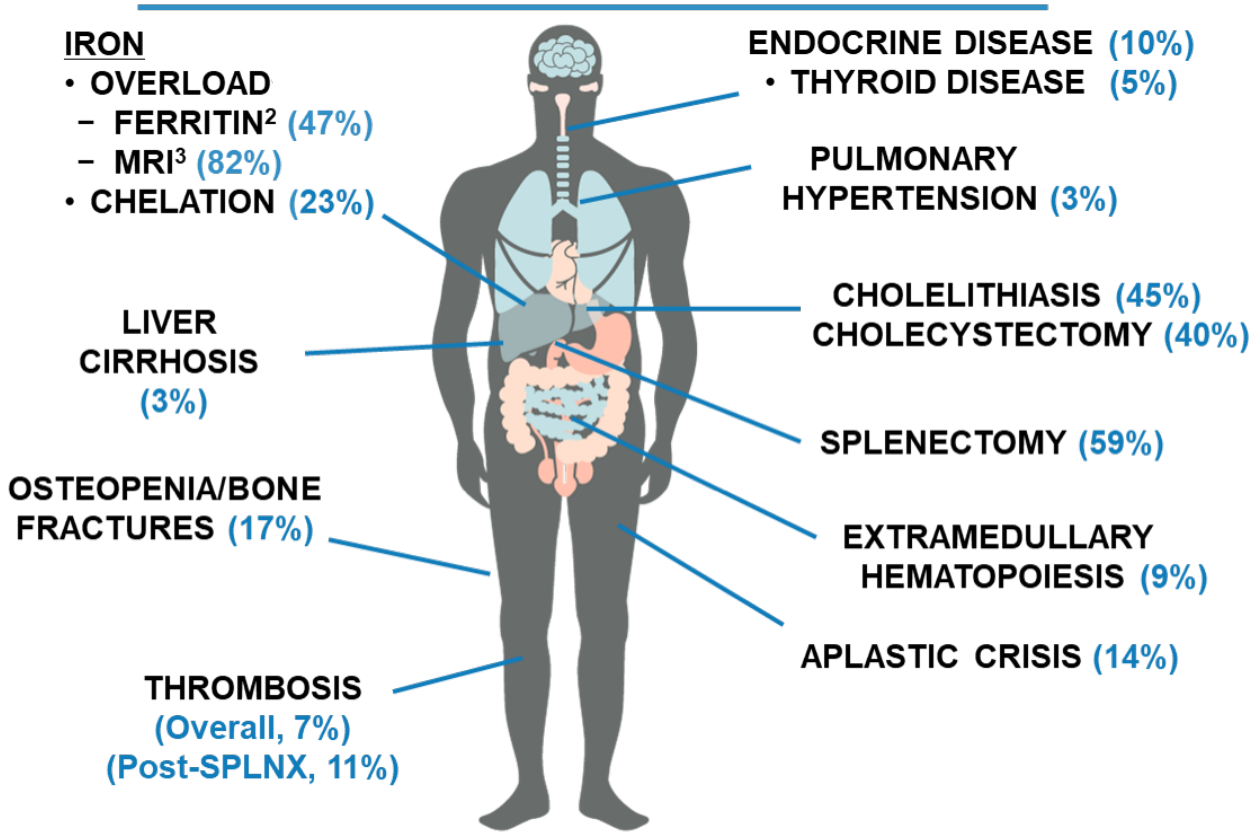
  - **John Porter**: No affiliations
  - **Sarah Gheuens, Vanessa Beynon, Emily Xu, Peter Hawkins, Erin Zagadailov**, and **Abdulafeez Oluyadi**: Agios – employees and shareholders
  - **W. Barcellini**: Agios, Alexion, Novartis – honoraria; Agios – research funding; Bioverativ, Incyte – board membership or advisory committee

Pyruvate kinase deficiency – disease overview

- Underrecognized, rare, hereditary chronic hemolytic anemia[1,2]
  - Characterized by mutations in the *PKLR* gene encoding PKR, which is critical for maintaining RBC energy levels and morphology, with defects in PKR causing chronic hemolysis[1–4]
- Associated with serious complications and a poor quality of life[3–6]
  - Current management strategies including RBC transfusions and splenectomy, are associated with both short- and long-term risks[3,7]
  - Regular transfusions are associated with iron overload and end organ damage[3,7]
- There are no approved disease-modifying drug therapies for PK deficiency

Comorbidities and long-term complications are common and affect multiple organ systems[6]

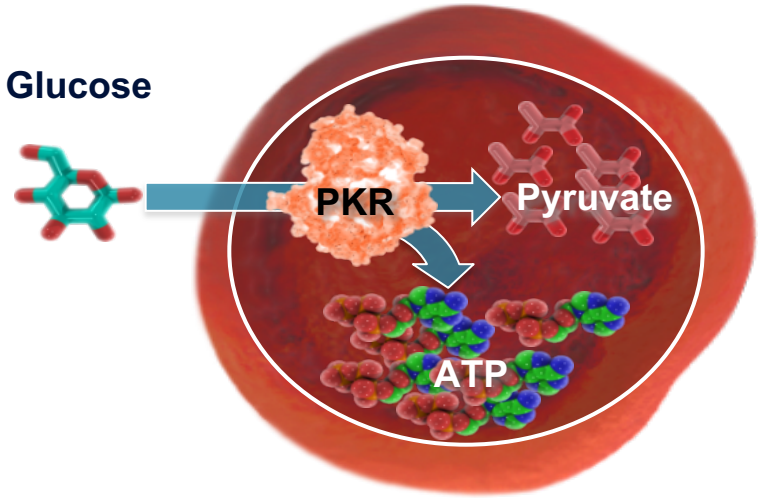


MRI = magnetic resonance imaging; PK = pyruvate kinase; PKR = PK in RBCs; *PKLR* = gene encoding the pyruvate kinase liver and red blood cell isozymes; RBC = red blood cell.

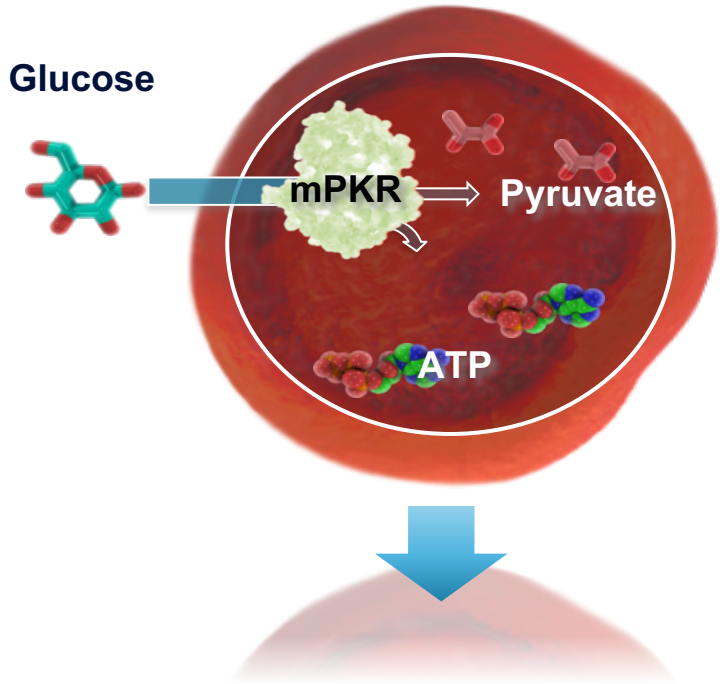
1. Grace RF, et al. *Am J Hematol*. 2015;90:825–30; **2.** Zanella A, et al. *Br J Haematol*. 2005;130:11–25; **3.** Grace RF, et al. *Blood*. 2018;131:2183–92; **4.** van Beers EJ, et al. *Haematologica*. 2019;104:e51–e3; **5.** Boscoe AN, et al. *EJH*. 2020;106:484–92; **6.** Grace RF, et al. *Eur J Haematol*. 2018;101:758–765; **7.** Grace RF, et al. *Br J Haematol*. 2019;184:721–34.

Mitapivat, an oral pyruvate kinase activator

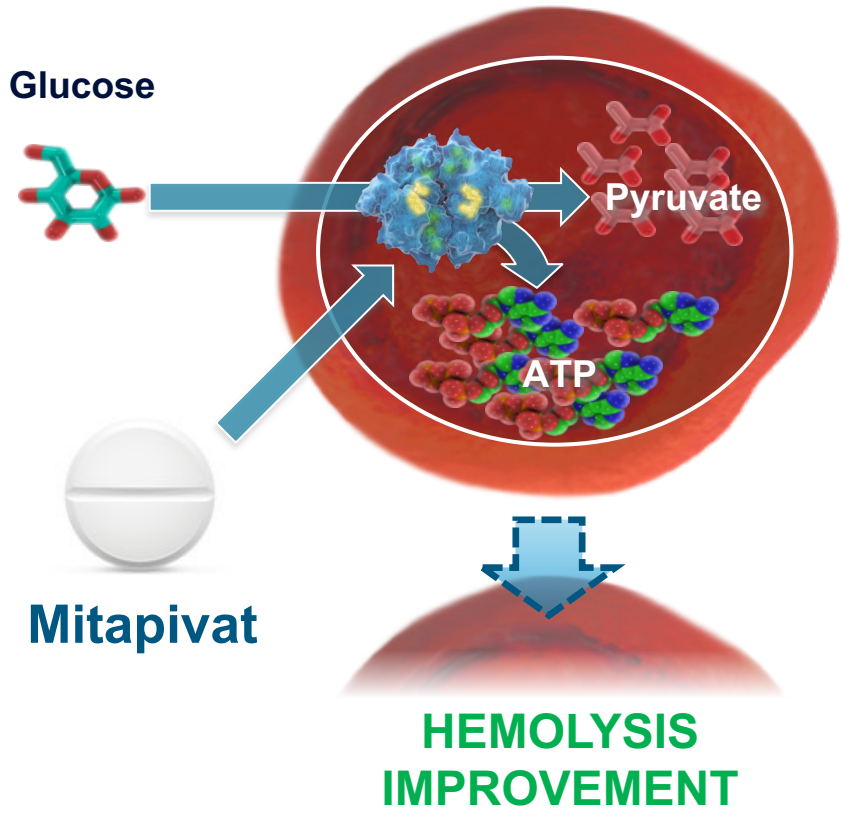
Healthy RBC, wild-type PKR



PK-deficient RBC, mPKR



RBC Post Mitapivat Treatment



ATP = adenosine triphosphate; Hb = hemoglobin; mPKR = mutant PKR; PK = pyruvate kinase; PKR = red blood cell-specific form of pyruvate kinase; RBC = red blood cell.

ACTIVATE-T was a Phase 3, open-label study that evaluated the efficacy and safety of mitapivat in adult patients with PK deficiency who were regularly transfused

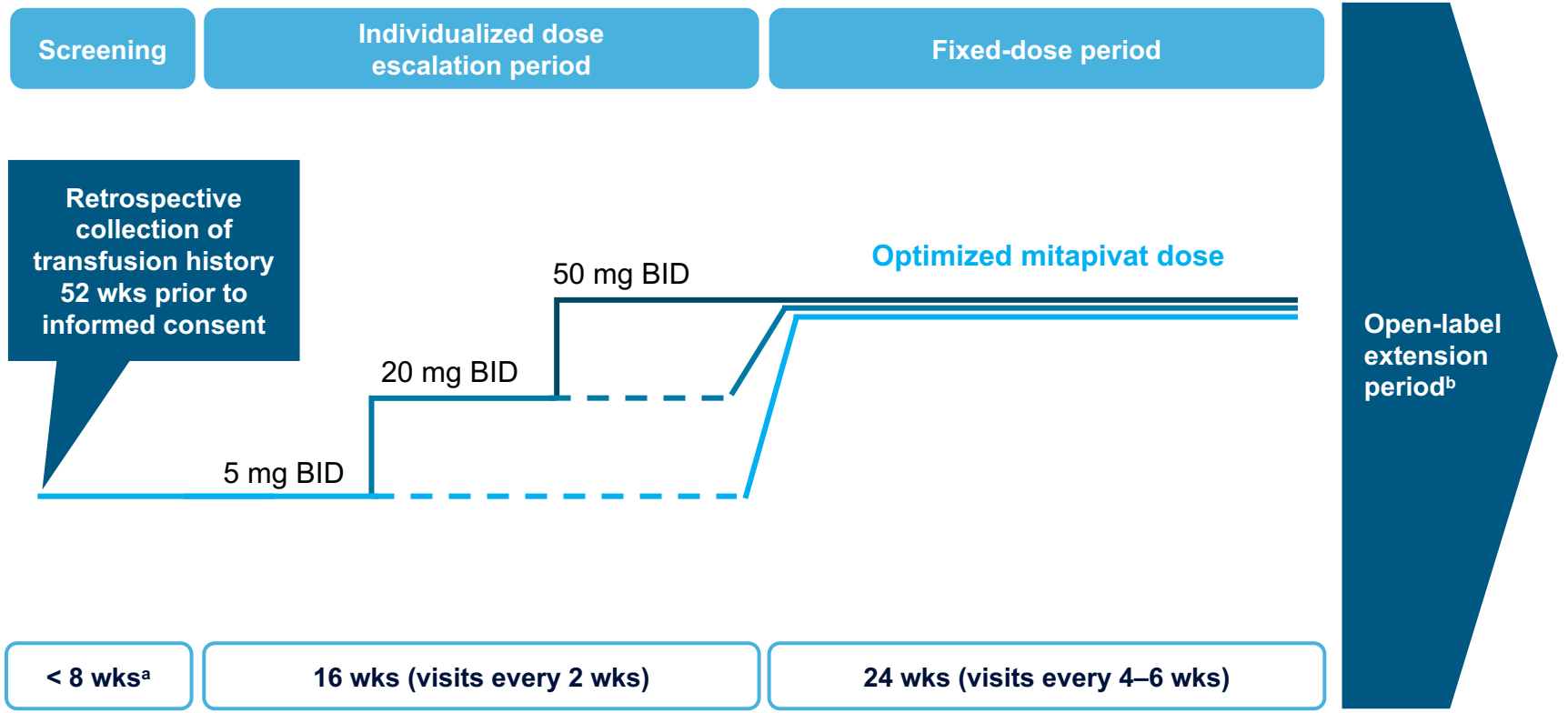
ACTIVATE-T

Key eligibility criteria:

- ≥ 18 yrs of age
- Documented ≥ 2 mutant alleles in *PKLR* (≥ 1 missense mutation)
- ≥ 6 transfusion episodes in the past 1 yr
- Complete records of transfusion history for the 52 wks prior to informed consent form
- Adequate organ function

Key exclusion criteria:

- Homozygous for R479H mutation or have 2 non-missense mutations, without another missense mutation, in *PKLR*
- > 1 transfusion episode every 3 wks in the past 1 yr
- Splenectomy during study, or within 12 months of enrollment



NB: ACTIVATE-T, ClinicalTrials.gov NCT03559699; [a]Screening may be extended beyond 8 wks if there is a delay in obtaining a patient's complete transfusion history or to ensure that the first dose of study drug can be administered 2–7 days after the most recent transfusion; [b]All patients who remain on study during Part 2 through the Week 24 visit may be eligible for an open-label extension study with mitapivat.
BID = twice daily; PK = pyruvate kinase; *PKLR* = gene encoding the pyruvate kinase liver and red blood cell isozymes; wks = weeks; yrs = years.

Primary and secondary efficacy endpoints

Primary Efficacy Endpoint: Achievement of transfusion burden reduction

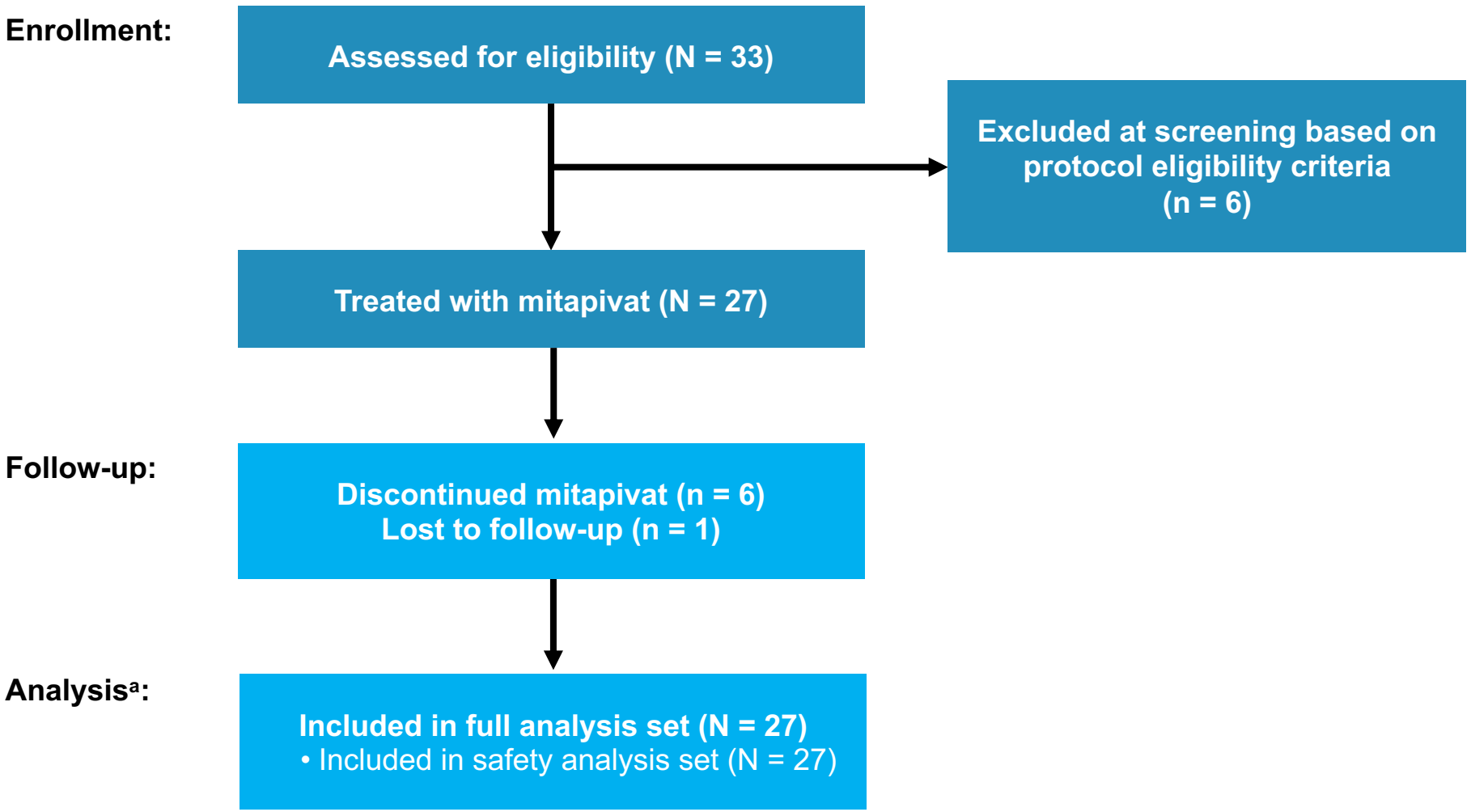
- Defined as a ≥ 33% reduction in the number of RBC units transfused during the fixed-dose period, compared with the patient's individual historical transfusion burden standardized to 24 wks

- **Secondary Efficacy Endpoints:**
  - Annualized total number of RBC units transfused during the study compared with the historical transfusion burden
  - Number of transfusion episodes during the fixed-dose period compared with the historical transfusion burden standardized to 24 wks
  - Becoming transfusion-free, defined as no transfusions during the fixed-dose period
  - Achieving Hb concentrations in the normal range at least once, 8 wks or more after a transfusion in the fixed-dose period

- **Exploratory Efficacy Endpoints:**
  - Change in markers of hemolysis including reticulocyte fraction, haptoglobin, LDH and indirect bilirubin
  - Change from baseline in PKDIA and PKDD, which are novel PK deficiency-specific patient-reported outcomes (PROs), developed to assess and capture changes in symptom burden and HRQoL impact in PK deficiency
    - For both PROs a higher score indicates more severe disease impact

AE = adverse events; Hb = hemoglobin; HRQoL = health-related quality of life; LDH = lactate dehydrogenase; PK = pyruvate kinase; PKDD = PK deficiency diary; PKDIA = PK deficiency impact assessment; PRO = patient-reported outcomes; RBC = red blood cells; wks = weeks.

Patient disposition



[a]Analysis set definitions: full and safety analysis sets included all patients who received at least 1 dose of mitapivat.

Patient demographics

Patient demographics	Total (N = 27)
Age (years)	
Median (range)	36.0 (18–68)
< 35, n (%)	13 (48.1)
≥ 35, n (%)	14 (51.9)
Sex, n (%)	
Male	7 (25.9)
Female	20 (74.1)
Race, n (%)	
White	20 (74.1)
Asian	3 (11.1)
America Indian or Alaska Native	0
Black or African American	0
Native Hawaiian or Other Pacific Islander	0
Not reported	4 (14.8)
Region, n (%)	
Western Europe	21 (77.8)
North America	4 (14.8)
Asia	2 (7.4)

Baseline characteristics

Baseline characteristics	Total (N = 27)
Hb (g/dL), mean (SD)	9.2 (0.98)
Ferritin (µg/L), mean (SD)[a]	1153.7 (1221.41)
Prior splenectomy, n (%)	21 (77.8)
Prior cholecystectomy, n (%)	23 (85.2)
Prior chelation therapy, n (%)[b]	24 (88.9)
DXA T-Score, mean (SD)[c]	
Femoral total[d]	–1.1 (0.83)
Adjusted spine	–1.4 (1.17)
***PKLR* mutation category, n (%)**	
Missense/Missense	20 (74.1)
Missense/Non-missense	7 (25.9)

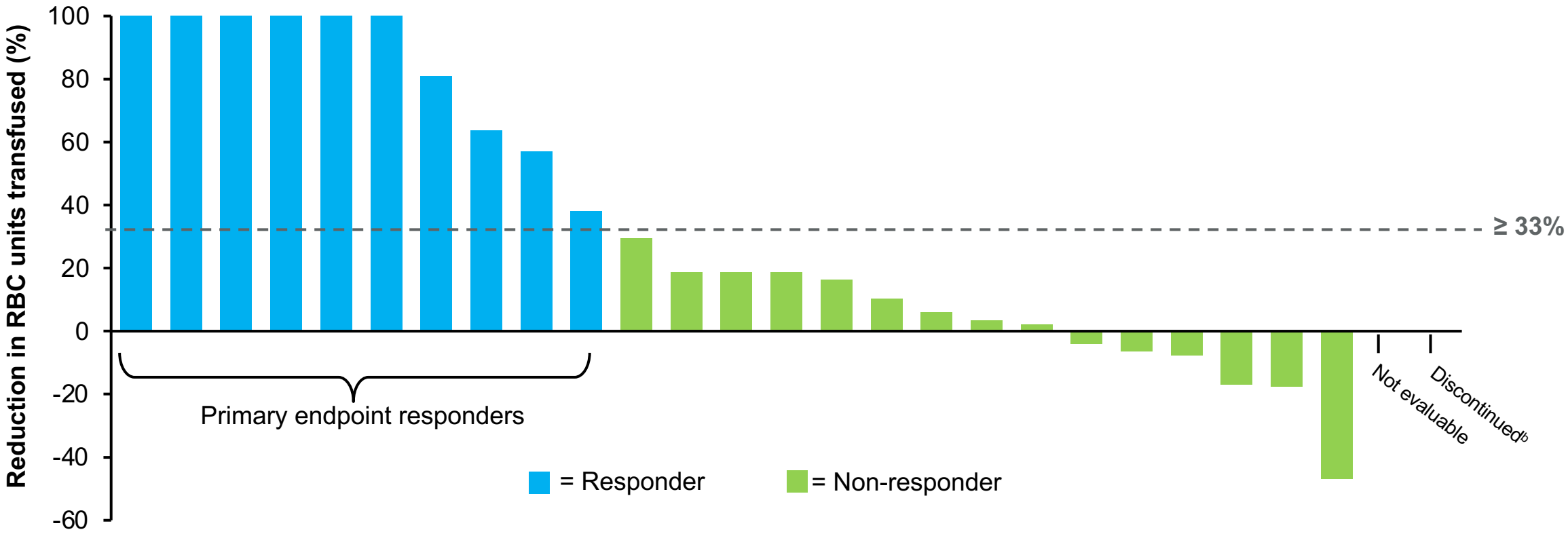
Transfusion history during 52 wks before Informed Consent	Total (N = 27)
No. RBC transfusion episodes[e], mean (SD)	9.7 (3.62)
No. RBC transfusion episodes[e], standardized to 24 wks, mean (SD)	4.5 (1.67)
No. RBC transfusion episodes[e], standardized to 24 wks, category	
≤ 6, n (%)	22 (81.5)
> 6, n (%)	5 (18.5)
No. RBC units transfused, mean (SD)	16.6 (8.63)
No. RBC units transfused, standardized to 24 wks, mean (SD)	7.7 (3.98)
No. RBC units transfused, standardized to 24 wks, category	
≤ 6, n (%)	12 (44.4)
> 6, n (%)	15 (55.6)

N is the number of subjects who received at least one dose of mitapivat; [a]evaluable patients for baseline ferritin, n = 18; [b]'Yes' if a patient has received chelation therapy within 52 wks (364 days) before first dose of study treatment; [c]evaluable patients for baseline DXA T-scores and bone mineral densities, n = 26; [d]femoral neck and total hip combined; [e]Transfusions received over up to 3 consecutive days are counted as one episode.
DXA = dual-energy x-ray absorptiometry; Hb = hemoglobin; LDH = lactate dehydrogenase; PKLR = gene encoding the pyruvate kinase liver and red blood cell isozymes; SD = standard deviation; wks = weeks.

Mitapivat met the primary endpoint, demonstrating a significant reduction in transfusion burden

10 patients (37%; 95% CI: 19–58) achieved a reduction in transfusion burden (1-sided p = 0.0002[a])

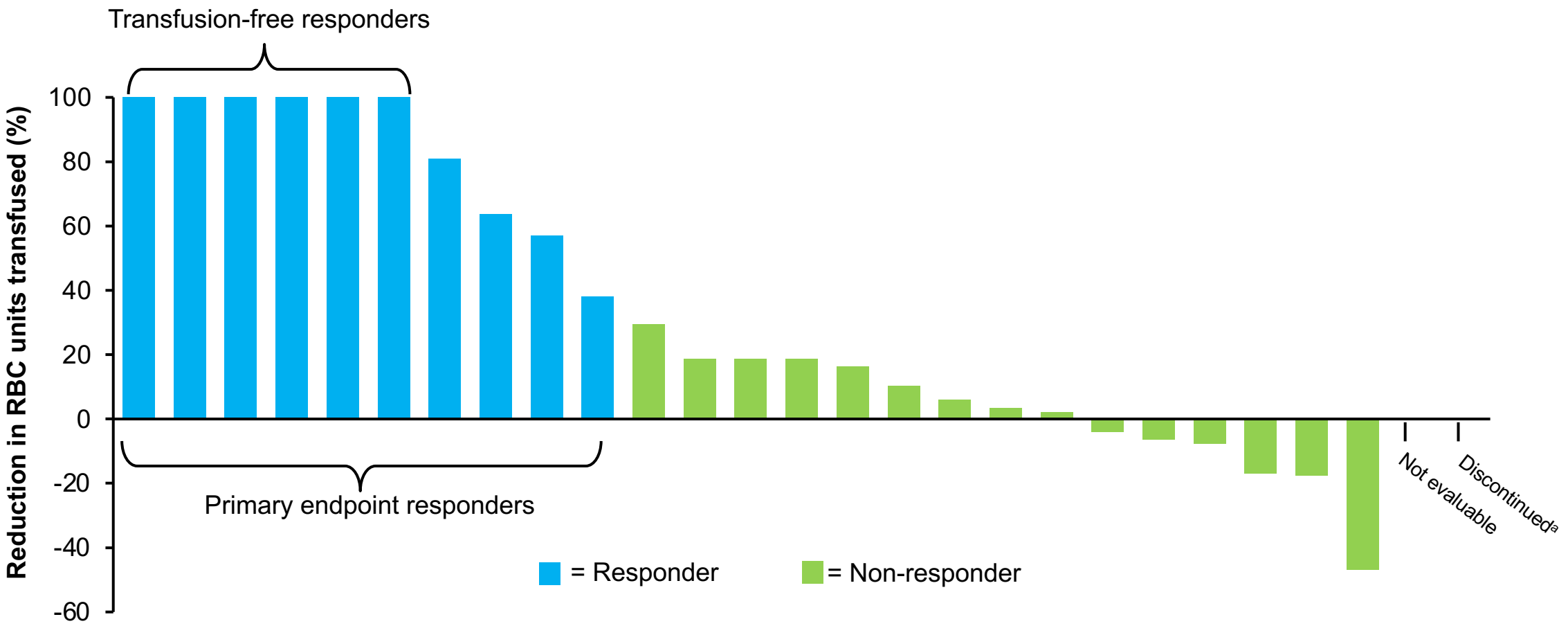
9 patients (33%) achieved ≥ 50% reduction in total number of RBC units transfused



[a]The p-value is based on the binomial exact test of H0: transfusion reduction response rate ≤ 10% vs. H1: transfusion reduction response rate > 10% at a 1-sided α = 0.025; [b]Patients who discontinued the study before completing 12 wks of treatment in the fixed-dose period were considered non-responders
CI = confidence interval; RBC = red blood cells.

Transfusion-free responders

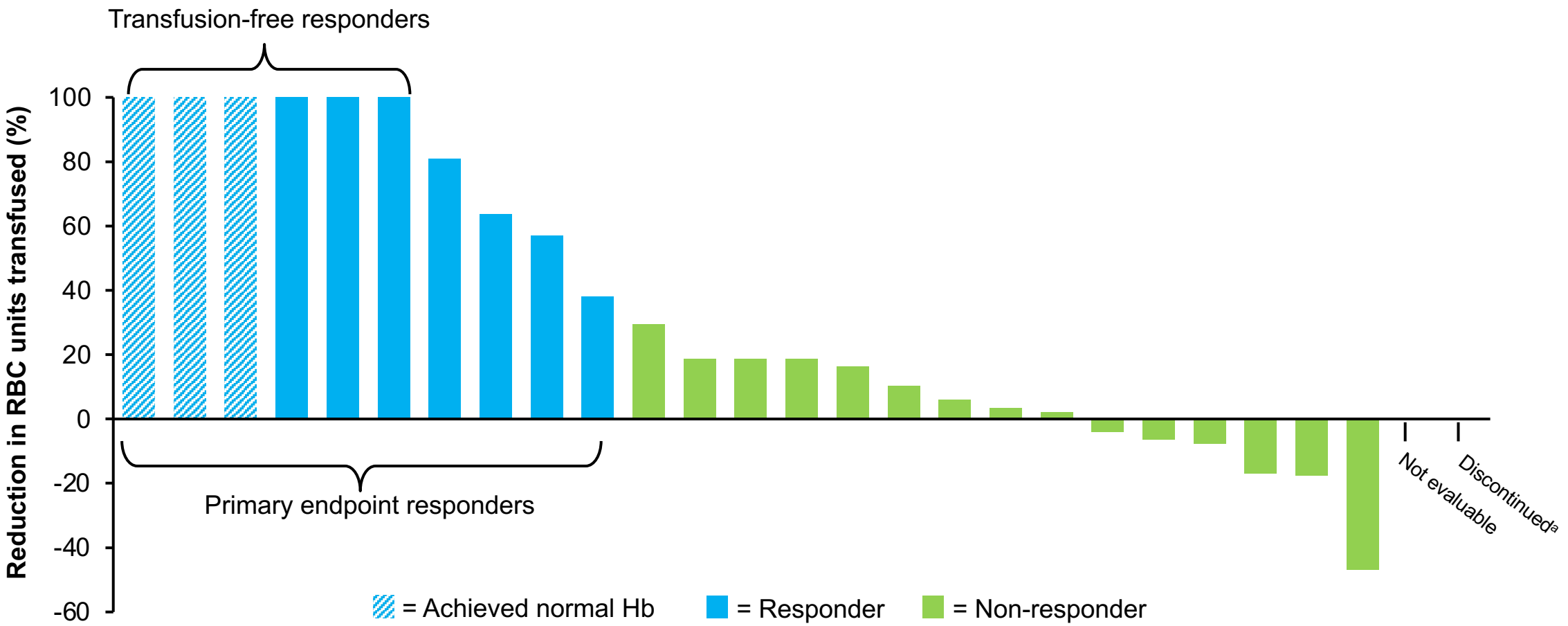
6 patients (22%; 95% CI: 9–42) achieved transfusion-free status during the 24 wk fixed-dose period



[a]Patients who discontinued the study before completing 12 wks of treatment in the fixed-dose period were considered non-responders
CI = confidence interval; RBC = red blood cells; wks = weeks.

Hb concentrations in normal range

3 patients (11%; 95% CI: 2–29) achieved Hb concentrations in the normal range at least once 8 weeks or more after transfusion in 24 wk fixed-dose period



[a]Patients who discontinued the study before completing 12 wks of treatment in the fixed-dose period were considered non-responders
CI = confidence interval; RBC = red blood cells; wks = weeks.

On-treatment transfusions compared to historical transfusions

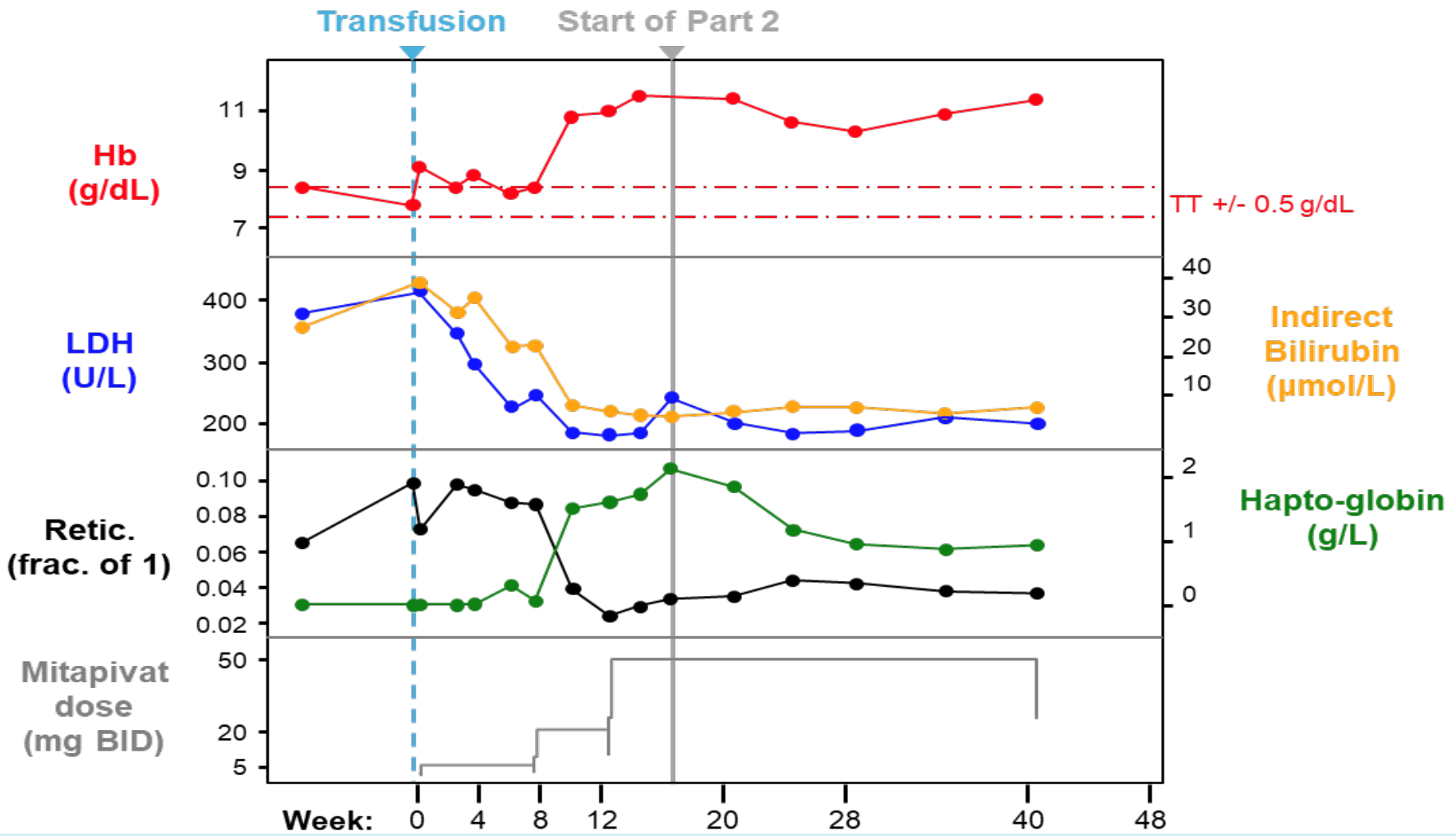
	Historical (standardized to 24 wks) (n = 27)	On-treatment[a] (24 wks) (n = 26)	% Reduction[b]
Number of transfusion episodes, Mean (SD)	4.46 (1.669)	2.88 (2.694)	39.57 (44.424)
RBC units transfused, Mean (SD)	7.68 (3.981)	5.40 (5.739)	37.09 (46.804)

Similar improvements were seen when comparing annualized RBC units transfused

NB: Transfusions received over up to 3 consecutive days were counted as one episode. Both historical transfusion episodes and number of transfusion episodes during the Fixed-Dose period (Part 2) were standardized to 24 wks.
[a]During the fixed-dose period; [b]Defined as percent reduction in the number of RBC units transfused during the fixed-dose period compared with the patient's individual historical transfusion burden standardized to 24 wks.
RBC = red blood cells; SD = standard deviation; wks = weeks.

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

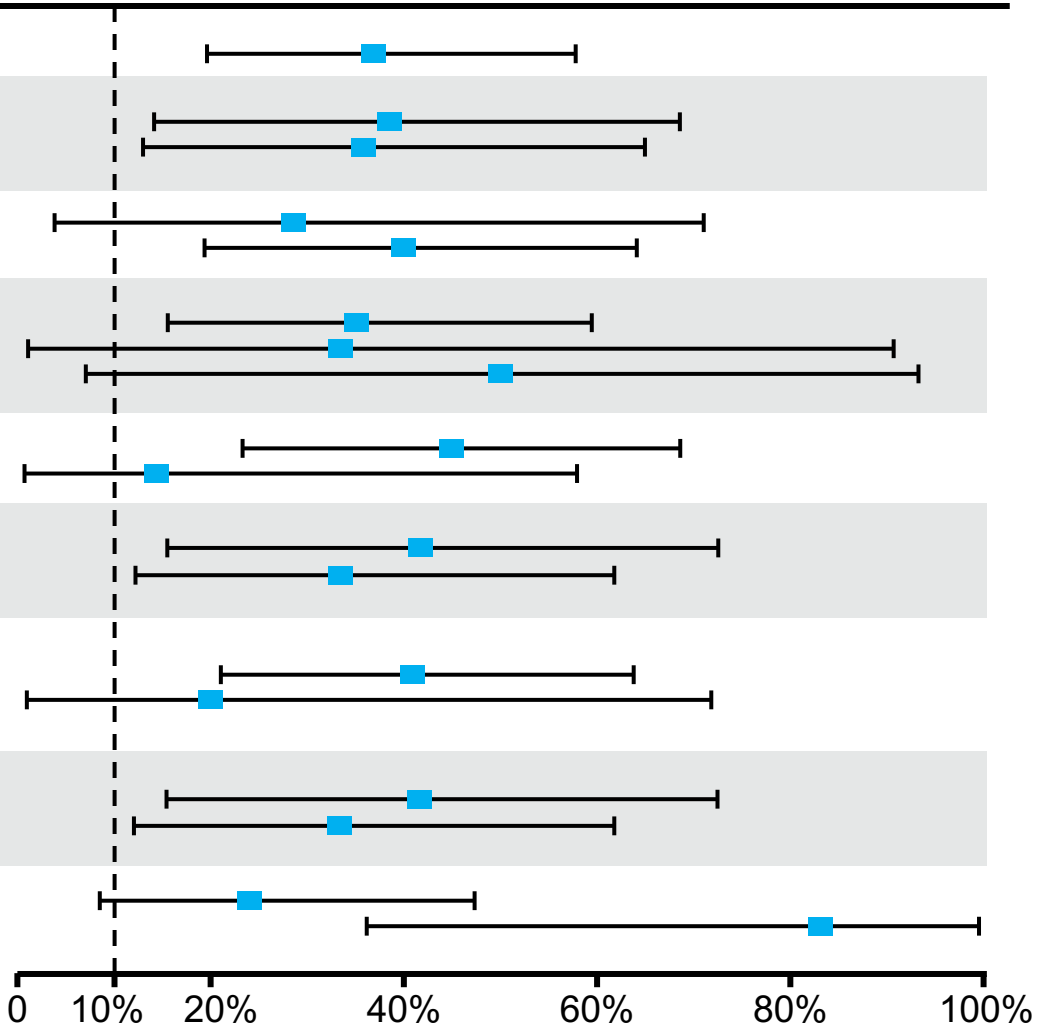
Hb and hemolysis markers over time in a transfusion-free[a] responder:



[a]Defined as a patient who was tranfusion-free during the Fixed-Dose period (Part 2).
BID = twice daily; Hb = hemoglobin; LDH = lactate dehydrogenase; Retic = reticulocyte/erythrocyte, fraction of 1; TT = transfusion trigger.

The benefit of mitapivat on the primary endpoint of reducing transfusion burden was seen across patient subgroups

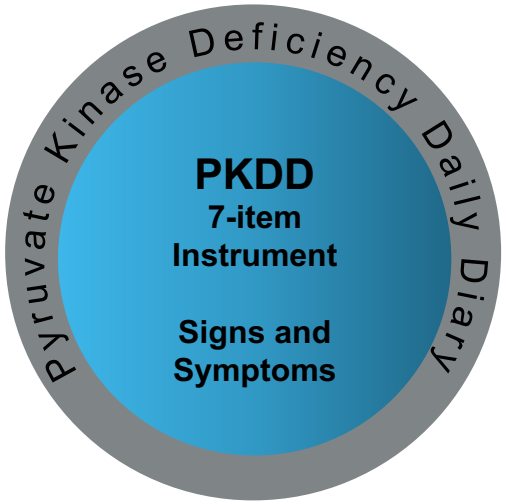
Characteristic	Subgroup	Response rate, % (n/N)[a]
Overall study population[a]:		37.0 (10/27)
Age at screening:	< 35 years ≥ 35 years	38.5 (5/13) 35.7 (5/14)
Sex:	Male Female	28.6 (2/7) 40.0 (8/20)
Race:	White Asian Other	35.0 (7/20) 33.3 (1/3) 50.0 (2/4)
***PKLR* mutation category:**	Missense/Missense Missense/Non-missense	45.0 (9/20) 14.3 (1/7)
Baseline individual transfusion trigger:	< 8.5 g/dL ≥ 8.5 g/dL	41.7 (5/12) 33.3 (5/15)
Individual historical transfusion burden, number of episodes[c]:	≤ 6 episodes > 6 episodes	40.9 (9/22) 20.0 (1/5)
Individual historical transfusion burden, number of RBC units[c]:	≤ 6 units > 6 units	41.7 (5/12) 33.3 (5/15)
Prior splenectomy:	Yes No	23.8 (5/21) 83.3 (5/6)



[a]Transfusion reduction responders defined as patients who had ≥ 33% reduction in the number of RBC units transfused during the fixed-dose period standardized to 24 wks compared with the historical number of RBC units transfused standardized to 24 wks; [b]The estimated 95% CI is based on the exact binomial distribution; [c]During the 52 wks before Informed Consent, standardized to 24 wks'.
CI = confidence interval; PKLR = gene encoding the pyruvate kinase liver and red blood cell isozymes; RBC = red blood cell; wks = weeks.

PKDD and PKDIA were developed to assess and capture changes in symptom burden and HRQoL impact in patients with PK deficiency

In-trial Validation

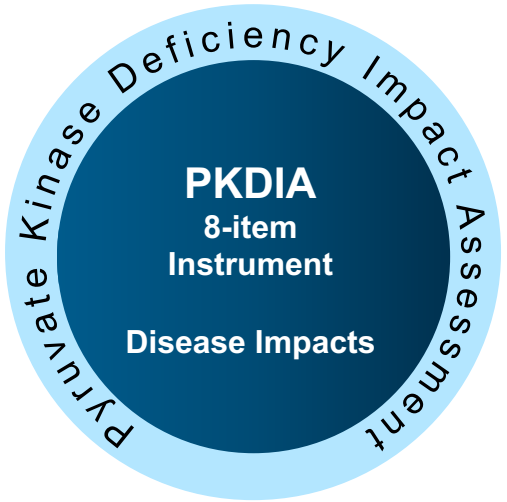


1. Tiredness at its worst
2. Tired after finishing daily activities
3. Jaundice
4. Bone pain
5. Shortness of breath
6. Energy level at beginning of day
7. Energy level at end of day

Daily Sum Score

Scoring Algorithm

T-score
Mean 50, SD 10
Min 25, Max 76



1. Starting things you wanted to get done
2. Household activities
3. Negative impact on social activities
4. Negative impact on leisure activities
5. Relationships with friends or family negatively affected
6. Difficulty concentrating
7. Difficulty performing moderate physical activity
8. Needing additional rest or sleep

Sum Score

Scoring Algorithm

T-score
Mean 50, SD 10
Min 30, Max 76

High internal consistency ☑

Excellent retest reliability ☑

Higher score = Higher disease burden

HRQoL; health related quality of life; PK = pyruvate kinase; PKDD = PK deficiency diary; PKDIA = PK deficiency impact assessment; SD = standard deviation.

Improvement in signs, symptoms, and disease impacts was observed throughout the study based on the PKDD and PKDIA

PRO Score by study visit	Total (N = 27)	
	PKDD	PKDIA
Baseline		
n	24	24
Mean (SD)	51.9 (8.51)	52.6 (7.88)
Change from baseline, dose escalation period Week 12		
n	23	23
Mean (SD)	–5.3 (11.63)	–4.9 (9.97)
Change from baseline, fixed-dose period Week 12		
n	17	17
Mean (SD)	–3.6 (12.22)	–6.0 (12.30)
Change from baseline, fixed-dose period Week 24		
n	14	14
Mean (SD)	–2.4 (11.30)	–9.1 (11.50)

N is the number of subjects who received at least one dose of mitapivat; n shows how many subjects are included at each visit.
PK = pyruvate kinase; PKDD = PK deficiency diary; PKDIA = PK deficiency impact assessment; SD = standard deviation.

Mitapivat was well tolerated and adverse events were consistent with previously reported data

Patients, n (%)	Total (N = 27)	
Any TEAE	27 (100)	
Grade ≥ 3 TEAE	8 (29.6)[a]	
Treatment-related TEAEs	18 (66.7)	
Grade ≥ 3 treatment-related TEAEs	2 (7.4)	
Serious TEAEs	3 (11.1)	
Serious treatment-related TEAEs	0	
TEAEs leading to discontinuation of study drug	0	
TEAEs leading to dose reduction of study drug	1 (3.7)	
TEAEs leading to interruption of study drug	0	
TEAEs leading to death	0	
Most common TEAEs (occurring in ≥ 15%)	**Any grade**	**Grade ≥ 3**
ALT increased	10 (37.0)	0
Headache	10 (37.0)	0
AST increased	5 (18.5)	1 (3.7)
Fatigue	5 (18.5)	0
Nausea	5 (18.5)	0

- The majority of TEAEs were Grade 1 or 2
- Two patients experienced Grade 3 treatment-related TEAEs[a]
  - AST increase; joint swelling
- There were no TEAEs leading to death and no patients discontinued or interrupted treatment due to an AE

NB: N is the number of subjects who received at least one dose of mitapivat; TEAEs classified according to MedDRA version 23.1; all assessments are based on investigator assessment;
[a]No Grade ≥3 AE was reported in more than one patient.
ALT = alanine aminotransferase; AST = aspartate aminotransferase; MedDRA = Medical Dictionary for Regulatory Activities; TEAE = treatment-emergent adverse event.

Mitapivat has the potential to be the first disease-modifying drug therapy for regularly-transfused patients with PK deficiency

- ACTIVATE-T was the first clinical study in patients with PK deficiency who are regularly transfused and demonstrated that mitapivat is an effective therapy for reducing transfusion burden in this population
  - 37% of patients achieved a transfusion reduction response in fixed-dose period
  - 22% of patients were transfusion-free during the fixed-dose period
  - 11% of patients achieved normal Hb concentrations during the fixed-dose period
  - PK deficiency-specific quality of life measures demonstrated improvements
- Mitapivat was well tolerated, and safety profile was consistent with previously reported data

Hb = hemoglobin; PK = pyruvate kinase.

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