# ACTIVATE: A Phase 3, Randomized, Multicenter, Double-blind, Placebo-Controlled Study Of Mitapivat In Adults With Pyruvate Kinase Deficiency Who Are Not Regularly Transfused

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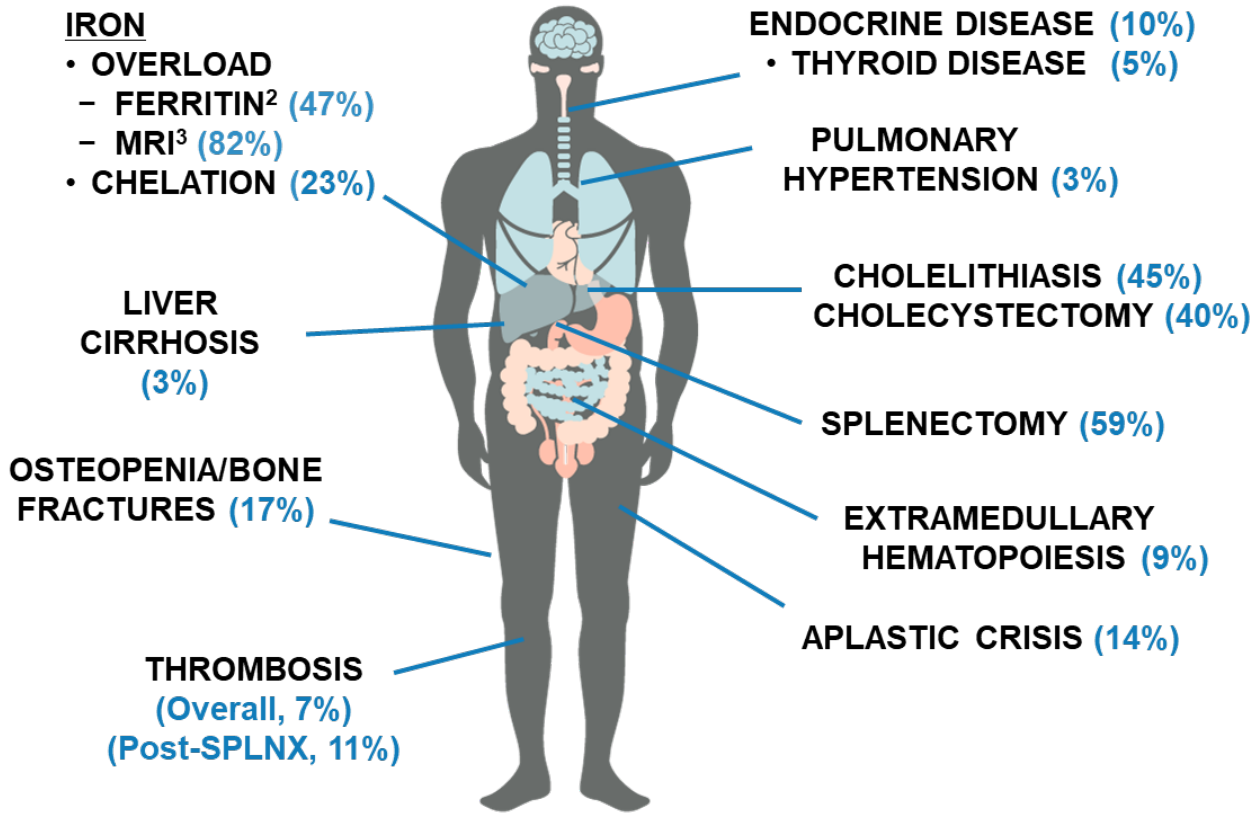
# Disclosures

- This study was funded by Agios Pharmaceuticals, Inc.
- Author conflict of interest disclosures as follows:
  - **Hanny Al-Samkari**: Agios, argenx, Dova, Novartis, Rigel, Sobi – consultancy; Agios, Dova, Amgen – research funding
  - **Frédéric Galactéros**: Addmedica – board membership or advisory committee
  - **Andreas Glenthøj**: Agios, bluebird bio, Celgene, Novartis – consultancy and advisory board member; Alexion – research grant; Novo Nordisk – honoraria
  - **Jennifer A. Rothman**: Pfizer – consultancy; Agios, Novartis, Pfizer – honoraria; Agios, bluebird bio, Novartis, Pfizer – research funding
  - **Oliver Andres**: Agios – Advisory board member
  - **Rachael F. Grace**: Agios, Novartis, Pfizer – research funding; Dova – membership of an entity's Board of Directors or advisory committees
  - **Marta Morado Arias**: Sanofi Genzyme – honoraria and other grants
  - **D. Mark Layton**: Agios, Novartis – consultancy; Agios, Cerus, Novartis – membership of an entity's Board of Directors or advisory committees
  - **Koichi Onodera**: No affiliations
  - **Madeleine Verhovsek**: Vertex – consultancy
  - **Wilma Barcellini**: Agios, Alexion, Novartis – honoraria; Agios – research funding; Bioverativ, Incyte – board membership or advisory committee
  - **Malia P. Judge, Vanessa Beynon, Emily Xu, Peter Hawkins, Erin Zagadailov, Sarah Gheuens**: Agios – employees and shareholders
  - **Eduard J. van Beers**: Agios – advisory board member; Agios, Novartis, Pfizer, RR Mechatronics – research funding

# Pyruvate kinase deficiency - disease overview

- Underrecognized, rare, hereditary chronic hemolytic anemia[1,2]
- Due to mutations in *PKLR,* resulting in chronic hemolysis[1–4]
- Numerous comorbidities and complications[3–6]
- Current management limited to supportive care and splenectomy[3,7]
- No approved disease-modifying agents

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

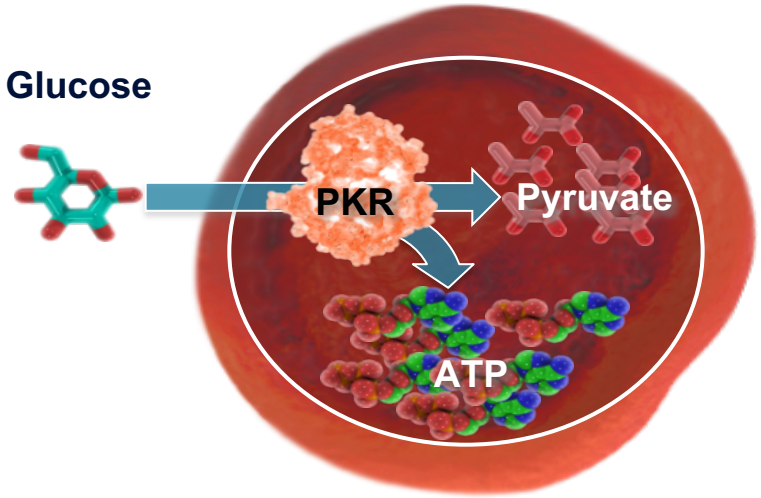



MRI = magnetic resonance imaging; PK = pyruvate kinase; PKR = red blood cell-specific form of pyruvate kinase; *PKLR* = gene encoding the pyruvate kinase liver and red blood cell isozymes.

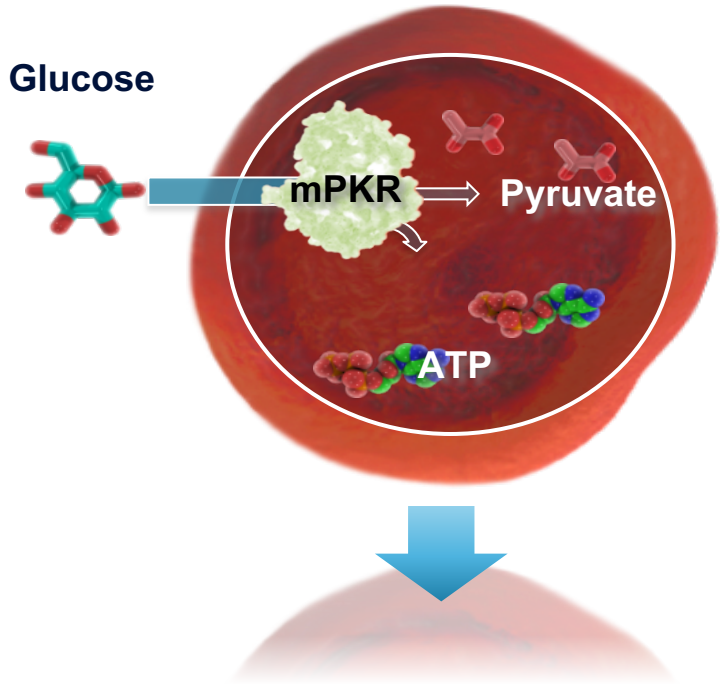
1. Grace RF, et al. *Am J Hematol*. 2015;90:825–30; 2. Zanella A, et al. *Br J Haematol*. 2005;130:11–25; 3. Grace RF, et al. *Blood*. 2018;131:2183–92; 4. van Beers EJ, et al. *Haematologica*. 2019;104:e51–e3; 5. Boscoe AN, et al. *EJH*. 2020;106:484–92; 6. Grace RF, et al. *Eur J Haematol*. 2018;101:758–765;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

# Mitapivat, an oral pyruvate kinase activator

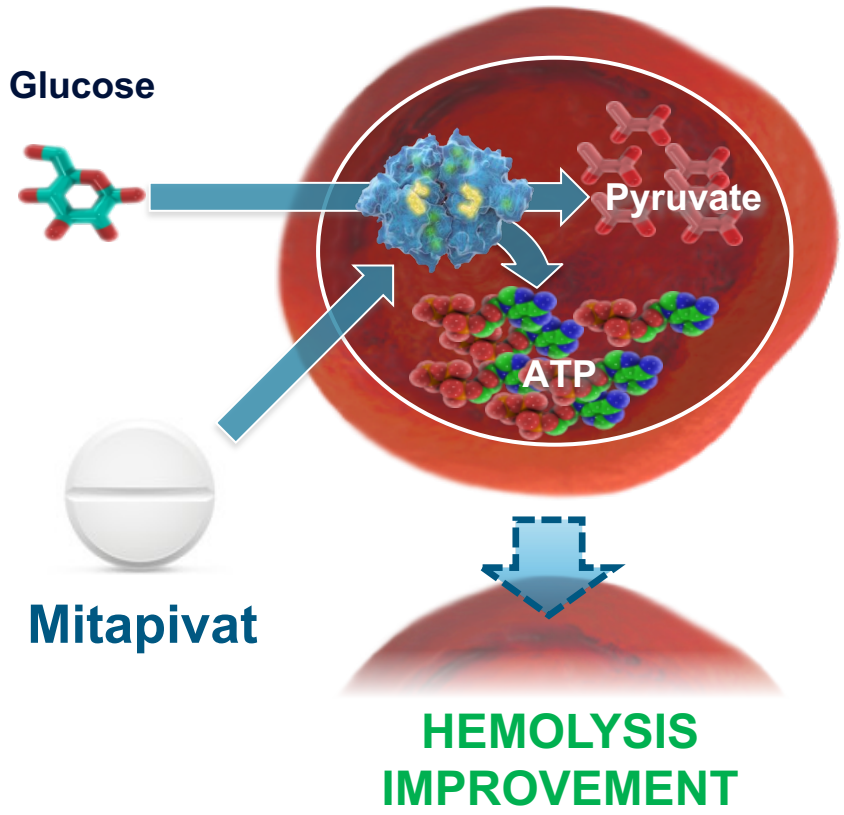
## Healthy RBC, wild-type PKR




## 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 was a Phase 3, randomized, double-blind, placebo-controlled study that evaluated the efficacy and safety of mitapivat in adult patients with PK deficiency who were not regularly transfused

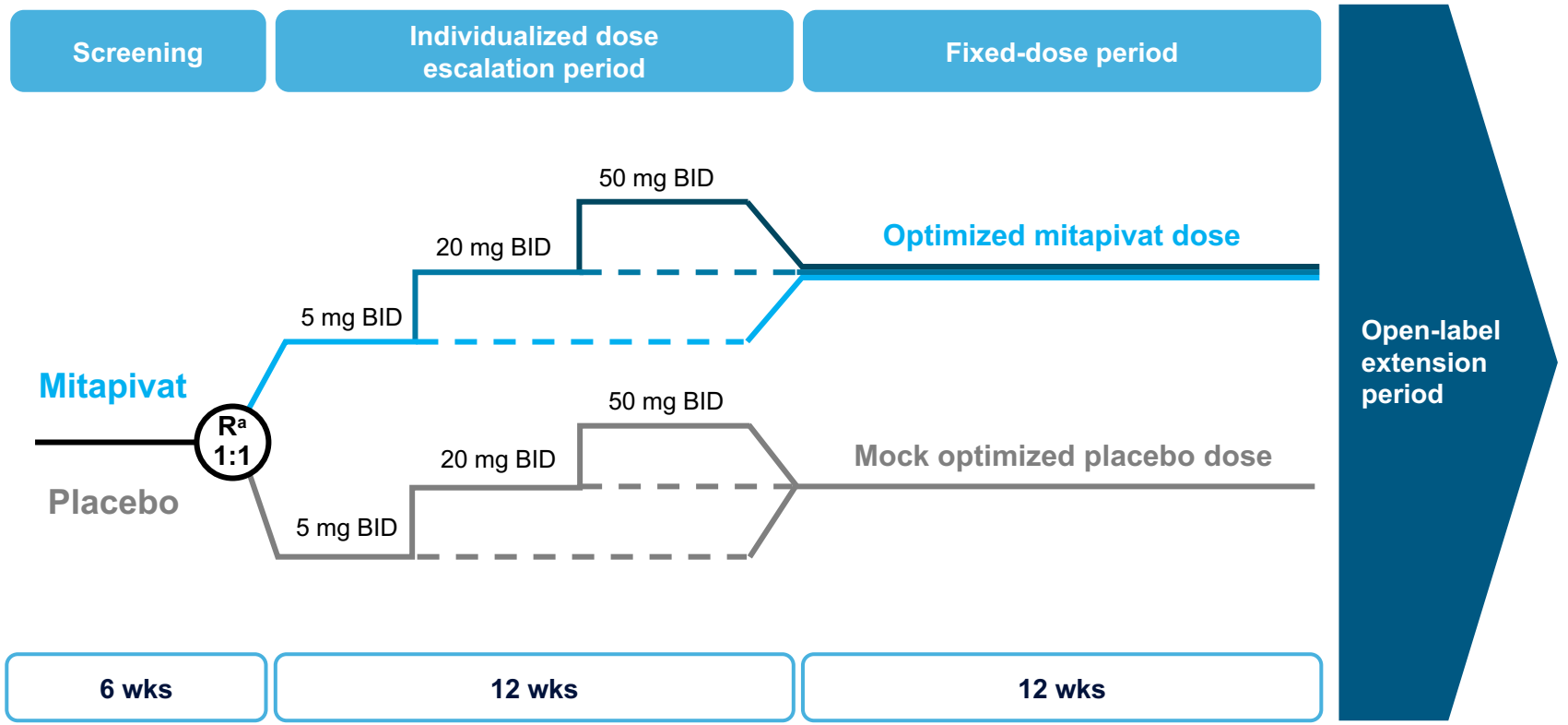
ACTIVATE

**Key eligibility criteria:**

- ≥ 18 yrs of age
- Documented ≥ 2 mutant alleles in *PKLR* (≥ 1 missense mutation)
- Not regularly transfused (≤ 4 transfusion episodes in previous year)
- Baseline Hb ≤ 10 g/dL
- Adequate organ function

**Key exclusion criteria:**

- Homozygous for R479H mutation or have 2 non-missense mutations, without another missense mutation, in *PKLR*
- Splenectomy during study, or within 12 months of enrollment
- Prior bone marrow or stem cell transplant




NB: ACTIVATE, ClinicalTrials.gov NCT03548220; [a]Stratified by average of screening Hb values (< 8.5 g/dL vs ≥ 8.5 g/dL) and *PKLR* gene mutation category (missense/missense vs missense/non-missense).
BID = twice daily; Hb = hemoglobin; PK = pyruvate kinase; *PKLR* = gene encoding the pyruvate kinase liver and red blood cell isozymes; R = randomized; wks = weeks; yrs = years.

# Primary and secondary efficacy endpoints

**Primary endpoint:** Hb response, defined as ≥ 1.5 g/dL increase in Hb concentration from BL sustained at ≥ 2 scheduled assessments at wks 16, 20, or 24 during fixed-dose period

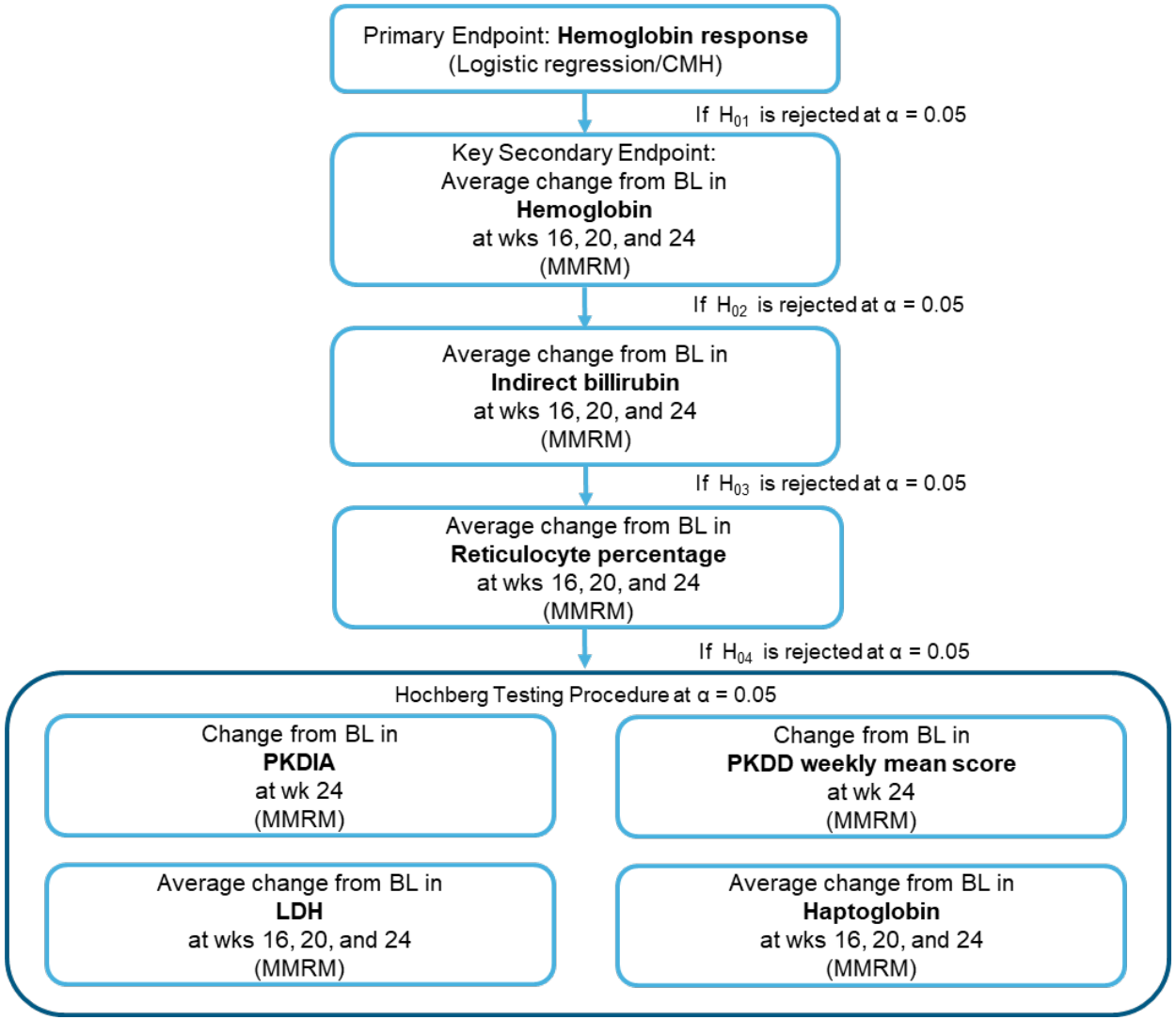
**Key secondary endpoint:** Average change from BL in Hb concentration at wks 16, 20, and 24

**Other secondary endpoints:**

- Average change from BL at wks 16, 20, and 24 in markers of hemolysis: bilirubin, LDH, and haptoglobin levels
- Average change from BL at wks 16, 20, and 24 in markers of hematopoietic activity: reticulocyte percentages (fraction of 1)
- Change from BL at wk 24 in HRQoL PRO scores: PKDIA and PKDD

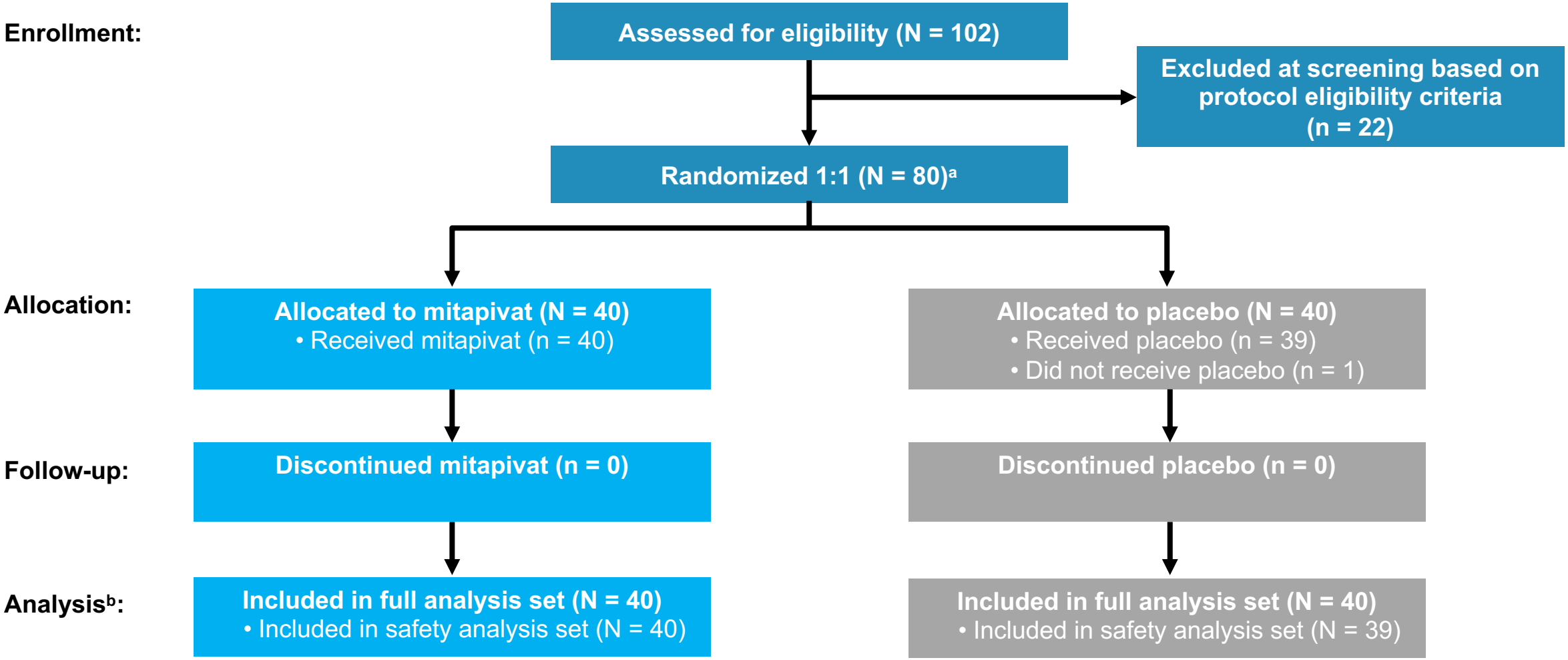
BL = baseline; Hb = hemoglobin; HRQoL = health related quality of life; LDH = lactate dehydrogenase; PK = pyruvate kinase; PKDD = PK deficiency diary; PKDIA = PK deficiency impact assessment; PRO = patient-reported outcomes; wks = weeks.

# Statistical testing strategy




H01: Hb Odds Ratio = 1; H0j: Difference in average of mean change from baseline = 0, for j≥ 2.
BL = baseline; CMH = Cochran-Mantel-Haenszel test; Hb = hemoglobin; HRQoL = health-related quality of life; LDH = lactate dehydrogenase; MMRM = Mixed-Effect Model Repeated Measure; PRO = patient-reported outcomes; PKDD = Pyruvate Kinase Deficiency Diary; PKDIA = Pyruvate Kinase Deficiency Impact Assessment; wks = weeks.

# Patient disposition




[a]Disposition for end of randomization reflects the disposition after randomization, but before start of study treatment; [b]Analysis set definitions: full analysis set included all patients who were randomized to treatment; safety analysis set included all patients who received at least 1 dose of study treatment.

# Demographics

| Patient demographics | Mitapivat N = 40 | Placebo N = 40 |
|---|---|---|
| **Age (years)** | | |
| Mean (SD) | 36.0 (15.2) | 37.2 (15.9) |
| Range | 18–70 | 19–78 |
| **Sex, n (%)** | | |
| Male | 16 (40.0) | 16 (40.0) |
| Female | 24 (60.0) | 24 (60.0) |
| **Race, n (%)** | | |
| White | 28 (70.0) | 32 (80.0) |
| Asian | 5 (12.5) | 3 (7.5) |
| Native Hawaiian or Other Pacific Islander | 1 (2.5) | 0 |
| American Indian or Alaska Native | 0 | 0 |
| Black or African American | 0 | 0 |
| Other | 0 | 1 (2.5) |
| Not reported | 6 (15.0) | 4 (10.0) |
| **Geographic Region, n (%)** | | |
| Western Europe | 19 (47.5) | 20 (50.0) |
| North America | 15 (37.5) | 16 (40.0) |
| Asia | 5 (12.5) | 3 (7.5) |
| Middle East | 0 | 1 (2.5) |
| Latin America | 1 (2.5) | 0 |

NB: Summarized using the full analysis set.
SD = standard deviation.

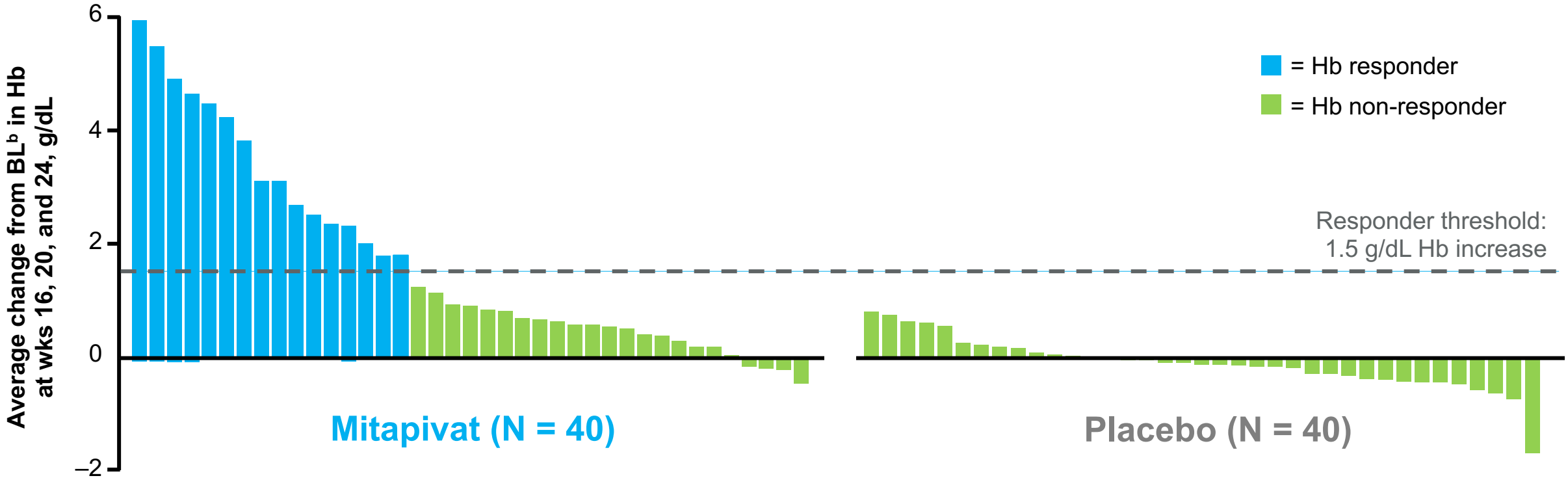
# Baseline characteristics

| Baseline characteristics | Mitapivat N = 40 | Placebo N = 40 |
|---|---|---|
| **Hb (g/dL), mean (SD)** | 8.6 (0.99) | 8.5 (0.85) |
| **Ferritin (µg/L), mean (SD)** | 748 (1116.2) | 688 (605.2) |
| **Hemolysis markers, mean (SD)** | | |
| Indirect bilirubin (µmol/L) | 81.8 (61.32) | 89.1 (61.79) |
| LDH (U/L) | 348 (276.0) | 260 (140.2) |
| Haptoglobin (g/L) | 0.08 (0.107) | 0.08 (0.138) |
| Reticulocyte (fraction of 1) | 0.37 (0.241) | 0.40 (0.222) |
| **Prior transfusions, n (%)** | | |
| 0 | 29 (72.5) | 30 (75.0) |
| 1 | 8 (20.0) | 7 (17.5) |
| 2 | 0 | 1 (2.5) |
| 3 | 3 (7.5) | 1 (2.5) |
| ≥4 | 0 | 1 (2.5) |
| **Prior splenectomy, n (%)** | 28 (70.0) | 30 (75.0) |
| **Prior cholecystectomy, n (%)** | 28 (70.0) | 30 (75.0) |
| **Prior chelation therapy, n (%)[a]** | 5 (12.5) | 10 (25.0) |
| **DXA T-Score, mean (SD)** | | |
| Femoral total[b] | –1.12 (1.081) | –0.79 (1.098) |
| Adjusted spine | –1.78 (1.104) | –1.14 (1.153) |
| ***PKLR* mutation category** | | |
| Missense/Missense | 28 (70.0) | 27 (67.5) |
| Missense/Non-missense | 12 (30.0) | 13 (32.5) |

NB: Summarized based on full analysis set (all patients who were randomized to treatment).
[a]"Yes' if a subject has received chelation therapy within 52 wks (364 days) before first dose of study treatment; [b]femoral neck and total hip combined.
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 higher hemoglobin response rate as compared with placebo

| | Mitapivat N = 40 | Placebo N = 40 | Difference[a] (95% CI) | 2-sided p-value |
|---|---|---|---|---|
| **Hemoglobin response n (%)** | 16 (40.0) | 0 (0) | 39.3 (24.1, 54.6) | < 0.0001 |

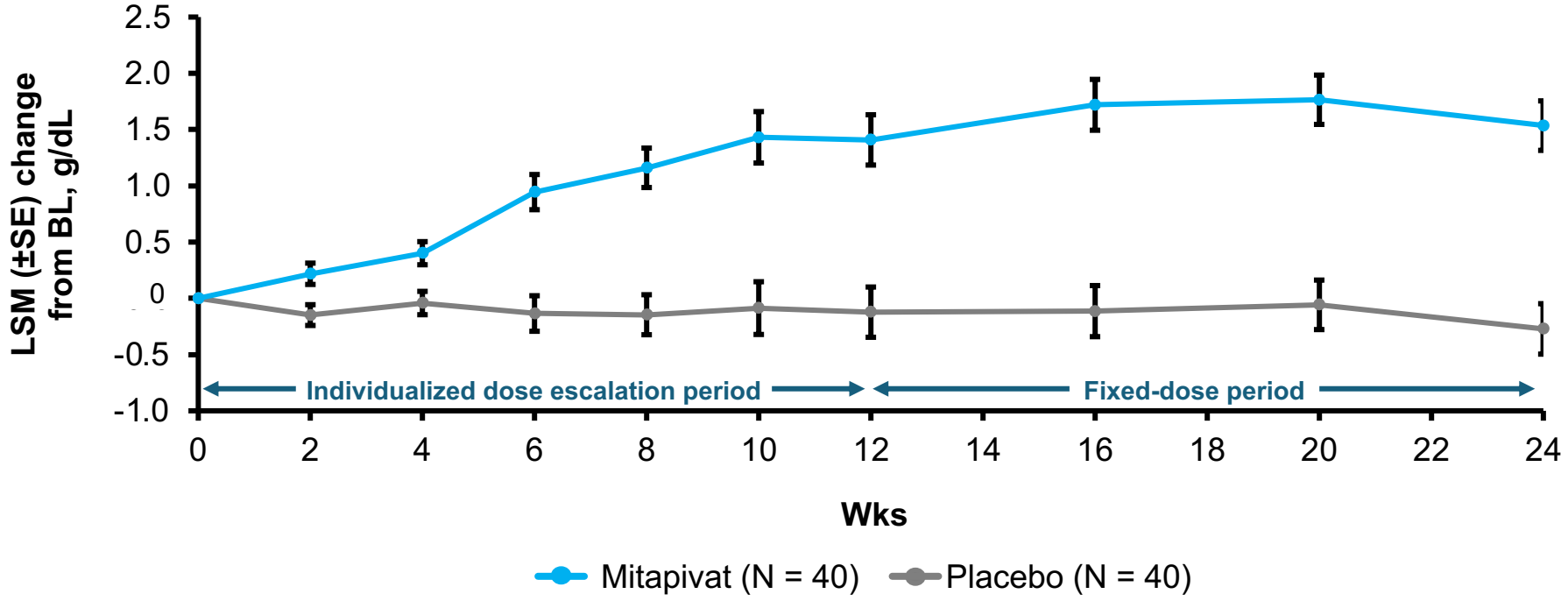



NB: Each bar represents an individual patient randomized to either mitapivat or placebo; summarized based on full analysis set (all patients who were randomized to treatment).
[a]Adjusted difference in response rate for primary endpoint; [b]BL is defined as the average of all screening assessments within 45 (42 + 3) days before randomization for subjects randomized and not dosed or before start of study treatment for subjects randomized and dosed.
BL = baseline; CI = confidence intervals; Hb = hemoglobin; wks = weeks.

# Mitapivat led to early and sustained improvement in Hb

## Average change from BL at wks 16, 20, and 24 in Hb

| | Mitapivat N = 40 | Placebo N = 40 | Difference in LSM (95% CI) | 2-sided p-value |
|---|---|---|---|---|
| **Hb (g/dL), LSM (95% CI)** | 1.67 (1.26, 2.09) | –0.15 (–0.56, 0.27) | 1.82 (1.24, 2.40) | < 0.0001 |




NB: Summarized based on full analysis set (all patients who were randomized to treatment); BL is defined as the average of all screening assessments within 45 (42 + 3) days before randomization for subjects randomized and not dosed or before start of study treatment for subjects randomized and dosed.
BL = baseline; CI= confidence interval; Hb = hemoglobin; LSM = least-squares mean; SE = standard error; wks = weeks.

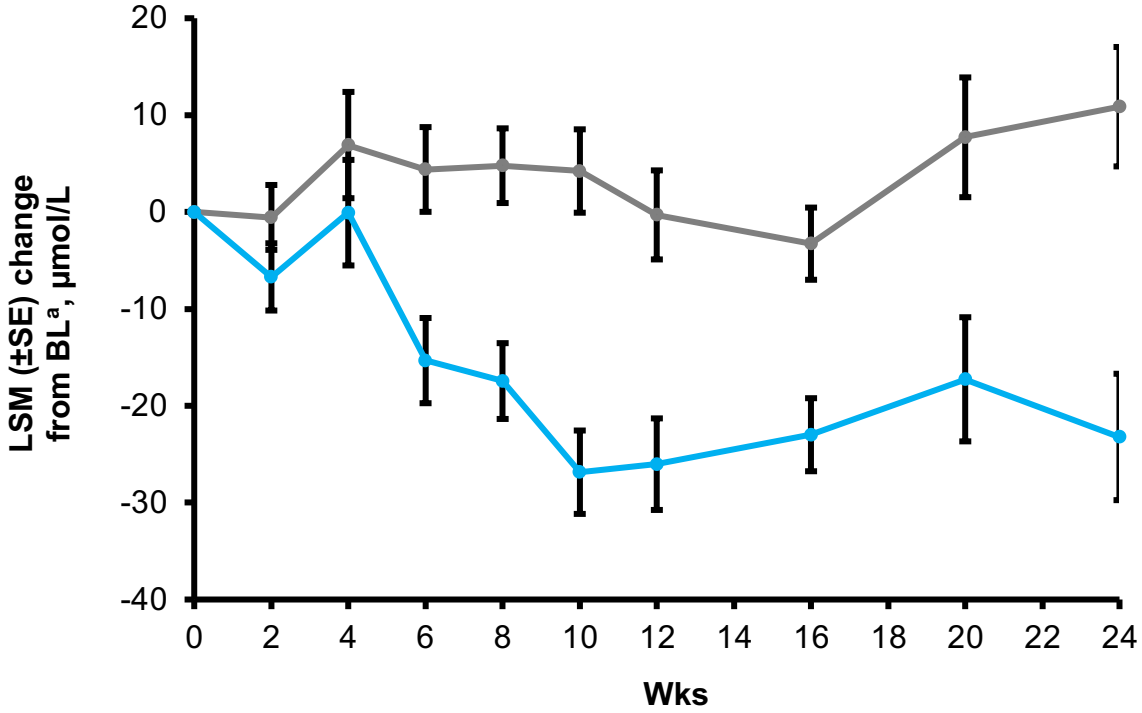
# Mitapivat led to improvements in markers of hemolysis

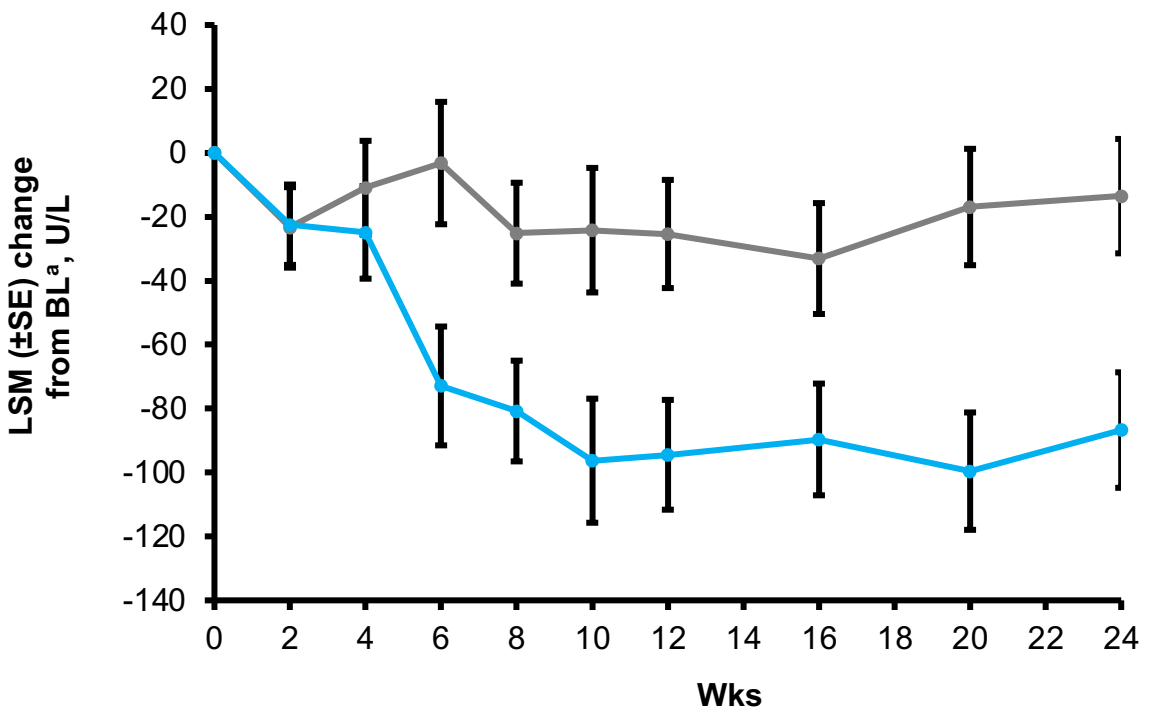
**Average change from BL at wks 16, 20, and 24 in indirect bilirubin**

| | Mitapivat N = 40 | Placebo N = 40 | Difference in LSM (95% CI) | 2-sided p-value |
|---|---|---|---|---|
| **Indirect bilirubin (µmol/L) LSM (95% CI)** | –21.16 (–29.59, –12.72) | 5.10 (–3.00, 13.21) | –26.26 (–37.82, –14.70) | < 0.0001 |

**Average change from BL at wks 16, 20, and 24 in LDH**

| | Mitapivat N = 40 | Placebo N = 40 | Difference in LSM (95% CI) | 2-sided p-value |
|---|---|---|---|---|
| **LDH (U/L) LSM (95% CI)** | –91.99 (–124.47, –59.50) | –21.18 (–53.30, 10.94) | –70.81 (–115.88, –25.74) | 0.0027 |




Mitapivat (N = 40) Placebo (N = 40)

NB: Summarized based on full analysis set (all patients who were randomized to treatment). [a]Baseline is defined as the average of all screening assessments within 45 (42 + 3) days before randomization for subjects randomized and not dosed or before start of study treatment for subjects randomized and dosed.
BL = baseline; CI = confidence interval; LDH = lactate dehydrogenase; LSM = least-squares mean; SE = standard error; Wks = weeks.

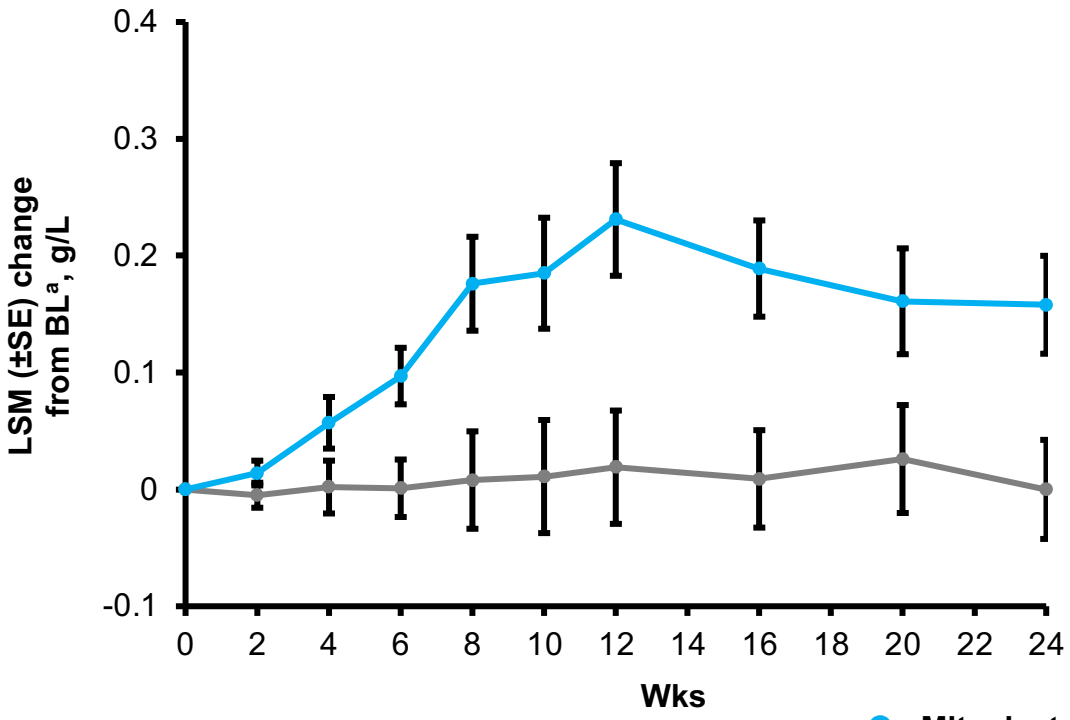
# Mitapivat led to improvements in markers of hemolysis and hematopoiesis

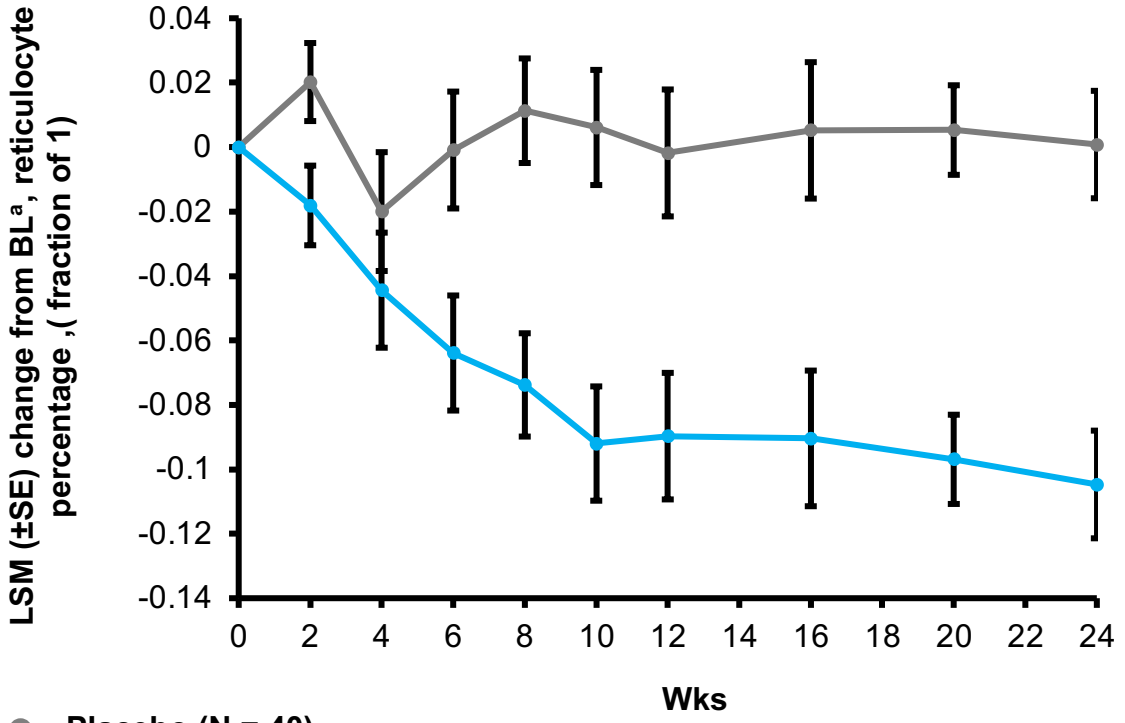
**Average change from BL at wks 16, 20, and 24 in haptoglobin**

| | Mitapivat N = 40 | Placebo N = 40 | Difference in LSM (95% CI) | 2-sided p-value |
|---|---|---|---|---|
| **Haptoglobin (g/L) LSM (95% CI)** | 0.169 (0.088, 0.251) | 0.012 (–0.070, 0.094) | 0.158 (0.043, 0.273) | 0.0079 |

**Average change from BL at wks 16, 20, and 24 in reticulocyte percentage (fraction of 1)**

| | Mitapivat N = 40 | Placebo N = 40 | Difference in LSM (95% CI) | 2-sided p-value |
|---|---|---|---|---|
| **Reticulocyte percentage (fraction of 1) LSM (95% CI)** | –0.0973 (–0.1252, –0.0694) | 0.0038 (–0.0239, 0.0315) | –0.1011 (–0.1391, –0.0632) | < 0.0001 |



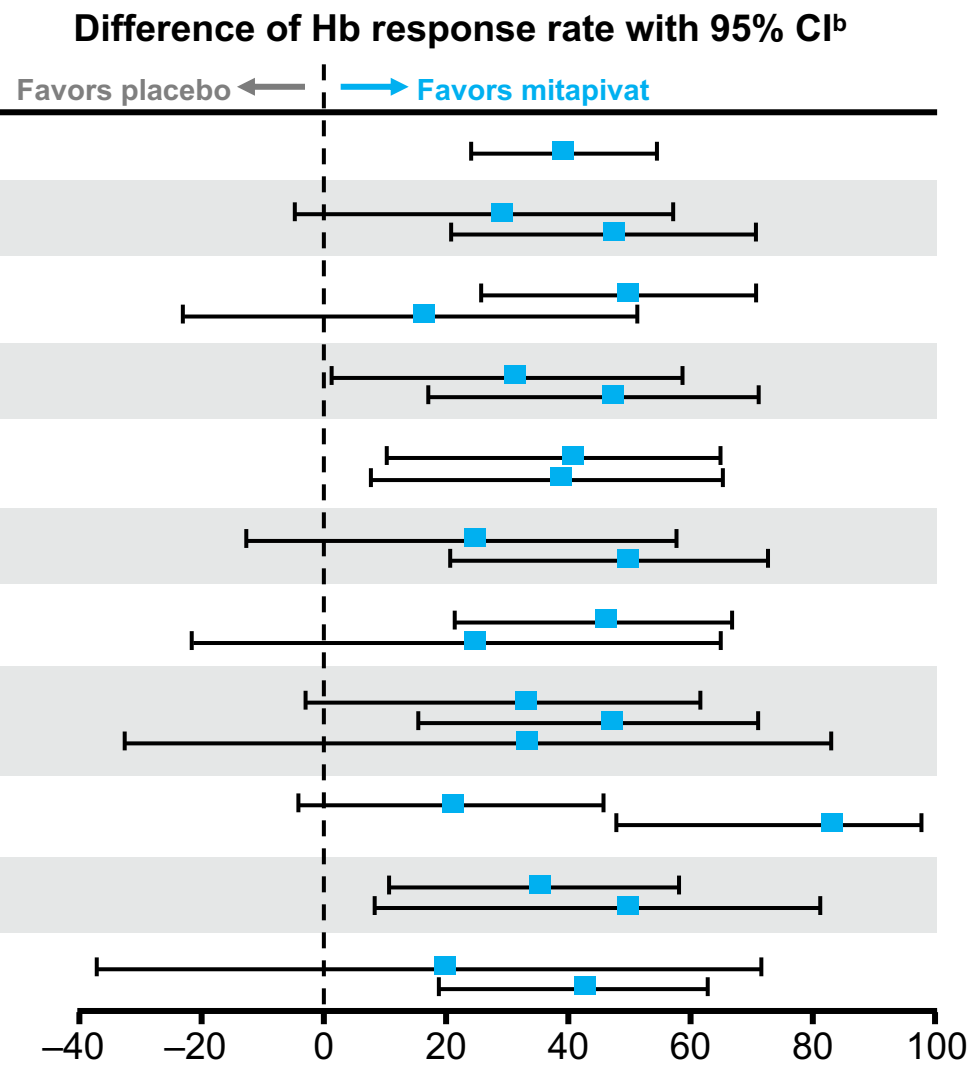




Mitapivat (N = 40) Placebo (N = 40)

NB: Summarized based on full analysis set (all patients who were randomized to treatment). [a]Baseline is defined as the average of all screening assessments within 45 (42 + 3) days before randomization for subjects randomized and not dosed or before start of study treatment for subjects randomized and dosed.
BL = baseline; CI = confidence interval; LSM = least-squares mean; SE = standard error; Wks = weeks.

# Hemoglobin response was seen across all pre-defined patient subgroups

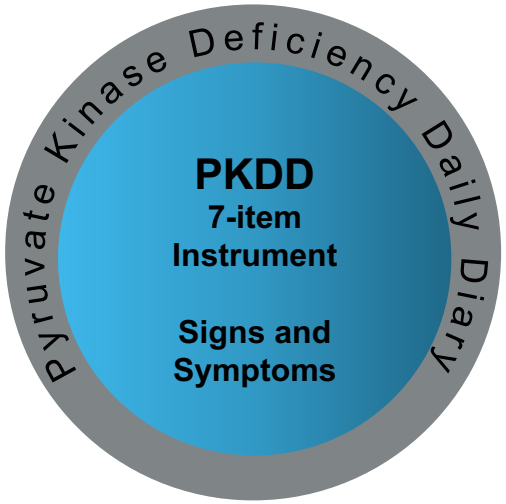
| Characteristic | Subgroup | Hb response rate, % (n/N) Mitapivat | Hb response rate, % (n/N) Placebo |
|---|---|---|---|
| **Overall study population[a]:** | | **40.0 (16/40)** | **0 (0/40)** |
| **Average of screening Hb:** | < 8.5 g/dL | 29.4 (5/17) | 0 (0/18) |
| | ≥ 8.5 g/dL | 47.8 (11/23) | 0 (0/22) |
| ***PKLR* mutation category:** | Missense/Missense | 50.0 (14/28) | 0 (0/27) |
| | Missense/Non-missense | 16.7 (2/12) | 0 (0/13) |
| **Baseline Hb:** | < 8.5 g/dL | 31.6 (6/19) | 0 (0/21) |
| | ≥ 8.5 g/dL | 47.6 (10/21) | 0 (0/19) |
| **Age at screening:** | < 35 years | 40.9 (9/22) | 0 (0/20) |
| | ≥ 35 years | 38.9 (7/18) | 0 (0/20) |
| **Sex:** | Male | 25.0 (4/16) | 0 (0/16) |
| | Female | 50.0 (12/24) | 0 (0/24) |
| **Race:** | White | 46.4 (13/28) | 0 (0/32) |
| | Other[c] | 25.0 (3/12) | 0 (0/8) |
| **Geographic region:** | North America | 33.3 (5/15) | 0 (0/16) |
| | Western Europe | 47.4 (9/19) | 0 (0/20) |
| | Rest of the World[c] | 33.3 (2/6) | 0 (0/4) |
| **Prior splenectomy:** | Yes | 21.4 (6/28) | 0 (0/30) |
| | No | 83.3 (10/12) | 0 (0/10) |
| **Prior cholecystectomy:** | Yes | 35.7 (10/28) | 0 (0/30) |
| | No | 50.0 (6/12) | 0 (0/10) |
| **Prior chelation therapy:** | Yes | 20.0 (1/5) | 0 (0/10) |
| | No | 42.9 (15/35) | 0 (0/30) |




NB: Summarized based on full analysis set (all patients who were randomized to treatment).
[a]Stratified by the Average of Screening Hb concentrations and PKLR gene mutation category; [b]For overall study population difference is based on Mantel-Haenszel stratum weighted method adjusting for randomization stratification factors; for subgroups difference is based on unstratified analyses; [c]Pre-specified subgroups with ≤10% of the subjects in the full analysis set were pooled (race, Asian and Other were pooled). CI = confidence interval; Hb = hemoglobin; N = number of patients randomized; *PKLR* = gene encoding the pyruvate kinase liver and red blood cell isozymes.

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

## In-trial Validation



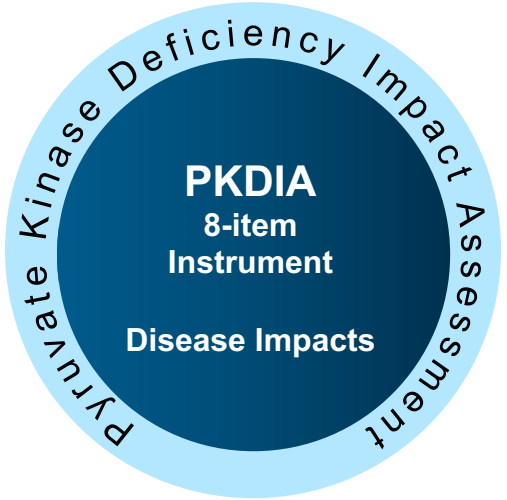

1. Tiredness at its worst
2. Tired after finishing daily activities
3. Jaundice
4. Bone pain
5. Shortness of breath
6. Energy level at beginning of day
7. Energy level at end of day

**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.

# Statistically significant improvement in change from baseline at Week 24 was demonstrated on PKDD and PKDIA mean weekly score

| PRO | Mitapivat | | Placebo | | LSM[a] Difference | 2-sided p-value |
|---|---|---|---|---|---|---|
| | BL Mean (SD) | LSM Change from BL at W24 | BL Mean (SD) | LSM Change from BL at W24 | | |
| PKDD | 50.45 (7.315) | –5.16 | 47.04 (8.103) | –2.05 | –3.11 (95% CI:–5.80, –0.41) | 0.0247 |
| PKDIA | 49.2 (9.00) | –4.65 | 48.5 (9.15) | –1.39 | –3.25 (95% CI: –6.39, –0.12) | 0.0421 |

NB: Summarized based on full analysis set (all patients who were randomized to treatment). [a]Difference in least square means (LSM) of change from BL at Week 24.
BL = baseline; CI = confidence interval; LSM = least square mean; PK = pyruvate kinase; PKDD = PK deficiency diary; PKDIA = PK deficiency impact assessment; PRO = patient-reported outcomes; SD = standard deviation; W = week.

# Safety

| Patients, n (%) | Mitapivat N = 40 | Placebo N = 39 |
|---|---|---|
| **Any TEAEs** | 35 (87.5) | 35 (89.7) |
| **Treatment-related TEAEs** | 23 (57.5) | 14 (35.9) |
| **Grade ≥ 3 TEAEs** | 10 (25.0) | 5 (12.8) |
| **Grade ≥ 3 treatment-related TEAEs** | 3 (7.5) | 0 |
| **Serious TEAEs** | 4 (10.0) | 2 (5.1) |
| **TEAEs leading to dose reduction of study drug** | 0 | 0 |
| **TEAEs leading to interruption of study drug** | 0 | 2 (5.1) |
| **TEAEs leading to discontinuation of study drug** | 0 | 0 |
| **TEAEs leading to death** | 0 | 0 |

NB: The denominator used to calculate percentages is N, the number of subjects in the Safety Analysis Set within each treatment arm.
TEAE = treatment-emergent adverse event.

# Most frequently reported (≥ 10%) Adverse Events in ACTIVATE

| Preferred Term | Mitapivat N = 40 | Placebo N = 39 |
|---|---|---|
| **Patients with events, n (%)** | 35 (87.5) | 35 (89.7) |
| Nausea | 7 (17.5) | 9 (23.1) |
| Headache | 6 (15.0) | 13 (33.3) |
| Nasopharyngitis | 5 (12.5) | 6 (15.4) |
| Fatigue | 5 (12.5) | 4 (10.3) |
| Back pain | 5 (12.5) | 3 (7.7) |
| Diarrhea | 4 (10.0) | 7 (17.9) |
| Dizziness | 4 (10.0) | 3 (7.7) |
| Abdominal pain | 4 (10.0) | 2 (5.1) |
| Arthralgia | 4 (10.0) | 2 (5.1) |
| Dyspnea | 3 (7.5) | 4 (10.3) |
| Alanine aminotransferase increased | 1 (2.5) | 6 (15.4) |
| Initial insomnia | 1 (2.5) | 4 (10.3) |
| Upper respiratory tract infection | 0 | 4 (10.3) |

NB: Summarized in order of decreasing frequency of subjects 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 subjects in the Safety Analysis Set within each treatment arm. Subjects with multiple adverse events within a PT were counted only once in that PT. For subjects with multiple occurrences of an adverse event, the adverse event with the worst CTCAE grade was included in the summary. MedDRA Version 23.1 and CTCAE Version 4.03 were used.
TEAE = treatment-emergent adverse event.

# Mitapivat has the potential to be the first disease-modifying drug therapy for patients with pyruvate kinase deficiency

- Mitapivat demonstrated sustained improvement in hemolytic anemia in non-regularly transfused patients with PK deficiency
  - 40% in mitapivat group achieved a Hb response compared to 0% in placebo group (2-sided $p < 0.0001$)
  - Increase in Hb occurred early and was sustained
  - The effect of mitapivat on Hb response compared to placebo was observed consistently across all predefined subgroups
- Statistically significant improvements were also demonstrated for the secondary endpoints, including:
  - Average change from baseline in Hb concentration
  - Average change from baseline in markers of hemolysis and hematopoietic activity
  - Change from baseline in novel, PK deficiency-specific PROs
- Mitapivat was well-tolerated with safety profile consistent with prior studies; no TEAEs leading to discontinuation

Hb = hemoglobin; PK = pyruvate kinase; PRO = patient reported outcomes; TEAE = treatment-emergent adverse event.

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