A Phase 2/3, Double-Blind, Randomized, Placebo-Controlled, Multicenter Study of Mitapivat in Patients With Sickle Cell Disease: RISE UP Phase 2 Results

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Sickle Cell Disease

- Sickle cell disease (SCD) is characterized by the presence of hemoglobin S (HbS), a structural variant caused by a mutation in the β-globin gene (*HBB)*[1]
- Deoxygenated HbS molecules rapidly polymerize into “fibers,” causing red blood cells (RBCs) to sickle and hemolyze[1,2]
  - Sickled RBCs have a shortened life span and impede blood flow to tissues, causing painful vaso-occlusive crises (VOCs)[1]
  - Recurrent microvascular damage and chronic hemolytic anemia result in progressive multi-organ damage (including the kidneys, heart, lung, and liver)[1]

HBB, β-globin gene; HbS, hemoglobin S; RBC, red blood cell; SCD, sickle cell disease; VOC, vaso-occlusive crisis.

1. Piel FB, et al. *N Eng J Med*. 2017;376(16):1561-1573. 2. Kaperonis AA, et al. *Am J Hematol*. 1986;21(3):269-275.

Sickle Cell Disease

- Approximately 8 million people are affected by SCD worldwide[1]; the life expectancy for patients with SCD is reduced by about 30 years and the quality of life is often poor[2]
- Common self-reported symptoms occurring in patients with SCD include fatigue (50% to 79%) and bone aches (43% to 66%)[3]
- A meta-analysis of 41 phase 2, 3, and 4 clinical trials in patients with SCD reported that an increase in Hb of ≥1.0 g/dL was associated with a 41% to 57% reduction in the risk for negative clinical outcomes and a 64% reduction in the risk of mortality[4]

Hb, hemoglobin; SCD, sickle cell disease.

1. GBD 2021 Sickle Cell Disease Collaborators. *Lancet Haematol*. 2023;10(8):e585-e589. 2. Piel FB, et al. *N Eng J Med*. 2017;376(16):1561-1573. 3. Osunkwo I, et al. *Am J Hematol*. 2022;97(8):1055-1064.
4. Ataga KI, et al. *PLoS One*. 2020;15(4):e0229959.

Pyruvate Kinase

- Pyruvate kinase (PK) is a key enzyme in RBC metabolism and the production of adenosine triphosphate (ATP)[1]
  - Sufficient ATP is needed to maintain RBC energy homeostasis, membrane integrity, and deformability[1,2]
  - A decrease in PK function leads to defects in glycolysis, including a buildup of 2,3-diphosphoglycerate (2,3-DPG) and reduced levels of ATP[1]
    - 2,3-DPG is an important regulator of the oxygen affinity of hemoglobin (Hb)[3]
- In RBCs of patients with SCD, PK activity and stability are reduced compared with healthy controls[3]

2,3,-DPG, 2,3-diphosphoglycerate; ATP, adenosine triphosphate; Hb, hemoglobin; PK, pyruvate kinase; RBC, red blood cell; SCD, sickle cell disease.

1. Zanella A, et al. *Br J Haematol*. 2005;130(1):11-25. 2. Betz T, et al. *Proc Natl Acad Sci U S A*. 2009;106(36):15320-15325. 3. Rab MAE, et al. *Blood*. 2021;137(21):2997-3001.

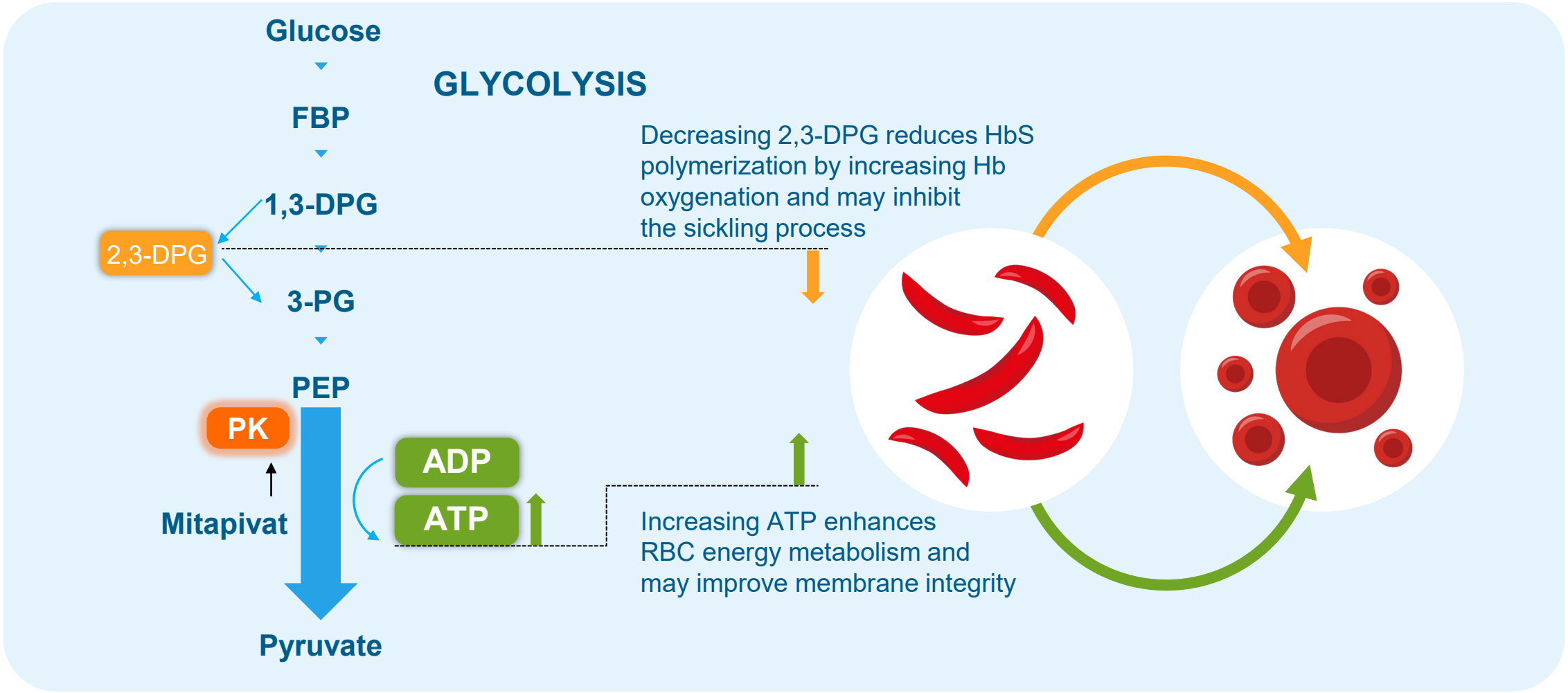
Mitapivat Mechanism of Action

- Mitapivat is a first-in-class, oral, small molecule allosteric activator of PK that is under investigation for the treatment of SCD
  - Mitapivat is approved in the United States for the treatment of hemolytic anemia in adults with PK deficiency and in the European Union and in the United Kingdom for the treatment of PK deficiency in adult patients[1-3]
- Mitapivat activates wild-type and mutant PK enzymes[4,5]
- By enhancing PK activity in SCD, mitapivat may improve anemia and reduce sickling through the dual mechanism of decreasing 2,3-DPG and increasing ATP[6]

ATP, adenosine triphosphate; 2,3,-DPG, 2,3-diphosphoglycerate; PK, pyruvate kinase; SCD, sickle cell disease.

1. Pyrukynd. Prescribing information. Agios Pharmaceuticals, Inc.; 2022. Accessed August 18, 2023. https://www.agios.com/prescribinginfo.pdf; 2. Pyrukynd. Product information. Agios Netherlands B.V.; 2022. Accessed August 18, 2023. https://www.ema.europa.eu/en/documents/product-information/pyrukynd-epar-product-information_en.pdf; 3. Pyrukynd. Orphan Register. Medicines and Healthcare Products Regulatory Agency; 2023. Accessed August 20, 2023. https://www.gov.uk/government/publications/orphan-registered-medicinal-products/orphan-register; 4. Kung C, et al. *Blood*. 2017;130(11):1347-1356; 5. Valentini G, et al. *J Biol Chem*. 2002;277(26):23807-23814; 6. Rab MAE, et al. *Blood*. 2021;137(21):2997-3001.

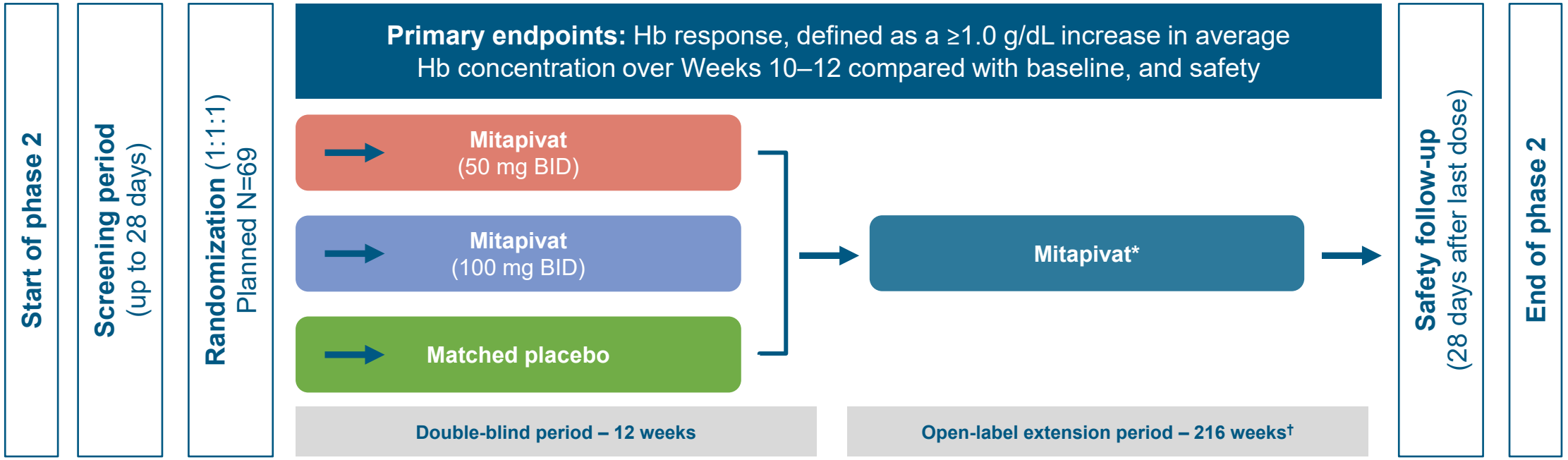
PK Activation in Sickle Cell Disease Modulates 2,3-DPG and ATP, Which May Improve Anemia and Reduce Sickling



ADP, adenosine diphosphate; ATP, adenosine triphosphate; 2,3,-DPG, 2,3-diphosphoglycerate; FBP, fructose bisphosphate; Hb, hemoglobin; HbS, hemoglobin S; PEP, phosphoenolpyruvate; PG, phosphoglycerate; PK, pyruvate kinase; RBC, red blood cell.

RISE UP Study Design (Phase 2 Portion)

- RISE UP is a global, phase 2/3, double-blind, randomized, placebo-controlled trial evaluating the efficacy and safety of mitapivat in patients with SCD (NCT05031780)
- The phase 2 portion of RISE UP is a dose-finding study evaluating 2 doses of mitapivat (50 mg BID and 100 mg BID) vs placebo to select the dose of mitapivat to be assessed in the phase 3 portion



*Patients who receive mitapivat in double-blind period will continue to receive the same dose of mitapivat in the open-label extension period; patients who receive placebo will be randomized 1:1 to mitapivat 50 mg BID or 100 mg BID.
†Patients who have completed the 12-week phase 2 double-blind period and do not have ongoing grade ≥3 TEAEs can receive mitapivat in the 216-week open-label extension period.

BID, twice daily; Hb, hemoglobin; SCD, sickle cell disease; TEAE, treatment-emergent adverse event.

Eligibility Criteria

Key Inclusion Criteria

- ≥16 years of age
- Confirmed diagnosis of SCD (any genotype)
- 2-10 sickle cell pain crises (SCPCs) in the prior 12 months, including:
  - Acute pain
  - Acute chest syndrome
  - Priapism
  - Hepatic or splenic sequestration
- Anemia (≥5.5 and ≤10.5 g/dL)
- If taking hydroxyurea (HU), the dose must be stable for ≥90 days before starting study drug

Key Exclusion Criteria

- Pregnant or breastfeeding
- Receiving regular RBC transfusion therapy
- Hospitalized for SCPC or other vaso-occlusive event ≤14 days prior to informed consent (IC) or during Screening
- Received disease-modifying treatment for SCD except HU or hematopoiesis-stimulating agents ≤90 days before randomization
- Cardiovascular or pulmonary disease

HU, hydroxyurea; IC, informed consent; RBC, red blood cell; SCD, sickle cell disease; SCPC, sickle cell pain crisis.

Primary Endpoints

- Primary endpoints:
  - Hb response, defined as ≥1.0 g/dL increase in average Hb concentration from Week 10 through Week 12 compared with baseline
  - Adverse events (AEs) and serious adverse events (SAEs), including type, severity, and relationship to study drug

AE, adverse event; Hb, hemoglobin; SAE, serious adverse event

Secondary Endpoints

- Prespecified secondary endpoints:
  - Average change from baseline from Week 10 through Week 12 in:
    - Hb levels
    - Indirect bilirubin
    - Lactate dehydrogenase (LDH)
    - Absolute reticulocyte count and percent reticulocytes
    - Erythropoietin
    - Patient-Reported Outcomes Measurement Information System® (PROMIS) Fatigue 13a Short Form (SF) score
  - Annualized rate of SCPCs

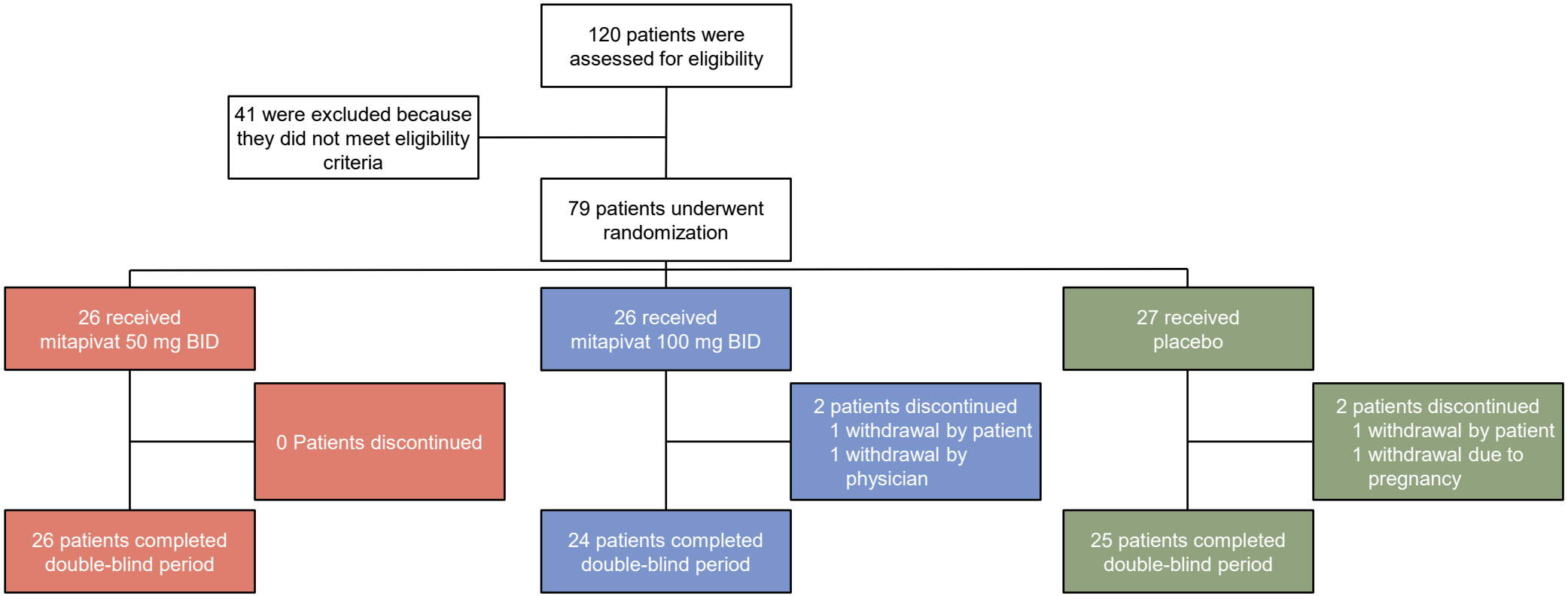
Hb, hemoglobin; LDH, lactate dehydrogenase; PROMIS, Patient-Reported Outcomes Measurement Information System; SCPC, sickle cell pain crisis; SF, Short Form.

Primary and Secondary Endpoints – Statistical Methods

- The difference in Hb response rates (proportion of patients with Hb response) between each of the mitapivat arms and the placebo arm was estimated and the exact 95% CIs and 2-sided p-values based on Fisher's exact test (significance level of 0.05) were calculated
- Secondary endpoints associated with change from baseline were analyzed based on a mixed model for repeated measures. The model included change from baseline as the dependent variable, baseline value as a covariate, treatment arm, study visit, and treatment-by-visit interaction as fixed factors, and subject as the random effect. The estimated treatment difference between each of the mitapivat arms and the placebo arm was estimated based on the LS mean and associated 95% CIs for each endpoint
- The annualized rates of SCPCs between each of the mitapivat arms and the placebo arm were compared based on a negative binomial regression model with natural log link. The model included the number of SCPCs as the response variable and the treatment arm as an independent variable

Hb, hemoglobin; LS, least squares; SCPC, sickle cell pain crisis.

Patient Disposition



BID, twice a day.

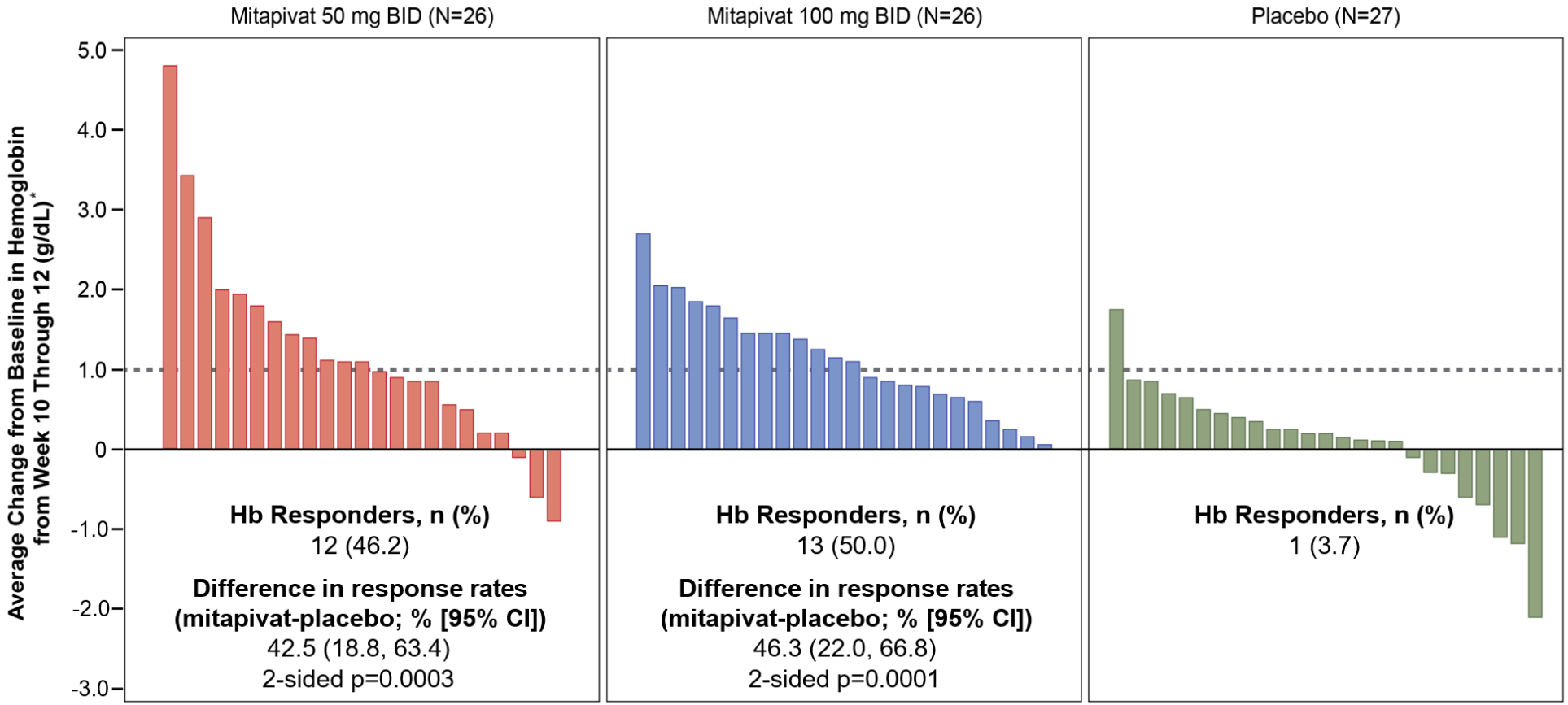
Demographics and Baseline Characteristics

	Mitapivat 50 mg BID N=26	Mitapivat 100 mg BID N=26	Placebo N=27
Age, mean (SD), years	29.9 (7.79)	30.2 (10.52)	28.5 (10.3)
Sex, n (%)			
Male	11 (42.3)	10 (38.5)	7 (25.9)
Female	15 (57.7)	16 (61.5)	20 (74.1)
Race, n (%)			
Black or African American	16 (61.5)	14 (53.8)	16 (59.3)
White	9 (34.6)	9 (34.6)	8 (29.6)
Asian	0	1 (3.8)	1 (3.7)
Multiracial	1 (3.8)	2 (7.7)	2 (7.4)
Hb, mean (SD), g/dL	8.76 (1.29)	8.82 (0.90)	8.49 (1.14)
Indirect bilirubin, mean (SD), µmol/L	31.51 (21.87)	31.27 (23.13)	30.42 (22.41)
LDH, mean (SD), U/L	403.15 (147.19)	422.10 (148.97)	381.25 (128.91)
Erythropoietin, mean (SD), IU/L	115.01 (125.88)	110.26 (128.36)	149.64 (285.09)
No. of SCPCs,* mean (SD)	3.1 (1.83)	3.2 (1.65)	3.4 (1.91)
Hydroxyurea use, n (%)	20 (76.9)	21 (80.8)	19 (70.4)

*Includes SCPCs within 12 months before IC and during screening.

BID, twice a day; Hb, hemoglobin; IC, informed consent; LDH, lactate dehydrogenase; No, number; SCPC, sickle cell pain crisis.

Mitapivat Met the Phase 2 Primary Endpoint, Demonstrating Higher Hb Response Rates Compared With Placebo



*Baseline was defined as the average of all assessments during the screening period up to the randomization date. Assessments collected within 8 weeks after an RBC transfusion were excluded from the baseline derivation and from the analysis. Subjects who do not have any Hb concentration assessments from Week 10 through Week 12 are considered as nonresponders.

BID, twice a day; Hb, hemoglobin; RBC, red blood cell.

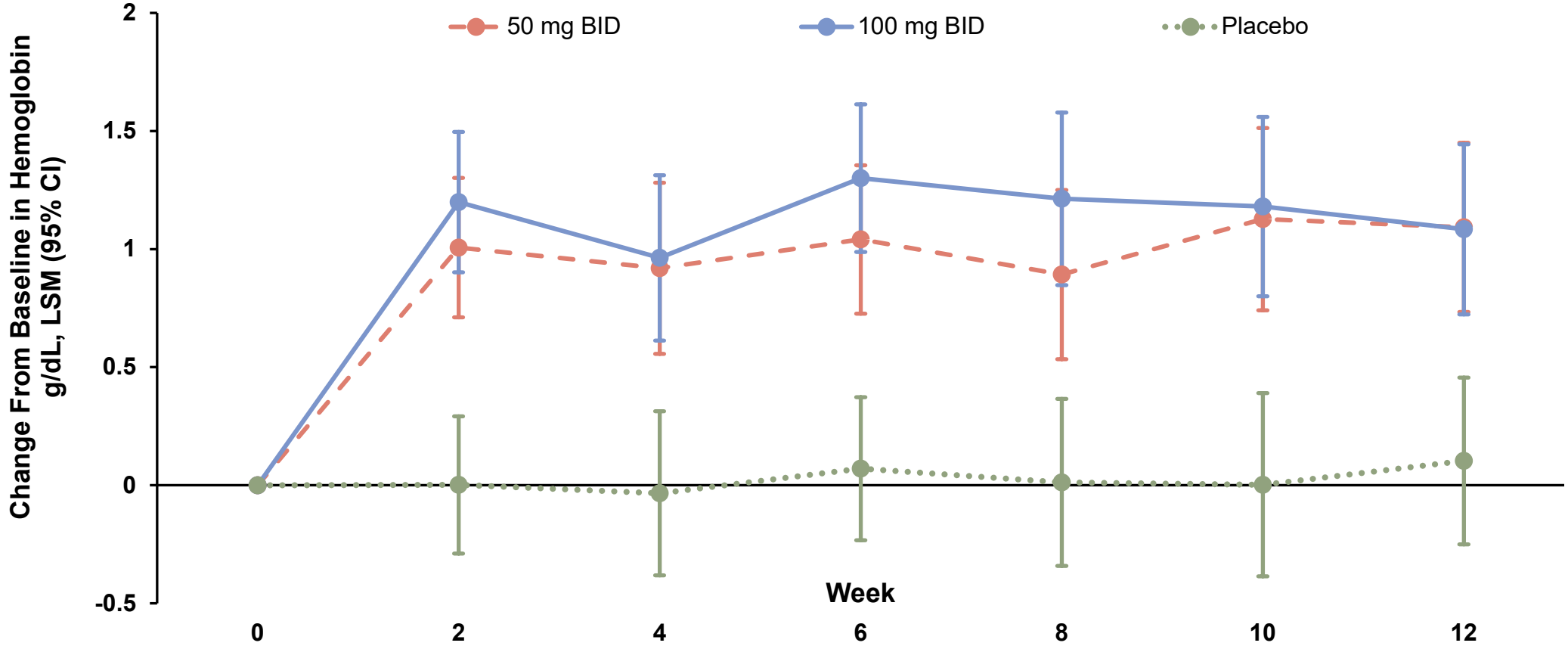
Improvements in Hb Levels Were Observed With Both Doses of Mitapivat Compared With Placebo

	Mitapivat 50 mg BID N=26	Mitapivat 100 mg BID N=26	Placebo N=27
Baseline Hb level (g/dL)			
Mean (SD)	8.76 (1.29)	8.82 (0.90)	8.49 (1.14)
Average change from baseline in Hb level from Week 10 through Week 12 (g/dL)			
LSM (95% CI)	1.11 (0.77, 1.45)	1.13 (0.79, 1.47)	0.05 (−0.28, 0.39)
Difference (LSM [95% CI]; mitapivat−placebo)	1.06 (0.58, 1.53)	1.08 (0.60, 1.56)	

NOTE: The estimates and 95% CIs are based on the mixed-effect model repeated measure (MMRM) method, which includes change from baseline as the dependent variable, baseline as a covariate, and treatment group, visit, treatment-by-visit interaction, and subject as the random effect.

BID, twice a day; Hb, hemoglobin; LSM, least squares mean.

Hemoglobin Levels Improved Early With Both Mitapivat Doses and Were Sustained Through Week 12



Mitapivat 100 mg BID, n=	26	23	23	24	23	23	23
Mitapivat 50 mg BID, n=	26	23	19	22	24	22	22
Placebo, n=	27	24	22	25	24	21	22

NOTE: The estimates and 95% CIs are based on the mixed-effect model repeated measure (MMRM) method, which includes change from baseline as the dependent variable, baseline as a covariate, and treatment group, visit, treatment-by-visit interaction, and subject as the random effect.

BID, twice a day; LSM, least squares mean.

Reductions in SCPCs Were Observed at Both Doses Compared With Placebo

	Mitapivat 50 mg BID N=26	Mitapivat 100 mg BID N=26	Placebo N=27
Sickle cell pain crises			
Annualized rate (95% CI)	0.83 (0.34, 1.99)	0.51 (0.16, 1.59)	1.71 (0.95, 3.08)
Mitapivat/placebo rate ratio (95% CI)	0.48 (0.17, 1.39)	0.30 (0.08, 1.07)	
Rate reduction (mitapivat vs placebo), % (95% CI)*	51.6 (−39.4, 83.2)	70.0 (−7.4, 91.6)	

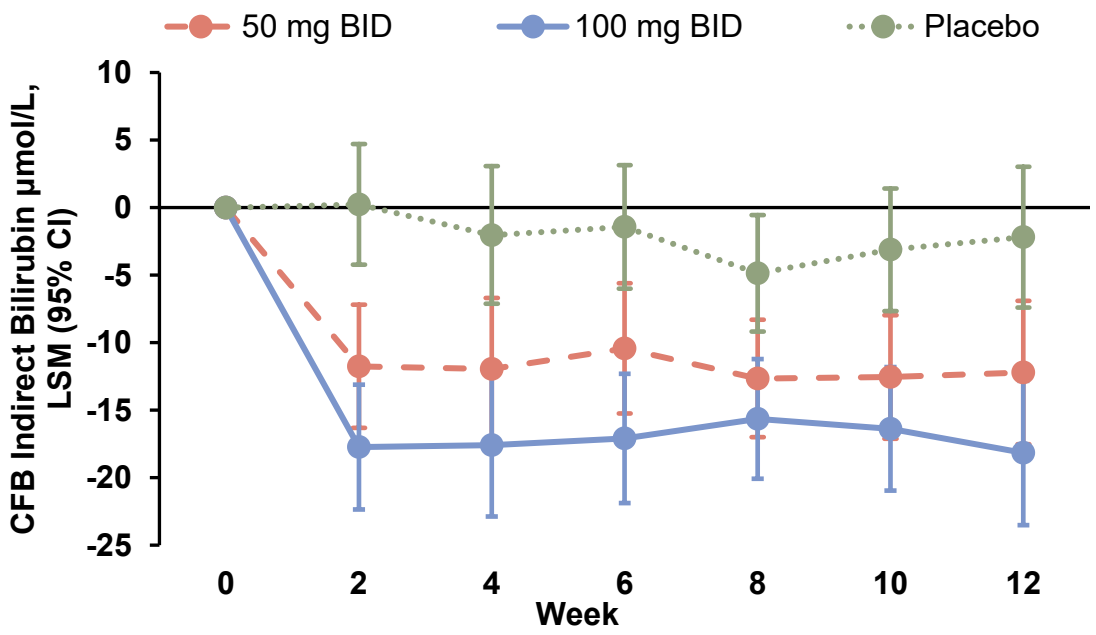
*Rate reduction is defined as 100% x 1−rate ratio).

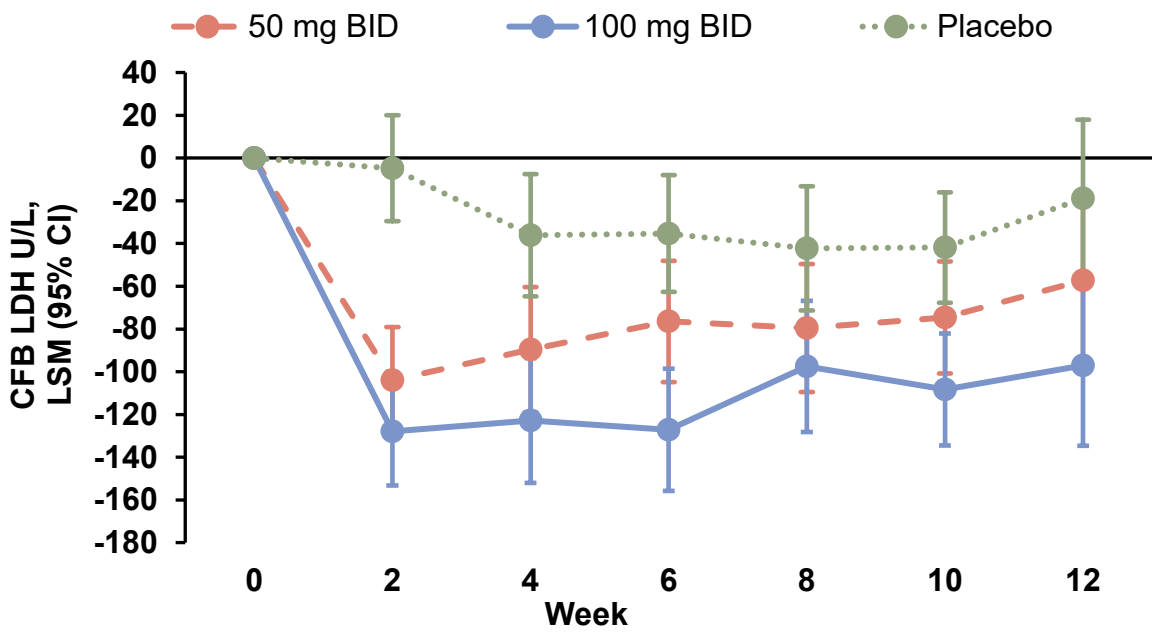
BID, twice a day; SCPCs, sickle cell pain crises.

Improvements in Markers of Hemolysis Were Observed With Both Doses of Mitapivat Compared With Placebo

Average CFB in indirect bilirubin from Week 10 through Week 12 (µmol/L)	Mitapivat 50 mg BID N=26	Mitapivat 100 mg BID N=26	Placebo N=27
LSM (95% CI)	−12.36 (−17.04, −7.69)	−17.26 (−21.98, −12.55)	−2.65 (−7.23, 1.93)
Difference (LSM [95% CI]; mitapivat−placebo)	−9.72 (−16.26, −3.17)	−14.62 (−21.19, −8.05)	

Average CFB in LDH from Week 10 through Week 12 (U/L)	Mitapivat 50 mg BID N=26	Mitapivat 100 mg BID N=26	Placebo N=27
LSM (95% CI)	−65.90 (−95.08, −36.72)	−102.71 (−132.17, −73.26)	−30.36 (−58.99, −1.73)
Difference (LSM [95% CI]; mitapivat−placebo)	−35.54 (−76.44, 5.36)	−72.35 (−113.54, −31.17)	





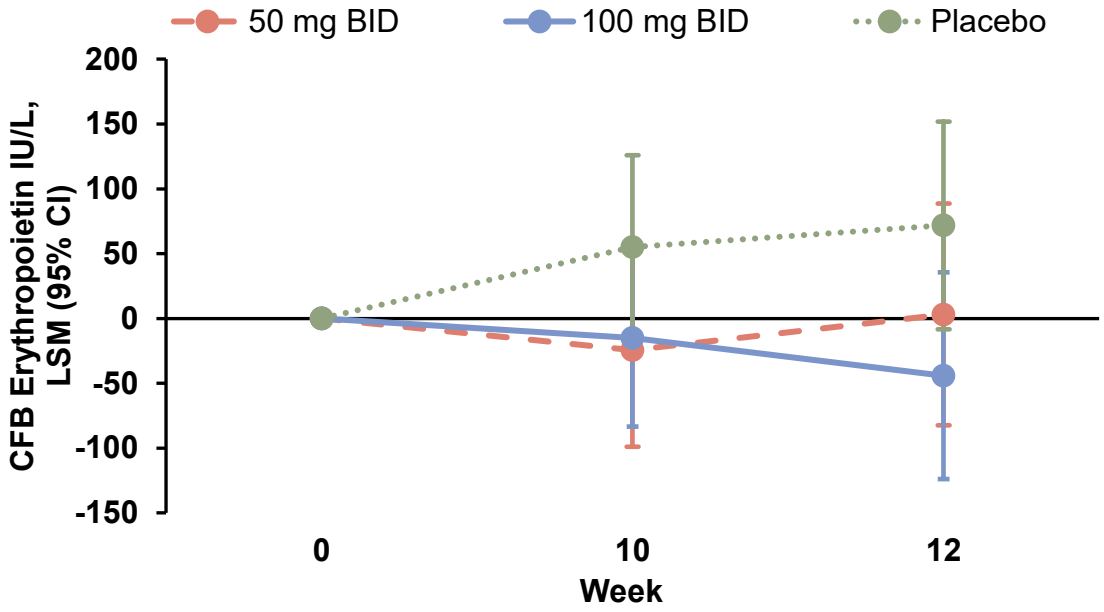
NOTE: The estimates and 95% CIs are based on the mixed-effect model repeated measure (MMRM) method, which includes CFB as the dependent variable, baseline as a covariate, and treatment group, visit, treatment-by-visit interaction, and subject as the random effect.

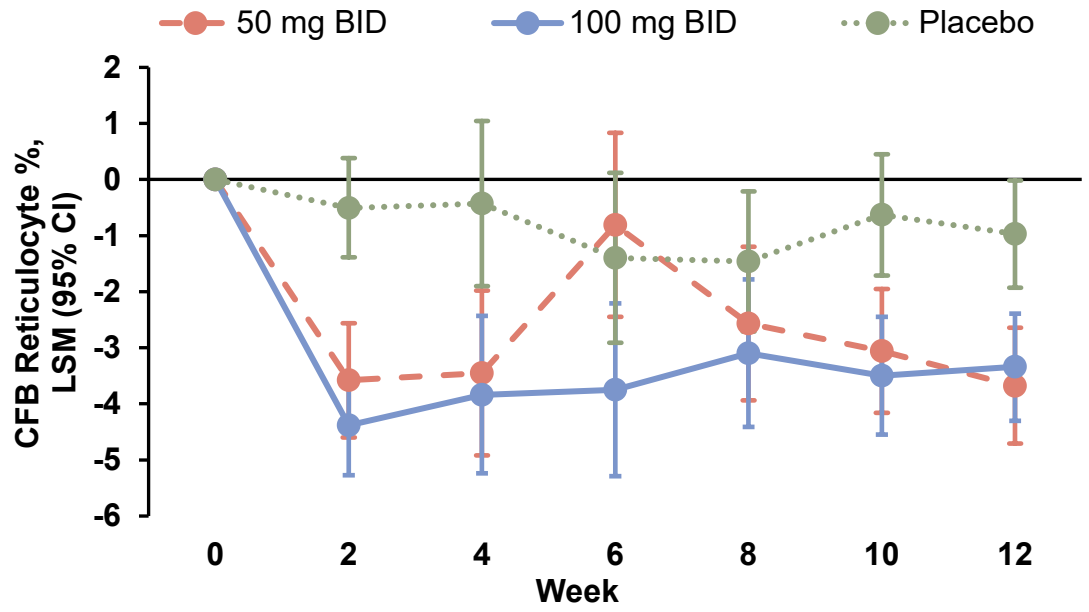
BID, twice a day; CFB, change from baseline; LDH, lactate dehydrogenase; LSM, least squares mean.

Improvements in Markers of Erythropoiesis Were Observed With Both Doses of Mitapivat Compared With Placebo

Average CFB in erythropoietin from Week 10 through Week 12 (IU/L)	Mitapivat 50 mg BID N=26	Mitapivat 100 mg BID N=26	Placebo N=27
LSM (95% CI)	−10.66 (−87.23, −65.91)	−29.66 (−100.16, 40.85)	63.47 (−7.72, 134.67)
Difference (LSM [95% CI]; mitapivat−placebo)	−74.13 (−178.92, 30.65)	−93.13 (−193.39, 7.13)	

Average CFB in percent reticulocytes from Week 10 through Week 12 (%)	Mitapivat 50 mg BID N=26	Mitapivat 100 mg BID N=26	Placebo N=27
LSM (95% CI)	−3.37 (−4.28, −2.47)	−3.42 (−4.27, −2.57)	−0.8 (−1.66, 0.06)
Difference (LSM [95% CI]; mitapivat−placebo)	−2.57 (−3.82, −1.32)	−2.62 (−3.83, −1.40)	





NOTE: The estimates and 95% CIs are based on the mixed-effect model repeated measure (MMRM) method, which includes CFB as the dependent variable, baseline as a covariate, and treatment group, visit, treatment-by-visit interaction, and subject as the random effect.

BID, twice a day; CFB, change from baseline; LSM, least squares mean.

Improvement in PROMIS Fatigue Scores Was Observed With Mitapivat 50 mg BID Compared With Placebo

Average CFB in PROMIS Fatigue 13a Short Form T score from Week 10 through Week 12	Mitapivat 50 mg BID N=26	Mitapivat 100 mg BID N=26	Placebo N=27
LSM (95% CI)	−3.80 (−7.16, −0.45)	−0.10 (−3.27, 3.08)	−0.17 (-3.40, 3.07)
Difference (LSM [95% CI]; mitapivat−placebo)	−3.64 (−8.30, 1.03)	0.07 (−4.46, 4.60)	

BID, twice a day; CFB, change from baseline; LSM, least squares mean; PROMIS, Patient-Reported Outcomes Measurement Information System.

Summary of Treatment-Emergent Adverse Events

	Mitapivat 50 mg BID N=26	Mitapivat 100 mg BID N=26	Placebo N=27
Any TEAEs, n (%)	19 (73.1)	23 (88.5)	22 (81.5)
Grade ≥3 TEAEs, n (%)	3 (11.5)	5 (19.2)	2 (7.4)
Treatment-related TEAEs, n (%)	10 (38.5)	8 (30.8)	7 (25.9)
Grade ≥3 treatment-related TEAEs, n (%)	0	0	0
Serious TEAEs, n (%)*	2 (7.7)	4 (15.4)	3 (11.1)
Serious treatment-related TEAEs, n (%)	0	0	0
TEAEs leading to discontinuation of study drug, n (%)	0	0	0
TEAEs leading to dose reduction	0	0	0
TEAEs leading to interruption of study drug	0	0	0
TEAEs leading to death	0	0	0
Treatment-related TEAEs leading to death	0	0	0

*Serious TEAEs included infections, bone fracture, pulmonary embolism, and anemia.

BID, twice a day; TEAE, treatment-emergent adverse event.

Mitapivat Was Generally Safe and Well Tolerated

Patients with most common TEAEs, n (%)*	Mitapivat 50 mg BID N=26	Mitapivat 100 mg BID N=26	Placebo N=27
Headache	6 (23.1)	6 (23.1)	7 (25.9)
Arthralgia	3 (11.5)	5 (19.2)	9 (33.3)
Dysmenorrhea	0	3 (11.5)	0
Pain	3 (11.5)	3 (11.5)	2 (7.4)
Pain in extremity	1 (3.8)	3 (11.5)	6 (22.2)
Back pain	4 (15.4)	2 (7.7)	3 (11.1)
Nausea	1 (3.8)	2 (7.7)	4 (14.8)
Fatigue	4 (15.4)	1 (3.8)	5 (18.5)
Influenza-like illness	1 (3.8)	1 (3.8)	3 (11.1)

*Most common TEAEs are those of any grade in ≥10% of patients in any treatment group.
NOTE: Patients with multiple occurrences of one AE type are counted once for that AE type.

AE, adverse event; BID, twice a day; TEAE, treatment-emergent adverse event.

Conclusions

- In the phase 2, 12-week, randomized, placebo-controlled, double-blind period of RISE UP, treatment with mitapivat demonstrated statistically significant and clinically meaningful improvements in Hb response at both dose levels (50 mg BID and 100 mg BID) compared with placebo
- Improvements in markers of hemolysis/erythropoiesis were observed in both mitapivat treatment arms compared with placebo
  - The magnitude of improvements were generally larger in the mitapivat 100-mg BID arm
- A reduction in the annualized rate of SCPCs was observed in both mitapivat treatment arms compared with placebo
- Mitapivat was safe and well tolerated, with an observed safety profile consistent with previously reported data of mitapivat in SCD and other hemolytic anemias
  - No AEs led to study drug reduction, discontinuation, interruption, or death

AE, adverse event; BID, twice a day; Hb, hemoglobin; SCD, sickle cell disease; SCPC, sickle cell pain crisis.

Conclusions

Mitapivat, through its dual mechanism of action, may provide clinical benefit to patients with SCD. Current phase 2 data support continued development in the phase 3* portion of the RISE UP trial evaluating a 100-mg BID dose

*The phase 3 portion of RISE UP is currently recruiting patients (NCT05031780).

BID, twice a day; SCD, sickle cell disease.

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Disclosures

- Conflicts of interest
  - MI reports receiving grants from Pfizer, Global Blood Therapeutics, Novartis, Agios, Novo Nordisk, Forma Therapeutics, and Alexion; consulting fees from Novo Nordisk, Global Blood Therapeutics, Novartis, Vertex, and bluebird bio; honoraria from Global Blood Therapeutics; and is on an advisory board for Global Blood Therapeutics
  - BA reports receiving grants from the American Society of Hematology, the Connecticut Department of Public Health, Forma Therapeutics, Global Blood Therapeutics, Hemanext, Health Resources & Services Administration (HRSA), Novartis, Patient-Centered Outcomes Research Institute (PCORI), and Pfizer; consulting fees from Accordant, Afimmune, Agios, bluebird bio, Emmaus, Forma Therapeutics, GlaxoSmithKline, Global Blood Therapeutics, Hemanext, Novartis, Novo Nordisk, Sanofi Genzyme, and Vertex
  - OEN reports being on an advisory board for Agios
  - AKG reports being an advisory board member for Bausch and Global Blood Therapeutics
  - PB reports being a consultant for bluebird bio, Roche, Emmaus, Global Blood Therapeutics, and Jazz Pharmaceuticals; a consultant and advisory board member for addmedica; a consultant, advisory board member, and steering committee member at Novartis; and co-founder of INNOVHEM

Disclosures (cont'd)

- Conflicts of interest (cont'd)
  - RC reports receiving grants from bluebird bio and Global Blood Therapeutics; receiving honoraria from Global Blood Therapeutics; being an advisory board member at addmedica, Novartis, and Global Blood Therapeutics; being a steering committee member for the Italian Association of Pediatric Hematology and Oncology (AIEOP); and a European Affairs Committee member for the European Haematology Association (EHA)
  - ATT reports being a consultant for and receiving research funding from Novartis, Bristol-Myers Squibb (Celgene), Vifor, Pharmacosmos, and Agios
  - MRA reports receiving grants or research funding from Novartis, Global Blood Therapeutics, and Forma; receiving honoraria from Global Blood Therapeutics; receiving travel grants from Emaus and Forma; and being an advisory board member for Novartis, Agios, and Vertex
  - WS reports being a consultant for Agios
  - AO, VI, SM, AMY, HS, SP, RU, AUZ, and OY are current or former employees of Agios Pharmaceuticals and may own stock
  - LO, BD, CLCL, SLT, AI, and STOS do not report any conflicts of interest