Results from a phase 2, open-label, multicenter study of the oral pyruvate kinase activator mitapivat in adults with non–transfusion-dependent alpha- or beta-thalassemia

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Disclosures

- **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
- **D. Mark Layton**: Agios, Novartis – consultancy; Agios, Cerus, Novartis – membership on an entity's Board of Directors or advisory committees
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- **Hanny Al-Samkari**: Agios, argenx, Dova, Novartis, Rigel, Sobi – consultancy; Agios, Dova, Amgen – research funding
- **Joy Bhatia, Bo Tong, Megan Lynch**, and **Katrin Uhlig**: Agios – employees and shareholders
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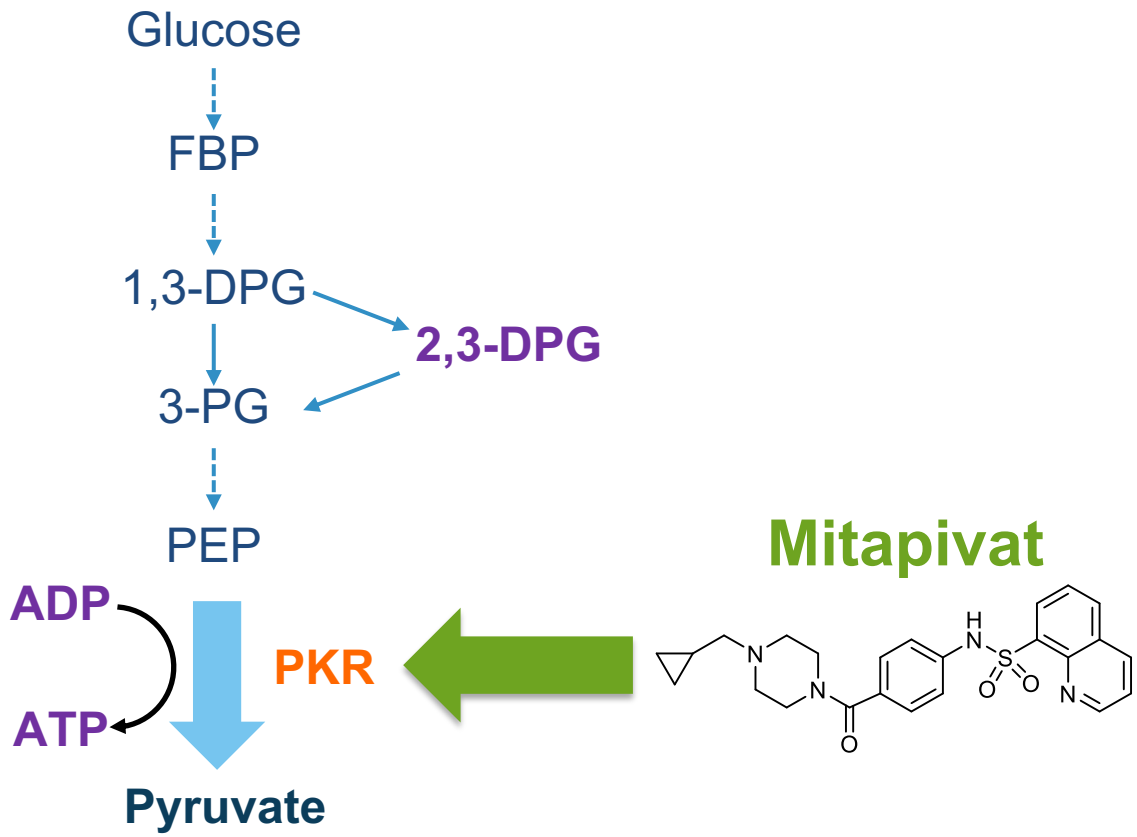
Mitapivat is an investigational, first-in-class, oral, small-molecule allosteric activator of PK

Mitapivat activates wild-type and mutant PKR[1] and increases RBC ATP levels[2]

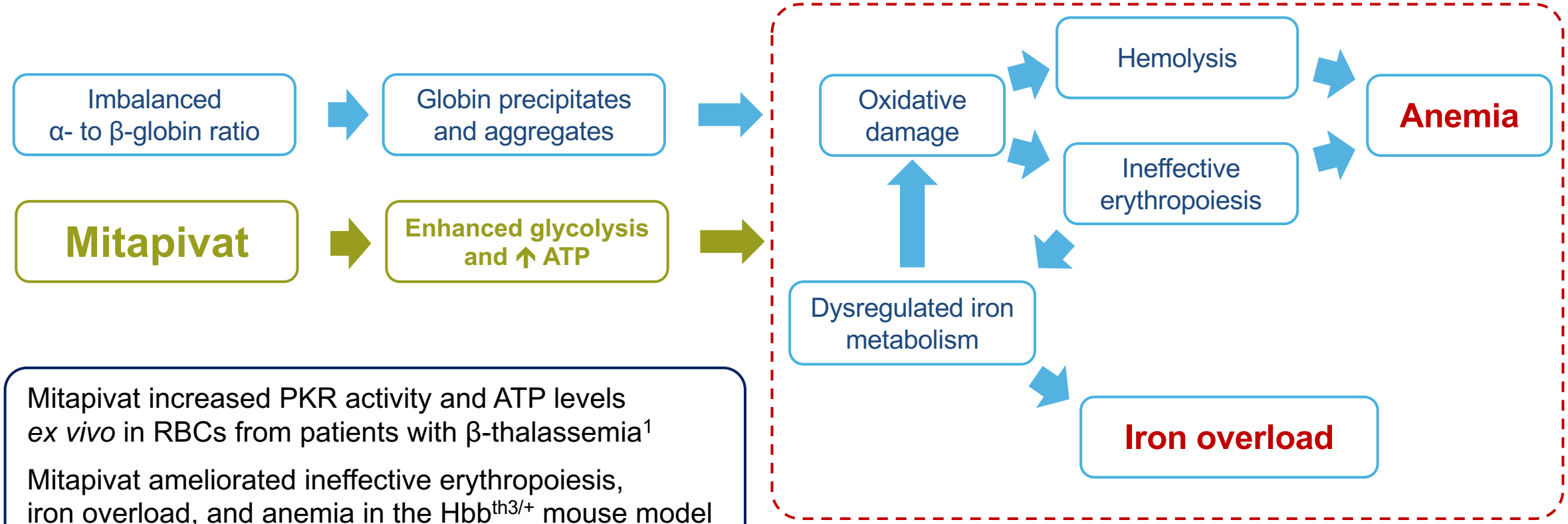


- ATP generation is essential for RBC functioning and stability[1,3]
- Mitapivat activates PKR, which catalyzes the final step of glycolysis in RBCs[2]
- In studies in patients with PK deficiency or sickle cell disease, BID dosing with mitapivat improved anemia with an acceptable tolerability profile[4–7]

ADP = adenosine diphosphate; ATP = adenosine triphosphate; BID = twice daily; DPG = diphosphoglyceric acid; FBP = fructose 1,6–bisphosphate; PEP = phosphoenolpyruvic acid; PG = phosphoglyceric acid; PK = pyruvate kinase; PKR = PK in RBCs; RBC = red blood cell.

1. Kung C et al. *Blood* 2017;130:1347—56; **2.** Yang H et al. *Clin Pharmacol Drug Dev* 2019;8:246–59; **3.** Valentini G et al. *J Biol Chem* 2002;277:23807–14; **4.** Grace RF et al. *EHA Congress* 2020, Abstract EP1561; **5.** Al-Samkari H et al. *EHA Congress* 2021. Abstract EHA-1873; **6.** Glenthøj A et al. *EHA Congress* 2021. Abstract EHA-2112; **7.** Xu JZ et al. *ASH 2020*. Abstract 681.

Hypothesis: mitapivat mechanism in thalassemia via activation of wild-type PKR



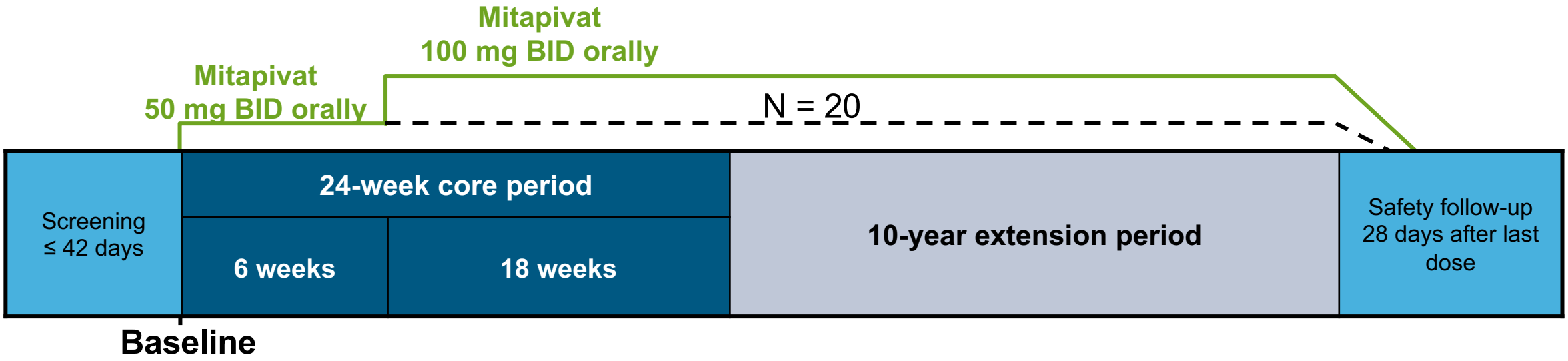
Mitapivat increased PKR activity and ATP levels *ex vivo* in RBCs from patients with β-thalassemia[1]

Mitapivat ameliorated ineffective erythropoiesis, iron overload, and anemia in the $Hbb^{th3/+}$ mouse model of β-thalassemia[2]

ATP = adenosine triphosphate; PK = pyruvate kinase; PKR = PK in RBCs; RBC = red blood cell.

1. Rab MAE et al. *ASH Congress* 2019, Abstract 3506; **2.** Matte A et al. *J Clin Invest* 2021;144206.

This phase 2, open-label, multicenter study investigated the efficacy and safety of mitapivat in non–transfusion-dependent α- and β-thalassemia[a]



Key inclusion criteria:

- β-thalassemia ± α-globin gene mutations, HbE β-thalassemia, or α-thalassemia (HbH disease)
- Hb ≤ 10.0 g/dL
- Non–transfusion-dependent[b]

Primary endpoint[c]

- Hb response, defined as increase of ≥ 1.0 g/dL from baseline at any time between Weeks 4–12, inclusive

Secondary and exploratory endpoints

- Sustained Hb response; delayed Hb response; markers of hemolysis and erythropoiesis; safety

[a]EudraCT 2018-002217-35, ClinicalTrials.gov: NCT03692052; [b]≤ 5 RBC units transfused in the preceding 24 weeks and none in the 8 weeks prior to study drug; [c]With the originally planned sample size of 17 patients, the study would have 80% power to reject a ≤ 30% response rate at a 1-sided 0.05 type 1 error rate.
BID = twice daily; dL = deciliter; Hb = hemoglobin; HbE = hemoglobin E; HbH = hemoglobin H; RBC = red blood cell.

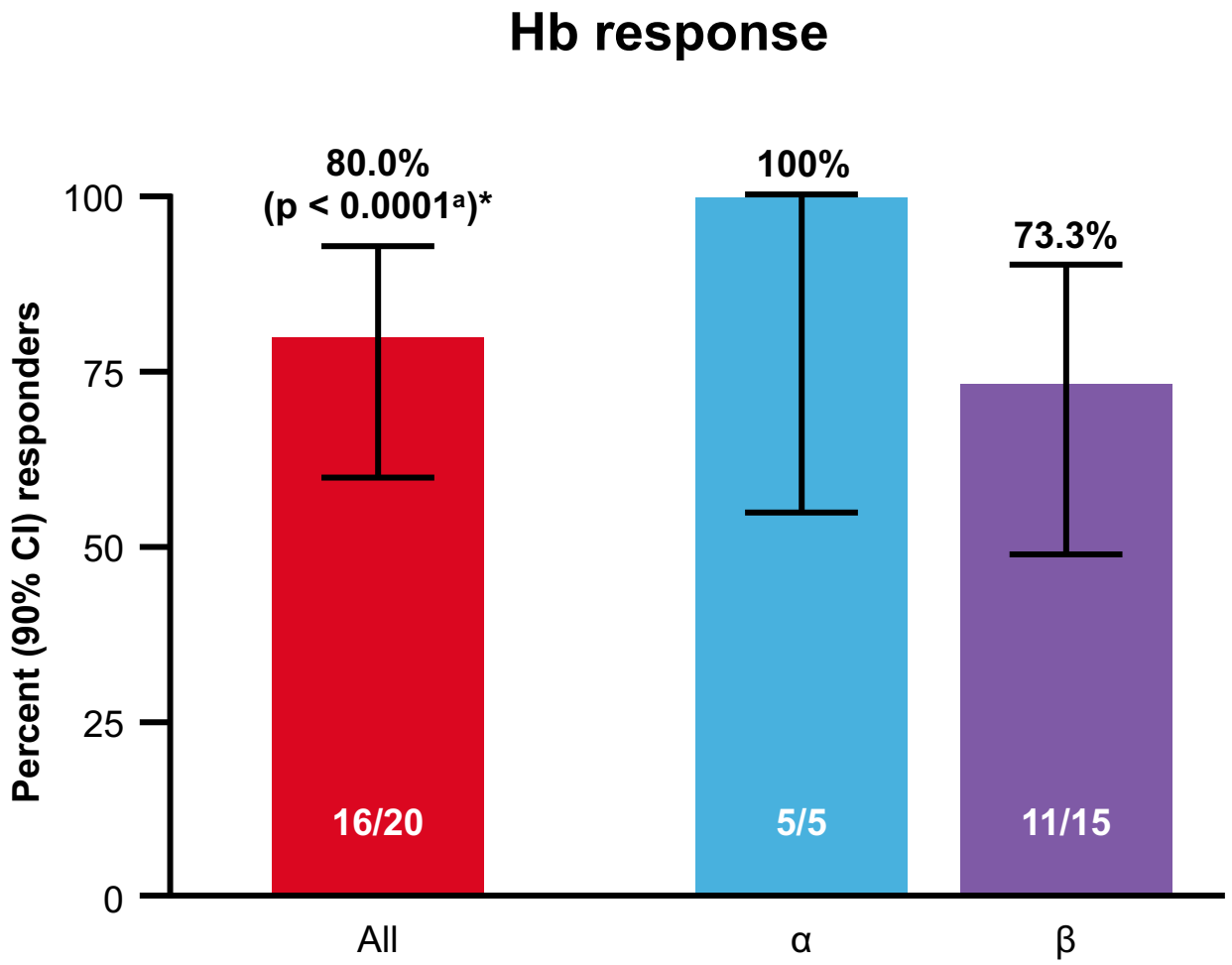
Patient demographics and baseline characteristics

Patient demographics and BL characteristics	All patients (N = 20)
Completed 24-week core treatment period, n (%)	19 (95)
Sex, n (%)	
Male	5 (25.0)
Female	15 (75.0)
Age, median (range), years	44.0 (29–67)
Race, n (%)	
Asian	10 (50.0)
White	4 (20.0)
Black or African American	1 (5.0)
Native Hawaiian or other Pacific Islander	1 (5.0)
American Indian or Alaska Native	0
Other	3 (15.0)
Not reported	1 (5.0)
Thalassemia type, n (%)	
α-thalassemia	5 (25%)
β-thalassemia	15 (75%)
Hb baseline, median (range), g/dL	8.43 (5.13–9.80)
Total bilirubin, median (range), µmol/L	31.00 (8.6–90.0)
LDH, median (range), U/L	249.00 (126.0–513.0)
Erythropoietin, median (range), IU/L	79.00 (15.0–11191.0)

Genotype	Patients (N = 18)[a]
β-thalassemia, n (%)	
Intermedia	6 (33.3)
Intermedia + α duplication	3 (16.7)
Trait/phenotypic β-thalassemia intermedia	2 (11.1)
HbE/β-thalassemia, n (%)	
HbE/β^0	2 (11.1)
α-thalassemia, n (%)	
Deletional	2 (11.1)
Non-deletional	3 (16.7)

[a]Genotype data is unknown for 2 patients.
AE = adverse event; BL = baseline; Hb = hemoglobin; HbE = hemoglobin E; IU = international units; LDH = lactate dehydrogenase; U = units.

Mitapivat met the primary endpoint of a Hb response in 80% of patients



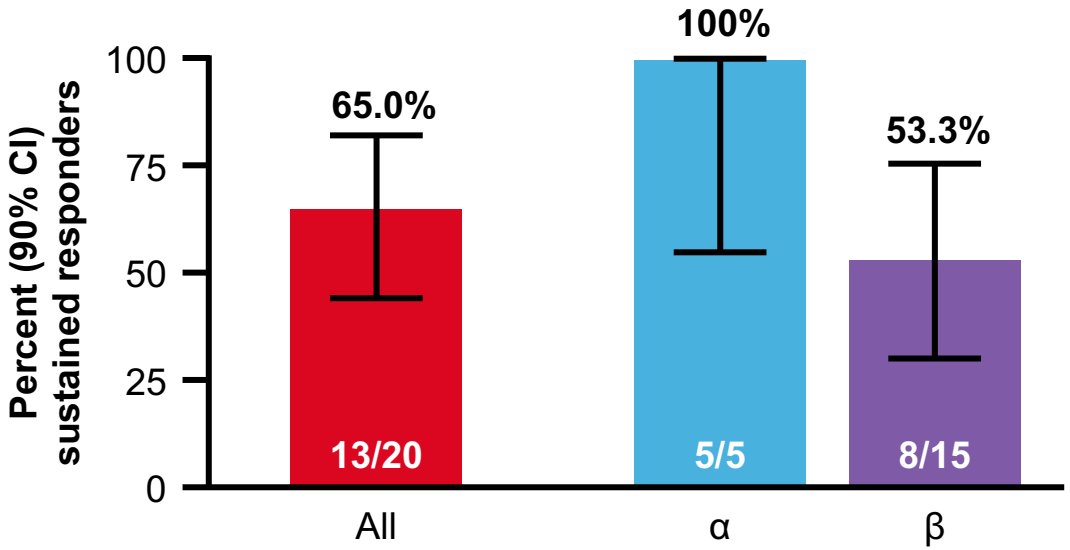
Primary endpoint

Hb response:
≥ 1.0 g/dL increase in Hb concentration from BL at ≥ 1 assessments between Weeks 4–12 (inclusive)

NB: Primary endpoint; Hb response, defined as a ≥1.0 g/dL increase in Hb concentration from baseline at 1 or more assessments between Week 4 and Week 12 (inclusive).
[a]1-sided p-value based on Clopper-Pearson method.
BL = baseline; CI = confidence interval; Hb = hemoglobin.

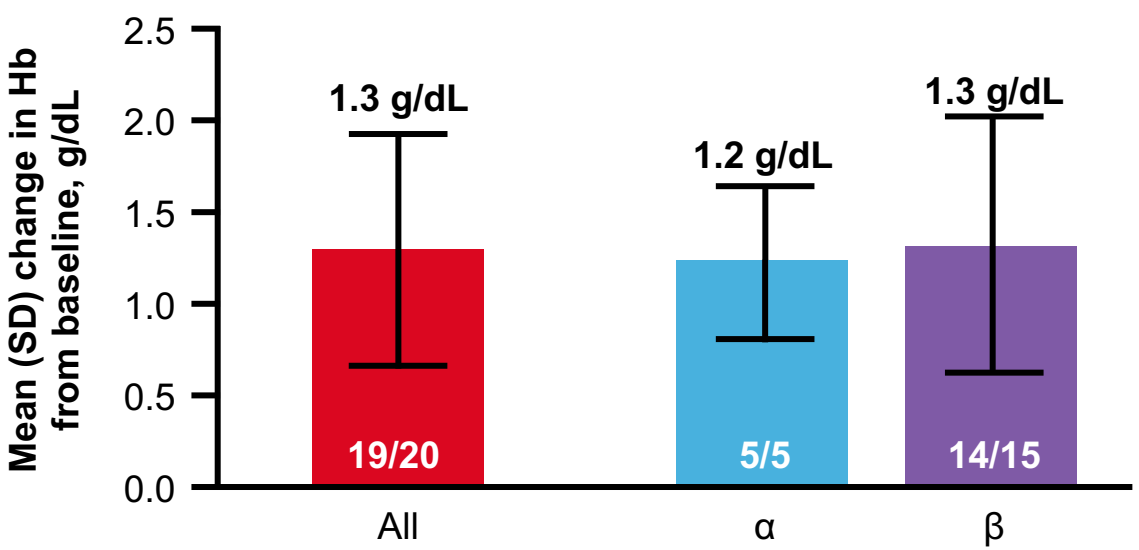
Secondary endpoints: sustained Hb response and consistent increases in mean Hb

Sustained Hb response



Sustained Hb response:
A primary endpoint response during Weeks 4–12 and a ≥ 1.0 g/dL increase in Hb concentration at ≥ 2 assessments between Weeks 12 and 24

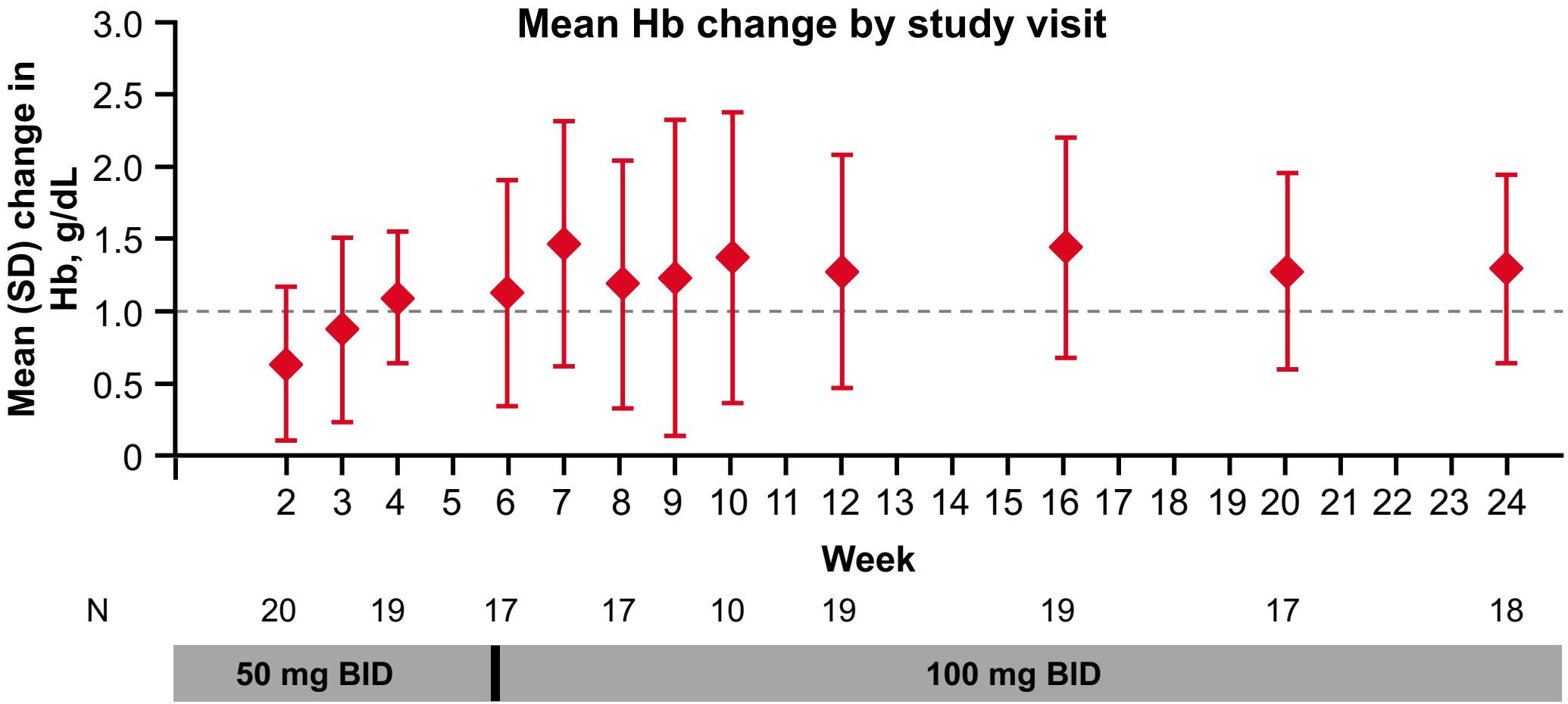
Mean Hb change



Mean Hb change:
Mean change from BL in Hb concentrations over a 12-week interval from Weeks 12 and 24

BL = baseline; CI = confidence interval; Hb = hemoglobin; SD = standard deviation.

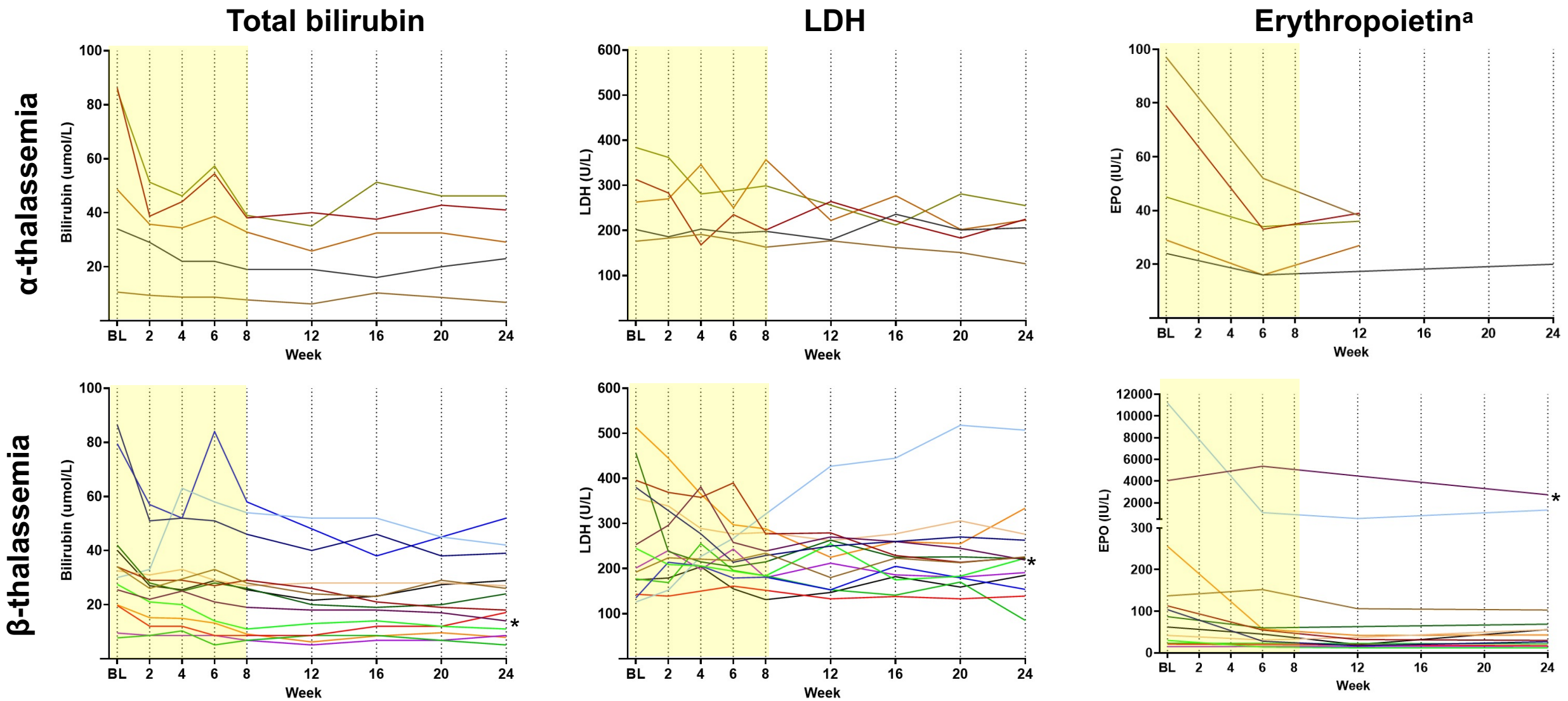
Improvements in Hb were rapid and maintained over the duration of the core treatment period



- Mean (SD) time to first Hb increase of ≥ 1 g/dL among responders was 4.5 (3.2) weeks

NB: Mean change from baseline in Hb concentrations over a continuous 12-week interval from Week 12 to Week 24
BID = twice daily; Hb = hemoglobin; SD = standard deviation.

Treatment with mitapivat improved markers of hemolysis and erythropoiesis in both α- and β-thalassemia



*Non-responder (purple line). [a]Week 24 data are missing for four of the five α-thalassemia patients, due to COVID-19.
NB: Predefined secondary endpoints, mean (SD) values of markers of hemolysis: bilirubin, LDH, and mean (SD) values of markers of erythropoietic activity: erythropoietin.
BL = baseline; EPO = erythropoietin; Hb = hemoglobin; IU = international units; LDH = lactate dehydrogenase; SD = standard deviation; U = units; µmol = micromole.

Improvements in ATP support mitapivat's proposed mechanism of action in thalassemia

Treatment dose	Visit	Mean (CV%) ATP change from baseline in blood, %
50 mg BID	Week 6 (n = 11)	78.2 (82.7)
100 mg BID	Week 8 (n = 12)	72.7 (67.9)
100 mg BID	Week 12 (n = 12)	86.7 (68.7)
100 mg BID	Week 24 (n = 8)	61.6 (62.7)

- Mean ATP percent increase from baseline was similar to that previously observed with mitapivat in healthy volunteers[1]

NB: Exploratory endpoint, change from baseline in ATP
ATP = adenosine triphosphate; BID = twice daily; CV = coefficient of variation.
1. Yang H et al. *Clin Pharmacol Drug Dev* 2019;8:246–59.

Common treatment-emergent adverse events reported

Most common TEAEs (any grade in ≥ 15% of patients)	All patients (N = 20)
	Any grade, n (%)
Patients with events	17 (85.0)
Initial insomnia	10 (50.0)
Dizziness	6 (30.0)
Headache	5 (25.0)
Cough	4 (20.0)
Dyspepsia	4 (20.0)
Fatigue	4 (20.0)
Nasal congestion	4 (20.0)
Upper respiratory tract infection	4 (20.0)
Abdominal pain	3 (15.0)
Diarrhea	3 (15.0)
Ocular icterus	3 (15.0)
Pain	3 (15.0)
Pain in extremity	3 (15.0)
Abdominal distension	3 (15.0)
Nausea	3 (15.0)
Oropharyngeal pain	3 (15.0)

MedDRA version 23.0 and CTCAE version 4.03 were used.
CTCAE = Common Terminology Criteria for Adverse Events; MedDRA = Medical Dictionary for Medical Regulatory Activities; TEAE = treatment-emergent adverse event.

Safety summary

All patients (n = 20)	Patients, n (%)	TEAEs[a]
Treatment-related TEAEs	13 (65.0)	Initial insomnia (n = 10), diarrhea (n = 3), dyspepsia (n = 3), abdominal distension (n = 3), nausea (n = 3)
Grade ≥ 3 TEAEs	5 (25.0)	Initial insomnia (n = 1), arthralgia (n = 1), renal impairment (n = 1), anemia (n = 1), vertigo positional (n = 1)
Grade ≥ 3 treatment-related TEAEs	1 (5.0)	Initial insomnia (grade 3)
Serious TEAEs	1 (5.0)	Renal impairment (grade 3)
TEAEs leading to study drug:		
Dose reduction	3 (15.0)	Abdominal distension and dyspepsia (both grade 2), initial insomnia (grade 3), renal impairment (grade 3)
Interruption	1 (5.0)	Vertigo positional (grade 3)
Discontinuation	1 (5.0)	Renal impairment (grade 3) Patient discontinued after the Week 4 visit

- The adverse event leading to study drug discontinuation was not treatment related
- There were no deaths during the study

Patients with multiple adverse events within a PT are counted only once in that PT; for patients with multiple occurrences of an adverse event, the adverse event with the worst CTCAE grade is included in the summary; MedDRA version 23.0 and CTCAE version 4.03 were used.

[a]TEAEs ≥ 20% listed for 'any TEAEs'; ≥ 20% listed for 'treatment-related TEAEs'; all TEAEs listed for other sections. CTCAE = Common Terminology Criteria for Adverse Events; MedDRA = Medical Dictionary for Medical Regulatory Activities; PT = preferred term; TEAE = treatment-emergent adverse event.

Conclusions

- This is the first clinical study evaluating PKR activation as a therapeutic option in α- and β-thalassemia, and is the first drug trial aimed at evaluating treatment in α-thalassemia
- The study met its primary endpoint, and demonstrated a sustained Hb response and improvements in hemolysis and ineffective erythropoiesis in patients with α- and β-thalassemia
- Mitapivat was well tolerated; the safety profile was consistent with previous studies
  - 17 patients continued to the extension period of the study and, as of 29 April 2021, 16 patients remain on study drug
- Mitapivat, through activation of wild-type PKR, may represent a novel therapeutic option for patients with α- or β-thalassemia
  - Two pivotal phase 3 trials, ENERGIZE (NTDT) and ENERGIZE-T (TDT), for patients with α- or β-thalassemia will be initiated in 2021

Hb = hemoglobin; NTDT = non-transfusion-dependent thalassemia; PK = pyruvate kinase; PKR = PK in RBCs; RBC = red blood cell; TDT = transfusion-dependent thalassemia..

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