EUROPEAN HEMATOLOGY ASSOCIATION

EHA25 VIRTUAL

Proof of concept for the oral pyruvate kinase activator mitapivat in adults with non–transfusion-dependent thalassemia: Interim results from an ongoing, phase 2, open-label, multicenter study

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Disclosures

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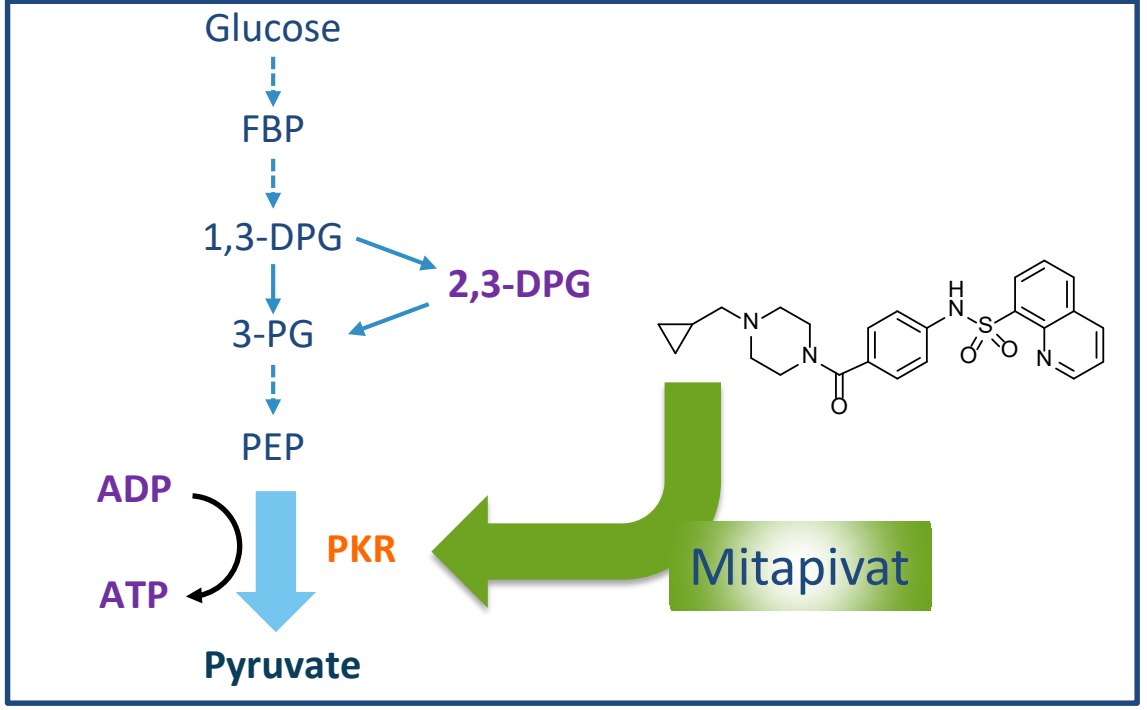
Mitapivat

- Mitapivat (AG-348) is an investigational, first-in-class, oral, small-molecule allosteric activator of pyruvate kinase (PK)R[1], which catalyzes the final step of glycolysis in RBCs[2]
- Mitapivat increased RBC ATP levels by 60% in healthy volunteers[3]
- In a phase 2 study in adult patients with PK deficiency, BID dosing with mitapivat:
  - Increased hemoglobin (Hb) by > 1.0 g/dL in 50% of patients[4]
  - Was well tolerated for up to 42 months[5]

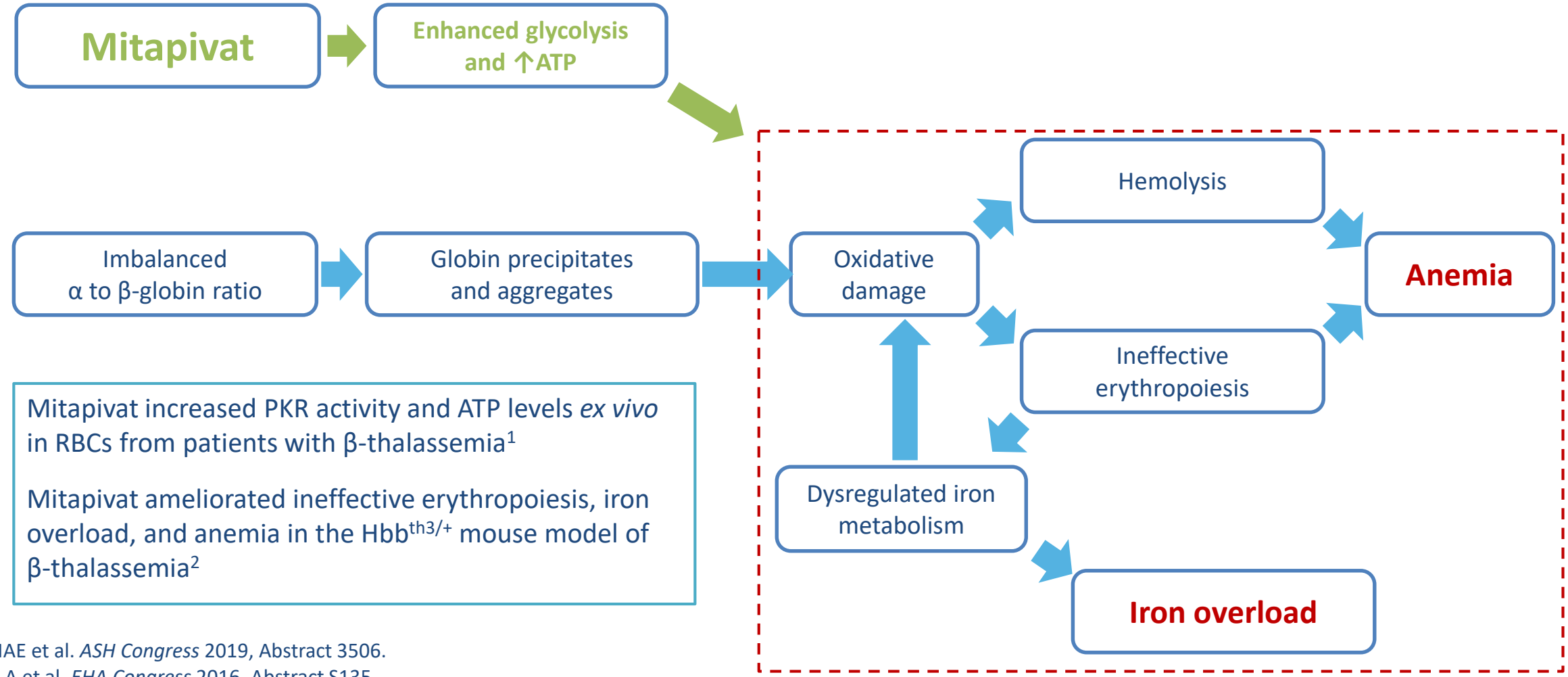
Mitapivat activates wild-type and mutant PKR enzymes[1]



ATP = adenosine triphosphate; BID = twice daily; RBC = red blood cell

1. Kung C et al. *Blood* 2017;130:1347. **2.** Valentini G et al. *J Biol Chem* 2002;277:23807. **3.** Yang H et al. *Clin Pharmacol Drug Dev* 2019;8:246.
4. Grace RF et al. *NEJM* 2019;381:933. **5.** Grace RF et al. *EHA Congress* 2020, Abstract EP1561

Hypothesis: Mitapivat mechanism in thalassemia



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]

1. Rab MAE et al. *ASH Congress* 2019, Abstract 3506.
2. Matte A et al. *EHA Congress* 2016, Abstract S135.

Study design: Open-label, phase 2, multicenter study

Key Inclusion Criteria

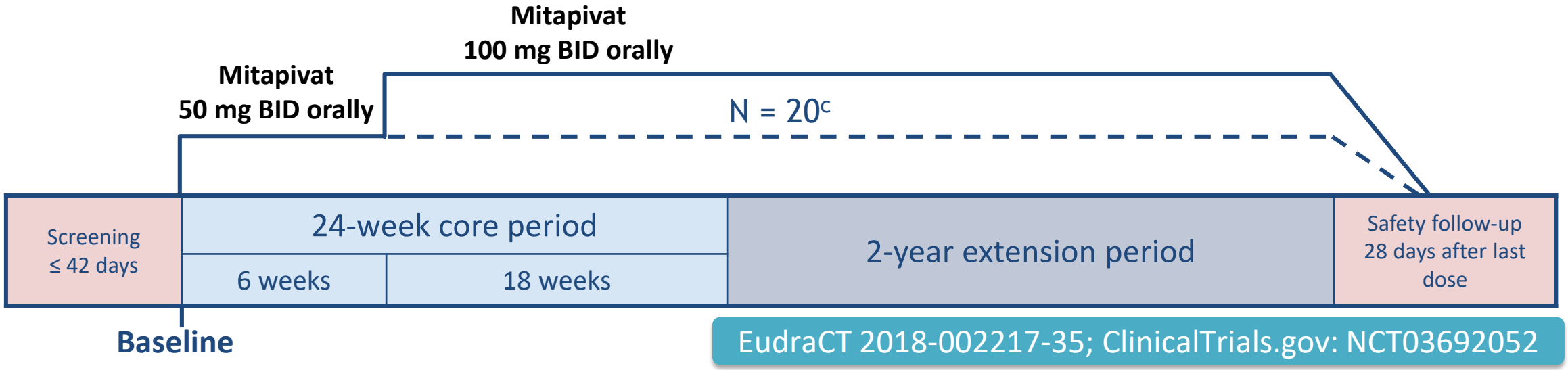
- β-thalassemia ± α-globin gene mutations, HbE β-thalassemia, or α-thalassemia (HbH disease)
- Hb ≤ 10.0 g/dL
- Non–transfusion-dependent[a]

Primary Endpoint[b]

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

Secondary/Exploratory Endpoints

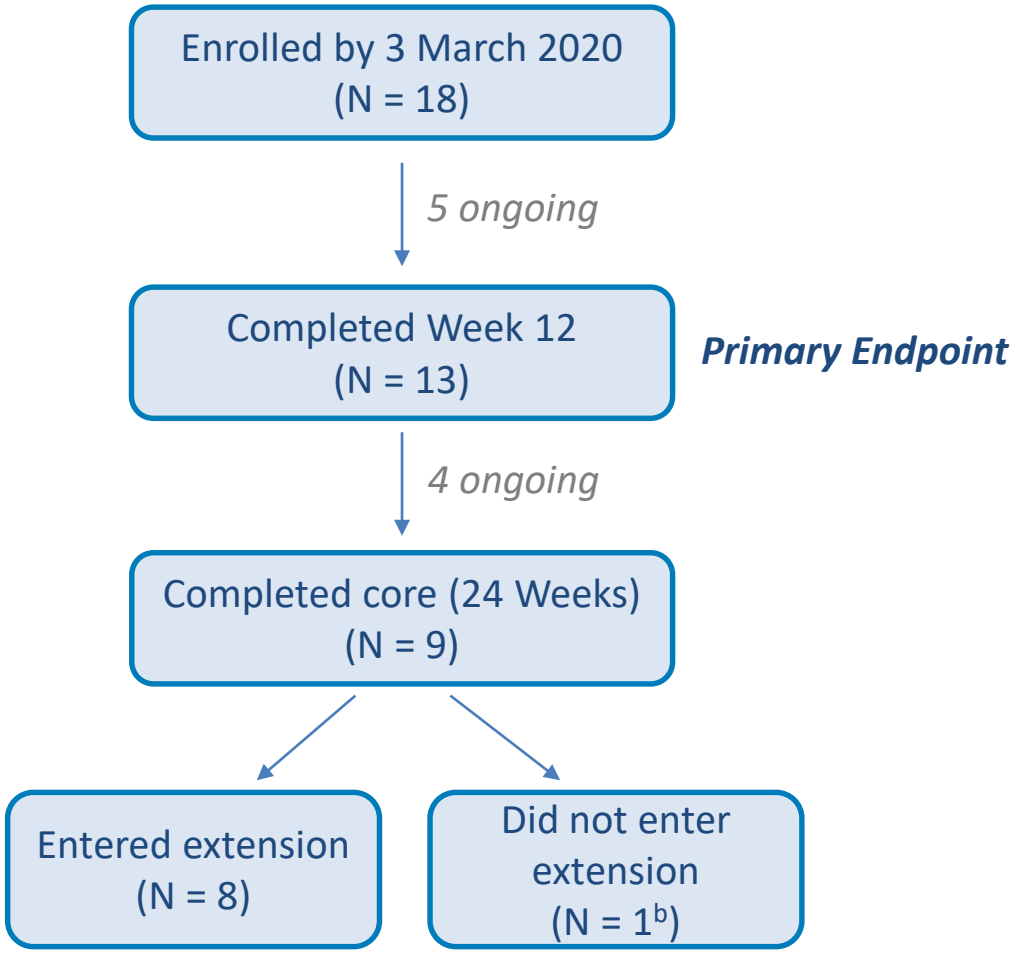
- Sustained Hb response; delayed Hb response; markers of hemolysis; hematopoietic activity; safety



[a]≤ 5 RBC units transfused in the preceding 24 weeks and none in the 8 weeks prior to study drug. [b]With the originally planned sample size of 17 patients enrolled, the study would have 80% power to reject a ≤ 30% response rate at a one-sided 0.05 type 1 error rate. [c]Fully enrolled. BID = twice daily

Demographics and disposition

Baseline characteristics		Total (N = 18)
Median (range) duration of treatment, weeks		20.6 (1.1–50.0)
Male/female, n		5/13
Age at informed consent, median (range), years		43.5 (29–67)
Race, n (%)	Asian	9 (50.0)
	White	4 (22.2)
	Native Hawaiian or other Pacific Islander	1 (5.6)
	Other[a]	4 (22.2)
Thalassemia type, n (%)	α	5 (27.8)
	β	13 (72.2)
Hb baseline, median (range), g/dL		8.43 (5.6–9.8)
Indirect bilirubin, median (range), mg/dL		1.17 (0.31–5.52)
Lactate dehydrogenase, median (range), U/L		249 (126–513)
Erythropoietin, median (range), mU/mL		70.5 (15–11,191)



Splenectomy and prior transfusions were reported in two patients each at baseline

[a]Includes patients who reported more than one category, and one not reported. [b]Investigator decision

Key efficacy results

Primary endpoint was met in 92.3% of patients

Endpoint	Genotype	N/N	%	90% CI
Hb responders during weeks 4–12 among those who completed 12 weeks	All	12/13	92.3	68.4, 99.6
	α	4/4	100	47.3, 100
	β	8/9	88.9	57.1, 99.4
Hb responders during weeks 12–24 among those who completed 24 weeks	β[a]	8/9	88.9	57.1, 99.4
Sustained responders: primary response and ≥ 2 Hb responses during weeks 12–24	β[a]	7/8	87.5	52.9, 99.4

Hb responder defined as a ≥ 1.0 g/dL Hb increase from baseline at least once

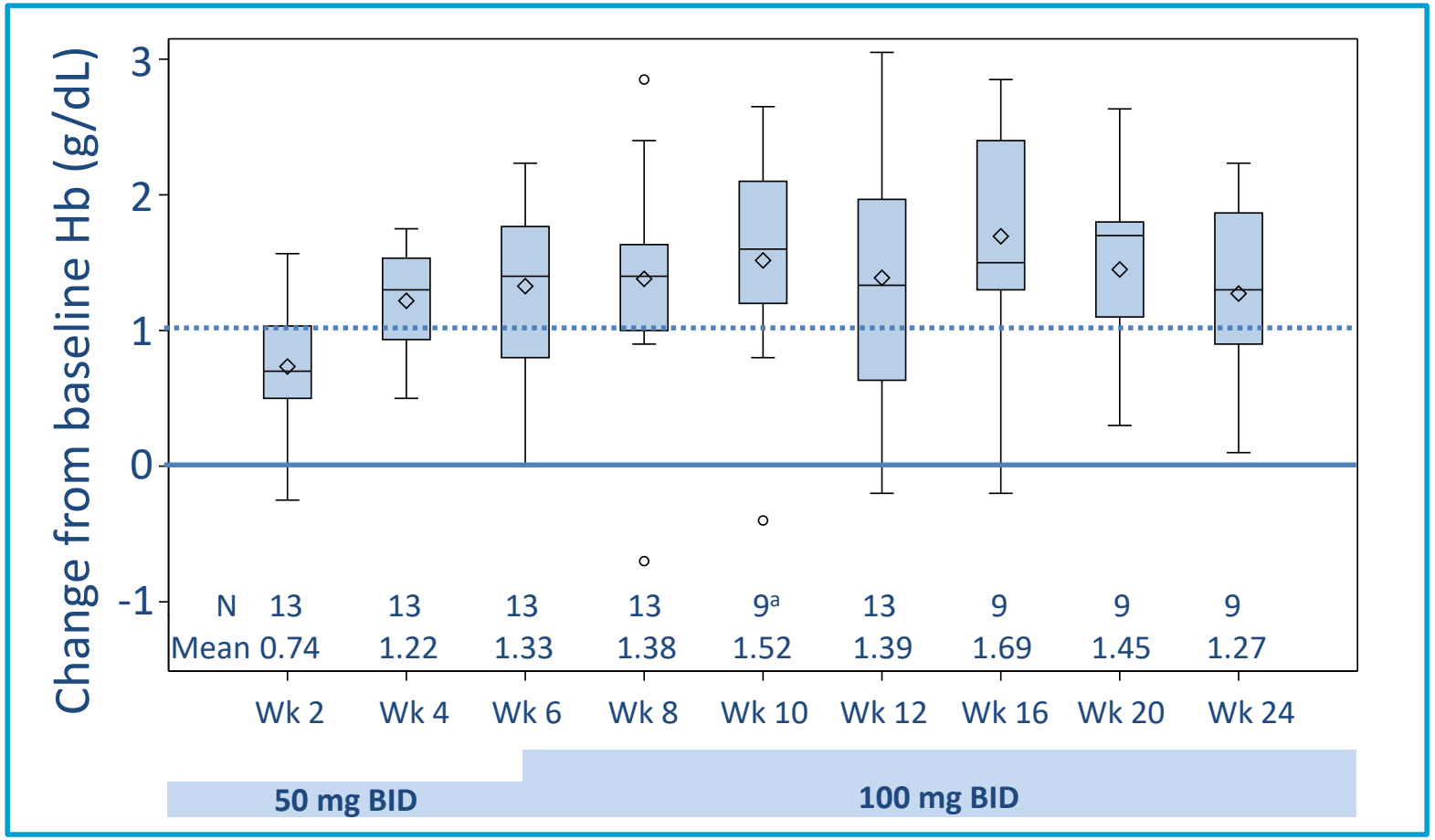
[a]Only patients with β-thalassemia had completed 24 weeks of treatment at the time of datacut

Hemoglobin change from baseline

Patient population	N	Weeks	Mean (SD) change from baseline Hb, g/dL
All patients	13	4–12	1.34 (0.7)
α-thalassemia	4	4–12	1.17 (0.4)
β-thalassemia	9	4–24	1.43 (0.8)

Median (range) time to Hb increase of ≥ 1 g/dL among responders was 3.1 (1.4–7.1) weeks

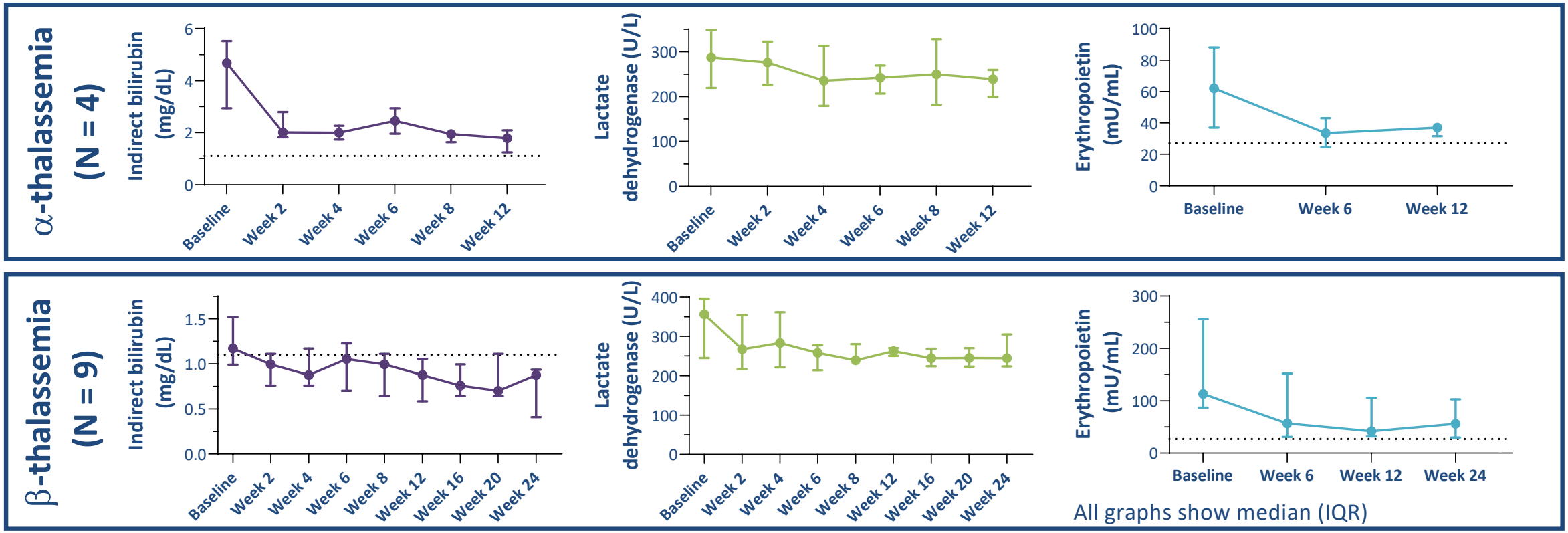
Hemoglobin change over time



Solid blue line indicates baseline, dashed blue line indicates Hb change required for primary endpoint. Boxes represent interquartile range, lines indicate medians, diamonds indicate means, whiskers and outliers (circles) calculated with Tukey's method. [a]4 patients were not evaluated at Week 10 due to a protocol amendment eliminating this visit
Wk = week

Markers of hemolysis and erythropoiesis

- The improvements in these markers correlated with the Hb increases



Dashed lines indicate upper limit of normal range. For α-thalassemia: N = 4 for lactate dehydrogenase and erythropoietin, for indirect bilirubin N = 3 at baseline, weeks 2, 8 and 12, and N = 2 at weeks 4 and 6; for β-thalassemia: N = 9 for erythropoietin, for lactate dehydrogenase N = 9 at baseline, weeks 6, 8, 12, and 20 and N = 8 at weeks 2, 4, 16, and 24, for indirect bilirubin N = 9 at baseline and N = 7 at the remaining times. IQR = interquartile range (25^{th}–75^{th} centiles)

ATP change with mitapivat

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

Treatment dose	Visit	Mean (CV%) ATP change from baseline in blood, %
50 mg	Week 6 (n = 9)	82.7 (85.8)
100 mg	Week 8 (n = 12)	76.8 (62.7)
100 mg	Week 12 (n = 12)	86.7 (68.7)
100 mg	Week 24 (n = 5)	92.3 (71.6)

1. Yang H et al. *Clin Pharmacol Drug Dev* 2019;8:246.
CV% = coefficient of variation, percent

Safety summary[a]

	Total (N = 18)
Patients with any AE, n (%)	13 (72.2)
Patients with any related AE, n (%)	11 (61.1)
Patients with AEs by maximum severity, n (%)	
Grade 1	4 (22.2)
Grade 2	7 (38.9)
Grade 3[b]	2 (11.1)

- There were no serious adverse events (AEs) and no AEs leading to treatment discontinuation as of the datacut
- Dose escalation to 100 mg BID was well tolerated and not associated with an increase in AEs
- Reported in one patient each:
  - AE leading to treatment interruption (grade 3, postural vertigo, not related)
  - AE leading to treatment modification (grade 2, bloating and heartburn, related)
- Post-datacut, one serious AE of renal dysfunction was reported, which resolved upon treatment discontinuation (grade 3, judged related by investigator)

AEs coded using MedDRA, version 22.0
[a]As of datacut of 3 March 2020
[b]Neither were judged related

Most common AEs[a]

AEs in ≥ 2 patients, number of patients (%)	Total (N = 18)
Insomnia	8 (44.4)
Dizziness	5 (27.8)
Cough	4 (22.2)
Dyspepsia	4 (22.2)
Fatigue	4 (22.2)
Headache	4 (22.2)
Nasal congestion	4 (22.2)
Nausea	4 (22.2)
Upper respiratory tract infection	4 (22.2)
Abdominal distension	3 (16.7)
Diarrhea	3 (16.7)
Ocular icterus	3 (16.7)
Oropharyngeal pain	3 (16.7)
Pain	3 (16.7)
Abdominal pain upper	2 (11.1)
Back pain	2 (11.1)
Pain in extremity	2 (11.1)
Pyrexia	2 (11.1)
Rash	2 (11.1)

- The safety profile was consistent with prior studies in healthy volunteers and patients with PK deficiency

[a]As of datacut of 3 March 2020
AEs coded using MedDRA, version 22.0

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 treating α-thalassemia
- Proof-of-concept was demonstrated
  - > 90% of patients met the primary endpoint showing a clinically significant Hb increase
  - All four α-thalassemia patients and eight of nine β-thalassemia patients were responders
  - A sustained Hb response was observed over time in patients with longer follow-up
  - Improvements in markers of hemolysis and erythropoiesis were consistent with mitapivat's mechanism of action
- Mitapivat was generally well tolerated; the safety profile was consistent with previous studies

These data indicate that activation of wild-type PKR by the oral agent mitapivat improved Hb and associated markers of hemolysis and erythropoiesis in patients with both α-and β-thalassemia, and that further investigation is warranted. Pivotal trials are in development.