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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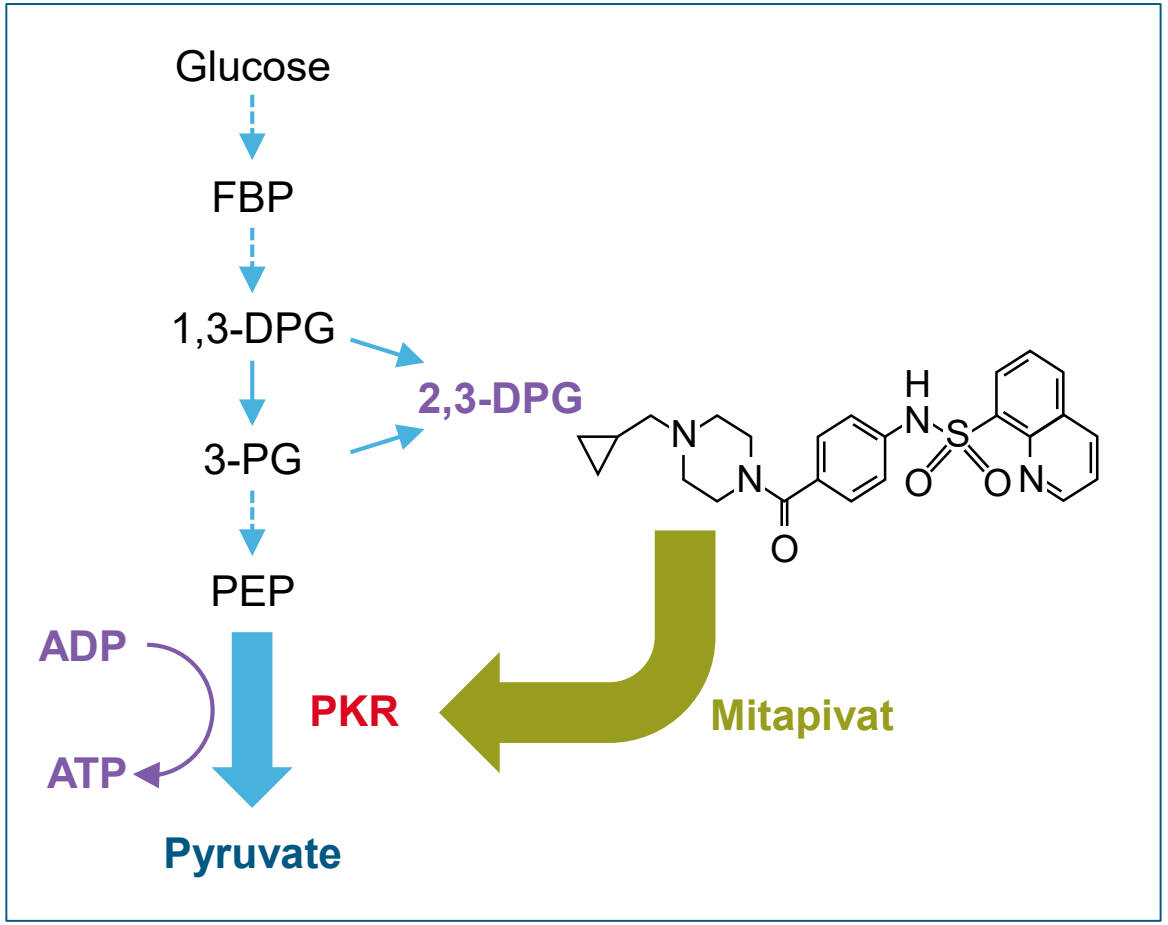
This study was funded by Agios Pharmaceuticals, Inc.

Mitapivat

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



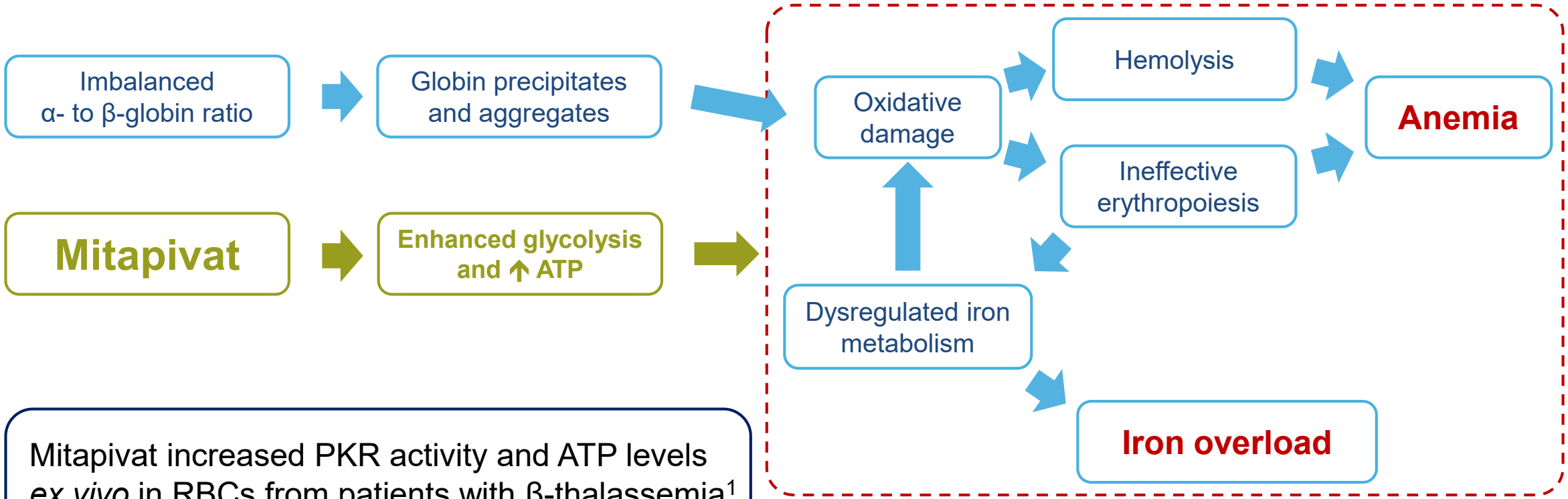
Mitapivat (AG-348) is an oral, allosteric activator of PKR, which catalyzes the final step of glycolysis in RBCs[1,2]

- Mitapivat increased whole blood ATP levels by 60% in healthy volunteers[3]
- In a phase 2 study in adult patients with pyruvate kinase deficiency, BID dosing with mitapivat:
  - Increased Hb by > 1.0 g/dL in 50% of patients[4]
  - Was well tolerated for up to 42 months[5]

ADP = adenosine diphosphate; ATP = adenosine triphosphate; BID = twice daily; DPG = diphosphoglyceric acid; FBP = fructose 1,6–bisphosphate; Hb = hemoglobin; 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.** Valentini G et al. *J Biol Chem* 2002;277:23807–14. **3.** Yang H et al. *Clin Pharmacol Drug Dev* 2019;8:246–59. **4.** Grace RF et al. *N Engl J Med* 2019;381:933–44. **5**. Grace RF et al. *EHA Congress* 2020, Abstract EP1561.

Hypothesis: Mitapivat mechanism in thalassemia



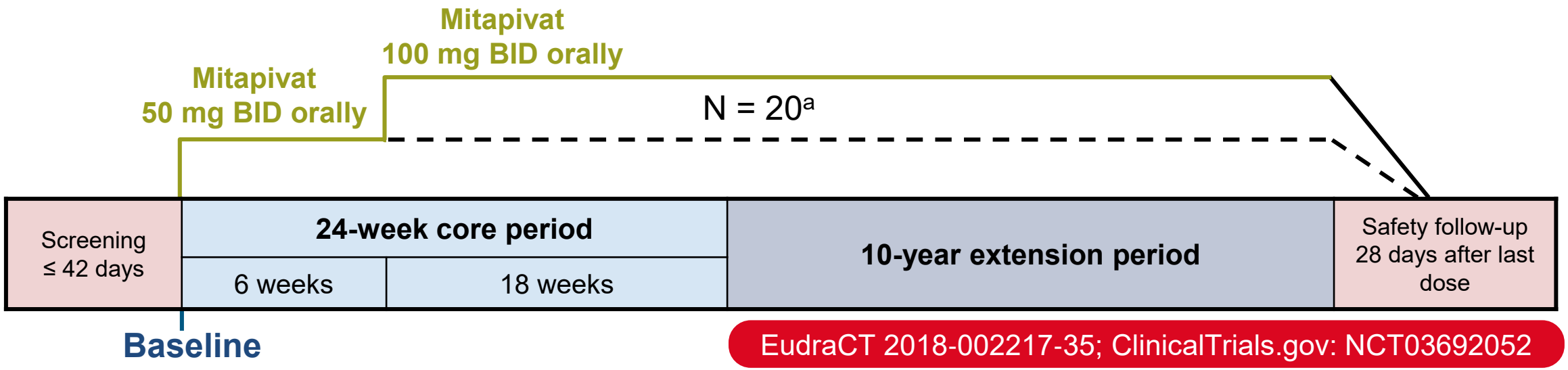
Mitapivat increased PKR activity and ATP levels *ex vivo* in RBCs from patients with β-thalassemia[1]

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

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

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[b]

Primary endpoint[c]

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

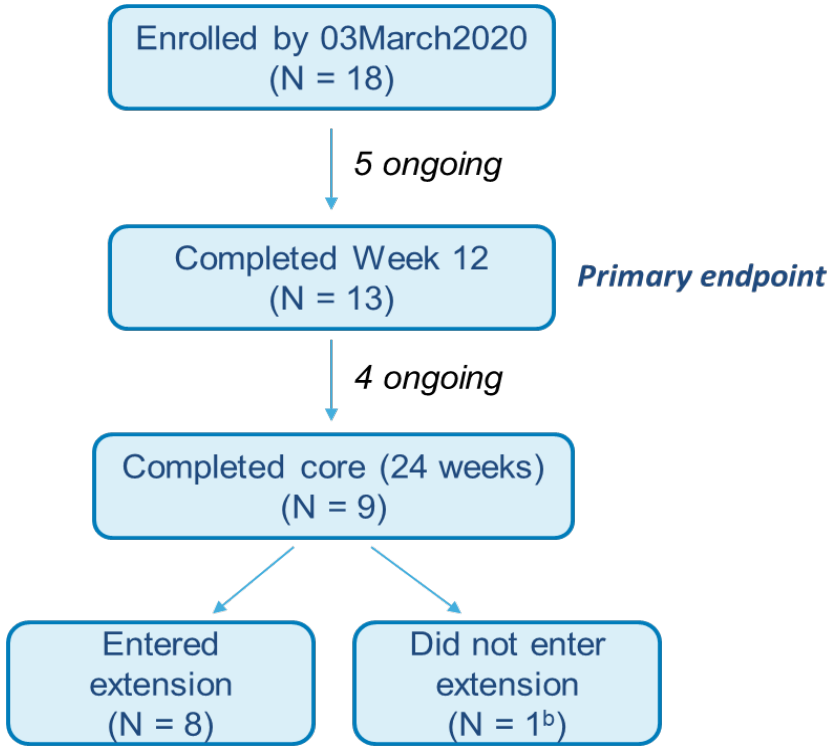
Secondary/exploratory endpoints

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

[a]Fully enrolled. [b]≤ 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.
BID = twice daily; Hb = hemoglobin; RBC = red blood cell.

Demographics and baseline characteristics

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 White Native Hawaiian or other Pacific Islander Other[a]	 9 (50.0) 4 (22.2) 1 (5.6) 4 (22.2)
Thalassemia type, n (%) α β	 5 (27.8) 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.
Hb = hemoglobin.

Key efficacy results

- Primary endpoint was met in 92.3% of patients

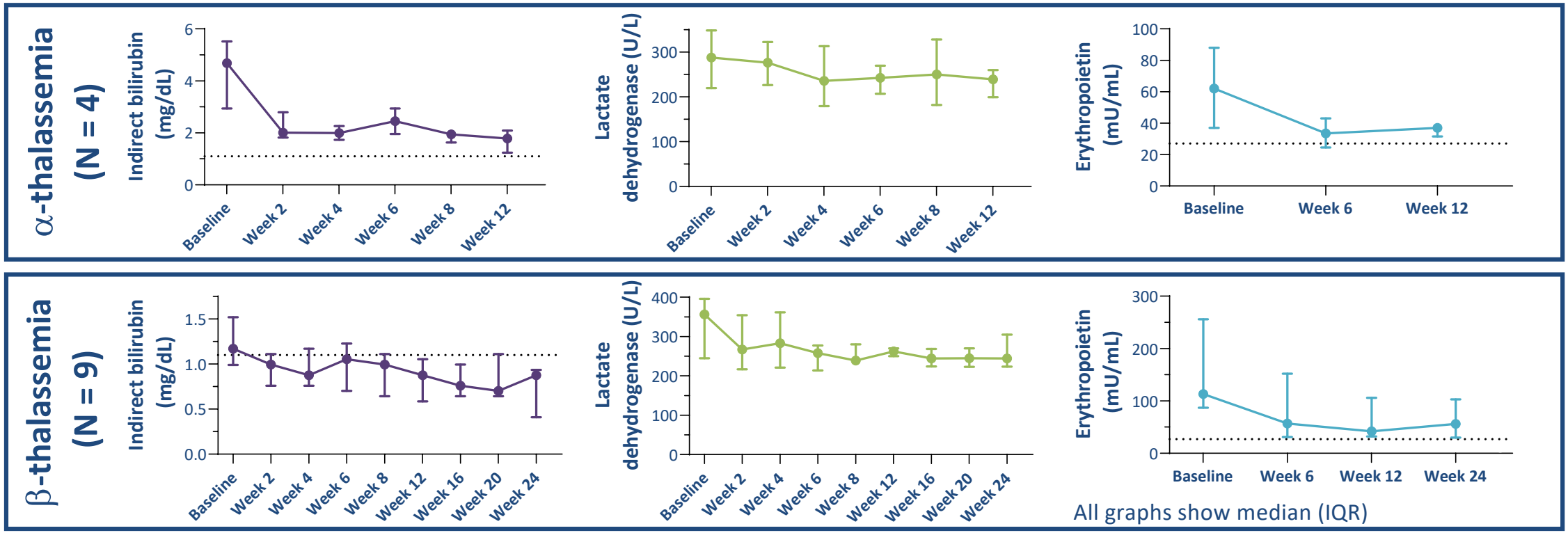
Endpoint	Genotype	n/N	%	90% CI
Hb responders during Weeks 4–12 (completed 12 weeks)	All	12/13	92.3	68.4, 99.6
	α	4/4	100	47.3, 100
	β	8/9	88.9	57.1, 99.4
Hb responders during Weeks 12–24 (completed 24 weeks)	β[a]	8/9	88.9	57.1, 99.4
Sustained responders: primary response and ≥ 2 Hb responses during Weeks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

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

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 data cut.
CI = confidence interval; Hb = hemoglobin.

Hb increases correlated with improvements in markers of hemolysis and erythropoiesis



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

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. ATP = adenosine triphosphate; Hb = hemoglobin; IQR = interquartile range (25th–75th centiles). **1.** Yang H et al. *Clin Pharmacol Drug Dev* 2019;8:246–59.

Safety summary[a]

- Dose escalation to 100 mg BID was well tolerated and not associated with an increase in AEs
- The most common AEs (> 25% of patients) were insomnia (8/18) and dizziness (5/18)
- There were no serious AEs and no AEs leading to treatment discontinuation
- 1 AE leading to treatment interruption (grade 3, postural vertigo, not treatment-related)
- 1 AE leading to treatment modification (grade 2, bloating and heartburn, treatment-related)
- A previously reported serious AE of renal dysfunction (grade 3) that occurred post-data cut was re-adjudicated by the investigator from treatment-related to not treatment-related

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

AEs coded using MedDRA, version 22.0.
[a]As of data cut of 03March2020. [b]Neither were considered treatment-related in the opinion of the investigator.
AE = adverse event; BID = twice daily; MedDRA = Medical Dictionary for Medical Regulatory Activities.

Summary

- 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 4 α-thalassemia patients and 8 of 9 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

Hb = hemoglobin; PKR = pyruvate kinase in RBC; RBC = red blood cell.

Acknowledgments and disclosures

- We would like to thank the patients taking part in this study
- This study was funded by Agios Pharmaceuticals, Inc. These data were previously presented at the *25th European Hematology Association (EHA) Annual Meeting*, June 11–21, 2020
- **Kevin H.M. Kuo** – Agios, Apellis, Bluebird Bio, Celgene, Pfizer – consultant; Alexion, Novartis – consultant, honoraria; Bioverativ – data safety monitoring board member; Pfizer – research support; **D. Mark Layton** – Agios, Novartis – consultant and advisory board member; Cerus – data safety monitoring board member; **Ashutosh Lal** – Bluebird Bio, Celgene, Insight Magnetics, La Jolla Pharmaceutical Company, Novartis, Protagonist Therapeutics, Terumo Corporations – research funding; Agios, Chiesi USA – consultancy; Celgene, Protagonist Therapeutics – membership on an entity's Board of Directors or advisory committees; **Hanny Al-Samkari** – Agios, Argenx, Dova, Rigel – consultant; Agios, Dova, Amgen – research funding; **Feng Tai** – Agios – employment and stockholder; **Megan Lynch** – Agios – employment and stockholder; **Katrin Uhlig** – Agios – employment and stockholder; **Elliot P. Vichinsky** – GBT, Pfizer, Novartis, Bluebird Bio, Agios – consultant and research funding
- Editorial assistance was provided by Julie B. Stimmel, PhD, Onyx Medica, London, UK, and supported by Agios Pharmaceuticals, Inc.