Agios´ mitapivat set to RISE UP to the challenge of sickle cell disease?

Market Event Summary

Georgia Constantinou, Ph.D. | November 2025

Mitapivat demonstrates modest efficacy in SCD

Background

- **Mitapivat**, marketed as Pyrukynd, is a first-in-class **PKR activator** developed by Agios Pharmaceuticals. It increases Hb and ATP in RBCs and reduces 2,3-diphosphoglycerate and hemolysis markers, thereby decreasing RBC sickling, hemolysis, and VOC events, while improving RBC hydration. It is approved for the treatment of pyruvate kinase deficiency and is currently in late-stage clinical development for SCD and thalassemia.

Event

- On November 19, 2025, Agios Pharmaceuticals announced that the **Phase 3 RISE UP trial** (NCT05031780) evaluating mitapivat in patients with sickle cell disease met the **first primary endpoint** of Hb response and various secondary endpoints but did not meet the **second primary endpoint** of annualized rate of sickle cell pain crises.
- No new safety concerns emerged; the drug was well tolerated.

Clinical results

- Mitapivat improved the Hb response in 40.6% of treated patients vs. 2.9% of patients receiving placebo (2-sided $P < 0.0001$).
- The annualized rate of pain crises was not significantly different between the mitapivat and placebo arms, 2.62 vs. 3.05, respectively (2-sided $P = 0.1213$).
- Mitapivat delivered a mean increase of 7.69 g/L in Hb concentration vs. 0.26 g/L with placebo ($P < 0.0001$).
- Patients receiving mitapivat showed a 16.03 µmol/L decrease in indirect bilirubin vs. 0.88 µmol/L increase in the placebo group ($P < 0.0001$).
- While mitapivat patients reported a -2.72 point change in PROMIS Fatigue scores vs. -2.25 points with placebo, the difference was not statistically significant ($P = 0.7112$) and did not meet the threshold for clinical relevance.

Clarivate's takeaways

Commercial outlook

- We expect regulatory approval of mitapivat for SCD in the United States in 2026 and in the EU5 in 2028.
- Based on the KOL optimism reported by Clarivate, along with the long-term efficacy and clean safety profile demonstrated in the RISE UP trial, we project mitapivat to garner approximately 8% of the targeted SCD therapy market in 2034.

Treatment dynamics

- If approved, mitapivat could transform SCD treatment by shifting care from transfusions and IV therapies to a more convenient, oral-based approach for patients who are not candidates for the potentially curative gene therapies.
- KOLs regard mitapivat as having an important mechanistic advance that fills a gap in Hb-raising strategies.
- We expect mitapivat to become an important addition to the SCD treatment armamentarium, but it will not replace established first-line therapies.

About the author

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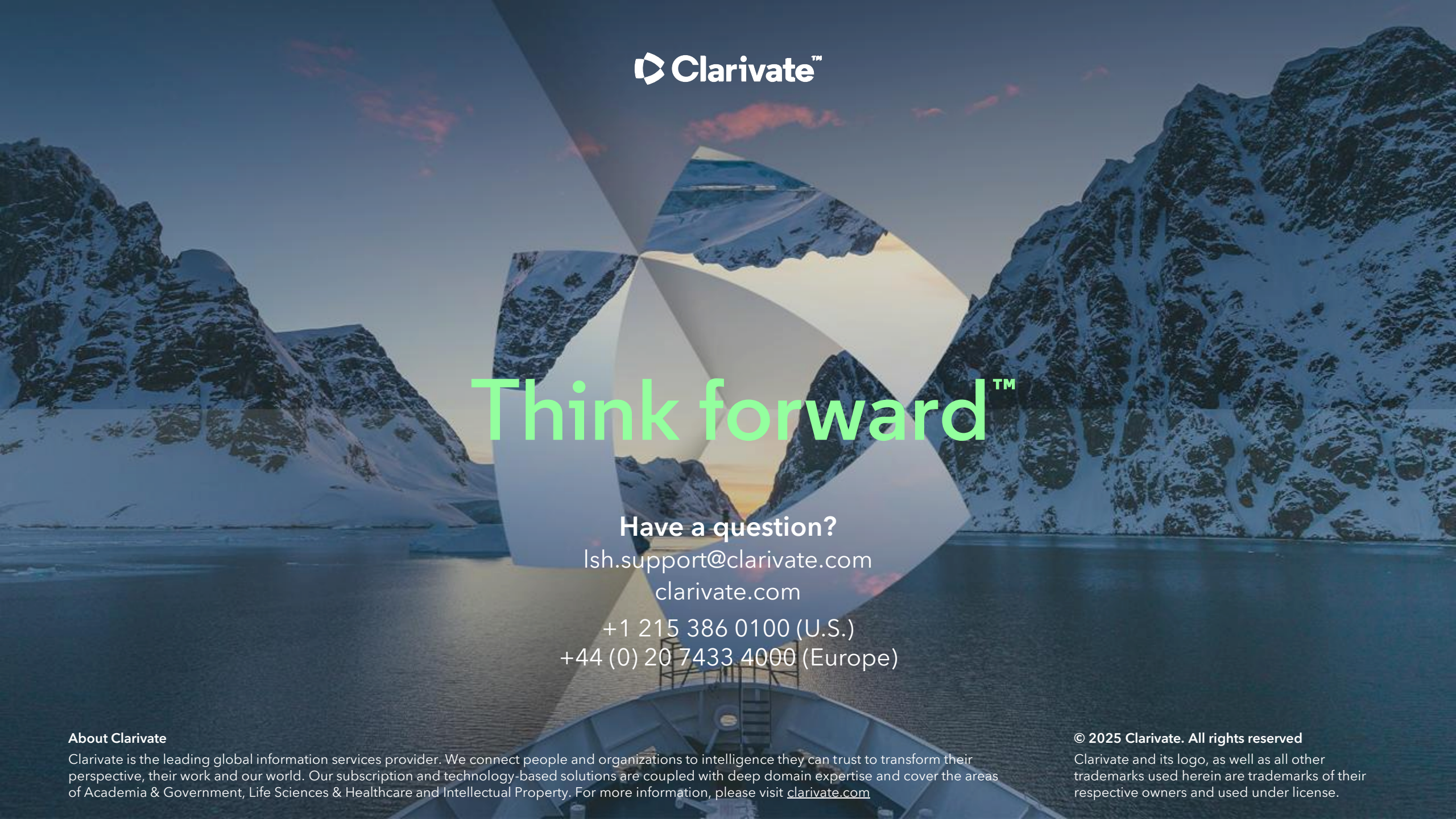
Georgia Constantinou, Ph.D., M.Sc., is a data analyst on the Infectious, Niche and Rare Diseases team at Clarivate. She has previous experience in life science consulting, offering research and analytical support to medical research funders of rare diseases. Georgia obtained her doctorate in immune-oncology, her master's degree in cancer, and her bachelor's degree in biomedical sciences from University College London.

Clarivate coverage of sickle cell disease

- Sickle Cell Disease Niche & Rare Disease Landscape & Forecast (US/EU5)
- Sickle Cell Disease Epidemiology data for mature markets
- Sickle Cell Disease Access & Reimbursement (US)



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