Agios Announces Topline Results from RISE UP Phase 3 Trial of Mitapivat in Sickle Cell Disease

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- Trial met primary endpoint of hemoglobin response and key secondary endpoints of change from baseline in hemoglobin concentration and indirect bilirubin
- Trial showed trend favoring mitapivat but did not meet statistical significance in primary endpoint of annualized rate of SCPCs (pain crises), and the key secondary endpoint of change from baseline in PROMIS Fatigue was not met
- Patients in the mitapivat arm who achieved hemoglobin response had clinically meaningful benefits in SCPC-related endpoints and PROMIS Fatigue
- Favorable safety profile observed in RISE UP Phase 3 trial was consistent with that observed in prior mitapivat sickle cell disease trials
- Company will share the comprehensive results from the RISE UP clinical program with the FDA and intends to submit for potential U.S. regulatory approval
- Company will host investor conference call and webcast today at 8:00 a.m. ET

CAMBRIDGE, Mass., Nov. 19, 2025 (GLOBE NEWSWIRE) -- Agios Pharmaceuticals, Inc. (Nasdaq: AGIO), a commercial-stage biopharmaceutical company focused on delivering innovative medicines for patients with rare diseases, today announced topline results from the 52-week double-blind period of the global RISE UP Phase 3 trial of mitapivat, an oral pyruvate kinase (PK) activator, in patients aged 16 years or older with sickle cell disease. RISE UP was designed with two primary endpoints and five key secondary endpoints to evaluate objective measures of hemolysis improvement as well as additional parameters of sickle cell disease. This comprehensive design enabled a broad assessment of the potential benefits of mitapivat across multiple aspects of the disease.

The trial met its primary endpoint of hemoglobin response, with mitapivat demonstrating a statistically significant improvement compared to placebo. While mitapivat also showed a reduction in the primary endpoint of annualized rate of sickle cell pain crises (SCPCs) compared to placebo, this trend did not achieve statistical significance.

Mitapivat also demonstrated statistically significant improvements in the first two key secondary endpoints, Week 24 through Week 52 average change from baseline in hemoglobin concentration and levels of indirect bilirubin, a marker of hemolysis, compared with placebo. The third key secondary endpoint of Week 24 through Week 52 average change from baseline on Patient Reported Outcome Measurement Information System Fatigue 13a (PROMIS Fatigue) score was not met.

The subset of patients in the mitapivat arm who achieved hemoglobin response also experienced clinically meaningful benefits in the endpoints of annualized rate of SCPCs, annualized rate of hospitalizations for SCPCs (the fourth key secondary endpoint of the trial), and PROMIS Fatigue, based on a post hoc analysis.

The safety profile of mitapivat in the RISE UP Phase 3 trial was consistent with that seen in prior mitapivat sickle cell disease trials.

“Sickle cell disease is a complex and devastating condition that has long lacked innovation. As a result, patients have very few effective treatments, contributing to poor outcomes and shortened lifespans,” said Biree Andemariam, M.D., Professor of Medicine and American Red Cross Endowed Chair in Transfusion Medicine, University of Connecticut Health, and a RISE UP trial investigator. “The data from RISE UP demonstrate that treatment with mitapivat significantly improved hemoglobin concentration and reduced hemolysis. We also see that patients who achieved the threshold of hemoglobin response also experienced clinically meaningful benefits in the rate of sickle cell pain crises and hospital visits for those events, as well as in fatigue. These strong results, coupled with a favorable safety profile, support the potential of mitapivat as a novel treatment option for patients with sickle cell disease.”

RISE UP Phase 3 Trial Results
The double-blind, randomized, placebo-controlled RISE UP Phase 3 trial enrolled 207 patients aged 16 years or older who are representative of the global sickle cell disease population. Participants were randomized 2:1 to receive mitapivat twice daily or matched-placebo. The 52-week double-blind treatment period was completed by 87.0% (n=120/138) of patients in the mitapivat arm and 81.2% (n=56/69) of patients in the placebo arm. All but two of these patients (174/176) opted to enter the ongoing 216-week open-label extension period of the study.

Primary Efficacy Endpoint Results

- **Hemoglobin Response:** 40.6% of patients in the mitapivat arm achieved a hemoglobin response, defined as a ≥1.0 g/dL increase from baseline in average hemoglobin from Week 24 through Week 52, compared to 2.9% of patients in the placebo arm, a statistically significant improvement (2-sided $p<0.0001$). In patients who achieved a hemoglobin response in the mitapivat arm, mean change from baseline in average hemoglobin concentration from Week 24 through Week 52 was 1.6 g/dL.

- **Annualized Rate of SCPCs:** The annualized rate of SCPCs, defined as acute pain needing medical contact, acute chest syndrome, priapism, hepatic, or splenic sequestration, was 2.62 in the mitapivat arm and 3.05 in the placebo arm (2-sided p=0.1213).

Key Secondary Efficacy Endpoint Results

- **Change from Baseline in Hemoglobin:** The average change from baseline in hemoglobin concentration from Week 24 through Week 52 was 7.69 g/L in the mitapivat arm and 0.26 g/L in the placebo arm, a statistically significant improvement (2-sided p<0.0001).
- **Change from Baseline in Indirect Bilirubin:** The average change from baseline in indirect bilirubin from Week 24 through Week 52 was -16.03 µmol/L in the mitapivat arm and 0.88 µmol/L in the placebo arm, a statistically significant improvement (2-sided p<0.0001). Elevated levels of indirect bilirubin in the blood can indicate increased hemolysis (red blood cell destruction), which is associated with increased morbidity and mortality in sickle cell disease.
- **Change from Baseline in PROMIS Fatigue Score:** The average change from baseline in PROMIS Fatigue score from Week 24 through Week 52 was -2.72 in the mitapivat arm and -2.25 in the placebo arm (2-sided p=0.7112). Negative change from baseline scores in the PROMIS Fatigue 13a scale indicate improvements in fatigue.

Results for the additional key secondary endpoints are summarized below; however, due to the hierarchical statistical testing strategy, no conclusions regarding statistical significance can be drawn.

- **Annualized Rate of Hospitalizations for SCPCs:** The annualized frequency of hospitalizations for SCPCs was 1.56 in the mitapivat arm and 1.81 in the placebo arm (2-sided nominal p=0.2498).
- **Change from Baseline in Percent Reticulocyte:** The average change from baseline in percent reticulocyte levels from Week 24 through Week 52 was -0.0236 (fraction of 1) in the mitapivat arm and -0.0013 (fraction of 1) in the placebo arm (2-sided nominal p=0.0001). Sickle cell disease often causes an elevated proportion of reticulocytes, a marker of erythropoiesis (process of red blood cell production), to compensate for the increased destruction of red blood cells; these results support that mitapivat improved hemolysis.

Hemoglobin Responders Post Hoc Analysis Results
In the subset of patients in the mitapivat arm achieving the primary endpoint of hemoglobin response the following was observed:

- **Annualized Rate of SCPCs:** The annualized rate of SCPCs was 2.20 for hemoglobin responders and 2.98 for non-hemoglobin responders (rate ratio [RR]=0.74, 95% confidence interval [CI]=0.58 to 0.94).
- **Annualized Rate of Hospitalizations for SCPCs:** The annualized frequency of hospitalizations for SCPCs was 1.16 for hemoglobin responders and 1.76 for non-hemoglobin responders (RR=0.66, 95% CI=0.48 to 0.91).
- **Change from Baseline in PROMIS Fatigue Score:** The average change in PROMIS Fatigue score between Week 24 and Week 52 was -5.19 for hemoglobin responders and -2.55 for non-hemoglobin responders (95% CI=-5.59 to 0.32). The results for hemoglobin responders in the mitapivat arm exceeded -4.1, the threshold for a clinically meaningful change from baseline for PROMIS Fatigue score.

Safety Results

- A similar proportion of patients on mitapivat (n=134, 97.1%) and placebo (n=68, 98.6%) had adverse events.
- Serious treatment emergent adverse events (TEAEs) were reported in 20.3% (n=28) and 29.0% (n=20) of patients on mitapivat and placebo, respectively; 0.7% (n=1) and 0.0% (n=0), respectively, were considered treatment-related.
- Liver abnormalities observed across the mitapivat and placebo arms were not suggestive of drug-induced hepatocellular injury (HCI), unlike what was observed in the mitapivat ENERGIZE and ENERGIZE-T Phase 3 trials.
- TEAEs led to treatment discontinuation in 4.3% (n=6) of patients on mitapivat and 2.9% (n=2) on placebo.
- Three deaths (2.2%) occurred in patients on mitapivat, and two (2.9%) on placebo. None were deemed related to study treatment by the trial investigator.

“The RISE UP Phase 3 results further support mitapivat’s strong anti-hemolytic profile, as demonstrated in other rare blood disease trials. These effects can help address debilitating features of sickle cell disease that can profoundly worsen quality of life and lead to early mortality,” said Sarah Gheuens, M.D., Ph.D., Chief Medical Officer and Head of R&D, Agios. “We plan to engage with the FDA to discuss these findings and our goal of bringing this innovative medicine to patients with sickle cell disease. On behalf of the entire Agios team, we extend our deepest gratitude to the patients, caregivers, investigators, and broader community for their trust, participation, and invaluable contributions to the RISE UP clinical program.”

Agios intends to submit a marketing application for mitapivat in the U.S. for sickle cell disease after having a pre-supplemental New Drug Application (sNDA) meeting with the U.S. Food and Drug Administration (FDA) in the first quarter of 2026. In addition, the company plans to submit detailed analyses from the RISE UP Phase 3 trial for presentation at future medical congresses.

Agios also remains focused on its other near-term commercial and pipeline milestones in 2025 and the first half of 2026 – including the potential U.S. approval of PYRUKYND® (mitapivat) for thalassemia, anticipated in early December 2025. To maximize the PYRUKYND thalassemia U.S. commercial launch and maintain a strong financial position, the company will take proactive steps to reduce operating expenses and provide an update by early 2026.

Conference Call Information
Agios will host a conference call and live webcast today at 8:00 a.m. ET to review the topline results from the RISE UP Phase 3 trial. The live webcast will be accessible on the Investors section of the company’s website (www.agios.com) under the “Events & Presentations” tab. A replay of the webcast will be available on the company’s website approximately two hours after the event.

About Sickle Cell Disease
Sickle cell disease is a rare, inherited blood disorder caused by the production of abnormal hemoglobin that disrupts the ability of red blood cells to carry oxygen throughout the body. As a result, red blood cells become rigid and sickle-shaped, causing deformation of red blood cell membranes and the premature death of the cells. These effects lead to chronic hemolytic anemia, vaso-occlusion, and a cascade of severe and life-threatening complications, including long-term damage to the lungs, kidneys, and cardiovascular system. Due to its physical toll, sickle cell disease imposes a profound burden on patients and their families, marked by increased healthcare needs and early mortality.

About Mitapivat in Sickle Cell Disease
Mitapivat, an oral pyruvate kinase (PK) activator, is designed to enhance the process by which red blood cells produce energy. This approach has the potential to improve red blood cell health by increasing ATP levels to support increased energy demands and lowering levels of a molecule called 2,3-diphosphoglycerate (2,3-DPG). In sickle cell disease, increased stress on red blood cells results in elevated levels of 2,3-DPG, which raises the likelihood that red blood cells develop the abnormal “sickle” shape that triggers vaso-occlusive crises.

About the RISE UP Phase 3 Trial
The global RISE UP Phase 3 trial (NCT05031780) is evaluating the efficacy and safety of mitapivat in patients aged 16 years or older with sickle cell disease. Eligible participants experienced between two and 10 sickle cell pain crises in the 12 months prior to screening and had a hemoglobin concentration between 5.5 and 10.5 g/dL during screening.

The trial includes a 52-week, double-blind, randomized, placebo-controlled phase in which 207 participants were randomized 2:1 to receive oral mitapivat (100 mg) twice daily (n=138) or matched-placebo (n=69). The primary endpoints are hemoglobin response, defined as a ≥1.0 g/dL increase from baseline in average hemoglobin concentration from Week 24 through Week 52, and annualized rate of sickle cell pain crises. The key secondary endpoints are:

- Average change from baseline in hemoglobin concentration from Week 24 through Week 52
- Average change from baseline in indirect bilirubin from Week 24 through Week 52
- Average change from baseline in Patient Reported Outcome Measurement Information System Fatigue 13a (PROMIS Fatigue) Short Form scores from Week 24 through Week 52
- Annualized frequency of hospitalizations for sickle cell pain crises
- Average change from baseline in percent reticulocyte levels from Week 24 through Week 52

Participants who completed the 52-week double-blind phase had the option to transition into a 216-week open-label extension phase, during which all participants receive mitapivat.

About PYRUKYND® (mitapivat)
U.S. INDICATION
PYRUKYND is a pyruvate kinase activator indicated for the treatment of hemolytic anemia in adults with pyruvate kinase (PK) deficiency.

U.S. IMPORTANT SAFETY INFORMATION
Acute Hemolysis: Acute hemolysis with subsequent anemia has been observed following abrupt interruption or discontinuation of PYRUKYND in a dose-ranging study. Avoid abruptly discontinuing PYRUKYND. Gradually taper the dose of PYRUKYND to discontinue treatment if possible. When discontinuing treatment, monitor patients for signs of acute hemolysis and anemia including jaundice, scleral icterus, dark urine, dizziness, confusion, fatigue, or shortness of breath.

Hepatocellular Injury in Another Condition: In patients with another condition treated with PYRUKYND at a higher dose than that recommended for patients with PK deficiency, liver injury has been observed. These events were characterized by a time to onset within the first 6 months of treatment with peak elevations of alanine aminotransferase of >5x upper limit of normal (ULN) with or without jaundice. All patients discontinued treatment with PYRUKYND, and these events improved upon treatment discontinuation.

Obtain liver tests prior to the initiation of PYRUKYND and monthly thereafter for the first 6 months and as clinically indicated. Interrupt PYRUKYND if clinically significant increases in liver tests are observed or alanine aminotransferase is >5x ULN. Discontinue PYRUKYND if hepatic injury due to PYRUKYND is suspected.

Adverse Reactions: The most common adverse reactions including laboratory abnormalities (≥10%) in patients with PK deficiency were estrone decreased (males), increased urate, back pain, estradiol decreased (males), and arthralgia.

Drug Interactions:

- Strong CYP3A Inhibitors and Inducers: Avoid concomitant use.
- Moderate CYP3A Inhibitors: Do not titrate PYRUKYND beyond 20 mg twice daily.
- Moderate CYP3A Inducers: Consider alternatives that are not moderate inducers. If there are no alternatives, adjust PYRUKYND dosage.
- Sensitive CYP3A, CYP2B6, CYP2C Substrates Including Hormonal Contraceptives: Avoid concomitant use with substrates that have narrow therapeutic index.
- UGT1A1 Substrates: Avoid concomitant use with substrates that have narrow therapeutic index.
- P-gp Substrates: Avoid concomitant use with substrates that have narrow therapeutic index.

Hepatic Impairment: Avoid use of PYRUKYND in patients with moderate and severe hepatic impairment.

Please see full Prescribing Information for PYRUKYND.

About Agios: Fueled by Connections to Transform Rare Diseases™
At Agios, our vision is to redefine the future of rare disease treatment. Fueled by connections, we build trusted partnerships with communities – collaborating to develop and deliver innovative medicines that have the potential to transform lives. With a foundation in hematology, we combine biological expertise with real-world insights to advance a growing pipeline of rare disease medicines that reflect the priorities of the people we serve. Agios is a commercial-stage biopharmaceutical company headquartered in Cambridge, Massachusetts. To learn more, visit www.agios.com and follow us on LinkedIn and X.

Cautionary Note Regarding Forward-Looking Statements
This press release contains forward-looking statements within the meaning of The Private Securities Litigation Reform Act of 1995. Such forward-looking statements include those regarding the potential benefits of mitapivat; Agios' plans for future meetings with, or submissions to, regulators, including the FDA; Agios' plans for the development of mitapivat; and Agios' strategic plans and focus. The words "anticipate," "expect," "goal," "hope," "milestone," "plan," "potential," "possible," "strategy," "will," "vision," and similar expressions are intended to identify forward-looking statements, although not all forward-looking statements contain these identifying words. Such statements are subject to numerous important factors, risks and uncertainties that may cause actual events or results to differ materially from Agios' current expectations and beliefs. For example, there can be no guarantee that any product candidate Agios is developing will successfully commence or complete necessary preclinical and clinical development phases, or that development of any of Agios' product candidates will successfully continue. There can be no guarantee that any positive developments in Agios' business will result in stock price appreciation. Management's expectations and, therefore, any forward-looking statements in this press release could also be affected by risks and uncertainties relating to a number of other important factors, including, without limitation: the content and timing of decisions made by the U.S. FDA, the EMA or other regulatory authorities, investigational review boards at clinical trial sites and publication review bodies; Agios' results of clinical trials and preclinical studies, including subsequent analysis of existing data and new data received from ongoing and future studies; risks and uncertainties related to the impact of pandemics or other public health emergencies to Agios' business, operations, strategy, goals and anticipated milestones, including its ongoing and planned research activities, ability to conduct ongoing and planned clinical trials, clinical supply of current or future drug candidates, commercial supply of current or future approved products, and launching, marketing and selling current or future approved products; Agios' ability to obtain and maintain requisite regulatory approvals and to enroll patients in its planned clinical trials; unplanned cash requirements and expenditures; competitive factors; Agios' ability to obtain, maintain and enforce patent and other intellectual property protection for any product candidates it is developing; Agios' ability to establish and maintain key collaborations; uncertainty regarding any royalty payments related to the sale of its oncology business or any milestone or royalty payments related to its in-licensing of AG-236, and the uncertainty of the timing of any such payments; uncertainty of the results and effectiveness of the use of Agios' cash and cash equivalents; and general economic and market conditions. These and other risks are described in greater detail under the caption "Risk Factors" included in Agios' public filings with the Securities and Exchange Commission. Any forward-looking statements contained in this press release speak only as of the date hereof, and Agios expressly disclaims any obligation to update any forward-looking statements, whether as a result of new information, future events or otherwise, except as required by law.

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