Agios Announces Positive Results from Phase 2 Portion of RISE UP Pivotal Study in Sickle Cell Disease with Both Mitapivat Dose Arms Achieving Statistically Significant Hemoglobin Response

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– Study's Primary Efficacy Endpoint Achieved, with 46.2% of Patients in the 50 mg BID Mitapivat Arm and 50.0% of Patients in the 100 mg BID Mitapivat Arm Achieving a Hemoglobin Response, Compared to 3.7% of Patients in the Placebo Arm –

– A Trend in Sickle Cell Pain Crisis Reduction was Observed in Both Mitapivat Dose Arms Compared to Placebo –

– Company Expects to Enroll First Patient in Phase 3 Portion of Study in Q4 2023, Report Phase 3 Data in 2025 and Potentially Receive U.S. Approval in 2026 –

– Agios to Host Investor Webcast Event Today at 8:00 a.m. ET –

CAMBRIDGE, Mass., June 26, 2023 (GLOBE NEWSWIRE) -- Agios Pharmaceuticals, Inc. (Nasdaq: AGIO), a leader in the field of cellular metabolism pioneering therapies for rare diseases, today announced that the Phase 2 portion of the global RISE UP study of mitapivat in sickle cell disease met its primary endpoint of hemoglobin response for patients in both the 50 mg and 100 mg twice daily (BID) mitapivat arms. The safety profile for mitapivat observed in the study was generally consistent with previously reported data in other studies of sickle cell disease and other hemolytic anemias. Improvements were observed in markers of hemolysis and erythropoiesis and annualized rates of sickle cell pain crises at both mitapivat doses compared to placebo. These results support proceeding with the Phase 3 portion of the study.

"We are pleased with the results of the Phase 2 portion of the RISE UP pivotal study in sickle cell disease, which bring us closer to our goal of providing a novel oral therapy that may improve anemia, reduce sickle cell pain crises and improve how patients feel and function," said Sarah Gheuens, M.D., Ph.D., chief medical officer and head of R&D. "We are grateful to all of the patients who participated in our trial, our collaborators, study investigators and advisors in the patient and clinical communities for their partnership in achieving this milestone. The Phase 2 RISE UP data further enhance the consistency of the dataset for mitapivat across a range of hemolytic anemias."

"It gives me great satisfaction to see the positive results from the Phase 2 portion of the RISE UP study. Mitapivat has a high potential to address aspects of the disease of greatest concern to patients," said Modupe Idowu, M.D., associate professor at The University of Texas Health Science Center at Houston and medical director of UT Physicians Comprehensive Sickle Cell Center, UT Houston. "Sickle cell disease is a complex and debilitating disease characterized by anemia, pain crises, fatigue, cognitive effects and more. The sickle cell community is in dire need of effective disease-modifying therapies – particularly novel oral therapies – to address these unmet needs. I look forward to continuing the Phase 3 RISE UP study and am hopeful this will deliver a potential new treatment option for sickle cell warriors."

The data from the Phase 2 RISE UP study, representing the first placebo-controlled trial of mitapivat in sickle cell disease, underscore the potential of mitapivat to be a safe and effective oral treatment option for people living with sickle cell disease. Based on the data reported to date, Agios plans to proceed with the Phase 3 portion of the RISE UP study, which is expected to enroll 198 patients. The operationally seamless Phase 2/3 study design allows Agios to leverage and create efficiencies in the start and conduct of the Phase 3 portion of RISE UP, with a goal of enrolling the first patient in Q4 of this year, reporting the Phase 3 data in 2025 and potentially receiving U.S. approval in 2026.

Results for the Phase 2 portion of RISE UP were as follows:

- A total of 79 patients were enrolled in the Phase 2 portion of the study, with 26 patients in the 50 mg BID mitapivat arm, 26 patients in the 100 mg BID mitapivat arm, and 27 patients in the placebo arm.
- Treatment with mitapivat demonstrated a statistically significant increase in hemoglobin response rate compared to placebo. Hemoglobin response was defined as an increase of ≥1 g/dL in average hemoglobin concentrations from Week 10 through Week 12 compared with baseline.
- 46.2 percent of patients (n=12) in the 50 mg BID mitapivat arm and 50.0 percent of patients (n=13) in the 100 mg BID mitapivat arm achieved a hemoglobin response, compared to 3.7 percent of patients (n=1) in the placebo arm (2-sided p=0.0003 and 0.0001, respectively).
- Over the course of this 12-week study, the annualized rates of sickle cell pain crises for patients in the 50 mg BID and 100 mg BID mitapivat arms were 0.83 and 0.51, respectively, compared to 1.71 for patients in the placebo arm.
- The safety profile for mitapivat observed in the study was generally consistent with previously reported data in other studies of sickle cell disease and other hemolytic anemias.
- There were no adverse events (AEs) leading to discontinuation in either the mitapivat or the placebo arms.
- Of the 79 patients enrolled in the study, 73 continued into the Phase 2 open-label extension period.

Given the promising data for both mitapivat dose arms, the company will continue to analyze the study data over the coming weeks to select a dose for the Phase 3 study. Agios plans to present a full analysis of the RISE UP Phase 2 data at an upcoming medical meeting.

About the Phase 2/3 RISE UP Study
The Phase 2/3 RISE UP study is evaluating the efficacy and safety of mitapivat in sickle cell disease patients who are 16 years of age or older, have had between two and 10 sickle cell pain crises in the past 12 months, and have hemoglobin within the range of 5.5 to 10.5 g/dL during screening. The Phase 2 and Phase 3 portions of the study are being conducted under a single protocol. The two portions of the study will enroll different participants

and will achieve operational efficiency through leveraging the same sites, vendors and other resources.

The Phase 2 portion included a 12-week randomized, placebo-controlled period in which participants were randomized in a 1:1:1 ratio to receive 50 mg mitapivat twice daily, 100 mg mitapivat twice daily or matched placebo. The primary endpoints were hemoglobin response, defined as ≥1 g/dL increase in average hemoglobin concentration from Week 10 through Week 12 compared to baseline, and safety.

The Phase 3 portion includes a 52-week randomized, placebo-controlled period in which participants will be randomized in a 2:1 ratio to receive the selected dose of mitapivat or placebo. The primary endpoints are hemoglobin response, defined as ≥1 g/dL increase in average hemoglobin from baseline to Week 52, and annualized rate of sickle cell pain crises. Participants who complete either the Phase 2 or Phase 3 portion will have the option to move into a 216-week open-label extension period to receive mitapivat.

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

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.

Adverse Reactions: Serious adverse reactions occurred in 10% of patients receiving PYRUKYND in the ACTIVATE trial, including atrial fibrillation, gastroenteritis, rib fracture, and musculoskeletal pain, each of which occurred in 1 patient. In the ACTIVATE trial, 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.

Conference Call Information
Agios will host a webcast investor event today at 8:00 a.m. ET to review the RISE UP Phase 2 data and next steps for the Phase 3 portion of the study. The event can be accessed under “Events & Presentations” in the Investors and Media section of the company's website at www.agios.com. The archived webcast will be available on the company's website beginning approximately two hours after the event.

About Agios
Agios is the pioneering leader in PK activation and is dedicated to developing and delivering transformative therapies for patients living with rare diseases. In the U.S., Agios markets a first-in-class pyruvate kinase (PK) activator for adults with PK deficiency, the first disease-modifying therapy for this rare, lifelong, debilitating hemolytic anemia. Building on the company's leadership in the field of cellular metabolism, Agios is advancing a robust clinical pipeline of investigational medicines with programs in alpha- and beta-thalassemia, sickle cell disease, pediatric PK deficiency and MDS-associated anemia. In addition to its clinical pipeline, Agios has a PAH stabilizer in preclinical development as a potential treatment for phenylketonuria (PKU) and deep scientific expertise in classical hematology. For more information, please visit the company’s website at www.agios.com.

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 the future clinical development of mitapivat in sickle cell disease; and Agios’ strategic plans and prospects. The words “anticipate,” “believe,” “estimate,” “expect,” “intend,” “may,” “plan,” “predict,” “project,” “would,” “could,” “potential,” “possible,” “hope” 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 or its collaborators 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: Agios’ results of clinical trials and preclinical studies, including subsequent analysis of existing data and new data received from ongoing and future studies; 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’ ability to obtain and maintain requisite regulatory approvals and to enroll patients in its planned clinical trials; unplanned cash requirements and expenditures and 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 collaborations; the failure of Agios to receive milestone or royalty payments related to the sale of its oncology business, the uncertainty of the timing of any receipt of any such payments, and the uncertainty of the results and effectiveness of the use of proceeds from the transaction with Servier; 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; 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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