Agios Presents Positive Results from Phase 2 Portion of the RISE UP Pivotal Study in Sickle Cell Disease at 65th ASH Annual Meeting and Exposition

December 10, 2023

– Treatment with Mitapivat Demonstrated Statistically Significant Improvement in Hemoglobin Response Compared to Placebo –

– Improvements Observed in Annualized Rates of Sickle Cell Pain Crises, Markers of Hemolysis and Erythropoiesis in Participants Treated with Mitapivat –

– Agios to Host Live and Webcast Investor Event on Dec. 11, 2023, at 7:00 a.m. Pacific Time –

CAMBRIDGE, Mass., Dec. 09, 2023 (GLOBE NEWSWIRE) -- Agios Pharmaceuticals, Inc. (Nasdaq: AGIO), a leader in the field of cellular metabolism pioneering therapies for rare diseases, today presented detailed results from the Phase 2 portion of the global RISE UP study of mitapivat in sickle cell disease in an oral presentation (abstract #271) at the 65th American Society of Hematology (ASH) Annual Meeting & Exposition, which is being hosted Dec. 9-12, 2023, in San Diego.

During the Phase 2 double-blind, placebo-controlled study, treatment with mitapivat demonstrated statistically significant improvement in hemoglobin response across both mitapivat dose levels (50 mg and 100 mg BID), compared to placebo. 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 annualized rates of sickle cell pain crises, and markers of hemolysis and erythropoiesis for both mitapivat treatment arms compared to placebo. Improvement in patient-reported fatigue scores was observed with mitapivat 50 mg BID compared to placebo.

“We are extremely pleased with the results of the Phase 2 portion of the RISE UP study and firmly believe that mitapivat has the potential to be a meaningful therapy for the sickle cell disease community,” said Sarah Gheuens, M.D., Ph.D., chief medical officer and head of R&D. “The data further add to the compelling and growing data set supporting the therapeutic potential of mitapivat, which has demonstrated consistent clinical and mechanistic improvements across three distinct hemolytic anemias. We look forward to building on these data through the Phase 3 portion of RISE UP and continuing to enroll patients around the world in this study.”

“Sickle cell disease is a tremendously burdensome disease that impacts all aspects of patients’ and families’ lives. New therapeutic options – particularly those with convenient and easy administration – are desperately needed for this underserved community,” Modupe Idowu, M.D., professor at The University of Texas Health Science Center at Houston and medical director of UT Physicians Comprehensive Sickle Cell Center, UT Houston. “Currently there are no approved oral therapies that address both sickle cell pain crises and chronic anemia, two of the hallmark symptoms of the disease. The RISE UP Phase 2 data suggest that mitapivat has the potential to address both of these aspects with the convenience of a pill. I look forward to supporting the Phase 3 portion of the study and to potentially having a much-needed new medicine for patients.”

Based on the Phase 2 data, Agios selected 100 mg BID as the Phase 3 dose and is currently enrolling patients in this portion of the RISE UP study. 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 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.
- Demographics and baseline characteristics for the participants in each arm were as follows:
    - Mean age (standard deviation) for participants in the 50 mg BID, 100 mg BID, and placebo arms, respectively, was: 29.9 (7.79), 30.2 (10.52), and 28.5 (10.30) years.
    - Percentage of female participants in the 50 mg BID, 100 mg BID, and placebo arms, respectively, was: 57.7%, 61.5%, and 74.1%.
    - Mean baseline hemoglobin (standard deviation) for participants in the 50 mg BID, 100 mg BID, and placebo arms, respectively, was: 8.76 (1.295), 8.82 (0.898), and 8.49 (1.141) g/dL.
    - Mean number of sickle cell pain crises during the previous year (standard deviation) for participants in the 50 mg BID, 100 mg BID, and placebo arms, respectively, was: 3.1 (1.83), 3.2 (1.65), and 3.4 (1.91).
- The study achieved its primary efficacy endpoint; 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% of patients (n=12) in the 50 mg BID mitapivat arm and 50.0% of patients (n=13) in the 100 mg BID mitapivat arm achieved a hemoglobin response, compared to 3.7% of patients (n=1) in the placebo arm (2-sided p=0.0003 and 0.0001, respectively).
    - Least-squares mean (95% confidence interval) for average change from baseline in hemoglobin levels, from Week 10 through Week 12, for participants in the 50 mg BID, 100 mg BID, and placebo arms, respectively, was: 1.11 (0.77, 1.45) g/dL, 1.13 (0.79, 1.47) g/dL, and 0.05 (−0.28, 0.39) g/dL.
- The annualized rate of sickle cell pain crises (95% confidence interval) for participants in the 50 mg BID and 100 mg BID,

arms, respectively, was 0.83 (0.34, 1.99) and 0.51 (0.16, 1.59), compared to 1.71 (0.95, 3.08) for participants in the placebo arm.
- Least-squares mean (95% confidence interval) for average changes from baseline in patient-reported fatigue score, from Week 10 through Week 12, for participants in the 50 mg BID, 100 mg BID, and placebo arms, respectively, was: −3.80 (−7.16, −0.45), −0.10 (−3.27, 3.08), and −0.17 (−3.40, 3.07).
- 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.
- The most common treatment-emergent adverse events (TEAEs) in the 50 mg BID, 100 mg BID, and placebo arms, respectively, were: headache (n=6, 6, 7), arthralgia (n=3, 5, 9), dysmenorrhea (n=0, 3, 0), pain (n=3, 3, 2), pain in extremity (n=1, 3, 6), back pain (n=4, 2, 3), nausea (n=1, 2, 4), fatigue (n=4, 1, 5), and influenza-like illness (n=1, 1, 3).
- No serious TEAEs were attributed to mitapivat treatment.
- There were no adverse events leading to drug reduction, discontinuation, interruption or death 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.

ASH Presentation Details
Title: A Phase 2/3, Double-Blind, Randomized, Placebo-Controlled, Multicenter Study of Mitapivat in Patients With Sickle Cell Disease: RISE UP Phase 2 Results
Presentation Time: Saturday, Dec. 9, 2023, at 4:00 p.m. PT
Oral Abstract Session: 114. Sickle Cell Disease, Sickle Cell Trait and Other Hemoglobinopathies, Excluding Thalassemias: Clinical and Epidemiological: Building on Momentum in Disease-Modifying Therapeutics for Sickle Cell Disease
Abstract: 271
Presenter: Modupe Idowu, MD; McGovern Medical School, UT Health, Houston, TX

Conference Call Information
Agios will host a live investor event on Dec. 11, 2023, at 7:00 a.m. PT in San Diego to review key oral and poster presentations from this year's ASH meeting, including the detailed RISE UP Phase 2 results. The event will be webcast live and 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 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 100 mg of mitapivat twice daily or matched 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 in the United States, and for the treatment of PK deficiency in adult patients in the European Union.

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 and Summary of Product Characteristics for PYRUKYND.

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 deep scientific expertise in classical hematology and leadership in the field of cellular metabolism and rare hematologic diseases, 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 is advancing a preclinical TMPRSS6 siRNA as a potential treatment for polycythemia vera, and a preclinical PAH stabilizer as a potential treatment for phenylketonuria (PKU). 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. Moreover, there can be no guarantee that any medicines ultimately commercialized by Agios will receive commercial acceptance. 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: 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' 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; 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 milestone or royalty payments related to the sale of Agios' oncology business or its in-licensing of TMPRSS6 siRNA, and the uncertainty of the timing of any such payments; uncertainty of the results and effectiveness of the use of proceeds from the transaction with Servier; competitive factors; 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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