Agios Announces Publication of Phase 3 ACTIVATE Study in New England Journal of Medicine Demonstrating Benefits of PYRUKYND® (mitapivat) for Adults with Pyruvate Kinase Deficiency

April 14, 2022

– In Adults with Pyruvate Kinase (PK) Deficiency Who Are Not Regularly Transfused, PYRUKYND® Significantly Increased Hemoglobin Level, Decreased Hemolysis and Improved Patient-Reported Outcomes –

– Following FDA Approval in February, PYRUKYND® Is the First and Only Disease-Modifying Treatment for Adults with PK Deficiency –

CAMBRIDGE, Mass., April 14, 2022 (GLOBE NEWSWIRE) -- Agios Pharmaceuticals, Inc. (NASDAQ: AGIO), a leader in the field of cellular metabolism pioneering therapies for genetically defined diseases, today announced that data from the core period of the pivotal Phase 3 ACTIVATE study of PYRUKYND® (mitapivat) in adults with pyruvate kinase (PK) deficiency who do not receive regular transfusions were published on April 14, 2022 in the *New England Journal of Medicine*. Data from this study were previously presented at the European Hematology Association (EHA) Virtual Congress held in June 2021. PYRUKYND® is a first-in-class, oral PK activator and the first and only approved disease-modifying treatment for this rare, debilitating, lifelong hemolytic anemia.

The publication can be accessed at the following link: https://www.nejm.org/doi/full/10.1056/NEJMoa2116634

"The results of the ACTIVATE study confirm that mitapivat, through its novel mechanism of activating pyruvate kinase and thus increasing ATP levels in red blood cells, successfully addressed the underlying cause of chronic hemolytic anemia in adults with PK deficiency with a wide array of genotypes," said Hanny Al-Samkari, M.D., hematologist and clinical investigator at the Mass General Cancer Center and Harvard Medical School, an investigator in the pivotal ACTIVATE Phase 3 study and first author of this publication. "Improvements in the PK deficiency–specific patient-reported outcome measures further support the clinical efficacy of mitapivat and its benefits on health-related quality of life and reduction in symptom severity."

"We have been pioneering the science of PK activation for more than a decade, and are pleased to have developed the first approved product for people with PK deficiency who previously had no disease-modifying treatment options," said Sarah Gheuens, M.D., Ph.D., chief medical officer at Agios. "The results of the ACTIVATE study underscore the clinical value of PYRUKYND® and support our current efforts to deliver this medicine to as many patients as possible who may benefit from it."

As reported in the publication, the ACTIVATE study met its primary endpoint, with 40 percent of patients randomized to PYRUKYND® achieving a hemoglobin response, defined as a ≥1.5 g/dL increase in hemoglobin concentration from baseline sustained at two or more scheduled assessments at Weeks 16, 20 and 24 during the fixed-dose period, compared to 0 patients randomized to placebo (2-sided p<0.001). Patients who received PYRUKYND® had a significantly greater response than those who received placebo with respect to each secondary endpoint, including average change from baseline in hemoglobin level; average change from baseline in markers of hemolysis including indirect bilirubin, lactate dehydrogenase (LDH) and haptoglobin levels; average change from baseline in markers of hematopoietic activity (reticulocyte percentage); and change from baseline in two PK deficiency–specific patient-reported outcome measures. The most common adverse events were nausea (in seven patients [18%] in the PYRUKYND® group and nine patients [23%] in the placebo group) and headache (in six patients [15%] and 13 patients [33%], respectively). Adverse events of grade 3 or higher occurred in 10 patients (25%) who received PYRUKYND® and five patients (13%) who received placebo.

PYRUKYND® was approved in February 2022 by the U.S. Food and Drug Administration (FDA) for the treatment of hemolytic anemia in adults with PK deficiency. PYRUKYND® is also under review by the European Medicines Agency (EMA) as a potential treatment for adults with PK deficiency, and Agios expects a regulatory decision in the EU by the end of 2022. Both the FDA and EMA have granted orphan drug designation to PYRUKYND® in PK deficiency. Learn more at www.PYRUKYND.com.

ACTIVATE Trial Design

ACTIVATE is a Phase 3 global, double-blind, placebo-controlled study with a 1:1 randomization evaluating the efficacy and safety of PYRUKYND® in adults with PK deficiency who do not receive regular transfusions. Patients were required to have a hemoglobin concentration less than or equal to 10.0g/dL. The trial randomized 80 patients.

The study was designed with two parts. Part 1 was a dose escalation period in which patients started at 5 mg of PYRUKYND® or placebo twice daily, with two potential dose escalations to 20 mg twice daily and 50 mg twice daily over a 12-week period. After the dose escalation period, patients received a fixed dose for an additional 12 weeks in Part 2.

The primary endpoint of the study was hemoglobin response, defined as a ≥1.5 g/dL increase in hemoglobin concentration from baseline that is sustained at two or more scheduled assessments at Weeks 16, 20 and 24 during Part 2 of the trial.

Agios conducted an additional pivotal Phase 3 study, ACTIVATE-T, in adults with PK deficiency who receive regular transfusions. The company is conducting an ongoing extension study for adults with PK deficiency previously enrolled in ACTIVATE or ACTIVATE-T, which is designed to evaluate the long-term safety, tolerability and efficacy of treatment with PYRUKYND®.

About PK Deficiency

Pyruvate kinase (PK) deficiency is a rare, inherited disease that presents as chronic hemolytic anemia, which is the accelerated destruction of red blood cells. The inherited mutation in the *PKLR* gene can cause a deficit in energy within the red blood cell, as evidenced by lower PK enzyme activity, a decline in adenosine triphosphate (ATP) levels and a build-up of upstream metabolites, including 2,3-DPG (2,3-diphosphoglycerate).

PK deficiency is associated with serious complications, including gallstones, pulmonary hypertension, extramedullary hematopoiesis, osteoporosis and iron overload and its sequelae, which can occur regardless of the degree of anemia or transfusion burden. PK deficiency can also cause quality of life problems, including challenges with work and school activities, social life and emotional health. Current management strategies for PK deficiency, including red blood cell transfusions and splenectomy, are associated with both short- and long-term risks. For more information, please visit the websites of two U.S.-based independent patient advocacy groups dedicated to PK deficiency: PK Deficiency Foundation and Thrive with PK Deficiency.

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.

About Agios
Agios is a biopharmaceutical company that is fueled by connections. The Agios team cultivates strong bonds with patient communities, healthcare professionals, partners and colleagues to discover, develop and deliver therapies for genetically defined 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 active and planned programs in alpha- and beta-thalassemia, sickle cell disease, pediatric PK deficiency and MDS-associated anemia. In addition to its clinical pipeline, Agios has multiple investigational therapies in preclinical development and an industry-leading research team with unmatched expertise in cellular metabolism and genetics. 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 PYRUKYND® (mitapivat); Agios' plans for the further clinical development of mitapivat and Agios' strategic plans and prospects. 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. 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 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; the impact of the COVID-19 pandemic on 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 future approved products, and launching, marketing and selling 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, including with respect to the regulatory submissions for PYRUKYND® (mitapivat), 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; 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, or SEC, including the risks and uncertainties set forth under the heading Risk Factors in our filings with the SEC. While the list of factors presented here is considered representative, this list should not be considered to be a complete statement of all potential risks and uncertainties. Any forward-looking statements contained in this press release are made only as of the date hereof, and we undertake no obligation to update forward-looking statements to reflect developments or information obtained after the date hereof and disclaim any obligation to do so other than as may be required by law.

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