Agios Announces Publication of Phase 3 ACTIVATE-T Data in The Lancet Haematology Demonstrating Benefits of PYRUKYND® (mitapivat) for Adults with Pyruvate Kinase Deficiency

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– In Adults with Pyruvate Kinase (PK) Deficiency Who Are Regularly Transfused, PYRUKYND® Demonstrated a Statistically Significant and Clinically Meaningful Reduction in Transfusion Burden –

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

CAMBRIDGE, Mass., Aug. 18, 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-T study of PYRUKYND® (mitapivat) in adults with pyruvate kinase (PK) deficiency who receive regular transfusions were published on August 18, 2022, in *The Lancet Haematology*. Data from this study were previously presented at the 2021 European Hematology Association (EHA) Annual Congress. 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.thelancet.com/journals/lanhae/article/PIIS2352-3026(22)00214-9/fulltext

“The results of the ACTIVATE-T study confirm that treatment with mitapivat substantially reduced the need for transfusions in PK deficiency patients who regularly receive them,” said Andreas Glenthøj, M.D., Ph.D., associate professor, Department of Hematology, Rigshospitalet, Copenhagen, Denmark, an investigator in the pivotal ACTIVATE-T 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.”

“With the approval of PYRUKYND® for the treatment of hemolytic anemia in adults with PK deficiency earlier this year, we delivered the very first approved medicine for patients who previously had no disease-modifying treatment options,” said Sarah Gheuens, M.D., Ph.D., head of R&D and chief medical officer at Agios. “The results of the ACTIVATE-T study underscore the clinical value of PYRUKYND®, particularly for patients who require regular transfusions to manage their disease, 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-T study met its primary endpoint, with 10 of 27 patients (37%; p=0.0002) receiving PYRUKYND® achieving a transfusion reduction response, defined as a ≥33% reduction in transfusion burden in the 24-week fixed dose period compared with individual historical transfusion burden standardized to 24 weeks. Nine of these responders achieved a ≥50% reduction. Additionally, six patients (22%) reached transfusion-free status during the fixed-dose period, and three patients (11%) achieved hemoglobin concentrations in the normal range at least once, eight weeks or more after a transfusion, during the fixed dose period. Improvements were also observed for two PK deficiency–specific patient-reported outcome measures. The safety profile of mitapivat was consistent with previously reported data. The most frequently reported adverse events in patients receiving mitapivat included alanine aminotransferase increase (37%), headache (37%), aspartate aminotransferase increase (18.5%), fatigue (18.5%) and nausea (18.5%). Adverse events of Grade 3 or higher occurred in 8 patients (30%) who received PYRUKYND®. No serious adverse events were considered by the investigator to be related to study treatment, and only one patient experienced an adverse event leading to dose reduction.

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-T Trial Design
ACTIVATE-T is a Phase 3 global, open-label study to evaluate the efficacy and safety of mitapivat as a potential treatment for adults with PK deficiency who are regularly transfused, defined as receiving six or more transfusions in the past 52 weeks. The trial enrolled 27 patients.

The study was designed with two parts. Part 1 was a dose escalation period in which patients started at 5 mg twice daily of mitapivat, with two potential dose increases to 20 mg twice daily and 50 mg twice daily for up to 16 weeks. After the dose escalation period, patients received a fixed dose for an additional 24 weeks in Part 2.

The primary endpoint of the study was reduction in transfusion burden, defined as a reduction of ≥33 percent in the number of red blood cell units transfused during the 24-week fixed dose period compared with the historical transfusion burden standardized to 24 weeks. Participants who discontinued the study before completing at least 12 weeks of treatment in the fixed dose period were considered non-responders. The p-value is based on the binomial exact test of H0: transfusion reduction response rate ≤10% vs. H1: transfusion reduction response rate >10% at a 1-sided α=0.025.

Agios conducted an additional pivotal Phase 3 study, ACTIVATE, in adults with PK deficiency who do not receive regular transfusions; these data were published in April 2022 in the *New England Journal of Medicine*. 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 Agios' plans, strategies and expectations for the preclinical, clinical and commercial advancement of its drug development programs, including PYRUKYND® (mitapivat); the potential benefits of Agios' products and product candidates, including PYRUKYND®; and the potential benefits of 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. 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 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®, 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; 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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