Agios Receives Positive CHMP Opinion for PYRUKYND® (mitapivat) for the Treatment of Pyruvate Kinase (PK) Deficiency in Adult Patients

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– Agios Expects a Decision on the Marketing Authorization Application by the European Commission within 67 Days of the Adoption of the Positive CHMP Opinion –

CAMBRIDGE, Mass., Sept. 16, 2022 (GLOBE NEWSWIRE) -- Agios Pharmaceuticals, Inc. (NASDAQ: AGIO), a leader in the field of cellular metabolism pioneering therapies for rare and genetically defined diseases, today announced that the Committee for Medicinal Products for Human Use (CHMP) of the European Medicines Agency (EMA) adopted a positive opinion on September 15, 2022, recommending the granting of a marketing authorization for PYRUKYND® (mitapivat) for the treatment of pyruvate kinase (PK) deficiency in adult patients. PK deficiency is a rare, debilitating, lifelong hemolytic anemia. PYRUKYND® is a first-in-class, oral PK activator that was recently approved by the U.S. Food and Drug Administration (FDA). If approved by the European Commission (EC), PYRUKYND® will be the first approved disease-modifying therapy for European patients with PK deficiency.

"The positive CHMP opinion for PYRUKYND® is a landmark event for European patients with PK deficiency, who currently have no disease-modifying treatment options," said Eduard J. van Beers, M.D., Ph.D., hematologist and associate professor at University Medical Center Utrecht. "PK deficiency is characterized by severe symptoms and complications, regardless of transfusion status, and has a significant impact on patients' quality of life. If approved, I look forward to having an oral medication available that has demonstrated clinically meaningful impact for patients with a range of PK deficiency symptoms and presentations."

"Today's positive CHMP opinion is an important step toward our goal of expanding PYRUKYND® access for adults with PK deficiency around the world," said Sarah Gheuens, M.D., Ph.D., head of R&D and chief medical officer at Agios Pharmaceuticals. "In addition to this milestone, we remain focused on our global clinical development programs for PYRUKYND® in thalassemia, sickle cell disease and pediatric PK deficiency and look forward to expanding the impact of this medication to even more patients."

PYRUKYND® was previously granted orphan drug designation by the EMA.

PYRUKYND® Safety and Efficacy Data
The positive CHMP opinion was based on results from two pivotal studies, ACTIVATE and ACTIVATE-T, conducted in not regularly transfused and regularly transfused adults with PK deficiency, respectively.

- The Phase 3 ACTIVATE trial of mitapivat achieved its primary endpoint. PYRUKYND® demonstrated a statistically significant increase in hemoglobin in patients with PK deficiency who are not regularly transfused.
  - 40 percent (n=16) of patients randomized to PYRUKYND® achieved a hemoglobin response, compared to 0 patients randomized to placebo (2-sided p<0.0001).
  - Statistically significant improvements compared to placebo were also demonstrated for all pre-specified secondary endpoints, including markers of hemolysis and ineffective erythropoiesis.
- The Phase 3 ACTIVATE-T trial of mitapivat achieved its primary endpoint. Mitapivat demonstrated a statistically significant and clinically meaningful reduction in transfusion burden for patients who are regularly transfused.
  - 37 percent (n=10) of patients achieved 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.
  - 22 percent (n=6) of patients were transfusion-free during the fixed-dose period.
- The most common adverse reaction across both studies was insomnia (19.4%), and the most common laboratory abnormalities observed were oestrone decreased (males) (43.5%) and oestradiol decreased (males) (8.7%).

A full analysis of these data was presented at the 2021 European Hematology Association (EHA) Virtual Congress, and results from ACTIVATE were published in the *New England Journal of Medicine*. An extension study for adults with PK deficiency previously enrolled in ACTIVATE or ACTIVATE-T is ongoing and designed to evaluate the long-term safety, tolerability and efficacy of treatment with mitapivat; initial results from the extension study were presented at the 2021 American Society of Hematology (ASH) Annual Meeting and Exposition.

The company is enrolling pediatric PK deficiency patients in two pivotal studies – ACTIVATE-kids and ACTIVATE-kidsT – in patients who are not regularly transfused and who are regularly transfused, respectively. Agios also continues to advance its Phase 3 ENERGIZE and ENERGIZE-T studies in not regularly transfused and regularly transfused adults with thalassemia, as well as its Phase 2/3 RISE UP study in sickle cell disease.

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 www.knowpkdeficiency.com.

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.

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 rare and 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 Agios' products, including PYRUKYND® (mitapivat), and its 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, 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. 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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