Agios Announces Publication of Phase 2 Data in The Lancet Demonstrating Safety and Efficacy of PYRUKYND® (mitapivat) in Non-transfusion-dependent α- and β-Thalassemia

August 11, 2022

– In Adults with Non-transfusion-dependent α- or β-Thalassemia, PYRUKYND® Induced ≥1.0 g/dL Hemoglobin Increase from Baseline in 16 of 20 (80%) Patients Between Weeks 4-12 –

– PYRUKYND® Safety Profile Consistent with Label for FDA-approved Indication in Pyruvate Kinase Deficiency –

– Actively Enrolling Phase 3 ENERGIZE and ENERGIZE-T Studies Evaluating PYRUKYND® in Adults with Non-transfusion-dependent and Transfusion-dependent α- or β-Thalassemia, Respectively –

CAMBRIDGE, Mass., Aug. 11, 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 open-label, Phase 2 study of PYRUKYND® (mitapivat) in adults with non-transfusion-dependent α- or β-thalassemia were published on August 11, 2022, in *The Lancet*. Data from this study were previously presented at the 2021 European Hematology Association (EHA) Annual Congress. PYRUKYND® is a first-in-class, investigational, oral, small molecule allosteric activator of wild-type and a variety of mutated pyruvate kinase (PK) enzymes.

The publication can be accessed at the following link: https://www.thelancet.com/journals/lancet/article/PIIS0140-6736(22)01337-X/fulltext

“Consistent with previously reported findings, the data reported today underscore the potential of PK activation to improve hallmarks of α- and β-thalassemia, including hemolysis and ineffective erythropoiesis,” said Kevin Kuo, M.D., hematologist at University of Toronto, Toronto General Hospital, and an investigator in the study. “Thalassemia is a rare, debilitating lifelong blood disorder characterized by severe complications, with no treatment options for those with α-thalassemia and limited options for those with β-thalassemia. These data demonstrate the potential clinical benefits of mitapivat for a broad spectrum of thalassemia patients and support its continued investigation in pivotal trials.”

“We are encouraged by *The Lancet*s publication of our Phase 2 thalassemia data for PYRUKYND ®, which has the potential to serve as several important firsts for patients: the first oral therapy for thalassemia, and first treatment for all types of thalassemia – α and β, transfusion-dependent and non-transfusion-dependent,” said Sarah Gheuens, M.D., Ph.D., head of R&D and chief medical officer at Agios. “Enrollment is underway for the Phase 3 ENERGIZE and ENERGIZE-T studies of PYRUKYND® in adults with non-transfusion-dependent or transfusion-dependent α- or β-thalassemia, respectively, and we expect to enroll a substantial portion of patients in the trials by year-end.”

As reported in the publication, 16 of 20 patients (80%; p<0.0001), including five of five (100%) with α-thalassemia and 11 of 15 (73%) with β-thalassemia, achieved the primary endpoint of hemoglobin response, a ≥1.0 g/dL increase in hemoglobin concentration from baseline at one or more assessment between Weeks 4–12. The mean time to hemoglobin response was 4.5 weeks. Of the 16 patients who achieved the primary endpoint, 13 had a sustained response, defined as ≥1.0 g/dL increase in hemoglobin at two or more assessments between Week 12 and Week 24. A trend in decreasing concentrations of markers of hemolysis (total bilirubin and LDH concentrations) was observed in both α- and β-thalassemia patients, with decreases observed as early as Week 2. Decreases in erythropoietin concentrations were also observed in both α- and β-thalassemia patients. The greatest change in markers of hemolysis and erythropoiesis was observed in the first 8 weeks of treatment, and improvements were maintained over the duration of the core period.

The most common adverse events were initial insomnia (50%, including 1 patient [5%] with Grade 3), dizziness (30%, all Grade 1) and headache (25%, all Grade 2 or lower). Initial insomnia was the only Grade 3 or worse treatment-emergent adverse event considered to be treatment-related. One patient who had β-thalassemia discontinued after Week 4 due to a treatment-emergent adverse event deemed unrelated to the study drug.

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. In addition, PYRUKYND® has been granted FDA orphan drug designation for the treatment of thalassemia and sickle cell disease, for which enrollment for ongoing pivotal studies is underway.

Mitapivat Phase 2 Study in Thalassemia
The open-label Phase 2 study evaluated the efficacy, safety, pharmacokinetics and pharmacodynamics of mitapivat treatment in adults with non-transfusion-dependent α- or β-thalassemia who have a baseline hemoglobin concentration of ≤10 g/dL. The trial enrolled 20 patients. All patients were treated with an initial dose of mitapivat 50 mg twice daily followed by a dose-level increase to 100 mg twice daily at the Week 6 visit based on safety evaluations and hemoglobin concentrations. Following the completion of the 24-week core period, patients had the opportunity to enroll in an optional 10-year extension period, which is evaluating long-term efficacy and safety of mitapivat in this population. Initial data from the extension period, which highlighted the long-term safety profile and durable improvement in hemoglobin and markers of hemolysis associated with mitapivat treatment in non-transfusion-dependent α- and β-thalassemia, were presented at the 2021 American Society of Hematology (ASH) Annual Meeting and Exposition.

About Thalassemia
Thalassemia is a rare, inherited blood disorder caused by mutations in either α- or β-globin genes, resulting in excessive destruction of red blood cells. Globin precipitates in thalassemia cause oxidative damage, leading to hemolytic anemia, ineffective erythropoiesis and iron overload.

Thalassemia is associated with serious complications, including fatigue, jaundice, facial bone deformities, delayed growth and development,

,abdominal swelling, dark urine and reduced life expectancy. Current management strategies for β-thalassemia can include red blood cell transfusions splenectomy and stem cell transplant, which are associated with short- and long-term risks. There are currently no approved therapies for α-thalassemia.

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.

Contacts

Investors:
Holly Manning, 617-844-6630

Senior Director, Investor Relations
Holly.Manning@agios.com

Media:
Jessica Rennekamp, 857-209-3286
Senior Director, Corporate Communications
Jessica.Rennekamp@agios.com

Source: Agios Pharmaceuticals, Inc.