Agios' Phase 3 ACTIVATE-Kids Study of Mitapivat in Children with Pyruvate Kinase (PK) Deficiency Not Regularly Transfused Met Primary Endpoint

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– ACTIVATE-Kids is the First Study to Demonstrate Efficacy of an Oral Therapy for Children with PK Deficiency Who Are Not Regularly Transfused –

– Safety Results Consistent with Safety Profile for Mitapivat Previously Observed in Adults with PK Deficiency Who Are Not Regularly Transfused –

– First Mitapivat Pediatric Clinical Program for a Rare Hemolytic Anemia; Double-blind Period Completed for Both PK Deficiency Trials ACTIVATE-Kids and ACTIVATE-KidsT –

CAMBRIDGE, Mass., Feb. 13, 2025 (GLOBE NEWSWIRE) -- Agios Pharmaceuticals, Inc. (Nasdaq: AGIO), a leader in cellular metabolism and pyruvate kinase (PK) activation pioneering therapies for rare diseases, today announced that the ACTIVATE-Kids Phase 3 study of mitapivat in children aged 1 to <18 years with PK deficiency who are not regularly transfused achieved its primary endpoint of hemoglobin response. In the ACTIVATE-Kids 20-week double-blind treatment period, the safety results were consistent with the safety profile for mitapivat previously observed for adult patients with PK deficiency who are not regularly transfused. In August 2024, Agios also reported topline results from the ACTIVATE-KidsT Phase 3 study of mitapivat in children aged 1 to <18 years with PK deficiency who are regularly transfused.

"The positive results for the ACTIVATE-Kids Phase 3 trial represent a very important step forward for the PK deficiency community, building on the clinical benefits demonstrated by mitapivat in adults with PK deficiency. The ACTIVATE-Kids and ACTIVATE-KidsT Phase 3 studies mark Agios' first pediatric clinical program for a rare hemolytic anemia, providing valuable insights that will help shape the company's future clinical programs evaluating mitapivat in pediatric patients with thalassemia and sickle cell disease," said Sarah Gheuens, M.D., Ph.D., chief medical officer and head of R&D at Agios. "We are deeply grateful to all who are contributing to the ACTIVATE-Kids and ACTIVATE-KidsT trials, especially the children who are participating in the studies and their caregivers. With data now available from the randomized, placebo-controlled, double-blind period of both Phase 3 pediatric PK deficiency studies, we look forward to sharing more detailed findings with the community and interacting with regulators."

Topline results for the Phase 3 ACTIVATE-Kids trial were as follows:

- A total of 30 patients aged 1 to <18 years were enrolled in the study, with 19 randomized to mitapivat twice-daily and 11 randomized to matched placebo.
- The primary endpoint of the study was hemoglobin response, defined as a ≥1.5 g/dL increase in hemoglobin concentration dfrom baseline that is sustained at two or more scheduled assessments at Weeks 12, 16, and 20 during the double-blin period.
    - The analysis of the primary endpoint was based on Bayesian statistical methodology whereby the hemoglobin response data from the adult ACTIVATE study inform and contribute to the analysis of hemoglobin response in the ACTIVATE-Kids study. The analysis was performed using a range of relative borrowing from the adult ACTIVATE study, representing the prior degree of belief in the similarity of the treatment effect in the pediatric and adult populations. The pre-specified statistical criterion for the primary endpoint in ACTIVATE-Kids was met for all possible borrowing weights (ranging from 0 to 1).
    - In addition, the pre-specified supportive analysis based on traditional methodology comparing the hemoglobin response rate for mitapivat versus placebo, provided further evidence that the primary endpoint was met. There were 31.6% (6/19) of patients in the mitapivat arm achieving a hemoglobin response compared to 0% (0/11) of patients in the placebo arm; the 95% confidence interval for the difference in hemoglobin response rates between mitapivat and placebo was >0 (95% CI=10.8% to 52.7%).
- In addition, improvements in changes from baseline for markers of hemolysis (indirect bilirubin, lactate dehydrogenase and haptoglobin) were observed in the mitapivat arm compared to the placebo arm.
- All patients in both treatment arms completed the 20-week double-blind period of the study.
- In the 20-week double-blind period of the study, a similar proportion of patients had adverse events (AEs) in the mitapivat and placebo arms and there were no discontinuations of study treatment due to AEs or for any reason.

"PK deficiency can lead to debilitating fatigue and a range of serious complications and symptoms, severely affecting and disrupting a child's quality of life," said Rachael F. Grace, M.D., MMSc; Dana-Farber/Boston Children's Cancer and Blood Disorder Center, Harvard Medical School, Boston, an investigator in the ACTIVATE-Kids study. "The efficacy and safety results from the ACTIVATE-Kids and ACTIVATE-KidsT Phase 3 studies demonstrate the potential for clinically meaningful benefits with mitapivat in children with PK deficiency who are and are not regularly transfused, improving anemia and reducing the need for transfusions."

Based on the clinically meaningful results observed in both the ACTIVATE-Kids and ACTIVATE-KidsT Phase 3 studies, Agios intends to submit a

marketing application for mitapivat in pediatric patients with PK deficiency. The company also plans to present more detailed analyses from both studies at upcoming medical conferences.

About PYRUKYND® (mitapivat)
U.S. INDICATION
PYRUKYND is a pyruvate kinase activator indicated for the treatment of hemolytic anemia in adults with pyruvate kinase (PK) deficiency.

U.S. 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.

Hepatocellular Injury in Another Condition: In patients with another condition treated with PYRUKYND at a higher dose than that recommended for patients with PK deficiency, liver injury has been observed. These events were characterized by a time to onset within the first 6 months of treatment with peak elevations of alanine aminotransferase of >5× upper limit of normal (ULN) with or without jaundice. All patients discontinued treatment with PYRUKYND, and these events improved upon treatment discontinuation.

Obtain liver tests prior to the initiation of PYRUKYND and monthly thereafter for the first 6 months and as clinically indicated. Interrupt PYRUKYND if clinically significant increases in liver tests are observed or alanine aminotransferase is >5x ULN. Discontinue PYRUKYND if hepatic injury due to PYRUKYND is suspected.

Adverse Reactions: 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 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, myelodysplastic syndrome (MDS)-associated anemia and phenylketonuria (PKU). In addition to its clinical pipeline, Agios is advancing a preclinical TMPRSS6 siRNA as a potential treatment for polycythemia vera. 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); 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. For example, there can be no guarantee that any product candidate Agios 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. 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; 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 key collaborations; uncertainty regarding any royalty payments related to the sale of its oncology business or any milestone or royalty payments related to its in-licensing of AG-236, and the uncertainty of the timing of any such payments; uncertainty of the results and effectiveness of the use of Agios' cash and cash equivalents; 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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