# Agios Announces Results from Phase 3 ACTIVATE-KidsT Study of Mitapivat in Children with PK Deficiency Who Are Regularly Transfused

August 1, 2024

*– ACTIVATE-KidsT is Agios' First Pediatric Data Readout;*
*Safety Results Consistent with Safety Profile for Mitapivat Previously Observed in Adults with PK Deficiency Who are Regularly Transfused –*

*– Prespecified Statistical Criterion for the Primary Endpoint in ACTIVATE-KidsT Was Not Met; Results Were Clinically Meaningful, with Observed Response Rates Higher for Mitapivat than Placebo for the Primary Endpoint of Transfusion Reduction Response and for the Secondary Endpoints of Transfusion-Free Response and Normal Hemoglobin Response –*

*– Enrollment Completed for Phase 3 ACTIVATE-Kids Study of Mitapivat in Children with PK Deficiency Who Are Not Regularly Transfused; Topline Data Expected in 2025 –*

CAMBRIDGE, Mass., Aug. 01, 2024 (GLOBE NEWSWIRE) -- Agios Pharmaceuticals, Inc. (Nasdaq: AGIO), a leader in cellular metabolism and pyruvate kinase (PK) activation pioneering therapies for rare diseases, today announced topline results from the global Phase 3 ACTIVATE-KidsT study of mitapivat in children aged 1 to <18 years with PK deficiency who are regularly transfused. Using Bayesian methodology, the prespecified statistical criterion for the primary endpoint in ACTIVATE-KidsT was not met using low or moderate borrowing of data from the ACTIVATE-T study in adults. In the ACTIVATE-KidsT study, 28.1% of patients in the mitapivat arm achieved the primary endpoint of transfusion reduction response, compared to 11.8% of patients in the placebo arm. Transfusion-free response and normal hemoglobin response were secondary endpoints in this study and only observed in patients in the mitapivat arm. In the 32-week double-blind treatment period, mitapivat was generally safe and well-tolerated, with safety results consistent with the safety profile for mitapivat previously observed in adults with PK deficiency who are regularly transfused.

"After years of working with the PK deficiency community and caregivers whose children have no disease-modifying therapies, it is gratifying to share encouraging efficacy and safety data that may support the potential of a first-ever pediatric treatment for this rare blood disorder," said Sarah Gheuens, M.D., Ph.D., chief medical officer and head of R&D at Agios. "We look forward to completing our pediatric PK deficiency clinical development program next year with the readout of the ACTIVATE-Kids study of mitapivat in children who are not regularly transfused. More broadly, the ACTIVATE-KidsT study represents Agios' first pediatric data readout. With our focus on lifelong, debilitating rare diseases, we hope that this study will be the first of several pediatric studies to make a positive impact in the lives of children facing rare hemolytic anemias, including PK deficiency, thalassemia and sickle cell disease."

"Children with PK deficiency can experience significant disease burden, including fatigue, the need for blood transfusions, and the risk of iron overload. Symptoms of PK deficiency, disease complications, and common supportive therapies can interfere with regular childhood activities," 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-KidsT study. "The ACTIVATE-KidsT trial is the first study of mitapivat in children who are regularly transfused and demonstrates the potential for meaningful clinical benefit, resolving the anemia and need for transfusions in a subset of children."

In addition, Agios has completed enrollment in the ACTIVATE-Kids study of mitapivat in children with PK deficiency who are not regularly transfused, and expects to report topline data in 2025.

Topline results for the Phase 3 ACTIVATE-KidsT study were as follows:

- A total of 49 patients aged 1 to <18 years were enrolled in the study, with 32 randomized to mitapivat twice-daily and 17 randomized to matched placebo. 30 patients (93.8%) in the mitapivat arm and 16 (94.1%) in the placebo arm completed the 32-week double-blind period of the study.
- The primary endpoint of the study was transfusion reduction response (TRR), defined as ≥33% reduction in the total red blood cell transfusion volume from Week 9 through Week 32 of the double-blind period normalized by weight and actual study drug duration compared with the historical transfusion volume standardized by weight and to 24 weeks.
    - The analysis of the primary endpoint was based on Bayesian statistical methodology whereby the TRR data from the adult ACTIVATE-T study inform and contribute to the analysis of TRR in the ACTIVATE-KidsT study. The analysis was performed using a range of relative weights of borrowing from the adult ACTIVATE-T study, representing the prior degree of belief in the similarity of the treatment effect in the pediatric and adult populations. The prespecified statistical criterion for the primary endpoint in ACTIVATE-KidsT was not met with low or moderate borrowing weights; however, the results were clinically meaningful.
    - 28.1% (9/32) of patients in the mitapivat arm achieved a transfusion reduction response, compared to 11.8% (2/17) of patients in the placebo arm.
- In addition, a higher proportion of patients in the mitapivat arm compared to the placebo arm achieved the secondary endpoints of transfusion-free response and normal hemoglobin response:
    - 6 patients (18.8%) in the mitapivat arm compared to 0 in the placebo arm had a transfusion-free response, defined as no red blood cell transfusions from Week 9 through Week 32 of the double-blind period.

    - 4 patients (12.5%) in the mitapivat arm compared to 0 in the placebo arm achieved a normal hemoglobin response, defined as hemoglobin concentrations within normal limits at least once, 8 weeks or more after a transfusion, from Week 9 through Week 32 of the double-blind period.
- In the 32-week double-blind treatment 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.
- Safety results in this pediatric study were consistent with the safety profile for mitapivat previously observed for adult patients with PK deficiency who are regularly transfused.

Agios plans to present a more detailed analysis of the Phase 3 ACTIVATE-KidsT data at an upcoming medical meeting.

**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, and for the treatment of PK deficiency in adult patients in the European Union.

**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 adult 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. The adverse reactions reported in the population of adult patients who were regularly transfused (ACTIVATE-T) were consistent with that seen in ACTIVATE.

**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 and Summary of Product Characteristics 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 and MDS-associated anemia. In addition to its clinical pipeline, Agios is advancing a preclinical TMPRSS6 siRNA as a potential treatment for polycythemia vera, and a preclinical PAH stabilizer as a potential treatment for phenylketonuria (PKU). 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 mitapivat; Agios' plans for the future clinical development of mitapivat in pyruvate kinase deficiency; and Agios' strategic plans and prospects. The words "anticipate," "believe," "estimate," "expect," "intend," "may," "plan," "predict," "project," "would," "could," "potential," "possible," "hope" 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 or its collaborators 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. Moreover, there can be no guarantee that any medicines ultimately commercialized by Agios will receive commercial acceptance. 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; 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 milestone or royalty payments

related to the sale of Agios' oncology business or its in-licensing of TMPRSS6 siRNA, and the uncertainty of the timing of any such payments; uncertainty of the results and effectiveness of the use of proceeds from the transaction with Servier; competitive factors; 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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