Agios Presents Positive Results from Phase 3 ENERGIZE-T Study of Mitapivat at ASH 2024 and Provides Regulatory Update on Mitapivat

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– ENERGIZE-T Study Achieved Primary and All Key Secondary Endpoints in Adult Patients with Transfusion-Dependent Alpha- or Beta-Thalassemia –

– ENERGIZE-T is First Phase 3 Study to Demonstrate Efficacy of an Oral, Disease-Modifying Treatment for Transfusion-Dependent Alpha- and Beta-Thalassemia –

– Company Filed for Regulatory Approval of Mitapivat (PYRUKYND®) for the Treatment of Adult Patients with Non-Transfusion-Dependent and Transfusion-Dependent Alpha- or Beta-Thalassemia in U.S., European Union, Kingdom of Saudi Arabia and United Arab Emirates –

– Live and Webcast Investor Event with Agios Leadership and Medical Experts will be Hosted in San Diego on Monday, December 9 at 7:00 a.m. PT –

CAMBRIDGE, Mass., Dec. 08, 2024 (GLOBE NEWSWIRE) -- Agios Pharmaceuticals, Inc. (Nasdaq: AGIO), a leader in cellular metabolism and pyruvate kinase (PK) activation pioneering therapies for rare diseases, today presented positive results from the Phase 3 ENERGIZE-T study investigating mitapivat, an oral, small molecule PK activator, in adults with transfusion-dependent alpha- or beta-thalassemia. These findings were shared in an oral presentation (abstract #409) at the 66th American Society of Hematology (ASH) Annual Meeting and Exposition in San Diego, California.

Thalassemia is a rare inherited blood disorder caused by genetic mutations that lead to a reduced production of healthy hemoglobin, compromising red blood cell development, health and survival, and resulting in chronic anemia. Patients with thalassemia often experience a range of debilitating complications, both from the disease itself and as secondary effects of common management strategies such as blood transfusions and iron chelation therapy, including organ damage, stroke, and other serious health issues.

In the ENERGIZE-T trial, mitapivat demonstrated a statistically significant reduction in transfusion burden compared to placebo in patients with transfusion-dependent alpha- or beta-thalassemia, achieving its primary endpoint. Additionally, the ENERGIZE-T study met all the key secondary endpoints, with mitapivat demonstrating a statistically significant reduction in additional measures of transfusion reduction response compared to placebo. In June 2024, Agios also presented positive results from the Phase 3 ENERGIZE study, which evaluated mitapivat in adults with non-transfusion-dependent alpha- or beta-thalassemia.

“Treatment options for patients with transfusion-dependent thalassemia are extremely limited, and transfusions carry serious risks, such as iron overload, infections and immune reactions. There is a significant need for alternative treatments to manage this debilitating disease,” said Maria Domenica Cappellini, M.D., professor, Internal Medicine, University of Milan, Italy. “The strong Phase 3 ENERGIZE-T results build on the positive findings from the Phase 3 ENERGIZE study in patients with non-transfusion-dependent alpha- or beta-thalassemia presented earlier this year, pointing to mitapivat as a potential transformative advancement in thalassemia care.”

Phase 3 ENERGIZE-T Study Results
ENERGIZE-T is a Phase 3, double-blind, randomized, placebo-controlled and multicenter 48-week study. A total of 258 patients were enrolled in the study worldwide, with 171 patients randomized to mitapivat 100 mg twice-daily (BID) and 87 patients randomized to matched placebo.

The study’s primary endpoint of transfusion reduction response (TRR) was defined as a ≥50% reduction in transfused red blood cell (RBC) units with a reduction of ≥2 units of transfused RBCs in any consecutive 12-week period through Week 48 compared with baseline. A TRR was achieved by 30.4% (n=52/171) of patients in the mitapivat arm compared to 12.6% (n=11/87) of patients in the placebo arm (2-sided p=0.0003).

Additionally, mitapivat demonstrated statistically significant reductions in transfusion burden compared with placebo as measured by the three key secondary endpoints of transfusion reduction response reflective of durability of response up to 36 weeks during the 48-week double-blind period. The key secondary endpoint TRR2, defined as a ≥50% reduction in transfused RBC units in any consecutive 24-week period through Week 48 compared with baseline, was achieved in 13.5% (n=23/171) versus 2.3% (n=2/87) of patients in the mitapivat and placebo arms, respectively (2-sided p=0.0003). The key secondary endpoints TRR3 and TRR4 were defined as a ≥33% and ≥50% reduction in transfused RBC units, respectively, from Week 13 through Week 48 compared with baseline. TRR3 was achieved in 14.6% (n=25/171) versus 1.1% (n=1/87) of patients in the mitapivat and placebo arms, respectively (2-sided p<0.0001), and TRR4 was achieved in 7.6% (n=13/171) versus 1.1% (n=1/87) of patients in the mitapivat and placebo arms, respectively (2-sided p=0.0056).

The results for the primary and key secondary endpoints were not driven by any of the individual prespecified subgroups, including but not limited to genotype and baseline transfusion burden, highlighting the overall robustness of the efficacy results.

Further, 17 patients (9.9%) in the mitapivat arm compared with one patient (1.1%) in the placebo arm achieved the secondary endpoint of transfusion independence (transfusion-free for 8 or more consecutive weeks through Week 48). Three patients in the mitapivat arm did not receive any transfusions during the 48-week double-blind period.

Overall, during the 48-week double-blind period, incidence of adverse events (AEs) was similar across the mitapivat and placebo arms. The proportion of patients with any treatment-emergent adverse events (TEAEs) was 90.1% (n=155) in patients on mitapivat and 83.5% (n=71) in patients on placebo. The most frequent TEAEs that occurred in at least 10% of patients on mitapivat were headache, upper respiratory tract infection, initial insomnia, diarrhea and fatigue. Serious treatment-emergent adverse events were reported in 11.0% (n=19) and 15.3% (n=13) of patients on mitapivat and placebo, respectively; 2.3% (n=4) and 1.2% (n=1), respectively, were considered treatment-related. There were 5.8% (n=10) of patients on

mitapivat and 1.2% (n=1) on placebo with TEAEs leading to treatment discontinuation. The TEAEs leading to discontinuation of mitapivat, each of which occurred in one patient, were diarrhea, paresthesia oral, concurrent anxiety and insomnia, initial insomnia, supraventricular tachycardia, fatigue, hypertransaminasemia, hepatitis C, hepatic cancer, and renal mass. The TEAE that led to discontinuation of the one patient on placebo was blood creatine phosphokinase increased.

Mitapivat Thalassemia Regulatory Next Steps
Currently, there are no disease-modifying therapies approved to treat the full spectrum of patients with thalassemia across transfusion requirements and genotypes. The standard of care for thalassemia remains centered on supportive care to address symptoms through transfusions, splenectomy, and/or iron chelation therapy, none of which address the underlying pathophysiology of the disease.

Based on the favorable benefit-risk profile observed in both the Phase 3 ENERGIZE and ENERGIZE-T studies, Agios filed regulatory applications for mitapivat (PYRUKYND®) for the treatment of adult patients with non-transfusion-dependent and transfusion-dependent alpha- or beta-thalassemia with the U.S., European Union, Kingdom of Saudi Arabia and United Arab Emirates health authorities.

The Phase 3 ENERGIZE and ENERGIZE-T trials enrolled a total of 452 patients reflective of the real-world thalassemia population. The results demonstrated that mitapivat improves hemolytic anemia and quality-of-life related measures, as measured by significant reductions in transfusion burden and significant improvements in hemoglobin and fatigue.

- The primary and all the key secondary efficacy endpoints were met, demonstrating the efficacy of mitapivat compared with placebo in the treatment of adult patients with non-transfusion-dependent and transfusion-dependent alpha- or beta-thalassemia.
- Overall, the incidence of AEs was similar for patients on mitapivat and patients on placebo. There were 4.7% (n=14) of patients on mitapivat and 0.7% (n=1) of patients on placebo with TEAEs leading to treatment discontinuation across the two studies.
- Two of 301 patients (0.66%) on mitapivat experienced AEs of hepatocellular injury within the first six months of exposure leading to treatment discontinuation. Liver tests improved following discontinuation of mitapivat. Based on the data from the ENERGIZE and ENERGIZE-T studies, Agios included, in its regulatory applications, hepatocellular injury as an important potential risk of mitapivat in patients with thalassemia and proposed monthly monitoring of liver tests for the first six months of treatment with mitapivat. In addition, mitapivat clinical trial protocols across all indications have been updated to incorporate similar monitoring.

“Informed by the robust data from both the Phase 3 ENERGIZE and ENERGIZE-T trials, we believe mitapivat has demonstrated an overall favorable benefit-risk profile in all subtypes of thalassemia, a disease where patients face debilitating challenges and have limited or no treatment options,” said Sarah Gheuens, M.D., Ph.D., chief medical officer and head of R&D at Agios. “We are confident that this comprehensive data package will highlight mitapivat’s effectiveness in treating patients with thalassemia with the convenience of an oral medication. We look forward to collaborating with regulators with the goal of bringing this novel therapy to patients with thalassemia as quickly as possible.”

Investor Event at ASH 2024
Agios will host a live and webcast investor event with the company’s leadership team and medical experts. The event will take place on Monday, December 9, in San Diego, starting at 7:00 a.m. PT (10:00 a.m. ET). The webcast will be accessible on the Investors section of the company's website (www.agios.com) under the “Events & Presentations” tab. The archived webcast will be available on the company's website approximately two hours after the event.

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 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 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, myelodysplastic syndromes (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); Agios' plans for the future clinical development and submission to regulators for approval of mitapivat in alpha-and-beta thalassemia; and Agios' strategic plans and prospects. 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 TMPRSS6 siRNA, 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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