Agios Announces Phase 3 ENERGIZE Study of Mitapivat Met Primary Endpoint and Both Key Secondary Endpoints in Adults with Non-Transfusion-Dependent Alpha- or Beta-Thalassemia

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–Mitapivat Demonstrated a Statistically Significant Increase in Hemoglobin Response Rate Compared to Placebo –

– Statistical Significance Also Achieved for Key Secondary Endpoints of Change From Baseline in Both FACIT-Fatigue Score and Hemoglobin Concentration –

– ENERGIZE is the First Phase 3 Study to Demonstrate Efficacy of an Oral Treatment for Non-Transfusion-Dependent Alpha- and Beta-Thalassemia –

– Agios to Host Investor Webcast Event Today at 8:00 a.m. ET–

CAMBRIDGE, Mass., Jan. 03, 2024 (GLOBE NEWSWIRE) -- Agios Pharmaceuticals, Inc. (Nasdaq: AGIO), a leader in the field of cellular metabolism and pioneering therapies for rare diseases, today announced that the global Phase 3 ENERGIZE study of mitapivat in adults with non-transfusion-dependent (NTD) alpha- or beta-thalassemia achieved its primary endpoint of hemoglobin response. Statistical significance was also achieved for both key secondary endpoints associated with change from baseline in FACIT-Fatigue Score and hemoglobin concentration.

“The results of the Phase 3 ENERGIZE study underscore the potential of mitapivat to be a meaningful treatment option for adults with non-transfusion dependent alpha- or beta-thalassemia. All subgroup analyses favored the mitapivat treatment arm compared to placebo,” said Sarah Gheuens, M.D., Ph.D., chief medical officer and head of R&D at Agios. “We are grateful to all of the patients who participated in this trial, our collaborators, study investigators and advisors in the patient and clinical communities for their partnership in achieving this milestone. These data bring us one step closer to a treatment for all thalassemia patients, and we look forward to the ENERGIZE-T readout mid-year.”

“The results of the ENERGIZE study support the potential of mitapivat to be the first oral therapy for all NTD thalassemia patients, including those with alpha- or beta-thalassemia,” said Ali Taher, M.D., Ph.D., Professor of Medicine, Hematology & Oncology and Director – Naef K. Basile Cancer Institute, American University of Beirut Medical Center in Beirut, Lebanon. “For NTD thalassemia patients across the globe, there are currently no approved oral treatments, and NTD thalassemia has consistently been associated with morbidity and mortality if left untreated. NTD thalassemia represents over half of clinically significant forms of thalassemia, so there is a tremendous unmet need. Based on the data reported to date, mitapivat has the potential to be a foundational treatment option for the thalassemia community.”

Agios is also advancing the fully enrolled Phase 3 ENERGIZE-T study of mitapivat in adults with transfusion-dependent alpha- or beta-thalassemia and expects to announce topline data from this 48-week study in mid-2024. Following the read-out of ENERGIZE-T, the company intends to file for regulatory approval of mitapivat as a treatment for thalassemia by the end of 2024, incorporating all available data from both studies.

Topline results for the Phase 3 ENERGIZE study were as follows:

- A total of 194 patients were enrolled in the study, with 130 randomized to mitapivat 100 mg twice-daily (BID) and 64 randomized to matched placebo. 122 (93.8%) in the mitapivat arm and 62 (96.9%) in the placebo arm completed the 24-week double-blind period of the study.
- The study met the primary endpoint of hemoglobin response. Hemoglobin response was defined as an increase of ≥1 g/dL in average hemoglobin concentrations from Week 12 through Week 24 compared with baseline.
    - Treatment with mitapivat demonstrated a statistically significant increase compared to placebo.
    - 42.3% of patients in the mitapivat arm achieved a hemoglobin response, compared to 1.6% of patients in the placebo arm (2-sided $p<0.0001$).
- Treatment with mitapivat also demonstrated statistically significant improvements compared to placebo for both key secondary endpoints:
    - Change from baseline in average FACIT-Fatigue (Functional Assessment of Chronic Illness Therapy-Fatigue) subscale score from Week 12 to Week 24.
    - Change from baseline in average hemoglobin concentration from Week 12 to Week 24.
- Overall, during the 24-week double-blind period, incidence of adverse events was similar across mitapivat and placebo arms. Four (3.1%) subjects in the mitapivat arm experienced adverse events (AEs) leading to discontinuation; there were no AEs leading to discontinuation in the placebo arm.

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

Conference Call Information
Agios will host a webcast investor event today at 8:00 a.m. ET to review the ENERGIZE Phase 3 data and next steps for the Phase 3 ENERGIZE-T study. The event can be accessed under “Events & Presentations” in the Investors and Media section of the company's website at www.agios.com. The archived webcast will be available on the company's website beginning 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 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 alpha-and-beta thalassemia; 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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