Agios Announces Data from Investigator-led Studies of Mitapivat in Adults with Sickle Cell Disease Demonstrating Improvements in Anemia, Hemolysis and Sickling Parameters at 63rd ASH Annual Meeting and Exposition

December 13, 2021

– Data Underscore Potential of Mitapivat to Provide Clinically Meaningful Outcomes for Patients –

– Safety Profile Consistent with Previously Reported Clinical Data –

– Agios Announces Initiation of Phase 2/3 RISE UP Study of Mitapivat in Adults with Sickle Cell Disease –

– Agios to Host Investor Webcast on Dec. 14, 2021, at 7:30 a.m. ET –

CAMBRIDGE, Mass., Dec. 13, 2021 (GLOBE NEWSWIRE) -- Agios Pharmaceuticals, Inc. (NASDAQ: AGIO), a leader in the field of cellular metabolism to treat genetically defined diseases, today announced new data from investigator-led studies of mitapivat, a first-in-class, investigational, oral, small molecule allosteric activator of wild-type and a variety of mutated pyruvate kinase (PK) enzymes, in adults with sickle cell disease. The data, reported by the National Institutes of Health (NIH) and University Medical Center (UMC) Utrecht, were featured in two presentations at the American Society of Hematology (ASH) Annual Meeting and Exposition, hosted virtually and in person from Dec. 11-14, 2021, in Atlanta. The data demonstrate the potential of mitapivat to provide clinically meaningful outcomes for patients, including improvements in anemia, hemolysis and red blood cell sickling.

Consistent with previously reported proof-of-concept data, mitapivat reduced 2,3-diphosphoglycerate (2,3-DPG) and increased adenosine triphosphate (ATP), and through this mechanism, may reduce hemoglobin S polymerization and red blood cell sickling. The safety profile observed in both studies was also generally consistent with previously published clinical data, including Phase 3 data in adults with pyruvate kinase deficiency.

“Results reported from these investigator-led studies provide additional efficacy, safety and translational data that continue to support the clinical development of mitapivat in people with sickle cell disease, a lifelong, debilitating condition with few treatment options,” said Sarah Gheuens, M.D., Ph.D., chief medical officer at Agios. “We’d like to thank our collaborators at the NIH and UMC Utrecht and look forward to building upon their contributions through our recently initiated Phase 2/3 RISE UP trial. In collaboration with the sickle cell disease community, we designed this trial to have a broad global reach, reduce barriers to participation and understand how mitapivat can impact the aspects of the disease that patients indicated were of greatest importance to them.”

Safety and Efficacy of Mitapivat (AG-348), An Oral Activator of Pyruvate Kinase-R, in Patients with Sickle Cell Disease: A Phase 2, Open-label Study (ESTIMATE) (Abstract #2005)
The Phase 2 ESTIMATE study being conducted by UMC Utrecht is designed to assess safety and efficacy of mitapivat in patients with sickle cell disease. The primary endpoints of the study are safety and point of sickling (point on the deoxygenation curve when sickling begins), and key secondary endpoints include changes in hemoglobin levels and clinical complication rates.

Key findings from six patients who completed the eight-week dose-finding period, all reaching 100 mg twice daily dosing, include:

- No serious adverse events (AEs) occurred, and all AEs were mild and mostly transient. One vaso-occlusive crisis (VOC) occurred without hospital admission and did not require dose reduction or discontinuation.
- All six patients had improvements in point of sickling.
- Observed changes in 2,3-DPG and ATP levels were consistent with proposed mechanism of action.
- Mitapivat increased hemoglobin and decreased hemolysis and sickling parameters.
    - Five out of six patients (83.3%) achieved hemoglobin response (≥ 1g/dL increase from baseline).
- Early improvements in albumin-to-creatinine ratio were observed.
- Follow-up data from the ongoing study will be reported at a later stage.

Mitapivat (AG-348) Demonstrates Safety, Tolerability and Improvements in Anemia, Hemolysis, Oxygen Affinity and Hemoglobin S Polymerization Kinetics in Adults with Sickle Cell Disease: A Phase 1 Dose Escalation Study (Abstract #10)
The Phase 1 study, which is being conducted in collaboration with the NIH as part of a cooperative research and development agreement, is designed to evaluate the efficacy, safety, pharmacokinetics and pharmacodynamics of treatment with mitapivat in adults with sickle cell disease. The primary endpoint of the study is safety and tolerability, as assessed by frequency and severity of AEs and laboratory parameters. Secondary endpoints include changes in hemoglobin, markers of hemolysis, 2,3-DPG and ATP levels and hemoglobin S polymerization.

Key findings from the 16 evaluable patients who completed the core period of the study, including up to eight weeks of dose escalation, dose taper and four-week safety follow-up, include:

- No AEs led to drug discontinuation.
    - No VOCs occurred during dose-escalation. Two VOCs occurred during drug taper, which were deemed possibly drug-related, and two VOCs occurred during the 28-day safety follow-up.
- Treatment with mitapivat demonstrated improvement in anemia and decreases in markers of hemolysis, including lactate dehydrogenase, total bilirubin, absolute reticulocyte count and aspartate aminotransferase.

    - Nine out of 16 patients (56.3%) achieved a hemoglobin response (≥1g/dL increase from baseline).
- Mitapivat reduced 2,3-DPG and increased ATP, with expected increase in oxygen affinity and decreased sickling rate.
- Long-term disease modifying effects being evaluated in an ongoing extension study.

Mitapivat is not approved for use by any regulatory authority.

Overview of Phase 2/3 RISE UP Study
The Phase 2/3 RISE UP study will evaluate the efficacy and safety of mitapivat in sickle cell disease patients who are 16 years of age or older, have had between two and 10 sickle cell pain crises in the past 12 months, and have hemoglobin within the range of 5.5 to 10.5 g/dL during screening.

The Phase 2 portion, which was recently initiated, includes a 12-week randomized, placebo-controlled period in which participants will be randomized in a 1:1:1 ratio to receive 50 mg mitapivat twice daily, 100 mg mitapivat twice daily or matched placebo. The primary endpoints are hemoglobin response, defined as ≥1 g/dL increase in average hemoglobin concentration from Week 10 through Week 12 compared to baseline, and safety. These data will be used to establish a clear dosing paradigm for the Phase 3 portion.

The Phase 3 portion includes a 52-week randomized, placebo-controlled period in which participants will be randomized in a 2:1 ratio to receive the recommended mitapivat dose level or placebo. The primary endpoints are hemoglobin response, defined as ≥1 g/dL increase in average hemoglobin from baseline to Week 52, and annualized rate of sickle cell pain crises. Participants who complete either the Phase 2 or Phase 3 portion will have the option to move into a 216-week open-label extension period to receive mitapivat.

Conference Call Information
Agios will host a virtual investor event at 7:30 a.m. ET on Dec. 14, 2021, to review the key clinical oral and poster presentations from this year's ASH meeting. The event will be webcast live and 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 Sickle Cell Disease
Sickle cell disease is caused by inherited mutations in the beta-globin gene, leading to sickle-shaped red blood cells that are rigid and prone to getting trapped in small vessels, slowing or stopping the flow of blood. People with sickle cell disease have inherited mutations in the beta-globin gene, which lead to elevated levels of the metabolite 2,3-DPG (2,3-diphosphoglycerate) and decreased adenosine triphosphate (ATP) levels.

Sickle cell disease can cause pain and is associated with serious complications, including anemia, increased risk of infection, acute chest syndrome ,and stroke. Current management strategies for sickle cell disease can include red blood cell transfusions, stem cell transplant and pain medications which are associated with short- and long-term risks. In addition, some disease-modifying therapies are available, but significant unmet need remains. Although sickle cell disease is considered a rare disease in the U.S. and EU, it is one of the most common genetic disorders in the world.

About Agios
Agios is focused on discovering and developing novel investigational medicines to treat genetically defined diseases through scientific leadership in the field of cellular metabolism. The company's most advanced drug candidate is a first-in-class pyruvate kinase (PK) activator, mitapivat, that is currently being evaluated for the treatment of three distinct hemolytic anemias. In addition to its active late-stage clinical pipeline, Agios has multiple novel, investigational therapies in clinical and preclinical development. 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 mitapivat; the potential benefits of Agios' products and product candidates, including 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. 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 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; the impact of the COVID-19 pandemic 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 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, 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; 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 communication 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.

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