Agios Presents Positive Results from Phase 2 Study of Mitapivat in Non-transfusion-dependent α- and β-Thalassemia at the European Hematology Association Virtual Congress

June 11, 2021

– Study Met Primary Endpoint; Treatment with Mitapivat Induced Hemoglobin Increase of ≥1.0 g/dL in 16 of 20 (80%) Patients During Weeks 4-12 –

– Mitapivat Safety Profile Consistent with Previously Published Studies –

– Agios to Host Investor Webcast Today at 7:30 a.m. ET –

CAMBRIDGE, Mass., June 11, 2021 (GLOBE NEWSWIRE) -- Agios Pharmaceuticals, Inc. (NASDAQ: AGIO), a leader in the field of cellular metabolism to treat genetically defined diseases, today announced positive results from its Phase 2, open-label, multicenter study of mitapivat in adults with non-transfusion dependent α- or β-thalassemia. Data from the study will be featured in an oral presentation on Tuesday, June 15, at the European Hematology Association (EHA) Virtual Congress.

Consistent with previously announced proof-of-concept data, the study met its primary endpoint, with 16 of the 20 patients (80%) achieving a hemoglobin increase of ≥1.0 g/dL from baseline at one or more assessments during Weeks 4-12. Additionally, a sustained hemoglobin response and improvements in hemolysis and ineffective erythropoiesis were observed in both α- or β-thalassemia patients treated with mitapivat. Mitapivat was well tolerated, and the safety profile was consistent with previous studies. Mitapivat is a first-in-class, investigational, oral, small molecule allosteric activator of wild-type and a variety of mutated pyruvate kinase R (PKR) enzymes.

“These data continue to validate the potential of PK activation as an entirely new mechanism for treating thalassemia, a disease for which there have been few medical advancements. In particular, we are excited to see data generated, for the first time, in α-thalassemia, demonstrating an increase in hemoglobin from baseline in all five patients in this subgroup,” said Kevin Kuo, M.D., hematologist at University Health Network, University of Toronto, and an investigator in the study. “The impressive results reported today underscore the potential of mitapivat to meaningfully improve hallmarks of this disease, including hemolysis and ineffective erythropoiesis.”

Mitapivat Phase 2 Proof-of-concept Study
The open-label Phase 2 study evaluated the efficacy, safety, pharmacokinetics and pharmacodynamics of mitapivat treatment in adults with either non-transfusion-dependent α- or β-thalassemia who have a baseline hemoglobin (Hb) concentration of ≤10 g/dL. The trial enrolled 20 patients. All patients were treated with an initial dose of mitapivat 50 mg twice daily followed by a dose-level increase to 100 mg twice daily at the Week 6 visit based on safety evaluations and hemoglobin concentrations. Following the completion of the 24-week core period, patients had the opportunity to enroll in an optional 10-year extension period which will evaluate long-term efficacy and safety of mitapivat in this population.

- Of the 20 patients, 5 patients had α-thalassemia, and 15 patients had β-thalassemia.
- Median hemoglobin at baseline was 8.43 (range 5.13-9.8) g/dL.
- Median age was 44 (range 29-67) years.

Efficacy Data

- The primary endpoint, defined as a ≥1.0 g/dL increase in hemoglobin concentration from baseline at one or more assessments between Week 4 and Week 12, was met by 16 of 20 (80%) patients (1-sided $p<0.0001$), including all 5 (100%) α-thalassemia patients and 11 of 15 (73.3%) β-thalassemia patients. The 1-sided p-value associated with the test of H_0: hemoglobin response rate =30% vs H_1: hemoglobin response rate >30%, based on the Clopper-Pearson method.
- The secondary endpoint of sustained hemoglobin response, defined as a primary endpoint response and a ≥1.0 g/dL increase in hemoglobin concentration from baseline at two or more assessments between Week 12 and Week 24, was met by 13 of 20 (65%) patients, including all 5 (100%) α-thalassemia patients and 8 of 15 (53.3%) patients with β-thalassemia.
- During Weeks 12-24, the mean hemoglobin change from baseline was 1.3 g/dL. The mean change was 1.2 g/dL for α-thalassemia patients, and 1.3 g/dL for β-thalassemia patients.
- Among hemoglobin responders, mean time to first ≥1.0 g/dL increase in hemoglobin concentration was 4.5 weeks.
- Markers of hemolysis and erythropoiesis – including indirect bilirubin, lactate dehydrogenase and erythropoietin – demonstrated improvements that were consistent with the hemoglobin increase in both α- and β-thalassemia patients.
- Adenosine triphosphate (ATP) levels showed mean increases of up to 86.7% from baseline.

Safety Data
The majority of adverse events (AEs) observed were consistent with previously published data for mitapivat in healthy volunteers and patients with pyruvate kinase (PK) deficiency.

- Dose escalation to 100 mg twice daily was well tolerated.
- The most commonly reported AEs were initial insomnia (n=10 [50%]), dizziness (n=6 [30%]) and headache (n=5 [25%]).
- One patient (5%) discontinued treatment during the study; the adverse event leading to study drug discontinuation was not treatment-related.

- Seventeen patients continued to the extension period of the study, and as of March 27, 2021, 17 patients remain on study drug.

“We are pleased to present data from our Phase 2 trial of mitapivat, which is the first clinical study of a PK activator in thalassemia and the first drug trial in α-thalassemia, and represents a potentially innovative therapeutic approach for these patients who are in need of new treatment options,” said Chris Bowden, chief medical officer at Agios. “Our focus now is to advance the development of mitapivat in thalassemia as quickly and efficiently as possible, with the initiation of two Phase 3 studies of mitapivat, ENERGIZE and ENERGIZE-T, in not regularly transfused and regularly transfused adults with thalassemia. Additionally, we look forward to further advancing mitapivat as a potential treatment for other underserved patients with hemolytic anemias, including individuals with pyruvate kinase deficiency, where our U.S. and EU regulatory filing plans are on track, and sickle cell disease, where our pivotal development program is on track to initiate by year-end.”

Oral Presentation Information

Title: Results from a Phase 2, open-label, multicenter study of the oral pyruvate kinase activator mitapivat in adults with non-transfusion dependent alpha- or beta-thalassemia
Live Q&A Session Date and Time: Tuesday, June 15, 2021, at 8:45 p.m. CEST / 2:45 p.m. ET
Oral Abstract Session: Changing the scene on thalassemias
Abstract: S267
Presenter: Kevin H. M. Kuo, M.D., Division of Hematology, University of Toronto, Toronto, Canada

Mitapivat Clinical Development
In addition to the Phase 2 extension study of mitapivat in adults with non-transfusion-dependent α- and β-thalassemia, Agios is initiating two Phase 3 studies of mitapivat in adults with thalassemia in the second half of 2021. They are:

- ENERGIZE: A placebo-controlled trial with a 2:1 randomization evaluating patients who do not receive regular transfusions. The primary endpoint of the trial is hemoglobin response, defined as a ≥1.0 g/dL increase in average hemoglobin concentration from Week 12 through Week 24 compared with baseline.
- ENERGIZE-T: A placebo-controlled trial with a 2:1 randomization evaluating patients who receive regular transfusions. The primary endpoint of the trial is transfusion reduction response, defined as a ≥50% reduction in transfused red blood cell units with a reduction of ≥2 units of transfused red blood cells in any consecutive 12-week period through Week 48 compared with baseline.

In addition to its Phase 2 study of mitapivat in adults with non-transfusion-dependent α- or β-thalassemia, Agios has completed two global, pivotal trials in adults with pyruvate kinase (PK) deficiency. Final data from these studies will be presented in an oral session at the EHA Virtual Congress. They are:

- ACTIVATE: A placebo-controlled trial with a 1:1 randomization evaluating patients who do not receive regular transfusions. The primary endpoint of the study was hemoglobin response, defined as a ≥1.5 g/dL increase in hemoglobin concentration from baseline that is sustained at two or more scheduled assessments at Weeks 16, 20 and 24 during the fixed dose period.
- ACTIVATE-T: A single arm trial of regularly transfused patients with a primary endpoint of reduction in transfusion burden, a reduction of ≥33 percent in the number of red blood cell units transfused during the 24-week fixed dose period compared with the historical transfusion burden standardized to 24 weeks.

ACTIVATE and ACTIVATE-T are intended to support global regulatory filings for mitapivat in adults with PK deficiency in the U.S. in the second quarter of 2021 and in the EU in mid-2021. Agios also is conducting an extension study for adults with PK deficiency previously enrolled in ACTIVATE or ACTIVATE-T, which is designed to evaluate the long-term safety, tolerability and efficacy of treatment with mitapivat.

In addition, mitapivat is being evaluated as a potential treatment for sickle cell disease under a Cooperative Research and Development Agreement (CRADA) with the U.S. National Institutes of Health. Mitapivat has been shown to decrease 2,3-diphosphoglycerate (2,3-DPG) and increase adenosine triphosphate (ATP), and through this mechanism, it may reduce hemoglobin S polymerization and red blood cell sickling. Preliminary clinical data establishing proof-of-concept for mitapivat in sickle cell disease were disclosed in June 2020, and updated data were presented at the American Society of Hematology (ASH) Annual Meeting in December 2020. Agios is initiating its pivotal Phase 2/3 study in sickle cell disease by year-end 2021.

Mitapivat has been granted orphan drug designation for the treatment of PK deficiency by the U.S. Food and Drug Administration (FDA) and the European Medicines Agency. Additionally, mitapivat has received orphan drug designation from the FDA for the treatment of thalassemia and sickle cell disease.

Mitapivat is not approved for use by any regulatory authority.

CONFERENCE CALL INFORMATION

Agios will host a virtual investor event today at 7:30 a.m. ET to review the mitapivat clinical data. 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 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 R (PKR) 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; Agios' key milestones and guidance for 2021; 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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