Agios Announces Clinical Proof-of-Concept Has Been Established in Phase 1 Study of Mitapivat, First-in Class PKR Activator, in Sickle Cell Disease

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– 5 of 8 (63%) Efficacy Evaluable Patients Achieved a Hemoglobin Increase of ≥1.0 g/dL From Baseline –

– Safety Profile Consistent with Previously Published Phase 2 Data for Mitapivat in Patients with Pyruvate Kinase Deficiency or Expected in the Context of Sickle Cell Disease –

– Pharmacodynamics and Biomarker Data Support Mitapivat's Proposed Mechanism of Action –

– Data Support Advancement of Mitapivat to Pivotal Development in Sickle Cell Disease –

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

CAMBRIDGE, Mass., June 12, 2020 (GLOBE NEWSWIRE) -- Agios Pharmaceuticals, Inc. (NASDAQ:AGIO), a leader in the field of cellular metabolism to treat cancer and rare genetic diseases, today announced that clinical proof-of-concept has been established based on a preliminary analysis in the Phase 1 trial of mitapivat (AG-348) in patients with sickle cell disease. The study is being conducted in collaboration with the National Institutes of Health (NIH) as part of a cooperative research and development agreement. Mitapivat is an investigational, first-in-class, oral, small molecule allosteric activator of wild-type and a variety of mutated pyruvate kinase-R (PKR) enzymes. 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 (Hb) S polymerization and red blood cell sickling.

The ongoing Phase 1 study has enrolled nine patients to date. Eight patients have completed all planned dose levels, and one patient discontinued within the first week due to a pre-existing condition and was subsequently lost to follow-up. Six patients were treated with three ascending dose levels of mitapivat (5 mg BID, 20 mg BID, 50 mg BID) for two weeks duration, respectively, followed by 9 or 12-day drug taper, and two patients received an additional ascending dose of 100 mg BID for two weeks before initiating the drug taper. Adverse events (AEs) reported during the study were generally consistent with those previously reported in pyruvate kinase (PK) deficiency or are to be expected in the context of sickle cell disease. One severe AE, a vaso-occlusive crisis, occurred during drug taper and was attributed as possibly related to the drug.

Seven of eight (88%) patients who completed all planned dose levels of mitapivat experienced a Hb increase, with five of eight patients (63%) achieving a hemoglobin increase of ≥1.0 g/dL from baseline (range 1.0-2.7 g/dL). All five patients who achieved a hemoglobin increase of ≥1.0 g/dL did so at doses of 50 mg BID or lower. Treatment with mitapivat was associated with decreases in hemolytic markers such as bilirubin, lactic acid dehydrogenase and reticulocytes. As expected, decreases in 2,3-DPG and increases in ATP levels were observed, consistent with the proposed mechanism of action and comparable to that observed in healthy volunteer studies with mitapivat. Evaluation of sickling curves (t50) and oxygen dissociation curves (p50) were consistent with decreases in both sickling and HbS polymerization, further supporting the proposed mechanism of action.

"The interim results from the Phase 1 study of mitapivat demonstrate for the first time that PKR activation has the potential to address chronic hemolytic anemia and impact markers of sickling in sickle cell disease patients as hypothesized based on the mechanism of action," said Swee Lay Thein, M.B.B.S., F.R.C.P., F.R.C.Path., D.Sc., chief of the Sickle Cell Branch of the National Heart, Lung, and Blood Institute, NIH, and the principal investigator of the study. "The safety profile of mitapivat continues to be consistent with prior studies in both mutated and wildtype PKR, and hemoglobin responses were seen in 63% of patients. We are excited about these preliminary results, and I look forward to continuing to collaborate with Agios to advance this treatment for sickle cell disease patients."

"First, I would like to thank the NIH and Dr. Thein for the incredible collaboration on this study. These data build on our six years of clinical experience with this mechanism and establish proof-of-concept for mitapivat as a potential novel approach for the treatment of sickle cell disease, a chronic lifelong condition with few treatment options," said Chris Bowden, M.D., chief medical officer at Agios. "Looking ahead, we are focused on advancing mitapivat to pivotal development, with the goal of initiating a pivotal study next year."

Mitapivat Phase 1 Trial in Sickle Cell Disease
The ongoing Phase 1 study, which can enroll up to 25 patients, is evaluating the efficacy, safety, pharmacokinetics and pharmacodynamics of treatment with mitapivat in adults with sickle cell disease. Six patients received three ascending dose levels of mitapivat (5 mg BID, 20 mg BID, 50 mg BID) for 2 weeks duration, respectively, followed by 9 or 12-day drug taper. The two patients most recently enrolled and all subsequent patients receive an additional ascending dose of 100 mg BID for two weeks before initiating the drug taper in order to further explore dose-response relationship. The primary endpoint of the study is safety and tolerability as assessed by frequency and severity of adverse events and laboratory parameters. Secondary endpoints included changes in hemoglobin, markers of hemolysis, 2,3-DPG and ATP levels and HbS polymerization.

Mitapivat Clinical Development
Agios has two ongoing global, pivotal trials in adults with PK deficiency that are fully enrolled.

- ACTIVATE: A placebo-controlled trial with a 1:1 randomization evaluating patients who do not receive regular transfusions. The primary endpoint of the trial is the proportion of patients who achieve a sustained hemoglobin increase of ≥1.5 g/dL.
- ACTIVATE-T: A single arm trial of regularly transfused patients with a primary endpoint of reduction in transfusion burden over six months compared to individual historical transfusion burden over prior 12 months.

In addition, mitapivat is being studied in an ongoing Phase 2 study in adults with non-transfusion-dependent β- and α-thalassemia. Interim results from

the study were reported today in an oral presentation at the 25th European Hematology Association Annual Congress (EHA).

Mitapivat is not approved for use by any regulatory authority.

Investor Webcast Information
Agios will host an investor webcast today at 7:30 a.m. ET to review the mitapivat proof-of-concept data in sickle cell disease and Phase 2 thalassemia data presented at EHA. The event will be webcast live and can be accessed under "Events & Presentations" in the Investors section of Agios' website at www.agios.com. The archived webcast will be available on Agios' website beginning approximately two hours after the event.

About Agios
Agios is focused on discovering and developing novel investigational medicines to treat cancer and rare genetic diseases through scientific leadership in the field of cellular metabolism. In addition to an active research and discovery pipeline across both therapeutic areas, Agios has two approved oncology precision medicines and multiple first-in-class investigational therapies in clinical and/or preclinical development. All Agios programs focus on genetically identified patient populations, leveraging our knowledge of metabolism, biology and genomics. 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 further clinical development of mitapivat; 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. 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 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 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 maintain key 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. 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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