



AgiOS Announces Updated Data from Phase 1 Study of Mitapivat, First-in-Class PKR Activator, in Sickle Cell Disease

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– Treatment with Mitapivat Induced Hemoglobin Increase of ≥ 1.0 g/dL in 6 of 11 (55%) Efficacy Evaluable Patients, Decreased Markers of Hemolysis, Reduced 2,3-DPG and Increased ATP –

– Safety Profile Generally Consistent with Previously Presented Data in Patients with Pyruvate Kinase Deficiency and Thalassemia –

– Data Support Advancement of Mitapivat to Pivotal Development in Sickle Cell Disease; Company Expects to Initiate Pivotal Program in 2021 –

– Company to Host Investor Event and Webcast Tomorrow, December 8, at 8:00 a.m. ET –

CAMBRIDGE, Mass., Dec. 07, 2020 (GLOBE NEWSWIRE) -- Agios Pharmaceuticals, Inc. (NASDAQ: AGIO), a leader in the field of cellular metabolism to treat cancer and rare genetic diseases, today reported updated data from a Phase 1 trial of mitapivat, the company's first-in-class pyruvate kinase R (PKR) activator, 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. Data from the study were featured in an oral presentation at the American Society of Hematology (ASH) Annual Meeting, which is being held virtually. Mitapivat is an investigational, oral, small molecule allosteric activator of wild-type and a variety of mutated PKR enzymes.

As of the October 6, 2020 data cut-off, six of 11 efficacy evaluable patients (55%) achieved a hemoglobin increase of ≥ 1.0 g/dL from baseline. The mean maximal hemoglobin increase among all efficacy evaluable patients was 1.3 g/dL, and the mean maximal hemoglobin increase among responders was 1.9 g/dL. Treatment with mitapivat was associated with decreases in hemolytic markers such as bilirubin, lactate dehydrogenase (LDH) and reticulocytes. As expected, dose-dependent decreases in 2,3-diphosphoglycerate (2,3-DPG) and increases in adenosine triphosphate (ATP) levels were observed, consistent with the proposed mechanism of action. Adverse events (AEs) reported during the study were generally consistent with those previously reported in pyruvate kinase (PK) deficiency and thalassemia studies.

"The hemoglobin improvement, in conjunction with improvements in markers of hemolysis, induced by mitapivat in sickle cell disease patients is highly encouraging, particularly given the short duration patients are on treatment at the higher dose levels," 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. "I believe mitapivat may be a promising sickle cell disease treatment option with a well-tolerated safety profile and convenient oral administration. I look forward to further investigating the long-term effects of mitapivat in an ongoing sickle cell disease extension study and to working with Agios to continue to advance mitapivat on behalf of this patient community, a historically under-served population in tremendous need of new treatment options."

"We are pleased to continue collaborating with Dr. Thein and her colleagues at the NIH to further elucidate mitapivat's potential to improve red blood cell health, energy and longevity for people living with sickle cell disease, a debilitating, inherited, lifelong red blood cell disorder," said Chris Bowden, M.D., chief medical officer at Agios. "We are excited by the updated results of this study and plan to build on our findings by initiating a pivotal study of mitapivat in adults with sickle cell disease next year."

Updated Data from the 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. As of the data cut-off, 12 patients were dosed and 11 were evaluable for efficacy. One patient discontinued within the first week due to a pre-existing condition and was subsequently lost to follow-up, one patient discontinued prior to completing the 100 mg BID dose level, one patient is ongoing and nine had completed all planned dose levels. All 11 efficacy evaluable patients have received three ascending dose levels of mitapivat (5 mg BID, 20 mg BID, 50 mg BID) for two weeks' duration, respectively, and of these, three patients have received an additional ascending dose of 100 mg BID for two weeks. All underwent a 12- or 15-day drug taper after completing the dosing.

Safety Data

A safety analysis conducted for all 12 patients as of the data cut-off demonstrated:

- The majority of treatment-related AEs were Grade 1-2 and generally consistent with previous studies in PK deficiency and thalassemia. The most common AEs of all grades were pain and hyperglycemia.
- As previously reported, one vaso-occlusive crisis (VOC) occurred during drug taper and was attributed as possibly related to the drug. Two other VOCs occurred during the 28-day safety follow-up post drug exposure and were not attributed to mitapivat. No VOCs were observed during dose escalation.
- One patient had hip pain at baseline, not attributed to study drug, that led to discontinuation prior to completing the 100 mg BID dose.
- One patient with a pre-existing pulmonary embolism was withdrawn from the study shortly after initiation.

Efficacy and Pharmacodynamic Data

An efficacy analysis conducted for 11 patients as of the data cut-off demonstrated:

- Six of 11 efficacy evaluable patients (55%) achieved a hemoglobin increase of ≥ 1.0 g/dL from baseline, all at doses of 50 mg or less.

- The mean maximal hemoglobin increase among all efficacy evaluable patients was 1.3 g/dL.
- The mean maximal hemoglobin increase among responders was 1.9 g/dL.
- Dose-dependent increases in ATP and decreases in 2,3-DPG were observed.
- Decreases in total bilirubin, LDH and absolute reticulocyte count were also observed.

Mitapivat Clinical Development

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 (NIH). Mitapivat has been shown to decrease 2,3-DPG and increase 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. The NIH is also running an extension study for individuals with sickle cell disease who participated in the Phase 1 trial. Agios expects to initiate a Phase 3, global, pivotal study of mitapivat in sickle cell disease in 2021.

In addition, Agios has two global, pivotal trials in adults with PK deficiency that are fully enrolled.

- **ACTIVATE:** A placebo-controlled trial with a 1:1 randomization evaluating mitapivat in patients who do not receive regular transfusions. The primary endpoint of the trial, defined as a sustained hemoglobin increase of ≥ 1.5 g/dL from baseline, was met, [as reported last week](#). Full results from the study will be presented at a medical meeting in 2021.
- **ACTIVATE-T:** A single arm trial evaluating mitapivat in patients who receive regular transfusions. The primary endpoint of the trial is the proportion of patients who achieve a reduction in transfusion burden compared to individual historical transfusion burden standardized to 24 weeks. Agios anticipates reporting topline ACTIVATE-T data in Q1 2021.

Agios is also conducting a Phase 2 study evaluating the efficacy, safety, pharmacokinetics and pharmacodynamics of treatment with mitapivat in adults with non-transfusion-dependent α - or β -thalassemia. The trial is fully enrolled with 20 patients, and the primary endpoint is hemoglobin response, defined as a ≥ 1.0 g/dL increase in Hb concentration from baseline. Agios expects to report the final results from this Phase 2 trial at a medical meeting in 2021. The company also expects to initiate a Phase 3 pivotal program evaluating mitapivat in thalassemia, including both α - and β -thalassemia, as well as transfusion dependent and non-transfusion dependent patient populations, in 2021.

Mitapivat has not received marketing authorization from any regulatory authority.

Investor Webcast Information

Agios will host an investor webcast tomorrow at 8:00 a.m. ET to review the mitapivat sickle cell disease data presented at ASH, the topline Phase 3 ACTIVATE data of mitapivat in pyruvate kinase deficiency and the company's pivotal development plans for mitapivat in thalassemia. 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 malignant hematology, solid tumors and rare genetic diseases through scientific leadership in the field of cellular metabolism. In addition to an active research and discovery pipeline across these three therapeutic areas, Agios has two approved oncology precision medicines and multiple first-in-class investigational therapies in clinical and/or 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: the potential benefits of mitapivat; Agios' plans for the further clinical development of mitapivat; Agios' plans for future data presentations; 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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