Agios First-in Class PKR Activator Mitapivat Demonstrates Sustained Hemoglobin Responses in Non-transfusion-dependent α- and β-Thalassemia in Phase 2 Study

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– Treatment with Mitapivat Induced Hemoglobin (Hb) Increase of ≥1.0 g/dL in 12 of 13 (92%) Evaluable Patients, Including 4 of 4 (100%) α-Thalassemia Patients, During Weeks 4-12 –

– 7 of 8 (88%) Evaluable Patients Achieved Sustained Hb Response During Weeks 12-24 –

– Thalassemia Pivotal Development Plan Expected to be Finalized by Year-End 2020 and Initiated in 2021 –

– 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 reported interim data from its ongoing Phase 2 study evaluating single agent mitapivat in non-transfusion-dependent α- and β-thalassemia. Data from the study were featured in an oral presentation at the 25th European Hematology Association Annual Congress, which is being held virtually. 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.

“These data are exciting and further validate the potential of PKR activation as an entirely new mechanism for treating thalassemia, including α-thalassemia, for which there have been few medical advancements,” said Kevin Kuo, M.D., hematologist at University Health Network, University of Toronto, and an investigator in the study. “Findings from the study indicate that activation of wild-type PKR by mitapivat, an oral treatment option, improved hemoglobin and associated markers of hemolysis and erythropoiesis in patients with α- and β-thalassemia. In addition, the safety profile was consistent with previously published data for mitapivat.”

“We are pleased to share the impressive interim results from our clinical study of mitapivat in α-and β-thalassemia, as the data validate pre-clinical work conducted in our laboratories and with academic collaborators and demonstrate the potential for PKR activators in hemoglobinopathies such as thalassemia and sickle cell disease,” said Chris Bowden, chief medical officer at Agios. “Our focus now is to advance the development of mitapivat for these patients as quickly and efficiently as possible. By the end of the year, we expect to finalize a robust pivotal development plan that spans both α-and β-thalassemia, as well as transfusion dependent and non-transfusion dependent patients, with a goal of initiating a pivotal program in 2021.”

Mitapivat Phase 2 Proof-of-concept Study

The ongoing, open-label Phase 2 study is evaluating the efficacy, safety, pharmacokinetics and pharmacodynamics of mitapivat treatment in adults with non-transfusion-dependent α- and β-thalassemia who have a baseline hemoglobin (Hb) concentration of ≤10 g/dL. The trial is fully enrolled with 20 patients, and includes a 24-week core period followed by a 2-year extension period for eligible participants. 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 Hb concentrations.

As of the March 3, 2020 data cutoff, 18 patients were dosed and 13 were evaluable for the primary endpoint of a increase of ≥1.0 g/dL from baseline in at least one assessment during weeks 4-12.

- Of the 18 patients dosed, 5 patients have α-thalassemia, 4 of which were evaluable for efficacy at the 12 week timepoint, and 13 patients have β-thalassemia, 9 of which were efficacy evaluable.
- Median Hb at baseline was 8.43 (range 5.6-9.8) g/dL.
- Median treatment duration was 20.6 (range 1.1-50.0) weeks.
- Median age was 43.5 (range 29-67) years.

Efficacy Data

Efficacy data from the 13 efficacy evaluable patients as of the data cutoff demonstrated:

- The primary endpoint defined as a ≥1.0 g/dL increase in Hb concentration from baseline at 1 or more assessments between week 4 and week 12 was met by 12 of 13 (92.3%) patients who had completed 12 weeks of treatment, including all 4 (100%) α-thalassemia patients and 8 of 9 (88.9%) patients with β-thalassemia.
- For the 9 β-thalassemia patients who completed 24 weeks of treatment, 8 of 9 achieved a Hb response defined as ≥1.0 g/dL increase in Hb concentration from baseline at 1 or more assessments between week 12 and week 24. Seven of 8 patients met the criteria for sustained response defined as primary response and Hb response in ≥2 assessments during weeks 12-24.
- The mean Hb change from baseline for all 13 efficacy evaluable patients was 1.34 g/dL over weeks 4-12. The mean change for α-thalassemia patients was 1.17 g/dL over weeks 4-12, and 1.43 g/dL for β-thalassemia patients over weeks 4-24.
- Median (range) time to Hb increase of >1 g/dL among the Hb responders was 3.1 (1.4-7.1) weeks.
- Preliminary results for markers of hemolysis and erythropoiesis demonstrated improvements that were consistent with the

Hb increase. Indirect bilirubin and lactate dehydrogenase showed declines in α- and β-thalassemia patients, and erythropoietin achieved near normal levels in both groups by week 6.
- Preliminary analysis of adenosine triphosphate (ATP) levels showed mean increases of up to 92%, consistent with mitapivat's enhancement of glycolysis.

Safety Data

The safety analysis conducted on the 18 patients dosed as of the data cutoff demonstrated that the majority of adverse events (AEs) were consistent with previously published Phase 2 data for mitapivat in patients with pyruvate kinase (PK) deficiency.

- Grade 3 AEs were reported in two patients and neither was judged to be related to treatment.
- There were no serious adverse events (SAEs) and no AEs leading to treatment discontinuation. Post-data cutoff, one Grade 3 AE of renal dysfunction was reported, which was judged to be related to treatment by the investigator and resolved upon treatment discontinuation.
- Dose escalation to 100 mg twice daily was well tolerated and not associated with an increase in AEs.

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 also being studied in sickle cell disease under a Cooperative Research and Development Agreement with the U.S. National Institutes of Health. Preliminary data establishing proof-of-concept for mitapivat in sickle cell disease were also disclosed today.

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 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 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 is developing will successfully commence or complete necessary preclinical and clinical development phases; that positive safety and efficacy findings observed in early stage clinical trials will be replicated in later stage trials; 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 and 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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