Agios Announces Phase 3 ACTIVATE-T Trial of Mitapivat Achieved Primary Endpoint in Adults with Pyruvate Kinase Deficiency Who Are Regularly Transfused

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– 37 Percent of Patients Treated with Mitapivat Achieved ≥33% Reduction in Transfusion Burden Compared to Individual Historical Transfusion Burden Standardized to 24 Weeks (1-Sided p=0.0002) –

– 22 Percent of Patients Treated with Mitapivat Were Transfusion-Free During the 24-Week Fixed Dose Period –

– Safety Profile Consistent with Previously Reported Data –

– Company Expects to File for Regulatory Approval for Mitapivat for the Treatment of Adults with Pyruvate Kinase (PK) Deficiency in the U.S. in Q2 2021 and in the EU in Mid-2021 –

CAMBRIDGE, Mass., Jan. 26, 2021 (GLOBE NEWSWIRE) -- Agios Pharmaceuticals, Inc. (NASDAQ: AGIO), a leader in the field of cellular metabolism to treat cancer and genetically defined diseases, today announced that the global, open-label Phase 3 ACTIVATE-T trial of mitapivat in regularly transfused adults with PK deficiency demonstrated a statistically significant and clinically meaningful reduction in transfusion burden. All 27 patients enrolled in the study were treated with mitapivat. In the 24-week fixed dose period, 37 percent (n = 10) achieved a ≥33% reduction in transfusion burden compared to individual historical transfusion burden standardized to 24 weeks (1-sided p=0.0002). In addition, 22 percent (n = 6) were transfusion-free during the 24-week fixed dose period. Mitapivat is a first-in-class, investigational, oral, small molecule allosteric activator of wild-type and a variety of mutated PKR enzymes.

Agios recently reported that its global, randomized, double-blind, placebo-controlled Phase 3 ACTIVATE trial of mitapivat in adults with PK deficiency who do not receive regular transfusions met its primary endpoint, with 40 percent of patients randomized to mitapivat achieving a hemoglobin response, defined as a ≥1.5 g/dL sustained increase in hemoglobin concentration from baseline, compared to 0 patients randomized to placebo (2-sided p<0.0001). Agios anticipates filing for regulatory approval based on data from ACTIVATE and ACTIVATE-T in the U.S. in Q2 2021 and in the EU in mid-2021, with a potential 2022 commercial launch in both geographies.

“Based on results from both the ACTIVATE and ACTIVATE-T Phase 3 trials, we believe mitapivat has the potential to make a meaningful difference for people living with pyruvate kinase deficiency, a debilitating, lifelong hemolytic anemia characterized by serious complications regardless of patients’ transfusion status. The ACTIVATE-T study represents our first study of mitapivat in regularly transfused patients, and when taken together with the ACTIVATE results, demonstrates mitapivat’s potential clinical benefit for patients regardless of transfusion burden,” said Chris Bowden, M.D., chief medical officer at Agios. “We look forward to working with regulatory authorities in both the U.S. and EU to rapidly bring mitapivat to patients as the first potentially disease-modifying therapy for this community that currently has limited treatment options.”

Results from the ACTIVATE-T trial were as follows:

- 37 percent of patients dosed with mitapivat (n = 10 of 27) achieved a ≥33% reduction in transfusion burden in the 24-week fixed dose period compared with individual historical transfusion burden standardized to 24 weeks (1-sided p=0.0002).
- 22 percent of patients dosed with mitapivat (n = 6 of 27) were transfusion-free during the 24-week fixed dose period.
- Treatment with mitapivat showed a reduction in the annualized total number of red blood cell units transfused during the study compared with the historical transfusion burden.
- The safety profile observed in the study was consistent with previously reported data.

Agios is conducting a full analysis of the ACTIVATE-T results and expects to submit the complete results of the trial for presentation at the European Hematology Association (EHA) Virtual Congress, which is being held June 9-17, 2021.

ACTIVATE-T Trial Design
ACTIVATE-T is a global, multicenter, open-label study to evaluate the efficacy and safety of mitapivat in adult patients with PK deficiency who are regularly transfused, defined as receiving six or more transfusions in the past 52 weeks. The trial enrolled 27 patients across North America, Europe and Asia.

The study was designed with two parts. Part 1 was a dose escalation period in which patients started at 5 mg twice daily of mitapivat, with two potential dose increases to 20 mg twice daily and 50 mg twice daily for up to 16 weeks. After the dose escalation period, patients received a fixed dose for an additional 24 weeks in Part 2.

The primary endpoint of the study was reduction in transfusion burden, defined as 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. Participants who discontinued the study before completing at least 12 weeks of treatment in the fixed dose period were considered non-responders. The p-value is based on the binomial exact test of H_0: transfusion reduction response rate≤10% vs. H_1: transfusion reduction response rate>10% at a 1-sided α=0.025.

Mitapivat Clinical Development
ACTIVATE-T is one of two studies intended to support a marketing application for mitapivat in patients with PK deficiency. In addition to the ACTIVATE-T trial, Agios recently reported topline results from the global Phase 3 ACTIVATE trial of mitapivat in adults with PK deficiency who do not receive regular transfusions. A full analysis of the data – including patient-reported outcomes (PRO) – is expected to be submitted for presentation at the EHA Virtual Congress. Agios is also 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.

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, and the primary endpoint is hemoglobin response, defined as a ≥1.0 g/dL increase in Hb concentration from baseline at one or more assessments between Week 4 and Week 12. Results from the study are expected to be submitted for presentation at the EHA Virtual Congress. Agios expects to initiate two Phase 3 studies of mitapivat, ENERGIZE and ENERGIZE-T, in not regularly transfused and regularly transfused adults with thalassemia in the second half of 2021.

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 expects to disclose its pivotal program in sickle cell disease in the first half of 2021 and initiate the study 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.

About PK Deficiency
Pyruvate kinase (PK) deficiency is a rare, inherited disease that presents as chronic hemolytic anemia, which is the accelerated destruction of red blood cells. The inherited mutations in PKR genes cause a deficit in cellular energy within the red blood cell, as evidenced by lower PK enzyme activity, a decline in adenosine triphosphate (ATP) levels and a build-up of upstream metabolites, including 2,3-DPG (2,3-diphosphoglycerate).

PK deficiency is associated with serious complications, including gallstones, pulmonary hypertension, extramedullary hematopoiesis, osteoporosis and iron overload and its sequelae, which can occur regardless of the degree of anemia or transfusion burden. PK deficiency can also cause quality of life problems, including challenges with work and school activities, social life and emotional health. Current management strategies for PK deficiency, including red blood cell transfusions and splenectomy, are associated with both short- and long-term risks. There are no currently approved therapies for PK deficiency. For more information, please visit www.knowpkdeficiency.com.

Agios, in partnership with PerkinElmer Genomics, launched the Anemia ID program to offer no-cost genetic testing to eligible patients in the U.S with suspected hereditary anemias, including PK deficiency. The program was created in response to feedback from patients, advocates and physicians about the need for improved diagnosis to inform disease management decisions. To learn more, please visit www.AnemiaID.com.

About Agios
Agios is focused on discovering and developing novel investigational medicines to treat malignant hematology, solid tumors and genetically defined 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 to file for regulatory approval based on data from ACTIVATE and ACTIVATE-T in the U.S. in Q2 2021 and in the EU in mid-2021; Agios' plans for the future clinical development of mitapivat in thalassemia and sickle cell disease; 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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