



AgiOS Announces the Phase 3 ACTIVATE Trial of Mitapivat Achieved Its Primary Endpoint in Adults with Pyruvate Kinase Deficiency Who Are Not Regularly Transfused

December 1, 2020

– 40 Percent of Patients Treated with Mitapivat Achieved a Sustained Hemoglobin Increase of ≥ 1.5 g/dL Compared to 0 Placebo Patients ($p < 0.0001$) –

– Safety Profile Consistent with Previously Reported Data –

– Topline Data from the Mitapivat Phase 3 ACTIVATE-T Trial in Regularly Transfused PK Deficiency Expected in Q1 2021 –

CAMBRIDGE, Mass., Dec. 01, 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 the global Phase 3 ACTIVATE trial of mitapivat in adults with pyruvate kinase (PK) deficiency who do not receive regular transfusions met its primary endpoint. Treatment with mitapivat demonstrated a statistically significant, sustained increase in hemoglobin compared to placebo. The safety profile observed in the study was generally consistent with previously published data. Mitapivat is a first-in-class, investigational, oral, small molecule allosteric activator of wild-type and a variety of mutated PKR enzymes.

"The robust, clinically meaningful efficacy and safety results from the ACTIVATE study underscore mitapivat's potential to be the first disease-modifying therapy for people with pyruvate kinase deficiency, a chronic, lifelong hemolytic anemia that often leads to serious physical and quality of life complications. With only supportive therapy currently available, there is tremendous unmet need in this community, and we are proud to advance a promising therapeutic candidate for these patients," said Chris Bowden, M.D., chief medical officer at Agios. "The results of this trial, which represent the first pivotal Phase 3 clinical data for mitapivat, support our hypothesis that mitapivat can improve the health, energy and longevity of red blood cells in patients with hemolytic anemias. We look forward to announcing ACTIVATE-T data in the first quarter of next year, and expect to file for regulatory approval in PK deficiency in both the U.S. and EU in 2021."

Results from the ACTIVATE trial were as follows:

- 40 percent of patients randomized to mitapivat achieved a 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, compared to 0 patients randomized to placebo (2-sided $p < 0.0001$)
- Treatment with mitapivat demonstrated statistically significant improvements over placebo across pre-specified key secondary endpoints, including average change from baseline in hemoglobin concentration at Weeks 16, 20, and 24 during the fixed-dose period; markers of hemolysis (indirect bilirubin, haptoglobin, serum lactate dehydrogenase [LDH] activity); and markers of hematopoietic activity (reticulocyte percentages).
- The safety profile observed in the study was generally consistent with previously reported data.
- There were no AEs leading to discontinuation in either the mitapivat or the placebo arm.

AgiOS is conducting a full analysis of the ACTIVATE data, including patient-reported outcomes (PRO) which are not yet available. The company 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.

AgiOS anticipates filing for U.S. and EU regulatory approval in adults with PK deficiency in 2021, with a potential 2022 commercial launch in both geographies.

ACTIVATE Trial Design

ACTIVATE is a Phase 3, global, double-blind, placebo-controlled trial with a 1:1 randomization evaluating the efficacy and safety of mitapivat as a potential treatment for adults with PK deficiency who do not receive regular transfusions. Patients were required to have a hemoglobin concentration less than or equal to 10.0g/dL. The trial randomized 80 patients.

The study was designed with two parts. Part 1 was a dose escalation period in which patients started at 5 mg of mitapivat or placebo twice daily, with two potential dose escalations to 20 mg twice daily and 50 mg twice daily over a 12-week period. After the dose escalation period, patients received a fixed dose for an additional 12 weeks in Part 2. 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 Part 2 of the trial.

[Multimedia Assets: Rare Diseases at Agios, Mitapivat Development, PK Deficiency Patient Testimonials](#)

Mitapivat Clinical Development

ACTIVATE is one of two studies intended to support a marketing application for mitapivat in patients with PK deficiency. In addition to the ACTIVATE trial, Agios has fully enrolled the global, pivotal Phase 3 ACTIVATE-T trial in adults with PK deficiency who receive regular transfusions. The primary endpoint of this single-arm 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 enrolling 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. Agios 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.

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](#) from this trial will be presented at the American Society of Hematology (ASH) Annual Meeting, which is being held virtually December 5-8. Agios expects to initiate a Phase 3, global, pivotal study of mitapivat in sickle cell disease in 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.

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 to file for regulatory approval in PK deficiency in both the U.S. and EU in 2021; 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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Source: Agios Pharmaceuticals, Inc.