Agios Announces Updated Data from ACTIVATE and ACTIVATE-T Phase 3 Studies of Mitapivat in Pyruvate Kinase (PK) Deficiency at the European Hematology Association Virtual Congress

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– Company Expects to File for Regulatory Approval for Mitapivat for the Treatment of Adults with PK Deficiency in the U.S. This Quarter and in the EU in Mid-2021 –

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

CAMBRIDGE, Mass., June 11, 2021 (GLOBE NEWSWIRE) -- Agios Pharmaceuticals, Inc. (NASDAQ: AGIO), a leader in the field of cellular metabolism to treat genetically defined diseases, today reported a full analysis of updated data, including patient-reported outcome (PRO) measures, from its global Phase 3 ACTIVATE and ACTIVATE-T studies of mitapivat in adults with pyruvate kinase (PK) deficiency. Data from the studies will be featured in oral presentations on Tuesday, June 15, at the European Hematology Association (EHA) Virtual Congress.

Consistent with previously announced topline data, the ACTIVATE and ACTIVATE-T studies met primary and secondary endpoints, including PRO outcomes that address symptom burden and quality-of-life impact of PK deficiency in adults. The safety profile observed in both studies 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 pyruvate kinase R (PKR) enzymes.

“Results from the ACTIVATE and ACTIVATE-T Phase 3 studies underscore the potential of mitapivat to be the first disease-modifying therapy for individuals with pyruvate kinase deficiency, a disease characterized by chronic hemolysis and associated long-term complications affecting multiple organ systems, regardless of the degree of anemia or transfusion status. New disease-modifying treatment approaches are needed, as current management strategies are supportive and include regular blood transfusions, which can lead to iron overload and splenectomy, which is also associated with short- and long-term risks,” said Andreas Glenthøj, M.D., Ph.D., associate professor, Department of Hematology, Rigshospitalet; Copenhagen, Denmark.

ACTIVATE Results Summary

- The Phase 3 ACTIVATE trial of mitapivat achieved its primary endpoint. Mitapivat demonstrated a sustained, statistically significant increase in hemoglobin in patients with PK deficiency who are not regularly transfused.
  - 40 percent (n=16) of patients randomized to mitapivat achieved a hemoglobin response, compared to 0 patients randomized to placebo (2-sided p<0.0001).
  - The effect of mitapivat on hemoglobin response compared to placebo was observed consistently across all predefined subgroups.
- Statistically significant improvements compared to placebo were also demonstrated for all pre-specified key secondary endpoints, including markers of hemolysis and ineffective erythropoiesis, as well as PRO measures.
  - The increase in hemoglobin occurred early and was sustained, with an average change from baseline of 1.67 g/dL for mitapivat compared with -0.15 g/dL for placebo (2-sided p<0.0001) at Weeks 16, 20 and 24.
  - Pyruvate Kinase Deficiency Daily Diary (PKDD), a daily diary of signs and symptoms, captures changes in symptom burden (e.g., tiredness, energy levels, jaundice, bone pain and shortness of breath).
  - Pyruvate Kinase Deficiency Impact Assessment (PKDIA), a weekly measure of disease impacts, measures health-related quality of life, (e.g., daily activities, concentration, physical activity and the need for additional rest or sleep).
- The safety profile of mitapivat was consistent with previously reported data.
  - The most common treatment-emergent adverse events (TEAEs) with mitapivat were nausea and headache, which were less frequent for mitapivat compared to placebo (n=7; 17.5% vs. n=9; 23.1% and n=6; 15.0% vs n=13; 33.3%, respectively).
  - There were no TEAEs leading to dose reduction, interruption, discontinuation or death in the mitapivat arm.

ACTIVATE-T Results Summary

- The Phase 3 ACTIVATE-T trial of mitapivat achieved its primary endpoint. Mitapivat demonstrated a statistically significant and clinically meaningful reduction in transfusion burden for patients who are regularly transfused.
  - 37 percent (n=10) of patients achieved a transfusion reduction response, defined as 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); 9 responders achieved a ≥50% reduction.
  - 22 percent (n=6) of patients were transfusion-free during the fixed-dose period.
  - 11 percent (n=3) of patients achieved hemoglobin concentrations in the normal range at least once, eight weeks or more after a transfusion, during the fixed dose period.
- Improvements were also observed for the PK deficiency-specific PRO measures, PKDD and PKDIA scores.
- The safety profile of mitapivat was consistent with previously reported data.
  - The most frequently reported adverse events in patients receiving mitapivat included alanine aminotransferase

increase (n=10; 37%), headache (n=10; 37%), aspartate aminotransferase increase (n=5; 18.5%), fatigue (n=5; 18.5%) and nausea (n=5; 18.5%).
- No serious TEAE was considered by the investigator to be related to study treatment.
- There were no TEAEs leading to interruption, discontinuation or death, and only one patient experienced a TEAE leading to dose reduction.

“For nearly a decade, Agios has been pioneering the science of PK activation. Results reported today from ACTIVATE and ACTIVATE-T continue to demonstrate the therapeutic impact of activating this pathway and provide the foundation for the first potential approval of a PK activator,” said Chris Bowden, M.D., chief medical officer at Agios. “In the weeks ahead, we look forward to working with regulatory authorities in both the U.S. and EU to rapidly bring mitapivat to pyruvate kinase deficiency patients as the first potentially disease-modifying therapy.”

Agios remains on track to submit a new drug application (NDA) in the U.S. in the second quarter of 2021 and a marketing authorization application (MAA) in the EU in mid-2021 for mitapivat in adults with PK deficiency.

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.

ACTIVATE-T Trial Design
ACTIVATE-T is a Phase 3 global, open-label study to evaluate the efficacy and safety of mitapivat as a potential treatment for adults with PK deficiency who are regularly transfused, defined as receiving six or more transfusions in the past 52 weeks. The trial enrolled 27 patients.

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.

Oral Presentation Information

Title: ACTIVATE: A Phase 3, randomized, multicenter, double-blind, placebo-controlled study of mitapivat in adults with pyruvate kinase deficiency who are not regularly transfused
Live Q&A Session Date and Time: Tuesday, June 15, 2021, at 7:45 p.m. CEST / 1:45 p.m. ET
Oral Abstract Session: Changing the scene in congenital anemias
Abstract: S270
Presenter: Hanny Al-Samkari, M.D., Division of Hematology, Massachusetts General Hospital, Harvard Medical School, Boston, MA, United States

Title: ACTIVATE-T: A Phase 3, open-label, multicenter study of mitapivat in adults with pyruvate kinase deficiency who are regularly transfused
Live Q&A Session Date and Time: Tuesday, June 15, 2021, at 7:45 p.m. CEST / 1:45 p.m. ET
Oral Abstract Session: Changing the scene on congenital anemias
Abstract: S271
Presenter: Andreas Glenthøj, M.D., Department of Hematology, Rigshospitalet Copenhagen, Denmark

Mitapivat Clinical Development
ACTIVATE and ACTIVATE-T are intended to support global regulatory filings for mitapivat in adults with PK deficiency in the U.S. in the second quarter of 2021 and the EU in mid-2021. Agios also is 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.

In addition, Agios completed 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 primary endpoint for the Phase 2 study was hemoglobin response, defined as a ≥1.0 g/dL increase in hemoglobin concentration from baseline at one or more assessments between Week 4 and Week 12. These results are also being reported as part of an oral presentation at the EHA Virtual Congress. Agios is conducting an extension study of mitapivat for adults previously enrolled in the Phase 2 study and is initiating two Phase 3 studies, ENERGIZE and ENERGIZE-T, in not regularly transfused and regularly transfused adults with thalassemia in the second half of 2021.

Mitapivat is also 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 is initiating its pivotal Phase 2/3 study in sickle cell disease 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.

CONFERENCE CALL INFORMATION

Agios will host a virtual investor event today at 7:30 a.m. ET to review the mitapivat clinical data. The event will be webcast live and can be accessed under "Events & Presentations" in the Investors and Media section of the company's website at www.agios.com. The archived webcast will be available on the company's website beginning approximately two hours after the event.

About Agios
Agios is focused on discovering and developing novel investigational medicines to treat genetically defined diseases through scientific leadership in the field of cellular metabolism. The company's most advanced drug candidate is a first-in-class pyruvate kinase R (PKR) activator, mitapivat, that is currently being evaluated for the treatment of three distinct hemolytic anemias. In addition to its active late-stage clinical pipeline, Agios has multiple novel, investigational therapies in clinical and 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 Agios' plans, strategies and expectations for the preclinical, clinical and commercial advancement of its drug development programs, including mitapivat; the potential benefits of Agios' products and product candidates, including mitapivat; Agios' key milestones and guidance for 2021; and the potential benefits of Agios' strategic plans and focus. The words "anticipate," "expect," "goal," "hope," "milestone," "plan," "potential," "possible," "strategy," "will," "vision," 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. 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 failure of Agios to receive milestone or royalty payments related to the sale of its oncology business, the uncertainty of the timing of any receipt of any such payments, and the uncertainty of the results and effectiveness of the use of proceeds from the transaction; 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 future approved products, and launching, marketing and selling 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 and 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 establish and maintain 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, or SEC, including the risks and uncertainties set forth under the heading Risk Factors in our filings with the SEC. While the list of factors presented here is considered representative, this list should not be considered to be a complete statement of all potential risks and uncertainties. Any forward-looking statements contained in this communication are made only as of the date hereof, and we undertake no obligation to update forward-looking statements to reflect developments or information obtained after the date hereof and disclaim any obligation to do so other than as may be required by law.

Contacts

Investors:
1AB
Steve Klass
steve@1abmedia.com

Media:
1AB
Josie Butler
josie@1abmedia.com

Source: Agios Pharmaceuticals, Inc.