Agios Announces Publication of Data for Mitapivat from Core and Extension Phases of the DRIVE PK Study in Patients with Pyruvate Kinase Deficiency in the New England Journal of Medicine

September 4, 2019

– Maximum Hemoglobin Increases >1.0 g/dL Observed in 50% of Patients in Core Period, Among Whom the Mean Maximum Hemoglobin Increase was 3.4 g/dL –

– Hemoglobin Responses Maintained in 19 Patients in the Extension Phase of the Study with Median Treatment Duration of 28.9 Months –

– Cumulative Safety Profile (Core Period plus Extension Phase) Continues to Support Long-term Twice Daily Dosing of Mitapivat –

CAMBRIDGE, Mass., Sept. 04, 2019 (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 new data from the core and extension phases of the DRIVE PK Phase 2 study of mitapivat (AG-348) in adults with pyruvate kinase (PK) deficiency were published in the September 5, 2019 issue of the*New England Journal of Medicine*. 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 that directly targets the underlying metabolic defect in PK deficiency, a rare, potentially debilitating, hemolytic anemia.

“The DRIVE PK study is the first clinical trial in adults with PK deficiency, which is a rare disease characterized by chronic hemolysis and long-term serious complications. Data from the study demonstrated rapid, clinically significant increases in hemoglobin in 50 percent of patients, and for patients in the extension phase, the response was sustained for up to 35 months,” said Rachael Grace, M.D., of the Dana-Farber/Boston Children's Cancer and Blood Disorder Center and a principal investigator for the study. “There are no approved therapies for PK deficiency, and there are significant risks associated with current disease management strategies. By directly targeting the underlying metabolic defect in PK deficiency, mitapivat has the potential to be the first disease-altering therapy for these patients.”

“Data from the extension phase of the DRIVE PK study showed that patients who respond to long-term treatment with mitapivat had continued evidence of decreased hemolysis as demonstrated by directionally appropriate changes over time in hemoglobin, absolute reticulocyte counts, indirect bilirubin, haptoglobin and lactate dehydrogenase,” said Chris Bowden, M.D., chief medical officer at Agios. “We are currently evaluating the safety and efficacy of mitapivat in adults with PK deficiency in our ongoing Phase 3 ACTIVATE and ACTIVATE-T studies, and we look forward to exploring mitapivat in the pediatric population.”

DRIVE PK is an ongoing global, open-label, Phase 2, safety and efficacy study evaluating mitapivat in adults with PK deficiency who do not receive regular transfusions. Patients were randomly assigned to receive either 50 mg or 300 mg of mitapivat twice daily for a 24-week core period and eligible patients could continue treatment in an ongoing extension phase. As of the August 31, 2018 data cutoff, 52 patients were randomized and 43 (83%) completed the core period. Thirty-six (69%) patients entered and 19 (37%) remain in the extension phase with a median treatment duration of 28.9 months [range 21.6-34.8]. The median baseline hemoglobin was 8.9 g/dL (range, 6.5–12.3 g/dL). Nearly half (48%) of the patients reported a history of treatment with iron chelation despite the absence of regular transfusions, while the majority of patients had a prior splenectomy (83%) and cholecystectomy (73%).

Safety Data
A safety analysis conducted for all 52 treated patients as of the data cut-off shows that adverse events associated with mitapivat were mainly low-grade and transient. The cumulative safety profile (core plus extension phase) remained similar to that observed in the core period and continues to support long-term twice daily dosing.

- The majority of adverse events (AEs) were Grade 1-2; the most frequent were headache (46%), insomnia (42%) and nausea (40%). These events resolved within seven days after the initiation of treatment in 92% of episodes of headache, 47% of episodes of insomnia, and 78% of episodes of nausea.
- Nine patients experienced Grade ≥3 treatment-related adverse events: hypertriglyceridemia (n=4), hemolytic anemia (n=2) and hemolysis, dizziness, headache, left renal cell carcinoma and insomnia (n=1 each).
- Changes from baseline in sex hormone levels were observed in men, the result of mild off-target aromatase inhibition, with most values of testosterone and estradiol remaining within the normal range. Interpretation of sex hormone data in females was confounded by variability in menopausal status and hormonal contraception use and will be assessed further in the Phase 3 studies.

Efficacy Data
In the efficacy analysis, 26 of 52 patients (50%) achieved a clinically significant maximum hemoglobin increase of >1.0 g/dL in the Core Period with improvement in other markers of hemolysis as of the data cutoff.

- In patients who had hemoglobin increases of >1.0 g/dL in the Core Period, the mean maximum hemoglobin increase was 3.4 g/dL (range, 1.1–5.8 g/dL).
- The median time to first hemoglobin increase of >1.0 g/dL was 10 days (range 7–187 days).
- Twenty patients maintained a hemoglobin response >1.0 g/dL for >50% of assessments in the Core Period.
- The hemoglobin response was maintained in 19 patients who continued to be treated in the extension phase, all of whom

had at least 21.6 months of treatment.
- In the patients with a hemoglobin response, directionally appropriate changes over time in absolute reticulocytes counts, indirect bilirubin, haptoglobin and lactate dehydrogenase provide additional evidence of decreased hemolysis with mitapivat treatment.

Mitapivat Pivotal Development Plan
Agios has two ongoing global, pivotal trials in adults with PK deficiency that are on track to complete enrollment by year-end 2019.

- ACTIVATE: A placebo-controlled trial with a 1:1 randomization, expected to enroll approximately 80 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 up to 40 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.

Learn more at activatetrials.com.

Mitapivat is not approved for use by any regulatory authority.

About Pyruvate Kinase Deficiency and Genetic Background
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 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, cirrhosis, osteoporosis, and iron overload and its sequelae, which occur regardless of the degree of anemia or transfusion burden. Current management strategies for PK deficiency, including blood transfusion and splenectomy, are associated with both short- and long-term risks.

More than 300 different mutations have been identified to date. The mutations observed in PK deficiency patients are classified in two main categories. A missense mutation causes a single amino acid change in the protein, generally resulting in some functional protein. A non-missense mutation is any mutation other than a missense mutation, generally resulting in little functional protein. It is estimated that 58 percent of patients with PK deficiency have two missense mutations, 27 percent have one missense and one non-missense mutation, and 15 percent have two non-missense mutations[1]. For more information about PK deficiency, including the signs and symptoms, how to test for it, and how it is currently managed, visit knowpkdeficiency.com.

The Peak Registry, a global, longitudinal study of children and adults with PK deficiency, has been established to better understand the full spectrum of disease variability, including impact on quality of life. The Registry is open and recruiting patients. Learn more at www.peakregistry.com.

About Agios
Agios is focused on discovering and developing novel investigational medicines to treat cancer and rare genetic diseases through scientific leadership in the field of cellular metabolism and adjacent areas of biology. In addition to an active research and discovery pipeline across both therapeutic areas, Agios has two approved oncology precision medicines and multiple first-in-class investigational therapies in clinical and/or preclinical development. All Agios programs focus on genetically identified patient populations, leveraging our knowledge of metabolism, biology and genomics. 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: 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.

---

[1] Bianchi P et al. poster, 2017 ASH Annual Meeting

Investor & Media Contact:
Holly Manning, 617-844-6630
Associate Director, Investor Relations

Holly.Manning@agios.com

A PDF accompanying this announcement is available at http://ml.globenewswire.com/Resource/Download/0fbe26a2-08f9-48c0-86f5-0b1640cdc726

Source: Agios Pharmaceuticals, Inc.