Agios Announces New Data from AG-348 and AG-519 Demonstrating Potential for First Disease-modifying Treatment for Patients with PK Deficiency

December 5, 2016

- AG-348 Is Well-Tolerated and Demonstrates Clinically Relevant, Rapid and Sustained Hemoglobin Increases in 15 of 26 Patients with at Least One Missense Mutation and 15 out of 32 Patients Overall -

- AG-519 Is Well-Tolerated and Demonstrates Robust Dose-Dependent Changes in ATP and 2,3-DPG Blood Levels in Normal Healthy Volunteers Consistent with PKR Enzyme Activation -

- Company to Host Investor Event and Webcast Today at 8:00 p.m. PT -

SAN DIEGO, Dec. 04, 2016 (GLOBE NEWSWIRE) -- Agios Pharmaceuticals, Inc. (Nasdaq:AGIO) presented new data on two molecules from its wholly owned PKR activator program demonstrating the potential for the first disease-modifying treatment for patients with PK Deficiency at the 2016 American Society of Hematology Annual Meeting and Exposition (ASH). Agios' PKR program consists of AG-348, which is being evaluated in the Phase 2 DRIVE PK study in patients with pyruvate kinase (PK) deficiency, and AG-519, a second PKR activator being evaluated in an ongoing Phase 1 trial in healthy volunteers. PK deficiency is a rare, potentially debilitating, congenital anemia. Data from these studies were last reported at the Congress of the European Hematology Association (EHA) in June 2016.

Updated data from DRIVE PK with additional patients and longer follow-up demonstrate that 47% of all efficacy evaluable patients (n=15/32) and 58% of evaluable patients with at least 1 missense mutation (n=15/26) treated with AG-348 experienced a maximum hemoglobin (Hb) increase from baseline of >1.0 gram per deciliter (g/dL). Efficacy evaluable patients were required to have received AG-348 for at least three weeks. Hb increases >1.0 g/dL were observed in patients randomized to two doses and the maximum increase ranged from 1.2–5.2 g/dL with a mean maximum increase of 3.6 g/dL. Hb increases were also rapid and sustained, with a median time to a hemoglobin increase of >1.0 g/dL of 1.4 weeks. Agios also presented the first data demonstrating a direct link between increases in hemoglobin levels and activation of the PKR pathway (rate of metabolism) in patients treated with AG-348.

In addition, data from the ongoing Phase 1 trial in healthy volunteers establish that AG-519 is well-tolerated and demonstrates clear proof-of-mechanism as a potent, oral, selective PKR activator. The robust dose-dependent changes in ATP (adenosine triphosphate) and 2,3-DPG (2,3-diphosphoglycerate) blood levels reported with AG-519 are consistent with PKR enzyme activation. The activity of AG-519 as an activator of both wild-type and mutant forms of PKR is similar to that of AG-348.

"With data from additional patients and longer follow-up, it is highly encouraging that AG-348 continues to demonstrate robust, rapid and sustained increases in hemoglobin in patients with PK deficiency," said Rachael Grace, M.D., of the Dana-Farber Boston Children's Cancer and Blood Disorder Center and a principal investigator for the study. "These findings are important for physicians and patients as they offer the potential for the first disease-modifying treatment for patients suffering from this chronic anemia and its associated complications."

"The rapid and sustained hemoglobin increases shown in DRIVE PK and AG-519's robust PK/PD profile continue to support moving a PKR activator into pivotal development next year," said Chris Bowden, M.D., chief medical officer at Agios. "In addition, our scientists continue to lead advances in the understanding of the biology of PK deficiency and have demonstrated the first data linking an increase in hemoglobin to direct activation of the PKR pathway."

Updated Phase 2 DRIVE-PK Data for AG-348

DRIVE PK is a global Phase 2, open-label safety and efficacy trial and the first study evaluating AG-348 in adult, transfusion-independent patients with PK deficiency. The study includes two arms of approximately 25 patients each, receiving a dose of 50 milligrams (mg) or 300 mg twice daily for at least six months (24 weeks). The target enrollment has been reached with a total of 52 patients enrolled. As of the September 23, 2016 data cut-off:

- Thirty-four patients had been treated in the study and are included in the safety analysis and 32 patients with at least 3 weeks of data are included in the efficacy analysis.
- Seventeen patients completed the initial 24 week treatment period.
- In the 32 patients for whom efficacy could be evaluated, the mean baseline Hb was 9.2 g/dL.
- Twenty-eight of the 34 patients (82%) had been splenectomized prior to study entry.

A safety analysis was conducted based on all 34 treated patients as of the data cut-off.

- AG-348 was well-tolerated, and the majority of treatment-related adverse events (AEs) were Grade 1-2; the most frequent being headache, nausea and insomnia.
- Two patients experienced serious adverse events (SAEs).
    - One Grade 2 AE of osteoporosis was previously reported in a patient with osteopenia at baseline assessment.
    - One patient experienced withdrawal hemolysis and anemia after AG-348 was temporarily discontinued due to a rapid treatment-related Hb increase, but stayed in the study and is continuing to receive treatment with AG-348 at a lower dose.
- Sex steroids were assessed at baseline, week 12 and week 24 for male and female patients. Increases in free

testosterone and decreases in estradiol indicate aromatase inhibition by AG-348. Bone density scan data (n = 17) show high variability and are inconclusive. Clinical significance of the aromatase inhibition remains unclear.

In the efficacy analysis (n=32), 15 of 32 total evaluable patients and 15 of 26 evaluable patients with at least one missense mutation achieved rapid, robust and sustained hemoglobin increases from baseline of >1.0 g/dL as of the data cut-off.

- In patients who had hemoglobin increases of >1.0 g/dL, the mean maximum hemoglobin increase was 3.6 g/dL (range 1.2–5.2 g/dL).
- The median time to a hemoglobin increase of >1.0 g/dL was 1.4 weeks (range 1.1–21.0 weeks).
- Further data are needed to obtain a greater understanding of the relationship between genotype and response. Preliminary observations show:
    - Of the 26 evaluable patients with at least one missense mutation, 15 have shown an increase in hemoglobin of >1.0 g/dL.
    - None of the six patients with two non-missense mutations showed increases in hemoglobin of >1.0 g/dL.
    - Five patients homozygous for R479H (missense-missense) were also non-responders.
- Additional studies were conducted on the red blood cells of eight DRIVE PK patients.
    - In this subset, four patients who had hemoglobin level increases >1.0 g/dL on AG-348 experienced a greater than 50% average increase in the rate of metabolism of the PKR pathway.
    - None of the four patients with <1.0 g/dL increase experienced significant metabolic changes.

Phase 1 Healthy Volunteer Study Results for AG-519

Data were reported from four single ascending dose (SAD) cohorts of healthy volunteers (eight per group, 32 volunteers total) receiving daily doses of 50 mg, 250 mg, 750 mg or 1250 mg of AG-519 or placebo. Data were also reported from five multiple ascending dose (MAD) cohorts of healthy volunteers (eight per group, 40 volunteers total) dosed twice daily with 10 mg, 25 mg, 125 mg, 300 mg or 375 mg of AG-519 or placebo for 14 days.

- AEs from the SAD and MAD cohorts were mild or moderate (Grade 1 or 2) in severity, the most common being headache.
    - A single case of Grade 2 thrombocytopenia was previously reported in a subject receiving 375 mg of AG-519 q12hr, which resolved spontaneously within seven days after the last dose.
    - After the data cut-off, one ongoing SAE of drug-related cholestatic hepatitis was reported in the bioavailability and food effect study after a dose of 300 mg. This event is being further evaluated.
- Pharmacodynamic data from the MAD cohorts showed a mean decrease of up to 61% in blood 2,3-DPG levels and a mean increase of up to 63% in blood ATP levels from baseline. In contrast, healthy volunteers receiving placebo showed minimal changes in 2,3-DPG or ATP levels.
- Volunteers treated with AG-519 exhibited no changes in sex steroids levels, consistent with a lack of aromatase enzyme inhibition.
- The study is ongoing with final data not yet available for the bioavailability and food effect study and a Japanese volunteer cohort. The study allows for an optional additional open-label, multiple-dose cohort, which has not yet been initiated.

About Pyruvate Kinase Deficiency and Genetic Background

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

The current standard of care for PK deficiency is supportive, including blood transfusions, splenectomy, chelation therapy to address iron overload and/or interventions for other treatment- and disease-related morbidities. There is no approved therapy to treat the underlying cause of PK deficiency.

PK deficiency is an autosomal recessive disease whereby all patients inherit two mutations, one from each parent. More than 250 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 53 percent of patients with PK deficiency have two missense mutations, 25 percent have one missense and one non-missense mutation, and 22 percent have two non-missense mutations[1].

Boston Children’s Hospital, in collaboration with Agios, is conducting a Natural History Study to better understand the symptoms and complications of PK deficiency, identify patients and treatment centers, and capture other clinical data, including quality of life measures and genetic information.

About Agios' PKR Activators

Agios has discovered and is currently evaluating two orally available, potent, selective small molecule activators of PKR in clinical trials, AG-348 and AG-519. Agios scientists previously reported that AG-348 is a potent activator of the wild-type and mutated PKR enzymes in humans. Agios retains worldwide development and commercialization rights to AG-348 and AG-519.

Investor Event and Webcast Information

Agios will host an investor event on Sunday, December 4, 2016 beginning at 8:00 p.m. PT (11:00 p.m. ET) in San Diego to review data presented at ASH, including new data from the ongoing studies of AG-348 and AG-519. 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.

About Agios

Agios is focused on discovering and developing novel investigational medicines to treat cancer and rare genetic metabolic disorders through scientific leadership in the field of cellular metabolism. In addition to an active research and discovery pipeline across both therapeutic areas, Agios has multiple first-in-class investigational medicines 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 Agios' product candidates targeting pyruvate kinase-R mutations, including AG-348 and AG-519; Agios' plans for the further clinical development of AG-348 and AG-519; 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, such as its agreements with Celgene; and general economic and market conditions. These and other risks are described in greater detail under the caption "Risk Factors" included in Agios' Quarterly Report on Form 10-Q for the quarter ended September 30, 2016, and other filings that Agios may make with the Securities and Exchange Commission in the future. 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.

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[1] Bianchi P et al. poster, 2015 ASH Annual Meeting

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