Agios Reports Positive Phase 1 Data in Healthy Volunteers for AG-348, a First-in-Class Investigational Medicine That Targets the Underlying Cause of Pyruvate Kinase (PK) Deficiency

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AG-348 Achieved Proof-of-Mechanism Through Substantial Effects on Two Key Biomarkers of Pyruvate Kinase Activity and Pathway Activation

Data Presented at ASH Support Initiation of a Phase 2 Trial in Patients with PK Deficiency in First Half 2015

Company to Host Investor Lunch and Webcast Today

SAN FRANCISCO, Dec. 8, 2014 (GLOBE NEWSWIRE) -- Agios Pharmaceuticals, Inc. (Nasdaq:AGIO), a leader in the fields of cancer metabolism and rare genetic disorders of metabolism, today presented the first clinical data from its Phase 1 single (SAD) and multiple ascending dose (MAD) clinical trials of AG-348 in healthy volunteers. These results provide early proof-of-mechanism for AG-348, a novel, first-in-class, oral activator of both wild type (normal) and mutated pyruvate kinase-R (PKR) enzymes. In these Phase 1 studies, dosing of AG-348 over 14-days in healthy volunteers resulted in a dose-dependent increase in the pyruvate kinase-R pathway as evidenced by a substantial increase in ATP and decrease in 2,3-DPG levels, which are key biomarkers of PKR activity and primary indicators of PK deficiency. These data support the hypothesis that AG-348 treatment may similarly enhance PKR activity in patients with PK deficiency and thus correct the underlying defect of the disease. Today's results will be presented during a poster session at the 56th Annual Meeting of the American Society of Hematology (ASH) Annual Meeting and Exposition in San Francisco, CA.

"PK deficiency is a serious form of inherited hemolytic anemia for which there are currently no approved or disease modifying treatments," said David Schenkein, M.D., chief executive officer of Agios. "We are pleased with the results we observed in healthy volunteers which showed that AG-348 was well tolerated. Since AG-348 targets both the mutant and wild-type PKR enzyme, the pharmacodynamic effect we observed provides evidence to support the mechanism of action of AG-348. In addition, these results inform dose selection in the planned Phase 2 study of AG-348 in PK deficiency patients, which we anticipate to begin in the first half of 2015. We look forward to advancing AG-348 into clinical trials in patients with PK deficiency with the hope of having a major beneficial effect in patients with this severe genetic disorder."

Pyruvate kinase deficiency is characterized by anemia from birth due to rapid red blood cell destruction. The inherited mutations in PKR enzymes cause a deficit in cellular energy within the red blood cell, as evidenced by a build-up of the metabolite 2,3-DPG (2,3-diphosphoglycerate) and a decline in the energy metabolite ATP (adenosine triphosphate). Agios scientists have previously reported that AG-348 is a potent activator of the wild-type and mutated PKR enzymes, resulting in restoration of ATP levels and a decrease in 2,3-DPG levels in blood sampled from patients with PK deficiency. The wild-type PKR activity of AG-348 allows the study of enzyme activation in healthy volunteers, providing an opportunity to understand the safety, dosing and pharmacodynamic activity of AG-348 prior to entering a proof-of-concept study in patients.

The results being reported are from 64 healthy volunteers who received either AG-348 or placebo, which includes 48 people from the completed SAD study and 16 people in the first two cohorts of the ongoing MAD study that recently completed enrollment. Complete safety results are being reported from the SAD Phase 1 study and showed that AG-348 was well tolerated. Although the MAD study remains blinded, no serious adverse events have been reported in the first two analyzed cohorts. AG-348 also showed a favorable pharmacokinetic profile with rapid absorption, low variability and dose-proportional increase in exposure following both single and multiple doses. The observed dose-dependent changes in 2,3-DPG and ATP blood levels seen are consistent with a substantial increase in PKR enzymatic activity.

The Phase 1 studies are randomized, double blind, placebo-controlled trials evaluating single ascending and multiple ascending oral doses for 14 days. The primary objectives of the studies are to assess safety and tolerability of AG-348 in healthy subjects (SAD study) and identify a safe and pharmacodynamically active dose and schedule for future studies in patients with PK deficiency (MAD study). Secondary objectives are designed to characterize the pharmacokinetics of AG-348 and the PK/PD relationship between AG-348, ATP, and 2,3-DPG. Both trials successfully met their respective primary endpoints.

SAD Phase 1 Final Results

- In the SAD study, six cohorts with doses of AG-348 ranging from 30 mg to 2500 mg were tested against placebo in 48 healthy volunteers. Safety events showed a favorable safety profile in all doses tested. There were no serious adverse events (SAE) reported, with all AE's being mild to moderate, and the most common being nausea and headache. In addition, there were no early discontinuations due to AG-348, no food effect was observed, and the maximum tolerated dose was not reached. In the SAD study, mean decreases in blood 2,3-DPG levels up to 49 percent from baseline were observed. ATP levels were not predicted to change after a single dose of AG-348.

MAD Phase 1 Preliminary Results

- The first two cohorts reported data from 16 healthy volunteers dosed twice daily with 120 mg and 360 mg multiple ascending doses of AG-348 or placebo. Safety data are being collected and will be analyzed at the end of the study but no SAE's (grade 3 or higher) have been reported in the blinded analysis of the first two cohorts. Pharmacodynamic data from these cohorts showed up to a 48 percent mean decrease in blood 2,3-DPG levels and up to a 52 percent mean increase in blood ATP levels from baseline. In contrast, healthy volunteers receiving placebo showed no changes in 2,3-DPG or

ATP levels. Enrollment has been completed with several additional dose cohorts undergoing analysis.

AG-348 Clinical Development Plans and Upcoming Milestones

It is hypothesized that healthy volunteers may predict the safety and pharmacodynamic responses that would be observed in PK deficiency patients treated with AG-348. Based on findings presented at ASH, Agios is planning to initiate a Phase 2 study of AG-348 in patients with PK deficiency in the first half of 2015. The doses will be determined based on the findings from the Phase 1 SAD and MAD studies. The company expects to provide final results from the MAD study in 2015. A natural history study of PK deficiency is also ongoing and patient enrollment is on track. Natural history studies are important to confirm and further understand clinical characteristics, symptoms and disease complications and potentially support the design of future clinical trials. Agios expects to report initial data from this study of the natural history of PK deficiency at a medical conference in 2015.

Additional ASH 2014 Poster Presentation

Additionally, a preclinical poster presentation at this year's ASH meeting showed that in mice AG-348 increased PKR activity levels by increasing ATP levels and reducing 2,3-DPG levels in a manner consistent with increased glycolytic pathway activity. These findings are consistent with the Phase 1 clinical data presented today.

Investor Event and Webcast

Agios will host a live event with webcast on Monday, December 8, 2014 at 12:00 p.m. PST (3:00 p.m. EST) to review the data being presented at ASH, including the new Phase 1 clinical data for AG-221 in IDH2-mutant positive advanced hematologic malignancies and data from the Phase 1 studies of AG-348 among healthy volunteers. The webcast can be accessed live or in archived form under "Events & Presentations" in the Investors & Media section of the company's website at www.agios.com.

About Agios Pharmaceuticals, Inc.

Agios Pharmaceuticals is focused on discovering and developing novel investigational medicines to treat cancer and rare genetic disorders of metabolism 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 the company's knowledge of metabolism, biology and genomics. For more information, please visit our website at 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: the potential of pyruvate kinase-R mutations as therapeutic targets; the potential benefits of Agios' drug candidate AG-348; its plans and timelines for the clinical development of AG-348; its plans regarding future data presentations; and the benefit of its strategic plans and focus. The words "anticipate," "believe," "estimate," "expect," "intend," "may," "plan," "predict," "project," "could," "potential," "would" 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, 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' Quarterly Report on Form 10-Q for the quarter ended September 30, 2014, 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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