



## **Agios Announces New Data from Ongoing Phase 1 Trial of AG-221 Showing Robust Clinical Activity in Patients with Advanced Hematologic Malignancies**

December 7, 2014

*Durable Responses Observed with Patients on Study for up to Eight Months and Ongoing in Advanced Acute Myeloid Leukemia and Other Blood Cancers*

*Company Expects Global Registration Program to Begin for IDH2 inhibitor AG-221 in 2015 and IDH1 inhibitor AG-120 by early 2016*

*Agios Announces 2015 Upcoming Milestones for IDH Programs*

SAN FRANCISCO, Dec. 7, 2014 (GLOBE NEWSWIRE) -- Agios Pharmaceuticals, Inc. (Nasdaq:AGIO), a leader in the fields of cancer metabolism and rare genetic disorders of metabolism, today announced new data from the ongoing Phase 1 dose escalation study of AG-221 as a single agent in patients with IDH2-mutant positive advanced hematologic malignancies. With additional patient enrollment and longer follow-up, the data continue to show a favorable safety profile as well as durable clinical activity for AG-221, with an overall response rate of 56 percent (25 of 45 evaluable patients) in advanced hematologic malignancies. Eytan Stein, M.D., lead investigator and attending physician in the leukemia service at Memorial Sloan Kettering Cancer Center, will present the data in an oral presentation today at the 56<sup>th</sup> Annual American Society of Hematology (ASH) Annual Meeting and Exposition being held in San Francisco. AG-221 is a first-in-class, oral, selective, potent inhibitor of the mutant IDH2 (isocitrate dehydrogenase-2) enzyme being developed in collaboration with Celgene.

"The durable responses observed for AG-221 with minimal toxicity being reported are impressive in this advanced disease setting," said Dr. Stein. "These findings build upon those presented throughout the year. In addition, they continue to provide evidence that AG-221 can inhibit the IDH2 mutant protein, stop production of the oncometabolite, 2-HG, and allow for cancer cells to become mature, functioning blood cells. This approach is different from traditional chemotherapy that attempts to non-selectively kill cancer cells. I believe AG-221's unique mechanism targeting a specific mutation is the way of the future and represents a highly specific oral therapy that may transform the treatment of a devastating group of blood cancers."

As of the data cut-off on October 1, 2014, the ongoing Phase 1 study of AG-221 had enrolled 73 patients, with a documented IDH2 mutation, in a broad range of advanced hematologic malignancies. Patients enrolled included those with relapsed or refractory acute myeloid leukemia (AML), myelodysplastic syndrome (MDS), chronic myelomonocytic leukemia (CMML) and untreated AML who decline intensive chemotherapy. At the time of the data cut-off, 45 patients were evaluable for an analysis of clinical activity. Twelve patients had initiated therapy too recently and were therefore not evaluable and 16 patients had discontinued without an evaluable day 28 assessment. The data showed that 25 out of 45 evaluable patients achieved investigator-assessed objective responses, including six complete remissions, nine complete remissions with various degrees of hematologic recovery and ten partial remissions. An estimated 90 percent of patients who responded had responses lasting for at least three months, with durations on AG-221 for as long as eight months and ongoing. For patients who achieved a complete remission, their cancer did not progress while on therapy. AG-221 was well tolerated and the overall safety profile observed was consistent with previously reported data. A maximum tolerated dose (MTD) had not been reached. These data form the basis for the planned initiation of a global registration program in 2015.

"We are making tremendous progress for patients with our AG-221 program, as the data from the Phase 1 study have consistently shown durable activity with a favorable safety profile in patients with several types of advanced hematologic malignancies, especially AML," said Chris Bowden, M.D., chief medical officer of Agios. "While the data we are presenting today and those recently reported for AG-120, our IDH1-mutant inhibitor, are still early, we believe they validate our approach of targeting dysregulated metabolic enzymes. Along with our partner Celgene, we expect to begin a global registration program for AG-221 in 2015 in IDH2-mutant positive hematologic malignancies followed by a global registration program for AG-120 in IDH1-mutant positive hematologic malignancies by early 2016. We feel strongly that these investigational medicines with their unique mechanisms of action have the potential to profoundly impact treatment for individuals with IDH-mutant cancers, and we are pleased to share the results of the additional data for AG-221 with the medical community."

### **About the Ongoing Phase 1 Trial for AG-221**

The primary goals of the Phase 1 trial are to establish the safety profile, determine the maximum tolerated dose and assess the preliminary clinical activity of AG-221 as a single agent administered orally in 28-day cycles. The study is only enrolling patients who have an IDH2-mutant hematologic malignancy. Secondary objectives include characterization of the pharmacokinetics (PK) and pharmacodynamics (PD), including inhibition of 2-hydroxyglutarate (or 2HG). The trial uses an open-label, dose-escalating design. Data reported are from patients receiving AG-221 in 10 dose escalation cohorts administered from 60 mg to 300 mg total daily doses as of October 1, 2014. Dose escalation continues, as the maximum tolerated dose has not been reached. The median age of these patients is 67 (range 33-90).

### **Safety Data**

- A safety analysis was conducted for all 73 treated patients as of October 1, 2014.
- The majority of adverse events reported by investigators were mild to moderate, with the most common being nausea, pyrexia, diarrhea and fatigue.
- The majority of serious adverse events (SAE) were disease related; SAE's possibly related to study drug were reported in 13 patients.
- 11 deaths were reported with nine unrelated to AG-221.
- Two deaths were reported as possibly related to study drug: one in a patient with sepsis and hypoxia and one with atrial

flutter.

## Efficacy Data

25 out of 45 efficacy evaluable patients achieved investigator assessed objective responses for an overall response rate of 56 percent as of the October 1, 2014 data cut-off date.

- Of the 25 patients who achieved an objective response, there were six complete remissions, four complete remissions with incomplete platelet recovery (CRp), four marrow complete remissions (mCR), one complete remission with incomplete hematologic recovery (CRi) and 10 partial remissions (PR).
- Responses were durable, with duration on study drug as long as eight months and ongoing. An estimated 90 percent of responses are three months or longer, with four responders on AG-221 beyond six months of treatment.
- Ten patients with stable disease remain on AG-221, with several patients on study as long as six months and ongoing
- There have been no relapses in patients with a complete remission.
- Five patients were removed from the study per the protocol following decision to undergo a potentially curative bone marrow transplant.
- Treatment with AG-221 showed substantial reduction in the plasma levels of 2-HG to the level observed in healthy volunteers.

"Throughout 2014, we made significant progress across our company, in particular the achievement of proof-of-concept for two distinct IDH inhibitors, AG-221 and AG-120," said David Schenkein, M.D., chief executive officer of Agios. "Over the coming year, we expect to expand the development programs into registration studies and in combination trials to explore the potential of broader use in patients who carry an IDH mutation. We also expect to present new data from multiple studies across our two lead IDH programs to help further define the potential of these investigational medicines to make a major impact on the treatment of cancer."

## Upcoming Milestones: Cancer Metabolism Program in Collaboration with Celgene

*AG-221 (IDH2 mutant inhibitor): Multiple studies of AG-221 planned for 2015 support speed and breadth in development for patients with an IDH2 mutation*

- **Phase 1 expansion cohorts:** In 2015, Agios expects to present data from the expansion cohorts in the ongoing Phase 1 study from 100 patients with IDH2-mutant hematologic malignancies, including AML.
- **Global registration program:** The company expects that a global registration program in hematologic malignancies will start in 2015.
- **Frontline therapy approach:** In 2015, Agios plans to initiate combination trials in patients with AML to evaluate the potential of AG-221 as a first line therapy for patients with hematologic malignancies.
- **Phase 1 solid tumor study:** The company expects the Phase 1 trial in patients with advanced solid tumors whose cancers carry an IDH2 mutation to remain on track.

*AG-120 (IDH1 mutant inhibitor): Multiple studies of AG-120 planned for 2015/2016 support speed and breadth in development for patients with an IDH1 mutation*

- **Phase 1 expansion cohorts:** Agios plans to initiate expansion cohorts in hematologic malignancies as part of ongoing Phase 1 study in first half of 2015.
- **Global registration program:** The company plans to initiate a global registration program in hematologic malignancies that harbor an IDH1 mutation by early 2016.
- **Frontline therapy approach:** Combination trials to evaluate potential frontline AML development are planned to begin in 2015.
- **Phase 1 solid tumor study:** The company remains on track to present the first data from the dose escalation portion of the Phase 1 advanced solid tumor trial at a medical conference in 2015.

## Additional Presentation Highlighting Agios' IDH Programs

A poster presentation characterizing the PK/PD clinical data for AG-221 was also presented at the ASH meeting. The results showed that AG-221 has an excellent PK profile following oral dosing, with a high plasma exposure and long half-life, which supports once daily (QD) dosing. In addition, AG 221 suppressed the production of 2-HG to the normal range found in healthy volunteers. The PK (AG-221 exposure) and PD (the inhibition of 2-HG production) correlation supports the selection of 100 mg QD dosing of AG-221 in the ongoing Phase 1 expansion cohorts in hematologic malignancies.

## Investor Event and Webcast

Agios will host a live event with webcast on Monday, December 8, 2014 at approximately 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](http://www.agios.com).

## About Agios/Celgene Collaboration

AG-221 is a part of Agios' global strategic collaboration with Celgene Corporation, an integrated global biopharmaceutical company. In June 2014, Celgene exercised its exclusive option to license AG-221 and gained worldwide development and commercialization rights for AG-221. Agios

continues to conduct early clinical development activities within the AG-221 development program. The companies are also collaborating on the development of AG-120, which is being studied in two Phase 1 trials in patients whose hematologic malignancies and solid tumors carry an IDH1 mutation. Agios retains U.S. development and commercialization rights for AG-120, and Celgene has an exclusive option to the ex-U.S. rights.

#### **About IDH Mutations and Cancer**

IDH1 and IDH2 are two metabolic enzymes that are mutated in a wide range of hematologic and solid tumor malignancies, including AML. Normally, IDH enzymes help to break down nutrients and generate energy for cells. When mutated, IDH increases production of an oncometabolite known as 2-hydroxyglutarate (2-HG) that alters the cells' genetic programming, and instead of maturing, the cells remain immature leukemic white blood cells, proliferate quickly and prevent mature infection-fighting white blood cells from developing. 2-HG has been found to be elevated in several tumor types. Agios believes that inhibition of the mutated IDH proteins may lead to clinical benefit for the subset of cancer patients whose tumors carry them. AG-221 was developed by Agios as a selective, potent inhibitor of the mutated IDH2 protein.

#### **About Acute Myelogenous Leukemia (AML)**

AML, a cancer of blood and bone marrow characterized by rapid disease progression, is the most common acute leukemia affecting adults. Undifferentiated blast cells proliferate in the bone marrow rather than mature into normal blood cells. AML incidence significantly increases with age, and according to the American Cancer Society the median age is 66. Less than 10 percent of U.S. patients are eligible for bone marrow transplant, and the vast majority of patients do not respond to chemotherapy and progress to relapsed/refractory AML. The five-year survival rate for AML is approximately 20 to 25 percent. IDH2 mutations are present in about 9 to 13 percent of AML cases. IDH mutations are also found in solid tumor cancers, including glioma, chondrosarcoma and intrahepatic cholangiocarcinoma.

#### **About Agios Pharmaceuticals, Inc.**

Agios Pharmaceuticals is focused on discovering and developing novel drugs 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 lead 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 [www.agios.com](http://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' expectations and beliefs about: the potential of IDH1/2 mutations as therapeutic targets; the potential benefits of Agios' product candidates targeting IDH1 or 2 mutations, including AG-221 and AG-120; its plans and timelines for the research and clinical development and data presentations of AG-221 and AG-120; including the timing of a global registration program for each product candidate; and the benefit of its strategic plans and focus. The words "anticipate," "believe," "estimate," "expect," "intend," "may," "plan," "predict," "potential," "could," "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, such as its agreement 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, 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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