Data from Agios' Phase 3 ClarIDHy Trial of TIBSOVO® Demonstrates Significant Improvement in Progression Free Survival (PFS) Compared to Placebo in Previously Treated IDH1 Mutant Cholangiocarcinoma Patients

September 30, 2019

– TIBSOVO® Reduced the Risk of Disease Progression or Death by 63% (HR=0.37, p<0.001); Median PFS for Patients Randomized to TIBSOVO® was 2.7 months Compared to 1.4 Months with Placebo –

– TIBSOVO® Patients Had 6-month PFS Rate of 32% and 12-month PFS Rate of 22%; No Placebo Patients Were Free From Progression for More Than Six Months –

– Supplemental New Drug Application on Track for Submission by End of 2019 –

– Company to Host Conference Call and Webcast on Monday, September 30 at 1p.m. ET / 7p.m. CET –

BARCELONA, Spain, Sept. 30, 2019 (GLOBE NEWSWIRE) -- Agios Pharmaceuticals, Inc. (NASDAQ:AGIO), a leader in the field of cellular metabolism to treat cancer and rare genetic diseases, today presented data from the global Phase 3 ClarIDHy trial of TIBSOVO® (ivosidenib) in previously treated cholangiocarcinoma patients with an isocitrate dehydrogenase 1 (IDH1) mutation in a Presidential Symposium at the European Society for Medical Oncology Congress (ESMO). Results from the ClarIDHy trial demonstrated a statistically significant improvement in progression-free survival (PFS) by independent radiology review of 2.7 months among patients randomized to TIBSOVO® compared with 1.4 months among placebo patients (hazard ratio [HR] 0.37; 95% CI [0.25, 0.54], p<0.001). The safety profile observed in the study was consistent with previously published data.

"Advanced cholangiocarcinoma is an aggressive disease oftentimes characterized by rapid progression following multiple lines of therapy, and there are no currently approved treatments," said Ghassan Abou-Alfa, M.D., medical oncologist at Memorial Sloan Kettering Cancer Center, who presented the data at ESMO. "The ClarIDHy study is the first randomized trial in previously treated IDH1 mutant cholangiocarcinoma patients and demonstrates that TIBSOVO® provides significant improvement in PFS compared to placebo, while also showing a favorable trend in overall survival. These critical data also provide strong justification for genomic testing in cholangiocarcinoma patients where a targeted therapeutic approach may provide benefit."

"Since we began clinical trials of TIBSOVO ® in solid tumors five years ago, we have hoped to provide benefit to cholangiocarcinoma patients who desperately need new treatment options. The results of the ClarIDHy trial help to establish the role that this targeted therapy may play in the treatment paradigm for patients with an IDH1 mutation," said Chris Bowden, M.D., chief medical officer at Agios. "Moving forward, we're focused on submitting our supplemental new drug application for previously treated IDH1 mutant cholangiocarcinoma patients by the end of the year."

ClarIDHy Phase 3 Trial
The ClarIDHy trial is a global, randomized Phase 3 trial in previously treated IDH1 mutant cholangiocarcinoma patients who have documented disease progression following one or two systemic therapies in the advanced setting. Patients were randomized 2:1 to receive either single-agent TIBSOVO® 500 mg once daily or placebo with crossover to TIBSOVO® permitted at the time of documented radiographic progression per RECIST 1.1. As of the January 31, 2019 data cutoff, 185 patients were randomized, with 124 patients in the TIBSOVO® arm and 61 patients in the placebo arm. Thirty-five patients randomized to placebo (57.4%) crossed over to open-label TIBSOVO® upon radiographic disease progression and unblinding.

Efficacy Results
Efficacy data as of the data cut-off showed:

- Median progression-free survival (PFS) for patients randomized to TIBSOVO® was 2.7 months compared to 1.4 months with placebo (hazard ratio [HR]=0.37; 95% CI [0.25, 0.54], p<0.001) as assessed by independent radiology review. PFS benefits were observed across all subgroups analyzed.

- The estimated PFS rate was 32% at six months and 22% at 12 months for patients randomized to TIBSOVO®, while no patients randomized to placebo were free from progression beyond these timepoints as of the data cut-off.

- In the TIBSOVO® arm, 2% of patients achieved a partial response and 51% had stable disease, compared to 28% with stable disease in the placebo arm.

- Median overall survival (OS) based on 78 events was 10.8 months for patients randomized to TIBSOVO® compared to 9.7 months for placebo patients (HR=0.69; 95% CI [0.44, 1.10], p=0.06). Using the rank-preserving structural failure time (RPSFT) method to reconstruct the survival curve for the placebo subjects as if they never crossed over to TIBSOVO®, the median OS with placebo adjusts to 6 months (HR=0.46; 95% CI [0.28, 0.75], p<0.001).

Safety Results
A safety analysis conducted for all patients as of the data cut-off demonstrated:

- Less than half of patients experienced a Grade 3 or above treatment-emergent adverse event (TEAE) in either arm (46.2% with total TIBSOVO® [includes patients who crossed over from placebo to TIBSOVO®] vs. 35.6% on placebo), with the most common being ascites (7.7% total TIBSOVO® vs. 6.8% placebo).
- TEAEs leading to discontinuation were more common with placebo compared with total TIBSOVO® (8.5% vs. 5.8%).
- TEAEs leading to dose reductions (2.6% vs. 0%) and interruptions (26.3% vs. 16.9%) were more common with total TIBSOVO® relative to placebo.
- The most common TEAEs of any grade for total TIBSOVO® were nausea (32%), diarrhea (29%) and fatigue (24%).

TIBSOVO® is not approved in any country for the treatment of patients with advanced cholangiocarcinoma.

Conference Call Information
Agios will host a conference call and live webcast with presentation slides today at 1 p.m. ET /7 p.m. CET to discuss the data from the ClarIDHy study. To participate in the conference call, please dial 1-877-377-7098 (domestic) or 1-631-291-4547 (international) and refer to conference ID 5209309. The live webcast can be accessed under “Events & Presentations” in the Investors 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 Cholangiocarcinoma
Cholangiocarcinoma (CC) is a rare cancer of the bile ducts within and outside of the liver. Cases that occur within the liver are known as intrahepatic cholangiocarcinoma (IHCC) and those that occur outside the liver are considered extrahepatic. Mutations in IDH1 occur in up to 20% of IHCC cases. Current treatment options for localized disease include surgery, radiation and/or other ablative treatments. There are no approved systemic therapies for cholangiocarcinoma and limited chemotherapy options are available in the advanced setting. Gemcitabine-based chemotherapy is often recommended for newly diagnosed advanced or metastatic disease.

About TIBSOVO® (ivosidenib)

TIBSOVO® is indicated for the treatment of acute myeloid leukemia (AML) with a susceptible isocitrate dehydrogenase-1 (IDH1) mutation as detected by an FDA-approved test in:

- Adult patients with newly-diagnosed AML who are ≥75 years old or who have comorbidities that preclude use of intensive induction chemotherapy.
- Adult patients with relapsed or refractory AML.

IMPORTANT SAFETY INFORMATION

WARNING: DIFFERENTIATION SYNDROME

Patients treated with TIBSOVO® have experienced symptoms of differentiation syndrome, which can be fatal if not treated. Symptoms may include fever, dyspnea, hypoxia, pulmonary infiltrates, pleural or pericardial effusions, rapid weight gain or peripheral edema, hypotension, and hepatic, renal, or multi-organ dysfunction. If differentiation syndrome is suspected, initiate corticosteroid therapy and hemodynamic monitoring until symptom resolution.

WARNINGS AND PRECAUTIONS

Differentiation Syndrome: See Boxed WARNING. In the clinical trial, 25% (7/28) of patients with newly diagnosed AML and 19% (34/179) of patients with relapsed or refractory AML treated with TIBSOVO® experienced differentiation syndrome. Differentiation syndrome is associated with rapid proliferation and differentiation of myeloid cells and may be life-threatening or fatal if not treated. Symptoms of differentiation syndrome in patients treated with TIBSOVO® included noninfectious leukocytosis, peripheral edema, pyrexia, dyspnea, pleural effusion, hypotension, hypoxia, pulmonary edema, pneumonitis, pericardial effusion, rash, fluid overload, tumor lysis syndrome, and creatinine increased. Of the 7 patients with newly diagnosed AML who experienced differentiation syndrome, 6 (86%) patients recovered. Of the 34 patients with relapsed or refractory AML who experienced differentiation syndrome, 27 (79%) patients recovered after treatment or after dose interruption of TIBSOVO®. Differentiation syndrome occurred as early as 1 day and up to 3 months after TIBSOVO® initiation and has been observed with or without concomitant leukocytosis.

If differentiation syndrome is suspected, initiate dexamethasone 10 mg IV every 12 hours (or an equivalent dose of an alternative oral or IV corticosteroid) and hemodynamic monitoring until improvement. If concomitant noninfectious leukocytosis is observed, initiate treatment with hydroxyurea or leukapheresis, as clinically indicated. Taper corticosteroids and hydroxyurea after resolution of symptoms and administer corticosteroids for a minimum of 3 days. Symptoms of differentiation syndrome may recur with premature discontinuation of corticosteroid and/or hydroxyurea treatment. If severe signs and/or symptoms persist for more than 48 hours after initiation of corticosteroids, interrupt TIBSOVO® until signs and symptoms are no longer severe.

QTc Interval Prolongation: Patients treated with TIBSOVO® can develop QT (QTc) prolongation and ventricular arrhythmias. One patient developed ventricular fibrillation attributed to TIBSOVO®. Concomitant use of TIBSOVO® with drugs known to prolong the QTc interval (e.g., anti-arrhythmic medicines, fluoroquinolones, triazole anti-fungals, 5-HT_3 receptor antagonists) and CYP3A4 inhibitors may increase the risk of QTc interval prolongation. Conduct monitoring of electrocardiograms (ECGs) and electrolytes. In patients with congenital long QTc syndrome, congestive heart failure, or electrolyte abnormalities, or in those who are taking medications known to prolong the QTc interval, more frequent monitoring may be necessary.

Interrupt TIBSOVO® if QTc increases to greater than 480 msec and less than 500 msec. Interrupt and reduce TIBSOVO® if QTc increases to greater than 500 msec. Permanently discontinue TIBSOVO® in patients who develop QTc interval prolongation with signs or symptoms of life-threatening arrhythmia.

Guillain-Barré Syndrome: Guillain-Barré syndrome occurred in <1% (2/258) of patients treated with TIBSOVO® in the clinical study. Monitor patients taking TIBSOVO® for onset of new signs or symptoms of motor and/or sensory neuropathy such as unilateral or bilateral weakness, sensory alterations, paresthesias, or difficulty breathing. Permanently discontinue TIBSOVO® in patients who are diagnosed with Guillain-Barré syndrome.

ADVERSE REACTIONS

- The most common adverse reactions including laboratory abnormalities (≥20%) were hemoglobin decreased (60%), fatigue (43%), arthralgia (39%), calcium decreased (39%), sodium decreased (39%), leukocytosis (38%), diarrhea (37%), magnesium decreased (36%), edema (34%), nausea (33%), dyspnea (32%), uric acid increased (32%), potassium decreased (32%), alkaline phosphatase increased (30%), mucositis (28%), aspartate aminotransferase increased (27%), phosphatase decreased (25%), electrocardiogram QT prolonged (24%), rash (24%), creatinine increased (24%), cough (23%), decreased appetite (22%), myalgia (21%), constipation (20%), and pyrexia (20%).
- **In patients with newly diagnosed AML,** the most frequently reported Grade ≥3 adverse reactions (≥5%) were fatigue (14%), differentiation syndrome (11%), electrocardiogram QT prolonged (11%), diarrhea (7%), nausea (7%), and leukocytosis (7%). Serious adverse reactions (≥5%) were differentiation syndrome (18%), electrocardiogram QT prolonged (7%), and fatigue (7%). There was one case of posterior reversible encephalopathy syndrome (PRES).
- **In patients with relapsed or refractory AML,** the most frequently reported Grade ≥3 adverse reactions (≥5%) were differentiation syndrome (13%), electrocardiogram QT prolonged (10%), dyspnea (9%), leukocytosis (8%), and tumor lysis syndrome (6%). Serious adverse reactions (≥5%) were differentiation syndrome (10%), leukocytosis (10%), and electrocardiogram QT prolonged (7%). There was one case of progressive multifocal leukoencephalopathy (PML).

DRUG INTERACTIONS

Strong or Moderate CYP3A4 Inhibitors: Reduce TIBSOVO® dose with strong CYP3A4 inhibitors. Monitor patients for increased risk of QTc interval prolongation.
Strong CYP3A4 Inducers: Avoid concomitant use with TIBSOVO®.
Sensitive CYP3A4 Substrates: Avoid concomitant use with TIBSOVO®.

QTc Prolonging Drugs: Avoid concomitant use with TIBSOVO®. If co-administration is unavoidable, monitor patients for increased risk of QTc interval prolongation.

LACTATION

Because many drugs are excreted in human milk and because of the potential for adverse reactions in breastfed children, advise women not to breastfeed during treatment with TIBSOVO® and for at least 1 month after the last dose.

Please see full Prescribing Information, including Boxed WARNING.

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 TIBSOVO® (ivosidenib); Agios' plans to submit a supplemental new drug application for TIBSOVO® in previously treated IDH1 mutant positive cholangiocarcinoma by the end of 2019; 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 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, 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.

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