Agios Presents New Pharmacodynamic and Response Data from Both Cohorts of the Perioperative Study of Vorasidenib and TIBSOVO® (ivosidenib) in Patients with IDH1 Mutant Positive Low-Grade Glioma

November 22, 2019

– Preliminary Efficacy Data Show 31% Overall Response Rate for Both Vorasidenib and TIBSOVO® with Postoperative Treatment –

– Vorasidenib and TIBSOVO® Showed 2-HG Suppression of Greater Than 90% in Resected IDH1 Mutant Gliomas Across All Doses Tested –

– Vorasidenib and TIBSOVO® Demonstrated Favorable Safety Profile at All Doses Tested –

– Registration-enabling Phase 3 INDIGO Study of Vorasidenib in Grade 2 Non-enhancing Glioma with an IDH mutation to Initiate by Year End –

PHOENIX, Nov. 22, 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 updated data from the ongoing perioperative study, confirming brain penetrance and robust biomarker suppression with treatment of single agent vorasidenib or TIBSOVO® (ivosidenib) in low-grade glioma with an IDH1 mutation. The data were featured in an oral presentation at the Society for Neuro-Oncology (SNO) Annual Meeting in Phoenix. Vorasidenib, an investigational, oral, selective, inhibitor of the mutant isocitrate dehydrogenase-1 (IDH1) and IDH2 enzymes, was designed for enhanced brain penetrance and selected for pivotal development in IDH mutant low-grade glioma.

“Now with data from both cohorts of the perioperative study, we have further evidence demonstrating that vorasidenib has excellent brain penetrance and suppresses 2-HG in IDH1 mutant gliomas,” said Ingo Mellinghoff, M.D., Memorial Sloan Kettering Cancer Center, an investigator for the study. “In addition, it is encouraging that the safety profile continues to be consistent, and preliminary efficacy data show objective tumor responses and durable disease control with postoperative treatment. These data support the selection of vorasidenib for pivotal development and help establish the potential role for IDH inhibitors in the treatment of low-grade glioma.”

“These data build on our initial findings that led us to the selection of vorasidenib for a pivotal study in low-grade glioma,” said Chris Bowden, M.D., chief medical officer at Agios. “Having now demonstrated brain penetrance, robust 2-HG suppression and an encouraging disease-control rate with vorasidenib, we’re confident in our ability to make a difference for patients with IDH mutant low-grade glioma and are on track to initiate the Phase 3 INDIGO study next month.”

Perioperative Study of Vorasidenib and TIBSOVO®

Vorasidenib and TIBSOVO® are being evaluated as a single agent in an ongoing perioperative study in IDH1 mutant Grade 2/3 glioma. The primary endpoint is 2-hydroxyglutarate (2-HG) concentration in tumors resected following presurgical treatment with vorasidenib and TIBSOVO® compared with untreated control tumors. Patients were randomized to 500 mg TIBSOVO® once daily, 50 mg vorasidenib once daily or the control arm in cohort 1; and 250 mg TIBSOVO® twice daily or 10 mg vorasidenib once daily in cohort 2. Patients were treated for four weeks prior to surgery and had the option to continue postoperative treatment until disease progression.

As of the July 26, 2019 data cutoff, 49 patients were randomized before surgery, and 39 remain on treatment. The median (range) postoperative treatment duration for all doses was 5.42 (0.9–13.5) months for vorasidenib and 6.93 (1.0–13.2) months for TIBSOVO®. Baseline characteristics were similar across the control and treated groups. Overall, 88% of patients had World Health Organization (WHO) classified Grade 2 tumors. Less than a third of patients had prior radiation therapy and approximately half had prior systemic therapy.

Safety Data

The safety analysis conducted for all 49 patients as of the data cut-off demonstrated that vorasidenib and TIBSOVO® continue to have favorable safety profiles consistent with the Phase 1 data.

- The most common adverse events (AE) occurring in >25% of patients in the vorasidenib arm were diarrhea (29.2%), fatigue (29.2%) and nausea (29.2%). In the TIBSOVO® arm, the most common AEs were headache (32%), diarrhea (28%) and anemia (28%).
- 8.3% of patients in the vorasidenib group developed transaminase elevations, including one Grade 3 transaminase elevation at 50 mg daily which resolved with dose interruption.
- Grade 3 or higher events occurred in six (25.0%) vorasidenib patients and four (16.0%) TIBSOVO® patients, with the majority related to postoperative complications.
- No patient discontinued treatment due to an AE.

Pharmacokinetics and Pharmacodynamics

- Vorasidenib and TIBSOVO® demonstrated brain penetrance, with mean brain:plasma ratios of 3.16 (vorasidenib 10 mg), 1.74 (vorasidenib 50 mg), 0.13 (TIBSOVO® 250 mg) and 0.10 (TIBSOVO® 500 mg).
- Mean percent reduction in 2-HG (95% CI) were 92.6% (76.1, 97.6) and 91.1% (72.0, 97.0), for vorasidenib 50 mg and TIBSOVO® 500 mg, respectively, relative to untreated samples.

Efficacy Data
Data from the 42 efficacy evaluable patients (21 in the vorasidenib arm; 21 in the TIBSOVO® arm) as of the data cut-off showed:

- Among patients treated post-operatively with 50 mg vorasidenib, four patients (31%) achieved objective tumor responses (two achieved a partial response, defined as tumor shrinkage based on T2/FLAIR signal of at least 50%, and two achieved a minor response, defined as tumor shrinkage based on T2/FLAIR signal of at least 25% but less than 50%) according to the investigator by Response Assessment in Neuro-Oncology for low-grade glioma (RANO-LGG).
- Among patients treated post-operatively with 500 mg TIBSOVO®, four patients (31%) achieved confirmed responses (two achieved a partial response and two achieved a minor response) according to the investigator by RANO-LGG.
- 15 patients treated with vorasidenib and 16 patients treated with TIBSOVO® experienced stable disease, resulting in disease control rates of 90% and 95% respectively.

About the Phase 3 INDIGO Study
The Phase 3 INDIGO study will evaluate 366 patients with IDH mutant Grade 2 non-enhancing glioma in a 1:1 double-blind randomization to either 50 mg of vorasidenib once daily or placebo.

- The primary endpoint is progression free survival, as assessed by a blinded independent review committee.
- Secondary endpoints include safety and tolerability, tumor growth rate as assessed by volume, overall response rate, time to next intervention and quality of life.
- Crossover from placebo to vorasidenib upon centrally confirmed radiographic progression will be permitted.

The study will initiate by the end of 2019.

TIBSOVO® and vorasidenib are not approved in any country for the treatment of patients with low-grade glioma.

About Glioma
Glioma presents in varying degrees of tumor aggressiveness, ranging from slower growing (low-grade glioma) to rapidly progressing (high-grade glioma-Glioblastoma Multiforme). Common symptoms include seizures, memory disturbance, sensory impairment and neurologic deficits. The long-term prognosis is poor, and regardless of treatment, the majority of patients with low-grade gliomas will have recurrent disease that will progress over time. Approximately 11,000 low-grade glioma patients are diagnosed annually in the U.S. and EU and approximately 80 percent have an IDH mutation.

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. 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 vorasidenib and TIBSOVO® (ivosidenib); Agios' plans for the further clinical development of vorasidenib and TIBSOVO® (ivosidenib); 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.

References

1. Mellinghoff et al. 2019 EANO Meeting Presentation

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