Agios Receives FDA Breakthrough Therapy Designation for TIBSOVO® (ivosidenib) for the Treatment of Adult Patients with Relapsed or Refractory Myelodysplastic Syndrome with an IDH1 Mutation

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CAMBRIDGE, Mass., Dec. 16, 2019 (GLOBE NEWSWIRE) -- Agios Pharmaceuticals, Inc. (NASDAQ:AGIO), a leader in the field of cellular metabolism to treat cancer and rare genetic diseases, today announced that the U.S. Food and Drug Administration (FDA) has granted Breakthrough Therapy designation for TIBSOVO® (ivosidenib) for the treatment of adult patients with relapsed or refractory myelodysplastic syndrome (MDS) with a susceptible IDH1 mutation as detected by an FDA-approved test. MDS is a group of bone marrow disorders that can cause severe complications, such as infections and uncontrolled bleeding, and can lead to the development of acute myelogenous leukemia (AML).

"There is a significant need for new targeted therapeutic approaches for individuals with MDS whose disease continues to progress despite treatment with standard of care," said Chris Bowden, M.D., chief medical officer at Agios. "The Breakthrough Therapy designation is based on results from the initial 12 patients in the MDS arm of our Phase 1 study in advanced hematologic malignancies with an IDH1 mutation and recognizes the potential for single-agent treatment with TIBSOVO® to make an impact on these patients. We recently re-opened the MDS arm of this study with the goal of generating sufficient data to pursue a regulatory filing in this indication."

The FDA's Breakthrough Therapy designation is intended to expedite the development and review of a drug candidate that is under investigation to treat a serious or life-threatening disease or condition when preliminary clinical evidence indicates that the drug may demonstrate substantial improvement over available therapies on one or more clinically significant endpoints.

Results from the MDS arm of the ongoing TIBSOVO® Phase 1 dose-escalation and expansion study in hematologic malignancies were presented at the 7th Society of Hematologic Oncology Annual Meeting, held September 11-14, 2019, in Houston, Texas. These demonstrate that TIBSOVO® administered as a monotherapy was well tolerated and associated with durable remissions as well as the achievement and maintenance of transfusion independence in patients with relapsed or refractory MDS with an IDH1 mutation. Among the 12 patients who received 500 mg of oral TIBSOVO® daily, the median treatment duration was 11.4 months. The median age was 72.5 years, and 42% of patients were age 75 or older. As of the November 2, 2018 data cut-off, 75% (9/12) of patients had a response and 42% (5/12) had a complete response (CR). The median duration of CR had not been reached (95% CI, 2.8 months, NE). Of the patients who had a CR, 60% remained relapse-free at 12 months. In addition, 9 (75%) patients were transfusion-independent for 56 days or longer during study treatment. The most common adverse events (AEs) of any grade were back pain, diarrhea, fatigue and rash. Grade 2 IDH differentiation syndrome was observed in 1 of 12 patients. No AEs resulted in permanent discontinuation of treatment.

TIBSOVO® Clinical Development in MDS

The MDS arm of the Phase 1 dose-escalation and expansion study evaluating TIBSOVO® (ivosidenib) in adults with advanced hematologic malignancies with IDH1 mutations is assessing the clinical activity, safety, tolerability, pharmacokinetics and pharmacodynamics of TIBSOVO® in adult patients with relapsed or refractory MDS with a susceptible IDH1 mutation. The arm was re-opened in October 2019 and will enroll up to 25 total patients with the goal of generating sufficient data to pursue a potential regulatory filing in this indication. Study recruitment is ongoing across 22 sites in the U.S. and France.

About Myelodysplastic Syndrome (MDS)

MDS comprises a diverse group of bone marrow disorders in which immature blood cells in the bone marrow do not mature or become healthy blood cells. The National Cancer Institute estimates that more than 10,000 people are diagnosed with MDS in the U.S. each year. Failure of the bone marrow to produce mature healthy cells is a gradual process, and reduced blood cell and/or reduced platelet counts may be accompanied by the loss of the body's ability to fight infections and control bleeding. For roughly 30 percent of the patients diagnosed with MDS, this bone marrow failure will progress to AML. Chemotherapy, hypomethylating agents and supportive blood products are used to treat MDS.

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

About TIBSOVO® (ivosidenib)

TIBSOVO® (ivosidenib) is an isocitrate dehydrogenase-1 (IDH1) inhibitor indicated for the treatment of adult patients with relapsed or refractory acute myeloid leukemia (AML) with a susceptible IDH1 mutation as detected by an FDA-approved test. For more information, visit TIBSOVO.com.

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, 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 34 patients who experienced differentiation syndrome, 27 (79%) 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, 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 (≥20%) of any grade were fatigue (39%), leukocytosis (38%), arthralgia (36%), diarrhea (34%), dyspnea (33%), edema (32%), nausea (31%), mucositis (28%), electrocardiogram QT prolonged (26%), rash (26%), pyrexia (23%), cough (22%), and constipation (20%).
- The most frequently reported ≥Grade 3 adverse reactions (≥5%) were electrocardiogram QT prolonged (10%), dyspnea (9%), leukocytosis (8%), tumor lysis syndrome (6%), and differentiation syndrome (5%).
- 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

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); and the benefit of Agios' strategic plans and focus. The words "expects," "anticipates," "believes," "intends," "estimates," "plans," "will," "outlook," "goal", "potential" 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, the FDA's Breakthrough Therapy designation for TIBSOVO® (ivosidenib) is not a guarantee of approval. 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, the EMA or 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, except as required by law.

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