Agios Announces FDA Approval of Supplemental New Drug Application (sNDA) for TIBSOVO® as Monotherapy for Newly Diagnosed Adult Patients with IDH1 Mutant Acute Myeloid Leukemia (AML) Not Eligible for Intensive Chemotherapy

– TIBSOVO® is the First and Only Therapy Approved for Newly Diagnosed AML Patients with an IDH1 Mutation who are Ineligible for Intensive Chemotherapy –

– sNDA Approval Based on 28 Newly Diagnosed Patients from Phase 1 Study of TIBSOVO® in Advanced Hematologic Malignancies with an IDH1 Mutation[1] –

– Single Agent TIBSOVO® Demonstrated CR Rate of 28.6% and CR+CRh Rate of 42.9%[1] –

CAMBRIDGE, Mass., May 2, 2019 -- Agios Pharmaceuticals, Inc. (NASDAQ:AGIO), a leader in the field of cellular metabolism to treat cancer and rare genetic diseases, today announced the U.S. Food and Drug Administration (FDA) approved a supplemental New Drug Application (sNDA) to update the U.S. Prescribing Information for TIBSOVO®, an isocitrate dehydrogenase-1 (IDH1) inhibitor, to include adult patients with newly diagnosed acute myeloid leukemia (AML) with a susceptible IDH1 mutation as detected by an FDA-approved test who are ≥ 75 years old or who have comorbidities that preclude use of intensive induction chemotherapy. The sNDA was granted Priority Review and accepted under the FDA's Real-Time Oncology Review pilot program, which aims to make the review of oncology drugs more efficient by allowing the FDA access to clinical trial data before the information is formally submitted to the agency. TIBSOVO® received initial FDA approval in July 2018 for adult patients with relapsed or refractory (R/R) AML and an IDH1 mutation[1].

"Despite several new AML medicines approved in the last two years, many newly diagnosed patients are still not eligible for existing therapies or combination regimens because of age and other comorbidities," said Chris Bowden, M.D., chief medical officer at Agios. "With today's additional TIBSOVO® approval, we are now able to provide a targeted, oral therapy to patients with an IDH1 mutation who may not have other treatment options. In addition, we are continuing our work to expand the utility of TIBSOVO® in newly diagnosed AML patients in ongoing Phase 3 trials in combination with both intensive chemotherapy and azacitidine. I would like to thank the patients, nurses, physicians and caregivers who participated in the clinical trial, as well as the tremendous employees at Agios whose focus on patients made this possible."

AML is a cancer of the blood and bone marrow marked by rapid disease progression and is the most common acute leukemia affecting adults with approximately 20,000 new cases estimated in the U.S. each year[2,3]. AML patients are typically older or have comorbidities that preclude the use of intensive chemotherapy[4]. These patients typically have a worse prognosis and poor outcomes[5]. The majority of patients with AML eventually relapse[6]. The five-year survival rate is approximately 28%[2]. For 6 to 10 percent of AML patients, the mutated IDH1 enzyme blocks normal blood stem cell differentiation, contributing to the genesis of acute leukemia[7]. IDH1 mutations have been associated with negative prognosis in AML[8,9].

"The Phase 1 results for TIBSOVO® demonstrated that this oral, single agent therapy can induce durable responses in newly diagnosed AML patients with an IDH1 mutation," said Gail J. Roboz, M.D., Professor of Medicine, Director of the Leukemia Program and a member of the Sandra and Edward Meyer Cancer Center at Weill Cornell Medicine and NewYork-Presbyterian/Weill Cornell Medical Center*. "Many patients included in the study had features associated with particularly aggressive and challenging forms of AML, including secondary disease, adverse risk genetics and prior treatment with hypomethylating agents."

TIBSOVO® Safety and Efficacy Data[1]

The efficacy of TIBSOVO® was evaluated in an open-label, single-arm, multicenter clinical trial (Study AG120-C-001, NCT02074839) that included 28 adult patients with newly diagnosed AML with an IDH1 mutation who were assigned to receive a 500 mg daily dose. The cohort included patients who were age 75 or older or had comorbidities that precluded the use of intensive induction chemotherapy (baseline Eastern Cooperative Oncology Group [ECOG] performance status of ≥2, severe cardiac or pulmonary disease, hepatic impairment with bilirubin >1.5 times the upper limit of normal, or creatinine clearance <45 mL/min). Patients had a median age of 77 years (range of 64 to 87) and 68% had AML with myelodysplasia-related changes. The primary endpoint is the combined complete remission (CR) and complete remission with partial hematologic improvement (CRh) rate. CRh is defined as <5% of blasts in the bone marrow, no evidence of disease and partial recovery of peripheral blood counts (platelets >50,000/microliter and ANC >500/microliter).

In this trial, TIBSOVO® demonstrated:

- CR+CRh rate of 42.9% (12 of 28 patients) (95% CI: 24.5, 62.8).
- The CR rate was 28.6% (8 of 28 patients) (95% CI 13.2, 48.7) and the CRh rate was 14.3% (4 of 28 patients) (95% CI 4.0, 32.7).
- Median durations of CR and CR+CRh were not estimable, with 5 patients (41.7%) who achieved CR or CRh remaining on TIBSOVO® treatment (treatment duration range: 20.3 to 40.9 months) as of the data cutoff.
- 58.3% (7 of 12) of patients who achieved CR or CRh were in remission at 1 year after receiving treatment.
- For patients who achieved a CR or CRh, the median time to best response of CR or CRh was 2.8 months (range, 1.9 to 12.9 months).
- Among the 17 patients who were dependent on red blood cell (RBC) and/or platelet transfusions at baseline, 7 (41.2%) became independent of RBC and platelet transfusions during any 56-day post-baseline period.
- Of the 11 patients who were independent of both RBC and platelet transfusions at baseline, 6 (54.5%) remained transfusion independent during any 56-day post-baseline period.

The safety profile of single-agent TIBSOVO® was evaluated in 28 patients with newly diagnosed AML with an IDH1 mutation treated with a dose of 500 mg daily. The median duration of

exposure to TIBSOVO® was 4.3 months (range, 0.3 to 40.9 months). In the clinical trial, 25% (7 of 28) of patients treated with TIBSOVO® experienced differentiation syndrome, which can be fatal if not treated. Of the 7 patients with newly diagnosed AML who experienced differentiation syndrome, 6 (86%) patients recovered. QTc interval prolongation occurred in patients treated with TIBSOVO®. The most common adverse reactions (≥20%) of any grade in patients with newly diagnosed AML were diarrhea, fatigue, decreased appetite, edema, nausea, leukocytosis, arthralgia, abdominal pain, dyspnea, myalgia, constipation, differentiation syndrome, dizziness, electrocardiogram QT prolonged, mucositis and vomiting.

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 Acute Myelogenous Leukemia (AML)
AML is a cancer of the blood and bone marrow marked by rapid disease progression and is the most common acute leukemia affecting adults with approximately 20,000 new cases estimated in the U.S. each year[2,3]. AML patients are typically older or have comorbidities that preclude the use of intensive chemotherapy[4]. These patients typically have a worse prognosis and poor outcomes[5]. The majority of patients with AML eventually relapse[6]. The five-year survival rate is approximately 28%[2]. For 6 to 10 percent of AML patients, the mutated IDH1 enzyme blocks normal blood stem cell differentiation, contributing to the genesis of acute leukemia[7]. IDH1 mutations have been associated with negative prognosis in AML[8,9].

About myAgios™ Patient Support Services
myAgios™ Patient Support Services is an expansive program that helps patients with access, reimbursement, and financial assistance for TIBSOVO® (ivosidenib). Healthcare providers and pharmacists can enroll patients at myAgios.com/enroll.

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.

**Dr. Roboz has served as a consultant for Celgene, Bayer, Otsuka, Pfizer, Astellas Pharmaceuticals, Argenx, Astex Pharmaceuticals, Hoffman-La Roche, Janssen, Novartis, Amphivena, AbbVie, Sandoz, Eisai, Jazz Pharmaceuticals, Celltrion, Orsenix and Daiichi Sankyo.*

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 Agios' products, including TIBSOVO® (ivosidenib), and its strategic plans and focus. The words “estimate,” “may,” “milestone,” “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, there can be no guarantee that development of any of Agios' product candidates will successfully continue, or 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 agreements with Celgene and CStone Pharmaceuticals; 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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