Agios Presents Final Data from Phase 3 ClarIDHy Study of TIBSOVO® (ivosidenib tablets) in Patients with Previously Treated IDH1-Mutant Cholangiocarcinoma

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– Supplemental New Drug Application Planned for Submission in Q1 2021 –

CAMBRIDGE, Mass., Jan. 17, 2021 (GLOBE NEWSWIRE) -- Agios Pharmaceuticals, Inc. (NASDAQ:AGIO), a leader in the field of cellular metabolism to treat cancer and genetically defined diseases, today reported a full analysis of the final data, including mature overall survival (OS) results, from its global Phase 3 ClarIDHy trial of TIBSOVO® (ivosidenib tablets) in patients with previously treated isocitrate dehydrogenase 1 (IDH1) mutated cholangiocarcinoma. Data from the study were featured in an oral presentation at the American Society of Clinical Oncology Gastrointestinal Cancers Symposium (ASCO-GI), which is being held virtually January 15-17, 2021.

The final analysis showed an improvement in the secondary endpoint of OS favoring patients randomized to TIBSOVO® compared to those randomized to placebo; however, statistical significance was not reached. The median OS for patients randomized to TIBSOVO® was 10.3 months compared to 7.5 months for patients randomized to placebo (hazard ratio [HR]=0.79; 95% CI [0.56–1.12], 1-sided p=0.093). The protocol specified that patients randomized to placebo could cross over to TIBSOVO® at the time of disease progression, and a high proportion of patients in the placebo arm (70.5%) crossed over to TIBSOVO®. The results of a pre-specified analysis to adjust for crossover, based on the rank-preserving structural failure time (RPSFT) model, showed a median OS for patients in the placebo arm of 5.1 months (HR=0.49, 95% CI 0.34–0.70, 1-sided p<0.0001). The safety profile observed in the study was consistent with previously published data. As previously announced, the study demonstrated a statistically significant improvement in the primary endpoint of progression-free survival (PFS) by independent radiology review.

“The progression-free survival and overall survival data from the ClarIDHy Phase 3 study, coupled with a tolerable safety profile and supportive patient-reported quality-of-life data, demonstrate that TIBSOVO® has the potential to be a clinically meaningful treatment option for patients with previously treated IDH1-mutant cholangiocarcinoma, an aggressive cancer with limited effective treatment options,” said Andrew Zhu, M.D., Ph.D., director emeritus of liver cancer research at Massachusetts General Hospital, director of Jiahui International Cancer Center and professor of medicine at Harvard Medical School. “Treatment with TIBSOVO ® resulted in a consistent trend in improved overall survival, despite the high rate of crossover from the placebo arm, and this improvement was further supported by the pre-specified statistical analysis to adjust for the crossover effect. I look forward to the potential of having a new treatment option for my patients with this devastating disease.”

“We are extremely pleased with the results of the ClarIDHy Phase 3 study, the first and only randomized Phase 3 trial for IDH1-mutant advanced cholangiocarcinoma, and believe TIBSOVO® has demonstrated compelling results for patients facing a grim prognosis who currently have few treatment options,” said Chris Bowden, M.D., chief medical officer at Agios. “We will collaborate closely with regulators to advance this potential new oral, non-cytotoxic, targeted treatment option, and we look forward to filing for U.S. approval later this quarter.”

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. The primary endpoint of the ClarIDHy trial is progression-free survival (PFS) as evaluated by independent radiology review. Secondary endpoints include investigator-evaluated PFS, safety and tolerability, overall response rate, OS, duration of response, pharmacokinetics, pharmacodynamics and quality of life assessments.

As of the May 31, 2020 data cutoff, 187 patients were randomized, with 126 patients in the TIBSOVO® arm and 61 patients in the placebo arm. Forty-three patients randomized to placebo (70.5%) crossed over to open-label TIBSOVO® upon radiographic disease progression and unblinding.

Updated Efficacy Data
Efficacy data as of the data cutoff showed:

- The median OS for patients in the TIBSOVO® arm was 10.3 months compared to 7.5 months for patients in the placebo arm (HR=0.79; 95% CI [0.56–1.12], 1-sided p=0.093).
- After adjusting for crossover from placebo to TIBSOVO® using the pre-specified analysis of rank-preserving structural failure time (RPSFT), the median OS for patients in the placebo arm was 5.1 months (HR=0.49; 95% CI [0.34–0.70], 1-sided p<0.0001).
- The 6-month survival rate for patients in the TIBSOVO® arm was 69 percent compared to 57 percent of patients in the placebo arm, not adjusted for crossover.
- The 12-month survival rate for patients in the TIBSOVO® arm was 43 percent compared to 36 percent for patients in the placebo arm, not adjusted for crossover.
- Treatment with TIBSOVO® preserved patients’ physical functioning from baseline, as assessed by the EORTC QLQ-C30 questionnaire, whereas patients in the placebo arm experienced decline from baseline at cycle 2, day 1 (2-sided p=0.002) and cycle 3, day 1 (2-sided p=0.004).
- Treatment with TIBSOVO® improved patients’ pain at cycle 2, day 1 compared to placebo, as assessed by the EORTC QLQ-BIL21 questionnaire (2-sided p=0.039); no difference was observed at cycle 3, day 1.

- Neither arm was favored on other pre-specified quality-of-life subscales (QLQ-C30 Appetite Loss and QLQ-BIL21 Pain and Eating).

Updated Safety Data

- Grade 3 or above treatment-emergent adverse events (TEAE) were reported in 53 percent of total TIBSOVO® patients, which includes patients originally randomized to TIBSOVO® and those who crossed over from placebo to TIBSOVO®, compared to 37.3 percent of patients on placebo, with the most common being ascites (9.0% total TIBSOVO® vs. 6.8% placebo), anemia (7.2% total TIBSOVO® vs. 0% placebo) and increased blood bilirubin (5.4% total TIBSOVO® vs. 1.7% placebo).
- TEAEs leading to discontinuation were more common with placebo compared with total TIBSOVO® (8.5% vs. 6.6%).
- TEAEs leading to dose reductions (3.0% vs. 0%) and interruptions (30.1% vs. 18.6%) were more common with total TIBSOVO® compared with placebo.
- The most common TEAEs of any grade for total TIBSOVO® were nausea (38.0%), diarrhea (33.1%) and fatigue (28.9%).

Previously Reported Data
Data from the study were previously presented at the European Society for Medical Oncology Congress (ESMO), held in September 2019 in Barcelona, Spain, and published in *The Lancet Oncology* on May 13, 2020. Results from the trial demonstrated a statistically significant improvement in the primary endpoint of PFS among patients randomized to TIBSOVO® compared with placebo patients (HR=0.37; 95% CI [0.25–0.54], p<0.0001), with a median PFS of 2.7 months in the TIBSOVO® arm versus a median PFS of 1.4 months in the placebo arm. The estimated PFS rate was 32 percent at six months and 22 percent at 12 months for patients randomized to TIBSOVO®, while no patients randomized to placebo were free from progression or death beyond six months as of the data cut-off.

Based on these data, the National Comprehensive Cancer Network (NCCN) guidelines, the French National Treatment Guidelines for Biliary Cancer and the Italian Clinical Practice Guidelines on Cholangiocarcinoma were updated to recommend treatment with TIBSOVO® for patients with advanced previously treated IDH1-mutant cholangiocarcinoma.

Agios plans to submit a supplemental new drug application for TIBSOVO® in previously treated IDH1-mutant cholangiocarcinoma in the first quarter of 2021.

TIBSOVO® is not approved in any country for the treatment of patients with previously treated advanced IDH1-mutant cholangiocarcinoma.

About Cholangiocarcinoma
Cholangiocarcinoma 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. IDH1 mutations occur in approximately 10% of cholangiocarcinoma cases. Current treatment options for localized disease include surgery, radiation and/or other ablative treatments. There are no approved systemic therapies for IDH1-mutated 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 AML 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 malignant hematology, solid tumors and genetically defined diseases through scientific leadership in the field of cellular metabolism. In addition to an active research and discovery pipeline across these three therapeutic areas, Agios has two approved oncology precision medicines and multiple first-in-class investigational therapies in clinical and/or preclinical development. 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 tablets); Agios' plans to submit a supplemental new drug application for TIBSOVO® in previously treated IDH1 mutant cholangiocarcinoma in the first quarter of 2021; 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 or its collaborators 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, without limitation: risks and uncertainties related to the impact of the COVID-19 pandemic to Agios' business, operations, strategy, goals and anticipated milestones, including its ongoing and planned research activities, ability to conduct ongoing and planned clinical trials, clinical supply of current or future drug candidates, commercial supply of current or future approved products, and launching, marketing and selling current or future approved products; 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.

Contacts

Investors:
Holly Manning, 617-844-6630
Director, Investor Relations
Holly.Manning@agios.com

Media:
Jessica Rennekamp, 857-209-3286
Associate Director, Corporate Communications
Jessica.Rennekamp@agios.com

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