

**UNITED STATES
SECURITIES AND EXCHANGE COMMISSION
WASHINGTON, D.C. 20549**

FORM 8-K

**CURRENT REPORT
Pursuant to Section 13 or 15(d)
of the Securities Exchange Act of 1934**

Date of Report (Date of earliest event reported): December 8, 2019

Agios Pharmaceuticals, Inc.

(Exact Name of Registrant as Specified in Charter)

Delaware
(State or Other Jurisdiction
of Incorporation)

001-36014
(Commission
File Number)

26-0662915
(IRS Employer
Identification No.)

88 Sidney Street, Cambridge, MA
(Address of Principal Executive Offices)

02139
(Zip Code)

Registrant's telephone number, including area code: (617) 649-8600

(Former Name or Former Address, if Changed Since Last Report)

Check the appropriate box below if the Form 8-K filing is intended to simultaneously satisfy the filing obligation of the registrant under any of the following provisions (*see* General Instruction A.2. below):

- Written communications pursuant to Rule 425 under the Securities Act (17 CFR 230.425)
- Soliciting material pursuant to Rule 14a-12 under the Exchange Act (17 CFR 240.14a-12)
- Pre-commencement communications pursuant to Rule 14d-2(b) under the Exchange Act (17 CFR 240.14d-2(b))
- Pre-commencement communications pursuant to Rule 13e-4(c) under the Exchange Act (17 CFR 240.13e-4(c))

Securities registered pursuant to Section 12(b) of the Act:

Title of each class	Trading symbol(s)	Name of each exchange on which registered
Common Stock, Par Value \$0.001 per share	AGIO	Nasdaq Global Select Market

Indicate by check mark whether the registrant is an emerging growth company as defined in Rule 405 of the Securities Act of 1933 (§230.405 of this chapter) or Rule 12b-2 of the Securities Exchange Act of 1934 (§240.12b-2 of this chapter).

Emerging growth company

If an emerging growth company, indicate by check mark if the registrant has elected not to use the extended transition period for complying with any new or revised financial accounting standards provided pursuant to Section 13(a) of the Exchange Act.

Item 8.01 Other Events.

On December 8, 2019, Agios Pharmaceuticals, Inc. (the “Company”) issued a press release announcing that clinical proof-of-concept has been established based on a preliminary analysis in the phase 2 trial of mitapivat in patients with non-transfusion-dependent thalassemia. On December 9, 2019, the Company issued press releases announcing data presented at the 2019 American Society of Hematology Annual Meeting, including (i) translational data describing molecular responses to treatment of TIBSOVO® (ivosidenib) and azacitidine and mechanisms of resistance and relapse to single agent treatment with TIBSOVO® in acute myeloid leukemia with an IDH1 mutation, and (ii) new data from the extension phase of the DRIVE PK phase 2 study of mitapivat in adults with pyruvate kinase, or PK, deficiency as well as data from the Natural History Study of PK deficiency that detailed the comorbidities and complications associated with the disease and the impact of transfusion history.

The full text of the press releases issued in connection with these announcements are attached as Exhibits 99.1, 99.2 and 99.3 to this Current Report on Form 8-K and incorporated herein by reference.

Item 9.01 Financial Statements and Exhibits.

(d) Exhibits.

<u>Exhibit No.</u>	<u>Description</u>
99.1	Press release issued December 8, 2019.
99.2	Press release issued December 9, 2019 (IDH-AML).
99.3	Press release issued December 9, 2019 (PK deficiency).
104	Cover Page Interactive Data File (embedded within the Inline XBRL document).

SIGNATURES

Pursuant to the requirements of the Securities Exchange Act of 1934, the registrant has duly caused this report to be signed on its behalf by the undersigned hereunto duly authorized.

AGIOS PHARMACEUTICALS, INC.

Date: December 9, 2019

By: /s/ Jacquelyn A. Fouse
Jacquelyn A. Fouse, Ph.D.
Chief Executive Officer



AgiOS Establishes Proof-of-Concept for Mitapivat in Non-transfusion-dependent Thalassemia Based on Preliminary Phase 2 Results

– Treatment with Mitapivat Induced Hemoglobin Increase of ³1.0 g/dL in 7 of 8 Evaluable Patients –

– Safety Profile Consistent with Previously Published Phase 2 Data for Mitapivat in Patients with Pyruvate Kinase Deficiency –

– Additional Data for the Phase 2 Study of Mitapivat in Thalassemia to be Presented at a Medical Meeting in the First Half of 2020 –

– Company to Host ASH Investor Event and Webcast Monday, December 9 at 8:00 p.m. ET –

CAMBRIDGE, Mass., December 8, 2019 — Agios Pharmaceuticals, Inc. (NASDAQ:AGIO), a leader in the field of cellular metabolism to treat cancer and rare genetic diseases, today announced that clinical proof-of-concept has been established based on a preliminary analysis of the Phase 2 trial of mitapivat (AG-348) in patients with non-transfusion-dependent thalassemia. Mitapivat is an investigational, first-in-class, oral, small molecule allosteric activator of wild-type and a variety of mutated pyruvate kinase-R (PKR) enzymes.

The Phase 2 study has enrolled 12 of the intended 17 patients (nine with β -thalassemia and three with α -thalassemia). As of the November 14, 2019 data cutoff date, eight patients, all with β -thalassemia, were evaluable for the primary endpoint of a hemoglobin increase of ³1.0 g/dL from baseline in at least one assessment during Weeks 4-12. All eight patients were treated with 50 mg of mitapivat twice daily for the first six weeks and escalated to 100 mg twice daily, and all patients remain on treatment (range 12.4-34.3 weeks). Seven of eight efficacy evaluable patients achieved a hemoglobin increase of ³1.0 g/dL, and for responders the mean hemoglobin increase from baseline was 1.76 g/dL (range, 0.9–3.3 g/dL) during Weeks 4-12. The majority of adverse events were Grade 1 or 2 and consistent with previously published Phase 2 data for mitapivat in patients with pyruvate kinase (PK) deficiency. Updated results from the Phase 2 thalassemia study will be presented at a medical meeting in the first half of 2020.

“These data demonstrate proof of concept that activation of wild-type PKR has the potential to convey clinical benefit in thalassemia and provides compelling evidence to broaden mitapivat clinical development in this disease,” said Chris Bowden, M.D., chief medical officer at Agios. “The safety and tolerability profile observed in this trial and in adults with pyruvate kinase deficiency supports the continued investigation of mitapivat treatment across severe, lifelong hemolytic anemias such as pyruvate kinase deficiency, thalassemia and sickle cell disease.”

Mitapivat Phase 2 Trial in Thalassemia

The ongoing Phase 2 study is evaluating the efficacy, safety, pharmacokinetics and pharmacodynamics of treatment with mitapivat in adults with non-transfusion-dependent β - and α -thalassemia (NTDT). This study includes a 24-week core period followed by a 2-year



extension period for eligible participants. The primary endpoint is hemoglobin response. Approximately 17 participants with NTDT who have a baseline hemoglobin concentration of ≤ 10 g/dL will be enrolled. The initial dose of mitapivat is 50 mg twice daily with one potential dose-level increase to 100 mg twice daily, at the week six visit based on the participant's safety and hemoglobin (Hb) concentrations. With a total of 17 patients enrolled, the study would have 80% power to reject a $\leq 30\%$ response rate at a one-sided 0.05 type 1 error rate.

Mitapivat Clinical Development

AgiOS has two ongoing global, pivotal trials in adults with PK deficiency that are on track to complete enrollment by year-end 2019. Learn more at activatetrials.com.

- **ACTIVATE:** A placebo-controlled trial with a 1:1 randomization, expected to enroll approximately 80 patients who do not receive regular transfusions. The primary endpoint of the trial is the proportion of patients who achieve a sustained hemoglobin increase of ≥ 1.5 g/dL.
- **ACTIVATE-T:** A single arm trial of up to 40 regularly transfused patients with a primary endpoint of reduction in transfusion burden over six months compared to individual historical transfusion burden over prior 12 months.

In addition to the thalassemia Phase 2 study, mitapivat is being studied in sickle cell disease under a Cooperative Research and Development Agreement (CRADA) with the U.S. National Institutes of Health.

Mitapivat is not approved for use by any regulatory authority.

Investor Event and Webcast Information

AgiOS will host an investor event on Monday, December 9, 2019 at 8:00 p.m. ET in Orlando, Fla. The event will be webcast live and 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 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 mitapivat; Agios' plans for the further clinical development of mitapivat 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.

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Investor & Media Contact:

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



AgiOS Presents Translational Data to Further Characterize the Role of TIBSOVO® (ivosidenib) Treatment in IDH1 Mutant Acute Myeloid Leukemia (AML)

– *Combination Therapy with TIBSOVO® and Azacitidine Results in Deep and Durable Molecular Remission in Newly Diagnosed IDH1 Mutant AML* –

– *Mechanisms of Resistance and Relapse to Single Agent IDH1 Inhibitors Are Complex and Multiclonal and Include Both IDH-dependent and IDH-independent Pathways* –

– *Company to Host Investor Event and Webcast Today at 8:00 p.m. ET* –

ORLANDO, Fla., December 9, 2019 — Agios Pharmaceuticals, Inc. (NASDAQ: AGIO), a leader in the field of cellular metabolism to treat cancer and rare genetic diseases, today presented translational data describing deep and durable molecular responses to treatment of TIBSOVO® (ivosidenib) and azacitidine and mechanisms of resistance and relapse to single agent treatment with TIBSOVO® in acute myeloid leukemia (AML) with an IDH1 mutation. The data were presented as part of the scientific program at the 2019 American Society of Hematology (ASH) Annual Meeting.

“For 10 years, we have pioneered the science behind the role of IDH mutations in AML, while bringing to patients new oral therapies for the approximately 20% of AML patients with an IDH mutation. We’re pleased to share a robust set of translational data at ASH that further elucidates our understanding of TIBSOVO® response and resistance mechanisms in patients with IDH1 mutant AML,” said Chris Bowden, M.D., chief medical officer at Agios. “These data show that combination treatment with TIBSOVO® and azacitidine in newly diagnosed IDH1 mutant AML can induce deep, durable remissions in patients with a number of molecular profiles. Our translational work has further elucidated mechanisms of relapse with IDH1 monotherapy in relapsed and refractory disease that includes both IDH-related and non-IDH related pathways.”

Treatment with TIBSOVO® and Azacitidine Results in High Rate of IDH1 Mutation Clearance and Measurable Residual Disease Negativity in Newly Diagnosed AML

As of the February 19, 2019 data cutoff, 23 patients have been treated in the ongoing Phase 1/2 study of TIBSOVO® in combination with azacitidine in patients with newly diagnosed IDH1 mutant AML ineligible for intensive chemotherapy. Results from the study show a complete response (CR) rate of 61% and a CR + CR with partial hematologic recovery (CRh) rate of 70%. Responses were durable, and the median duration of CR (95% CI 9.3 months, NE) as well as CR+CRh (95% CI 12.2 months, NE) had not been reached. In patients with CR, 10 of 14 (71%) had IDH1 mutation clearance in bone marrow mononuclear cells measured by BEAMing digital PCR (limit of detection 0.02-0.04%). Additionally, the majority of CR patients with IDH1 mutation clearance demonstrated measurable residual disease (MRD) negativity by flow cytometry or next-generation sequencing. Five patients were shown to have RTK pathway mutations (*KRAS*, *NRAS*, *PTPN11*), and three of these patients achieved CR/CRh with TIBSOVO® and azacitidine combination therapy.



Mechanisms of Resistance to Single Agent IDH1 Inhibitors in Relapsed/Refractory AML

Comprehensive genomic profiling was conducted using patient samples from the Phase 1 study of TIBSOVO® in IDH1 mutant relapsed/refractory AML to characterize the molecular predictors of response and mechanisms of relapse to TIBSOVO monotherapy. The analysis found that multiple mechanisms contribute to relapse or progression. RTK pathway mutations NRAS and PTPN11 at baseline were associated with a lower likelihood of clinical response to TIBSOVO® monotherapy in relapsed/refractory AML, while patients with JAK2 mutations were more likely to achieve a response. Acquired resistance is mediated by diverse mechanisms, and mutations are acquired in multiple pathways, most frequently in RTK and 2-HG–restoring pathways (IDH2 and second-site IDH1 mutations).

Single cell mutation profiling was conducted to explore the evolution of mutant IDH2 clones under the selective pressure of TIBSOVO® monotherapy in a subset of patients. The analysis revealed multiple evolutionary mechanisms by which mutant IDH2 contributes to relapse and reinforced the key role of 2-HG production in mutant IDH AML.

Taken together, these results inform the design of combination or sequential treatment strategies with TIBSOVO® in IDH1 mutant AML and reinforce the importance of genomic testing for both IDH1 and IDH2 mutations at relapse.

TIBSOVO® is not approved in any country for the treatment of patients with newly diagnosed AML in combination with azacitidine.

Investor Event and Webcast Information

AgiOS will host an investor event today at 8:00 p.m. ET in Orlando, Fla. to review the IDH and PKR data presented at ASH. The event will be webcast live and 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 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-HT₃ 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 (³20%) 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 ³3 adverse reactions (³5%) were fatigue (14%), differentiation syndrome (11%), electrocardiogram QT prolonged (11%), diarrhea (7%), nausea (7%), and leukocytosis (7%). Serious adverse reactions (³5%) 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 ³3 adverse reactions (³5%) were differentiation syndrome (13%), electrocardiogram QT prolonged (10%), dyspnea (9%), leukocytosis (8%), and tumor lysis syndrome (6%). Serious adverse reactions (³5%) 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 Myeloid 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. AML patients are typically older or have comorbidities that preclude the use of intensive chemotherapy. These patients typically have a worse prognosis and poor outcomes. The majority of patients with AML eventually relapse. The five-year survival rate is approximately 28%. 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. IDH1 mutations have been associated with negative prognosis in AML.

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 for the further clinical development of 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.

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Investor & Media Contact:

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



AgiOS Presents Updated Data for Mitapivat from Extension Phase of the DRIVE PK Study in Patients with Pyruvate Kinase Deficiency

– Robust Hemoglobin Increases Maintained in 18 Patients in the Extension Phase of the Study with Median Treatment Duration of Three Years –

– Cumulative Safety Profile (Core Period plus Extension Phase) Continues to Support Long-term Twice Daily Dosing of Mitapivat –

– Data from the Natural History Study Demonstrate that PK Deficiency Patients, Regardless of Transfusion Status, Have Higher Rates of Select Comorbidities and Complications –

– Company to Host Investor Event and Webcast Today at 8:00 p.m. ET –

ORLANDO, Fla., December 9, 2019 — Agios Pharmaceuticals, Inc. (NASDAQ: AGIO), a leader in the field of cellular metabolism to treat cancer and rare genetic diseases, today reported new data from the extension phase of the DRIVE PK Phase 2 study of mitapivat (AG-348) in adults with pyruvate kinase (PK) deficiency at the 2019 American Society of Hematology (ASH) Annual Meeting. Mitapivat is an investigational, first-in-class, oral, small molecule allosteric activator of wild-type and a variety of mutated pyruvate kinase-R (PKR) enzymes that directly targets the underlying metabolic defect in PK deficiency, a rare, potentially debilitating, hemolytic anemia. In addition, data was shared from the Agios-sponsored Natural History Study of PK deficiency that detailed the comorbidities and complications associated with the disease and the impact of transfusion history.

“DRIVE PK was the first clinical trial aimed at addressing the metabolic defect in PK deficiency, and demonstrated that clinically meaningful and robust increases in hemoglobin can be achieved with an oral PKR activator,” said Eduard J. van Beers, M.D., Ph.D., University Medical Center Utrecht and an investigator in the study. “These new data demonstrate that chronic treatment with mitapivat is well tolerated and can lead to a reduction in hemolysis as demonstrated by sustained improvements in hemoglobin and other markers for more than three years.”

“As a rare hemolytic anemia, PK deficiency has historically been under diagnosed and not well characterized. The new and emerging data from the Natural History Study demonstrate that adults with PK deficiency are at increased risk of comorbidities and complications resulting from chronic hemolysis and iron overload, regardless of transfusion history,” said Chris Bowden, M.D., chief medical officer at Agios. “We are committed to advancing the first potential disease-modifying therapy for these patients and are on track to complete enrollment in both of our pivotal Phase 3 trials of mitapivat in PK deficiency by the end of the year. In addition, we are exploring the utility of wildtype PKR activation in other hemolytic anemias, such as thalassemia and sickle cell disease.”

Data from the Extension Phase of the DRIVE PK Study of Mitapivat

DRIVE PK is an ongoing global, open-label, Phase 2, safety and efficacy study evaluating mitapivat in adults with PK deficiency who do not receive regular transfusions. Patients were randomly assigned to receive either 50 mg or 300 mg of mitapivat twice daily for a 24-week core period and eligible patients could continue treatment in an ongoing extension phase. In the extension phase, patients treated with mitapivat doses >25 mg twice daily in the core period undergo a dose taper and continue on a dose that maintained their Hb level at no lower than 1.0 g/dL below their pre-taper level. As of the March 27, 2019 data cutoff, 18 of the 36 patients remain in the extension phase with a median treatment duration of 35.6 months (range 28.7-41.9).

For the 18 patients in the extension phase, improvements in hemoglobin and other markers of hemolysis including reticulocytes, indirect bilirubin and haptoglobin achieved during the core period were sustained during the extension period up to 42 months, as of the data cutoff.

Adverse events (AEs) for patients who continued in the study (n=18) were comparable in the core and extension periods. In the extension, the most common AEs were headache (39%), insomnia (28%), fatigue (28%) and nasopharyngitis (28%). No new safety signals were identified in the extension period.

Data from the Natural History Study Evaluating Comorbidities and Complications in Adults with PK Deficiency

The ongoing PK Deficiency Natural History Study (NHS) evaluated 254 patients (131 adults) at 31 centers in six countries who enrolled from June 2014 through April 2017². Data reported at ASH compare baseline rates of comorbidities and complications in adult patients from the NHS with the general population (U.S.-based IBM MarketScan® claims database), and assess the impact of transfusion frequency on the prevalence of these comorbidities and complications. Individuals from the general population were matched 10:1 to patients with PK deficiency based on age, gender and year of enrollment in the NHS. The analysis showed that patients with PK deficiency, regardless of current or prior transfusion status, have higher rates of the following comorbidities and complications than observed in the general population.

- Adults with PK deficiency had higher lifetime rates of pulmonary hypertension (4.6% compared to 0.3% in the general population), osteoporosis (15.6% compared to 0%) and liver cirrhosis (5.6% compared to 0.4%).
- Adults with PK deficiency had higher rates of splenectomy (4.9% compared to 0.2% in the general population), cholecystectomy (13.1% compared to 3.6%) and gallstones (16.9% compared to 4.3%) over the preceding eight years.
- Rates of current prophylactic antibiotic and anticoagulant use were significantly higher among patients with PK deficiency.
- It was observed that for some conditions, a gradient is seen across PK deficiency transfusion cohorts, with the highest rates observed in patients who receive regular transfusions (³ 6 per year). However, even patients with PK deficiency who have never received blood transfusion are at increased risk of complications of the disease and its treatment.

Mitapivat Clinical Development

Agios has two ongoing global, pivotal trials in adults with PK deficiency that are on track to complete enrollment by year-end 2019. Learn more at activatetrials.com.

- **ACTIVATE:** A placebo-controlled trial with a 1:1 randomization, expected to enroll approximately 80 patients who do not receive regular transfusions. The primary endpoint of the trial is the proportion of patients who achieve a sustained hemoglobin increase of ≥ 1.5 g/dL.
- **ACTIVATE-T:** A single arm trial of up to 40 regularly transfused patients with a primary endpoint of reduction in transfusion burden over six months compared to individual historical transfusion burden over prior 12 months.

In addition, Agios is conducting a Phase 2 study evaluating the efficacy, safety, pharmacokinetics and pharmacodynamics of treatment with mitapivat in adults with non-transfusion-dependent β - and α -thalassemia (NTDT). The primary endpoint is hemoglobin response, and approximately 17 participants with NTDT will be enrolled. Mitapivat is also being studied in sickle cell disease under a Cooperative Research and Development Agreement (CRADA) with the U.S. National Institutes of Health.

Mitapivat is not approved for use by any regulatory authority.

About Pyruvate Kinase Deficiency and Genetic Background

Pyruvate kinase (PK) deficiency is a rare, inherited disease that presents as chronic hemolytic anemia, which is the accelerated destruction of red blood cells. The inherited mutations in PKR genes cause a deficit in cellular energy within the red blood cell, as evidenced by lower PK enzyme activity, a decline in adenosine triphosphate levels and a build-up of upstream metabolites, including 2,3-DPG (2,3-diphosphoglycerate).

PK deficiency is associated with chronic hemolysis leading to complications including gallstones, pulmonary hypertension, extramedullary hematopoiesis, cirrhosis, osteoporosis, and iron overload and its sequelae, which occur regardless of transfusion burden. Current management strategies for PK deficiency, including blood transfusion and splenectomy, are associated with both short- and long-term risks.

More than 300 different mutations have been identified to date. The mutations observed in PK deficiency patients are classified in two main categories. A missense mutation causes a single amino acid change in the protein, generally resulting in some functional protein. A non-missense mutation is any mutation other than a missense mutation, generally resulting in little functional protein. It is estimated that 58 percent of patients with PK deficiency have two missense mutations, 27 percent have one missense and one non-missense mutation, and 15 percent have two non-missense mutations¹. For more information about PK deficiency, including the signs and symptoms, how to test for it (including a free testing option), and how it is currently managed, visit knowpkdeficiency.com.



The Peak Registry, a global, longitudinal study of children and adults with PK deficiency, has been established to better understand the full spectrum of disease variability, including impact on quality of life. The Registry is open and recruiting patients. Learn more at www.peakregistry.com.

Investor Event and Webcast Information

AgiOS will host an investor event today at 8:00 p.m. ET in Orlando, Fla. to review the IDH and PKR data presented at ASH. The event will be webcast live and 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 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 mitapivat; Agios’ plans for the further clinical development of mitapivat; 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.

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¹ Bianchi P et al. poster, 2017 ASH Annual Meeting

² Grace RF et al. Blood 2018;131:2183-92

Investor & Media Contact:

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