AGIOS PHARMACEUTICALS INC
Form 424B5
December 09, 2014
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Filed Pursuant to Rule 424(b)(5)
File No. 333-200822

The information in this preliminary prospectus supplement is not complete and may be changed. The registration statement filed with the Securities and Exchange Commission relating to these securities is effective. This preliminary prospectus supplement is not an offer to sell these securities and we are not soliciting offers to buy these securities in any state or jurisdiction where the offer or sale is not permitted.

Subject to completion, dated December 9, 2014

Preliminary prospectus supplement

(To Prospectus dated December 9, 2014)

$175,000,000

Common Stock

Agios Pharmaceuticals, Inc. is offering $175,000,000 of shares of its common stock.

Our common stock is listed on The NASDAQ Global Select Market under the symbol AGIO. The last reported sale price of our common stock on The NASDAQ Global Select Market on December 8, 2014 was $107.30 per share.

We are an emerging growth company as that term is used in the Jumpstart Our Business Startups Act of 2012, and as such, have elected to comply with certain reduced public reporting requirements.

Investing in our common stock involves risks. See Risk factors beginning on page S-10 of this prospectus supplement, as well as those contained in the accompanying prospectus and the documents incorporated herein and therein.

	Per share	Total
Public offering price	$	$
Underwriting discounts(1)	$	$
Proceeds, before expenses, to Agios Pharmaceuticals, Inc.	$	$

(1) We have agreed to reimburse the underwriters for certain FINRA-related expenses. See Underwriting beginning on page S-21 of this prospectus supplement.

We have granted the underwriters the right to purchase up to an additional $26,250,000 of shares of our common stock at the public offering price less the underwriting discounts and commissions. The underwriters can exercise this right at any time within 30 days after the date of this prospectus supplement.

Celgene Corporation, or Celgene, an affiliate of two of our existing stockholders and our cancer metabolism strategic alliance partner, has indicated an interest in purchasing an aggregate of up to approximately $26,250,000 of shares of our common stock in this offering at the public offering price. However, because indications of interest are not binding agreements or commitments to purchase, Celgene may determine to purchase fewer shares than they have indicated an interest in purchasing or not to purchase any shares in this offering. In addition, the underwriters could determine to sell fewer shares to Celgene than Celgene indicated an interest in purchasing or not to sell any shares to Celgene. The underwriters will receive the same underwriting discount on any shares purchased by Celgene as they will on any other shares sold to the public in this offering. Any shares sold to Celgene will be subject to the lock-up agreements described under Underwriting.

Neither the Securities and Exchange Commission nor any other regulatory body has approved or disapproved of these securities or passed upon the accuracy or adequacy of this prospectus supplement or the accompanying prospectus. Any representation to the contrary is a criminal offense.

The underwriters expect to deliver the shares of common stock to investors on or about December , 2014.

J.P. Morgan **Goldman, Sachs & Co.**

Cowen and Company **Leerink Partners**

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PROSPECTUS SUPPLEMENT

PROSPECTUS

Neither we nor the underwriters have authorized anyone to provide you with information other than that contained in this prospectus supplement and the accompanying prospectus or in any free writing prospectus prepared by or on behalf of us or to which we have referred you. We and the underwriters take

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no responsibility for, and can provide no assurance as to the reliability of, any other information that others may give to you. We are offering to sell, and seeking offers to buy, shares of our common stock only in jurisdictions where offers and sales are permitted. The information contained or incorporated by reference in this prospectus supplement and the accompanying prospectus is accurate only as of its date, regardless of the time of delivery of this prospectus supplement and the accompanying prospectus or any sale of our common stock. Our business, financial condition, results of operations and prospects may have changed since that date.

No action is being taken in any jurisdiction outside the United States to permit a public offering of our common stock or possession or distribution of this prospectus supplement and the accompanying prospectus in that jurisdiction. Persons who come into possession of this prospectus supplement and the accompanying prospectus in jurisdictions outside the United States are required to inform themselves about and to observe any restrictions as to this offering and the distribution of this prospectus supplement and the accompanying prospectus applicable to that jurisdiction.

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About this prospectus supplement

This document is in two parts. The first part is this prospectus supplement, which describes the specific terms of this common stock offering and also adds to and updates information contained in the accompanying prospectus and the documents incorporated by reference herein. The second part, the accompanying prospectus, provides more general information. Generally, when we refer to this prospectus, we are referring to both parts of this document combined. To the extent there is a conflict between the information contained in this prospectus supplement and the information contained in the accompanying prospectus or any document incorporated by reference therein filed prior to the date of this prospectus supplement, you should rely on the information in this prospectus supplement; provided that if any statement in one of these documents is inconsistent with a statement in another document having a later date for example, a document incorporated by reference in the accompanying prospectus the statement in the document having the later date modifies or supersedes the earlier statement.

We further note that the representations, warranties and covenants made by us in any agreement that is filed as an exhibit to any document that is incorporated by reference herein were made solely for the benefit of the parties to such agreement, including, in some cases, for the purpose of allocating risk among the parties to such agreements, and should not be deemed to be a representation, warranty or covenant to you. Moreover, such representations, warranties or covenants were accurate only as of the date when made. Accordingly, such representations, warranties and covenants should not be relied on as accurately representing the current state of our affairs.

You should rely only on the information contained in this prospectus supplement or the accompanying prospectus, or incorporated by reference herein. We have not authorized, and the underwriters have not authorized, anyone to provide you with information that is different. The information contained in this prospectus supplement or the accompanying prospectus, or incorporated by reference herein is accurate only as of the respective dates thereof, regardless of the time of delivery of this prospectus supplement and the accompanying prospectus or of any sale of our common stock. It is important for you to read and consider all information contained in this prospectus supplement and the accompanying prospectus, including the documents incorporated by reference herein, in making your investment decision. You should also read and consider the information in the documents to which we have referred you in the sections entitled Where you can find more information and Incorporation of documents by reference in this prospectus supplement and in the accompanying prospectus.

We are offering to sell, and seeking offers to buy, shares of our common stock only in jurisdictions where offers and sales are permitted. The distribution of this prospectus supplement and the accompanying prospectus and the offering of the common stock in certain jurisdictions may be restricted by law. Persons outside the United States who come into possession of this prospectus supplement and the accompanying prospectus must inform themselves about, and observe any restrictions relating to, the offering of the common stock and the distribution of this prospectus supplement and the accompanying prospectus outside the United States. This prospectus supplement and the accompanying prospectus do not constitute, and may not be used in connection with, an offer to sell, or a solicitation of an offer to buy, any securities offered by this prospectus supplement and the accompanying prospectus by any person in any jurisdiction in which it is unlawful for such person to make such an offer or solicitation.

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Prospectus supplement summary

This summary does not contain all of the information that you should consider before investing in our common stock. You should read this entire prospectus supplement and the accompanying prospectus carefully, including the financial statements and other information incorporated by reference in this prospectus supplement and the accompanying prospectus, before making an investment decision. In addition, please read the Risk factors section of this prospectus supplement beginning on page S-10 and the risk factors contained in our Annual Report on Form 10-K for the year ended December 31, 2013 and our Quarterly Reports on Form 10-Q for the quarterly periods ended March 31, 2014, June 30, 2014 and September 30, 2014.

Overview

We are a biopharmaceutical company committed to applying our scientific leadership in the field of cellular metabolism to transform the lives of patients with cancer and rare genetic disorders of metabolism, which are a subset of orphan genetic metabolic diseases. Metabolism is a complex biological process involving the uptake and assimilation of nutrients in cells to produce energy and facilitate many of the processes required for cellular division and growth. We focus our efforts on using cellular metabolism, an unexploited area of biological research with disruptive potential, as a platform for developing potentially transformative small molecule medicines. Our most advanced cancer product candidates, AG-221 and AG-120, target mutant isocitrate dehydrogenase 2 and 1, or IDH2 and IDH1, respectively. These mutations have been found in a wide range of hematological malignancies and solid tumors. The lead candidate in our rare genetic disorders program, AG-348, targets pyruvate kinase for the treatment of pyruvate kinase deficiency. Pyruvate kinase deficiency is a rare disorder which often results in severe hemolytic anemia due to inherited mutations in the pyruvate kinase enzyme within red blood cells.

Targeting isocitrate dehydrogenase (IDH) for the treatment of cancer

The isocitrate dehydrogenase, or IDH, protein is a critical enzyme in the citric acid cycle, also known as the tricarboxylic acid, or Krebs, cycle. The Krebs cycle is centrally important to many biochemical pathways, and is one of the earliest established components of cellular metabolism. The Krebs cycle converts an essential cellular metabolite called isocitrate into another metabolite, alpha-ketoglutarate (μ-ketoglutarate), both of which are critically important for cellular function and the creation of energy. In humans, there are three forms of the IDH enzyme, IDH1, IDH2, and IDH3, but only IDH1 and IDH2 appear to be mutated in cancers. IDH1 and IDH2 catalyze the same reaction but in different cellular compartments: IDH1 is found in the cytoplasm of the cell and IDH2 in the mitochondria. Tumor cells are generally observed to carry either an IDH1 or IDH2 mutation, but not both.

Using our proprietary metabolic platform, we and our collaborators examined the mutated pathway and discovered that the mutated IDH enzymes had adopted a novel gain of function activity that allows only the mutated IDH enzyme to produce large amounts of a metabolite called 2 hydroxygluturate, or 2HG. We believe that the excessive levels of the metabolite 2HG produced by the tumor fuel cancer growth and survival via multiple cellular changes that lead to a block in cell maturation, or differentiation. We believe that inhibition of these mutated proteins will lead to clinical benefit for the subset of cancer patients whose tumors carry these mutations. We have identified selective development candidates that target and inhibit the mutated forms of IDH1 and IDH2. To date our preclinical *in vitro* and *in vivo* efficacy data and early clinical data of AG-221 and AG-120, our lead inhibitors of mutant IDH2 and IDH1, respectively demonstrate a mechanism of response that is consistent with preclinical studies, including substantial reduction of plasma 2HG levels, as well as evidence of cellular differentiation and normalization of cell counts in the bone marrow and blood. This differentiation effect is distinct from that seen with traditional chemotherapeutics commonly used to treat AML.

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AG-221: lead IDH2 program

AG-221 is an orally available, selective, potent inhibitor of the mutated IDH2 protein, making it a highly targeted therapeutic candidate for the treatment of patients with cancers that harbor IDH2 mutations, including those with AML. On June 16, 2014, the U.S. Food and Drug Administration (FDA) granted us orphan drug designation for AG-221 for treatment of patients with AML. On August 13, 2014, we announced that the U.S. FDA granted Fast Track designation to AG-221 for treatment of patients with AML that harbor an IDH2 mutation. We have been evaluating AG-221 in several phase 1b dose escalation trials evaluating both hematological and solid tumor cancers with IDH2 mutations. To date, all clinical data reported by us highlights that the mechanism of response is consistent with preclinical studies, including substantial reduction of plasma 2HG levels, as well as evidence of cellular differentiation and normalization of cell counts in the bone marrow and blood. This differentiation effect is distinct from that seen with traditional chemotherapeutics commonly used to treat AML. We intend to begin a global registration program for AG-221 in 2015 for IDH2-mutant positive hematologic malignancies.

In September 2013, we initiated our first phase 1 study for AG-221 in patients with advanced hematologic malignancies with an IDH2 mutation and in April 2014, we reported initial findings from the first two cohorts of patients treated with AG-221 at the American Association for Cancer Research (AACR) Annual Meeting 2014 in San Diego, California. As of March 20, 2014, a total of 22 patients with relapsed or refractory AML, which means that their disease had progressed after, or was refractory to, between one and four prior therapies, were treated with either 30 mg or 50 mg of AG-221 orally twice daily. At the time of data submission to the AACR Annual Meeting 2014, seven of 10 patients were evaluable for efficacy as they had completed the first 28 day cycle of therapy. Within the first dose cohort at the 30 mg twice-daily dose, three patients did not complete a full 28-day cycle of therapy and died due to complications of disease-related infection common in patients with relapsed or refractory AML. Of the seven evaluable patients, six patients had investigator-assessed objective responses, including three patients who achieved complete remission (CR), two patients who achieved complete remission with incomplete platelet recovery (CRp) and one patient with a partial response (PR). A complete remission is determined by using well-established criteria, which requires no evidence of leukemia in the bone marrow and blood accompanied by full restoration of all blood counts to normal ranges. A complete remission with incomplete platelet recovery means all the criteria for CR are met except that platelet counts are outside of the normal range. Platelets are one of the three major types of blood cells. A partial response means all the criteria for CR are met except that the immature defective blood cells, or leukemia, in the bone marrow are in the 5% to 25% range and are decreased by at least 50% over pretreatment. One patient with a CR elected to be removed from the study to undergo a bone marrow transplant; all other patients with objective responses continued to receive the drug. AG-221 demonstrated favorable drug exposure and pharmacokinetics with substantial reductions in plasma levels of 2HG. Preliminary analysis of pharmacokinetics at the 30 mg and 50 mg dose levels demonstrated excellent oral AG-221 exposure and a mean plasma half-life of greater than 40 hours. Given the long half-life observed, we announced that we intended to expand the trial to include once daily dosing cohorts, beginning with 100 mg.

On June 14, 2014, we presented additional clinical data from the phase 1 study of AG-221 at the 19th Congress of the European Hematology Association in Milan, Italy. These data built upon previously presented data on AG-221 s clinical activity, safety profile and unique mechanism of action and included 35 patients with IDH2-mutant positive advanced hematologic malignancies. The new data showed investigator-assessed objective responses in 14 out of 25 evaluable patients on AG-221 and an additional five patients with stable disease. In six patients who achieved a complete remission, evidence of durability was observed, ranging from one to four months in duration. AG-221 continued to show favorable drug exposure and pharmacokinetics at all doses tested with substantial reductions in plasma levels of 2HG. There were no discontinuations of AG-221 due to adverse events. In June 2014, Celgene exercised its option to an exclusive global license for development and commercialization of AG-221.

In October 2014, we initiated four expansion cohorts in our ongoing phase 1 study of AG-221 in patients with IDH2-mutant hematologic malignancies to assess the safety and tolerability of AG-221 at 100 mg once daily oral

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dose in approximately 100 patients with IDH2-mutant hematologic malignancies, including AML. The expansion cohorts are evaluating relapsed or refractory AML patients 60 years of age and older, relapsed or refractory AML patients under age 60, untreated AML patients who decline standard of care chemotherapy and patients with other IDH2-mutant positive advanced hematologic malignancies. In October 2014, we announced the initiation of a phase 1/2 multicenter study of AG-221 in patients with advanced solid tumors, including gliomas, as well as angioimmunoblastic T-cell lymphoma (AITL), in each case, that carry an IDH2 mutation. This phase 1/2 multicenter, open-label, dose-escalation clinical trial of AG-221, which is being conducted by Agios, is designed to assess the safety, clinical activity, and tolerability of AG-221 among patients who have an IDH2-mutant advanced solid tumor. The phase 1/2 trial is expected to include a dose expansion phase where three cohorts of patients with glioma, AITL and other solid tumors that are IDH2-mutant positive will receive AG-221 to further evaluate safety, tolerability and clinical activity in advanced solid tumors.

On December 7, 2014, we reported additional clinical data from the phase 1 study of AG-221, which included 73 enrolled patients with IDH2-mutant positive advanced hematologic malignancies. The data were presented at the 56th Annual Meeting of the American Society of Hematology (ASH) Annual Meeting and Exposition in San Francisco, California. The new data showed investigator-assessed objective responses in 25 out of 45 evaluable patients on AG-221. Of the 25 patients who achieved an objective response, there were six complete remissions, four complete remissions with incomplete platelet recovery (CRp), four marrow complete remissions (mCR), one complete remission with incomplete hematologic recovery (CRi) and ten partial remissions (PR). In the six patients who achieved a complete remission, evidence of durability was observed as long as eight months in duration and there have been no relapses in these patients. An estimated 90 percent of responses are three months or longer, with four responders on AG-221 beyond six months of treatment. Ten patients with stable disease remain on AG-221, with several patients on study as long as six months and ongoing. Five patients were removed from the study per the protocol following decision to undergo a potentially curative bone marrow transplant. AG-221 continued to show favorable drug exposure and pharmacokinetics at all doses tested with substantial reductions in plasma levels of 2HG. There were no discontinuations of AG-221 due to adverse events. The maximum tolerated dose had not yet been reached and the dose escalation continued. In addition, on December 7, 2014, we announced our intention to initiate a global registration program for AG-221 in 2015 as well as to initiate combination trials of AG-221 for the treatment of frontline hematological malignancies.

AG-120: lead IDH1 program

AG-120 is an orally available, selective, potent inhibitor of the mutated IDH1 protein, making it a highly targeted therapeutic candidate for the treatment of patients with cancers that harbor IDH1 mutations. Mutations in IDH1 have been identified in difficult to treat liquid and solid tumor cancers, including AML, chondrosarcoma and cholangiocarcinoma where both the treatment options and prognosis for patients are poor. In March 2014, we initiated two phase 1 studies for AG-120, one in patients with advanced hematologic malignancies and the second in patients with advanced solid tumors; both trials are only enrolling patients that carry an IDH1 mutation.

In November 2014, we reported initial clinical data from the ongoing AG-120 phase 1 study in advanced hematologic malignancies at the 26th EORTC-NCI-AACR Symposium on Molecular Targets and Cancer Therapeutics. As of October 17, 2014, a total of 17 patients with a documented IDH1 mutation whose cancer relapsed or were refractory, meaning they failed to respond to at least one prior treatment regimen were treated with AG-120. At the time of the data cut, 14 patients with relapsed and/or refractory AML were evaluable; three patients recently initiated therapy and were not evaluable. The initial data showed investigator-assessed objective responses in seven out of 14 evaluable patients, including four complete remissions, with responses observed across the four dose levels tested. In the four patients who achieved a complete remission, durability ranging from 15 days to five months was observed. All responding patients remain on AG-120. One patient with stable disease remains on AG-120. AG-120 was well

tolerated, with the majority of adverse events reported as mild to

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moderate. The maximum tolerated dose has not yet been reached. One patient had a dose limiting toxicity of asymptomatic grade 3 QT prolongation at the highest dose tested to date, which improved to grade 1 after AG-120 dose reduction according to treatment protocol. This patient is in complete remission and remains on AG-120. AG-120 showed favorable drug exposure and pharmacokinetics at all doses tested and also substantially reduced plasma levels of the oncometabolite 2-hydroxyglutarate (2HG), which is produced by the mutant IDH1 protein, to the level observed in healthy volunteers. The mechanism of response is consistent with differentiation, as evidenced by the maturation of the leukemic cells into infection fighting white blood cells, or neutrophils. Based on these findings, we plan to initiate multiple expansion cohorts in the first half of 2015. We intend to initiate a global registration program for AG-120 in IDH1-mutant positive hematologic malignancies by early 2016.

AG-348: Pyruvate Kinase (PK) Deficiency Program

PK deficiency, a rare genetic disorder, manifests by mild to severe forms of anemia caused by the excessive premature destruction of red blood cells. The inherited mutations in PKR enzymes cause a deficit in cellular energy within the red blood cell, as evidenced by a build-up of the metabolite 2,3-DPG (2,3-diphosphoglycerate) and a decline in the energy metabolite ATP (adenosine triphosphate).

We are developing AG-348 as an orally available small molecule and a potent activator of the pyruvate kinase, or PKR, enzyme, an isoform of PK that when mutated leads to PK deficiency. Agios scientists have previously reported that AG-348 is a potent activator of the wild-type and mutated PKR enzymes, resulting in restoration of ATP levels and a decrease in 2,3-DPG levels in blood sampled from patients with PK deficiency. The wild-type PKR activity of AG-348 allows the study of enzyme activation in healthy volunteers, providing an opportunity to understand the safety, dosing and pharmacodynamic activity of AG-348 prior to entering a proof-of-concept study in patients.

In April 2014, we initiated a single ascending dose, or SAD, escalation phase 1 clinical trial for AG-348 in healthy volunteers and in June 2014, we initiated a multiple ascending dose, or MAD, escalation phase 1 clinical trial for healthy volunteers. The SAD trial is complete and has met its primary endpoint. The MAD trial, while still ongoing, has also met its primary endpoint. The primary endpoint is defined in the protocol to identify a safe and pharmacodynamically active dose and schedule for AG-348 to be used in subsequent clinical studies in patients with pyruvate kinase deficiency.

On December 8, 2014, during a poster session at ASH 2014, we reported first clinical data from the phase 1 SAD and MAD clinical trials of AG-348 in healthy volunteers. These results provided early proof-of-mechanism for AG-348 as a novel, first-in-class, oral activator of both wild-type (normal) and mutated PKR enzymes. In these phase 1 studies, dosing of AG-348 over 14-days in healthy volunteers resulted in a dose-dependent increase in the PKR pathway as evidenced by a substantial increase in ATP and decrease in 2,3-DPG levels, which are key biomarkers of PKR activity and primary indicators of PK deficiency. These data support the hypothesis that AG-348 treatment may similarly enhance PKR activity in patients with PK deficiency and thus correct the underlying defect of the disease. Results presented are from 64 healthy volunteers who received either AG-348 or placebo, which includes 48 people from the completed SAD study and 16 people in the first two cohorts of the ongoing MAD study that recently completed enrollment. Complete safety results are being reported from the SAD phase 1 study and showed that AG-348 was well tolerated. Although the MAD study remains blinded, no serious adverse events have been reported in the first two analyzed cohorts. AG-348 also showed a favorable pharmacokinetic profile with rapid absorption, low variability and dose-proportional increase in exposure following both single and multiple doses. The observed dose-dependent changes in 2,3-DPG and ATP blood levels seen are consistent with a substantial increase in PKR enzymatic activity. We expect to provide final results from the MAD study in 2015 and to initiate a phase 2 study of AG-348 in patients with PK deficiency in the first half of 2015. A natural history study of PK deficiency is also ongoing and patient enrollment is on track.

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Collaboration with Celgene

In April 2010, we entered into a discovery and development collaboration and license agreement with Celgene, focused on targeting cancer metabolism. The goal of the collaboration is to discover, develop and commercialize disease-altering therapies in oncology arising out of our cancer metabolism research platform that have achieved development candidate status. On December 8, 2014, Celgene elected to extend the period of its exclusivity for an additional year to April 2016. The extension marks the final year for the discovery phase and Celgene will maintain its exclusive option to drug candidates that emerge from our cancer metabolism research platform through April 2016. We will receive a $20 million payment as a result of the extension.

Following this extension, the discovery portion of the collaboration will expire on April 14, 2016. Under the terms of the original agreement, we lead research, preclinical and early development efforts through phase 1, while Celgene receives an option to obtain exclusive rights either upon IND acceptance or at the end of phase 1, to further development and commercialize medicines emerging from our cancer metabolism research. Celgene would lead and fund global development and commercialization of some of these drugs, and we would retain development and commercialization rights for certain drugs in the U.S. On all programs, we are eligible to receive up to $120 million in milestone-based payments as well as royalties on any sales.

AG-221 and AG-120 are two drug candidates that have been nominated to date during the discovery phase of the collaboration. In June 2014, Celgene exercised its exclusive option to license AG-221 and gained worldwide development and commercialization rights for AG-221. We continue to conduct early clinical development activities within the AG-221 development program. We are also collaborating with Celgene on the development of AG-120. We retain U.S. development and commercialization rights for AG-120, and Celgene has an exclusive option to the ex-U.S. rights.

Our strategy

We aim to build a multi-product company, based on our expertise in cellular metabolism, that discovers, develops and commercializes first- and best-in-class medicines to treat cancer and rare genetic disorders. Key elements of our strategy include:

- Aggressively pursuing the development of novel medicines to transform the lives of patients with cancer and rare genetic disorders.

- Maintaining our competitive advantage and singular focus in the field of cellular metabolism.

- Continuing to build a product engine for cancer and rare genetic disorders to generate novel and important medicines.

- Building a preeminent independent biopharmaceutical company by engaging in discovery, development and commercialization of our medicines.

Maintaining a commitment to precision medicine in drug development.

Our guiding principles

We aim to build a long-term company with a disciplined focus on developing medicines that transform the lives of patients with cancer and rare genetic disorders. We maintain a culture of high integrity that embraces the following guiding principles, which we believe will provide long-term benefits for all our stakeholders:

Follow the science and do what is right for patients.

Maintain a culture of incisive decision-making driven by deep scientific interrogation and respectful irreverence.

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Foster collaborative spirit that includes all employees regardless of function or level.

Leverage deep strategic relationships with our academic and commercial partners to improve the quality of our discovery and development efforts.

Risks associated with our business

Our business is subject to a number of risks of which you should be aware before making an investment decision. These risks are discussed more fully in the Risk factors section of this prospectus supplement immediately following this prospectus supplement summary. These risks include the following:

We have incurred significant losses since inception. We expect to incur losses for the foreseeable future and may never achieve or maintain profitability. As of September 30, 2014, we had an accumulated deficit of $140.3 million.

We will need substantial additional funding. If we are unable to raise capital when needed, we would be forced to delay, reduce or eliminate our product development programs or commercialization efforts.

Our short operating history may make it difficult for you to evaluate the success of our business to date and to assess our future viability.

Our approach to the discovery and development of product candidates that target cellular metabolism and is unproven, and we do not know whether we will be able to develop any medicines of commercial value.

If clinical trials of our product candidates fail to demonstrate safety and efficacy to the satisfaction of regulatory authorities or do not otherwise produce positive results, we may incur additional costs or experience delays in completing, or ultimately be unable to complete, the development and commercialization of our product candidates.

We depend on our collaboration with Celgene and may depend on collaborations with additional third parties for the development and commercialization of our product candidates. If those collaborations are not successful, we may not be able to capitalize on the market potential of these product candidates.

If we are unable to obtain and maintain patent or trade secret protection for our medicines and technology, or if the scope of the patent protection obtained is not sufficiently broad, our competitors could develop and commercialize medicines and technology similar or identical to ours, and our ability to successfully commercialize our medicines and technology may be adversely affected. We currently have patent protection for one of our lead product candidates in the United States, and do not own or license any issued patents for our other lead product candidates in major markets such as the United States and Europe.

If we are not able to obtain, or if there are delays in obtaining, required regulatory approvals, we will not be able to commercialize, or will be delayed in commercializing, our product candidates, and our ability to generate revenue will be materially impaired.

Our corporate information

We were incorporated under the laws of the State of Delaware in August 2007. Our executive offices are located at 38 Sidney Street, 2nd Floor, Cambridge, Massachusetts 02139, and our telephone number is (617) 649-8600. Our website address is www.agios.com. The information contained in, or accessible through, our website does not constitute part of this prospectus supplement. We have included our website address in this prospectus supplement solely as an inactive textual reference.

As used in this prospectus supplement, unless the context otherwise requires, references to Agios, we, us, our and similar references refer to Agios Pharmaceuticals, Inc. and, where appropriate, our consolidated subsidiary. The trademarks, trade names and service marks appearing in this prospectus supplement are the property of their respective owners.

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The offering

Common stock offered	shares
Common stock to be outstanding after this offering	shares
Option to purchase additional shares	The underwriters have an option for a period of 30 days to purchase up to $26,250,000 of additional shares of our common stock.
Use of proceeds	We intend to use the net proceeds from this offering as follows: approximately $70-100 million to fund the costs of phase 1 clinical development of AG-120, and initiating a global registration program; approximately $20-30 million to fund the phase 1/2 clinical development activities for AG-348; approximately $50-70 million to fund research and development to advance our pipeline of earlier-stage cancer metabolism and rare genetic disorders programs; and the remainder for working capital and other general corporate purposes. See Use of proceeds for more information.
Risk factors	See Risk factors beginning on page S-10 and the other information included in, or incorporated by reference into, this prospectus supplement and the accompanying prospectus for a discussion of certain factors you should carefully consider before deciding to invest in shares of our common stock.
The NASDAQ Global Select Market symbol	AGIO

The number of shares of our common stock to be outstanding after this offering is based on 34,642,539 shares of our common stock outstanding as of September 30, 2014.

The number of shares of our common stock to be outstanding after this offering excludes:

- 3,816,834 shares of common stock issuable upon exercise of stock options outstanding as of September 30, 2014 at a weighted-average exercise price of $13.74 per share;
- 799,270 shares of common stock reserved as of September 30, 2014 for future issuance under our equity incentive plans; and
- 327,272 shares of common stock reserved as of September 30, 2014 for future issuance under our 2013 employee stock purchase plan.

Unless otherwise indicated, this prospectus supplement reflects and assumes the following:

- no exercise of the outstanding options described above; and
- no exercise by the underwriters of their option to purchase additional shares.

Celgene Corporation, or Celgene, an affiliate of two of our existing stockholders and our cancer metabolism strategic alliance partner, has indicated an interest in purchasing an aggregate of up to approximately $26,250,000 of shares of our common stock in this offering at the public offering price. However, because indications of interest are not binding agreements or commitments to purchase, Celgene may determine to purchase fewer shares than they have indicated an interest in purchasing or not to purchase any shares in this offering. In addition, the underwriters could determine to sell fewer shares to Celgene than Celgene indicated an interest in purchasing or not to sell any shares to Celgene. Any shares sold to Celgene will be subject to the lock-up agreements described under Underwriting.

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Summary consolidated financial data

The following table summarizes our consolidated financial data. We have derived the following summary of our consolidated statement of operations data for the nine months ended September 30, 2014 and the consolidated balance sheet data as of September 30, 2014 from our unaudited condensed consolidated financial statements incorporated by reference in this prospectus supplement from our Quarterly Report on Form 10-Q for the quarterly period ended September 30, 2014. We derived the consolidated statement of operations data for the years ended December 31, 2013, 2012 and 2011 from our audited consolidated financial statements incorporated by reference in this prospectus supplement from our Annual Report on Form 10-K for the year ended December 31, 2013. You should read this data together with our audited consolidated financial statements and related notes and the information under the captions Selected Consolidated Financial Data and Management s Discussion and Analysis of Financial Condition and Results of Operations, which are included in our Annual Report on Form 10-K for the year ended December 31, 2013 and our unaudited Quarterly Report on Form 10-Q for the nine months ended September 30, 2014 and incorporated by reference in this prospectus supplement. For more details on how you can obtain the documents incorporated by reference in this prospectus supplement, see Where you can find more information and Incorporation of documents by reference appearing elsewhere in this prospectus supplement. Our historical results are not necessarily indicative of future results.

(in thousands, except share and per share amounts)	Nine months ended September 30, 2014	Year Ended December 31, 2013	2012	2011
Consolidated statement of operations data:				
Revenue related party	$ 50,722	$ 25,548	$ 25,106	$ 21,837
Operating expenses:				
Research and development	65,509	54,502	41,037	31,253
General and administrative	12,619	9,929	7,064	7,215
Total operating expenses	78,128	64,431	48,101	38,468
Loss from operations	(27,406)	(38,883)	(22,995)	(16,631)
Interest income	118	55	69	132
Loss before provision (benefit) for income taxes	(27,288)	(38,828)	(22,926)	(16,499)
Provision (benefit) for income taxes	(448)	579	(2,824)	7,207
Net loss	(26,840)	(39,407)	(20,102)	(23,706)
Cumulative preferred stock dividends		(4,162)	(7,190)	(3,100)
Net loss applicable to common stockholders	$ (26,840)	$ (43,569)	$ (27,292)	$ (26,806)

Net loss per share applicable to common stockholders basic and diluted	$ (0.81)	$ (2.83)	$ (8.02)	$ (8.90)
Weighted-average number of common shares used in net loss per share applicable to common stockholders basic and diluted	33,176,801	15,415,373	3,401,719	3,013,366

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(in thousands)	As of September 30, 2014 Actual	As Adjusted(1)
Consolidated balance sheet data:		
Cash, cash equivalents and marketable securities	$ 237,887	$
Total assets	269,608	
Total liabilities	61,859	61,859
Common stock	35	
Additional paid-in capital	347,947	
Accumulated deficit	(140,284)	(140,284)
Total stockholders equity	207,749	

(1) The as adjusted consolidated balance sheet data gives effect to the issuance and sale of shares of our common stock in this offering at the public offering price of $ per share, after deducting underwriting discounts and commissions and estimated offering expenses payable by us.

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Risk factors

An investment in our common stock involves risks. You should carefully consider the following risk factors, as well as the risk factors included in our Annual Report on Form 10-K for the year ended December 31, 2013 and our Quarterly Reports on Form 10-Q for the quarterly periods ended March 31, 2014, June 30, 2014 and September 30, 2014, together with all of the other information included in, or incorporated by reference into, this prospectus supplement and the accompanying prospectus in evaluating an investment in our common stock. If any of the following risks were to occur, our business, financial condition or results of operations could be materially adversely affected. In that case, the trading price of our common stock could decline and you could lose all or part of your investment.

Risks related to our common stock and this offering

Following this offering, our executive officers, directors and principal stockholders will continue to own a significant percentage of our stock and will be able to control matters submitted to stockholders for approval.

Upon completion of this offering, our executive officers, directors and a small number of our stockholders will continue to own more than a majority of our outstanding common stock. As a result, if these stockholders were to choose to act together, they would be able to control all matters submitted to our stockholders for approval, as well as our management and affairs. For example, these persons, if they choose to act together, would control the election of directors and approval of any merger, consolidation or sale of all or substantially all of our assets. This concentration of voting power could delay or prevent an acquisition of our company on terms that you may desire.

If you purchase shares of common stock in this offering, you will suffer immediate dilution of your investment.

The public offering price of our common stock is substantially higher than the net tangible book value per share of our common stock. Therefore, if you purchase shares of our common stock in this offering, you will pay a price per share that substantially exceeds our net tangible book value per share after giving effect to this offering. If you purchase common stock in this offering, you will incur an immediate and substantial dilution in net tangible book value of $ per share, after giving effect to the sale by us of shares in this offering at the public offering price of $ per share. In the past, we have issued options to acquire common stock at prices significantly below this offering price. To the extent these outstanding options are ultimately exercised, you will incur additional dilution.

We have broad discretion in the use of the net proceeds from this offering and may not use them effectively.

Our management will have broad discretion in the application of the net proceeds from this offering and could spend the proceeds in ways that do not improve our results of operations or enhance the value of our common stock. The failure by our management to apply these funds effectively could result in financial losses, and these financial losses could have a material adverse effect on our business, cause the price of our common stock to decline and delay the development of our product candidates. Pending their use, we may invest the net proceeds from this offering in a manner that does not produce income or that loses value.

Because we do not anticipate paying any cash dividends on our capital stock in the foreseeable future, capital appreciation, if any, will be your sole source of gain.

We have never declared or paid cash dividends on our capital stock. We currently intend to retain all of our future earnings, if any, to finance the growth and development of our business. In addition, the terms of any future debt agreements may preclude us from paying dividends. As a result, capital appreciation, if any, of our common stock will

be your sole source of gain for the foreseeable future.

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Cautionary note regarding forward-looking statements

This prospectus supplement, the accompanying prospectus and the documents incorporated by reference herein and therein contain forward-looking statements that involve substantial risks and uncertainties. All statements, other than statements of historical facts, contained in this prospectus supplement, the accompanying prospectus and the documents incorporated by reference herein and therein, including statements regarding our strategy, future operations, future financial position, future revenue, projected costs, prospects, plans and objectives of management are forward-looking statements. These statements involve known and unknown risks, uncertainties and other important factors that may cause our actual results, performance or achievements to be materially different from any future results, performance or achievements expressed or implied by the forward-looking statements.

The words anticipate, believe, estimate, expect, intend, may, plan, predict, project, target, poten should, continue and similar expressions are intended to identify forward-looking statements, although not all forward-looking statements contain these identifying words. These forward-looking statements include, among other things, statements about:

- the initiation, timing, progress and results of future preclinical studies and clinical trials, and our research and development programs;
- our plans to develop and commercialize our product candidates;
- our collaboration with Celgene Corporation;
- our ability to establish and maintain additional collaborations or obtain additional funding;
- the timing or likelihood of regulatory filings and approvals;
- the implementation of our business model, strategic plans for our business, product candidates and technology;
- our commercialization, marketing and manufacturing capabilities and strategy;
- the rate and degree of market acceptance and clinical utility of our products;
- our competitive position;
- our intellectual property position;

developments and projections relating to our competitors and our industry;

the potential of IDH1/IDH2 and pyruvate kinase-R mutations as therapeutic targets;

the potential benefits of our drug candidates targeting IDH1/IDH2 or pyruvate kinase-R mutations, including AG-221, AG-120 and AG-348;

our expectations related to the use of proceeds from this offering; and

our estimates regarding expenses, future