

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

**Amendment No. 1 to
FORM S-1
REGISTRATION STATEMENT
UNDER
THE SECURITIES ACT OF 1933**

AGIOS PHARMACEUTICALS, INC.

(Exact name of registrant as specified in its charter)

Delaware
(State or other jurisdiction of
incorporation or organization)

2834
(Primary Standard Industrial
Classification Code Number)

26-0662915
(I.R.S. Employer
Identification No.)

38 Sidney Street, 2nd Floor
Cambridge, MA 02139
(617) 649-8600

(Address, including zip code, and telephone number, including area code, of registrant's principal executive offices)

David P. Schenkein, M.D.
Chief Executive Officer
AgiOS Pharmaceuticals, Inc.
38 Sidney Street, 2nd Floor
Cambridge, MA 02139
(617) 649-8600

(Name, address, including zip code, and telephone number, including area code, of agent for service)

Copies to:

Steven D. Singer, Esq.
Cynthia T. Mazareas, Esq.
Wilmer Cutler Pickering Hale and Dorr LLP
60 State Street
Boston, MA 02109
Telephone: (617) 526-6000

Richard D. Truesdell, Jr., Esq.
Davis Polk & Wardwell LLP
450 Lexington Avenue
New York, NY 10017
Telephone: (212) 450-4000

Approximate date of commencement of proposed sale to the public: As soon as practicable after this Registration Statement is declared effective.

If any of the securities being registered on this form are to be offered on a delayed or continuous basis pursuant to Rule 415 under the Securities Act of 1933, check the following box.

If this form is filed to register additional securities for an offering pursuant to Rule 462(b) under the Securities Act, check the following box and list the Securities Act registration statement number of the earlier effective registration statement for the same offering.

If this form is a post-effective amendment filed pursuant to Rule 462(c) under the Securities Act, check the following box and list the Securities Act registration statement number of the earlier effective registration statement for the same offering.

If this form is a post-effective amendment filed pursuant to Rule 462(d) under the Securities Act, check the following box and list the Securities Act registration statement number of the earlier effective registration statement for the same offering.

Indicate by check mark whether the registrant is a large accelerated filer, an accelerated filer, a non-accelerated filer, or a smaller reporting company. See the definitions of "large accelerated filer," "accelerated filer" and "smaller reporting company" in Rule 12b-2 of the Exchange Act.

Large accelerated filer Accelerated filer
Non-accelerated filer (Do not check if a smaller reporting company) Smaller reporting company

CALCULATION OF REGISTRATION FEE

Class of securities to be registered	Number of Shares to be Registered(1)	Proposed Maximum Offering Price Per Share(2)	Proposed maximum aggregate offering price(1)	Amount of registration fee(3)
Common Stock, \$0.001 par value per share	2,300,000	\$39.78	\$91,494,000	\$11,785

- Estimated solely for the purpose of calculating the registration fee in accordance with Rule 457(a) under the Securities Act of 1933, as amended. Includes shares that the underwriters have the option to purchase.
- Estimated solely for the purpose of calculating the registration fee pursuant to Rule 457(c) under the Securities Act of 1933, as amended and based on the average of the high and low sales price of the registrant's common stock as reported on The NASDAQ Global Select Market on April 16, 2014.
- \$11,109 previously paid on April 9, 2014. \$676 paid herewith.

The Registrant hereby amends this Registration Statement on such date or dates as may be necessary to delay its effective date until the Registrant shall file a further amendment which specifically states that this Registration Statement shall thereafter become effective in accordance with Section 8(a) of the Securities Act of 1933 or until the Registration Statement shall become effective on such date as the Commission, acting pursuant to said Section 8(a), may determine.

[Table of Contents](#)

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

Subject to completion, dated April 21, 2014

Prospectus



AgiOS Pharmaceuticals, Inc. is offering 2,000,000 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 April 17, 2014 was \$40.67 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 11 of this prospectus.

	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 63 of this prospectus.

We have granted the underwriters the right to purchase up to an additional 300,000 shares of our common stock. The underwriters can exercise this right at any time within 30 days after the date of this prospectus.

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 296,800 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 "Shares eligible for future sale—Lock-up agreements."

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. Any representation to the contrary is a criminal offense.

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

J.P. Morgan
Cowen and Company

Goldman, Sachs & Co.
Leerink Partners

The date of this prospectus is _____, 2014.

Agios is passionately committed to the fundamental transformation of patients' lives through scientific leadership in the field of cancer metabolism and inborn errors of metabolism.



The people pictured here are some of the many friends and family of Agios employees affected by cancer. All of us at Agios are passionate about transforming patients' lives. This is our vision and what motivates, inspires, and drives us.

[Table of Contents](#)

Table of contents

Prospectus summary	1
Risk factors	11
Cautionary note regarding forward-looking statements	13
Use of proceeds	14
Price range of common stock	15
Dividend policy	15
Industry and other data	15
Capitalization	16
Business	18
Description of capital stock	52
Shares eligible for future sale	56
Material U.S. tax considerations for non-U.S. holders of common stock	59
Underwriting	63
Legal matters	70
Experts	70
Where you can find more information	70
Incorporation of documents by reference	70

Neither we nor the underwriters have authorized anyone to provide you with information other than that contained in this 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 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 is accurate only as of its date, regardless of the time of delivery of this 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 in that jurisdiction. Persons who come into possession of this 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 applicable to that jurisdiction.

Prospectus summary

This summary highlights information contained elsewhere in this prospectus or incorporated by reference into this prospectus from our Annual Report on Form 10-K for the year ended December 31, 2013 and our other filings with the Securities and Exchange Commission listed in the section of this prospectus entitled "Incorporation of documents by reference" and does not contain all of the information you should consider before investing in our common stock. You should also consider, among other things, the matters described under "Risk factors" and "Management's Discussion and Analysis of Financial Condition and Results of Operations," in each case appearing elsewhere in this prospectus or in our Annual Report on Form 10-K for the year ended December 31, 2013, incorporated by reference herein.

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 inborn errors of metabolism, or IEMs, 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 believe that dysregulation of normal cellular metabolism plays a crucial role in many diseases, including certain cancers and IEMs. We singularly 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 for cancer and IEMs. The lead product candidates in our most advanced programs are aimed at druggable targets which have undergone rigorous validation processes. Our most advanced cancer product candidates, AG-221 and AG-120, which target mutant isocitrate dehydrogenase 2 and 1, or IDH2 and IDH1, respectively, have demonstrated strong proof of concept in preclinical models. In September 2013, we initiated a phase 1 study for AG-221 in patients with advanced hematologic malignancies with an IDH2 mutation. 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 acute myelogenous leukemia or AML. On April 6, 2014, we announced in a press release, as well as presented, the initial findings from the dose escalation portion of the ongoing phase 1 study of AG-221 at the American Association for Cancer Research (AACR) Annual Meeting 2014 in San Diego, California.

This multi-center global study is evaluating multiple ascending doses of AG-221, as a single agent, in patients with advanced hematologic malignancies with a confirmed IDH2 mutation. This study includes both a dose escalation phase and an expansion phase with multiple expansion cohorts. The goals of the study are to primarily assess safety and tolerability. Secondary endpoints aim to evaluate the pharmacokinetics and pharmacodynamics properties of AG-221 and determine if preliminary efficacy signals can be measured.

The initial phase 1 data from the first two cohorts of patients treated with AG-221 were presented during a symposium titled "Novel Immune and Targeted Therapies for Hematological Malignancies and Solid Tumors" at the AACR Annual Meeting 2014. A total of 10 patients with relapsed or refractory AML, which means 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, seven of the 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 to 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 a 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

[Table of Contents](#)

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 are continuing to receive drug.

The mechanism of response is consistent with preclinical studies, including substantial reduction of plasma 2HG, 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.

AG-221 has been well tolerated to date, with no dose-limiting toxicities reported. Within the 22 patients enrolled as of March 20, 2014, possible drug-related severe adverse events were reported in two patients. These included one patient with an abnormally elevated white blood count and one patient with confusion and respiratory failure concomitant with infection common in patients with AML and related diseases due to a lack of infection-fighting white blood cells.

We are encouraged by the degree of clinical activity and tolerability observed in the first two cohorts of patients (30 mg and 50 mg twice a day). Preliminary analysis of pharmacokinetics (PK) 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. As the maximum tolerated dose has not been reached for AG-221, the dose escalation portion of the trial continues. Given the long half-life observed, we have expanded the trial to include once daily dosing cohorts, beginning with 100 mg. We will continue to enroll patients in escalating dose cohorts to evaluate both tolerability and clinical activity. Multiple expansion cohorts are expected to begin later this year after an appropriate dose and schedule are selected.

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 only enrolling patients with an IDH1 mutation. The lead candidate in our IEM program, AG-348, targets pyruvate kinase for the treatment of pyruvate kinase deficiency. We have completed IND-enabling studies and initiated a phase 1 clinical trial for AG-348 in April 2014.

Our ability to identify, validate and drug novel targets is enabled by a set of core capabilities. Key proprietary aspects of our core capabilities in cellular metabolism include the ability to measure the activities of numerous metabolic pathways in cells or tissues in a high throughput fashion and expertise in “flux biochemistry.” This refers to the dynamic analysis of how metabolites, which are intermediates or small molecule products of metabolism, accumulate or diminish as they are created or chemically altered by multiple networks of metabolic enzymes. Complex mathematical modeling of metabolic pathways, enzymatic activity and the flux of metabolites through metabolic enzymatic reactions within diseased tissues allow us to identify novel biological parameters that can be measured to characterize a disease state or the effect of therapy, or biomarkers, and targets for drug discovery.

Our understanding of metabolism within diseased tissues enables the development of methods to measure the effect of a drug on the target of interest and the patient, or pharmacodynamic markers, and patient selection strategies for clinical development. Utilizing our approach we identify altered metabolic pathways within abnormal cells. Altered metabolic pathways generate disease-specific metabolic fingerprints, comprising patterns of metabolite levels, which are the amounts of particular metabolites, that can be exploited in both discovery and development of novel therapeutics. Metabolites make ideal biomarkers because they are readily measured in the target tissues and blood. Metabolic biomarkers can identify appropriate patients for clinical trials, serve as pharmacodynamic markers to characterize medicine/target engagement in patients, and permit the monitoring of patient response to therapy. The clinical development strategy for all of our product candidates will always

[Table of Contents](#)

include initial study designs that allow for genetically or biomarker defined patient populations, enabling the potential for proof of concept early in clinical development, along with the potential for accelerated approval.

We have assembled a set of core capabilities at the intersection of cellular biology and metabolism, centered on the expertise of our founding scientists who are widely considered to be the thought leaders in cancer metabolism—Lewis Cantley, Ph.D. (Director of the Cancer Center at Weill Cornell Medical College and New York Presbyterian Hospital), Tak Mak, Ph.D. (Professor of Medical Biophysics, University of Toronto) and Craig Thompson, M.D. (President and CEO of Memorial Sloan-Kettering Cancer Center)—as well as on the strength of our management team, including our CEO, David Schenkein, M.D., and a group of world class scientists. We have built an exceptional team of cancer biologists, enzymologists and a core group of metabolomic experts that interrogate cellular metabolism to identify key metabolic targets and biomarkers in cancer and IEMs. Our scientists have published numerous scientific papers since 2009, including several in both *Nature* and *Science*. We have also established an intellectual property portfolio consisting of over 100 patent applications worldwide, including multiple patent applications directed to our lead product candidates, together with trade secrets, know-how and continuing technological innovation.

Our initial therapeutic area of focus is cancer. We are leveraging our expertise in metabolic pathways to discover, validate, develop and commercialize a pipeline of novel drug candidates. In April 2010, and subsequently amended in October 2011, we entered into a collaboration agreement with Celgene Corporation, or Celgene, focused on cancer metabolism. Under the collaboration, we are leading discovery, preclinical and early clinical development for all cancer metabolism programs. The discovery phase of the collaboration was initially set to expire in April 2014, subject to Celgene's option to extend the discovery phase for up to two additional years. In December 2013, Celgene notified us of its intent to extend the discovery phase for an additional year through April 2015. Celgene has the option to obtain exclusive rights for the further development and commercialization of certain of these programs, and we will retain rights to the others. For the programs that Celgene chooses to license, we may elect to participate in a portion of sales activities for the medicines from such programs in the United States. In addition, for certain of these programs, we may elect to retain full rights to develop and commercialize medicines from these programs in the United States. Through December 31, 2013, we have received approximately \$141.2 million in payments from Celgene and \$50.3 million in equity investments and are entitled to a \$20.0 million payment in 2014 as a result of the discovery term extension exercised in December 2013. We are also eligible to receive an additional extension payment, payments upon the successful achievement of specified milestones, reimbursements for certain development expenses and royalties on certain product sales.

We believe that our competitive advantage and singular focus in understanding cellular metabolism has created disruptive knowledge in biology that we can exploit for the development of transformative medicines in cancer. Because there has not previously been a systematic approach to drug discovery in this field, we have had to demonstrate significant major advances, including:

- identification of unique and specific metabolic enzymes that are altered from normal cells within cancer cells and are directly involved in the pathogenesis of cancer;
- creation of selective small molecules with drug-like properties that preferentially target disease-associated enzymes;
- achievement of pharmacologic efficacy in *in vivo* models and our phase 1 study of AG-221; and
- discovery of novel biomarkers that identify the appropriate patients for clinical trials.

Our two most advanced cancer programs are targeting mutations in the enzymes isocitrate dehydrogenase 1 and 2, referred to as IDH1 and IDH2, respectively. Both program targets are genetically validated, which means the importance of such targets have been demonstrated based on genetics, and represent two of the most promising metabolic targets in cancer biology, as concluded by the leading scientific journal *Nature* in 2011. Extensive

[Table of Contents](#)

publications led by Agios scientists validate our belief that these mutations are initiating and driving events in many cancers. These two otherwise normal metabolic enzymes are mutated in a wide range of cancers, including both solid tumors and hematological malignancies. Our drug candidates are selective for the mutated form of IDH1 and IDH2 found in cancer cells. In September 2013, we initiated a phase 1 study for AG-221, the lead candidate in our IDH2 program, in patients with advanced hematologic malignancies with an IDH2-mutation, and in April 2014, we reported initial findings at the AACR Annual Meeting 2014 from the first two cohorts of patients treated with AG-221. We believe that the data we presented at AACR Annual Meeting 2014 corroborate our approach in treating cancers that express specific mutations utilizing a precision medicine based approach. In March 2014, we initiated two phase 1 studies for our lead development candidate in the IDH1 program, AG-120, one in patients with advanced hematologic malignancies and the second in patients with advanced solid tumors, both trials only enrolling patients with an IDH1 mutation. In January 2014, we elected to exercise the option to obtain U.S. development and commercial rights for AG-120, in accordance with the terms of our agreement with Celgene, with Celgene retaining its option to ex-U.S. rights.

We are also focused on developing medicines to address IEMs, with a novel approach to orphan diseases for which no effective or disease-modifying therapy is currently available. A hallmark of IEMs is abnormal cellular metabolic activity due to a genetic defect, which results in the accumulation or deficit of certain metabolites or proteins, disrupting normal metabolic functions. We utilize stringent criteria when identifying which IEMs we will pursue. We focus on IEMs with a common set of attributes:

- single gene, single disease (i.e., monogenic disorders);
- high unmet medical need with evidence that there is progressive disease post-birth that can be addressed with therapy; and
- an adequate number of patients for prospective clinical trials.

We apply our core capabilities in exploring cellular metabolism to identify key cellular targets in affected cells and design novel small molecules with the potential to correct the metabolic defect in patients afflicted with these diseases. We have successfully used this approach in our most advanced IEM program—pyruvate kinase deficiency, or PK deficiency, a rare form of hereditary hemolytic anemia. The disease is characterized by mild to severe forms of anemia. There are no currently available treatments other than supportive care, which includes splenectomy, transfusion support and chelation, which refers to the removal of excess iron from the human body with a therapeutic agent. Our lead development candidate, AG-348, is a potent, orally available small molecule activator of the PKR enzyme, an isoform of PK that, when mutated, leads to PK deficiency. We started a single ascending dose-escalation phase 1 clinical trial for AG-348 in healthy volunteers in April 2014 and expect to start a multiple ascending dose-escalation phase 1 clinical trial in healthy volunteers in mid-2014.

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 IEMs. Key elements of our strategy include:

- *Aggressively pursuing the development of novel medicines to transform the lives of patients with cancer and IEMs.*
- *Maintaining our competitive advantage and singular focus in the field of cellular metabolism.*
- *Continuing to build a product engine for cancer and IEMs 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 IEMs. 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.”*
- *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 immediately following this prospectus summary and in our Annual Report on Form 10-K for the year ended December 31, 2013, incorporated by reference herein. 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 December 31, 2013, we had an accumulated deficit of \$113.4 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 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 do not own or license any issued patents for our 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.

[Table of Contents](#)

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. We have included our website address in this prospectus solely as an inactive textual reference.

As used in this prospectus, 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 are the property of their respective owners.

[Table of Contents](#)

The offering

Common stock offered	2,000,000 shares
Common stock to be outstanding after this offering	33,202,542 shares
Option to purchase additional shares	The underwriters have an option for a period of 30 days to purchase up to 300,000 additional shares of our common stock.
Use of proceeds	We intend to use the net proceeds from this offering as follows: approximately \$20 million to fund the costs of phase 1 clinical development of AG-221; approximately \$20-25 million to fund our share of development costs for AG-120; approximately \$15-20 million to fund the phase 1/2 clinical development activities for AG-348; approximately \$10-20 million to fund research and development to advance our pipeline of earlier-stage cancer metabolism and IEM programs; and the remainder for working capital and other general corporate purposes. See “Use of proceeds” for more information.
Risk factors	You should read the “Risk factors” section of this prospectus and our Annual Report on Form 10-K for the year ended December 31, 2013, incorporated by reference herein, for a discussion of factors to consider carefully 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 31,202,542 shares of our common stock outstanding as of December 31, 2013.

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

- 3,846,168 shares of common stock issuable upon exercise of stock options outstanding as of December 31, 2013 at a weighted-average exercise price of \$4.14 per share;
- 655,036 shares of common stock reserved as of December 31, 2013 for future issuance under our equity incentive plans;
- 327,272 shares of common stock reserved as of December 31, 2013 for future issuance under our 2013 employee stock purchase plan; and
- 1,242,966 additional shares of common stock that were reserved for future issuance under our equity incentive plans as of January 1, 2014.

[Table of Contents](#)

Unless otherwise indicated, this prospectus 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 296,800 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 “Shares eligible for future sale—Lock-up agreements.”

[Table of Contents](#)

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 years ended December 31, 2013, 2012 and 2011 and the consolidated balance sheet data as of December 31, 2013 from our audited consolidated financial statements incorporated by reference in this prospectus 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,” all included elsewhere or incorporated by reference in this prospectus. For more details on how you can obtain the documents incorporated by reference in this prospectus, see “Where you can find more information” and “Incorporation of documents by reference” appearing elsewhere in this prospectus. Our historical results are not necessarily indicative of future results.

	Year Ended December 31,		
	2013	2012	2011
<i>(in thousands, except share and per share amounts)</i>			
Consolidated statement of operations data:			
Revenue	\$ 25,548	\$ 25,106	\$ 21,837
Operating expenses:			
Research and development	54,502	41,037	31,253
General and administrative	9,929	7,064	7,215
Total operating expenses	64,431	48,101	38,468
Loss from operations	(38,883)	(22,995)	(16,631)
Interest income	55	69	132
Loss before provision (benefit) for income taxes	(38,828)	(22,926)	(16,499)
Provision (benefit) for income taxes	579	(2,824)	7,207
Net loss	(39,407)	(20,102)	(23,706)
Cumulative preferred stock dividends	(4,162)	(7,190)	(3,100)
Net loss applicable to common stockholders	\$ (43,569)	\$ (27,292)	\$ (26,806)
Net loss per share applicable to common stockholders—basic and diluted	\$ (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	15,415,373	3,401,719	3,013,366

<i>(in thousands)</i>	As of December 31, 2013	
	Actual	As Adjusted(1)
Consolidated balance sheet data:		
Cash, cash equivalents and marketable securities	\$ 193,894	\$ 269,944
Total assets	201,205	277,255
Total liabilities	69,723	69,723
Common stock	31	33
Additional paid-in capital	244,881	320,929
Accumulated deficit	(113,444)	(113,444)
Total stockholders’ equity	131,482	207,532

[Table of Contents](#)

- (1) The as adjusted consolidated balance sheet data give effect to our issuance of 2,000,000 shares of common stock being offered by us at an assumed public offering price of \$40.67 per share, the last reported sale price of our common stock on The NASDAQ Global Select Market on April 17, 2014, after deducting estimated underwriting discounts and commissions and estimated offering expenses payable by us.
- (2) A \$1.00 increase (decrease) in the assumed public offering price of \$40.67 per share, the last reported sale price of our common stock on The NASDAQ Global Select Market on April 17, 2014, would increase (decrease) the as adjusted amount of each of cash, cash equivalents and marketable securities, total assets and total stockholders' equity by approximately \$1.9 million, assuming that the number of shares offered by us, as set forth on the cover of this prospectus, remains the same and after deducting estimated underwriting discounts and commissions and estimated offering expenses payable by us. Similarly, each increase (decrease) of 200,000 shares offered by us would increase (decrease) the net proceeds to us from this offering by approximately \$7.6 million, assuming the assumed public offering price remains the same and after deducting estimated underwriting discounts and commissions and estimated offering expenses payable by us. A 200,000 share increase in the number of shares offered by us together with a concomitant \$1.00 increase in the assumed public offering price of \$40.67 per share, the last reported sale price of our common stock on The NASDAQ Global Select Market on April 17, 2014, would increase the as adjusted amount of each of cash, cash equivalents and marketable securities, total assets and total stockholders' equity by approximately \$9.7 million after deducting estimated underwriting discounts and commissions and estimated offering expenses payable by us. Conversely, a 200,000 share decrease in the number of shares offered by us together with a concomitant \$1.00 decrease in the assumed public offering price of \$40.67 per share, the last reported sale price of our common stock on The NASDAQ Global Select Market on April 17, 2014, would decrease the as adjusted amount of each of cash, cash equivalents and marketable securities, total assets and total stockholders' equity by approximately \$9.3 million after deducting estimated underwriting discounts and commissions and estimated offering expenses payable by us.

Risk factors

Investing in our common stock involves a high degree of risk. Before investing in our common stock, you should consider carefully the risks described below, together with the other information contained in this prospectus or incorporated by reference in this prospectus, including the risks and uncertainties discussed under "Risk Factors" in our Annual Report on Form 10-K for the year ended December 31, 2013, which are incorporated by reference herein in their entirety. If any of the following risks occur, our business, financial condition, results of operations and future growth prospects could be materially and adversely affected. In these circumstances, the market price of our common stock could decline, and you may 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. To the extent shares are issued under outstanding options, you will incur further dilution. Based on an assumed public offering price of \$40.67 per share, which was the last reported sale price of our common stock on The NASDAQ Global Select Market on April 17, 2014, you will experience immediate dilution of \$34.42 per share, representing the difference between our as adjusted net tangible book value per share after giving effect to this offering at the assumed public offering price.

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.

[Table of Contents](#)

A significant portion of our total outstanding shares may be sold into the market in the near future, which could cause the market price of our common stock to drop significantly, even if our business is doing well.

Sales of a substantial number of shares of our common stock in the public market could occur at any time. These sales, or the perception in the market that holders of a large number of shares intend to sell shares, could reduce the market price of our common stock. After this offering, we will have outstanding 33,202,542 shares of common stock based on the number of shares outstanding as of December 31, 2013. This includes the shares that we are issuing and selling in this offering, which shares may be resold in the public market immediately without restriction, unless purchased by our affiliates. Of the remaining shares, 24,301,947 shares are “restricted securities” under Rule 144. Of these shares, 19,088,669 shares are subject to lock-up agreements entered into in connection with this offering, not including any shares that may be purchased by Celgene in this offering. After the lock-up period, these restricted securities may be sold in the public market only if registered or if they qualify for an exemption from registration under Rule 144 or 701 under the Securities Act or any other exemption. See the “Shares eligible for future sale” section of this prospectus. Moreover, following this offering, assuming that the underwriters do not exercise their option to purchase additional shares of common stock, based on information we have available to us, we believe holders of an aggregate of 19,262,768 shares of our common stock will have rights, subject to some conditions, to require us to file registration statements covering their shares or to include their shares in registration statements that we may file for ourselves or other stockholders. We have also registered shares of common stock that we have issued upon the exercise of stock options outstanding on December 31, 2013, and may in the future issue, under our equity compensation plans. These can be freely sold in the public market upon issuance, subject to volume limitations applicable to affiliates and the lock-up agreements described in the “Underwriting” section of this prospectus.

Cautionary note regarding forward-looking statements

This prospectus and the documents incorporated by reference into it contain forward-looking statements that involve substantial risks and uncertainties. All statements, other than statements of historical facts, contained in this prospectus, 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,” “potential,” “will,” “would,” “could,” “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;
- our expectations regarding the time during which we will be an emerging growth company under the JOBS Act;
- our expectations related to the use of proceeds from this offering; and
- our estimates regarding expenses, future revenue, capital requirements and needs for additional financing.

We may not actually achieve the plans, intentions or expectations disclosed in our forward-looking statements, and you should not place undue reliance on our forward-looking statements. Actual results or events could differ materially from the plans, intentions and expectations disclosed in the forward-looking statements we make. We have included important factors in the cautionary statements included in this prospectus, particularly in the “Risk factors” section and other documents incorporated by reference herein, that could cause actual results or events to differ materially from the forward-looking statements that we make. Our forward-looking statements do not reflect the potential impact of any future acquisitions, mergers, dispositions, joint ventures or investments that we may make.

You should read this prospectus, other documents incorporated by reference herein, and the documents that we have filed as exhibits to the registration statement of which this prospectus is a part completely and with the understanding that our actual future results may be materially different from what we expect. We do not assume any obligation to update any forward-looking statements, whether as a result of new information, future events or otherwise, except as required by law.

Use of proceeds

We estimate that the net proceeds from our issuance and sale of 2,000,000 shares of our common stock in this offering will be approximately \$76.0 million based upon an assumed public offering price of \$40.67 per share, the last reported sale price of our common stock on The NASDAQ Global Select Market on April 17, 2014, and after deducting the estimated underwriting discounts and commissions and estimated offering expenses payable by us. If the underwriters exercise their option to purchase additional shares in full, we estimate that our net proceeds will be approximately \$87.5 million, after deducting estimated underwriting discounts and commissions and estimated offering expenses payable by us.

We intend to use the net proceeds from this offering as follows:

- approximately \$20 million to fund the costs of phase 1 clinical development of AG-221;
- approximately \$20-25 million to fund our share of development costs for AG-120;
- approximately \$15-20 million to fund the phase 1/2 clinical development activities for AG-348;
- approximately \$10-20 million to fund research and development to advance our pipeline of earlier-stage cancer metabolism and IEM programs; and
- the remainder for working capital and other general corporate purposes.

This expected use of net proceeds from this offering represents our intentions based upon our current plans and business conditions, which could change in the future as our plans and business conditions evolve. The amounts and timing of our actual expenditures may vary significantly depending on numerous factors, including the progress of our development, the status of and results from clinical trials, as well as any additional collaborations that we may enter into with third parties for our product candidates, and any unforeseen cash needs. As a result, our management will retain broad discretion over the allocation of the net proceeds from this offering.

We believe opportunities may exist from time to time to expand our current business through acquisitions or in-licenses of complementary companies, medicines or technologies. While we have no current agreements, commitments or understandings for any specific acquisitions or in-licenses at this time, we may use a portion of the net proceeds for these purposes.

Pending use of the proceeds as described above, we intend to invest the proceeds in a variety of capital preservation investments, including short-term, interest-bearing, investment-grade instruments and U.S. government securities.

Price range of common stock

Our common stock began trading on The NASDAQ Global Select Market under the symbol “AGIO” on July 24, 2013. Prior to that time, there was no public market for our common stock. The following table sets forth the high and low sale prices per share of our common stock, as reported on The NASDAQ Global Select Market, for the periods indicated.

	<u>High</u>	<u>Low</u>
Year Ended December 31, 2013		
Third quarter (from July 24, 2013)	\$33.45	\$22.34
Fourth quarter	\$33.59	\$15.77
Year Ending December 31, 2014		
First quarter	\$49.79	\$21.70
Second quarter (through April 17, 2014)	\$48.98	\$31.42

On April 17, 2014, the last reported sale price of our common stock as reported on The NASDAQ Global Select Market was \$40.67 per share. As of the date of this prospectus, we had approximately 38 holders of record of our common stock. The actual number of stockholders is greater than this number of record holders and includes stockholders who are beneficial owners but whose shares are held in street name by brokers and other nominees. This number of holders of record also does not include stockholders whose shares may be held in trust by other entities.

Dividend policy

We have not declared or paid any cash dividends on our capital stock since our inception. We intend to retain future earnings, if any, to finance the operation and expansion of our business and do not anticipate paying any cash dividends to holders of common stock in the foreseeable future.

Industry and other data

We obtained the industry, market and competitive position data in this prospectus from our own internal estimates and research as well as from industry and general publications and research, surveys and studies conducted by third parties. Industry publications, studies and surveys generally state that they have been obtained from sources believed to be reliable, although they do not guarantee the accuracy or completeness of such information. While we believe that the data contained in each of these studies and publications are reliable, we have not independently verified market and industry data from third-party sources. While we believe our internal company research is reliable and that our internal estimates are reasonable, such research has not been verified by any independent source and our internal estimates are based on our good faith beliefs as of the respective dates of such estimates.

Capitalization

The following table sets forth our consolidated cash, cash equivalents and marketable securities and capitalization as of December 31, 2013, as follows:

- on an actual basis; and
- on an as adjusted basis to give effect to our issuance and sale of 2,000,000 shares of our common stock in this offering at an assumed public offering price of \$40.67 per share, which was the last reported sale price of our common stock on The NASDAQ Global Select Market on April 17, 2014, after deducting estimated underwriting discounts and commissions and estimated offering expenses payable by us.

You should read the following table together with “Description of capital stock” appearing elsewhere in this prospectus, and our consolidated financial statements and related notes to those statements and the “Management’s Discussion and Analysis of Financial Condition and Results of Operations” in our Annual Report on Form 10-K for the year ended December 31, 2013, which is incorporated by reference in this prospectus.

(in thousands, except share and per share data)	As of December 31, 2013	
	Actual	As Adjusted
Cash, cash equivalents and marketable securities	\$ 193,894	\$ 269,944
Preferred stock, par value \$0.001 per share; 25,000,000 shares authorized, no shares issued or outstanding, actual and as adjusted	\$ —	\$ —
Common stock, par value \$0.001 per share; 125,000,000 shares authorized, actual and as adjusted, 31,202,542 shares issued and outstanding, actual; 33,202,542 shares issued and outstanding, as adjusted	31	33
Additional paid-in capital	244,881	320,929
Accumulated other comprehensive income	14	14
Accumulated deficit	(113,444)	(113,444)
Total stockholders’ equity	\$ 131,482	\$ 207,532
Total capitalization	\$ 131,482	\$ 207,532

The table above does not include:

- 3,846,168 shares of common stock issuable upon exercise of stock options outstanding as of December 31, 2013, at a weighted-average exercise price of \$4.14 per share;
- 655,036 shares of common stock reserved as of December 31, 2013, for future issuance under our stock incentive plans;
- 327,272 shares of common stock reserved as of December 31, 2013 for future issuance under our 2013 employee stock purchase plan; and
- 1,242,966 additional shares of common stock reserved for future issuance under our equity incentive plans as of January 1, 2014.

A \$1.00 increase (decrease) in the assumed public offering price of \$40.67 per share, the last reported sale price of our common stock on The NASDAQ Global Select Market on April 17, 2014, would increase (decrease) the amount of cash, cash equivalents and marketable securities, total stockholders’ equity and total capitalization on an as adjusted basis by approximately \$1.9 million, assuming the number of shares offered by us, as set forth on the cover page of this prospectus, remains the same and after deducting estimated underwriting discounts and commissions and estimated offering expenses payable by us. Similarly, each increase (decrease) of 200,000 shares offered by us would increase (decrease) cash, cash equivalents and marketable securities, total stockholders’ equity and total capitalization on an as adjusted basis by approximately \$7.6 million, assuming the assumed public offering price remains the same, and after deducting estimated underwriting discounts and commissions and estimated offering expenses payable by us. A 200,000 share increase in the number of shares offered by us together with a concomitant \$1.00

[Table of Contents](#)

increase in the assumed public offering price of \$40.67 per share, the last reported sale price of our common stock on The NASDAQ Global Select Market on April 17, 2014, would increase each of cash, cash equivalents and marketable securities, total stockholders' equity and total capitalization on an as adjusted basis by approximately \$9.7 million after deducting estimated underwriting discounts and commissions and estimated offering expenses payable by us. Conversely, a 200,000 share decrease in the number of shares offered by us together with a concomitant \$1.00 decrease in the assumed public offering price of \$40.67 per share, the last reported sale price of our common stock on The NASDAQ Global Select Market on April 17, 2014, would decrease each of cash, cash equivalents and marketable securities, total stockholders' equity and total capitalization on an as adjusted basis by approximately \$9.3 million after deducting estimated underwriting discounts and commissions and estimated offering expenses payable by us. The as adjusted information discussed above is illustrative only and will be adjusted based on the actual offering price and other terms of this offering determined at pricing.

Business

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 inborn errors of metabolism, or IEMs, 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 believe that dysregulation of normal cellular metabolism plays a crucial role in many diseases, including certain cancers and IEMs. We singularly 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 for cancer and IEMs. The lead product candidates in our most advanced programs are aimed at druggable targets which have undergone rigorous validation processes. Our most advanced cancer product candidates, AG-221 and AG-120, which target mutant isocitrate dehydrogenase 2 and 1, or IDH2 and IDH1, respectively, have demonstrated strong proof of concept in preclinical models. In September 2013, we initiated a phase 1 study for AG-221 in patients with advanced hematologic malignancies with an IDH2 mutation. 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 acute myelogenous leukemia or AML. On April 6, 2014, we announced in a press release, as well as presented, the initial findings from the dose escalation portion of the ongoing phase 1 study of AG-221 at the American Association for Cancer Research (AACR) Annual Meeting 2014 in San Diego, California.

This multi-center global study is evaluating multiple ascending doses of AG-221, as a single agent, in patients with advanced hematologic malignancies with a confirmed IDH2 mutation. This study includes both a dose escalation phase and an expansion phase with multiple expansion cohorts. The goals of the study are to primarily assess safety and tolerability. Secondary endpoints aim to evaluate the pharmacokinetics and pharmacodynamics properties of AG-221 and determine if preliminary efficacy signals can be measured.

The initial phase 1 data from the first two cohorts of patients treated with AG-221 were presented during a symposium titled “Novel Immune and Targeted Therapies for Hematological Malignancies and Solid Tumors” at the AACR Annual Meeting 2014. A total of 10 patients with relapsed or refractory AML, which means 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, seven of the 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 to 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 a 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 are continuing to receive drug.

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.

AG-221 has been well tolerated to date, with no dose-limiting toxicities reported. Within the 22 patients enrolled as of March 20, 2014, possible drug-related severe adverse events were reported in two patients. These included

[Table of Contents](#)

one patient with an abnormally elevated white blood count and one patient with confusion and respiratory failure concomitant with infection common in patients with AML and related diseases due to a lack of infection-fighting white blood cells.

We are encouraged by the degree of clinical activity and tolerability observed in the first two cohorts of patients (30 mg and 50 mg twice a day). Preliminary analysis of pharmacokinetics (PK) 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. As the maximum tolerated dose has not been reached for AG-221, the dose escalation portion of the trial continues. Given the long half-life observed, we have expanded the trial to include once daily dosing cohorts, beginning with 100 mg. We will continue to enroll patients in escalating dose cohorts to evaluate both tolerability and clinical activity. Multiple expansion cohorts are expected to begin later this year after an appropriate dose and schedule are selected.

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 only enrolling patients with an IDH1 mutation. The lead candidate in our IEM program, AG-348, targets pyruvate kinase for the treatment of pyruvate kinase deficiency. We have completed IND-enabling studies and initiated a phase 1 clinical trial for AG-348 in April 2014.

Our ability to identify, validate and drug novel targets is enabled by a set of core capabilities. Key proprietary aspects of our core capabilities in cellular metabolism include the ability to measure the activities of numerous metabolic pathways in cells or tissues in a high throughput fashion and expertise in “flux biochemistry.” This refers to the dynamic analysis of how metabolites, which are intermediates or small molecule products of metabolism, accumulate or diminish as they are created or chemically altered by multiple networks of metabolic enzymes. Complex mathematical modeling of metabolic pathways, enzymatic activity and the flux of metabolites through metabolic enzymatic reactions within diseased tissues allow us to identify novel biological parameters that can be measured to characterize a disease state or the effect of therapy, or biomarkers, and targets for drug discovery.

Our understanding of metabolism within diseased tissues enables the development of methods to measure the effect of a drug on the target of interest and the patient, or pharmacodynamic markers, and patient selection strategies for clinical development. Utilizing our approach we identify altered metabolic pathways within abnormal cells. Altered metabolic pathways generate disease-specific metabolic fingerprints, comprising patterns of metabolite levels, which are the amounts of particular metabolites, that can be exploited in both discovery and development of novel therapeutics. Metabolites make ideal biomarkers because they are readily measured in the target tissues and blood. Metabolic biomarkers can identify appropriate patients for clinical trials, serve as pharmacodynamic markers to characterize medicine/target engagement in patients, and permit the monitoring of patient response to therapy. The clinical development strategy for all of our product candidates will always include initial study designs that allow for genetically or biomarker defined patient populations, enabling the potential for proof of concept early in clinical development, along with the potential for accelerated approval.

We have assembled a set of core capabilities at the intersection of cellular biology and metabolism, centered on the expertise of our founding scientists who are widely considered to be the thought leaders in cancer metabolism—Lewis Cantley, Ph.D. (Director of the Cancer Center at Weill Cornell Medical College and New York Presbyterian Hospital), Tak Mak, Ph.D. (Professor of Medical Biophysics, University of Toronto) and Craig Thompson, M.D. (President and CEO of Memorial Sloan-Kettering Cancer Center)—as well as on the strength of our management team, including our CEO, David Schenkein, M.D., and a group of world class scientists. We have built an exceptional team of cancer biologists, enzymologists and a core group of metabolomic experts that interrogate cellular metabolism to identify key metabolic targets and biomarkers in cancer and IEMs. Our scientists have published numerous scientific papers since 2009, including several in both *Nature* and *Science*. We have also established an intellectual property portfolio consisting of over 100 patent applications worldwide, including multiple patent applications directed to our lead product candidates, together with trade secrets, know-how and continuing technological innovation.

[Table of Contents](#)

Our initial therapeutic area of focus is cancer. We are leveraging our expertise in metabolic pathways to discover, validate, develop and commercialize a pipeline of novel drug candidates. In April 2010, and subsequently amended in October 2011, we entered into a collaboration agreement with Celgene Corporation, or Celgene, focused on cancer metabolism. Under the collaboration, we are leading discovery, preclinical and early clinical development for all cancer metabolism programs. The discovery phase of the collaboration was initially set to expire in April 2014, subject to Celgene's option to extend the discovery phase for up to two additional years. In December 2013, Celgene notified us of its intent to extend the discovery phase for an additional year through April 2015. Celgene has the option to obtain exclusive rights for the further development and commercialization of certain of these programs, and we will retain rights to the others. For the programs that Celgene chooses to license, we may elect to participate in a portion of sales activities for the medicines from such programs in the United States. In addition, for certain of these programs, we may elect to retain full rights to develop and commercialize medicines from these programs in the United States. Through December 31, 2013, we have received approximately \$141.2 million in payments from Celgene and \$50.3 million in equity investments and are entitled to a \$20.0 million payment in 2014 as a result of the discovery term extension exercised in December 2013. We are also eligible to receive an additional extension payment, payments upon the successful achievement of specified milestones, reimbursements for certain development expenses and royalties on any product sales.

We believe that our competitive advantage and singular focus in understanding cellular metabolism has created disruptive knowledge in biology that we can exploit for the development of transformative medicines in cancer. Because there has not previously been a systematic approach to drug discovery in this field, we have had to demonstrate significant major advances, including:

- identification of unique and specific metabolic enzymes that are altered from normal cells within cancer cells and are directly involved in the pathogenesis of cancer;
- creation of selective small molecules with drug-like properties that preferentially target disease-associated enzymes;
- achievement of pharmacologic efficacy in *in vivo* models and our phase 1 study of AG-221; and
- discovery of novel biomarkers that identify the appropriate patients for clinical trials.

Our two most advanced cancer programs are targeting mutations in the enzymes isocitrate dehydrogenase 1 and 2, referred to as IDH1 and IDH2, respectively. Both program targets are genetically validated, which means the importance of such targets have been demonstrated based on genetics, and represent two of the most promising metabolic targets in cancer biology, as concluded by the leading scientific journal *Nature* in 2011. Extensive publications led by Agios scientists validate our belief that these mutations are initiating and driving events in many cancers. These two otherwise normal metabolic enzymes are mutated in a wide range of cancers, including both solid tumors and hematological malignancies. Our drug candidates are selective for the mutated form of IDH1 and IDH2 found in cancer cells. In September 2013, we initiated a phase 1 study for AG-221, the lead candidate in our IDH2 program, in patients with advanced hematologic malignancies with an IDH2-mutation, and in April 2014, we reported initial findings at the AACR Annual Meeting 2014 from the first two cohorts of patients treated with AG-221. We believe that the data we presented at the AACR Annual Meeting 2014 corroborate our approach in treating cancers that express specific mutations utilizing a precision medicine based approach. In March 2014, we initiated two phase 1 studies for our lead development candidate in the IDH1 program, AG-120, one in patients with either advanced hematologic malignancies and the second in patients with advanced solid tumors, both trials only enrolling patients with an IDH1 mutation. We exercised our option to obtain U.S. development and commercial rights for AG-120, in accordance with the terms of our agreement with Celgene, with Celgene retaining its option to ex-U.S. rights.

We are also focused on developing medicines to address IEMs, with a novel approach to orphan diseases for which no effective or disease-modifying therapy is currently available. A hallmark of IEMs is abnormal cellular metabolic activity due to a genetic defect, which results in the accumulation or deficit of certain metabolites or

[Table of Contents](#)

proteins, disrupting normal metabolic functions. We utilize stringent criteria when identifying which IEMs Agios will pursue. We focus on IEMs with a common set of attributes:

- single gene, single disease (i.e., monogenic disorders);
- high unmet medical need with evidence that there is progressive disease post-birth that can be addressed with therapy; and
- an adequate number of patients for prospective clinical trials.

We apply our core capabilities in exploring cellular metabolism to identify key cellular targets in affected cells and design novel small molecules with the potential to correct the metabolic defect in patients afflicted with these diseases. We have successfully used this approach in our most advanced IEM program—pyruvate kinase deficiency, or PK deficiency, a rare form of hereditary hemolytic anemia. The disease is characterized by mild to severe forms of anemia. There are no currently available treatments other than supportive care, which includes splenectomy, transfusion support and chelation, which refers to the removal of excess iron from the human body with a therapeutic agent. Our lead development candidate, AG-348, is a potent, orally available small molecule activator of the PKR enzyme, an isoform of PK that, when mutated, leads to PK deficiency. We started a single ascending dose-escalation phase I clinical trial for AG-348 in healthy volunteers in April 2014 and expect to start a multiple ascending dose-escalation phase I clinical trial in healthy volunteers in mid-2014.

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 IEMs. 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.”*
- *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.*

Our focus—cellular metabolism

Cellular metabolism refers to the set of life-sustaining chemical transformations within the cells of living organisms. The conversion of nutrients into energy via enzyme-catalyzed reactions allows organisms to grow and reproduce, maintain their structures, and respond to their environments. The chemical reactions of metabolism are organized into metabolic pathways, in which one chemical is transformed through a series of steps into another chemical, by a sequence of enzymes. Enzymes catalyze quick and efficient reactions, serve as key regulators of metabolic pathways, and respond to changes in the cell’s environment or signals from other cells. We believe our deep understanding of metabolic pathways within normal cells enables us to identify altered metabolic pathways within abnormal cells such as in rapidly proliferating cancers and IEMs.

Fundamental differences in the metabolism of normal cells and rapidly proliferating cancer cells were first discovered by Otto Warburg more than 80 years ago—an observation that earned him the Nobel Prize. Warburg demonstrated that in contrast to normal cells, which convert nutrients, such as sugar, into energy via a process known as the Krebs cycle, cancer cells ferment their sugar into lactic acid—a process known as aerobic glycolysis. It is now known that this allows the cancer cells to generate the building blocks they need to grow rapidly. The ability of the cancer cell to “rewire” its metabolic pathways to fuel its growth and survival has spawned an entirely new field of cancer biology known as cancer metabolism or tumor metabolism. It is only in

[Table of Contents](#)

the last decade that scientists have developed sophisticated tools to interrogate and evaluate metabolism within cancer or rapidly dividing cells. Agios' founders and scientific advisors have largely driven this intense focus on studying the metabolism of cancer cells.

Cancer metabolism is a new and exciting field of biology that provides a fundamentally different approach to treating cancer. Cancers become addicted to certain fuel sources and inherently alter their cellular machinery to change how they consume and utilize nutrients. Cancer cells increase the transport of nutrients into the cell by 200 - 400 fold compared to normal cells while also mutating metabolic enzymes to generate metabolites that fuel growth and altering gene expression of enzymes to divert energy production. Collectively, these changes afford cancer cells the ability to generate the building blocks that drive tumor growth. Inhibiting key enzymes in cancer cell specific metabolic pathways has the potential to disrupt tumor cell proliferation and survival without affecting normal cells, thus providing a powerful new intervention point for discovery and development of novel targeted, cancer therapeutics. We believe that this is an entirely novel approach to treating cancer, and our research is directed at identifying such metabolic targets and discovering medicines against them.

Validation of the concept of cancer cell metabolic rewiring and excessive nutrient uptake comes from the widespread use of positron emission tomography, or PET, to detect cancers. This medical imaging technology relies on the uptake of nutrients, namely sugar, into cells. Patients are injected with a radioactively labeled form of sugar, which is more rapidly consumed by cancer cells given their profound requirement for nutrients relative to normal tissues. PET imaging precisely locates cancerous areas throughout the body and provides for both a diagnostic and prognostic tool throughout cancer therapy.

The metabolic rewiring of cancer cells can also be linked to specific genetic alterations in oncogenes (which are genes that transform normal cells into tumor cells) and tumor suppressor genes (which are genes that are anti-oncogenic) responsible for cell signaling. These mutations in signaling pathways can drive excessive uptake of nutrients and altered metabolic pathways, thereby causing cancer formation. This cross-talk between cell signaling and metabolism offers multiple opportunities to treat cancer by combining Agios therapies directed against metabolic enzymes with existing or emerging standards of care.

In cancer, our target universe for creating novel transformative medicines is derived from the human cellular metabolic machinery, referred to as the "metabolome," containing 2,000 - 3,000 cellular metabolic enzymes, from which we anticipate that there will likely be between 50 - 100 novel targets for oncology. This represents one of the largest unexploited new classes of important targets in oncology. The Agios team has already studied more than 50 metabolic enzymes as possible important cancer targets. With our focus on targets that are distinct in cancer versus normal cells, we believe that they are likely to fall within three broad categories:

- a mutation leading to a unique metabolic enzyme only found in cancer;
- unique isoforms of metabolic enzymes that are found in the cancer and that are different in normal cells; and
- dysregulation of an entire metabolic pathway to feed the cancer's need for a specific metabolite or nutrient.

An understanding of metabolic pathways based solely on traditional biochemistry would underestimate the pervasive role of metabolism in essentially every aspect of biology. Recent work has demonstrated that many human diseases involve altered cellular metabolism—often genetically programmed—that disrupts normal physiology and leads to severe tissue dysfunction. Another area of unmet medical need is IEMs, severe and often life-threatening inherited childhood and adult diseases caused by a defect in a metabolic enzyme or pathway. Our core capabilities to interrogate the metabolic pathway of the disease have allowed us to create potential medicines that can restore the metabolic balance and potentially lead to disease-modifying therapies for these orphan diseases. Our approach is designed to develop treatment for the "right" patient identified by the genetic and metabolic alteration marked by their inherited disease.

[Table of Contents](#)

Our core capabilities and science

We believe that our capabilities in understanding both static and dynamic aspects of cellular metabolism are unique in the industry as demonstrated by our ability to identify and validate four novel, druggable targets. Among our key core capabilities to identify and validate novel enzyme targets are:

- ***Measurement of metabolites and metabolic pathways in cells and tissues using high throughput mass spectrometry.***
- ***Identification of candidate metabolic enzymes using flux biochemistry:*** In many circumstances, cancers and normal cells utilize multiple routes to produce the same metabolite. To identify the relevant target, we evaluate the kinetics of enzymes to determine the speed at which metabolites are moving along enzymatic pathways. This critically important technology is called “flux biochemistry” and is distinguished from the more conventional “static” metabolomics view. Flux biochemistry, by labeling the nutrients, allows us to create a pathway map by measuring the rate of filling and emptying of metabolic pools. This methodology, which precisely measures the rate at which a nutrient source is broken down and reassembled into cellular building blocks and biochemical energy, has been automated in a high throughput fashion at Agios. Experimental data is integrated with mathematical modeling of enzyme pathways to generate an accurate understanding of the metabolic dysregulation. This allows us to determine which enzyme is the “Achilles’ Heel” of a particular cancer or IEM.
- ***Mining of genomic data emerging from the public cancer genome sequencing efforts, utilizing our state of the art genomics and bioinformatics capabilities, to identify metabolic enzymes that are mutated or amplified in tumors:*** This provides insight into novel targets for therapy while facilitating a precision medicine approach to patient selection based on the genetic defect (e.g., mutant IDH1 and IDH2).
- ***Development of a multiplexed, barcoded RNAi depletion screening strategy, enabling us to interrogate the entire metabolome in a single experiment, both in cells and in tumor bearing animals:*** This technology allows us to identify novel targets in cancers of interest.
- ***Inhibition and activation of metabolic enzymes using structure-based design from crystal structures, computational chemistry, and high throughput chemical and fragment library screening.***

Our approach to drug discovery and development, and the utilization of precision medicine

We intend to apply our deep understanding of metabolism, coupled with our ability to create medicines that can inhibit or activate metabolic enzymes, to fundamentally change the way cancer and IEMs are treated. We have the ability to identify and validate novel and druggable targets in both cancer and IEMs.

We begin the process to find and validate new targets by evaluating a cancer’s dependency on certain nutrients or enzymes in comparison to normal cells. We then utilize a number of techniques to determine if the cancer is dependent on the identified enzyme. The candidate enzyme target is inactivated, or turned off using genetic tools, first in tissue culture and then in xenograft models, in which representative tumors have been implanted in animals. Once inactivated, we can determine if turning off the enzyme stops the growth of the cancer cells *in vitro* and slows or stops the growth of a tumor in the xenograft model. If our findings are positive, we begin the process of searching for biomarkers that will enable our precision medicine approach of identifying the right patients to be eventually treated. In the early stages of biomarker development, we create a responder hypothesis, comparing the molecular genetics and metabolite patterns between cancers that respond to treatment to those that do not respond to enzyme inhibition. The process to design a small molecule drug candidate begins by determining the crystal structure of the enzyme. We create candidate molecules using structure-based design coupled with high throughput chemical screening, searching for small molecules that can inhibit the enzyme. The decision to enter the final and most expensive part of drug discovery, which is the refinement of the small molecule product candidates, is only made when we have completed all of these critical steps. The target is then

[Table of Contents](#)

considered “validated”. This rigorous process only allows the most promising programs to enter the last stage of drug discovery.

In our IEM portfolio, we use an equally rigorous set of validation techniques. We begin with an assessment of scientific literature and disease and genomic databases, applying text and data mining techniques, to identify IEMs that are caused by a mutation in a single metabolic enzyme, referred to as monogenic disorders. We perform a full evaluation of the clinical aspects of the disease, which includes an understanding of the severity of the disease, the progression of the disease manifestations post-birth and currently available treatments. We intend to focus only on diseases of a severe nature for which there are no available effective treatments, where intervention is likely to ameliorate disease manifestations, and where there are an adequate number of patients to conduct appropriate clinical trials. We conduct a detailed mutational and structural analysis of the metabolic enzyme and the entire pathway of interest to determine the scientific feasibility of intervention using small molecules to restore metabolic balance within the diseased cell. As in our efforts to develop therapeutics for cancer, we create a crystal structure of the enzyme to begin the process of drug design. We make candidate tool molecules using structure-based design coupled with high throughput chemical screening. To fully evaluate the potential of our lead molecules to lead to disease modifying effects we strive to develop an animal model of the disease by genetically inserting the mutated enzyme into animals (“knock-in mouse model”). Agios has selected a product candidate, AG-348, for the treatment of PK deficiency to advance into clinical development. We are currently conducting drug discovery for several other IEMs which are in various stages of research.

We will only progress drug candidates forward into phase 1 trials if we have the ability to select patients who are most likely to respond to a given therapy based on genetic or metabolic biomarkers. While many factors are considered critical to maximize the probability of technical success in the drug development process, perhaps none is more important than identifying highly specific and selective molecules aimed at the best possible targets for therapy coupled with the patients most likely to respond to that therapy. Our goal is to develop increasing confidence in the target and the patient population prior to entering human clinical trials and then initiate those first human trials in a patient population that has been selected based on target dependence using a biomarker. This approach, known as personalized or precision medicine, is used in the industry to lead to the potential for clear proof of concept in early human trials.

We believe our approach to drug discovery and development will lead to transformative medicines for patients. We plan to partner closely with worldwide regulatory authorities and to utilize all available methodologies such as orphan, fast track, accelerated approval and/or breakthrough therapy designations as appropriate. We expect that conducting clinical trials with a targeted agent in the appropriate clinical population has the potential to lead to very rapid development timelines. There are now multiple examples within oncology of drugs against novel targets that have progressed from first in human trial to regulatory approval in less than five years (e.g., Gleevec®, VELCADE® and Xalkori®).

Our development programs

We have leveraged our core capabilities in cellular metabolism to build a research and development engine that is focused in the therapeutic areas of cancer and IEMs. This engine has permitted us to discover proprietary first-in-class orally available small molecules as potential lead product candidates for each of several novel programs in development. All of our lead programs focus on diagnostically-identified patient populations with the potential for early clinical proof of concept and accelerated approval paths.

[Table of Contents](#)

The following table summarizes key information about our most advanced product candidates, each of which is described and discussed in further detail below:

Product candidate	Biomarker(s)	Initial indications	Stage of development	Commercial rights
Cancer metabolism programs:				
AG-221 (IDH2 mutant inhibitor)	Genotyping of IDH2 mutation; 2HG	All cancer patients with an IDH2 mutation in the following diseases: acute myelogenous leukemia, high risk myelodysplasia and myeloproliferative disorders, angio-immunoblastic non-Hodgkins T cell lymphoma, glioma, chondrosarcoma and other solid tumors	Phase 1 on-going	Agios: milestones and royalties Celgene: worldwide
AG-120 (IDH1 mutant inhibitor)	Genotyping of IDH1 mutation; 2HG	All cancer patients with an IDH1 mutation in the following diseases: glioma, chondrosarcoma, cholangiocarcinoma, acute myelogenous leukemia, high risk myelodysplasia and myeloproliferative disorders, and other hematological and solid tumors	Phase 1 on-going	Agios: milestones, cross-royalties, and U.S. rights Celgene: ex-U.S. rights
Inborn errors of metabolism programs:				
AG-348 (Pyruvate kinase (R) activator)	Genetic testing for mutation in the pyruvate kinase R gene	Patients with pyruvate kinase deficiency	Phase 1 initiated in April 2014	Agios: worldwide
AG-221 or other mutant inhibitor (IDH2 mutant inhibitor)	Genotyping of IDH2 mutation; 2HG	Patients with Type II D-2-hydroxyglutaric aciduria	Research	Agios: milestones and royalties Celgene: worldwide

Cancer

Background

In most cases of advanced cancer, the diagnosis still represents a death sentence to patients and their families. The American Cancer Society estimates that 1.66 million new cancer cases will be diagnosed in the U.S. in 2013. According to the Society, approximately 580,000 Americans and 7.1 million people worldwide will die of cancer in 2013. Cancer is the second leading cause of death in the United States, exceeded only by heart disease. Lung, colon and rectal, breast, and prostate cancer are the most prevalent cancers. Causes of cancer include environmental factors such as tobacco, chemicals, radiation and diet, genetic factors, such as inherited mutations, and endogenous hormone levels, and associated medical conditions such as certain viral infections and immunodeficiency.

Cancer is a disease characterized by unregulated cell growth. Cancer typically develops when the repair of genetic material in normal cells begins to fail and genes that regulate cell growth become disrupted. Carcinogens, or cancer causing agents, such as radiation, chemicals and hormones, can trigger changes to the genetic material of a cell, and typically prompt this disruption. Cells that have been disrupted may become cancerous, leading to

[Table of Contents](#)

changes in the cells' DNA, and ultimately uncontrolled growth. Cancer cells can spread to other areas of the body, or metastasize, and form tumors, which can destroy normal tissue or organs. Risk factors for cancer include family history, age, diet, and exogenous factors, such as exposure to ultraviolet sunlight and smoking. Cancers can be classified in stages to document disease severity, measured in stages of I to IV, generally based on tumor size, involvement of lymph nodes, and metastases.

The most common methods of treating patients with cancer are surgery, radiation and drug therapy. A cancer patient often receives treatment with a combination of these methods. Surgery and radiation therapy are particularly effective in patients in whom the disease is localized. Physicians generally use systemic drug therapies in situations in which the cancer has spread beyond the primary site or cannot otherwise be treated through surgery. The goal of drug therapy is to kill cancer cells or to damage cellular components required for rapid growth and survival of cancer cells. In many cases, drug therapy entails the administration of several different drugs in combination. Over the past several decades, drug therapy has evolved from non-specific drugs that kill both healthy and cancerous cells to drugs that target specific molecular pathways involved in cancer.

Cytotoxic chemotherapies

The earliest approach to cancer treatment was to develop drugs, referred to as cytotoxic drugs, that kill rapidly proliferating cancer cells through non-specific mechanisms, such as disrupting cell metabolism or causing damage to cellular components required for survival and rapid growth. While these drugs, (e.g. CYTOXAN®, Adriamycin®) have been effective in the treatment of some cancers they act in an indiscriminate manner, killing healthy as well as cancerous cells. Due to their mechanism of action, many cytotoxic drugs have a narrow dose range above which the toxicity causes unacceptable or even fatal levels of damage and below which the drugs are not effective in eradicating cancer cells.

Targeted therapies

The next approach to pharmacological cancer treatment was to develop drugs, referred to as targeted therapeutics, that target specific biological molecules in the human body that play a role in rapid cell growth and the spread of cancer. Targeted therapeutics are designed to preferentially kill cancer cells and spare normal cells, to improve efficacy and minimize side effects. The drugs are designed to either attack a target that causes uncontrolled growth of cancer cells because of either a specific genetic alteration primarily found in cancer cells but not in normal cells or a target that cancer cells are more dependent on for their growth in comparison to normal cells. Examples of effective targeted therapies include Herceptin®, Avastin® and Zelboraf®.

Emerging areas

Several new approaches to develop novel cancer treatments are underway. They include: treatment with drugs or other methods that stimulate the normal immune system to attack the cancer; antibody drug conjugates (Kadcyla™) that carry a powerful chemotherapy payload that is only released into the cancer cell; and drugs that target the changes in gene activity that occurs in cancer cells (epigenetics).

We believe that interrogating altered cellular metabolism—the way cancers take up and break down their nutrients—will lead to a new wave of important cancer treatments. Further, we believe that we must utilize a precision medicine approach, which will enable us to only enroll patients in clinical trials based on a biomarker likely to predict response and benefit.

Programs in isocitrate dehydrogenase (IDH)

The isocitrate dehydrogenase (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 (α -ketoglutarate), both of which are

Table of Contents

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.

We have identified selective development candidates that target the mutated forms of IDH1 and IDH2 which are each found in a wide range of solid and hematological cancers. We and our collaborators have demonstrated that these mutations initiate and drive cancer growth by blocking differentiation, also referred to as maturation, of primitive cells which leads to tumor formation and maintenance. We believe that inhibition of these mutated proteins will lead to clinical benefit for the subset of cancer patients whose tumors carry these mutations.

Agios research in IDH mutations in cancer

Academic researchers first identified mutations in either IDH1 or IDH2 in over 70% of patients with brain tumors, also known as gliomas. They also demonstrated that the mutated form of the enzyme IDH was no longer able to conduct its normal function of converting the metabolite isocitrate into alpha-ketoglutarate. Our scientists decided to examine the mutated pathway using our metabolic platform 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-hydroxyglutarate, or 2HG. This discovery was the subject of the first Agios publication in the scientific journal *Nature* (Dang et al 2009), and was subsequently deemed by *Nature* to be one of the most important recent discoveries in cancer research.

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. Recently, two published preclinical studies confirm that 2HG promotes tumorigenesis and that the effects of 2HG can be reversed with an IDH1 or IDH2 mutant specific inhibitor. 2HG is also an ideal biomarker to identify and follow cancer patients as they receive treatment with an IDH mutant specific inhibitor. In normal cells, 2HG is present at extremely low levels. However, in cancer cells that carry the IDH mutation, 2HG is produced at massively higher levels than in normal cells. It can easily be detected in samples from cancer specimens and in the blood of certain cancer patients. In patients with brain tumors it can also be imaged on an MRI.

In a cell based model it was demonstrated that the IDH1 mutation (R132H) promotes growth factor independence (i.e., transformation into cancerous cells) and blocks differentiation in hematopoietic cells. It was also demonstrated in this model that the cell’s transformation into cancer could be driven solely by the metabolite 2HG without any mutant enzyme. Lastly the transformation by IDH1 mutation was reversible with the use of an IDH1 mutant inhibitor. (Science Kaelin et al 2013). These results are illustrated in the graph below.

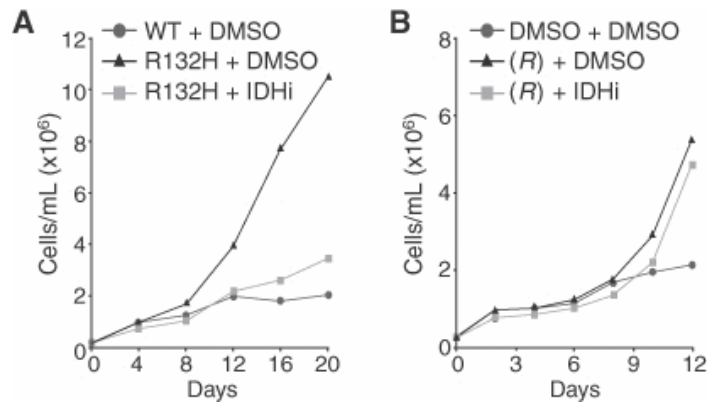
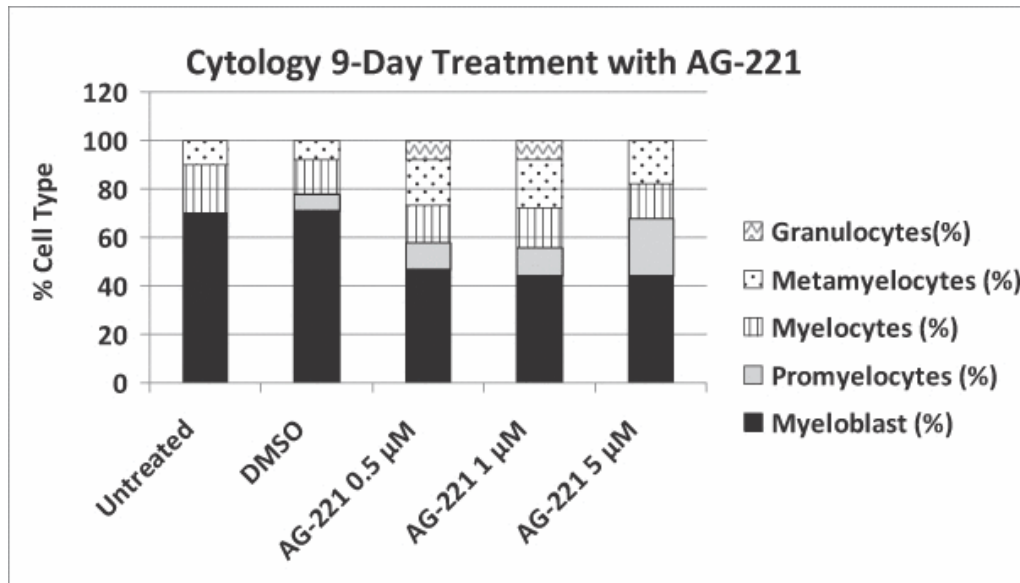


Table of Contents

Figure A demonstrates that insertion of R132H IDH1 mutation into TF-1 cells leads to growth factor independence which can be reversed by the addition of an Agios IDH1 mutant inhibitor. **Figure B** demonstrates that this transformation to growth factor independence can be replicated solely by the addition of 2HG(R). As expected, the IDH1 mutant inhibitor has no effect on the ability of exogenously administered 2HG to transform cells.

An *ex vivo* model is shown in the figure below, in which human acute myelogenous leukemia, or AML, bone marrow cells removed directly from a patient with a leukemia positive for an IDH2 mutation were maintained in short term culture. Treatment with the Agios clinical candidate AG-221 at concentrations achievable *in vivo* revealed a significant decrease in leukemia cells (myeloblasts) associated with evidence that normal cell maturation is returning, as noted by the increase in normal maturing cells (promyelocytes, myelocytes, metamyelocytes and granulocytes). These data provide *ex vivo* proof of concept that inhibitors targeting mutant IDH2 could induce differentiation in cells previously destined to form undifferentiated leukemic cells.



Taken together, these data provide compelling evidence that IDH1 or IDH2 mutant inhibitors induce differentiation in both cell based models and primary patient samples. The best example of an approved treatment that can reverse the block in differentiation induced by a mutation is all trans-retinoic acid (ATRA) for the treatment of acute promyelocytic leukemia. This single agent leads to complete responses in this form of leukemia, which is driven by a genetic alteration in the retinoic acid receptor, and is proof of principle that differentiation therapy can lead to major clinical activity in patients with acute leukemia.

In addition we have been able to generate AML mouse models leveraging primary samples from both IDH1 and IDH2 mutant positive patients. In an IDH1 mutant positive AML model, after 28 days of treatment with an Agios IDH1 mutant inhibitor, we were able to demonstrate early signs of single agent activity and synergy in combination with chemotherapy. In an IDH2 mutant positive AML model, we were able to reproduce an aggressive form of leukemia. Using our lead IDH2 mutant inhibitor AG-221, we demonstrated a dose dependent survival advantage in comparison to standard chemotherapy. The group of animals receiving the highest dose of AG-221 all survived until the study was completed. A dose dependent decrease in leukemia and evidence of normal differentiation was seen in all AG-221 treated animals. As we enter clinical development, these models

[Table of Contents](#)

help to inform our early strategies in designing single agent and combination clinical studies. In April 2014, we reported initial findings at the AACR Annual Meeting 2014 from the first two cohorts of patients treated with AG-221 in our first phase 1 clinical trial of patients with advanced hematological malignancies with an IDH2 mutation. 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.

Incidence of IDH mutations

To date, IDH1 and IDH2 mutations have been found to be prevalent in both solid and hematologic tumors. Mutations in IDH1 were identified through a genome-wide mutation analysis in glioblastoma multiforme, or GBM, the most common and aggressive type of brain cancer. High throughput deep sequencing revealed the presence of mutations in either IDH1 or IDH2 in more than 70% of grade II-III gliomas and secondary glioblastomas. Subsequent sequencing efforts revealed alterations in these two genes across additional cancers, including hematologic malignancies. Mutations in IDH1 and IDH2 are generally mutually exclusive and occur at very early stages of tumor development suggesting that they can promote tumorigenesis.

- IDH2 mutations appear to be most prevalent in hematologic tumors. Among patients with AML, IDH2 mutations have been observed in 15% of adult patients. Outside of AML, IDH2 mutations are found in a subset of other hematologic and non-hematologic cancers. Sequence analysis has shown that IDH2 mutations occur in approximately 5% of patients with myelodysplastic syndrome, or MDS, or myeloproliferative neoplasms, or MPN. IDH2 mutations have also been found in several solid tumor types such as melanoma, glioma and chondrosarcoma.
- IDH1 mutations appear to be most prevalent in solid tumors. Among patients with gliomas (low grade glioma and secondary glioblastoma), IDH1 mutations have been observed in 70% of patients. Outside of gliomas, mutations have been found in a subset of other solid and hematologic cancers. Importantly, mutations in IDH1 have been identified in difficult to treat cancers such as chondrosarcoma and cholangiocarcinoma where both the treatment options and prognosis for patients are poor. IDH1 mutations have also been found in several other solid tumor types such as colon, melanoma and lung.

Table of Contents

The following table summarizes our current initial estimates on the prevalence of IDH2 and IDH1 mutations in hematologic and solid tumors. We believe our estimates may expand as more cancer treatment centers screen for these IDH mutations.

<u>Mutation</u>	<u>Indications</u>	<u>% with IDH mutations</u>	<u>Estimated patient numbers(1)</u>
IDH2	Acute Myeloid Leukemia (AML)	15%	7,200
	MDS/MPN	5%	2,000
	Angio-immunoblastic T cell NHL	25%	400
	Others (melanoma, glioma, chondrosarcoma)	3-5%	1,500
Total			11,100
IDH1	Grade II, III glioma & secondary GBM	70%	11,000
	Chondrosarcoma	>50%	4,600
	AML	7.50%	3,600
	MDS/MPN	5%	2,000
	Intrahepatic Cholangiocarcinoma	20%	1,600
	Others (colon, melanoma, lung)	1-2%	8,000
	Total		

(1) Estimated U.S., Europe and Japan incidence

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. Based on our established non-clinically-based target profiling, as well as non-clinical *in vitro* and *in vivo* efficacy data, there is a clear rationale to develop AG-221 in defined target populations that harbor the IDH2 mutation.

We have conducted exploratory pharmacology studies to develop a model of IDH2 mutant-induced tumorigenesis and to characterize the binding, inhibition, and selectivity of AG-221. AG-221 is a potent inhibitor of the IDH2 mutant protein. We have demonstrated in *in vitro* experiments and in *in vivo* models that exposure to AG-221 reduces 2HG levels to those found in normal cells, reverses 2HG-induced histone hypermethylation, and induces differentiation in multiple leukemia cell models. Targeted inhibition of the IDH2 mutant also reversed the differentiation block in both TF-1 leukemia cells and primary AML cells derived from patients.

During 2013, we successfully completed IND-enabling studies on AG-221. The molecule has excellent pharmacological properties with a wide therapeutic index. In September 2013, we initiated our first phase 1 study for AG-221 in patients with advanced hematologic malignancies with an IDH2 mutation. This multi-center, global, multiple ascending dose trial primarily assesses safety and tolerability for AG-221 in adults with AML or related diseases. Secondary endpoints will evaluate the pharmacokinetics and pharmacodynamics properties of AG-221 and determine if preliminary efficacy signals can be measured. The initial proof of mechanism will require the reduction of the metabolite 2HG in response to drug treatment. In April 2014, we reported initial findings from the first two cohorts of patients treated with AG-221. The initial phase 1 data were presented during a symposium titled “Novel Immune and Targeted Therapies for Hematological Malignancies and Solid Tumors” at the AACR Annual Meeting 2014. A total of 10 patients with relapsed or refractory AML, which

[Table of Contents](#)

means that 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 the 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 to 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 a 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 are continuing to receive drug.

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.

AG-221 has been well tolerated to date, with no dose-limiting toxicities reported. Within the 22 patients enrolled as of March 20, 2014, possible drug-related severe adverse events were reported in two patients. These included one patient with an abnormally elevated white blood count and one patient with confusion and respiratory failure concomitant with infection common in patients with AML and related diseases due to a lack of infection-fighting white blood cells.

We are encouraged by the degree of clinical activity and tolerability observed in the first two cohorts of patients (30 mg and 50 mg twice a day). 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. As the maximum tolerated dose has not been reached for AG-221, the dose escalation portion of the trial continues. Given the long half-life observed, we have expanded the trial to include once daily dosing cohorts, beginning with 100 mg. Multiple expansion cohorts are expected to begin later this year after an appropriate dose and schedule are selected.

We intend to conduct subsequent trials in patients with other cancers carrying the IDH2 mutation and in combination with other anti-cancer agents. We plan to pursue additional clinical studies, evaluating both single-agent as well as combination therapy in patients with serious and life-threatening hematological and solid tumors that harbor IDH2 mutation, in the most efficient manner as we seek to establish the safety and effectiveness of AG-221. The potential regulatory pathway (i.e., conventional or accelerated approval) will be determined by data emerging from the early development program.

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. Importantly, mutations in IDH1 have been identified in difficult to treat cancers such as chondrosarcoma and cholangiocarcinoma where both the treatment options and prognosis for patients are poor. These are indications where the standard of care treatment options are limited, thus providing an opportunity for more rapid development of an IDH1 mutant inhibitor. Based on our nonclinical *in vitro* and *in vivo* efficacy data, there is a clear rationale to develop AG-120 in defined target populations that harbor the IDH1 gene mutation.

[Table of Contents](#)

We have successfully filed an IND for AG-120 that has been accepted by the FDA. The molecule has excellent pharmacological properties with a wide therapeutic index. 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 will only enroll patients that carry an IDH1 mutation.

Other programs

In addition to our lead IDH2 and IDH1 programs, we are in earlier stages of validation and drug discovery on multiple novel programs.

Inborn errors of metabolism

Background

IEMs are a broad group of more than 600 orphan genetic diseases caused by mutations of single metabolic genes. In these disorders, the defect of a single metabolic enzyme disrupts the normal functioning of a metabolic pathway, leading to either aberrant accumulation of “upstream” metabolites which may be toxic or interfere with normal function or reduced ability to synthesize essential “downstream” metabolites or other critical cellular components. IEMs are also referred to as congenital metabolic diseases or rare genetic metabolic diseases.

The term inborn error of metabolism was coined by a British physician, Archibald Garrod (1857–1936), in the early 20th century. He is known for work that prefigured the “one gene-one enzyme” hypothesis, and his seminal text, *Inborn Errors of Metabolism*, was published in 1923. Traditionally, IEMs were categorized as disorders of carbohydrate metabolism, amino acid metabolism, organic acid metabolism, or lysosomal storage diseases. In recent decades, hundreds of new IEMs have been discovered and the categories have proliferated.

Most of these diseases are rare or ultra-rare orphan diseases, often with severe or life-threatening features. A disorder is considered orphan if it affects fewer than 200,000 people in the United States, or fewer than five per 10,000 people in the European Union. In a study in British Columbia, the overall incidence of IEMs was estimated to be 70 per 100,000 live births or one in 1,400 births, overall representing more than approximately 15% of single gene disorders in the population. Incidence of a single IEM can vary widely but is generally rare, usually equal to or less than one per 100,000 births. Many IEMs are likely to be under-diagnosed given the lack of available therapies or diagnostics and the rarity of the condition.

Current treatment options for these disorders are limited. Diet modification or nutrient supplementation can be beneficial in some IEMs. Several of these disorders, from a group known as lysosomal storage diseases, have been treated successfully with enzyme replacement therapy, or ERT, the therapeutic administration of a functional version of the defective enzyme. Examples of ERTs for lysosomal storage disorders include Fabrazyme® for Fabry disease, Myozyme® for Pompe disease, Cerezyme® for Gaucher disease, and Elaprase® for Hunter syndrome.

Unfortunately, most mutations driving IEMs are intracellular and not amenable for treatment with enzyme replacement therapies. As a result, despite the promising progress made for patients with a small group of these diseases, the vast majority of patients with IEMs have few therapeutic options available, and the standard of care is palliative, meaning treatment of symptoms with no effect on underlying disease mechanisms. We are taking a novel small molecule approach to correct the metabolic defects within diseased cells with a goal of developing transformative medicines for patients.

Pyruvate kinase deficiency program

Pyruvate kinase, or PK, is the enzyme involved in the second to last reaction in glycolysis—the conversion of glucose into lactic acid. This enzyme is critical for the survival of the cell and has several tissue-specific isoforms (PKR, PKL, PKM1 and PKM2). PKR is the isoform of pyruvate kinase which is present in red blood cells. Mutations in PKR cause defects in red cell glycolysis and leads to a hematological IEM known as pyruvate kinase deficiency, or PK deficiency. Glycolysis is the only pathway available for red blood cells to maintain the production of ATP, or Adenosine-5'-triphosphate, which transports chemical energy within cells for metabolism. Accordingly, total absence of the PKR gene is not compatible with life. PK deficiency leads to a shortened life-

[Table of Contents](#)

span for red blood cells and is the most common form of non-spherocytic hemolytic anemia in humans. The disease is autosomal recessive, meaning children inherit one mutated form of PKR from one parent and the second mutated form from the other parent. Children with the disease produce PKR enzyme that has only a fraction of the normal level of activity (generally <50%). Parents of affected children have only one copy of the mutated PKR enzyme and are clinically normal.

PK deficiency is a rare disorder and disease understanding is still evolving. Several published epidemiology studies estimated prevalence of PK deficiency between three to nine affected patients per million. Agios estimates that between 1,000-3,000 diagnosed patients are alive in the U.S., with similar numbers in Europe, and we believe that the disease is likely under-diagnosed. There is no unique ethnic or geographic representation of the disease. The disease manifests by mild to severe forms of anemia caused by the excessive premature destruction of red blood cells. The precise mechanism for the destruction is not well understood but is thought to result from membrane instability secondary to the metabolic defect caused by the low level of PKR enzyme. The hemolysis is “extra-vascular” in that the red blood cells are destroyed in small capillaries or organs and not spontaneously breaking open in the circulation.

The disease typically presents during early infancy with jaundice and severe anemia, which can require immediate life-saving intervention via replacement of the infant’s entire blood system with a donor’s blood, referred to as an exchange transfusion. Children are classified as either severe disease (hemoglobin <8gm/dl and life-long need for transfusions) or moderate (hemoglobin levels of 8-10 gm/dl and intermittent or rare transfusion support). Adults also fall into two similar categories: severe, which requires chronic transfusions, often monthly, or moderate, which requires intermittent transfusions. Both moderate and severe patients may develop a severe hemolytic crisis in the face of infections or other “stressful” situations and face life-long anemia with an impact on the quality of life.

There is no treatment for this disease other than transfusion support and the disease is life-long. The true natural history and impact of life-long hemolysis is unknown. Chronic iron overload related to transfusions and possibly the disease itself can lead to life-threatening complications. Splenectomy, which refers to removal of the spleen, can modify the symptoms of the disease in some patients but has minimal impact on the ongoing hemolysis. Agios has commissioned and initiated a natural history study that will collect retrospective medical history, routine clinical, and quality of life measures for patients with PK deficiency.

AG-348: lead PKR program

Our development candidate AG-348 is an orally available, potent small molecule activator of PKR. Preclinical *in vitro* data demonstrate that these activators can significantly enhance both the activity and the stability of the majority of the common PKR mutants. This degree of enzyme activation leads to a meaningful correction of the metabolic imbalance normally found within mutant cells. Red blood cells have been obtained from patients with severe and moderate PK deficiency where *ex vivo* studies have demonstrated enzyme activation and metabolic improvement. We have successfully completed IND-enabling studies on AG-348 and the molecule has excellent pharmacological properties with a wide therapeutic index. We started a single ascending dose-escalation phase 1 clinical trial for AG-348 in healthy volunteers in April 2014 and expect to start a multiple ascending dose-escalation phase 1 clinical trial in healthy volunteers in mid-2014.

We believe the clinical and regulatory strategy for our PK deficiency program has well established primary and secondary endpoints similar to that of other approved medicines developed for the treatment of other anemias.

Type II D-2 hydroxyglutaric aciduria: IDH2 non-cancer indication

A germline mutation in IDH2, identical to that of cancer patients, has recently been discovered in patients with an ultra-rare, extremely debilitating, and uniformly fatal, genetic neurometabolic disorder called Type II D-2 hydroxyglutaric aciduria. Type II D-2-HGA patients develop a range of medical complications, including

[Table of Contents](#)

developmental delay, seizures, hypotonia, epilepsy, cardiomyopathy, and dysmorphic features. Few affected patients survive past their teens, with the majority dying from cardiac and/or central nervous system disease.

In addition to our planned cancer development program, we will potentially evaluate the use of AG-221 for Type II D-2 HGA. We have initiated collaborations with global metabolic clinical centers to further explore the prevalence and incidence of the disease. There have been potentially 50 reported cases globally, however there is uncertainty as to the number of patients. In addition, we have created a genetically derived mouse model that appears to replicate the disease. This model should allow us to conduct profiling and efficacy studies with AG-221 and other IDH2 mutant specific compounds.

Other preclinical IEM programs

Our approach is to identify a series of IEMs which share the following common set of features:

- single gene defect;
- severe clinical presentation with evidence that disease damage is progressive but potentially reversible;
- adequate number of patients identified for prospective clinical trials; and
- an assessment of the target, based upon a detailed mutational, structural, and metabolomic analysis, to determine if a small molecule approach to correcting the disease is possible.

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 or before April 14, 2014. Celgene has the option to extend such period through April 14, 2016 and in December 2013, notified us of its intention to extend the period through April 14, 2015. We refer to such four to six year period as the discovery phase of the collaboration. We are leading discovery, preclinical and early clinical development for all cancer metabolism programs under the collaboration. We have nominated two development candidates, AG-221 and AG-120, during the discovery phase and both development candidates have been confirmed by a joint research committee, or JRC, pursuant to the agreement—our IDH1 and IDH2 development candidates. Primarily all of our revenues for the years ended December 31, 2013, 2012 and 2011 are from payments received under our agreement with Celgene.

Discovery programs with development candidates. Celgene may elect to progress into preclinical development each discovery program for which we nominate and the JRC confirms a development candidate during the discovery phase. If Celgene makes such an election, we will, at our expense, conduct studies required to meet the requirements for filing an IND, or IND-enabling studies, and, following their successful completion as confirmed by the JRC, we will file an IND to commence clinical studies of such development candidate. If the FDA accepts the IND, Celgene may request that we conduct an initial phase 1 study at our expense, for which Celgene will pay us at least \$5 million upon enrollment of the last patient in such study unless such program becomes a split licensed program, as described below.

Celgene may elect to convert each discovery program for which we have nominated a development candidate into a co-commercialized licensed program, the attributes of which are described below. We have the right, exercisable during a specified period following FDA acceptance of the applicable IND, to convert one of every three co-commercialized licensed programs into a split licensed program, for which we retain the United States rights, other attributes of which are further described below. Our IDH2 program is not a split licensed program. We may elect to opt out of any split licensed program, after which such split licensed program will revert to a co-commercialized licensed program, and Celgene will have the right, but not the obligation, to commercialize medicines from such program in the United States. We have chosen AG-120, and our IDH1 program, as our first split licensed program.

[Table of Contents](#)

We will retain our rights to the development candidate and certain other compounds from any discovery program for which we nominate and the JRC confirms a development candidate and that Celgene does not elect to progress into preclinical development or convert into a co-commercialized licensed program. In addition, if the JRC or Celgene elects not to continue collaboration activities with respect to a particular target, either we or Celgene would have the right independently to undertake a discovery program on such target and would have rights to specified compounds from such program, subject to certain “buy-in” rights granted to the other party.

Further development and commercialization of programs. The agreement provides for three types of licensed programs discussed above: co-commercialized licensed programs, split licensed programs, and buy-in programs. Celgene’s and our rights and obligations under each licensed program vary depending on the type of licensed program, as described below.

- *Co-commercialized licensed programs:* Celgene will lead and, following either IND acceptance by the FDA or, if Celgene requests us to conduct the initial phase 1 study, completion of such study, will fund global development and commercialization of each co-commercialized licensed program. We have the right to participate in a portion of sales activities in the United States for medicines from co-commercialized programs in accordance with the applicable commercialization plan.
- *Split licensed programs:* Celgene will lead development and commercialization outside the United States, and we will lead development and commercialization in the United States, for each split licensed program. We and Celgene will equally fund the global development costs of each split licensed program that are not specific to any particular region or country, Celgene will be responsible for development and commercialization costs specific to countries outside the United States, and we will be responsible for development and commercialization costs specific to the United States.
- *Buy-in programs:* The party that was conducting an independent program that became a buy-in program will lead the development and commercialization of such program. The party that elects to buy in to such program will be responsible for funding a portion of development costs incurred after acceptance of an IND for a buy-in program compound, and the lead party will be responsible for all other development costs and all commercialization costs for medicines from such buy-in program.

In addition, Celgene may license certain discovery programs for which we did not nominate or the JRC did not confirm a development candidate during the discovery phase and for which Celgene will lead and fund global development and commercialization. We refer to these as picked licensed programs.

Collaboration governance. The collaboration is managed by a set of joint committees comprised of equal numbers of representatives from each of us and Celgene. The joint steering committee, or JSC, oversees and coordinates the overall conduct of the collaboration. The JRC oversees and coordinates discovery, research and preclinical activities with respect to each discovery program during the discovery phase. A joint development committee, or JDC, for each licensed program will oversee and coordinate development (including manufacturing of clinical supply) of medicines under such licensed program. The joint commercialization committee, or JCC, will oversee the commercialization (including manufacturing of commercial supply) of medicines under the licensed programs.

Diligence. We and Celgene each must use commercially reasonable efforts to perform all activities for which such party is responsible under the collaboration.

Exclusivity. During the discovery phase, we may not directly or indirectly develop, manufacture or commercialize, except pursuant to the agreement, any product or product candidate for any cancer indication with specified activity against certain metabolic targets (except in connection with certain specified third-party collaborations), or with specified activity against any collaboration target (or any target for which Celgene is conducting an independent program that we elected not to buy in to) for any indication. Following the discovery phase until termination or expiration of the agreement, either in its entirety or with respect to the relevant program, we may not directly or indirectly develop, manufacture or commercialize, outside of the collaboration, any therapeutic modality with specified activity against any collaboration target that is within a licensed program

[Table of Contents](#)

or against any former collaboration target against which Celgene is conducting an independent program under the agreement. Pursuant to the terms of the first amendment to the agreement, we have the right to develop, manufacture and commercialize outside of the collaboration certain medicines directed against PKR for certain indications, including PK deficiency, subject to specified conditions, including a right of first negotiation that Celgene may exercise if we intend to license our PKR program to any third party.

Financial terms. Under the terms of the agreement, we received an upfront payment of approximately \$121.2 million. In addition, Celgene purchased 5,190,551 shares of our series B convertible preferred stock at a price of \$1.70 per share, resulting in net proceeds to us of approximately \$8.8 million. Celgene made a payment to us of \$20.0 million pursuant to an October 2011 amendment in consideration of extending the discovery phase until April 14, 2014. In December 2013, Celgene notified us of its intent to extend the discovery phase of the strategic collaboration by one year, extending the initial period of exclusivity from four years to five years. As a result of the extension, we are entitled to, and expect to receive a \$20.0 million extension payment from Celgene in May 2014.

We may be eligible to receive an additional \$20.0 million through a final extension payment to extend the discovery phase until April 2016. We may also be eligible to receive up to \$120.0 million in potential milestone payments payable for each licensed program other than buy-in programs. The potential milestone payments under the agreement for such licensed program are comprised of: (i) a \$25.0 million milestone payment upon achievement of a specified clinical development milestone event, (ii) up to \$70.0 million in milestone payments upon achievement of specified regulatory milestone events, and (iii) a \$25.0 million milestone payment upon achievement of a specified commercial milestone event (for co-commercialized and certain other licensed programs only). In addition, we are eligible to receive a payment of \$22.5 million upon achievement of an early clinical development milestone event for certain co-commercialized licensed programs. We are also eligible to receive a one-time payment of \$25.0 million upon dosing of the last patient in a phase 2 study for the first split licensed program, our IDH1 Program, AG-120.

We are eligible to receive royalties at tiered, low- to mid-teen percentage rates on Celgene's net sales of medicines from licensed programs. We are also eligible to receive royalties at a fixed, mid-single digit percentage rate on net sales of medicines from certain Celgene independent programs. We may be obligated to pay Celgene royalties at tiered, low- to mid-teen percentage rates on our net sales in the United States of medicines from split licensed programs and on net sales of medicines from buy-in programs for which we are the commercializing party.

Termination. Celgene may terminate the agreement for convenience in its entirety or with respect to one or more programs upon ninety days written notice to us. Either we or Celgene may terminate the agreement, in its entirety or with respect to one or more programs, if the other party is in material breach and fails to cure such breach within the specified cure period; however, if such breach relates solely to a specific program, the non-breaching party may terminate the agreement solely with respect to such program. Either we or Celgene may terminate the agreement in the event of specified insolvency events involving the other party.

If Celgene terminates the agreement as a result of our uncured material breach, then certain of our rights and certain of Celgene's obligations described above would change with respect to the terminated program(s), including, for example: the licenses we granted to Celgene would become perpetual; milestone payments to which we may be entitled may be reduced or eliminated; royalties to which we may be entitled may be reduced or eliminated; we would lose the development and commercialization rights for the United States for any terminated split licensed program; and we would grant Celgene specified rights, and take specified actions, to assist Celgene in continuing the development, manufacture and commercialization of medicines for the United States from each terminated split licensed program.

If Celgene terminates the agreement for convenience or if we terminate the agreement as a result of Celgene's uncured material breach, the licenses we granted to Celgene with respect to the terminated program(s) will end,

[Table of Contents](#)

and we will have specified rights for, and Celgene will take specified actions to assist us in continuing, the development, manufacture and commercialization of medicines from each terminated program.

Intellectual property

Our commercial success depends in part on our ability to obtain and maintain proprietary or intellectual property protection for our product candidates and our core technologies, including novel biomarker and diagnostic discoveries, and other know-how, to operate without infringing on the proprietary rights of others and to prevent others from infringing our proprietary or intellectual property rights. Our policy is to seek to protect our proprietary and intellectual property position by, among other methods, filing U.S., international and foreign patent applications related to our proprietary technology, inventions and improvements that are important to the development and implementation of our business. We also rely on trade secrets, know-how and continuing technological innovation to develop and maintain our proprietary and intellectual property position.

We file patent applications directed to our key product candidates, including AG-221, AG-120 and AG-348, in an effort to establish intellectual property positions regarding new chemical entities relating to these product candidates as well as uses of new chemical entities in the treatment of diseases. We also seek patent protection with respect to biomarkers that may be useful in selecting the right patient population for therapies with our product candidates. As of December 31, 2013, we had a portfolio of pending U.S. provisional and non-provisional patent applications and foreign patent applications. Any patents that may issue from these applications would expire between 2027 and 2035. A significant portion of our pending patent applications pertain to our key development programs, including AG-221, AG-120 and AG-348.

In addition to the pending patent applications covering our most advanced product candidates, our portfolio also includes pending patent applications relating to diagnostic methods for detecting various IDH1 and IDH2 mutations, as well as compositions of matter and methods of use directed to modulating other metabolic targets.

The term of individual patents depends upon the legal term for patents in the countries in which they are obtained. In most countries, including the United States, the patent term is 20 years from the earliest filing date of a non-provisional patent application. In the United States, a patent's term may be lengthened by patent term adjustment, which compensates a patentee for administrative delays by the U.S. Patent and Trademark Office, or the USPTO, in examining and granting a patent, or may be shortened if a patent is terminally disclaimed over an earlier filed patent. The term of a patent that covers a drug or biological product may also be eligible for patent term extension when FDA approval is granted, provided statutory and regulatory requirements are met. In the future, if and when our product candidates receive approval by the FDA or foreign regulatory authorities, we expect to apply for patent term extensions on issued patents covering those products, depending upon the length of the clinical trials for each medicine and other factors. There can be no assurance that any of our pending patent applications will issue or that we will benefit from any patent term extension or favorable adjustment to the term of any of our patents.

As with other biotechnology and pharmaceutical companies, our ability to maintain and solidify our proprietary and intellectual property position for our product candidates and technologies will depend on our success in obtaining effective patent claims and enforcing those claims if granted. However, patent applications that we may file or license from third parties may not result in the issuance of patents. We also cannot predict the breadth of claims that may be allowed or enforced in our patents. Any issued patents that we may receive in the future may be challenged, invalidated or circumvented. For example, we cannot be certain of the priority of inventions covered by pending third-party patent applications. If third parties prepare and file patent applications in the United States that also claim technology or therapeutics to which we have rights, we may have to participate in interference proceedings in the USPTO to determine priority of invention, which could result in substantial costs to us, even if the eventual outcome is favorable to us. In addition, because of the extensive time required for clinical development and regulatory review of a product candidate we may develop, it is possible that, before any of our product candidates can be commercialized, any related patent may expire or remain in force for only a short period following commercialization, thereby reducing any advantage of any such patent.

In addition to patents, we rely upon unpatented trade secrets and know-how and continuing technological innovation to develop and maintain our competitive position. We seek to protect our proprietary information, in

[Table of Contents](#)

part, using confidentiality agreements with our collaborators, scientific advisors, employees and consultants, and invention assignment agreements with our employees. We also have agreements requiring assignment of inventions with selected consultants, scientific advisors and collaborators. The confidentiality agreements are designed to protect our proprietary information and, in the case of agreements or clauses requiring invention assignment, to grant us ownership of technologies that are developed through a relationship with a third party.

With respect to our proprietary cellular metabolism technology platform, we consider trade secrets and know-how to be our primary intellectual property. Trade secrets and know-how can be difficult to protect. In particular, we anticipate that with respect to this technology platform, these trade secrets and know-how will over time be disseminated within the industry through independent development, the publication of journal articles describing the methodology, and the movement of personnel skilled in the art from academic to industry scientific positions.

Competition

The pharmaceutical and biotechnology industries are characterized by rapidly advancing technologies, intense competition and a strong emphasis on proprietary products. While we believe that our technology, development experience and scientific knowledge provide us with competitive advantages, we face potential competition from many different sources, including major pharmaceutical, specialty pharmaceutical and biotechnology companies, academic institutions and governmental agencies and public and private research institutions. Any product candidates that we successfully develop and commercialize will compete with existing therapies and new therapies that may become available in the future.

We compete in the segments of the pharmaceutical, biotechnology and other related markets that address cancer metabolism and IEMs. There are other companies working to develop therapies in the field of cancer metabolism and IEMs. These companies include divisions of large pharmaceutical companies and biotechnology companies of various sizes.

Cancer metabolism. In the field of cancer metabolism, our principal competitors include AstraZeneca, Calithera Biosciences, Cornerstone Pharmaceuticals, Inc., Eli Lilly and Company, Forma Therapeutics Holdings, LLC, GlaxoSmithKline plc, Merck & Co., Novartis International AG, Pfizer, Inc., and Roche Holdings, Inc., and its subsidiary Genentech, Inc.

The most common methods of treating patients with cancer are surgery, radiation and drug therapy, including chemotherapy, hormone therapy and targeted drug therapy. There are a variety of available drug therapies marketed for cancer. In many cases, these drugs are administered in combination to enhance efficacy. While our product candidates may compete with many existing drug and other therapies, to the extent they are ultimately used in combination with or as an adjunct to these therapies, our product candidates will not be competitive with them. Some of the currently approved drug therapies are branded and subject to patent protection, and others are available on a generic basis. Many of these approved drugs are well established therapies and are widely accepted by physicians, patients and third-party payors. In general, although there has been considerable progress over the past few decades in the treatment of cancer and the currently marketed therapies provide benefits to many patients, these therapies all are limited to some extent in their efficacy and frequency of adverse events, and none are successful in treating all patients. As a result, the level of morbidity and mortality from cancer remains high.

In addition to currently marketed therapies, there are also a number of medicines in late stage clinical development to treat cancer. These medicines in development may provide efficacy, safety, convenience and other benefits that are not provided by currently marketed therapies. As a result, they may provide significant competition for any of our product candidates for which we obtain market approval.

Inborn errors of metabolism. In the field of IEMs, our principal competitors include Alexion Pharmaceuticals, Inc., BioMarin Pharmaceutical, Inc., Genzyme, a Sanofi company, and Shire Biochem, Inc.

[Table of Contents](#)

The most common methods for treating patients with IEMs are dietary restriction, dietary supplementation or replacement, treatment of symptoms and complications, gene therapy, organ transplant and enzyme replacement therapies. There are a number of marketed enzyme replacement therapies available for treating patients with IEMs. In some cases, these treatment methods are used in combination to improve efficacy. While our product candidates may compete with existing medicines and other therapies, to the extent they are ultimately used in combination with or as an adjunct to these therapies, our product candidates will not be competitive with them. In addition to currently marketed therapies, there are also a number of products that are either enzyme replacement therapies or gene therapies in various stages of clinical development to treat IEMs. These products in development may provide efficacy, safety, convenience and other benefits that are not provided by currently marketed therapies. As a result, they may provide significant competition for any of our product candidates for which we obtain market approval.

Many of our competitors may have significantly greater financial resources and expertise in research and development, manufacturing, preclinical testing, conducting clinical trials, obtaining regulatory approvals and marketing approved medicines than we do. Mergers and acquisitions in the pharmaceutical, biotechnology and diagnostic industries may result in even more resources being concentrated among a smaller number of our competitors. These competitors also compete with us in recruiting and retaining qualified scientific and management personnel and establishing clinical trial sites and patient registration for clinical trials, as well as in acquiring technologies complementary to, or necessary for, our programs. Smaller or early stage companies may also prove to be significant competitors, particularly through collaborative arrangements with large and established companies.

The key competitive factors affecting the success of all of our product candidates, if approved, are likely to be their efficacy, safety, convenience, price, the effectiveness of companion diagnostics in guiding the use of related therapeutics, the level of generic competition and the availability of reimbursement from government and other third-party payors.

Our commercial opportunity could be reduced or eliminated if our competitors develop and commercialize medicines that are safer, more effective, have fewer or less severe side effects, are more convenient or are less expensive than any medicines that we may develop. Our competitors also may obtain FDA or other regulatory approval for their medicines more rapidly than we may obtain approval for ours, which could result in our competitors establishing a strong market position before we are able to enter the market. In addition, our ability to compete may be affected in many cases by insurers or other third-party payors seeking to encourage the use of generic medicines. There are many generic medicines currently on the market for the indications that we are pursuing, and additional medicines are expected to become available on a generic basis over the coming years. If our therapeutic product candidates are approved, we expect that they will be priced at a significant premium over competitive generic medicines.

Manufacturing

We do not own or operate, and currently have no plans to establish, any manufacturing facilities. We currently rely, and expect to continue to rely, on third parties for the manufacture of our product candidates for preclinical and clinical testing, as well as for commercial manufacture of any products that we may commercialize. To date, we have obtained materials for AG-221, AG-120 and AG-348 for our ongoing phase 1 testing from third party manufacturers. We obtain our supplies from these manufacturers on a purchase order basis and do not have a long-term supply arrangement in place. We do not currently have arrangements in place for redundant supply for bulk drug substance. For all of our product candidates, we intend to identify and qualify additional manufacturers to provide the active pharmaceutical ingredient and fill-and-finish services prior to submission of a new drug application to the FDA.

AG-221, AG-120 and AG-348 are organic compounds of low molecular weight, generally called small molecules. They can be manufactured in reliable and reproducible synthetic processes from readily available starting materials. The chemistry is amenable to scale-up and does not require unusual equipment in the

[Table of Contents](#)

manufacturing process. We expect to continue to develop drug candidates that can be produced cost-effectively at contract manufacturing facilities.

We generally expect to rely on third parties for the manufacture of any companion diagnostics we develop.

Research and development expenses

For the years ended December 31, 2013, 2012 and 2011, company-sponsored research and development expenses were \$54.5 million, \$41.0 million and \$31.3 million, respectively.

Government regulation

Government authorities in the United States, at the federal, state and local level, and in other countries extensively regulate, among other things, the research, development, testing, manufacture, including any manufacturing changes, packaging, storage, recordkeeping, labeling, advertising, promotion, distribution, marketing, post-approval monitoring and reporting, import and export of pharmaceutical products, such as those we are developing.

United States drug approval process

In the United States, the FDA regulates drugs under the Federal Food, Drug, and Cosmetic Act, or FDCA, and implementing regulations. The process of obtaining regulatory approvals and the subsequent compliance with appropriate federal, state, local and foreign statutes and regulations requires the expenditure of substantial time and financial resources. Failure to comply with the applicable United States requirements at any time during the product development process, approval process or after approval, may subject an applicant to a variety of administrative or judicial sanctions, such as the FDA's refusal to approve pending applications, withdrawal of an approval, imposition of a clinical hold, issuance of warning letters and untitled letters, product recalls, product seizures, total or partial suspension of production or distribution injunctions, fines, refusals of government contracts, restitution, disgorgement of profits or civil or criminal penalties.

The process required by the FDA before a drug may be marketed in the United States generally involves the following:

- completion of preclinical laboratory tests, animal studies and formulation studies in compliance with the FDA's good laboratory practice, or GLP, regulations;
- submission to the FDA of an IND, which must become effective before human clinical trials may begin;
- approval by an independent institutional review board, or IRB, at each clinical site before each trial may be initiated;
- performance of adequate and well-controlled human clinical trials in accordance with good clinical practices, or GCP, to establish the safety and efficacy of the proposed drug for each indication;
- submission to the FDA of a new drug application, or NDA;
- satisfactory completion of an FDA inspection of the manufacturing facility or facilities at which the product is produced to assess compliance with current good manufacturing practices, or cGMP, requirements and to assure that the facilities, methods and controls are adequate to preserve the drug's identity, strength, quality and purity; and
- FDA review and approval of the NDA.

Preclinical studies and IND

Preclinical studies include laboratory evaluation of product chemistry and formulation, as well as *in vitro* and animal studies to assess the potential for adverse events and in some cases to establish a rationale for therapeutic

[Table of Contents](#)

use. The conduct of preclinical studies is subject to federal regulations and requirements, including GLP regulations for safety/toxicology studies. An IND sponsor must submit the results of the preclinical tests, together with manufacturing information, analytical data, any available clinical data or literature and plans for clinical studies, among other things, to the FDA as part of an IND. Some long-term preclinical testing, such as animal tests of reproductive adverse events and carcinogenicity, may continue after the IND is submitted. An IND automatically becomes effective 30 days after receipt by the FDA, unless before that time the FDA raises concerns or questions related to one or more proposed clinical trials and places the trial on clinical hold. In such a case, the IND sponsor and the FDA must resolve any outstanding concerns before the clinical trial can begin. As a result, submission of an IND may not result in the FDA allowing clinical trials to commence.

Clinical trials

Clinical trials involve the administration of the investigational new drug to human subjects under the supervision of qualified investigators in accordance with GCP requirements, which include, among other things, the requirement that all research subjects provide their informed consent in writing before their participation in any clinical trial. Clinical trials are conducted under written study protocols detailing, among other things, the objectives of the study, the parameters to be used in monitoring safety and the effectiveness criteria to be evaluated. A protocol for each clinical trial and any subsequent protocol amendments must be submitted to the FDA as part of the IND. In addition, an IRB at each institution participating in the clinical trial must review and approve the plan for any clinical trial before it commences at that institution, and the IRB must conduct continuing review. The IRB must review and approve, among other things, the study protocol and informed consent information to be provided to study subjects. An IRB must operate in compliance with FDA regulations. Information about certain clinical trials must be submitted within specific timeframes to the National Institutes of Health for public dissemination at www.clinicaltrials.gov.

Human clinical trials are typically conducted in three sequential phases, which may overlap or be combined:

- *Phase 1:* The drug is initially introduced into healthy human subjects or patients with the target disease or condition and tested for safety, dosage tolerance, absorption, metabolism, distribution, excretion and, if possible, to gain an early indication of its effectiveness.
- *Phase 2:* The drug is administered to a limited patient population to identify possible adverse effects and safety risks, to preliminarily evaluate the efficacy of the product for specific targeted diseases and to determine dosage tolerance and optimal dosage.
- *Phase 3:* The drug is administered to an expanded patient population in adequate and well-controlled clinical trials to generate sufficient data to statistically confirm the efficacy and safety of the product for approval, to establish the overall risk-benefit profile of the product and to provide adequate information for the labeling of the product.

Progress reports detailing the results of the clinical trials must be submitted at least annually to the FDA and, more frequently, if serious adverse events occur. Phase 1, phase 2 and phase 3 clinical trials may not be completed successfully within any specified period, or at all. Furthermore, the FDA or the sponsor may suspend or terminate a clinical trial at any time on various grounds, including a finding that the research subjects are being exposed to an unacceptable health risk. Similarly, an IRB can suspend or terminate approval of a clinical trial at its institution if the clinical trial is not being conducted in accordance with the IRB's requirements or if the drug has been associated with unexpected serious harm to patients.

Marketing approval

Assuming successful completion of the required clinical testing, the results of the preclinical and clinical studies, together with detailed information relating to the product's chemistry, manufacture, controls and proposed labeling, among other things, are submitted to the FDA as part of an NDA requesting approval to market the

[Table of Contents](#)

product for one or more indications. Under federal law, the submission of most NDAs is additionally subject to a substantial application user fee, currently exceeding \$1.8 million, and the sponsor of an approved NDA is also subject to annual product and establishment user fees, currently exceeding \$98,000 per product and \$520,000 per establishment. These fees are typically increased annually.

The FDA conducts a preliminary review of all NDAs within the first 60 days after submission before accepting them for filing to determine whether they are sufficiently complete to permit substantive review. The FDA may request additional information rather than accept an NDA for filing. In this event, the application must be resubmitted with the additional information. The resubmitted application is also subject to review before the FDA accepts it for filing. Once the submission is accepted for filing, the FDA begins an in-depth substantive review. The FDA has agreed to specified performance goals in the review of NDAs. Under these goals, the FDA has committed to review most such applications for non-priority products within 10 months, and most applications for priority review products, that is, drugs that the FDA determines represent a significant improvement over existing therapy, within six months. The review process may be extended by the FDA for three additional months to consider certain information or clarification regarding information already provided in the submission. The FDA may also refer applications for novel drugs or products that present difficult questions of safety or efficacy to an advisory committee, typically a panel that includes clinicians and other experts, for review, evaluation and a recommendation as to whether the application should be approved. The FDA is not bound by the recommendations of an advisory committee, but it considers such recommendations carefully when making decisions.

Before approving an NDA, the FDA typically will inspect the facility or facilities where the product is manufactured. The FDA will not approve an application unless it determines that the manufacturing processes and facilities are in compliance with cGMP requirements and adequate to assure consistent production of the product within required specifications. In addition, before approving an NDA, the FDA will typically inspect one or more clinical sites to assure compliance with GCP and integrity of the clinical data submitted.

The testing and approval process requires substantial time, effort and financial resources, and each may take many years to complete. Data obtained from clinical activities are not always conclusive and may be susceptible to varying interpretations, which could delay, limit or prevent regulatory approval. The FDA may not grant approval on a timely basis, or at all. We may encounter difficulties or unanticipated costs in our efforts to develop our product candidates and secure necessary governmental approvals, which could delay or preclude us from marketing our products.

After the FDA's evaluation of the NDA and inspection of the manufacturing facilities, the FDA may issue an approval letter or a complete response letter. An approval letter authorizes commercial marketing of the drug with specific prescribing information for specific indications. A complete response letter generally outlines the deficiencies in the submission and may require substantial additional testing or information in order for the FDA to reconsider the application. If and when those deficiencies have been addressed to the FDA's satisfaction in a resubmission of the NDA, the FDA will issue an approval letter. The FDA has committed to reviewing such resubmissions in two or six months depending on the type of information included. Even with submission of this additional information, the FDA ultimately may decide that the application does not satisfy the regulatory criteria for approval and refuse to approve the NDA. Even if the FDA approves a product, it may limit the approved indications for use for the product, require that contraindications, warnings or precautions be included in the product labeling, require that post-approval studies, including phase 4 clinical trials, be conducted to further assess a drug's safety after approval, require testing and surveillance programs to monitor the product after commercialization, or impose other conditions, including distribution restrictions or other risk management mechanisms, including Risk Evaluation and Mitigation Strategies, or REMs, which can materially affect the potential market and profitability of the product. The FDA may prevent or limit further marketing of a product based on the results of post-market studies or surveillance programs. After approval, some types of changes to the approved product, such as adding new indications, manufacturing changes and additional labeling claims, are subject to further testing requirements and FDA review and approval.

[Table of Contents](#)

Fast track designation

The FDA is required to facilitate the development and expedite the review of drugs that are intended for the treatment of a serious or life-threatening condition for which there is no effective treatment and which demonstrate the potential to address unmet medical needs for the condition. Under the fast track program, the sponsor of a new drug candidate may request the FDA to designate the product for a specific indication as a fast track product concurrent with or after the filing of the IND for the product candidate. The FDA must determine if the product candidate qualifies for fast track designation within 60 days after receipt of the sponsor's request.

In addition to other benefits, such as the ability to use surrogate endpoints and have greater interactions with the FDA, the FDA may initiate review of sections of a fast track product's NDA before the application is complete. This rolling review is available if the applicant provides and the FDA approves a schedule for the submission of the remaining information and the applicant pays applicable user fees. However, the FDA's time period goal for reviewing a fast track application does not begin until the last section of the NDA is submitted. In addition, the fast track designation may be withdrawn by the FDA if the FDA believes that the designation is no longer supported by data emerging in the clinical trial process.

Priority review

Under FDA policies, a product candidate may be eligible for priority review, or review generally within a six-month time frame from the time a complete application is received. Products regulated by the FDA's Center for Drug Evaluation and Research, or CDER, are eligible for priority review if they provide a significant improvement compared to marketed products in the treatment, diagnosis or prevention of a disease. A fast track designated product candidate would ordinarily meet the FDA's criteria for priority review.

Accelerated approval

Under the FDA's accelerated approval regulations, the FDA may approve a drug for a serious or life-threatening illness that provides meaningful therapeutic benefit to patients over existing treatments based upon a surrogate endpoint that is reasonably likely to predict clinical benefit. In clinical trials, a surrogate endpoint is a measurement of laboratory or clinical signs of a disease or condition that substitutes for a direct measurement of how a patient feels, functions or survives. Surrogate endpoints can often be measured more easily or more rapidly than clinical endpoints. A product candidate approved on this basis is subject to rigorous post-marketing compliance requirements, including the completion of phase 4 or post-approval clinical trials to confirm the effect on the clinical endpoint. Failure to conduct required post-approval studies, or confirm a clinical benefit during post-marketing studies, would allow the FDA to withdraw the drug from the market on an expedited basis. All promotional materials for drug candidates approved under accelerated regulations are subject to prior review by the FDA.

Breakthrough therapy designation

Under the provisions of the new Food and Drug Administration Safety and Innovation Act, or FDASIA, enacted in 2012, a sponsor can request designation of a product candidate as a "breakthrough therapy." A breakthrough therapy is defined as a drug that is intended, alone or in combination with one or more other drugs, to treat a serious or life-threatening disease or condition, and preliminary clinical evidence indicates that the drug may demonstrate substantial improvement over existing therapies on one or more clinically significant endpoints, such as substantial treatment effects observed early in clinical development. Drugs designated as breakthrough therapies are also eligible for accelerated approval. The FDA must take certain actions, such as holding timely meetings and providing advice, intended to expedite the development and review of an application for approval of a breakthrough therapy. Even if a product qualifies for one or more of these programs, the FDA may later decide that the product no longer meets the conditions for qualification or decide that the time period for FDA review or approval will not be shortened.

[Table of Contents](#)

Orphan drugs

Under the Orphan Drug Act, the FDA may grant orphan drug designation to drugs intended to treat a rare disease or condition, which is generally defined as a disease or condition that affects fewer than 200,000 individuals in the United States. Orphan drug designation must be requested before submitting an NDA. After the FDA grants orphan drug designation, the generic identity of the drug and its potential orphan use are disclosed publicly by the FDA. Orphan drug designation does not convey any advantage in, or shorten the duration of, the regulatory review and approval process. The first NDA applicant to receive FDA approval for a particular active ingredient to treat a particular disease with FDA orphan drug designation is entitled to a seven-year exclusive marketing period in the United States for that product, for that indication. During the seven-year exclusivity period, the FDA may not approve any other applications to market the same drug for the same orphan indication, except in limited circumstances, such as a showing of clinical superiority to the product with orphan drug exclusivity in that it is shown to be safer, more effective or makes a major contribution to patient care. Orphan drug exclusivity does not prevent the FDA from approving a different drug for the same disease or condition, or the same drug for a different disease or condition. Among the other benefits of orphan drug designation are tax credits for certain research and a waiver of the NDA application user fee.

Pediatric information

Under the Pediatric Research Equity Act of 2003, as amended and reauthorized by the Food and Drug Administration Amendments Act of 2007, or the FDAAA, an NDA or supplement to an NDA must contain data that are adequate to assess the safety and effectiveness of the drug for the claimed indications in all relevant pediatric subpopulations, and to support dosing and administration for each pediatric subpopulation for which the product is safe and effective. The FDA may, on its own initiative or at the request of the applicant, grant deferrals for submission of some or all pediatric data until after approval of the product for use in adults, or full or partial waivers from the pediatric data requirements. Unless otherwise required by regulation, the pediatric data requirements do not apply to products with orphan drug designation.

Combination products

The FDA regulates combinations of products that cross FDA centers, such as drug, biologic or medical device components that are physically, chemically or otherwise combined into a single entity, as a combination product. The FDA center with primary jurisdiction for the combination product will take the lead in the premarket review of the product, with the other center consulting or collaborating with the lead center.

The FDA's Office of Combination Products, or OCP, determines which center will have primary jurisdiction for the combination product based on the combination product's "primary mode of action." A mode of action is the means by which a product achieves an intended therapeutic effect or action. The primary mode of action is the mode of action that provides the most important therapeutic action of the combination product, or the mode of action expected to make the greatest contribution to the overall intended therapeutic effects of the combination product.

Often it is difficult for the OCP to determine with reasonable certainty the most important therapeutic action of the combination product. In those difficult cases, the OCP will consider consistency with other combination products raising similar types of safety and effectiveness questions, or which center has the most expertise to evaluate the most significant safety and effectiveness questions raised by the combination product.

A sponsor may use a voluntary formal process, known as a Request for Designation, when the product classification is unclear or in dispute, to obtain a binding decision as to which center will regulate the combination product. If the sponsor objects to that decision, it may request that the agency reconsider that decision.

[Table of Contents](#)

Overview of FDA regulation of companion diagnostics

We may seek to develop *in vitro* and *in vivo* companion diagnostics for use in selecting the patients that we believe will respond to our therapeutics.

FDA officials have issued draft guidance that, when finalized, would address issues critical to developing *in vitro* companion diagnostics, such as biomarker qualification, establishing clinical validity, the use of retrospective data, the appropriate patient population and when the FDA will require that the device and the drug be approved simultaneously. The draft guidance issued in July 2011 states that if safe and effective use of a therapeutic product depends on an *in vitro* diagnostic, then the FDA generally will require approval or clearance of the diagnostic at the same time that the FDA approves the therapeutic product. The FDA has yet to issue further guidance, and it is unclear whether it will do so, or what the scope would be.

The FDA previously has required *in vitro* companion diagnostics intended to select the patients who will respond to the cancer treatment to obtain Pre-Market Approval, or PMA, simultaneously with approval of the drug.

PMA approval pathway

A medical device, including an *in vitro* diagnostic, or IVD, to be commercially distributed in the United States must receive either 510(k) clearance or PMA approval from the FDA prior to marketing. Devices deemed by the FDA to pose the greatest risk, such as life-sustaining, life supporting or implantable devices, or devices deemed not substantially equivalent to a previously 510(k) cleared device or a pre-amendment class III device for which PMA applications have not been called, are placed in Class III requiring PMA approval. The PMA approval pathway requires proof of the safety and effectiveness of the device to the FDA's satisfaction.

The PMA approval pathway generally takes from one to three years or even longer from submission of the application.

A PMA application for an IVD must provide extensive preclinical and clinical trial data. Preclinical data for an IVD includes many different tests, including how reproducible the results are when the same sample is tested multiple times by multiple users at multiple laboratories. The clinical data need to establish that the test is sufficiently safe, effective and reliable in the intended use population. In addition, the FDA must be convinced that a device has clinical utility, meaning that an IVD provides information that is clinically meaningful. A biomarker's clinical significance may be obvious, or the applicant may be able to rely upon published literature or submit data to show clinical utility.

A PMA application also must provide information about the device and its components regarding, among other things, device design, manufacturing and labeling. The sponsor must pay an application fee.

As part of the PMA review, the FDA will typically inspect the manufacturer's facilities for compliance with Quality System Regulation, or QSR, requirements, which impose elaborate testing, control, documentation and other quality assurance procedures.

Upon submission, the FDA determines if the PMA application is sufficiently complete to permit a substantive review, and, if so, the FDA accepts the application for filing. The FDA then commences an in-depth review of the PMA application. The entire process typically takes one to three years, but may take longer. The review time is often significantly extended as a result of the FDA asking for more information or clarification of information already provided. The FDA also may respond with a not approvable determination based on deficiencies in the application and require additional clinical trials that are often expensive and time-consuming and can substantially delay approval.

During the review period, an FDA advisory committee, typically a panel of clinicians, may be convened to review the application and recommend to the FDA whether, or upon what conditions, the device should be

[Table of Contents](#)

approved. Although the FDA is not bound by the advisory panel decision, the panel's recommendation is important to the FDA's overall decision making process.

If the FDA's evaluation of the PMA application is favorable, the FDA typically issues an approvable letter requiring the applicant's agreement to specific conditions, such as changes in labeling, or specific additional information, such as submission of final labeling, in order to secure final approval of the PMA. If the FDA concludes that the applicable criteria have been met, the FDA will issue a PMA for the approved indications, which can be more limited than those originally sought by the manufacturer. The PMA can include post-approval conditions that the FDA believes necessary to ensure the safety and effectiveness of the device, including, among other things, restrictions on labeling, promotion, sale and distribution. Failure to comply with the conditions of approval can result in material adverse enforcement action, including the loss or withdrawal of the approval.

Even after approval of a PMA, a new PMA or PMA supplement may be required in the event of a modification to the device, its labeling or its manufacturing process. Supplements to a PMA often require the submission of the same type of information required for an original PMA, except that the supplement is generally limited to the information needed to support the proposed change from the product covered by the original PMA.

Clinical trials

A clinical trial is almost always required to support a PMA application. In some cases, one or more smaller Investigational Device Exemption, or IDE, studies may precede a pivotal clinical trial intended to demonstrate the safety and efficacy of the investigational device.

All clinical studies of investigational devices must be conducted in compliance with the FDA's requirements. If an investigational device could pose a significant risk to patients pursuant to FDA regulations, the FDA must approve an IDE application prior to initiation of investigational use. IVD trials usually do not require an IDE, as the FDA does not judge them to be a significant risk because the results do not affect the patients in the study. However, for a trial where the IVD result directs the therapeutic care of patients with cancer, we believe that the FDA would consider the investigation to present significant risk.

An IDE application must be supported by appropriate data, such as laboratory test results, showing that it is safe to test the device in humans and that the testing protocol is scientifically sound. The FDA typically grants IDE approval for a specified number of patients. A non-significant risk device does not require FDA approval of an IDE. Both significant risk and non-significant risk investigational devices require approval from IRBs at the study centers where the device will be used.

During the trial, the sponsor must comply with the FDA's IDE requirements for investigator selection, trial monitoring, reporting and record keeping. The investigators must obtain patient informed consent, rigorously follow the investigational plan and study protocol, control the disposition of investigational devices and comply with all reporting and record keeping requirements. Prior to granting PMA approval, the FDA typically inspects the records relating to the conduct of the study and the clinical data supporting the PMA application for compliance with applicable requirements.

Although the QSR does not fully apply to investigational devices, the requirement for controls on design and development does apply. The sponsor also must manufacture the investigational device in conformity with the quality controls described in the IDE application and any conditions of IDE approval that the FDA may impose with respect to manufacturing.

Post-market

After a device is on the market, numerous regulatory requirements apply. These requirements include: the QSR, labeling regulations, the FDA's general prohibition against promoting products for unapproved or "off label"

[Table of Contents](#)

uses, the Medical Device Reporting regulation, which requires that manufacturers report to the FDA if their device may have caused or contributed to a death or serious injury or malfunctioned in a way that would likely cause or contribute to a death or serious injury if it were to recur, and the Reports of Corrections and Removals regulation, which requires manufacturers to report recalls and field actions to the FDA if initiated to reduce a risk to health posed by the device or to remedy a violation of the FDCA.

The FDA enforces these requirements by inspection and market surveillance. If the FDA finds a violation, it can institute a wide variety of enforcement actions, ranging from a public warning letter to more severe sanctions such as: fines, injunctions and civil penalties; recall or seizure of products; operating restrictions, partial suspension or total shutdown of production; refusing requests for PMA approval of new products; withdrawing PMA approvals already granted; and criminal prosecution.

Other regulatory requirements

Any drug manufactured or distributed by us pursuant to FDA approvals are subject to pervasive and continuing regulation by the FDA, including, among other things, requirements relating to recordkeeping, periodic reporting, product sampling and distribution, advertising and promotion and reporting of adverse experiences with the product. After approval, most changes to the approved product, such as adding new indications or other labeling claims are subject to prior FDA review and approval.

The FDA may impose a number of post-approval requirements, including REMs, as a condition of approval of an NDA. For example, the FDA may require post-marketing testing, including phase 4 clinical trials, and surveillance to further assess and monitor the product's safety and effectiveness after commercialization. Regulatory approval of oncology products often requires that patients in clinical trials be followed for long periods to determine the overall survival benefit of the drug.

In addition, drug manufacturers and other entities involved in the manufacture and distribution of approved drugs are required to register their establishments with the FDA and state agencies, and are subject to periodic unannounced inspections by the FDA and these state agencies for compliance with cGMP requirements. Changes to the manufacturing process are strictly regulated and often require prior FDA approval before being implemented. FDA regulations also require investigation and correction of any deviations from cGMP and impose reporting and documentation requirements upon us and any third-party manufacturers that we may decide to use. Accordingly, manufacturers must continue to expend time, money and effort in the areas of production and quality control to maintain cGMP compliance.

Once an approval is granted, the FDA may withdraw the approval if compliance with regulatory requirements and standards is not maintained or if problems occur after the product reaches the market. Later discovery of previously unknown problems with a product, including adverse events of unanticipated severity or frequency, or with manufacturing processes, or failure to comply with regulatory requirements, may result in revisions to the approved labeling to add new safety information, imposition of post-market studies or clinical trials to assess new safety risks or imposition of distribution or other restrictions under a Risk Evaluation and Mitigation Strategy program. Other potential consequences include, among other things:

- restrictions on the marketing or manufacturing of the product, complete withdrawal of the product from the market or product recalls;
- fines, warning letters or holds on post-approval clinical trials;
- refusal of the FDA to approve pending applications or supplements to approved applications, or suspension or revocation of product license approvals;
- product seizure or detention, or refusal to permit the import or export of products; or
- consent decrees, injunctions or the imposition of civil or criminal penalties.

[Table of Contents](#)

The FDA strictly regulates marketing, labeling, advertising and promotion of products that are placed on the market. Drugs may be promoted only for the approved indications and in accordance with the provisions of the approved label. The FDA and other agencies actively enforce the laws and regulations prohibiting the promotion of off label uses, and a company that is found to have improperly promoted off label uses may be subject to significant liability.

Additional provisions

In addition to FDA restrictions on marketing of pharmaceutical products, several other types of state and federal laws have been applied to restrict certain marketing practices in the pharmaceutical industry in recent years. These laws include anti-kickback statutes and false claims statutes. The federal healthcare program anti-kickback statute prohibits, among other things, knowingly and willfully offering, paying, soliciting or receiving remuneration to induce or in return for purchasing, leasing, ordering or arranging for the purchase, lease or order of any healthcare item or service reimbursable under Medicare, Medicaid or other federally financed healthcare programs. This statute has been interpreted to apply to arrangements between pharmaceutical manufacturers on the one hand and prescribers, purchasers and formulary managers on the other. Violations of the anti-kickback statute are punishable by imprisonment, criminal fines, civil monetary penalties and exclusion from participation in federal healthcare programs. Although there are a number of statutory exemptions and regulatory safe harbors protecting certain common activities from prosecution or other regulatory sanctions, the exemptions and safe harbors are drawn narrowly, and practices that involve remuneration intended to induce prescribing, purchases or recommendations may be subject to scrutiny if they do not qualify for an exemption or safe harbor.

Federal false claims laws prohibit any person from knowingly presenting, or causing to be presented, a false claim for payment to the federal government, or knowingly making, or causing to be made, a false statement to have a false claim paid. Recently, several pharmaceutical and other healthcare companies have been prosecuted under these laws for allegedly inflating drug prices they report to pricing services, which in turn were used by the government to set Medicare and Medicaid reimbursement rates, and for allegedly providing free product to customers with the expectation that the customers would bill federal programs for the product. In addition, certain marketing practices, including off-label promotion, may also violate false claims laws. The majority of states also have statutes or regulations similar to the federal anti-kickback law and false claims laws, which apply to items and services reimbursed under Medicaid and other state programs, or, in several states, apply regardless of the payor.

Physician drug samples

As part of the sales and marketing process, pharmaceutical companies frequently provide samples of approved drugs to physicians. The Prescription Drug Marketing Act, or the PDMA, imposes requirements and limitations upon the provision of drug samples to physicians, as well as prohibits states from licensing distributors of prescription drugs unless the state licensing program meets certain federal guidelines that include minimum standards for storage, handling and record keeping. In addition, the PDMA sets forth civil and criminal penalties for violations.

Foreign regulation

In order to market any product outside of the United States, we would need to comply with numerous and varying regulatory requirements of other countries regarding safety and efficacy and governing, among other things, clinical trials, marketing authorization, commercial sales and distribution of our products. Whether or not we obtain FDA approval for a product, we would need to obtain the necessary approvals by the comparable regulatory authorities of foreign countries before we can commence clinical trials or marketing of the product in those countries. The approval process varies from country to country and can involve additional product testing and additional administrative review periods. The time required to obtain approval in other countries might differ from and be longer than that required to obtain FDA approval. Regulatory approval in one country does not

[Table of Contents](#)

ensure regulatory approval in another, but a failure or delay in obtaining regulatory approval in one country may negatively impact the regulatory process in others.

New legislation and regulations

From time to time, legislation is drafted, introduced and passed in Congress that could significantly change the statutory provisions governing the testing, approval, manufacturing and marketing of products regulated by the FDA. In addition to new legislation, FDA regulations and policies are often revised or interpreted by the agency in ways that may significantly affect our business and our products. It is impossible to predict whether further legislative changes will be enacted or whether FDA regulations, guidance, policies or interpretations changed or what the effect of such changes, if any, may be.

Pharmaceutical coverage, pricing and reimbursement

Significant uncertainty exists as to the coverage and reimbursement status of any drug products for which we obtain regulatory approval. Sales of any of our product candidates, if approved, will depend, in part, on the extent to which the costs of the products will be covered by third-party payors, including government health programs such as Medicare and Medicaid, commercial health insurers and managed care organizations. The process for determining whether a payor will provide coverage for a drug product may be separate from the process for setting the price or reimbursement rate that the payor will pay for the drug product once coverage is approved. Third-party payors may limit coverage to specific drug products on an approved list, or formulary, which might not include all of the approved drugs for a particular indication.

In order to secure coverage and reimbursement for any product that might be approved for sale, we may need to conduct expensive pharmacoeconomic studies in order to demonstrate the medical necessity and cost-effectiveness of the product, in addition to the costs required to obtain FDA or other comparable regulatory approvals. Our product candidates may not be considered medically necessary or cost-effective. A payor's decision to provide coverage for a drug product does not imply that an adequate reimbursement rate will be approved. Third-party reimbursement may not be sufficient to enable us to maintain price levels high enough to realize an appropriate return on our investment in product development.

The containment of healthcare costs has become a priority of federal, state and foreign governments, and the prices of drugs have been a focus in this effort. Third-party payors are increasingly challenging the prices charged for medical products and services and examining the medical necessity and cost-effectiveness of medical products and services, in addition to their safety and efficacy. If these third-party payors do not consider our products to be cost-effective compared to other available therapies, they may not cover our products after approval as a benefit under their plans or, if they do, the level of payment may not be sufficient to allow us to sell our products at a profit. The U.S. government, state legislatures and foreign governments have shown significant interest in implementing cost containment programs to limit the growth of government-paid health care costs, including price controls, restrictions on reimbursement and requirements for substitution of generic products for branded prescription drugs. Adoption of such controls and measures, and tightening of restrictive policies in jurisdictions with existing controls and measures, could limit payments for pharmaceuticals such as the drug candidates that we are developing and could adversely affect our net revenue and results.

Pricing and reimbursement schemes vary widely from country to country. Some countries provide that drug products may be marketed only after a reimbursement price has been agreed. Some countries may require the completion of additional studies that compare the cost-effectiveness of a particular product candidate to currently available therapies. For example, the European Union provides options for its member states to restrict the range of drug products for which their national health insurance systems provide reimbursement and to control the prices of medicinal products for human use. European Union member states may approve a specific price for a drug product or may instead adopt a system of direct or indirect controls on the profitability of the company placing the drug product on the market. Other member states allow companies to fix their own prices for drug

[Table of Contents](#)

products, but monitor and control company profits. The downward pressure on health care costs in general, particularly prescription drugs, has become very intense. As a result, increasingly high barriers are being erected to the entry of new products. In addition, in some countries, cross-border imports from low-priced markets exert competitive pressure that may reduce pricing within a country. There can be no assurance that any country that has price controls or reimbursement limitations for drug products will allow favorable reimbursement and pricing arrangements for any of our products.

The marketability of any products for which we receive regulatory approval for commercial sale may suffer if the government and third-party payors fail to provide adequate coverage and reimbursement. In addition, an increasing emphasis on managed care in the United States has increased and we expect will continue to increase the pressure on drug pricing. Coverage policies, third-party reimbursement rates and drug pricing regulation may change at any time. In particular, the Patient Protection and Affordable Care Act was enacted in the United States in March 2010 and contain provisions that may reduce the profitability of drug products, including, for example, increased rebates for drugs sold to Medicaid programs, extension of Medicaid rebates to Medicaid managed care plans, mandatory discounts for certain Medicare Part D beneficiaries and annual fees based on pharmaceutical companies' share of sales to federal health care programs. Even if favorable coverage and reimbursement status is attained for one or more products for which we receive regulatory approval, less favorable coverage policies and reimbursement rates may be implemented in the future.

Our scientific founders and advisors

Founders

The founders of Agios are eminent scientists and authorities in cancer who have pioneered key advances in the field of cancer metabolism. Together, they provide scientific leadership and expertise in this field.

Lewis C. Cantley, Ph.D. Dr. Cantley is director of the Cancer Center at Weill Cornell Medical College and New York-Presbyterian Hospital and a member of the National Academy of Sciences and American Academy of Arts and Sciences. Dr. Cantley is a foremost expert in understanding the biochemical pathways linking cancer and energy metabolism. His key contributions include:

- discovering the phosphatidylinositol-3-kinase (PI3K) signaling pathway;
- characterizing the mechanism by which PI3K is activated by growth factors and oncogenes and elucidating pathways downstream of PI3K, including the AKT/PKB signaling pathway;
- pioneering the application of fluorescence resonance energy transfer (FRET) for studying small molecule cell membrane transport; and
- discovering pyruvate kinase M2 (PKM2) as a “hub” to integrate growth factor signaling and aerobic glycolysis, an evolution in the understanding of the Warburg effect.

Tak W. Mak, Ph.D. Dr. Mak is professor of medical biophysics, University of Toronto; director of the Advanced Medical Discovery Institute; director of the Campbell Family Institute for Breast Cancer Research; foreign associate of the National Academy of Sciences; and fellow of the Royal Society. Dr. Mak is a preeminent researcher of the biology of the immune system, the biology of apoptosis and the pathogenesis of cancer. His key contributions include:

- discovering the T-Cell receptor;
- characterizing the tumorigenic functions of the tumor suppressor protein p53 and the kinase Chk2;
- identifying CPT1C as a tumor-specific gene product that plays an important role in the utilization of fatty acids as an alternative energy source of cancer cells; and
- discovery of the function of CTLA-4.

[Table of Contents](#)

Craig B. Thompson, M.D. Dr. Thompson is president and CEO of Memorial Sloan-Kettering Cancer Center; and a member of the National Academy of Sciences, American Academy of Arts and Sciences and Institute of Medicine. Dr. Thompson is an authority in the study of how genes regulate apoptosis and metabolism and investigates their application in treating cancer. His key contributions include:

- elucidating the role of the Bcl-2 family of oncogenes in regulating cell survival;
- identifying the roles of aerobic glycolysis, fatty acid synthesis and autophagy in the metabolic adaptation by cancer cells as part of carcinogenesis; and
- proposing the concept that most oncogenes and tumor suppressors evolved to regulate cellular metabolism.

Scientific advisors

We have assembled a world-class scientific advisory board that includes renowned experts in cancer metabolism, oncology, drug discovery and translational medicine. These advisors work in close collaboration with our scientists to identify new research directions and accelerate our target validation and drug discovery programs.

<u>Name</u>	<u>Primary affiliation</u>
Craig B. Thompson, M.D.	Memorial Sloan-Kettering Cancer Center
Joan Brugge, Ph.D.	Harvard Medical School
Lewis C. Cantley, Ph.D.	The Cancer Center at Weill Cornell Medical College and New York-Presbyterian Hospital
Jeffrey Engelman, M.D., Ph.D.	Massachusetts General Hospital and Harvard Medical School
William G. Kaelin, Jr., M.D.	Dana-Farber Cancer Institute and Harvard Medical School
Tak W. Mak, Ph.D.	University of Toronto and the Campbell Family Institute for Breast Cancer Research
Pier Paolo Pandolfi, M.D., Ph.D.	Beth Israel Deaconess Medical Center
David M. Sabatini, M.D., Ph.D.	Whitehead Institute and Massachusetts Institute of Technology
Charles Sawyers, M.D.	Memorial Sloan-Kettering Cancer Center
Matthew Vander Heiden, M.D., Ph.D.	Koch Institute for Integrative Cancer Research at MIT

Employees

As of December 31, 2013, we had 96 full-time employees, including 44 employees with M.D. or Ph.D. degrees. Of these full-time employees, 73 employees are engaged in research and development activities. None of our employees is represented by a labor union or covered by a collective bargaining agreement. We consider our relationship with our employees to be good.

Properties

Our principal facilities consist of approximately 39,000 square feet of office and laboratory space located at 38 Sidney Street, Cambridge, Massachusetts. The lease on all this space expires in April 2016. We have the option to extend the lease for two additional consecutive terms of five years. We believe our existing facilities are adequate for our current needs and that additional space will be available in the future on commercially reasonable terms as needed.

Legal proceedings

We are not currently a party to any material legal proceedings.

Description of capital stock

General

Our authorized capital stock consists of 125,000,000 shares of common stock, par value \$0.001 per share, and 25,000,000 shares of preferred stock, par value \$0.001 per share, all of which preferred stock is undesignated.

The following description of our capital stock and provisions of our certificate of incorporation and by-laws are summaries and are qualified by reference to the certificate of incorporation and by-laws. Copies of these documents have been filed with the Securities and Exchange Commission as exhibits to our registration statement, of which this prospectus forms a part.

As of December 31, 2013, we had issued and outstanding 31,202,542 shares of our common stock held of record by 107 stockholders.

Common stock

Holders of our common stock are entitled to one vote for each share held on all matters submitted to a vote of stockholders and do not have cumulative voting rights. An election of directors by our stockholders shall be determined by a plurality of the votes cast by the stockholders entitled to vote on the election. Holders of common stock are entitled to receive proportionately any dividends as may be declared by our board of directors, subject to any preferential dividend rights of any series of preferred stock that we may designate and issue in the future.

In the event of our liquidation or dissolution, the holders of common stock are entitled to receive proportionately our net assets available for distribution to stockholders after the payment of all debts and other liabilities and subject to the prior rights of any outstanding preferred stock. Holders of common stock have no preemptive, subscription, redemption or conversion rights. Our outstanding shares of common stock are, and the shares offered by us in this offering will be, when issued and paid for, validly issued, fully paid and nonassessable. The rights, preferences and privileges of holders of common stock are subject to and may be adversely affected by the rights of the holders of shares of any series of preferred stock that we may designate and issue in the future.

Preferred stock

Under the terms of our certificate of incorporation, our board of directors is authorized to direct us to issue shares of preferred stock in one or more series without stockholder approval. Our board of directors has the discretion to determine the rights, preferences, privileges and restrictions, including voting rights, dividend rights, conversion rights, redemption privileges and liquidation preferences, of each series of preferred stock.

The purpose of authorizing our board of directors to issue preferred stock and determine its rights and preferences is to eliminate delays associated with a stockholder vote on specific issuances. The issuance of preferred stock, while providing flexibility in connection with possible acquisitions, future financings and other corporate purposes, could have the effect of making it more difficult for a third party to acquire, or could discourage a third party from seeking to acquire, a majority of our outstanding voting stock. As of December 31, 2013, there are no shares of preferred stock outstanding, and we have no present plans to issue any shares of preferred stock.

Options

As of December 31, 2013, options to purchase 3,846,168 shares of our common stock at a weighted average exercise price of \$4.14 per share were outstanding.

[Table of Contents](#)

Registration rights

We have entered into a second amended and restated investor rights agreement, dated November 16, 2011, which we refer to as the investor rights agreement, with certain holders of our common stock. Following this offering, assuming that the underwriters do not exercise their option to purchase additional shares of common stock, based on information we have available to us, we believe that, based on shares outstanding as of December 31, 2013, holders of an aggregate of 19,262,768 shares of our common stock will have the right to require us to register these shares under the Securities Act of 1933, as amended, or Securities Act, and to participate in future registrations of securities by us, under the circumstances described below. After registration pursuant to these rights, these shares will become freely tradable without restriction under the Securities Act. If not otherwise exercised, the rights described below will expire in July 2018, which is five years after the closing of our initial public offering.

Demand registration rights

Beginning January 24, 2014, subject to specified limitations set forth in the investor rights agreement, at any time, the holders of a majority of the then outstanding shares having rights under the investor rights agreement, which we refer to as registrable shares, may at any time demand in writing that we register all or a portion of the registrable shares under the Securities Act if the total amount of registrable shares registered have an aggregate offering price of at least \$5 million (based on the then current market price). We are not obligated to file a registration statement pursuant to this provision on more than two occasions.

In addition, subject to specified limitations set forth in the investor rights agreement, at any time after we become eligible to file a registration statement on Form S-3, holders of at least 25% of the registrable shares then outstanding may request that we register their registrable securities on Form S-3 for purposes of a public offering if the total amount of registrable shares registered have an aggregate offering price of at least \$5 million (based on the then current market price). We are not obligated to file a registration statement pursuant to this provision on more than two occasions in any 12-month period.

Incidental registration rights

If we propose to file a registration statement to register any of our securities under the Securities Act, either for our own account or for the account of any of our stockholders, other than pursuant to the demand registration rights described above and other than pursuant to a Form S-4 or Form S-8, the holders of our registrable securities are entitled to notice of registration and, subject to specified exceptions, we will be required upon the holder's request to use our best efforts to register their then held registrable securities.

In the event that any registration in which the holders of registrable shares participate pursuant to our investor rights agreement is an underwritten public offering, we agree to enter into an underwriting agreement containing customary representation and warranties and covenants, including without limitation customary provisions with respect to indemnification of the underwriters of such offering.

In the event that any registration in which the holders of registrable shares participate pursuant to our investor rights agreement is an underwritten public offering, we will use our best efforts to include the requested registrable shares to be included, but may be limited by market conditions.

Expenses

Pursuant to the investor rights agreement, we are required to pay all registration and filing fees, exchange listing fees, printing expenses, fees and expenses of one counsel to represent the selling stockholders, state Blue Sky fees and expenses, and the expense of any special audits incident to or required by any such registration, but

[Table of Contents](#)

excluding underwriting discounts, selling commissions and the fees and expenses of selling stockholders' own counsel (other than the counsel selected to represent all selling stockholders). We are not required to pay registration expenses if a demand registration request under the investor rights agreement is withdrawn at the request of holders who exercise their demand right to register the registrable securities, unless the withdrawal is due to discovery of a materially adverse change in our business.

The investor rights agreement contains customary cross-indemnification provisions, pursuant to which we are obligated to indemnify the selling stockholders in the event of material misstatements or omissions in the registration statement attributable to us, and they are obligated to indemnify us for material misstatements or omissions in the registration statement attributable to them.

Delaware Anti-takeover law and certain charter and by-law provisions

Delaware business combination statute

We are subject to Section 203 of the Delaware General Corporation Law. Subject to certain exceptions, Section 203 prevents a publicly held Delaware corporation from engaging in a "business combination" with any "interested stockholder" for three years following the date that the person became an interested stockholder, unless the interested stockholder attained such status with the approval of our board of directors or unless the business combination is approved in a prescribed manner or the interested stockholder acquired at least 85% of our outstanding voting stock in the transaction in which it became an interested stockholder. A "business combination" includes, among other things, a merger or consolidation involving us and the "interested stockholder" and the sale of more than 10% of our assets. In general, an "interested stockholder" is any entity or person beneficially owning 15% or more of our outstanding voting stock and any entity or person affiliated with or controlling or controlled by such entity or person.

Staggered board; removal of directors

Our certificate of incorporation and our bylaws divide our board of directors into three classes with staggered three-year terms. In addition, such certificate of incorporation and bylaws provide that a director may be removed only for cause and only by the affirmative vote of the holders of at least 75% of the votes that all our stockholders would be entitled to cast in an annual election of directors. Under our certificate of incorporation and bylaws, any vacancy on our board of directors, including a vacancy resulting from an enlargement of our board of directors, may be filled only by vote of a majority of our directors then in office. Furthermore, our certificate of incorporation provides that the authorized number of directors may be changed only by the resolution of our board of directors.

The classification of our board of directors and the limitations on the removal of directors and filling of vacancies could make it more difficult for a third party to acquire, or discourage a third party from seeking to acquire, control of our company.

Super-majority voting

The Delaware General Corporation Law provides generally that the affirmative vote of a majority of the shares entitled to vote on any matter is required to amend a corporation's certificate of incorporation or by-laws, unless a corporation's certificate of incorporation or by-laws, as the case may be, requires a greater percentage. Our by-laws may be amended or repealed by a majority vote of our board of directors or the affirmative vote of the holders of at least 75% of the votes that all our stockholders would be entitled to cast in an annual election of directors. In addition, the affirmative vote of the holders of at least 75% of the votes which all our stockholders would be entitled to cast in an election of directors is required to amend or repeal or to adopt any provisions inconsistent with any of the provisions of our certificate of incorporation described in the prior two paragraphs.

[Table of Contents](#)

Stockholder action; special meeting of stockholders; advance notice requirements for stockholder proposals and director nominations

Our certificate of incorporation and our bylaws provide that any action required or permitted to be taken by our stockholders at an annual meeting or special meeting of stockholders may only be taken if it is properly brought before such meeting and may not be taken by written action in lieu of a meeting. Our certificate of incorporation and our bylaws also provide that, except as otherwise required by law, special meetings of the stockholders can only be called by our chairman of the board, our president or chief executive officer or our board of directors. In addition, our bylaws establish an advance notice procedure for stockholder proposals to be brought before an annual meeting of stockholders, including proposed nominations of candidates for election to our board of directors. Stockholders at an annual meeting may only consider proposals or nominations specified in the notice of meeting or brought before the meeting by or at the direction of our board of directors, or by a stockholder of record on the record date for the meeting, who is entitled to vote at the meeting and who has delivered timely written notice in proper form to our secretary of the stockholder's intention to bring such business before the meeting. These provisions could have the effect of delaying until the next stockholder meeting stockholder actions that are favored by the holders of a majority of our outstanding voting securities. These provisions also could discourage a third party from making a tender offer for our common stock, because even if it acquired a majority of our outstanding voting stock, it would be able to take action as a stockholder, such as electing new directors or approving a merger, only at a duly called stockholders meeting and not by written consent.

Authorized but unissued shares

The authorized but unissued shares of common stock and preferred stock are available for future issuance without stockholder approval, subject to any limitations imposed by the listing standards of The NASDAQ Global Select Market. These additional shares may be used for a variety of corporate finance transactions, acquisitions and employee benefit plans. The existence of authorized but unissued and unreserved common stock and preferred stock could make more difficult or discourage an attempt to obtain control of us by means of a proxy contest, tender offer, merger or otherwise.

Transfer agent and registrar

The transfer agent and registrar for our common stock is American Stock Transfer & Trust Company, LLC.

The NASDAQ Global Select Market

Our common stock is listed on The NASDAQ Global Select Market under the symbol "AGIO."

Shares eligible for future sale

Future sales of substantial amounts of our common stock, including shares issued upon exercise of outstanding options or purchased in the public market after this offering, or the anticipation of these sales, could adversely affect market prices prevailing from time to time and could impair our ability to raise capital through sales of equity securities. Our common stock is listed on The NASDAQ Global Select Market under the symbol "AGIO."

Upon the closing of this offering, we will have outstanding an aggregate of 33,202,542 shares of our common stock, after giving effect to the issuance by us of 2,000,000 shares of our common stock in this offering, assuming no exercise by the underwriters of their option to purchase additional shares and no exercise of options outstanding as of December 31, 2013.

Of the shares to be outstanding immediately after the closing of this offering, 8,900,595 shares of common stock, including 2,000,000 shares to be sold by us in this offering, will be freely tradable without restriction under the Securities Act unless purchased by our "affiliates," as that term is defined in Rule 144 under the Securities Act.

The remaining 24,301,947 shares of our common stock are "restricted securities" under Rule 144. Of these shares 19,088,669 (as well as any additional shares that may be purchased by Celgene or its affiliates in this offering) are subject to lock-up agreements entered into in connection with this offering. See "Underwriting."

After the lock-up period, these restricted securities may be sold in the public market only if registered or if they qualify for an exemption from registration under Rule 144 or 701 under the Securities Act or any other exemption.

Rule 144

In general, under Rule 144, any person who is not our affiliate and has held their shares for at least six months, including the holding period of any prior owner other than one of our affiliates, may sell those shares without restriction, subject to the availability of current public information about us. In addition, under Rule 144, any person who is not our affiliate and has not been our affiliate at any time during the preceding three months and has held their shares for at least one year, including the holding period of any prior owner other than one of our affiliates, would be entitled to sell an unlimited number of shares immediately upon the closing of this offering without regard to whether current public information about us is available.

A person who is our affiliate or who was our affiliate at any time during the preceding three months and who has beneficially owned restricted securities for at least six months, including the holding period of any prior owner other than one of our affiliates, is entitled to sell a number of shares within any three-month period that does not exceed the greater of:

- 1% of the number of shares of our common stock then outstanding, which will equal 332,025 shares immediately after this offering assuming no exercise by the underwriters of their option to purchase additional shares and no exercise of options outstanding as of December 31, 2013; or
- the average weekly trading volume in our common stock on The NASDAQ Global Select Market during the four calendar weeks preceding the date of filing of a Notice of Proposed Sale of Securities Pursuant to Rule 144 with respect to the sale.

Sales under Rule 144 by our affiliates are also subject to manner of sale provisions and notice requirements and to the availability of current public information about us.

Upon the expiration of the lock-up agreements entered into in connection with this offering by certain of our existing stockholders, which expire upon the earlier of 60 days from the date of this prospectus and June 22, 2014 and are further described below, 18,005,149 shares of our common stock will be eligible for sale under Rule 144, based on shares outstanding as of December 31, 2013. Upon the expiration of the 90-day lock-up agreements

[Table of Contents](#)

entered into in connection with this offering by our directors and officers, as described below, 1,083,520 additional shares of our common stock will be eligible for sale under Rule 144, based on shares outstanding as of December 31, 2013. We cannot estimate the number of shares of our common stock that our existing stockholders will elect to sell under Rule 144.

Rule 701

In general, under Rule 701 of the Securities Act, any of our employees, directors, officers, consultants or advisors, other than our affiliates, who purchased shares from us in connection with a qualified compensatory stock plan or other written agreement before our initial public offering is eligible to resell these shares in reliance on Rule 144, but without compliance with various restrictions, including minimum holding periods and, for non-affiliates, the availability of public information about us, contained in Rule 144. Subject to the lock-up agreements described below, 1,335,892 shares of our common stock will be eligible for sale in accordance with Rule 701, based on shares outstanding as of December 31, 2013, including 23,295 shares of unvested restricted stock which would not be eligible for sale until vested.

Lock-up agreements

We and each of our directors and executive officers have agreed that, without the prior written consent of J.P. Morgan Securities LLC and Goldman, Sachs & Co. on behalf of the underwriters for this offering, we and they will not, subject to limited exceptions, during the period ending 90 days after the date of this prospectus:

- offer, pledge, sell, contract to sell, sell any option or contract to purchase, purchase any option or contract to sell, grant any option, right or warrant to purchase, lend, or otherwise transfer or dispose of, directly or indirectly, any shares of our common stock; or
- enter into any swap or other arrangement that transfers to another, in whole or in part, any of the economic consequences of ownership of our common stock.

Additionally, holders of a majority of our outstanding common stock have agreed that, without the prior written consent of J.P. Morgan Securities LLC and Goldman, Sachs & Co. on behalf of the underwriters for this offering, they will not, subject to limited exceptions, during the period ending the earlier of 60 days after the date of this prospectus and the June 22, 2014:

- offer, pledge, sell, contract to sell, sell any option or contract to purchase, purchase any option or contract to sell, grant any option, right or warrant to purchase, lend, or otherwise transfer or dispose of, directly or indirectly, any shares of our common stock; or
- enter into any swap or other arrangement that transfers to another, in whole or in part, any of the economic consequences of ownership of our common stock.

A total of 19,088,669 outstanding shares of common stock will be subject to these lock-up arrangements (not including any shares that may be purchased by Celgene in this offering), based on shares outstanding as of December 31, 2013.

See “Underwriting” for a further description of the lock-up agreements applicable to our common stock.

Registration rights

Subject to the lock-up agreements described above, following this offering, assuming that the underwriters do not exercise their option to purchase additional shares of common stock, based on information we have available to us, we believe that, based on shares outstanding as of December 31, 2013, holders of an aggregate of 19,262,768 shares of our common stock have rights, subject to some conditions, to require us to file registration statements covering their shares or to include their shares in registration statements that we may file for ourselves or other stockholders. After registration pursuant to these rights, these shares will become freely tradable without restriction under the Securities Act. See “Description of capital stock—Registration rights” in this prospectus for additional information regarding these registration rights.

Stock options and Form S-8 registration statement

As of December 31, 2013, we had outstanding options to purchase an aggregate of 3,846,168 shares of our common stock, of which options to purchase 2,161,333 shares were vested. We have filed a registration statement on Form S-8 under the Securities Act to register all of the shares of our common stock subject to outstanding options and options and other awards issuable pursuant to our 2007 Plan and our 2013 Plan. For additional information regarding these plans, see the information set forth under the caption “Executive Compensation—Equity Compensation Plans and Other Benefits” in our Proxy Statement for our 2014 annual meeting of stockholders, which is incorporated by reference in this prospectus. Accordingly, shares of our common stock registered under the registration statements will be available for sale in the open market, subject to Rule 144 volume limitations applicable to affiliates, and subject to any vesting restrictions and lock-up agreements applicable to these shares.

Material U.S. tax considerations for non-U.S. holders of common stock

The following is a general discussion of material U.S. federal income and estate tax considerations relating to the ownership and disposition of our common stock by a non-U.S. holder. For purposes of this discussion, the term “non-U.S. holder” means a beneficial owner of our common stock that is not, for U.S. federal income tax purposes:

- an individual who is a citizen or resident of the United States;
- a corporation, or other entity treated as a corporation for U.S. federal income tax purposes, created or organized in or under the laws of the United States or of any political subdivision of the United States;
- an estate the income of which is subject to U.S. federal income taxation regardless of its source; or
- a trust, if a U.S. court is able to exercise primary supervision over the administration of the trust and one or more U.S. persons have authority to control all substantial decisions of the trust or if the trust has a valid election to be treated as a U.S. person under applicable U.S. Treasury Regulations.

An individual may be treated as a resident instead of a nonresident of the United States in any calendar year for U.S. federal income tax purposes if the individual was present in the United States for at least 31 days in that calendar year and for an aggregate of at least 183 days during the three-year period ending with the current calendar year. For purposes of this calculation, all of the days present in the current year, one-third of the days present in the immediately preceding year and one-sixth of the days present in the second preceding year are counted. Residents are taxed for U.S. federal income tax purposes as if they were U.S. citizens.

This discussion is based on current provisions of the U.S. Internal Revenue Code of 1986, as amended, which we refer to as the Code, existing and proposed U.S. Treasury Regulations promulgated thereunder, current administrative rulings and judicial decisions, all as in effect as of the date of this prospectus and all of which are subject to change or to differing interpretation, possibly with retroactive effect. Any change could alter the tax consequences to non-U.S. holders described in this prospectus. In addition, the Internal Revenue Service, or the IRS, could challenge one or more of the tax consequences described in this prospectus.

We assume in this discussion that each non-U.S. holder holds shares of our common stock as a capital asset (generally, property held for investment). This discussion does not address all aspects of U.S. federal income and estate taxation that may be relevant to a particular non-U.S. holder in light of that non-U.S. holder’s individual circumstances nor does it address any aspects of U.S. state, local or non-U.S. taxes. This discussion also does not consider any specific facts or circumstances that may apply to a non-U.S. holder and does not address the special tax rules applicable to particular non-U.S. holders, such as:

- insurance companies;
- tax-exempt organizations;
- financial institutions;
- brokers or dealers in securities;
- regulated investment companies;
- pension plans;
- controlled foreign corporations;
- passive foreign investment companies;
- owners that hold our common stock as part of a straddle, hedge, conversion transaction, synthetic security or other integrated investment; and
- certain U.S. expatriates.

[Table of Contents](#)

In addition, this discussion does not address the tax treatment of partnerships or persons who hold their common stock through partnerships or other entities that are pass-through entities for U.S. federal income tax purposes. A partner in a partnership or other pass-through entity that will hold our common stock should consult his, her or its own tax advisor regarding the tax consequences of the ownership and disposition of our common stock through a partnership or other pass-through entity, as applicable.

Dividends

If we pay distributions on our common stock, those distributions generally will constitute dividends for U.S. federal income tax purposes to the extent paid from our current or accumulated earnings and profits, as determined under U.S. federal income tax principles. If a distribution exceeds our current and accumulated earnings and profits, the excess will be treated as a tax-free return of the non-U.S. holder's investment, up to such holder's tax basis in the common stock. Any remaining excess will be treated as capital gain, subject to the tax treatment described below under the heading "Gain on disposition of common stock." Any such distribution made after June 30, 2014 will also be subject to the discussion below under the heading "Withholding and information reporting requirements—FATCA."

Dividends paid to a non-U.S. holder generally will be subject to withholding of U.S. federal income tax at a 30% rate or such lower rate as may be specified by an applicable income tax treaty between the United States and such holder's country of residence. If we determine, at a time reasonably close to the date of payment of a distribution on our common stock, that the distribution will not constitute a dividend because we do not anticipate having current or accumulated earnings and profits, we intend not to treat such distribution as subject to withholding of any U.S. federal income tax as permitted by U.S. Treasury Regulations.

Dividends that are treated as effectively connected with a trade or business conducted by a non-U.S. holder within the United States, and, if an applicable income tax treaty so provides, that are attributable to a permanent establishment or a fixed base maintained by the non-U.S. holder within the United States, are generally exempt from the 30% withholding tax if the non-U.S. holder satisfies applicable certification and disclosure requirements. However, such U.S. effectively connected income, net of specified deductions and credits, is taxed at the same graduated U.S. federal income tax rates applicable to U.S. persons (as defined in the Code). Any U.S. effectively connected income received by a non-U.S. holder that is a corporation may also, under certain circumstances, be subject to an additional "branch profits tax" at a 30% rate or such lower rate as may be specified by an applicable income tax treaty between the United States and such holder's country of residence.

A non-U.S. holder of our common stock who claims the benefit of an applicable income tax treaty between the United States and such holder's country of residence generally will be required to provide a properly executed IRS Form W-8BEN (or successor form) and satisfy applicable certification and other requirements. Non-U.S. holders are urged to consult their own tax advisors regarding their entitlement to benefits under a relevant income tax treaty.

A non-U.S. holder that is eligible for a reduced rate of U.S. withholding tax under an income tax treaty may obtain a refund or credit of any excess amounts withheld by timely filing an appropriate claim with the IRS.

Gain on disposition of common stock

A non-U.S. holder generally will not be subject to U.S. federal income tax on gain recognized on a disposition of our common stock unless:

- the gain is effectively connected with the non-U.S. holder's conduct of a trade or business in the United States, and, if an applicable income tax treaty so provides, the gain is attributable to a permanent establishment or fixed base maintained by the non-U.S. holder in the United States; in these cases, the non-U.S. holder will be taxed on a net income basis at the regular graduated rates and in the manner applicable

[Table of Contents](#)

to U.S. persons, and, if the non-U.S. holder is a foreign corporation, an additional branch profits tax at a rate of 30%, or a lower rate as may be specified by an applicable income tax treaty, may also apply;

- the non-U.S. holder is an individual present in the United States for 183 days or more in the taxable year of the disposition and certain other requirements are met, in which case the non-U.S. holder will be subject to a 30% tax (or such lower rate as may be specified by an applicable income tax treaty) on the net gain derived from the disposition, which may be offset by U.S.—source capital losses of the non-U.S. holder, if any; or
- we are or have been, at any time during the five-year period preceding such disposition (or the non-U.S. holder’s holding period, if shorter) a “U.S. real property holding corporation” unless our common stock is regularly traded on an established securities market and the non-U.S. holder held no more than 5% of our outstanding common stock, directly or indirectly, during the shorter of the 5-year period ending on the date of the disposition or the period that the non-U.S. holder held our common stock. Generally, a corporation is a “U.S. real property holding corporation” if the fair market value of its “U.S. real property interests” equals or exceeds 50% of the sum of the fair market value of its worldwide real property interests plus its other assets used or held for use in a trade or business. Although there can be no assurance, we believe that we are not currently, and we do not anticipate becoming, a “U.S. real property holding corporation” for U.S. federal income tax purposes. No assurance can be provided that our common stock will be regularly traded on an established securities market for purposes of the rule described above.

Information reporting and backup withholding

The gross amount of the distributions on our common stock paid to each non-U.S. holder and the tax withheld, if any, with respect to such distributions must be reported annually to the IRS. Non-U.S. holders may have to comply with specific certification procedures to establish that the holder is not a U.S. person (as defined in the Code) in order to avoid backup withholding at the applicable rate, currently 28%, with respect to dividends on our common stock. Generally, a holder will comply with such procedures if it provides a properly executed IRS Form W-8BEN (or other applicable Form W-8) or otherwise meets documentary evidence requirements for establishing that it is a non-U.S. holder, or otherwise establishes an exemption. Dividends paid to non-U.S. holders subject to withholding of U.S. federal income tax, as described above under the heading “Dividends,” will generally be exempt from backup withholding.

Information reporting and backup withholding generally will apply to the proceeds of a disposition of our common stock by a non-U.S. holder effected by or through the U.S. office of any broker, U.S. or foreign, unless the holder certifies its status as a non-U.S. holder and satisfies certain other requirements, or otherwise establishes an exemption. Generally, information reporting and backup withholding will not apply to a payment of disposition proceeds to a non-U.S. holder where the transaction is effected outside the United States through a non-U.S. office of a broker. However, for information reporting purposes, dispositions effected through a non-U.S. office of a broker with substantial U.S. ownership or operations generally will be treated in a manner similar to dispositions effected through a U.S. office of a broker. Non-U.S. holders should consult their own tax advisors regarding the application of the information reporting and backup withholding rules to them.

Copies of information returns may be made available to the tax authorities of the country in which the non-U.S. holder resides or is incorporated under the provisions of a specific treaty or agreement.

Backup withholding is not an additional tax. Any amounts withheld under the backup withholding rules from a payment to a non-U.S. holder can be refunded or credited against the non-U.S. holder’s U.S. federal income tax liability, if any, provided that an appropriate claim is timely filed with the IRS.

Withholding and information reporting requirements—FATCA

Recently enacted legislation (commonly referred to as “FATCA”) will impose U.S. federal withholding tax of 30% on payments of dividends on, and gross proceeds from the sale or disposition of, our common stock if paid

[Table of Contents](#)

to a foreign entity unless (i) in the case of a foreign entity that is a “foreign financial institution” (as defined under FATCA), the foreign entity undertakes certain due diligence, reporting, withholding, and certification obligations, (ii) in the case of a foreign entity that is not a foreign financial institution, the foreign entity identifies certain of its U.S. investors, or (iii) the foreign entity is otherwise exempt under FATCA. Although this legislation is effective with respect to amounts paid after December 31, 2012, under applicable U.S. Treasury Regulations, withholding under FATCA will only apply (1) to payments of dividends on our common stock made after June 30, 2014 and (2) to payments of gross proceeds from a sale or other disposition of our common stock made after December 31, 2016. Under certain circumstances, a non-U.S. holder may be eligible for refunds or credits of such taxes.

Prospective investors should consult their own tax advisors regarding the possible impact of the FATCA rules on their investment in our common stock and on the entities through which they hold our common stock including, without limitation, the process and deadlines for meeting the applicable requirements to prevent the imposition of the 30% withholding tax under FATCA.

Federal estate tax

Common stock owned or treated as owned by an individual (including by reason of holding interests in certain entities) who is a non-U.S. holder (as specially defined for U.S. federal estate tax purposes) at the time of death will be included in the individual’s gross estate for U.S. federal estate tax purposes and, therefore, may be subject to U.S. federal estate tax, unless an applicable estate tax or other treaty provides otherwise.

The preceding discussion of material U.S. federal tax considerations is for general information only. It is not tax advice. Prospective investors should consult their own tax advisors regarding the particular U.S. federal, state, local and non-U.S. tax consequences of purchasing, holding and disposing of our common stock, including the consequences of any proposed changes in applicable laws.

[Table of Contents](#)

Underwriting

We are offering the shares of common stock described in this prospectus through a number of underwriters. J.P. Morgan Securities LLC and Goldman, Sachs & Co. are acting as joint book-running managers of the offering and as representatives of the underwriters. We have entered into an underwriting agreement with the underwriters. Subject to the terms and conditions of the underwriting agreement, we have agreed to sell to the underwriters, and each underwriter has severally agreed to purchase, at the public offering price less the underwriting discounts and commissions set forth on the cover page of this prospectus, the number of shares of common stock listed next to its name in the following table:

<u>Name</u>	<u>Number of Shares</u>
J.P. Morgan Securities LLC	
Goldman, Sachs & Co.	
Cowen and Company, LLC	
Leerink Partners LLC	
Total	<u>2,000,000</u>

The underwriters are committed to purchase all the common shares offered by us if they purchase any shares. The underwriting agreement also provides that if an underwriter defaults, the purchase commitments of non-defaulting underwriters may also be increased or the offering may be terminated.

The underwriters propose to offer the common shares directly to the public at the public offering price set forth on the cover page of this prospectus and to certain dealers at that price less a concession not in excess of \$ _____ per share. After the public offering of the shares, the offering price and other selling terms may be changed by the underwriters. Sales of shares made outside of the United States may be made by affiliates of the underwriters.

The underwriters have an option to buy up to 300,000 additional shares of common stock. The underwriters have 30 days from the date of this prospectus to exercise this option. If any shares are purchased with this option, the underwriters will purchase shares in approximately the same proportion as shown in the table above. If any additional shares of common stock are purchased, the underwriters will offer the additional shares on the same terms as those on which the shares are being offered.

The underwriting fee is equal to the public offering price per share of common stock less the amount paid by the underwriters to us per share of common stock. The underwriting fee is \$ _____ per share. The following table shows the per share and total public offering price, underwriting discounts and commissions to be paid to the underwriters and proceeds before expenses to us assuming both no exercise and full exercise of the underwriters' option to purchase additional shares.

	<u>Per Share</u>	<u>Total</u>	
		<u>No Exercise</u>	<u>Full Exercise</u>
Public offering price	\$ _____	\$ _____	\$ _____
Underwriting discounts and commissions to be paid by us	\$ _____	\$ _____	\$ _____
Proceeds, before expenses, to us	\$ _____	\$ _____	\$ _____

We estimate that the total expenses of this offering, including registration, filing and listing fees, printing fees and legal and accounting expenses, but excluding the underwriting discounts and commissions, will be approximately \$410,000. We have agreed to reimburse the underwriters \$ _____ for expenses related to any filing with, and the clearance of this offering by, the Financial Industry Regulatory Authority, Inc.

A prospectus in electronic format may be made available on the web sites maintained by one or more underwriters, or selling group members, if any, participating in the offering. The underwriters may agree to

[Table of Contents](#)

allocate a number of shares to underwriters and selling group members for sale to their online brokerage account holders. Internet distributions will be allocated by the representatives to underwriters and selling group members that may make Internet distributions on the same basis as other allocations.

We have agreed that we will not (i) offer, pledge, sell, contract to sell, sell any option or contract to purchase, purchase any option or contract to sell, grant any option, right or warrant to purchase or otherwise transfer or dispose of, directly or indirectly, or file with the Securities and Exchange Commission a registration statement under the Securities Act relating to, any shares of our common stock or securities convertible into or exchangeable or exercisable for any shares of our common stock, or publicly disclose the intention to make any offer, sale, pledge, disposition or filing, or (ii) enter into any swap or other arrangement that transfers all or a portion of the economic consequences associated with the ownership of any shares of our common stock or any such other securities (regardless of whether any of these transactions are to be settled by the delivery of shares of our common stock or such other securities, in cash or otherwise), in each case without the prior written consent of J.P. Morgan Securities LLC and Goldman, Sachs & Co. for a period of 90 days after the date of this prospectus, other than (A) the shares of our common stock to be sold hereunder, (B) any shares of our common stock issued upon the exercise of options granted under company stock plans or warrants described as outstanding in this prospectus, (C) any options and other awards granted under company stock plans, (D) our filing of a registration statement on Form S-8 or a successor form thereto relating to the shares of our common stock granted pursuant to or reserved for issuance under company stock plans and (E) shares of our common stock or other securities issued in connection with a transaction that includes a commercial relationship (including joint ventures, marketing or distribution arrangements, collaboration agreements or intellectual property license agreements) or any acquisition of assets or not less than a majority or controlling portion of the equity of another entity; provided that the aggregate number of shares of our common stock issued pursuant to clause (E) shall not exceed 5.0% of the total number of outstanding shares of our common stock immediately following the issuance and sale of the underwritten shares pursuant to the underwriting agreement provided, further, the recipient of any such shares of our common stock and securities issued pursuant to clause (E) during the 90-day restricted period described above shall enter into an agreement substantially in the form described thereby.

Our directors and executive officers have entered into lock-up agreements with the underwriters prior to the commencement of this offering pursuant to which each of these persons or entities, for a period of 90 days after the date of this prospectus, may not, without the prior written consent of J.P. Morgan Securities LLC and Goldman, Sachs & Co., (1) offer, pledge, sell, contract to sell, sell any option or contract to purchase, purchase any option or contract to sell, grant any option, right or warrant to purchase, or otherwise transfer or dispose of, directly or indirectly, any shares of our common stock or any securities convertible into or exercisable or exchangeable for our common stock (including, without limitation, common stock or such other securities which may be deemed to be beneficially owned by such directors and officers in accordance with the rules and regulations of the SEC and securities which may be issued upon exercise of a stock option or warrant), or publicly disclose the intention to make any offer, sale, pledge or disposition, (2) enter into any swap or other agreement that transfers, in whole or in part, any of the economic consequences of ownership of our common stock or such other securities, whether any such transaction described in clause (1) or (2) above is to be settled by delivery of our common stock or such other securities, in cash or otherwise or (3) make any demand for or exercise any right with respect to the registration of any shares of our common stock or any security convertible into or exercisable or exchangeable for our common stock, in each case subject to certain exceptions, including (A) transfers of shares of our common stock or other securities as bona fide gifts, (B) transfers or dispositions of shares of our common stock or other securities to any trust for the direct or indirect benefit of the director or officer or the immediate family of such person in a transaction not involving a disposition for value, (C) transfers or dispositions of shares of our common stock or other securities to any corporation, partnership, limited liability company or other entity all of the beneficial ownership interests of which are held by the director or officer or the immediate family of such person in a transaction not involving a disposition for value, (D) transfers or dispositions of shares of our common stock or other securities by will, other testamentary document or intestate succession to the legal representative, heir, beneficiary or a member of the immediate family of the director or

[Table of Contents](#)

officer, (E) distributions of shares of our common stock or other securities to partners, members or stockholders of the shareholder and (F) the exercise of options to purchase shares of common stock granted under any stock incentive plan described in this prospectus, provided that the underlying common stock issued upon such exercise continues to be subject to the restrictions described herein. In the case of any transfer, disposition or distribution pursuant to clause (A), (B), (C), (D) or (E), each transferee, donee or distributee must execute and deliver to J.P. Morgan Securities LLC and Goldman, Sachs & Co. a lock-up agreement. In addition, in the case of any transfer, disposition or distribution pursuant to clause (A), (B), (C), (D) or (E), no filing by any party under the Exchange Act, or other public announcement may be required or voluntarily made in connection with such transfer, disposition or distribution, other than a filing on a Form 5 made after the expiration of the 90-day restricted period referred to above. In addition, notwithstanding the foregoing restrictions, the director or officer may (i) transfer such person's shares of our common stock or any security convertible into or exercisable or exchangeable for our common stock to us pursuant to any contractual arrangement in effect on the date of the lock-up agreement that provides for the repurchase of such person's common stock or such other securities by us or in connection with such person's termination of employment with us, provided that no filing by any party under the Exchange Act, or other public announcement may be required or voluntarily made in connection with such transfer, other than a filing on a Form 5 made after the expiration of the 90-day restricted period referred to above, (ii) establish a trading plan pursuant to Rule 10b5-1 under the Exchange Act for the transfer of common stock, provided that such plan does not provide for any transfers of common stock, and no filing with the SEC or other public announcement shall be required or voluntarily made by the director or officer or any other person in connection therewith, in each case during the 90-day restricted period or any extension thereof pursuant to the lock-up agreement, and (iii) transfer or dispose of shares of our common stock on the open market following the offering, provided that no filing by any party under the Exchange Act, or other public announcement reporting a reduction in the beneficial ownership of common stock held by the director or officer may be required or voluntarily made in connection with such transfer, other than a filing on a Form 5 made after the expiration of the 90-day restricted period referred to above and (iv) transfer shares of common stock pursuant to sales in the public market undertaken by such person under a trading plan pursuant to Rule 10b5-1 under the Exchange Act, provided that such trading plan shall have been in effect prior to the date of the lock-up agreement, and, that to the extent a public announcement or filing under the Exchange Act, if any, is required or voluntarily made by or on behalf of such person or us regarding any such sales, such announcement or filing shall include a statement to the effect that the sale was made pursuant to a trading plan pursuant to Rule 10b5-1 under the Exchange Act.

Holders of a majority of our outstanding common stock have entered into lock-up agreements with the underwriters prior to the commencement of this offering pursuant to which each of these persons or entities, for a period ending the earlier of (x) 60 days after the prospectus and (y) June 22, 2014, may not, without the prior written consent of J.P. Morgan Securities LLC and Goldman, Sachs & Co., (1) offer, pledge, sell, contract to sell, sell any option or contract to purchase, purchase any option or contract to sell, grant any option, right or warrant to purchase, or otherwise transfer or dispose of, directly or indirectly, any shares of our common stock or any securities convertible into or exercisable or exchangeable for our common stock (including, without limitation, common stock or such other securities which may be deemed to be beneficially owned by such shareholders in accordance with the rules and regulations of the SEC and securities which may be issued upon exercise of a stock option or warrant), or publicly disclose the intention to make any offer, sale, pledge or disposition, (2) enter into any swap or other agreement that transfers, in whole or in part, any of the economic consequences of ownership of our common stock or such other securities, whether any such transaction described in clause (1) or (2) above is to be settled by delivery of our common stock or such other securities, in cash or otherwise or (3) make any demand for or exercise any right with respect to the registration of any shares of our common stock or any security convertible into or exercisable or exchangeable for our common stock, in each case subject to certain exceptions, including (A) transfers of shares of our common stock or other securities as bona fide gifts, (B) transfers or dispositions of shares of our common stock or other securities to any trust for the direct or indirect benefit of the shareholder or the immediate family of such person in a transaction not involving a disposition for value, (C) transfers or dispositions of shares of our common stock or other securities to any corporation, partnership, limited liability company or other entity all of the beneficial ownership interests of which are held by the shareholder or the immediate family of such person in a transaction not involving a

[Table of Contents](#)

disposition for value, (D) transfers or dispositions of shares of our common stock or other securities by will, other testamentary document or intestate succession to the legal representative, heir, beneficiary or a member of the immediate family of the shareholder, and (E) distributions of shares of our common stock or other securities to partners, members or stockholders of the shareholder. In the case of any transfer, disposition or distribution pursuant to clause (A), (B), (C), (D) or (E), each transferee, donee or distributee must execute and deliver to J.P. Morgan Securities LLC and Goldman, Sachs & Co. a lock-up agreement. In addition, in the case of any transfer, disposition or distribution pursuant to clause (A), (B), (C), (D) or (E), no filing by any party under the Exchange Act, or other public announcement may be required or voluntarily made in connection with such transfer, disposition or distribution, other than a filing on a Form 5 made after the expiration of the restricted period referred to above. In addition, notwithstanding the foregoing restrictions, the shareholder may (i) transfer such person's shares of our common stock or any security convertible into or exercisable or exchangeable for our common stock to us pursuant to any contractual arrangement in effect on the date of the lock-up agreement that provides for the repurchase of such person's common stock or such other securities by us or in connection with such person's termination of employment with us, provided that no filing by any party under the Exchange Act, or other public announcement may be required or voluntarily made in connection with such transfer, other than a filing on a Form 5 made after the expiration of the restricted period referred to above, (ii) establish a trading plan pursuant to Rule 10b5-1 under the Exchange Act for the transfer of common stock, provided that such plan does not provide for any transfers of common stock, and no filing with the SEC or other public announcement shall be required or voluntarily made by the shareholder or any other person in connection therewith, in each case during the restricted period or any extension thereof pursuant to the lock-up agreement, and (iii) transfer or dispose of shares of our common stock on the open market following the offering, provided that no filing by any party under the Exchange Act, or other public announcement reporting a reduction in the beneficial ownership of common stock held by the shareholder may be required or voluntarily made in connection with such transfer, other than a filing on a Form 5 made after the expiration of the restricted period referred to above.

We have agreed to indemnify the underwriters against certain liabilities, including liabilities under the Securities Act of 1933.

Our common stock is listed on The NASDAQ Global Select Market under the symbol "AGIO."

In connection with this offering, the underwriters may engage in stabilizing transactions, which involves making bids for, purchasing and selling shares of common stock in the open market for the purpose of preventing or retarding a decline in the market price of the common stock while this offering is in progress. These stabilizing transactions may include making short sales of the common stock, which involves the sale by the underwriters of a greater number of shares of common stock than they are required to purchase in this offering, and purchasing shares of common stock on the open market to cover positions created by short sales. Short sales may be "covered" shorts, which are short positions in an amount not greater than the underwriters' option referred to above, or may be "naked" shorts, which are short positions in excess of that amount. The underwriters may close out any covered short position either by exercising their option, in whole or in part, or by purchasing shares in the open market. In making this determination, the underwriters will consider, among other things, the price of shares available for purchase in the open market compared to the price at which the underwriters may purchase shares through the option. A naked short position is more likely to be created if the underwriters are concerned that there may be downward pressure on the price of the common stock in the open market that could adversely affect investors who purchase in this offering. To the extent that the underwriters create a naked short position, they will purchase shares in the open market to cover the position.

The underwriters have advised us that, pursuant to Regulation M of the Securities Act of 1933, they may also engage in other activities that stabilize, maintain or otherwise affect the price of the common stock, including the imposition of penalty bids. This means that if the representatives of the underwriters purchase common stock in the open market in stabilizing transactions or to cover short sales, the representatives can require the underwriters that sold those shares as part of this offering to repay the underwriting discount received by them.

[Table of Contents](#)

These activities may have the effect of raising or maintaining the market price of the common stock or preventing or retarding a decline in the market price of the common stock, and, as a result, the price of the common stock may be higher than the price that otherwise might exist in the open market. If the underwriters commence these activities, they may discontinue them at any time. The underwriters may carry out these transactions on The NASDAQ Global Select Market, in the over-the-counter market or otherwise.

In addition, in connection with this offering certain of the underwriters (and selling group members) may engage in passive market making transactions in our common stock on The NASDAQ Global Select Market prior to the pricing and completion of this offering. Passive market making consists of displaying bids on The NASDAQ Global Select Market no higher than the bid prices of independent market makers and making purchases at prices no higher than these independent bids and effected in response to order flow. Net purchases by a passive market maker on each day are generally limited to a specified percentage of the passive market maker's average daily trading volume in the common stock during a specified period and must be discontinued when such limit is reached. Passive market making may cause the price of our common stock to be higher than the price that otherwise would exist in the open market in the absence of these transactions. If passive market making is commenced, it may be discontinued at any time.

The underwriters and their respective affiliates are full-service financial institutions engaged in various activities, which may include securities trading, commercial and investment banking, financial advisory, investment management, investment research, principal investment, hedging, financing and brokerage activities. Certain of the underwriters and their affiliates have provided in the past to us and our affiliates and may provide from time to time in the future certain commercial banking, financial advisory, investment banking and other services for us and such affiliates in the ordinary course of their business, for which they have received and may continue to receive customary fees and commissions. In addition, in the ordinary course of their various business activities, the underwriters and their respective affiliates, officers, directors and employees may purchase, sell or hold a broad array of investments and actively trade securities, derivatives, loans, commodities, currencies, credit default swaps and other financial instruments for their own account and for the accounts of their customers, and such investment and trading activities may involve or relate to our assets, securities and/or instruments (directly, as collateral securing other obligations or otherwise) and/or persons and entities with relationships with us. The underwriters and their respective affiliates may also communicate independent investment recommendations, market color or trading ideas and/or publish or express independent research views in respect of such assets, securities or instruments and may at any time hold, or recommend to clients that they should acquire, long and/or short positions in such assets, securities and instruments.

Selling restrictions

General

Other than in the United States, no action has been taken by us or the underwriters that would permit a public offering of the securities offered by this prospectus in any jurisdiction where action for that purpose is required. The securities offered by this prospectus may not be offered or sold, directly or indirectly, nor may this prospectus or any other offering material or advertisements in connection with the offer and sale of any such securities be distributed or published in any jurisdiction, except under circumstances that will result in compliance with the applicable rules and regulations of that jurisdiction. Persons into whose possession this prospectus comes are advised to inform themselves about and to observe any restrictions relating to the offering and the distribution of this prospectus. This prospectus does not constitute an offer to sell or a solicitation of an offer to buy any securities offered by this prospectus in any jurisdiction in which such an offer or a solicitation is unlawful.

[Table of Contents](#)

United Kingdom

Each underwriter has represented and agreed that:

- (1) it has only communicated or caused to be communicated and will only communicate or cause to be communicated an invitation or inducement to engage in investment activity (within the meaning of Section 21 of the FSMA) received by it in connection with the issue or sale of our common shares in circumstances in which Section 21(1) of the FSMA does not apply to us; and
- (2) it has complied and will comply with all applicable provisions of the FSMA with respect to anything done by it in relation to our common shares in, from or otherwise involving the United Kingdom.

European Economic Area

In relation to each Member State of the European Economic Area which has implemented the Prospectus Directive (each, a “Relevant Member State”), an offer to the public of any shares which are the subject of the offering contemplated by this prospectus (the “Shares”) may not be made in that Relevant Member State, except that an offer to the public in that Relevant Member State of any Shares may be made at any time under the following exemptions under the Prospectus Directive, if they have been implemented in that Relevant Member State:

- (1) to any legal entity which is a qualified investor as defined in the Prospectus Directive;
- (2) to fewer than 100 or, if the Relevant Member State has implemented the relevant provision of the 2010 PD Amending Directive, 150, natural or legal persons (other than qualified investors as defined in the Prospectus Directive), as permitted under the Prospectus Directive, subject to obtaining the prior consent of the representatives for any such offer; or
- (3) in any other circumstances falling within Article 3(2) of the Prospectus Directive,

provided that no such offer of Shares shall result in a requirement for the publication by us or any underwriter of a prospectus pursuant to Article 3 of the Prospectus Directive.

For the purposes of this provision, the expression an “offer to the public” in relation to any Shares in any Relevant Member State means the communication in any form and by any means of sufficient information on the terms of the offer and any Shares to be offered so as to enable an investor to decide to purchase any Shares, as the same may be varied in that Member State by any measure implementing the Prospectus Directive in that Member State, the expression “Prospectus Directive” means Directive 2003/71/EC (and amendments thereto, including the 2010 PD Amending Directive, to the extent implemented in the Relevant Member State), and includes any relevant implementing measure in the Relevant Member State, and the expression “2010 PD Amending Directive” means Directive 2010/73/EU.

Hong Kong

The shares may not be offered or sold by means of any document other than (i) in circumstances which do not constitute an offer to the public within the meaning of the Companies Ordinance (Cap.32, Laws of Hong Kong), or (ii) to “professional investors” within the meaning of the Securities and Futures Ordinance (Cap.571, Laws of Hong Kong) and any rules made thereunder, or (iii) in other circumstances which do not result in the document being a “prospectus” within the meaning of the Companies Ordinance (Cap.32, Laws of Hong Kong), and no advertisement, invitation or document relating to the shares may be issued or may be in the possession of any person for the purpose of issue (in each case whether in Hong Kong or elsewhere), which is directed at, or the contents of which are likely to be accessed or read by, the public in Hong Kong (except if permitted to do so under the laws of Hong Kong) other than with respect to shares which are or are intended to be disposed of only

[Table of Contents](#)

to persons outside Hong Kong or only to “professional investors” within the meaning of the Securities and Futures Ordinance (Cap. 571, Laws of Hong Kong) and any rules made thereunder.

Singapore

This prospectus has not been registered as a prospectus with the Monetary Authority of Singapore. Accordingly, this prospectus and any other document or material in connection with the offer or sale, or invitation for subscription or purchase, of the shares may not be circulated or distributed, nor may the shares be offered or sold, or be made the subject of an invitation for subscription or purchase, whether directly or indirectly, to persons in Singapore other than (i) to an institutional investor under Section 274 of the Securities and Futures Act, Chapter 289 of Singapore (the “SFA”), (ii) to a relevant person, or any person pursuant to Section 275(1A), and in accordance with the conditions, specified in Section 275 of the SFA or (iii) otherwise pursuant to, and in accordance with the conditions of, any other applicable provision of the SFA.

Where the shares are subscribed or purchased under Section 275 by a relevant person which is: (a) a corporation (which is not an accredited investor) the sole business of which is to hold investments and the entire share capital of which is owned by one or more individuals, each of whom is an accredited investor; or (b) a trust (where the trustee is not an accredited investor) whose sole purpose is to hold investments and each beneficiary is an accredited investor, shares, debentures and units of shares and debentures of that corporation or the beneficiaries’ rights and interest in that trust shall not be transferable for 6 months after that corporation or that trust has acquired the shares under Section 275 except: (1) to an institutional investor under Section 274 of the SFA or to a relevant person, or any person pursuant to Section 275(1A), and in accordance with the conditions, specified in Section 275 of the SFA; (2) where no consideration is given for the transfer; or (3) by operation of law.

Japan

The securities have not been and will not be registered under the Financial Instruments and Exchange Law of Japan (the Financial Instruments and Exchange Law) and each underwriter has agreed that it will not offer or sell any securities, directly or indirectly, in Japan or to, or for the benefit of, any resident of Japan (which term as used herein means any person resident in Japan, including any corporation or other entity organized under the laws of Japan), or to others for re-offering or resale, directly or indirectly, in Japan or to a resident of Japan, except pursuant to an exemption from the registration requirements of, and otherwise in compliance with, the Financial Instruments and Exchange Law and any other applicable laws, regulations and ministerial guidelines of Japan.

Legal matters

The validity of the shares of common stock offered hereby will be passed upon for us by Wilmer Cutler Pickering Hale and Dorr LLP, Boston, Massachusetts. Davis Polk & Wardwell LLP, New York, New York, has acted as counsel for the underwriters in connection with certain matters relating to this offering.

Experts

The consolidated financial statements of Agios Pharmaceuticals, Inc. appearing in Agios Pharmaceuticals, Inc.'s Annual Report on Form 10-K for the year ended December 31, 2013 have been audited by Ernst & Young LLP, independent registered public accounting firm, as set for in their report thereon, included therein, and incorporated herein by reference. Such consolidated financial statements are incorporated herein by reference in reliance upon such report given on the authority of such firm as experts in accounting and auditing.

Where you can find more information

We have filed with the Securities and Exchange Commission a registration statement on Form S-1 under the Securities Act with respect to the shares of common stock offered hereby. This prospectus, which constitutes a part of the registration statement, does not contain all the information set forth in the registration statement or the exhibits and schedules filed therewith. For further information about us and the common stock offered hereby, we refer you to the registration statement and the exhibits and schedules filed thereto. Statements contained in this prospectus regarding the contents of any contract or any other document that is filed as an exhibit to the registration statement or incorporated herein by reference are not necessarily complete, and each such statement is qualified in all respects by reference to the full text of such contract or other document filed as an exhibit to the registration statement or incorporated herein by reference.

We are required to file periodic reports, proxy statements, and other information with the Securities and Exchange Commission pursuant to the Securities Exchange Act of 1934. You may read and copy this information at the Public Reference Room of the Securities and Exchange Commission, 100 F. Street, N.E., Room 1580, Washington, D.C. 20549. You may obtain information on the operation of the public reference rooms by calling the Securities and Exchange Commission at 1-800-SEC-0330. The Securities and Exchange Commission also maintains an Internet website that contains reports, proxy statements and other information about

We also maintain a website at <http://www.agios.com> and make available free of charge through this website our Annual Report on Form 10-K, quarterly reports on Form 10-Q, current reports on Form 8-K and amendments to those reports filed or furnished pursuant to Sections 13(a) and 15(d) of the Exchange Act. We make these reports available through our website as soon as reasonably practicable after we electronically file such reports with, or furnish such reports to, the SEC. The information contained on, or that can be accessed through, our website is not a part of this prospectus. The reference to our web address does not constitute incorporation by reference of the information contained in, or that can be accessed through, our website.

Incorporation of documents by reference

The SEC allows us to "incorporate by reference" information from other documents that we file with it, which means that we can disclose important information to you by referring you to those documents. The information incorporated by reference is considered to be part of this prospectus. Information in this prospectus supersedes information incorporated by reference that we filed with the SEC prior to the date of this prospectus.

We incorporate by reference into this prospectus and the registration statement of which this prospectus is a part the information or documents listed below that we have filed with the SEC.

Table of Contents

- our Annual Report on Form 10-K for the fiscal year ended December 31, 2013 filed on March 18, 2014;
- our Current Reports on Form 8-K filed on April 7, 2014 and April 17, 2014;
- our Proxy Statement for our 2014 annual meeting of stockholders filed on April 7, 2014 (solely to the extent incorporated by reference into part III of our Annual Report on Form 10-K); and
- the description of our common stock contained in our Registration Statement on Form 8-A filed on July 19, 2013, including any amendment or report filed for the purpose of updating such description.

Any statement contained in a document incorporated or deemed to be incorporated by reference in this prospectus will be deemed modified, superseded or replaced for purposes of this prospectus to the extent that a statement contained in this prospectus modifies, supersedes or replaces such statement.

You may request, orally or in writing, a copy of any or all of the documents incorporated herein by reference. These documents will be provided to you at no cost, by contacting: Investor Relations, Agios Pharmaceuticals, Inc. 38 Sidney Street, 2nd Floor, Cambridge, MA 02139, (617) 649-8600 email address: investors@agios.com. In addition, copies of any or all of the documents incorporated herein by reference may be accessed at our website at www.agios.com. The information contained in, or accessible through, our website does not constitute part of this prospectus.



Part II

Information not required in prospectus

Item 13. Other expenses of issuance and distribution.

The following table indicates the expenses to be incurred in connection with the offering described in this registration statement, other than underwriting discounts and commissions, all of which will be paid by us. All amounts are estimated except the Securities and Exchange Commission registration fee and the Financial Industry Regulatory Authority, Inc. ("FINRA") filing fee.

	Amount
Securities and Exchange Commission registration fee	\$ 11,785
FINRA filing fee	14,225
Accountants' fees and expenses	50,000
Legal fees and expenses	200,000
Blue Sky fees and expenses	30,000
Transfer agent's fees and expenses	10,000
Printing and engraving expenses	50,000
Miscellaneous	43,990
Total expenses	<u>\$410,000</u>

Item 14. Indemnification of directors and officers.

Section 102 of the General Corporation Law of the State of Delaware permits a corporation to eliminate the personal liability of directors of a corporation to the corporation or its stockholders for monetary damages for a breach of fiduciary duty as a director, except where the director breached his duty of loyalty, failed to act in good faith, engaged in intentional misconduct or knowingly violated a law, authorized the payment of a dividend or approved a stock repurchase in violation of Delaware corporate law or obtained an improper personal benefit. Our certificate of incorporation provides that no director of the Registrant shall be personally liable to it or its stockholders for monetary damages for any breach of fiduciary duty as a director, notwithstanding any provision of law imposing such liability, except to the extent that the General Corporation Law of the State of Delaware prohibits the elimination or limitation of liability of directors for breaches of fiduciary duty.

Section 145 of the General Corporation Law of the State of Delaware provides that a corporation has the power to indemnify a director, officer, employee, or agent of the corporation, or a person serving at the request of the corporation for another corporation, partnership, joint venture, trust or other enterprise in related capacities against expenses (including attorneys' fees), judgments, fines and amounts paid in settlement actually and reasonably incurred by the person in connection with an action, suit or proceeding to which he was or is a party or is threatened to be made a party to any threatened, ending or completed action, suit or proceeding by reason of such position, if such person acted in good faith and in a manner he reasonably believed to be in or not opposed to the best interests of the corporation, and, in any criminal action or proceeding, had no reasonable cause to believe his conduct was unlawful, except that, in the case of actions brought by or in the right of the corporation, no indemnification shall be made with respect to any claim, issue or matter as to which such person shall have been adjudged to be liable to the corporation unless and only to the extent that the Court of Chancery or other adjudicating court determines that, despite the adjudication of liability but in view of all of the circumstances of the case, such person is fairly and reasonably entitled to indemnity for such expenses which the Court of Chancery or such other court shall deem proper.

Our certificate of incorporation provides that we will indemnify each person who was or is a party or threatened to be made a party to any threatened, pending or completed action, suit or proceeding (other than an action by or

[Table of Contents](#)

in the right of us) by reason of the fact that he or she is or was, or has agreed to become, a director or officer, or is or was serving, or has agreed to serve, at our request as a director, officer, partner, employee or trustee of, or in a similar capacity with, another corporation, partnership, joint venture, trust or other enterprise (all such persons being referred to as an "Indemnitee"), or by reason of any action alleged to have been taken or omitted in such capacity, against all expenses (including attorneys' fees), judgments, fines and amounts paid in settlement actually and reasonably incurred in connection with such action, suit or proceeding and any appeal therefrom, if such Indemnitee acted in good faith and in a manner he or she reasonably believed to be in, or not opposed to, our best interests, and, with respect to any criminal action or proceeding, he or she had no reasonable cause to believe his or her conduct was unlawful. Our certificate of incorporation provides that we will indemnify any Indemnitee who was or is a party to an action or suit by or in the right of us to procure a judgment in our favor by reason of the fact that the Indemnitee is or was, or has agreed to become, a director or officer, or is or was serving, or has agreed to serve, at our request as a director, officer, partner, employee or trustee of, or in a similar capacity with, another corporation, partnership, joint venture, trust or other enterprise, or by reason of any action alleged to have been taken or omitted in such capacity, against all expenses (including attorneys' fees) and, to the extent permitted by law, amounts paid in settlement actually and reasonably incurred in connection with such action, suit or proceeding, and any appeal therefrom, if the Indemnitee acted in good faith and in a manner he or she reasonably believed to be in, or not opposed to, our best interests, except that no indemnification shall be made with respect to any claim, issue or matter as to which such person shall have been adjudged to be liable to us, unless a court determines that, despite such adjudication but in view of all of the circumstances, he or she is entitled to indemnification of such expenses. Notwithstanding the foregoing, to the extent that any Indemnitee has been successful, on the merits or otherwise, he or she will be indemnified by us against all expenses (including attorneys' fees) actually and reasonably incurred in connection therewith. Expenses must be advanced to an Indemnitee under certain circumstances.

We have entered into indemnification agreements with each of our directors and executive officers. These indemnification agreements may require us, among other things, to indemnify our directors and officers for some expenses, including attorneys' fees, judgments, fines and settlement amounts incurred by a director or officer in any action or proceeding arising out of his or her service as one of our directors or officers, or any of our subsidiaries or any other company or enterprise to which the person provides services at our request.

We maintain a general liability insurance policy that covers certain liabilities of directors and officers of our corporation arising out of claims based on acts or omissions in their capacities as directors or officers.

In any underwriting agreement we enter into in connection with the sale of common stock being registered hereby, the underwriters will agree to indemnify, under certain conditions, us, our directors, our officers and persons who control us within the meaning of the Securities Act of 1933, as amended (the "Securities Act"), against certain liabilities.

Item 15. Recent sales of unregistered securities.

Set forth below is information regarding securities issued by us within the past three years. Also included is the consideration received by us for such securities and information relating to the section of the Securities Act, or rule of the Securities and Exchange Commission, under which exemption from registration was claimed.

(a) Issuances of preferred stock

In November 2011, we issued and sold an aggregate of 7,395,829 shares of our series C-1 preferred stock and 8,486,560 shares of our series C-2 preferred stock, each at a purchase price per share of \$4.9111, for an aggregate purchase price of \$78.0 million.

No underwriters were involved in the sale of these securities. The securities described in this section (a) of Item 15 were issued to investors in reliance upon the exemption from the registration requirements of the

[Table of Contents](#)

Securities Act, as set forth in Section 4(a)(2) under the Securities Act and Regulation D promulgated thereunder relative to transactions by an issuer not involving any public offering, to the extent an exemption from such registration was required. All purchasers of shares of preferred stock described above represented to us in connection with their purchase that they were accredited investors and were acquiring the shares for their own account for investment purposes only and not with a view to, or for sale in connection with, any distribution thereof and that they could bear the risks of the investment and could hold the securities for an indefinite period of time. The purchasers received written disclosures that the securities had not been registered under the Securities Act and that any resale must be made pursuant to a registration statement or an available exemption from such registration.

(b) Issuances of common stock

Since January 1, 2011 through the filing of our registration statement on Form S-8 on July 24, 2013, we issued to certain employees an aggregate of 52,098 shares of unregistered restricted common stock at a purchase price ranging from \$0.4675 to \$2.34 per share. The issuances of common stock described in this section (b) of Item 15 were issued pursuant to written compensatory plans or arrangements with our employees in reliance on the exemption from the registration requirements of the Securities Act provided by Rule 701 promulgated under the Securities Act, or pursuant to Section 4(a)(2) under the Securities Act, relative to transactions by an issuer not involving any public offering, to the extent an exemption from such registration was required. All recipients either received adequate information about us or had access, through employment relationships, to such information.

(c) Stock option grants

Since January 1, 2011, (i) we have issued to certain employees, directors and consultants options to purchase an aggregate of 3,002,642 shares of common stock, (ii) through the filing of our registration statement on Form S-8 on July 24, 2013, options to purchase 550,596 shares of common stock were exercised and (iii) options to purchase 244,026 shares of common stock have been forfeited or cancelled. As of April 17, 2014, options to purchase 3,826,410 shares of common stock remained outstanding at a weighted-average exercise price of \$10.36 per share.

The issuance of stock options and the common stock issuable upon the exercise of such options as described in this section (c) of Item 15 were issued pursuant to written compensatory plans or arrangements with our employees, directors and consultants, in reliance on the exemption from the registration requirements of the Securities Act provided by either Section 4(a)(2) of the Securities Act or Rule 701 promulgated under the Securities Act, or pursuant to Section 4(a)(2) under the Securities Act, relative to transactions by an issuer not involving any public offering, to the extent an exemption from such registration was required. All recipients either received adequate information about us or had access, through employment or other relationships, to such information.

Item 16. Exhibits and financial statement schedules.

(a) Exhibits.

The exhibits to the registration statement are listed in the Exhibit Index attached hereto and incorporated by reference herein.

Item 17. Undertakings.

(a) Insofar as indemnification for liabilities arising under the Securities Act may be permitted to directors, officers and controlling persons of the registrant pursuant to the foregoing provisions, or otherwise, the registrant has been advised that in the opinion of the Securities and Exchange Commission such indemnification is against public policy as expressed in the Securities Act and is, therefore, unenforceable. In the event that a claim for

[Table of Contents](#)

indemnification against such liabilities (other than the payment by the registrant of expenses incurred or paid by a director, officer or controlling person of the registrant in the successful defense of any action, suit or proceeding) is asserted by such director, officer or controlling person in connection with the securities being registered, the registrant will, unless in the opinion of its counsel the matter has been settled by controlling precedent, submit to a court of appropriate jurisdiction the question whether such indemnification by it is against public policy as expressed in the Securities Act and will be governed by the final adjudication of such issue.

(b) The undersigned hereby undertakes that:

- (1) For purposes of determining any liability under the Securities Act, the information omitted from the form of prospectus filed as part of this registration statement in reliance upon Rule 430A and contained in a form of prospectus filed by the registrant pursuant to Rule 424(b)(1) or (4) or 497(h) under the Securities Act shall be deemed to be part of this registration statement as of the time it was declared effective.
- (2) For the purpose of determining any liability under the Securities Act, each post-effective amendment that contains a form of prospectus shall be deemed to be a new registration statement relating to the securities offered therein, and the offering of such securities at that time shall be deemed to be the initial bona fide offering thereof.

[Table of Contents](#)

Signatures

Pursuant to the requirements of the Securities Act, the registrant has duly caused Amendment No. 1 to the Registration Statement to be signed on its behalf by the undersigned, thereunto duly authorized, in the City of Cambridge, Commonwealth of Massachusetts, on this 21st day of April, 2014.

AGIOS PHARMACEUTICALS, INC.

By: /s/ David P. Schenkein, M.D.

David P. Schenkein, M.D.
Chief Executive Officer

Pursuant to the requirements of the Securities Act of 1933, Amendment No. 1 to the Registration Statement has been signed by the following persons in the capacities held on the dates indicated.

<u>Signature</u>	<u>Title</u>	<u>Date</u>
<u>/s/ David P. Schenkein, M.D.</u> David P. Schenkein, M.D.	Chief Executive Officer and Director (Principal executive officer)	Date: April 21, 2014
<u>/s/ Glenn Goddard</u> Glenn Goddard	Senior Vice President, Finance (Principal financial and accounting officer)	Date: April 21, 2014
<u>*</u> Lewis C. Cantley, Ph.D.	Director	Date: April 21, 2014
<u>*</u> Paul J. Clancy	Director	Date: April 21, 2014
<u>*</u> Douglas G. Cole, M.D.	Director	Date: April 21, 2014
<u>*</u> Perry Karsen	Director	Date: April 21, 2014
<u>John M. Maraganore, M.D.</u>	Director	Date: April 21, 2014
<u>*</u> Robert T. Nelsen	Director	Date: April 21, 2014
<u>*</u> Kevin P. Starr	Director	Date: April 21, 2014
<u>*</u> Marc Tessier-Lavigne, Ph.D.	Director	Date: April 21, 2014
<u>*By: /s/ Glenn Goddard</u> Glenn Goddard <i>Attorney-in-Fact</i>		

EXHIBIT INDEX

Exhibit Number	Description of Exhibit	Incorporated by Reference			Exhibit Number	Filed Herewith
		Form	File Number	Date of Filing		
1.1	Form of Underwriting Agreement					X
3.1	Restated Certificate of Incorporation of the Registrant	8-K	001-36014	July 29, 2013	3.1	
3.2	Amended and Restated By-Laws	8-K	001-36014	July 29, 2013	3.2	
4.1	Specimen Stock Certificate evidencing the shares of common stock	S-1	333-189216	June 24, 2013	4.1	
4.2	Second Amended and Restated Investor Rights Agreement dated as of November 16, 2011	S-1	333-189216	June 10, 2013	4.2	
5.1	Opinion of Wilmer Cutler Pickering Hale and Dorr LLP					X
10.1#	2007 Stock Incentive Plan	S-1	333-189216	June 24, 2013	10.1	
10.2#	Form of Incentive Stock Option Agreement under 2007 Stock Incentive Plan	S-1	333-189216	June 10, 2013	10.2	
10.3#	Form of Nonstatutory Stock Option Agreement under 2007 Stock Incentive Plan	S-1	333-189216	June 10, 2013	10.3	
10.4#	2013 Stock Incentive Plan	S-1	333-189216	June 24, 2013	10.4	
10.5#	Form of Incentive Stock Option Agreement under 2013 Stock Incentive Plan	S-1	333-189216	June 24, 2013	10.5	
10.6#	Form of Nonstatutory Stock Option Agreement under 2013 Stock Incentive Plan	S-1	333-189216	June 24, 2013	10.6	
10.7#	2013 Employee Stock Purchase Plan	S-1	333-189216	June 24, 2013	10.7	
10.8#	Letter Agreement, dated as of April 17, 2009, between the Registrant and Duncan Higgons	S-1	333-189216	July 11, 2013	10.8	
10.9#	Letter Agreement, dated as of May 6, 2009, between the Registrant and David P. Schenkein, M.D.	S-1	333-189216	July 11, 2013	10.9	
10.10#	Letter Agreement, dated as of July 22, 2010, between the Registrant and Scott Biller, Ph.D.	S-1	333-189216	July 11, 2013	10.10	
10.11#	Letter of Agreement, dated May 4, 2010 between the Registrant and Glenn Goddard	S-1	333-189216	June 10, 2013	10.11	
10.12	Form of Indemnification Agreement between the Registrant and each of its Executive Officers and Directors	S-1	333-189216	July 11, 2013	10.12	

[Table of Contents](#)

Exhibit Number	Description of Exhibit	Incorporated by Reference			Filed Herewith
		Form	File Number	Date of Filing	
10.13	Lease, dated as of August 2, 2010, between the Registrant and Thirty-Eight Sidney Street Limited Partnership	S-1	333-189216	June 10, 2013	10.12
10.14†	Discovery and Development Collaboration and License Agreement, dated as of April 14, 2010, as amended on October 3, 2011, between the Registrant and Celgene Corporation	S-1	333-189216	July 16, 2013	10.14
10.15	Common Stock Purchase Agreement, dated as of July 16, 2013, between the Registrant and Celgene Alpine Investment Co., LLC	S-1	333-189216	July 16, 2013	10.15
21.1	Subsidiaries of the Registrant	10-K	001-36014	March 18, 2014	21.1
23.1	Consent of Ernst & Young LLP				X
23.2	Consent of Wilmer Cutler Pickering Hale and Dorr LLP (included in Exhibit 5.1)				X
24.1	Power of Attorney (included in signature page)	S-1	333-195174	April 10, 2014	24.1
101.INS**	XBRL Instance Document	10-K	001-36014	March 18, 2014	101.INS
101.SCH**	XBRL Taxonomy Extension Schema Document	10-K	001-36014	March 18, 2014	101.SCH
101.CAL**	XBRL Taxonomy Calculation Linkbase Document	10-K	001-36014	March 18, 2014	101.CAL
101.DEF**	XBRL Taxonomy Extension Definition Linkbase Document	10-K	001-36014	March 18, 2014	101.DEF
101.LAB**	XBRL Taxonomy Label Linkbase Document	10-K	001-36014	March 18, 2014	101.LAB
101.PRE**	XBRL Taxonomy Presentation Linkbase Document	10-K	001-36014	March 18, 2014	101.PRE

Indicates management contract or compensatory plan or arrangement.

† Confidential treatment has been granted by the Securities and Exchange Commission as to certain portions, which portions have been omitted and filed separately with the Securities and Exchange Commission.

* To be filed by amendment.

** In accordance with Rule 406T of Regulation S-T, XBRL (eXtensible Business Reporting Language) information is furnished and not filed or a part of this Registration Statement for purposes of Sections 11 or 12 of the Securities Act of 1933, as amended, is deemed not filed for purposes of Section 18 of the Securities Exchange Act of 1934, as amended, and is not otherwise subject to liability under these sections.

AGIOS PHARMACEUTICALS, INC.

[✕] Shares of Common Stock

Underwriting Agreement

April [✕], 2014

J.P. Morgan Securities LLC
Goldman, Sachs & Co.
As Representatives of the
several Underwriters listed
in Schedule 1 hereto

c/o J.P. Morgan Securities LLC
383 Madison Avenue
New York, New York 10179

c/o Goldman, Sachs & Co.
200 West Street
New York, New York 10282

Ladies and Gentlemen:

Agios Pharmaceuticals, Inc., a Delaware corporation (the “Company”), proposes to issue and sell to the several Underwriters listed in Schedule 1 hereto (the “Underwriters”), for whom you are acting as representatives (the “Representatives”), an aggregate of [✕] shares of common stock, par value \$0.001 per share, of the Company (the “Underwritten Shares”), and at the option of the Underwriters, up to an additional [✕] shares of common stock of the Company (the “Option Shares”). The Underwritten Shares and the Option Shares are herein referred to as the “Shares”. The shares of common stock, par value \$0.001 per share, of the Company to be outstanding after giving effect to the sale of the Shares are referred to herein as the “Stock”.

The Company hereby confirms its agreement with the several Underwriters concerning the purchase and sale of the Shares, as follows:

1. Registration Statement. The Company has prepared and filed with the Securities and Exchange Commission (the “Commission”) under the Securities Act of 1933, as amended, and the rules and regulations of the Commission thereunder (collectively, the “Securities Act”), a registration statement (File No. 333-195174), including a prospectus, relating to the Shares. Such registration statement, as amended at the time it became effective, including the information, if any, deemed pursuant to Rule 430A, 430B or 430C under the Securities Act to be part of the registration statement at the time of its effectiveness (“Rule 430 Information”), is referred to herein as the “Registration Statement”; and as used herein, the term “Preliminary Prospectus” means each prospectus included in such registration statement (and any amendments thereto) before effectiveness, any prospectus filed with the Commission pursuant to Rule 424(a) under the Securities Act and the prospectus included in the Registration Statement at the time of its effectiveness that omits Rule 430 Information, and the term “Prospectus” means the prospectus in the form first used (or made available upon request of purchasers pursuant to Rule 173 under the Securities Act) in connection with confirmation of sales of the Shares. If the Company has filed an abbreviated registration statement pursuant to Rule 462(b) under the Securities Act (the “Rule 462 Registration Statement”), then any reference herein to the term “Registration Statement” shall be deemed to include such Rule 462 Registration Statement. Capitalized terms used but not defined herein shall have the meanings given to such terms in the Registration Statement and the Prospectus.

At or prior to the Applicable Time (as defined below), the Company had prepared the following information (collectively with the pricing information set forth on Annex B, the "Pricing Disclosure Package"): a Preliminary Prospectus dated April [x], 2014 and each "free-writing prospectus" (as defined pursuant to Rule 405 under the Securities Act) listed on Annex B hereto.

"Applicable Time" means [x] P.M., New York City time, on April [x], 2014.

2. Purchase of the Shares by the Underwriters.

(a) The Company agrees to issue and sell the Underwritten Shares to the several Underwriters as provided in this Agreement, and each Underwriter, on the basis of the representations, warranties and agreements set forth herein and subject to the conditions set forth herein, agrees, severally and not jointly, to purchase from the Company the respective number of Underwritten Shares set forth opposite such Underwriter's name in Schedule 1 hereto at a price per share (the "Purchase Price") of \$[x].

In addition, the Company agrees to issue and sell the Option Shares to the several Underwriters as provided in this Agreement, and the Underwriters, on the basis of the representations, warranties and agreements set forth herein and subject to the conditions set forth herein, shall have the option to purchase, severally and not jointly, from the Company the Option Shares at the Purchase Price less an amount per share equal to any dividends or distributions declared by the Company and payable on the Underwritten Shares but not payable on the Option Shares.

If any Option Shares are to be purchased, the number of Option Shares to be purchased by each Underwriter shall be the number of Option Shares which bears the same ratio to the aggregate number of Option Shares being purchased as the number of Underwritten Shares set forth opposite the name of such Underwriter in Schedule 1 hereto (or such number increased as set forth in Section 10 hereof) bears to the aggregate number of Underwritten Shares being purchased from the Company by the several Underwriters, subject, however, to such adjustments to eliminate any fractional Shares as the Representatives in their sole discretion shall make.

The Underwriters may exercise the option to purchase Option Shares at any time in whole, or from time to time in part, on or before the thirtieth day following the date of the Prospectus, by written notice from the Representatives to the Company. Such notice shall set forth the aggregate number of Option Shares as to which the option is being exercised and the date and time when the Option Shares are to be delivered and paid for, which may be the same date and time as the Closing Date (as hereinafter defined) but shall not be earlier than the Closing Date or later than the tenth full business day (as hereinafter defined) after the date of such notice (unless such time and date are postponed in accordance with the provisions of Section 10 hereof). Any such notice shall be given at least two business days prior to the date and time of delivery specified therein.

(b) The Company understands that the Underwriters intend to make a public offering of the Shares as soon after the effectiveness of this Agreement as in the judgment of the Representatives is advisable, and initially to offer the Shares on the terms set forth in the Prospectus. The Company acknowledges and agrees that the Underwriters may offer and sell Shares to or through any affiliate of an Underwriter.

(c) Payment for the Shares shall be made by wire transfer in immediately available funds to the account specified by the Company to the Representatives in the case of the Underwritten Shares, at the offices of Davis Polk & Wardwell LLP, 450 Lexington Avenue, New York, New York 10017 at 10:00 A.M. New York City time, on [X], 2014, or at such other time or place on the same or such other date, not later than the fifth business day thereafter, as the Representatives and the Company may agree upon in writing or, in the case of the Option Shares, on the date and at the time and place specified by the Representatives in the written notice of the Underwriters' election to purchase such Option Shares. The time and date of such payment for the Underwritten Shares is referred to herein as the "Closing Date", and the time and date for such payment for the Option Shares, if other than the Closing Date, is herein referred to as the "Additional Closing Date".

Payment for the Shares to be purchased on the Closing Date or the Additional Closing Date, as the case may be, shall be made against delivery to the Representatives for the respective accounts of the several Underwriters of the Shares to be purchased on such date or the Additional Closing Date, as the case may be, with any transfer taxes payable in connection with the sale of such Shares duly paid by the Company. Delivery of the Shares shall be made through the facilities of The Depository Trust Company ("DTC") unless the Representatives shall otherwise instruct. The certificates for the Shares will be made available for inspection and packaging by the Representatives at the office of DTC or its designated custodian not later than 1:00 P.M., New York City time, on the business day prior to the Closing Date or the Additional Closing Date, as the case may be.

(d) The Company acknowledges and agrees that the Underwriters are acting solely in the capacity of an arm's length contractual counterparty to the Company with respect to the offering of Shares contemplated hereby (including in connection with determining the terms of the offering) and not as a financial advisor or a fiduciary to, or an agent of, the Company or any other person. Additionally, neither the Representatives nor any other Underwriter is advising the Company or any other person as to any legal, tax, investment, accounting or regulatory matters in any jurisdiction. The Company shall consult with its own advisors concerning such matters and shall be responsible for making its own independent investigation and appraisal of the transactions contemplated hereby, and the Underwriters shall have no responsibility or liability to the Company with respect thereto. Any review by the Underwriters of the Company, the transactions contemplated hereby or other matters relating to such transactions will be performed solely for the benefit of the Underwriters and shall not be on behalf of the Company.

3. Representations and Warranties of the Company. The Company represents and warrants to each Underwriter that:

(a) *Preliminary Prospectus.* No order preventing or suspending the use of any Preliminary Prospectus has been issued by the Commission, and each Preliminary Prospectus included in the Pricing Disclosure Package, at the time of filing thereof, complied in all material respects with the Securities Act, and no Preliminary Prospectus, at the time of filing thereof, contained any untrue statement of a material fact or omitted to state a material fact necessary in order to make the statements therein, in the light of the circumstances under which they were made, not misleading; provided that the Company makes no representation and warranty with respect to any statements or omissions made in reliance upon and in conformity with information relating to any Underwriter furnished to the Company in writing by such Underwriter through the Representatives expressly for use in any Preliminary Prospectus, it being understood and agreed that the only such information furnished by any Underwriter consists of the information described as such in Section 7(b) hereof.

(b) *Pricing Disclosure Package.* The Pricing Disclosure Package as of the Applicable Time did not, and as of the Closing Date and as of the Additional Closing Date, as the case may be, will not, contain any untrue statement of a material fact or omit to state a material fact necessary in order to make the statements therein, in the light of the circumstances under which they were made, not misleading; provided that the Company makes no representation and warranty with respect to any statements or omissions made in reliance upon and in conformity with information relating to any Underwriter furnished to the Company in writing by such Underwriter through the Representatives expressly for use in such Pricing Disclosure Package, it being understood and agreed that the only such information furnished by any Underwriter consists of the information described as such in Section 7(b) hereof.

(c) *Issuer Free Writing Prospectus.* Other than the Registration Statement, the Preliminary Prospectus and the Prospectus, the Company (including its agents and representatives, other than the Underwriters in their capacity as such) has not prepared, used, authorized, approved or referred to and will not prepare, use, authorize, approve or refer to any “written communication” (as defined in Rule 405 under the Securities Act) that constitutes an offer to sell or solicitation of an offer to buy the Shares (each such communication by the Company or its agents and representatives (other than a communication referred to in clause (i) below) an “Issuer Free Writing Prospectus”) other than (i) any document not constituting a prospectus pursuant to Section 2(a)(10)(a) of the Securities Act or Rule 134 under the Securities Act or (ii) the documents listed on Annex B hereto, each electronic road show and any other written communications approved in writing in advance by the Representatives. Each such Issuer Free Writing Prospectus complied in all material respects with the Securities Act, has been or will be (within the time period specified in Rule 433) filed in accordance with the Securities Act (to the extent required thereby) and, when taken together with the Preliminary Prospectus accompanying, or delivered prior to delivery of, such Issuer Free Writing Prospectus, did not, and as of the Closing Date and as of the Additional Closing Date, as the case may be, will not, contain any untrue statement of a material fact or omit to state a material fact necessary in order to make the statements therein, in the light of the circumstances under which they were made, not misleading; provided that the Company makes no representation and warranty with respect to any statements or omissions made in each such Issuer Free Writing Prospectus or Preliminary Prospectus in reliance upon and in conformity with information relating to any Underwriter furnished to the Company in writing by such Underwriter through the Representatives expressly for use in such Issuer Free Writing Prospectus or Preliminary Prospectus, it being understood and agreed that the only such information furnished by any Underwriter consists of the information described as such in Section 7(b) hereof.

(d) *Emerging Growth Company.* From the time of initial confidential submission of the registration statement relating to the Company’s initial public offering to the Commission (or, if earlier, the first date on which the Company engaged directly or through any person authorized to act on its behalf in any Testing-the-Waters Communication, as defined below) through the date hereof, the Company has been and is an “emerging growth company,” as defined in Section 2(a)(19) of the Securities Act (an “Emerging Growth Company”). “Testing-the-Waters Communication” means any oral or written communication with potential investors undertaken in reliance on Section 5(d) of the Securities Act.

(e) *Testing-the-Waters Materials.* The Company (i) has not alone engaged in any Testing-the-Waters Communications other than Testing-the-Waters Communications of which the Company notified the Representatives in writing with entities that are qualified institutional buyers within the meaning of Rule 144A under the Securities Act or institutions that are

accredited investors within the meaning of Rule 501 under the Securities Act and (ii) has not authorized anyone other than the Representatives to engage in Testing-the-Waters Communications. The Company reconfirms that the Representatives have been authorized to act on its behalf in undertaking Testing-the-Waters Communications. The Company has not distributed or approved for distribution any Written Testing-the-Waters Communications other than those listed on Annex C hereto. "Written Testing-the-Waters Communication" means any Testing-the-Waters Communication that is a written communication within the meaning of Rule 405 under the Securities Act. Any individual Written Testing-the-Waters Communication does not conflict with the information contained in the Registration Statement or the Pricing Disclosure Package, complied in all material respects with the Securities Act, and when taken together with the Pricing Disclosure Package as of the Applicable Time, did not, and as of the Closing Date and as of the Additional Closing Date, as the case may be, will not, contain any untrue statement of a material fact or omit to state a material fact necessary in order to make the statements therein, in the light of the circumstances under which they were made, not misleading; provided that the Company makes no representation and warranty with respect to any statements or omissions made in each such Written Testing-the-Waters Communication in reliance upon and in conformity with written information furnished to the Company in writing by such Underwriter through the Representatives expressly for use in such Written Testing-the-Waters Communications, it being understood and agreed that the only such information furnished by any Underwriter consists of the information described as such in Section 7(b) hereof.

(f) *Registration Statement and Prospectus.* The Registration Statement has been declared effective by the Commission. No order suspending the effectiveness of the Registration Statement has been issued by the Commission, and no proceeding for that purpose or pursuant to Section 8A of the Securities Act against the Company or related to the offering of the Shares has been initiated or, to the knowledge of the Company, threatened by the Commission; as of the applicable effective date of the Registration Statement and any post-effective amendment thereto, the Registration Statement and any such post-effective amendment complied and will comply in all material respects with the Securities Act, and did not and will not contain any untrue statement of a material fact or omit to state a material fact required to be stated therein or necessary in order to make the statements therein not misleading; and as of the date of the Prospectus and any amendment or supplement thereto and as of the Closing Date and as of the Additional Closing Date, as the case may be, the Prospectus will not contain any untrue statement of a material fact or omit to state a material fact necessary in order to make the statements therein, in the light of the circumstances under which they were made, not misleading; provided that the Company makes no representation and warranty with respect to any statements or omissions made in reliance upon and in conformity with information relating to any Underwriter furnished to the Company in writing by such Underwriter through the Representatives expressly for use in the Registration Statement and the Prospectus and any amendment or supplement thereto, it being understood and agreed that the only such information furnished by any Underwriter consists of the information described as such in Section 7(b) hereof.

(g) *Incorporated Documents.* The documents incorporated by reference in the Registration Statement, the Prospectus and the Pricing Disclosure Package, when they were filed with the Commission conformed in all material respects to the requirements of the Exchange Act, and none of such documents contained any untrue statement of a material fact or omitted to state a material fact necessary to make the statements therein, in the light of the circumstances under which they were made, not misleading.

(h) *Financial Statements.* The financial statements (including the related notes thereto) of the Company and its consolidated subsidiaries included in the Registration Statement, the Pricing Disclosure Package and the Prospectus comply in all material respects with the applicable requirements of the Securities Act and present fairly the financial position of the Company and its consolidated subsidiaries as of the dates indicated and the results of their operations and the changes in their cash flows for the periods specified; such financial statements have been prepared in conformity with generally accepted accounting principles in the United States applied on a consistent basis throughout the periods covered thereby, except as otherwise disclosed therein, and, in the case of unaudited, interim financial statements, subject to normal year-end audit adjustments and the exclusion of certain footnotes, and any supporting schedules included in the Registration Statement present fairly the information required to be stated therein; and the other financial information included in the Registration Statement, the Pricing Disclosure Package and the Prospectus has been derived from the accounting records of the Company and its consolidated subsidiaries and presents fairly the information shown thereby.

(i) *No Material Adverse Change.* Since the date of the most recent financial statements of the Company included in the Registration Statement, the Pricing Disclosure Package and the Prospectus, (i) there has not been any material change in the capital stock (other than the issuance of shares of common stock upon exercise of stock options and warrants described as outstanding in, and the grant of options and awards under existing equity incentive plans described in, the Registration Statement, the Pricing Disclosure Package and the Prospectus), short-term debt or long-term debt of the Company or any of its subsidiaries, or any dividend or distribution of any kind declared, set aside for payment, paid or made by the Company on any class of capital stock, or any material adverse change, or any development that would reasonably be expected to result in a material adverse change, in or affecting the business, properties, management, financial position, stockholders' equity, results of operations or prospects of the Company and its subsidiaries taken as a whole; (ii) neither the Company nor any of its subsidiaries has entered into any transaction or agreement (whether or not in the ordinary course of business) that is material to the Company and its subsidiaries taken as a whole or incurred any liability or obligation, direct or contingent, that is material to the Company and its subsidiaries taken as a whole; and (iii) neither the Company nor any of its subsidiaries has sustained any loss or interference with its business that is material to the Company and its subsidiaries taken as a whole and that is either from fire, explosion, flood or other calamity, whether or not covered by insurance, or from any labor disturbance or dispute or any action, order or decree of any court or arbitrator or governmental or regulatory authority, except in each case as otherwise disclosed in the Registration Statement, the Pricing Disclosure Package and the Prospectus.

(j) *Organization and Good Standing.* The Company and each of its subsidiaries have been duly organized and are validly existing and in good standing under the laws of their respective jurisdictions of organization, are duly qualified to do business and are in good standing in each jurisdiction in which their respective ownership or lease of property or the conduct of their respective businesses requires such qualification, and have all power and authority necessary to own or hold their respective properties and to conduct the businesses in which they are engaged, except where the failure to be so qualified or in good standing or have such power or authority would not, individually or in the aggregate, have a material adverse effect on the business, properties, management, financial position, stockholders' equity, results of operations or prospects of the Company and its subsidiaries taken as a whole or on the performance by the Company of its obligations under this Agreement (a "Material Adverse Effect"). The Company does not own or control, directly or indirectly, any corporation, association or other entity other than the subsidiaries incorporated by reference into Exhibit 21 to the Registration Statement.

(k) *Capitalization.* The Company has an authorized capitalization as set forth in the Registration Statement, the Pricing Disclosure Package and the Prospectus under the heading “Capitalization”; all the outstanding shares of capital stock of the Company have been duly and validly authorized and issued and are fully paid and non-assessable and are not subject to any pre-emptive or similar rights; except as described in or expressly contemplated by the Pricing Disclosure Package and the Prospectus, there are no outstanding rights (including, without limitation, pre-emptive rights), warrants or options to acquire, or instruments convertible into or exchangeable for, any shares of capital stock or other equity interest in the Company or any of its subsidiaries, or any contract, commitment, agreement, understanding or arrangement of any kind relating to the issuance of any capital stock of the Company or any such subsidiary, any such convertible or exchangeable securities or any such rights, warrants or options; the capital stock of the Company conforms in all material respects to the description thereof contained in the Registration Statement, the Pricing Disclosure Package and the Prospectus; and all the outstanding shares of capital stock or other equity interests of each subsidiary owned, directly or indirectly, by the Company have been duly and validly authorized and issued, are fully paid and non-assessable (except, in the case of any foreign subsidiary, for directors’ qualifying shares) and are owned directly or indirectly by the Company, free and clear of any lien, charge, encumbrance, security interest, restriction on voting or transfer or any other claim of any third party.

(l) *Stock Options.* With respect to the stock options (the “Stock Options”) granted pursuant to the stock-based compensation plans of the Company and its subsidiaries (the “Company Stock Plans”), (i) to the knowledge of the Company, each Stock Option intended to qualify as an “incentive stock option” under Section 422 of the Internal Revenue Code of 1986, as amended (the “Code”) so qualifies, (ii) each grant of a Stock Option was duly authorized no later than the date on which the grant of such Stock Option was by its terms to be effective (the “Grant Date”) by all necessary corporate action, including, as applicable, approval by the board of directors of the Company (or a duly constituted and authorized committee thereof) and any required stockholder approval by the necessary number of votes or written consents, and, to the knowledge of the Company (other than with respect to due execution and delivery by the Company), the award agreement governing such grant (if any) was duly executed and delivered by each party thereto, (iii) each such grant was made in accordance with the terms of the Company Stock Plans, and (iv) each such grant was properly accounted for in accordance with generally accepted accounting principles in the United States in the financial statements (including the related notes) of the Company.

(m) *Due Authorization.* The Company has full right, power and authority to execute and deliver this Agreement and to perform its obligations hereunder; and all action required to be taken for the due and proper authorization, execution and delivery by it of this Agreement and the consummation by it of the transactions contemplated hereby has been duly and validly taken.

(n) *Underwriting Agreement.* This Agreement has been duly authorized, executed and delivered by the Company.

(o) *The Shares.* The Shares to be issued and sold by the Company hereunder have been duly authorized and, when issued and delivered and paid for as provided herein, will be duly and validly issued, will be fully paid and nonassessable and will conform in all material respects to the descriptions thereof in the Registration Statement, the Pricing Disclosure Package and the Prospectus; and the issuance of the Shares is not subject to any preemptive or similar rights that have not been validly waived.

(p) *Descriptions of the Underwriting Agreement.* This Agreement conforms in all material respects to the description thereof contained in the Registration Statement, the Pricing Disclosure Package and the Prospectus.

(q) *No Violation or Default.* Neither the Company nor any of its subsidiaries is (i) in violation of its charter or by-laws or similar organizational documents; (ii) in default, and no event has occurred that, with notice or lapse of time or both, would constitute such a default, in the due performance or observance of any term, covenant or condition contained in any indenture, mortgage, deed of trust, loan agreement or other agreement or instrument to which the Company or any of its subsidiaries is a party or by which the Company or any of its subsidiaries is bound or to which any of the property or assets of the Company or any of its subsidiaries is subject; or (iii) in violation of any law or statute or any judgment, order, rule or regulation of any court or arbitrator or governmental or regulatory authority having jurisdiction over the Company or any of its subsidiaries, except, in the case of clauses (ii) and (iii) above, for any such default or violation that would not, individually or in the aggregate, have a Material Adverse Effect.

(r) *No Conflicts.* The execution, delivery and performance by the Company of this Agreement, the issuance and sale of the Shares and the consummation of the transactions contemplated by this Agreement will not (i) conflict with or result in a breach or violation of any of the terms or provisions of, or constitute a default under, or result in the creation or imposition of any lien, charge or encumbrance upon any property or assets of the Company or any of its subsidiaries pursuant to, any indenture, mortgage, deed of trust, loan agreement or other agreement or instrument to which the Company or any of its subsidiaries is a party or by which the Company or any of its subsidiaries is bound or to which any of the property or assets of the Company or any of its subsidiaries is subject, (ii) result in any violation of the provisions of the charter or by-laws or similar organizational documents of the Company or any of its subsidiaries or (iii) result in the violation of any law or statute or any judgment, order, rule or regulation of any court or arbitrator or governmental or regulatory authority having jurisdiction over the Company or any of its subsidiaries, except, in the case of clauses (i) and (iii) above, for any such conflict, breach, violation or default that would not, individually or in the aggregate, have a Material Adverse Effect.

(s) *No Consents Required.* No consent, approval, authorization, order, license, registration or qualification of or with any court or arbitrator or governmental or regulatory authority is required for the execution, delivery and performance by the Company of this Agreement, the issuance and sale of the Shares and the consummation of the transactions contemplated by this Agreement, except for the registration of the Shares under the Securities Act and such consents, approvals, authorizations, orders and registrations or qualifications as have already been obtained or made or as may be required by the Financial Industry Regulatory Authority, Inc. ("FINRA") or the Nasdaq Stock Market or under applicable state securities laws in connection with the purchase and distribution of the Shares by the Underwriters.

(t) *Legal Proceedings.* There are no legal, governmental or regulatory investigations, actions, suits or proceedings pending to which the Company or any of its subsidiaries is a party or to which any property of the Company or any of its subsidiaries is subject that, individually or in the aggregate, would reasonably be expected to have a Material Adverse Effect; to the knowledge of the Company, no such investigations, actions, suits or

proceedings are threatened or contemplated by any governmental or regulatory authority or threatened by others; and (i) there are no current or pending legal, governmental or regulatory actions, suits or proceedings that are required under the Securities Act to be described in the Registration Statement, the Pricing Disclosure Package or the Prospectus that are not so described in the Registration Statement, the Pricing Disclosure Package and the Prospectus and (ii) there are no statutes, regulations or contracts or other documents that are required under the Securities Act to be filed as exhibits to the Registration Statement or described in the Registration Statement, the Pricing Disclosure Package or the Prospectus that are not so filed as exhibits to the Registration Statement or described in the Registration Statement, the Pricing Disclosure Package and the Prospectus.

(u) *Independent Accountants.* Ernst & Young LLP, who have certified certain financial statements of the Company and its subsidiaries is an independent registered public accounting firm with respect to the Company and its subsidiaries within the applicable rules and regulations adopted by the Commission and the Public Company Accounting Oversight Board (United States) and as required by the Securities Act.

(v) *Title to Real and Personal Property.* Except as described in the Registration Statement, the Pricing Disclosure Package and the Prospectus, the Company and its subsidiaries have good title in fee simple (in the case of real property) to, or have valid rights to lease or otherwise use, all items of real and personal property and assets that are material to the business of the Company and its subsidiaries taken as a whole, in each case free and clear of all liens, encumbrances, claims and defects and imperfections of title except those that (i) do not materially interfere with the use made and proposed to be made of such property by the Company and its subsidiaries or (ii) would not reasonably be expected, individually or in the aggregate, to have a Material Adverse Effect.

(w) *Title to Intellectual Property.* Except as described in the Registration Statement, the Pricing Disclosure Package and the Prospectus, the Company and its subsidiaries own or possess, or can acquire on reasonable terms, adequate rights to use all patents, patent rights, trademarks, service marks, trade names, domain names, goodwill associated with the foregoing, copyrights, licenses, know-how and other similar intellectual property rights (including, trade secrets and other unpatented and/or unpatentable proprietary or confidential information, systems or procedures) and all registrations and applications for registration of the foregoing (collectively, "Intellectual Property"), in each case necessary for the conduct of the business of the Company and its subsidiaries taken as whole in all material respects as currently conducted and as proposed to be conducted, and, to the knowledge of the Company, the conduct of the businesses of the Company and its subsidiaries has not conflicted with, infringed, misappropriated or otherwise violated any Intellectual Property of any third party in any material respect. The Company is not aware of any facts that would inform a reasonable basis for a claim that the commercialization of any of the Company's product candidates would infringe, misappropriate or otherwise violate any Intellectual Property of any third party in any material respect. The Company and its subsidiaries have not received any written notice of any claim of infringement, misappropriation or other violation of any Intellectual Property of any third party or any written notice challenging the validity, scope or enforceability of their respective patents or rights therein, in each case, which would reasonably be expected to result in a Material Adverse Effect. Except as described in the Registration Statement, the Pricing Disclosure Package and the Prospectus, the Company is not aware of any specific facts or combination of facts that cause the Company to reasonably conclude that any of the material patent applications owned by or licensed to the Company or any of its subsidiaries would, if issued, be invalid or unenforceable.

(x) *No Undisclosed Relationships.* No relationship, direct or indirect, exists between or among the Company or any of its subsidiaries, on the one hand, and the directors, officers, stockholders, customers or suppliers of the Company or any of its subsidiaries, on the other, that is required by the Securities Act to be described in the Registration Statement and the Prospectus and that is not so described in such documents and in the Pricing Disclosure Package.

(y) *Investment Company Act.* The Company is not and, after giving effect to the offering and sale of the Shares and the application of the proceeds thereof as described in the Registration Statement, the Pricing Disclosure Package and the Prospectus, will not be required to register as an “investment company” or an entity “controlled” by an “investment company” within the meaning of the Investment Company Act of 1940, as amended, and the rules and regulations of the Commission thereunder (collectively, the “Investment Company Act”).

(z) *Taxes.* The Company and its subsidiaries have filed all federal, state, local and foreign tax returns required to be filed through the date hereof. The Company and its subsidiaries have paid all taxes shown as due on such returns, except for taxes being contested in good faith and for which adequate reserves have been taken, and except as would not, individually or in the aggregate, have a Material Adverse Effect. Except as otherwise disclosed in the Registration Statement, the Pricing Disclosure Package and the Prospectus, there is no tax deficiency that has been, or would reasonably be expected to be, asserted against the Company or any of its subsidiaries or any of their respective properties or assets, in each case, except as would not have a Material Adverse Effect.

(aa) *Licenses and Permits.* The Company and its subsidiaries possess all licenses, certificates, permits and other authorizations issued by, and have made all declarations and filings with, the appropriate federal, state, local or foreign governmental or regulatory authorities that are necessary for the ownership or lease of their respective properties or the conduct of their respective businesses as described in the Registration Statement, the Pricing Disclosure Package and the Prospectus, except where the failure to possess or make the same would not, individually or in the aggregate, have a Material Adverse Effect; and except as described in the Registration Statement, the Pricing Disclosure Package and the Prospectus, neither the Company nor any of its subsidiaries has received notice of any revocation or modification of any such license, certificate, permit or authorization or has any reason to believe that any such license, certificate, permit or authorization will not be renewed in the ordinary course. Except as described in the Registration Statement, the Pricing Disclosure Package and the Prospectus, as applicable, the Company and its subsidiaries (i) are, and at all times have been, in compliance with all statutes, rules and regulations applicable to the ownership, testing, development, manufacture, packaging, processing, use, distribution, storage, import, export or disposal of any product manufactured or distributed by the Company or its subsidiaries (“Applicable Laws”), except where such noncompliance would not, individually or in the aggregate, reasonably be expected to have a Material Adverse Effect; and (ii) have not received any U.S. Food and Drug Administration (“FDA”) Form 483, written notice of adverse finding, warning letter, untitled letter or other correspondence or written notice from any court or arbitrator or governmental or regulatory authority alleging or asserting non-compliance with (x) any Applicable Laws or (y) any licenses, exemptions, certificates, approvals, clearances, authorizations, permits and supplements or amendments thereto required by any such Applicable Laws.

(bb) *No Labor Disputes.* No labor disturbance by or dispute with employees of the Company or any of its subsidiaries exists or, to the knowledge of the Company, is contemplated or threatened, and the Company is not aware of any existing or imminent labor disturbance by, or dispute with, the employees of any of its or its subsidiaries’ principal suppliers, contractors or customers, except as would not have a Material Adverse Effect.

(cc) *Compliance with and Liability under Environmental Laws.* (i) The Company and its subsidiaries (a) are, and at all prior times were, in compliance with any and all applicable federal, state, local and foreign laws, rules, regulations, requirements, decisions, judgments, decrees, orders and the common law relating to pollution or the protection of the environment, natural resources or human health or safety, including those relating to the generation, storage, treatment, use, handling, transportation, Release or threat of Release of Hazardous Materials (collectively, “Environmental Laws”), (b) have received and are in compliance with all permits, licenses, certificates or other authorizations or approvals required of them under applicable Environmental Laws to conduct their respective businesses, (c) have not received notice of any actual or potential liability under or relating to, or actual or potential violation of, any Environmental Laws, including for the investigation or remediation of any Release or threat of Release of Hazardous Materials, and have no knowledge of any event or condition that would reasonably be expected to result in any such notice, (d) are not conducting or paying for, in whole or in part, any investigation, remediation or other corrective action pursuant to any Environmental Law at any location, and (e) are not a party to any order, decree or agreement that imposes any obligation or liability under any Environmental Law, and (ii) there are no costs or liabilities associated with Environmental Laws of or relating to the Company or its subsidiaries, except in the case of each of (i) and (ii) above, for any such matter, as would not, individually or in the aggregate, reasonably be expected to have a Material Adverse Effect; and (iii) except as described in the Registration Statement, the Pricing Disclosure Package and the Prospectus, (a) there are no proceedings that are pending, or, to the knowledge of the Company, contemplated, against the Company or any of its subsidiaries under any Environmental Laws in which a governmental entity is also a party, other than such proceedings regarding which it is reasonably believed no monetary sanctions of \$100,000 or more will be imposed, (b) the Company and its subsidiaries are not aware of any facts or issues regarding compliance with Environmental Laws, or liabilities or other obligations under Environmental Laws, including the Release or threat of Release of Hazardous Materials, that would reasonably be expected to have a material effect on the capital expenditures, earnings or competitive position of the Company and its subsidiaries, and (c) none of the Company and its subsidiaries anticipates material capital expenditures relating to any Environmental Laws.

(dd) *Hazardous Materials.* There has been no storage, generation, transportation, use, handling, treatment, Release or threat of Release of Hazardous Materials by, relating to or caused by the Company or any of its subsidiaries (or, to the knowledge of the Company and its subsidiaries, any other entity (including any predecessor) for whose acts or omissions the Company or any of its subsidiaries is or would reasonably be expected to be liable) at, on, under or from any property or facility now or previously owned, operated or leased by the Company or any of its subsidiaries, or at, on, under or from any other property or facility, in violation of any Environmental Laws or in a manner or amount or to a location that would reasonably be expected to result in any liability under any Environmental Law, except for any violation or liability which would not, individually or in the aggregate, reasonably be expected to have a Material Adverse Effect. “Hazardous Materials” means any material, chemical, substance, waste, pollutant, contaminant, compound, mixture, or constituent thereof, in any form or amount, including petroleum (including crude oil or any fraction thereof) and petroleum products, natural gas liquids, asbestos and asbestos containing materials, naturally occurring radioactive materials, brine, and drilling mud, regulated or which can give rise to liability under any Environmental Law. “Release” means any spilling, leaking, seepage, pumping, pouring, emitting, emptying, discharging, injecting, escaping, leaching, dumping, disposing, depositing, dispersing, or migrating in, into or through the environment, or in, into from or through any building or structure.

(ee) *Compliance with ERISA.* (i) Each employee benefit plan, within the meaning of Section 3(3) of the Employee Retirement Income Security Act of 1974, as amended (“ERISA”), for which the Company or any member of its “Controlled Group” (defined as any organization which is a member of a controlled group of corporations within the meaning of Section 414 of the Code) would have any liability (each, a “Plan”) has been maintained in compliance with its terms and the requirements of any applicable statutes, orders, rules and regulations, including but not limited to ERISA and the Code, except for noncompliance that would not reasonably be expected to result in material liability to the Company or its subsidiaries; (ii) no prohibited transaction, within the meaning of Section 406 of ERISA or Section 4975 of the Code, has occurred with respect to any Plan excluding transactions effected pursuant to a statutory or administrative exemption that would reasonably be expected to result in a material liability to the Company or its subsidiaries; (iii) for each Plan that is subject to the funding rules of Section 412 of the Code or Section 302 of ERISA, the minimum funding standard of Section 412 of the Code or Section 302 of ERISA, as applicable, has been satisfied (without taking into account any waiver thereof or extension of any amortization period) and is reasonably expected to be satisfied in the future (without taking into account any waiver thereof or extension of any amortization period); (iv) the fair market value of the assets of each Plan that is required to be funded exceeds the present value of all benefits accrued under such Plan (determined based on those assumptions used to fund such Plan); (v) no “reportable event” (within the meaning of Section 4043(c) of ERISA) has occurred or is reasonably expected to occur that either has resulted, or would reasonably be expected to result, in material liability to the Company or its subsidiaries; (vi) neither the Company nor any member of the Controlled Group has incurred, nor reasonably expects to incur, any liability under Title IV of ERISA (other than contributions to the Plan or premiums to the Pension Benefit Guaranty Corporation, in the ordinary course and without default) in respect of a Plan (including a “multiemployer plan”, within the meaning of Section 4001(a)(3) of ERISA); and (vii) there is no pending audit or investigation by the Internal Revenue Service, the U.S. Department of Labor, the Pension Benefit Guaranty Corporation or any other governmental agency or any foreign regulatory agency with respect to any Plan that would reasonably be expected to result in material liability to the Company or its subsidiaries. None of the following events has occurred or is reasonably likely to occur: (x) a material increase in the aggregate amount of contributions required to be made to all Plans by the Company or its subsidiaries in the current fiscal year of the Company and its subsidiaries compared to the amount of such contributions made in the Company and its subsidiaries’ most recently completed fiscal year, other than an increase solely attributable to (A) an increase in the number of employees covered by such Plans or (B) an increase arising from the renewal in the ordinary course of business of contracts with vendors, insurers, plan administrators or other similar service providers under which the benefits of the Plans are provided; or (y) a material increase in the Company and its subsidiaries’ “accumulated post-retirement benefit obligations” (within the meaning of Statement of Financial Accounting Standards 106) compared to the amount of such obligations in the Company and its subsidiaries’ most recently completed fiscal year.

(ff) *Disclosure Controls.* The Company and its subsidiaries have established an effective system of “disclosure controls and procedures” (as defined in Rule 13a-15(e) of the Securities Exchange Act of 1934, as amended, and the rules and regulations of the Commission thereunder (collectively, the “Exchange Act”)) that complies with the requirements of the Exchange Act and that has been designed to ensure that information required to be disclosed by

the Company in reports that it files or submits under the Exchange Act is recorded, processed, summarized and reported within the time periods specified in the Commission's rules and forms, including controls and procedures designed to ensure that such information is accumulated and communicated to the Company's management as appropriate to allow timely decisions regarding required disclosure.

(gg) *Accounting Controls.* The Company and its subsidiaries have established systems of "internal control over financial reporting" (as defined in Rule 13a-15(f) of the Exchange Act) that have been designed by, or under the supervision of, their respective principal executive and principal financial officers, or persons performing similar functions, to provide reasonable assurance regarding the reliability of financial reporting and the preparation of financial statements for external purposes in accordance with generally accepted accounting principles, including, but not limited to, internal accounting controls sufficient to provide reasonable assurance that (i) transactions are executed in accordance with management's general or specific authorizations; (ii) transactions are recorded as necessary to permit preparation of financial statements in conformity with generally accepted accounting principles and to maintain asset accountability; (iii) access to assets is permitted only in accordance with management's general or specific authorization; (iv) the recorded accountability for assets is compared with the existing assets at reasonable intervals and appropriate action is taken with respect to any differences; and (v) the interactive data in eXtensible Business Reporting Language included or incorporated by reference in the Registration Statement is accurate. Except as disclosed in the Registration Statement, the Pricing Disclosure Package and the Prospectus, there are no material weaknesses in the Company's internal controls. The Company's auditors and the Audit Committee of the Board of Directors of the Company have been advised of: (i) all significant deficiencies and material weaknesses in the design or operation of internal controls over financial reporting which have adversely affected or are reasonably likely to adversely affect the Company's ability to record, process, summarize and report financial information; and (ii) any fraud, whether or not material, that involves management or other employees who have a significant role in the Company's internal controls over financial reporting.

(hh) *Insurance.* Except as described in the Registration Statement, the Pricing Disclosure Package and the Prospectus, the Company and its subsidiaries have insurance covering their respective properties, operations, personnel and businesses, including business interruption insurance, which insurance is in amounts and insures against such losses and risks as the Company reasonably believes are adequate to protect the Company and its subsidiaries and their respective businesses; and neither the Company nor any of its subsidiaries has (i) received notice from any insurer or agent of such insurer that material capital improvements or other expenditures are required or necessary to be made in order to continue such insurance or (ii) any reason to believe that it will not be able to renew its existing insurance coverage as and when such coverage expires or to obtain similar coverage at reasonable cost from similar insurers as may be necessary to continue its business.

(ii) *No Unlawful Payments.* Neither the Company nor any of its subsidiaries, nor any director, officer or employee of the Company or any of its subsidiaries nor, to the knowledge of the Company, any agent, affiliate or other person associated with or acting on behalf of the Company or any of its subsidiaries has (i) used any corporate funds for any unlawful contribution, gift, entertainment or other unlawful expense relating to political activity; (ii) made or taken an act in furtherance of an offer, promise or authorization of any direct or indirect unlawful payment of corporate funds or benefit to any foreign or domestic government official or employee, including of any government-owned or controlled entity or of a public international organization,

or any person acting in an official capacity for or on behalf of any of the foregoing, or any political party or party official or candidate for political office; (iii) violated or is in violation of any provision of the Foreign Corrupt Practices Act of 1977, as amended, or any applicable law or regulation implementing the OECD Convention on Combating Bribery of Foreign Public Officials in International Business Transactions, or committed an offence under the Bribery Act 2010 of the United Kingdom, or any other applicable anti-bribery or anti-corruption law; or (iv) made, offered, agreed, requested or taken an act in furtherance of any unlawful bribe or other unlawful benefit, including, without limitation, any rebate, payoff, influence payment, kickback or other unlawful or improper payment or benefit. The Company and its subsidiaries have instituted, maintain and enforce, and will continue to maintain and enforce policies and procedures designed to promote and ensure compliance with all applicable laws and regulations.

(jj) *Compliance with Anti-Money Laundering Laws.* The operations of the Company and its subsidiaries are and have been conducted at all times in compliance with applicable financial recordkeeping and reporting requirements, including those of the Currency and Foreign Transactions Reporting Act of 1970, as amended, the applicable money laundering statutes of all jurisdictions where the Company or any of its subsidiaries conducts business, the rules and regulations thereunder and any related or similar rules, regulations or guidelines, issued, administered or enforced by any governmental agency (collectively, the “Anti-Money Laundering Laws”), and no action, suit or proceeding by or before any court or governmental agency, authority or body or any arbitrator involving the Company or any of its subsidiaries with respect to the Anti-Money Laundering Laws is pending or, to the knowledge of the Company, threatened.

(kk) *No Conflicts with Sanctions Laws.* Neither the Company nor any of its subsidiaries, directors, officers or employees, nor, to the knowledge of the Company, any agent, affiliate or other person associated with or acting on behalf of the Company or any of its subsidiaries is currently the subject or the target of any sanctions administered or enforced by the U.S. government (including, without limitation, the Office of Foreign Assets Control of the U.S. Department of the Treasury (“OFAC”) or the U.S. Department of State and including, without limitation, the designation as a “specially designated national” or “blocked person”), the United Nations Security Council (“UNSC”), the European Union, Her Majesty’s Treasury (“HMT”) or other relevant sanctions authority (collectively, “Sanctions”), nor is the Company, any of its subsidiaries located, organized or resident in a country or territory that is the subject or target of Sanctions, including, without limitation, Cuba, Iran, North Korea, Sudan and Syria (each, a “Sanctioned Country”); and the Company will not directly or indirectly use the proceeds of the offering of the Shares hereunder, or lend, contribute or otherwise make available such proceeds to any subsidiary, joint venture partner or other person or entity (i) to fund or facilitate any activities of or business with any person that, at the time of such funding or facilitation, is the subject or target of Sanctions, (ii) to fund or facilitate any activities of or business in any Sanctioned Country or (iii) in any other manner that will result in a violation by any person (including any person participating in the transaction, whether as underwriter, advisor, investor or otherwise) of Sanctions. For the past five years, the Company and its subsidiaries have not knowingly engaged in and are not now knowingly engaged in any dealings or transactions with any person that at the time of the dealing or transaction is or was the subject or the target of Sanctions or with any Sanctioned Country.

(ll) *No Restrictions on Subsidiaries.* Except as described in the Registration Statement, the Pricing Disclosure Package and the Prospectus, no subsidiary of the Company is currently prohibited, directly or indirectly, under any agreement or other instrument to which it is a party or is subject, from paying any dividends to the Company, from making any other

distribution on such subsidiary's capital stock, from repaying to the Company any loans or advances to such subsidiary from the Company or from transferring any of such subsidiary's properties or assets to the Company or any other subsidiary of the Company.

(mm) *No Broker's Fees.* Neither the Company nor any of its subsidiaries is a party to any contract, agreement or understanding with any person (other than this Agreement) that would give rise to a valid claim against the Company or any of its subsidiaries or any Underwriter for a brokerage commission, finder's fee or like payment in connection with the offering and sale of the Shares.

(nn) *No Registration Rights.* Except as described in the Registration Statement, the Pricing Disclosure Package and the Prospectus, no person has the right to require the Company or any of its subsidiaries to register any securities for sale under the Securities Act by reason of the filing of the Registration Statement with the Commission or the issuance and sale of the Shares, other than rights that have been validly waived.

(oo) *No Stabilization.* The Company has not taken, directly or indirectly, without giving effect to activities by the Underwriters, any action designed to or that would reasonably be expected to cause or result in any stabilization or manipulation of the price of the Shares.

(pp) *Margin Rules.* The application of the proceeds received by the Company from the issuance, sale and delivery of the Shares as described in the Registration Statement, the Pricing Disclosure Package and the Prospectus will not violate Regulation T, U or X of the Board of Governors of the Federal Reserve System or any other regulation of such Board of Governors.

(qq) *Forward-Looking Statements.* No forward-looking statement (within the meaning of Section 27A of the Securities Act and Section 21E of the Exchange Act) contained in the Registration Statement, the Pricing Disclosure Package or the Prospectus has been made or reaffirmed without a reasonable basis or has been disclosed other than in good faith.

(rr) *Statistical and Market Data.* Nothing has come to the attention of the Company that has caused the Company to believe that the statistical and market-related data included in the Registration Statement, the Pricing Disclosure Package and the Prospectus is not based on or derived from sources that are reliable and accurate in all material respects.

(ss) *Clinical Trials.* The clinical and pre-clinical trials conducted by or, to the knowledge of the Company, on behalf of or sponsored by the Company or its subsidiaries, or in which the Company or its subsidiaries have participated, that are described in the Registration Statement, the Pricing Disclosure Package and the Prospectus, or the results of which are referred to in the Registration Statement, the Pricing Disclosure Package and the Prospectus, as applicable, were, and if still pending are, being conducted in all material respects in accordance with standard medical and scientific research standards and procedures for products or product candidates comparable to those being developed by the Company and all applicable statutes and all applicable rules and regulations of the FDA and comparable regulatory agencies outside of the United States to which they are subject, including the European Medicines Agency (collectively, the "Regulatory Authorities"), and current Good Clinical Practices and Good Laboratory Practices; the descriptions in the Registration Statement, the Pricing Disclosure Package and the Prospectus of the results of such studies and tests are accurate and complete descriptions in all material respects and fairly present the data derived therefrom; the Company has no knowledge of any other trials not described in the Registration Statement, the Pricing Disclosure Package and

the Prospectus, the results of which are inconsistent with or call into question the results described or referred to in the Registration Statement, the Pricing Disclosure Package and the Prospectus; the Company and its subsidiaries have operated at all times and are currently in compliance in all material respects with all applicable statutes, rules and regulations of the Regulatory Authorities; neither the Company nor any of its subsidiaries have received any written notices, correspondence or other communications from the Regulatory Authorities or any other governmental agency requiring or threatening the termination, material modification or suspension of any clinical or pre-clinical trials that are described in the Registration Statement, the Pricing Disclosure Package and the Prospectus or the results of which are referred to in the Registration Statement, the Pricing Disclosure Package and the Prospectus, other than ordinary course communications with respect to modifications in connection with the design and implementation of such trials, and, to the Company's knowledge, there are no reasonable grounds for the same.

(tt) *Regulatory Filings*. The Company has not failed to file with the Regulatory Authorities any required filing, declaration, listing, registration, report or submission with respect to the Company's product candidates that are described or referred to in the Registration Statement, the Pricing Disclosure Package and the Prospectus; all such filings, declarations, listings, registrations, reports or submissions were in material compliance with applicable laws when filed; and no deficiencies regarding compliance with applicable law have been asserted by any applicable regulatory authority with respect to any such filings, declarations, listings, registrations, reports or submissions.

(uu) *Sarbanes-Oxley Act*. There is and has been no failure on the part of the Company or, to the knowledge of the Company, any of the Company's directors or officers, in their capacities as such, to comply with any provision of the Sarbanes-Oxley Act of 2002 and the rules and regulations promulgated in connection therewith (the "Sarbanes-Oxley Act"), including Section 402 related to loans.

(vv) *Status under the Securities Act*. At the time of filing the Registration Statement and any post-effective amendment thereto, at the earliest time thereafter that the Company or any offering participant made a *bona fide* offer (within the meaning of Rule 164(h)(2) under the Securities Act) of the Shares and at the date hereof, the Company was not and is not an "ineligible issuer," as defined in Rule 405 under the Securities Act.

(ww) The interactive data in eXtensible Business Reporting Language included or incorporated by reference in the Registration Statement fairly presents the information called for in all material respects and has been prepared in accordance with the Commission's rules and guidelines applicable thereto.

4. Further Agreements of the Company. The Company covenants and agrees with each Underwriter that:

(a) *Required Filings*. The Company will file the final Prospectus with the Commission within the time periods specified by Rule 424(b) and Rule 430A, 430B or 430C under the Securities Act, will file any Issuer Free Writing Prospectus to the extent required by Rule 433 under the Securities Act; and will furnish copies of the Prospectus and each Issuer Free Writing Prospectus (to the extent not previously delivered) to the Underwriters in New York City as soon as practicable, in such quantities as the Representatives may reasonably request.

(b) *Delivery of Copies.* The Company will, upon request of the Representatives, deliver, without charge, (i) to the Representatives, three signed copies of the Registration Statement as originally filed and each amendment thereto, in each case including all exhibits and consents filed therewith; and (ii) to each Underwriter (A) a conformed copy of the Registration Statement as originally filed and each amendment thereto (without exhibits) and (B) during the Prospectus Delivery Period (as defined below), as many copies of the Prospectus (including all amendments and supplements thereto and each Issuer Free Writing Prospectus) as the Representatives may reasonably request. As used herein, the term “Prospectus Delivery Period” means such period of time after the first date of the public offering of the Shares as in the opinion of counsel for the Underwriters a prospectus relating to the Shares is required by law to be delivered (or required to be delivered but for Rule 172 under the Securities Act) in connection with sales of the Shares by any Underwriter or dealer.

(c) *Amendments or Supplements, Issuer Free Writing Prospectuses.* Before preparing, using, authorizing, approving, referring to or filing any Issuer Free Writing Prospectus, and before filing any amendment or supplement to the Registration Statement or the Prospectus, the Company will furnish to the Representatives and counsel for the Underwriters a copy of the proposed Issuer Free Writing Prospectus, amendment or supplement for review and will not prepare, use, authorize, approve, refer to or file any such Issuer Free Writing Prospectus or file any such proposed amendment or supplement to which the Representatives reasonably object.

(d) *Notice to the Representatives.* The Company will advise the Representatives promptly, and confirm such advice in writing, (i) when the Registration Statement has become effective; (ii) when any amendment to the Registration Statement has been filed or becomes effective; (iii) when any supplement to the Prospectus, any Issuer Free Writing Prospectus or any Written Testing-the-Waters Communication or any amendment to the Prospectus has been filed or distributed; (iv) of any request by the Commission for any amendment to the Registration Statement or any amendment or supplement to the Prospectus or the receipt of any comments from the Commission relating to the Registration Statement or any other request by the Commission for any additional information including, but not limited to, any request for information concerning any Testing-the-Waters Communication; (v) of the issuance by the Commission of any order suspending the effectiveness of the Registration Statement or preventing or suspending the use of any Preliminary Prospectus, any of the Pricing Disclosure Package, the Prospectus or any Written Testing-the-Waters Communication or the initiation or threatening of any proceeding for that purpose or pursuant to Section 8A of the Securities Act; (vi) of the occurrence of any event or development within the Prospectus Delivery Period as a result of which the Prospectus, the Pricing Disclosure Package, any Issuer Free Writing Prospectus or any Written Testing-the-Waters Communication as then amended or supplemented would include any untrue statement of a material fact or omit to state a material fact necessary in order to make the statements therein, in the light of the circumstances existing when the Prospectus, the Pricing Disclosure Package, any such Issuer Free Writing Prospectus or Written Testing-the-Waters Communication is delivered to a purchaser, not misleading; and (vii) of the receipt by the Company of any notice with respect to any suspension of the qualification of the Shares for offer and sale in any jurisdiction or the initiation or threatening of any proceeding for such purpose; and the Company will use its best efforts to prevent the issuance of any such order suspending the effectiveness of the Registration Statement, preventing or suspending the use of any Preliminary Prospectus, any of the Pricing Disclosure Package or the Prospectus or any Written Testing-the-Waters Communication or suspending any such qualification of the Shares and, if any such order is issued, will use its reasonable best efforts to obtain as soon as possible the withdrawal thereof.

(e) *Ongoing Compliance.* (1) If during the Prospectus Delivery Period (i) any event or development shall occur or condition shall exist as a result of which the Prospectus as then amended or supplemented would include any untrue statement of a material fact or omit to state any material fact necessary in order to make the statements therein, in the light of the circumstances existing when the Prospectus is delivered to a purchaser, not misleading or (ii) it is necessary to amend or supplement the Prospectus to comply with law, the Company will immediately notify the Underwriters thereof and forthwith prepare and, subject to paragraph (c) above, file with the Commission and furnish to the Underwriters and to such dealers as the Representatives may designate such amendments or supplements to the Prospectus as may be necessary so that the statements in the Prospectus as so amended or supplemented will not, in the light of the circumstances existing when the Prospectus is delivered to a purchaser, be misleading or so that the Prospectus will comply with law and (2) if at any time prior to the Closing Date (i) any event or development shall occur or condition shall exist as a result of which the Pricing Disclosure Package as then amended or supplemented would include any untrue statement of a material fact or omit to state any material fact necessary in order to make the statements therein, in the light of the circumstances existing when the Pricing Disclosure Package is delivered to a purchaser, not misleading or (ii) it is necessary to amend or supplement the Pricing Disclosure Package to comply with law, the Company will immediately notify the Underwriters thereof and forthwith prepare and, subject to paragraph (c) above, file with the Commission (to the extent required) and furnish to the Underwriters and to such dealers as the Representatives may designate such amendments or supplements to the Pricing Disclosure Package as may be necessary so that the statements in the Pricing Disclosure Package as so amended or supplemented will not, in the light of the circumstances existing when the Pricing Disclosure Package is delivered to a purchaser, be misleading or so that the Pricing Disclosure Package will comply with law.

(f) *Blue Sky Compliance.* The Company will qualify the Shares for offer and sale under the securities or Blue Sky laws of such jurisdictions as the Representatives shall reasonably request and will continue such qualifications in effect so long as required for distribution of the Shares; provided that the Company shall not be required to (i) qualify as a foreign corporation or other entity or as a dealer in securities in any such jurisdiction where it would not otherwise be required to so qualify, (ii) file any general consent to service of process in any such jurisdiction or (iii) subject itself to taxation in any such jurisdiction if it is not otherwise so subject.

(g) *Earning Statement.* The Company will make generally available to its security holders and the Representatives as soon as practicable an earnings statement that satisfies the provisions of Section 11(a) of the Securities Act and Rule 158 of the Commission promulgated thereunder covering a period of at least twelve months beginning with the first fiscal quarter of the Company occurring after the “effective date” (as defined in Rule 158) of the Registration Statement.

(h) *Clear Market.* For a period of 90 days after the date of the Prospectus, the Company will not (i) offer, pledge, sell, contract to sell, sell any option or contract to purchase, purchase any option or contract to sell, grant any option, right or warrant to purchase, or otherwise transfer or dispose of, directly or indirectly, or file with the Commission a registration statement under the Securities Act relating to, any shares of Stock or any securities convertible into or exercisable or exchangeable for Stock, or publicly disclose the intention to make any offer, sale, pledge, disposition or filing, or (ii) enter into any swap or other agreement that transfers, in whole or in part, any of the economic consequences of ownership of the Stock or any such other securities, whether any such transaction described in clause (i) or (ii) above is to be

settled by delivery of Stock or such other securities, in cash or otherwise, without the prior written consent of J.P. Morgan Securities LLC and Goldman, Sachs & Co., other than (A) the Shares to be sold hereunder, (B) any shares of Stock of the Company issued upon the exercise of options granted under Company Stock Plans described in the Registration Statement, the Pricing Disclosure Package and the Prospectus or warrants described as outstanding in the Registration Statement, the Pricing Disclosure Package and the Prospectus, (C) any options and other awards granted under Company Stock Plans described in the Registration Statement, the Pricing Disclosure Package and the Prospectus, (D) the filing by the Company of any registration statement on Form S-8 or a successor form thereto relating to the shares of Stock granted pursuant to or reserved for issuance under Company Stock Plans described in the Registration Statement, the Pricing Disclosure Package and the Prospectus and (E) shares of Stock or other securities issued in connection with a transaction that includes a commercial relationship (including joint ventures, marketing or distribution arrangements, collaboration agreements or intellectual property license agreements) or any acquisition of assets or not less than a majority or controlling portion of the equity of another entity, provided that (x) the aggregate number of shares of Stock issued pursuant to this clause (E) shall not exceed 5.0% of the total number of outstanding shares of Stock immediately following the issuance and sale of the Underwritten Shares pursuant hereto and (y) the recipient of any such shares of Stock and securities issued pursuant to this clause (E) during the 90-day restricted period described above shall enter into an agreement substantially in the form of Exhibit A hereto.

(i) *Use of Proceeds*. The Company will apply the net proceeds from the sale of the Shares in all material respects as described in the Registration Statement, the Pricing Disclosure Package and the Prospectus under the heading "Use of proceeds".

(j) *No Stabilization*. The Company will not take, directly or indirectly, without giving effect to activities by the Underwriters, any action designed to or that would reasonably be expected to cause or result in any stabilization or manipulation of the price of the Stock.

(k) *Reports*. During a period of two years from the date hereof, the Company will furnish to the Representatives, as soon as they are available, copies of all reports or other communications (financial or other) furnished to holders of the Shares, and copies of any reports and financial statements furnished to or filed with the Commission or any national securities exchange or automatic quotation system; provided the Company will be deemed to have furnished such reports and financial statements to the Representatives to the extent they are filed on the Commission's Electronic Data Gathering, Analysis, and Retrieval system or any successor system.

(l) *Record Retention*. The Company will, pursuant to reasonable procedures developed in good faith, retain copies of each Issuer Free Writing Prospectus that is not filed with the Commission in accordance with Rule 433 under the Securities Act.

(m) *Filings*. The Company will file with the Commission such reports as may be required by Rule 463 under the Securities Act.

(n) *Emerging Growth Company*. The Company will promptly notify the Representatives if the Company ceases to be an Emerging Growth Company at any time prior to the later of (i) completion of the distribution of Shares within the meaning of the Securities Act and (ii) completion of the 90-day restricted period referred to in Section 4(h) hereof.

5. Certain Agreements of the Underwriters. Each Underwriter hereby represents and agrees that:

(a) It has not used, authorized use of, referred to or participated in the planning for use of, and will not use, authorize use of, refer to or participate in the planning for use of, any “free writing prospectus”, as defined in Rule 405 under the Securities Act (which term includes use of any written information furnished to the Commission by the Company and not incorporated by reference into the Registration Statement and any press release issued by the Company) other than (i) a free writing prospectus that contains no “issuer information” (as defined in Rule 433(h)(2) under the Securities Act) that was not included in the Preliminary Prospectus or a previously filed Issuer Free Writing Prospectus, (ii) any Issuer Free Writing Prospectus listed on Annex B or prepared pursuant to Section 3(c) or Section 4(c) above (including any electronic road show), or (iii) any free writing prospectus prepared by such underwriter and approved by the Company in advance in writing (each such free writing prospectus referred to in clauses (i) or (iii), an “Underwriter Free Writing Prospectus”).

(b) It has not and will not, without the prior written consent of the Company, use any free writing prospectus that contains the final terms of the Shares unless such terms have previously been included in a free writing prospectus filed with the Commission.

(c) It is not subject to any pending proceeding under Section 8A of the Securities Act with respect to the offering (and will promptly notify the Company if any such proceeding against it is initiated during the Prospectus Delivery Period).

6. Conditions of Underwriters’ Obligations. The obligation of each Underwriter to purchase the Underwritten Shares on the Closing Date or the Option Shares on the Additional Closing Date, as the case may be, as provided herein is subject to the performance by the Company of its covenants and other obligations hereunder and to the following additional conditions:

(a) *Registration Compliance; No Stop Order.* No order suspending the effectiveness of the Registration Statement shall be in effect, and no proceeding for such purpose or pursuant to Section 8A under the Securities Act shall be pending before or threatened by the Commission; the Prospectus and each Issuer Free Writing Prospectus shall have been timely filed with the Commission under the Securities Act (in the case of an Issuer Free Writing Prospectus, to the extent required by Rule 433 under the Securities Act) and in accordance with Section 4(a) hereof; and all requests by the Commission for additional information shall have been complied with to the reasonable satisfaction of the Representatives.

(b) *Representations and Warranties.* The representations and warranties of the Company contained herein shall be true and correct on the date hereof and on and as of the Closing Date or the Additional Closing Date, as the case may be; and the statements of the Company and its officers made in any certificates delivered pursuant to this Agreement shall be true and correct on and as of the Closing Date or the Additional Closing Date, as the case may be.

(c) *No Downgrade.* Subsequent to the earlier of (A) the Applicable Time and (B) the execution and delivery of this Agreement, if there are any debt securities or preferred stock of, or guaranteed by, the Company or any of its subsidiaries that are rated by a “nationally recognized statistical rating organization,” as such term is defined in Section 3(a)(62) of the Exchange Act, (i) no downgrading shall have occurred in the rating accorded any such debt securities or preferred stock and (ii) no such organization shall have publicly announced that it

has under surveillance or review, or has changed its outlook with respect to, its rating of any such debt securities or preferred stock (other than an announcement with positive implications of a possible upgrading).

(d) *No Material Adverse Change.* No event or condition of a type described in Section 3(i) hereof shall have occurred or shall exist, which event or condition is not described in the Pricing Disclosure Package (excluding any amendment or supplement thereto) and the Prospectus (excluding any amendment or supplement thereto) and the effect of which in the judgment of the Representatives makes it impracticable or inadvisable to proceed with the offering, sale or delivery of the Shares on the Closing Date or the Additional Closing Date, as the case may be, on the terms and in the manner contemplated by this Agreement, the Pricing Disclosure Package and the Prospectus.

(e) *Officers' Certificate.* The Representatives shall have received on and as of the Closing Date or the Additional Closing Date, as the case may be, a certificate on behalf of the Company of the principal financial and accounting officer of the Company and one additional senior executive officer of the Company who is reasonably satisfactory to the Representatives (i) confirming that such officers have carefully reviewed the Registration Statement, the Pricing Disclosure Package and the Prospectus and, to the knowledge of such officers, the representations set forth in Sections 3(b) and 3(f) hereof are true and correct, (ii) confirming that the other representations and warranties of the Company in this Agreement are true and correct and that the Company has in all material respects complied with all agreements and satisfied all conditions on its part to be performed or satisfied hereunder at or prior to the Closing Date or the Additional Closing Date, as the case may be, and (iii) to the effect set forth in paragraphs (a), (c) and (d) above.

(f) *Comfort Letters.* On the date of this Agreement and on the Closing Date or the Additional Closing Date, as the case may be, Ernst & Young LLP shall have furnished to the Representatives, at the request of the Company, letters, dated the respective dates of delivery thereof and addressed to the Underwriters, in form and substance reasonably satisfactory to the Representatives, containing statements and information of the type customarily included in accountants' "comfort letters" to underwriters with respect to the financial statements and certain financial information contained in the Registration Statement, the Pricing Disclosure Package and the Prospectus; provided, that the letter delivered on the Closing Date or the Additional Closing Date, as the case may be, shall use a "cut-off" date no more than three business days prior to such Closing Date or such Additional Closing Date, as the case may be.

(g) *Opinion and 10b-5 Statement of Counsel for the Company.* Wilmer Cutler Pickering Hale and Dorr LLP, counsel for the Company, shall have furnished to the Representatives, at the request of the Company, their written opinion and 10b-5 statement, dated the Closing Date or the Additional Closing Date, as the case may be, and addressed to the Underwriters, in form and substance reasonably satisfactory to the Representatives, to the effect set forth in Annex A-1 hereto.

(h) *Opinion of Intellectual Property Counsel for the Company.* Lando & Anastasi, LLP, special counsel for the Company with respect to intellectual property matters, shall have furnished to the Representatives, at the request of the Company, their written opinion and 10b-5 statement, dated the Closing Date or the Additional Closing Date, as the case may be, and addressed to the Underwriters, in form and substance reasonably satisfactory to the Representatives, to the effect set forth in Annex A-2 hereto.

(i) *Opinion and 10b-5 Statement of Counsel for the Underwriters.* The Representatives shall have received on and as of the Closing Date or the Additional Closing Date, as the case may be, an opinion and 10b-5 statement of Davis Polk & Wardwell LLP, counsel for the Underwriters, with respect to such matters as the Representatives may reasonably request, and such counsel shall have received such documents and information as they may reasonably request to enable them to pass upon such matters.

(j) *No Legal Impediment to Issuance.* No action shall have been taken and no statute, rule, regulation or order shall have been enacted, adopted or issued by any federal, state or foreign governmental or regulatory authority that would, as of the Closing Date or the Additional Closing Date, as the case may be, prevent the issuance or sale of the Shares; and no injunction or order of any federal, state or foreign court shall have been issued that would, as of the Closing Date or the Additional Closing Date, as the case may be, prevent the issuance or sale of the Shares.

(k) *Good Standing.* The Representatives shall have received on and as of the Closing Date or the Additional Closing Date, as the case may be, satisfactory evidence of the good standing of the Company and its subsidiaries in their respective jurisdictions of organization and their good standing as foreign entities in such other jurisdictions as the Representatives may reasonably request, in each case in writing or any standard form of telecommunication from the appropriate governmental authorities of such jurisdictions.

(l) *Exchange Listing.* The Shares to be delivered on the Closing Date or Additional Closing Date, as the case may be, are listed on the Nasdaq Global Market.

(m) *Lock-up Agreements.* The “lock-up” agreements between you and the officers and directors of the Company, each substantially in the form of Exhibit A-1 hereto, and between you and certain other stockholders, each substantially in the form of Exhibit A-2 hereto, relating to sales and certain other dispositions of shares of Stock or certain other securities, delivered to you on or before the date hereof, shall be in full force and effect on the Closing Date or Additional Closing Date, as the case may be.

(n) *Additional Documents.* On or prior to the Closing Date or the Additional Closing Date, as the case may be, the Company shall have furnished to the Representatives such further certificates and documents as the Representatives may reasonably request.

All opinions, letters, certificates and evidence mentioned above or elsewhere in this Agreement shall be deemed to be in compliance with the provisions hereof only if they are in form and substance reasonably satisfactory to counsel for the Underwriters.

7. Indemnification and Contribution.

(a) *Indemnification of the Underwriters.* The Company agrees to indemnify and hold harmless each Underwriter, its affiliates, directors and officers and each person, if any, who controls such Underwriter within the meaning of Section 15 of the Securities Act or Section 20 of the Exchange Act, from and against any and all losses, claims, damages and liabilities (including, without limitation, reasonable legal fees and other reasonable expenses incurred in connection with any suit, action or proceeding or any claim asserted, as such fees and expenses are incurred), joint or several, that arise out of, or are based upon, (i) any untrue statement or alleged untrue statement of a material fact contained in the Registration Statement or caused by any omission or alleged omission to state therein a material fact

required to be stated therein or necessary in order to make the statements therein, not misleading, (ii) or any untrue statement or alleged untrue statement of a material fact contained in the Prospectus (or any amendment or supplement thereto), any Issuer Free Writing Prospectus, any “issuer information” filed or required to be filed pursuant to Rule 433(d) under the Securities Act, any Written Testing-the-Waters Communication, any road show as defined in Rule 433(h) under the Securities Act (a “road show”) or any Pricing Disclosure Package (including any Pricing Disclosure Package that has subsequently been amended), or caused by any omission or alleged omission to state therein a material fact necessary in order to make the statements therein, in light of the circumstances under which they were made, not misleading, in each case except insofar as such losses, claims, damages or liabilities arise out of, or are based upon, any untrue statement or omission or alleged untrue statement or omission made in reliance upon and in conformity with any information relating to any Underwriter furnished to the Company in writing by such Underwriter through the Representatives expressly for use therein, it being understood and agreed that the only such information furnished by any Underwriter consists of the information described as such in subsection (b) below.

(b) *Indemnification of the Company.* Each Underwriter agrees, severally and not jointly, to indemnify and hold harmless the Company, its directors, its officers who signed the Registration Statement, and each person, if any, who controls the Company within the meaning of Section 15 of the Securities Act or Section 20 of the Exchange Act to the same extent as the indemnity set forth in paragraph (a) above, but only with respect to any losses, claims, damages or liabilities that arise out of, or are based upon, any untrue statement or omission or alleged untrue statement or omission made in reliance upon and in conformity with any information relating to such Underwriter furnished to the Company in writing by such Underwriter through the Representatives expressly for use in the Registration Statement, the Prospectus (or any amendment or supplement thereto), any Issuer Free Writing Prospectus, any Written Testing-the-Waters Communication, any road show or any Pricing Disclosure Package (including any Pricing Disclosure Package that has subsequently been amended), it being understood and agreed upon that the only such information furnished by any Underwriter consists of the following information in the Prospectus furnished on behalf of each Underwriter: the concession and reallowance figures appearing in the third paragraph under the caption “Underwriting” and the information contained in the seventh, thirteenth, fourteenth and sixteenth paragraphs under the caption “Underwriting”.

(c) *Notice and Procedures.* If any suit, action, proceeding (including any governmental or regulatory investigation), claim or demand shall be brought or asserted against any person in respect of which indemnification may be sought pursuant to either paragraph (a) or (b) above, such person (the “Indemnified Person”) shall promptly notify the person against whom such indemnification may be sought (the “Indemnifying Person”) in writing; provided that the failure to notify the Indemnifying Person shall not relieve it from any liability that it may have under paragraph (a) or (b) above except to the extent that it has been materially prejudiced (through the forfeiture of substantive rights or defenses) by such failure; and provided, further, that the failure to notify the Indemnifying Person shall not relieve it from any liability that it may have to an Indemnified Person otherwise than under paragraph (a) or (b) above. If any such proceeding shall be brought or asserted against an Indemnified Person and it shall have notified the Indemnifying Person thereof, the Indemnifying Person shall retain counsel reasonably satisfactory to the Indemnified Person (who shall not, without the consent of the Indemnified Person, be counsel to the Indemnifying Person) to represent the Indemnified Person in such proceeding and shall pay the reasonable fees and expenses of such counsel related to such proceeding, as incurred. In any such proceeding, any Indemnified Person shall have the right to retain its own counsel, but the fees and expenses of such counsel shall be at the expense of such Indemnified Person unless (i) the Indemnifying Person and the Indemnified Person shall have mutually agreed to the contrary; (ii) the Indemnifying Person has failed within a reasonable time to retain counsel reasonably satisfactory to the Indemnified

Person; (iii) the Indemnified Person shall have reasonably concluded that there may be legal defenses available to it that are different from or in addition to those available to the Indemnifying Person; or (iv) the named parties in any such proceeding (including any impleaded parties) include both the Indemnifying Person and the Indemnified Person and representation of both parties by the same counsel would be inappropriate due to actual or potential differing interest between them. It is understood and agreed that the Indemnifying Person shall not, in connection with any proceeding or related proceedings in the same jurisdiction, be liable for the reasonable fees and expenses of more than one separate firm (in addition to any local counsel) for all Indemnified Persons, and that all such reasonable fees and expenses shall be paid or reimbursed as they are incurred. Any such separate firm for any Underwriter, its affiliates, directors and officers and any control persons of such Underwriter shall be designated in writing by the Representatives and any such separate firm for the Company, its directors, its officers who signed the Registration Statement and any control persons of the Company shall be designated in writing by the Company. The Indemnifying Person shall not be liable for any settlement of any proceeding effected without its written consent, but if settled with such consent or if there be a final judgment for the plaintiff, the Indemnifying Person agrees to indemnify each Indemnified Person from and against any loss or liability by reason of such settlement or judgment. Notwithstanding the foregoing sentence, if at any time an Indemnified Person shall have requested that an Indemnifying Person reimburse the Indemnified Person for fees and expenses of counsel as contemplated by this paragraph, the Indemnifying Person shall be liable for any settlement of any proceeding effected without its written consent if (i) such settlement is entered into (A) more than 60 days after receipt by the Indemnifying Person of such request and (B) more than 30 days after receipt by the Indemnifying Person of the proposed terms of such settlement and (ii) the Indemnifying Person shall not have reimbursed the Indemnified Person in accordance with such request prior to the date of such settlement. No Indemnifying Person shall, without the written consent of the Indemnified Person, effect any settlement of any pending or threatened proceeding in respect of which any Indemnified Person is or could have been a party and indemnification could have been sought hereunder by such Indemnified Person, unless such settlement (x) includes an unconditional release of such Indemnified Person, in form and substance reasonably satisfactory to such Indemnified Person, from all liability on claims that are the subject matter of such proceeding and (y) does not include any statement as to or any admission of fault, culpability or a failure to act by or on behalf of any Indemnified Person.

(d) *Contribution.* If the indemnification provided for in paragraphs (a) and (b) above is unavailable to an Indemnified Person or insufficient in respect of any losses, claims, damages or liabilities referred to therein, then each Indemnifying Person under such paragraph, in lieu of indemnifying such Indemnified Person thereunder, shall contribute to the amount paid or payable by such Indemnified Person as a result of such losses, claims, damages or liabilities (i) in such proportion as is appropriate to reflect the relative benefits received by the Company on the one hand, and the Underwriters on the other, from the offering of the Shares or (ii) if the allocation provided by clause (i) is not permitted by applicable law, in such proportion as is appropriate to reflect not only the relative benefits referred to in clause (i) but also the relative fault of the Company, on the one hand, and the Underwriters on the other, in connection with the statements or omissions that resulted in such losses, claims, damages or liabilities, as well as any other relevant equitable considerations. The relative benefits received by the Company, on the one hand, and the Underwriters on the other, shall be deemed to be in the same respective proportions as the net proceeds (before deducting expenses) received by the Company from the sale of the Shares and the total underwriting discounts and commissions received by the Underwriters in connection therewith, in each case as set forth in the table on the cover of the Prospectus, bear to the aggregate public offering price of the Shares. The relative fault of the Company, on the one hand, and the Underwriters on the other, shall be determined by reference to, among other things, whether the untrue or alleged untrue statement of a material fact or the omission or alleged omission to state a material fact relates to information supplied by the Company or by the Underwriters and the parties' relative intent, knowledge, access to information and opportunity to correct or prevent such statement or omission.

(e) *Limitation on Liability.* The Company and the Underwriters agree that it would not be just and equitable if contribution pursuant to paragraph (d) above were determined by pro rata allocation (even if the Underwriters were treated as one entity for such purpose) or by any other method of allocation that does not take account of the equitable considerations referred to in paragraph (d) above. The amount paid or payable by an Indemnified Person as a result of the losses, claims, damages and liabilities referred to in paragraph (d) above shall be deemed to include, subject to the limitations set forth above, any reasonable legal or other expenses incurred by such Indemnified Person in connection with any such action or claim. Notwithstanding the provisions of paragraphs (d) and (e), in no event shall an Underwriter be required to contribute any amount in excess of the amount by which the total underwriting discounts and commissions received by such Underwriter with respect to the offering of the Shares exceeds the amount of any damages that such Underwriter has otherwise been required to pay by reason of such untrue or alleged untrue statement or omission or alleged omission. No person guilty of fraudulent misrepresentation (within the meaning of Section 11(f) of the Securities Act) shall be entitled to contribution from any person who was not guilty of such fraudulent misrepresentation. The Underwriters' obligations to contribute pursuant to paragraphs (d) and (e) are several in proportion to their respective purchase obligations hereunder and not joint.

(f) *Non-Exclusive Remedies.* The remedies provided for in this Section 7 are not exclusive and shall not limit any rights or remedies which may otherwise be available to any Indemnified Person at law or in equity.

8. Effectiveness of Agreement. This Agreement shall become effective upon the execution and delivery hereof by the parties hereto.

9. Termination. This Agreement may be terminated in the absolute discretion of the Representatives, by notice to the Company, if after the execution and delivery of this Agreement and prior to the Closing Date or, in the case of the Option Shares, prior to the Additional Closing Date (i) trading generally shall have been suspended or materially limited on or by any of the New York Stock Exchange, the American Stock Exchange, the Nasdaq Stock Market, the Chicago Board Options Exchange, the Chicago Mercantile Exchange or the Chicago Board of Trade; (ii) trading of any securities issued or guaranteed by the Company shall have been suspended on any exchange or in any over-the-counter market; (iii) a general moratorium on commercial banking activities shall have been declared by federal or New York State authorities; or (iv) there shall have occurred any outbreak or escalation of hostilities or any change in financial markets or any calamity or crisis, either within or outside the United States, that, in the judgment of the Representatives, is material and adverse and makes it impracticable or inadvisable to proceed with the offering, sale or delivery of the Shares on the Closing Date or the Additional Closing Date, as the case may be, on the terms and in the manner contemplated by this Agreement, the Pricing Disclosure Package and the Prospectus.

10. Defaulting Underwriter.

(a) If, on the Closing Date or the Additional Closing Date, as the case may be, any Underwriter defaults on its obligation to purchase the Shares that it has agreed to purchase hereunder on such date, the non-defaulting Underwriters may in their discretion arrange for the purchase of such Shares by other persons satisfactory to the Company on the terms contained in this Agreement. If, within 36 hours after any such default by any Underwriter, the non-defaulting Underwriters do not arrange for the purchase of such Shares, then the Company shall be entitled to a further period of 36 hours within which

to procure other persons satisfactory to the non-defaulting Underwriters to purchase such Shares on such terms. If other persons become obligated or agree to purchase the Shares of a defaulting Underwriter, either the non-defaulting Underwriters or the Company may postpone the Closing Date or the Additional Closing Date, as the case may be, for up to five full business days in order to effect any changes that in the opinion of counsel for the Company or counsel for the Underwriters may be necessary in the Registration Statement and the Prospectus or in any other document or arrangement, and the Company agrees to promptly prepare any amendment or supplement to the Registration Statement and the Prospectus that effects any such changes. As used in this Agreement, the term "Underwriter" includes, for all purposes of this Agreement unless the context otherwise requires, any person not listed in Schedule 1 hereto that, pursuant to this Section 10, purchases Shares that a defaulting Underwriter agreed but failed to purchase.

(b) If, after giving effect to any arrangements for the purchase of the Shares of a defaulting Underwriter or Underwriters by the non-defaulting Underwriters and the Company as provided in paragraph (a) above, the aggregate number of Shares that remain unpurchased on the Closing Date or the Additional Closing Date, as the case may be, does not exceed one-eleventh of the aggregate number of Shares to be purchased on such date, then the Company shall have the right to require each non-defaulting Underwriter to purchase the number of Shares that such Underwriter agreed to purchase hereunder on such date plus such Underwriter's pro rata share (based on the number of Shares that such Underwriter agreed to purchase on such date) of the Shares of such defaulting Underwriter or Underwriters for which such arrangements have not been made.

(c) If, after giving effect to any arrangements for the purchase of the Shares of a defaulting Underwriter or Underwriters by the non-defaulting Underwriters and the Company as provided in paragraph (a) above, the aggregate number of Shares that remain unpurchased on the Closing Date or the Additional Closing Date, as the case may be, exceeds one-eleventh of the aggregate amount of Shares to be purchased on such date, or if the Company shall not exercise the right described in paragraph (b) above, then this Agreement or, with respect to any Additional Closing Date, the obligation of the Underwriters to purchase Shares on the Additional Closing Date, shall terminate without liability on the part of the non-defaulting Underwriters. Any termination of this Agreement pursuant to this Section 10 shall be without liability on the part of the Company, except that the provisions of Section 7 hereof shall not terminate and shall remain in effect.

(d) Nothing contained herein shall relieve a defaulting Underwriter of any liability it may have to the Company or any non-defaulting Underwriter for damages caused by its default.

11. Payment of Expenses.

(a) Whether or not the transactions contemplated by this Agreement are consummated or this Agreement is terminated, the Company will pay or cause to be paid all costs and expenses incident to the performance of its obligations hereunder, including without limitation, (i) the costs incident to the authorization, issuance, sale, preparation and delivery of the Shares and any taxes payable in that connection; (ii) the costs incident to the preparation, printing and filing under the Securities Act of the Registration Statement, the Preliminary Prospectus, any Issuer Free Writing Prospectus, any Pricing Disclosure Package and the Prospectus (including all exhibits, amendments and supplements thereto) and the distribution thereof; (iii) the costs of reproducing and distributing this Agreement; (iv) the fees and expenses of the Company's counsel and independent accountants; (v) the reasonable fees and expenses incurred in connection with the registration or qualification of the Shares under the state or foreign securities or blue sky laws of such jurisdictions as the Representatives may designate and the preparation, printing and distribution of a Blue Sky Memorandum (including the related fees and expenses of counsel for the

Underwriters); (vi) the cost of preparing stock certificates; (vii) the costs and charges of any transfer agent and any registrar; (viii) all expenses and application fees incurred in connection with any filing with, and clearance of the offering by, FINRA in an amount not to exceed \$30,000; (ix) all expenses incurred by the Company in connection with any “road show” presentation to potential investors; (x) all expenses and application fees related to the listing of the Shares on the Nasdaq Global Select Market and (xi) all other costs and expenses incident to the performance of the obligations of the Company hereunder for which provision is not otherwise made in this Section.

(b) If (i) this Agreement is terminated pursuant to clause (i) or (ii) of Section 9, (ii) the Company for any reason fails to tender the Shares for delivery to the Underwriters or (iii) the Underwriters decline to purchase the Shares for any reason permitted under this Agreement (other than following termination of this Agreement pursuant to clause (iii) or (iv) of Section 9), the Company agrees to reimburse the Underwriters for all out-of-pocket costs and expenses (including the fees and expenses of their counsel) reasonably incurred by the Underwriters in connection with this Agreement and the offering contemplated hereby.

12. Persons Entitled to Benefit of Agreement. This Agreement shall inure to the benefit of and be binding upon the parties hereto and their respective successors and the officers and directors and any controlling persons referred to in Section 7 hereof. Nothing in this Agreement is intended or shall be construed to give any other person any legal or equitable right, remedy or claim under or in respect of this Agreement or any provision contained herein. No purchaser of Shares from any Underwriter shall be deemed to be a successor merely by reason of such purchase.

13. Survival. The respective indemnities, rights of contribution, representations, warranties and agreements of the Company and the Underwriters contained in this Agreement or made by or on behalf of the Company or the Underwriters pursuant to this Agreement or any certificate delivered pursuant hereto shall survive the delivery of and payment for the Shares and shall remain in full force and effect, regardless of any termination of this Agreement or any investigation made by or on behalf of the Company or the Underwriters.

14. Certain Defined Terms. For purposes of this Agreement, (a) except where otherwise expressly provided, the term “affiliate” has the meaning set forth in Rule 405 under the Securities Act; (b) the term “business day” means any day other than a day on which banks are permitted or required to be closed in New York City; and (c) the term “subsidiary” has the meaning set forth in Rule 405 under the Securities Act.

15. Miscellaneous.

(a) Notices. All notices and other communications hereunder shall be in writing and shall be deemed to have been duly given if mailed or transmitted and confirmed by any standard form of telecommunication. Notices to the Underwriters shall be given to the Representatives c/o J.P. Morgan Securities LLC, 383 Madison Avenue, New York, New York 10179 (fax: (212) 622-8358); Attention: Equity Syndicate Desk and c/o Goldman, Sachs & Co., 200 West Street, New York, New York 10282; Attention: Registration Department. Notices to the Company shall be given to it at Agios Pharmaceuticals, Inc., 38 Sidney Street, Cambridge, Massachusetts 02139 (fax: (617) 649-8618); Attention: Chief Executive Officer.

(b) Governing Law. This Agreement and any claim, controversy or dispute arising under or related to this Agreement shall be governed by and construed in accordance with the laws of the State of New York applicable to agreements made and to be performed in such state.

(c) *Counterparts*. This Agreement may be signed in counterparts (which may include counterparts delivered by any standard form of telecommunication), each of which shall be an original and all of which together shall constitute one and the same instrument.

(d) *Amendments or Waivers*. No amendment or waiver of any provision of this Agreement, nor any consent or approval to any departure therefrom, shall in any event be effective unless the same shall be in writing and signed by the parties hereto.

(e) *Headings*. The headings herein are included for convenience of reference only and are not intended to be part of, or to affect the meaning or interpretation of, this Agreement.

(f) *Patriot Act*. In accordance with the requirements of the USA Patriot Act (Title III of Pub. L. 107-56 (signed into law October 26, 2001)), the Underwriters are required to obtain, verify and record information that identifies their respective clients, including the Company, which information may include the name and address of their respective clients, as well as other information that will allow the Underwriters to properly identify their respective clients.

If the foregoing is in accordance with your understanding, please indicate your acceptance of this Agreement by signing in the space provided below.

Very truly yours,

AGIOS PHARMACEUTICALS, INC.

By: _____

Name: David P. Schenkein, M.D.

Title: Chief Executive Officer

[Signature page to Underwriting Agreement]

Accepted: As of the date first written above

J.P. MORGAN SECURITIES LLC
GOLDMAN, SACHS & CO.

For themselves and on behalf of the
several Underwriters listed
in Schedule 1 hereto.

J.P. MORGAN SECURITIES LLC

By: _____
Authorized Signatory

Name:
Title:

GOLDMAN, SACHS & CO.

By: _____
Authorized Signatory

Name:
Title:

[Signature page to Underwriting Agreement]

Underwriter	Number of Underwritten Shares
J.P. Morgan Securities LLC	[x]
Goldman, Sachs & Co.	[x]
Cowen and Company, LLC	[x]
Leerink Partners LLC	[x]
Total	[x]

[Form of Opinion of Wilmer Cutler Pickering Hale and Dorr LLP, Counsel for the Company]

Annex A-1-1

Annex A-2-1

- a. **Pricing Disclosure Package**

- b. **Pricing Information Provided Orally by Underwriters**

Annex B-1

Written Testing-the-Waters Communications

Annex C-1

FORM OF LOCK-UP AGREEMENT

(Directors and Officers)

, 2014

J.P. Morgan Securities LLC
Goldman, Sachs & Co.
As Representatives of
the several Underwriters listed in
Schedule 1 to the Underwriting
Agreement referred to below

c/o J.P. Morgan Securities LLC
383 Madison Avenue
New York, New York 10179

c/o Goldman, Sachs & Co.
200 West Street
New York, New York 10282

Re: Agios Pharmaceuticals, Inc. — Public Offering

Ladies and Gentlemen:

The undersigned understands that you, as Representatives of the several Underwriters, propose to enter into an Underwriting Agreement (the “Underwriting Agreement”) with Agios Pharmaceuticals, Inc., a Delaware corporation (the “Company”), providing for the public offering (the “Public Offering”) by the several Underwriters named in Schedule 1 to the Underwriting Agreement (the “Underwriters”), of common stock, of the Company (the “Securities”). Capitalized terms used herein and not otherwise defined shall have the meanings set forth in the Underwriting Agreement.

In consideration of the Underwriters’ agreement to purchase and make the Public Offering of the Securities, and for other good and valuable consideration receipt of which is hereby acknowledged, the undersigned hereby agrees that, without the prior written consent of J.P. Morgan Securities LLC and Goldman, Sachs & Co. on behalf of the Underwriters (the “Representatives”), the undersigned will not, during the period commencing on the date hereof and ending 90 days after the date of the final prospectus relating to the Public Offering (the “Prospectus”), (1) offer, pledge, sell, contract to sell, sell any option or contract to purchase, purchase any option or contract to sell, grant any option, right or warrant to purchase, or otherwise transfer or dispose of, directly or indirectly, any shares of common stock, \$0.001 per share par value, of the Company (the “Common Stock”) or any securities convertible into or exercisable or exchangeable for Common Stock (including without limitation, Common Stock or such other securities which may be deemed to be beneficially owned by the undersigned in accordance with the rules and regulations of the Securities and Exchange Commission (the “Commission”) and securities which may be issued upon exercise of a stock option or warrant), or publicly disclose the intention to make any offer, sale, pledge or disposition, (2) enter into any swap or other agreement that transfers, in

Exhibit A-1-1

whole or in part, any of the economic consequences of ownership of the Common Stock or such other securities, whether any such transaction described in clause (1) or (2) above is to be settled by delivery of Common Stock or such other securities, in cash or otherwise or (3) make any demand for or exercise any right with respect to the registration of any shares of Common Stock or any security convertible into or exercisable or exchangeable for Common Stock, in each case other than (A) transfers of shares of Common Stock or such other securities as a bona fide gift or gifts, (B) transfers or dispositions of shares of Common Stock or such other securities to any trust for the direct or indirect benefit of the undersigned or the immediate family of the undersigned in a transaction not involving a disposition for value, (C) transfers or dispositions of shares of Common Stock or such other securities to any corporation, partnership, limited liability company or other entity all of the beneficial ownership interests of which are held by the undersigned or the immediate family of the undersigned in a transaction not involving a disposition for value, (D) transfers or dispositions of shares of Common Stock or such other securities by will, other testamentary document or intestate succession to the legal representative, heir, beneficiary or a member of the immediate family of the undersigned, (E) distributions of shares of Common Stock or such other securities to partners, members or stockholders of the undersigned and (F) the exercise of options to purchase shares of Common Stock granted under a stock incentive plan described in the Prospectus, provided that the underlying Common Stock issued upon such exercise continues to be subject to the restrictions set forth in this Letter Agreement on the terms set forth herein; provided that in the case of any transfer, disposition or distribution pursuant to clause (A), (B), (C), (D) or (E) each transferee, donee or distributee shall execute and deliver to the Representatives a lock-up letter in the form of this paragraph; and provided, further, that in the case of any transfer, disposition or distribution pursuant to clause (A), (B), (C), (D) or (E), no filing by any party (donor, donee, transferor or transferee) under the Securities Exchange Act of 1934, as amended (the "Exchange Act"), or other public announcement shall be required or shall be made voluntarily in connection with such transfer, disposition or distribution (other than a filing on a Form 5 made after the expiration of the 90-day period referred to above). For purposes of this Letter Agreement, "immediate family" shall mean any relationship by blood, marriage or adoption, not more remote than first cousin. Furthermore, notwithstanding the restrictions imposed by this Letter Agreement, the undersigned may, without the prior written consent of the Representatives, (i) transfer the undersigned's Common Stock or any security convertible into or exercisable or exchangeable for Common Stock to the Company pursuant to any contractual arrangement in effect on the date of this Letter Agreement that provides for the repurchase of the undersigned's Common Stock or such other securities by the Company or in connection with the termination of the undersigned's employment with the Company, provided that no filing by any party under the Exchange Act or other public announcement shall be required or shall be made voluntarily in connection with such transfer, disposition or distribution (other than a filing on a Form 5 made after the expiration of the 90-day period referred to above), (ii) establish a trading plan pursuant to Rule 10b5-1 under the Exchange Act for the transfer of Common Stock, provided that such plan does not provide for any transfers of Common Stock during the 90-day restricted period or any extension thereof pursuant to this Letter Agreement and provided, further, that no filing with the Commission or other public announcement shall be required or voluntarily made by the undersigned or any other person in connection therewith, (iii) transfer or dispose of shares of Common Stock acquired on the open market following the Public Offering, provided that no filing by any party under the Exchange Act or other public announcement reporting a reduction in the beneficial ownership of Common Stock held by the undersigned shall be required or shall be made voluntarily in connection with such transfer or disposition (other than a filing on Form 5 made after the expiration of the 90-day period referred to above) and (iv) transfer shares of Common Stock pursuant to sales in the public market undertaken by the undersigned under a trading plan pursuant to Rule 10b5-1 under the Exchange Act, provided that such trading plan shall have been in effect prior to the date hereof, and provided, further, that to the extent a public announcement or filing under the Exchange Act, if any, is required or voluntarily made by or on behalf of the undersigned or the Company regarding any such sales, such announcement or filing shall include a statement to the effect that the sale was made pursuant to a trading plan pursuant to Rule 10b5-1 under the Exchange Act.

The Representatives, on behalf of the Underwriters agree that, at least three business days before the effective date of any release or waiver of the foregoing restrictions in connection with a transfer of shares of Common Stock, the Representatives, on behalf of the Underwriters will notify the Company of the impending release or waiver, and the Company has agreed in the Underwriting Agreement to announce the impending release or waiver by press release through a major news service at least two business days before the effective date of the release or waiver. Any release or waiver granted by the Representatives on behalf of the Underwriters hereunder to any such officer or director shall only be effective two business days after the publication date of such press release. The provisions of this paragraph will not apply if (a) the release or waiver is effected solely to permit a transfer not for consideration and (b) the transferee has agreed in writing to be bound by the same terms described in this Letter Agreement to the extent and for the duration that such terms remain in effect at the time of the transfer.

In furtherance of the foregoing, the Company and any duly appointed transfer agent for the registration or transfer of the securities described herein, are hereby authorized to decline to make any transfer of securities if such transfer would constitute a violation or breach of this Letter Agreement.

The undersigned hereby represents and warrants that the undersigned has full power and authority to enter into this Letter Agreement. All authority herein conferred or agreed to be conferred and any obligations of the undersigned shall be binding upon the successors, assigns, heirs or personal representatives of the undersigned.

This Letter Agreement shall automatically terminate and the undersigned shall be released from all obligations under this Letter Agreement upon the earliest to occur, if any, of: (a) either the Company, on the one hand, or either the Representatives, on the other hand, advising the other in writing, prior to the execution of the Underwriting Agreement, that they have determined not to proceed with the Public Offering, (b) termination of the Underwriting Agreement (other than the provisions thereof which survive termination) prior to the sale of any of the Securities to the Underwriters, and (c) the registration statement filed with the Commission with respect to the Public Offering is withdrawn. The undersigned understands that the Underwriters are entering into the Underwriting Agreement and proceeding with the Public Offering in reliance upon this Letter Agreement.

This Letter Agreement and any claim, controversy or dispute arising under or related to this Letter Agreement shall be governed by and construed in accordance with the laws of the State of New York, without regard to the conflict of laws principles thereof.

Very truly yours,

[NAME OF STOCKHOLDER]

By: _____

Name:

Title:

Exhibit A-1-3

FORM OF LOCK-UP AGREEMENT

(Shareholders)

, 2014

J.P. Morgan Securities LLC
Goldman, Sachs & Co.
As Representatives of
the several Underwriters listed in
Schedule 1 to the Underwriting
Agreement referred to below

c/o J.P. Morgan Securities LLC
383 Madison Avenue
New York, New York 10179

c/o Goldman, Sachs & Co.
200 West Street
New York, New York 10282

Re: Agios Pharmaceuticals, Inc. — Public Offering

Ladies and Gentlemen:

The undersigned understands that you, as Representatives of the several Underwriters, propose to enter into an Underwriting Agreement (the "Underwriting Agreement") with Agios Pharmaceuticals, Inc., a Delaware corporation (the "Company"), providing for the public offering (the "Public Offering") by the several Underwriters named in Schedule 1 to the Underwriting Agreement (the "Underwriters"), of common stock, of the Company (the "Securities"). Capitalized terms used herein and not otherwise defined shall have the meanings set forth in the Underwriting Agreement.

In consideration of the Underwriters' agreement to purchase and make the Public Offering of the Securities, and for other good and valuable consideration receipt of which is hereby acknowledged, the undersigned hereby agrees that, without the prior written consent of J.P. Morgan Securities LLC and Goldman, Sachs & Co. on behalf of the Underwriters (the "Representatives"), the undersigned will not, during the period commencing on the date hereof and ending on the earlier of (x) 60 days after the date of the final prospectus relating to the Public Offering (the "Prospectus") and (y) June 22, 2014 (such period, the "Restricted Period"), (1) offer, pledge, sell, contract to sell, sell any option or contract to purchase, purchase any option or contract to sell, grant any option, right or warrant to purchase, or otherwise transfer or dispose of, directly or indirectly, any shares of common stock, \$0.001 per share par value, of the Company (the "Common Stock") or any securities convertible into or exercisable or exchangeable for Common Stock (including without limitation, Common Stock or such other securities which may be deemed to be beneficially owned by the undersigned in accordance with the rules and regulations of the Securities and Exchange Commission (the "Commission") and securities which may be issued upon exercise of a stock option or warrant), or publicly disclose the intention to make any offer, sale, pledge or

Exhibit A-2-1

disposition, (2) enter into any swap or other agreement that transfers, in whole or in part, any of the economic consequences of ownership of the Common Stock or such other securities, whether any such transaction described in clause (1) or (2) above is to be settled by delivery of Common Stock or such other securities, in cash or otherwise or (3) make any demand for or exercise any right with respect to the registration of any shares of Common Stock or any security convertible into or exercisable or exchangeable for Common Stock, in each case other than (A) transfers of shares of Common Stock or such other securities as a bona fide gift or gifts, (B) transfers or dispositions of shares of Common Stock or such other securities to any trust for the direct or indirect benefit of the undersigned or the immediate family of the undersigned in a transaction not involving a disposition for value, (C) transfers or dispositions of shares of Common Stock or such other securities to any corporation, partnership, limited liability company or other entity all of the beneficial ownership interests of which are held by the undersigned or the immediate family of the undersigned in a transaction not involving a disposition for value, (D) transfers or dispositions of shares of Common Stock or such other securities by will, other testamentary document or intestate succession to the legal representative, heir, beneficiary or a member of the immediate family of the undersigned, and (E) distributions of shares of Common Stock or such other securities to partners, members or stockholders of the undersigned; provided that in the case of any transfer, disposition or distribution pursuant to clause (A), (B), (C), (D) or (E) each transferee, donee or distributee shall execute and deliver to the Representatives a lock-up letter in the form of this paragraph; and provided, further, that in the case of any transfer, disposition or distribution pursuant to clause (A), (B), (C), (D) or (E), no filing by any party (donor, donee, transferor or transferee) under the Securities Exchange Act of 1934, as amended (the "Exchange Act"), or other public announcement shall be required or shall be made voluntarily in connection with such transfer, disposition or distribution (other than a filing on a Form 5 made after the expiration of the Restricted Period). For purposes of this Letter Agreement, "immediate family" shall mean any relationship by blood, marriage or adoption, not more remote than first cousin. Furthermore, notwithstanding the restrictions imposed by this Letter Agreement, the undersigned may, without the prior written consent of the Representatives, (i) transfer the undersigned's Common Stock or any security convertible into or exercisable or exchangeable for Common Stock to the Company pursuant to any contractual arrangement in effect on the date of this Letter Agreement that provides for the repurchase of the undersigned's Common Stock or such other securities by the Company or in connection with the termination of the undersigned's employment with the Company, provided that no filing by any party under the Exchange Act or other public announcement shall be required or shall be made voluntarily in connection with such transfer, disposition or distribution (other than a filing on a Form 5 made after the expiration of the Restricted Period), (ii) establish a trading plan pursuant to Rule 10b5-1 under the Exchange Act for the transfer of Common Stock, provided that such plan does not provide for any transfers of Common Stock during the Restricted Period or any extension thereof pursuant to this Letter Agreement and provided, further, that no filing with the Commission or other public announcement shall be required or voluntarily made by the undersigned or any other person in connection therewith and (iii) transfer or dispose of shares of Common Stock acquired on the open market following the Public Offering, provided that no filing by any party under the Exchange Act or other public announcement reporting a reduction in the beneficial ownership of Common Stock held by the undersigned shall be required or shall be made voluntarily in connection with such transfer or disposition (other than a filing on Form 5 made after the expiration of the Restricted Period referred to above).

In the event that during the Restricted Period, the Representatives waive any prohibition on the transfer of shares of Common Stock held by any director or executive officer of the Company or any person or entity that beneficially owns 5% or more of the outstanding shares of Common Stock, the Representatives shall be deemed to have also waived the prohibitions set forth in this Letter Agreement that would otherwise have applied to the undersigned with respect to the same percentage of the undersigned's shares of Common Stock as the relative percentage of aggregate shares held by such party receiving the waiver which are subject to such waiver. The provisions of this paragraph will not apply: (1)

unless and until Representatives have first waived more than 0.5% of the Company's total outstanding shares of Common Stock from such prohibitions, (2) (a) if the release or waiver is effected solely to permit a transfer not for consideration and (b) the transferee has agreed in writing to be bound by the same terms described in this Letter Agreement to the extent and for the duration that such terms remain in effect at the time of the transfer, or (3) if the release or waiver is granted to a holder of Common Stock in connection with a follow-on public offering of such Securities pursuant to a registration statement on Form S-1 that is filed with the Commission. In the event that, as a result of this paragraph, any shares of Common Stock held by the undersigned are released from the restrictions imposed by this Letter Agreement, Representatives shall use their commercially reasonable efforts to notify the undersigned within three business days that the same percentage of shares of Common Stock held by the undersigned has been released; provided that the failure to give such notice shall not give rise to any claim or liability against Representatives or the Underwriters.

In furtherance of the foregoing, the Company and any duly appointed transfer agent for the registration or transfer of the securities described herein, are hereby authorized to decline to make any transfer of securities if such transfer would constitute a violation or breach of this Letter Agreement.

The undersigned hereby represents and warrants that the undersigned has full power and authority to enter into this Letter Agreement. All authority herein conferred or agreed to be conferred and any obligations of the undersigned shall be binding upon the successors, assigns, heirs or personal representatives of the undersigned.

This Letter Agreement shall automatically terminate and the undersigned shall be released from all obligations under this Letter Agreement upon the earliest to occur, if any, of: (a) either the Company, on the one hand, or either the Representatives, on the other hand, advising the other in writing, prior to the execution of the Underwriting Agreement, that they have determined not to proceed with the Public Offering, (b) termination of the Underwriting Agreement (other than the provisions thereof which survive termination) prior to the sale of any of the Securities to the Underwriters, and (c) the registration statement filed with the Commission with respect to the Public Offering is withdrawn. The undersigned understands that the Underwriters are entering into the Underwriting Agreement and proceeding with the Public Offering in reliance upon this Letter Agreement.

Very truly yours,

[NAME OF STOCKHOLDER]

By: _____

Name:

Title:

WILMERHALE

+1 617 526 6000 (t)
+1 617 526 5000 (f)
wilmerhale.com

April 21, 2014

Agios Pharmaceuticals, Inc.
38 Sidney Street, 2nd floor
Cambridge, MA 02139

Re: Registration Statement on Form S-1

Ladies and Gentlemen:

This opinion is furnished to you in connection with a Registration Statement on Form S-1 (File No. 333-195174) (the "Registration Statement") filed with the Securities and Exchange Commission (the "Commission") under the Securities Act of 1933, as amended (the "Securities Act"), for the registration of 2,300,000 shares of Common Stock, \$0.001 par value per share (the "Shares"), of Agios Pharmaceuticals, Inc, a Delaware corporation (the "Company"), including 300,000 Shares issuable upon exercise of an over-allotment option granted by the Company.

The Shares are to be sold by the Company pursuant to an underwriting agreement (the "Underwriting Agreement") to be entered into by and among the Company and the several underwriters named on Schedule A thereto, for whom J. P. Morgan and Goldman, Sachs & Co., are acting as representatives, the form of which is filed as Exhibit 1.1 to the Registration Statement.

We are acting as counsel for the Company in connection with the issuance and sale by the Company of the Shares. We have examined signed copies of the Registration Statement as filed with the Commission. We have also examined and relied upon the Underwriting Agreement, minutes of meetings of the stockholders and the Board of Directors of the Company as provided to us by the Company, stock record books of the Company as provided to us by the Company, the Certificate of Incorporation and By-Laws of the Company, each as restated and/or amended to date, and such other documents as we have deemed necessary for purposes of rendering the opinions hereinafter set forth.

In our examination of the foregoing documents, we have assumed the genuineness of all signatures, the authenticity of all documents submitted to us as originals, the conformity to original documents of all documents submitted to us as copies, the authenticity of the originals of such latter documents and the legal competence of all signatories to such documents.

Wilmer Cutler Pickering Hale and Dorr LLP, 7 World Trade Center, 250 Greenwich Street, New York, New York 10007
Beijing Berlin Boston Brussels Frankfurt London Los Angeles New York Oxford Palo Alto Waltham Washington

We express no opinion herein as to the laws of any state or jurisdiction other than the state laws of the State of New York, the General Corporation Law of the State of Delaware and the federal laws of the United States of America.

Based upon and subject to the foregoing, we are of the opinion that the Shares have been duly authorized for issuance and, when the Shares are issued and paid for in accordance with the terms and conditions of the Underwriting Agreement, the Shares will be validly issued, fully paid and nonassessable.

Please note that we are opining only as to the matters expressly set forth herein, and no opinion should be inferred as to any other matters. This opinion is based upon currently existing statutes, rules, regulations and judicial decisions, and we disclaim any obligation to advise you of any change in any of these sources of law or subsequent legal or factual developments which might affect any matters or opinions set forth herein.

We hereby consent to the filing of this opinion with the Commission as an exhibit to the Registration Statement in accordance with the requirements of Item 601(b)(5) of Regulation S-K under the Securities Act and to the use of our name therein and in the related Prospectus under the caption "Legal matters." In giving such consent, we do not hereby admit that we are in the category of persons whose consent is required under Section 7 of the Securities Act or the rules and regulations of the Commission.

Very truly yours,

WILMER CUTLER PICKERING
HALE AND DORR LLP

By: /s/ Steven D. Singer
Steven D. Singer, a Partner

Consent of Independent Registered Public Accounting Firm

We consent to the reference to our firm under the caption "Experts" in Amendment No. 1 to the Registration Statement (Form S-1 No. 333-195174) and related Prospectus of Agios Pharmaceuticals, Inc. for the registration of common stock and to the incorporation by reference therein of our report dated March 18, 2014 with respect to the consolidated financial statements of Agios Pharmaceuticals, Inc. included in its Annual Report (Form 10-K) for the year ended December 31, 2013, filed with the Securities and Exchange Commission.

/s/ Ernst & Young LLP

Boston, Massachusetts
April 18, 2014