AGIOS PHARMACEUTICALS INC
Form 10-K
February 24, 2015
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**UNITED STATES SECURITIES AND EXCHANGE COMMISSION**

**Washington, DC 20549**

**Form 10-K**

(Mark One)

þ **ANNUAL REPORT PURSUANT TO SECTION 13 OR 15(d) OF THE SECURITIES EXCHANGE ACT OF 1934**
**For the fiscal year ended December 31, 2014**

**OR**

¨ **TRANSITION REPORT PURSUANT TO SECTION 13 OR 15(d) OF THE SECURITIES EXCHANGE ACT OF 1934**
**Commission File Number:**

**001-36014**

**AGIOS PHARMACEUTICALS, INC.**

*(Exact name of registrant as specified in its charter)*

| **Delaware** | **26-0662915** |
|---|---|
| *(State or other jurisdiction of incorporation or organization)* | *(IRS Employer Identification No.)* |
| **38 Sidney Street, 2nd Floor** | **02139** |
| **Cambridge, MA** | |
| *(Address of principal executive offices)* | *(Zip Code)* |

Registrant s telephone number, including area code:

**(617) 649-8600**

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

| Title of Class | Name of Exchange on Which Registered |
|---|---|
| **Common Stock, Par Value $0.001 per share** | **NASDAQ Global Select Market** |

Securities registered pursuant to Section 12(g) of the Act: **None**

Indicate by check mark if the registrant is a well-known seasoned issuer, as defined in Rule 405 of the Securities Act. Yes þ No ¨

Indicate by check mark if the registrant is not required to file reports pursuant to Section 13 or Section 15(d) of the Act. Yes ¨ No þ

Indicate by check mark whether the registrant (1) has filed all reports required to be filed by Section 13 or 15(d) of the Securities Exchange Act of 1934 during the preceding 12 months (or for such shorter period that the registrant was required to file such reports), and (2) has been subject to such filing requirements for the past 90 days. Yes þ No ¨

Indicate by check mark whether the registrant has submitted electronically and posted on its corporate Web site, if any, every Interactive Data File required to be submitted and posted pursuant to Rule 405 of Regulation S-T (§ 232.405 of this chapter) during the preceding 12 months (or for such shorter period that the registrant was required to submit and post such files). Yes þ No ¨

Indicate by check mark if disclosure of delinquent filers pursuant to Item 405 of Regulation S-K is not contained herein, and will not be contained, to the best of registrant s knowledge, in definitive proxy or information statements incorporated by reference in Part III of this Form 10-K or any amendment to this Form 10-K. ¨

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 definitions of large accelerated filer, accelerated filer and smaller reporting company in Rule 12b-2 of the Exchange Act. (Check one):

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

Indicate by check mark whether the registrant is a shell company (as defined in Rule 12b-2 of the Act). Yes ¨ No þ

The aggregate market value of the voting and non-voting Common Stock held by non-affiliates of the registrant computed by reference to the price of the registrant s Common Stock as of June 30, 2014 (based on the last reported sale price on the NASDAQ Global Select Market as of such date) was $876,210,178.

As of February 20, 2015, there were 37,218,456 shares of Common Stock, $0.001 par value per share, outstanding.

**DOCUMENTS INCORPORATED BY REFERENCE**

Portions of the registrant s definitive proxy statement for its 2015 Annual Meeting of Stockholders to be filed pursuant to Regulation 14A within 120 days of the end of the registrant s fiscal year ended December 31, 2014 are incorporated by reference into Part III of this Annual Report on Form 10-K to the extent stated herein.

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**References to Agios**

Throughout this Annual Report on Form 10-K, the Company, Agios, we, us, and our, except where the context requires otherwise, refer to Agios Pharmaceuticals, Inc. and its consolidated subsidiary, and our board of directors refers to the board of directors of Agios Pharmaceuticals, Inc.

**Forward-Looking Information**

This Annual Report on Form 10-K contains forward-looking statements that involve substantial risks and uncertainties. All statements, other than statements of historical facts, contained in this Annual Report on Form 10-K, including statements regarding our strategy, future operations, future financial position, future revenues, projected costs, prospects, plans and objectives of management, are forward-looking statements. The words anticipate, believe, estimate, expect, intend, may, plan, predict, project, target, potential, will, would, could, s expressions are intended to identify forward-looking statements, although not all forward-looking statements contain these identifying words.

The forward-looking statements in this Annual Report on Form 10-K 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;
- the potential of IDH1/IDH2 and pyruvate kinase-R mutations as therapeutic targets;
- the potential benefits of our product candidates targeting IDH1/IDH2 or pyruvate kinase-R mutations, including AG-120, AG-221, and AG-348;
- 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; 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 Annual Report on Form 10-K, particularly in the Risk Factors section, 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 we may make.

You should read this Annual Report on Form 10-K and the documents that we have filed as exhibits to this Annual Report on Form 10-K 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.

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## Item 1. 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 rare genetic disorders of metabolism, or RGDs, which are a subset of rare genetic 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 RGDs. We focus our efforts on using cellular metabolism an unexploited area of biological research with disruptive potential, as a platform for developing potentially transformative small molecule medicines. Our most advanced cancer product candidates, AG-221 and AG-120, target mutant isocitrate dehydrogenase 2 and 1, or IDH2 and IDH1, respectively. These mutations have been found in a wide range of hematological malignancies and solid tumors. The lead candidate in our RGD program, AG-348, targets pyruvate kinase-R for the treatment of pyruvate kinase deficiency. Pyruvate kinase deficiency is a rare genetic disorder that often results in severe hemolytic anemia due to inherited mutations in the pyruvate kinase-R enzyme within red blood cells.

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 our ability to measure the activities of numerous metabolic pathways in cells or tissues in a high throughput fashion and our 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. The clinical development strategy for all of our product candidates includes a precision approach with 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.

### 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 RGDs. Key elements of our strategy include:

- Aggressively pursuing the development of novel medicines to transform the lives of patients with cancer and RGDs.
- Maintaining our competitive advantage and singular focus in the field of cellular metabolism.
- Continuing to build a product engine for cancer and RGDs 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 RGDs. We maintain a culture of high integrity that embraces the following guiding principles, which we believe will provide long-term benefits for all our stakeholders:

*Follow the science and do what is right for patients.*

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

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

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

**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 RGDs.

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.

***Cancer and cancer metabolism***

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 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. These treatment regimens are often associated with side effects, including fatigue, infection, nausea and vomiting and pain. 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.

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*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 (immuno-oncology); antibody drug conjugates (e.g., 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).

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. 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 our therapies directed against metabolic enzymes with existing or emerging standards of care.

***Rare genetic disorders of metabolism***

Rare genetic disorders of metabolism, or RGDs, 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. RGDs are also referred to as congenital metabolic diseases or rare genetic

metabolic diseases.

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

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10,000 people in the European Union. In a study in British Columbia, the overall incidence of RGDs 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 RGD can vary widely but is generally rare, usually equal to or less than one per 100,000 births. Many RGDs 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 RGDs. 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, Myozome® for Pompe disease, Cerezyme® for Gaucher disease, and Elaprase® for Hunter syndrome.

Unfortunately, most mutations driving RGDs 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 RGDs 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.

We focus on RGDs that 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 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.

**Precision Medicine Approach**

Our understanding of cellular 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 pharmacodynamics markers to characterize medicine/target engagement in patients, and permit the monitoring of patient response to therapy.

We will only progress our 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, along with the potential for accelerated approval.

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**Our Development Programs**

We believe that by leveraging our core capabilities in cellular metabolism combined with a precision medicine approach has significantly enhanced our ability to build a research and development engine that is focused in the therapeutic areas of cancer and RGDs. 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.

The following table summarizes key information about our most advanced product candidates as of February 1, 2015, each of which is described and discussed in further detail below:

| Product Candidate | Biomarker(s) | Initial Indications | Stage of Development | Commercial Rights |
|---|---|---|---|---|
| **Cancer metabolism:** | | | | |
| AG-221<br><br>(IDH2 mutant inhibitor) | Genotyping of IDH2 mutation; 2HG | IDH2-mutant positive hematologic malignancies | Phase 1 study on-going; early clinical proof of concept achieved | Agios: milestones and royalties<br><br>Celgene: worldwide |
| | | IDH2-mutant positive solid tumors | Phase 1 study on-going | Agios: milestones and royalties<br><br>Celgene: worldwide |
| AG-120 (IDH1 mutant inhibitor) | Genotyping of IDH1 mutation; 2HG | IDH1-mutant positive hematologic malignancies | Phase 1 study on-going; early clinical proof of concept achieved | Agios: Milestones, cross-royalties, and U.S. rights<br><br>Celgene: ex-U.S. rights, cross-royalties |
| | | IDH1-mutant positive solid tumors | Phase 1 study on-going | Agios: Milestones, cross-royalties, and U.S. rights |

| | | | | |
|---|---|---|---|---|
| | | | | Celgene: ex-U.S. rights, cross-royalties |
| **Rare genetic disorders of metabolism:** | | | | |
| AG-348 (Pyruvate kinase-R activator) | Genetic testing for mutation in the pyruvate kinase-R gene | Patients with pyruvate kinase deficiency | Phase 1 single ascending dose study completed; phase 1 multiple ascending dose study dosing completed | Agios: worldwide |

**Targeting isocitrate dehydrogenase (IDH) for the treatment of cancer**

The isocitrate dehydrogenase, or IDH, protein is a critical enzyme in the citric acid cycle, also known as the tricarboxylic acid, or Krebs, cycle. The Krebs cycle is centrally important to many biochemical pathways and is one of the earliest established components of cellular metabolism. The Krebs cycle converts an essential cellular metabolite

called isocitrate into another metabolite, alpha-ketoglutarate (a-ketoglutarate), both of which are critically important for cellular function and the creation of energy. In humans, there are three forms of the IDH enzyme, IDH1, IDH2, and IDH3, but only IDH1 and IDH2 appear to be mutated in cancers. IDH1 and IDH2 catalyze the

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same reaction but in different cellular compartments: IDH1 is found in the cytoplasm of the cell and IDH2 in the mitochondria. Tumor cells are generally observed to carry either an IDH1 or IDH2 mutation, but not both.

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

To date, IDH1 and IDH2 mutations have been found to be prevalent in a broad range of advanced hematologic and solid tumors. The following tables summarize our current initial estimates on the occurrence 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.

| Mutation | Indications | % with IDH mutations |
|---|---|---|
| **IDH1** | Low grade glioma & 2$^{ary}$ Glioblastomas (GBM) | 68-74 |
| | Chondrosarcoma | 40-52 |
| | Acute Myeloid Leukemia (AML) | 6-10 |
| | Myelodysplastic Syndromes (MDS) / Myeloproliferative neoplasms (MPN) | 3 |
| | Intrahepatic Cholangiocarcinoma | 11-24 |
| | Ollier/Maffucci | 80 |
| | Others* (colon, melanoma, lung, prostate) | 1-3 |
| **IDH2** | Acute Myeloid Leukemia (AML) | 9-13 |
| | MDS/MPN | 3-6 |
| | Angio-immunoblastic non-Hodgkin lymphoma (NHL) | 30 |
| | Intrahepatic Cholangiocarcinoma | 2-6 |
| | Giant Cell Tumor of the Bone | 80 |
| | D-2-hydroxyglutarate (D2HG) Aciduria | 50 |
| | Others* (melanoma, glioma) | 3-5 |

Based on literature analysis. Estimates will continue to evolve with additional future data.

* Includes basket of emerging unconfirmed indications

***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 who have a historically poor prognosis. On June 16, 2014, the U.S. Food and Drug Administration (FDA) granted us orphan drug designation for AG-221 for treatment of patients with AML. On August 13, 2014, we announced that the FDA granted Fast Track designation to AG-221 for treatment of patients with AML that harbor an IDH2 mutation. We have been evaluating AG-221 in several phase 1 dose escalation trials evaluating both hematological and solid tumor cancers with IDH2 mutations. To date, all clinical data reported by us highlights that the mechanism of response is consistent with preclinical studies, including substantial reduction of

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plasma 2HG levels, as well as evidence of cellular differentiation and normalization of cell counts in the bone marrow and blood. This differentiation effect is distinct from that seen with traditional chemotherapeutics commonly used to treat AML. We intend to begin a global registration program for AG-221 in 2015 for IDH2-mutant positive hematologic malignancies.

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

On June 14, 2014, we presented additional clinical data from the phase 1 study of AG-221 at the 19th Congress of the European Hematology Association in Milan, Italy. These data built upon previously presented data on AG-221 s clinical activity, safety profile and unique mechanism of action and included 35 patients with IDH2-mutant positive advanced hematologic malignancies. The new data showed investigator-assessed objective responses in 14 out of 25 evaluable patients on AG-221 and an additional five patients with stable disease. In six patients who achieved a complete remission, evidence of durability was observed, ranging from one to four months in duration. AG-221 continued to show favorable drug exposure and pharmacokinetics at all doses tested with substantial reductions in plasma levels of 2HG.

In June 2014, Celgene Corporation, or Celgene, exercised its option to an exclusive global license for development and commercialization of AG-221 under our collaboration agreement. Under the collaboration agreement, Celgene is responsible for all development costs for AG-221. We are eligible to receive up to $120 million in milestone payments and a tiered royalty on any net sales of products containing AG-221. We also have the right to conduct a portion of any commercialization activities for AG-221 in the United States. In addition to contributing our scientific and translational expertise, we will continue to conduct early clinical development and regulatory activities within the AG-221 development program in collaboration with Celgene.

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

in approximately 100 patients with IDH2-mutant hematologic malignancies, including AML. The expansion cohorts are evaluating relapsed or refractory AML patients 60 years of age and older, relapsed or refractory AML

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

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

***AG-120: lead IDH1 program***

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

In November 2014, we reported initial clinical data from the ongoing AG-120 phase 1 study in advanced hematologic malignancies at the 26th EORTC-NCI-AACR Symposium on Molecular Targets and Cancer Therapeutics. As of October 17, 2014, a total of 17 patients with a documented IDH1 mutation whose cancer relapsed or were refractory, meaning they failed to respond to at least one prior treatment regimen, were treated with AG-120. At the time of the data cutoff, 14 patients with relapsed and/or refractory AML were evaluable; and three patients had recently initiated therapy and were not evaluable. The initial data showed investigator-assessed objective responses in seven out of 14 evaluable patients, including four complete remissions, with responses observed across the four dose levels tested. In the four patients who achieved a complete remission, durability ranging from 15 days to five months was observed. All responding patients remain on AG-120. One patient with stable disease was reported on AG-120. AG-120 was well tolerated, with the majority of adverse events reported as mild to moderate. The maximum tolerated dose has not yet been reached. One patient had a dose limiting toxicity of asymptomatic grade 3 QT prolongation at the highest

dose tested to date, which improved to grade 1 after AG- 120 dose reduction according to treatment protocol. This patient achieved

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complete remission and remained on AG-120. AG-120 showed favorable drug exposure and pharmacokinetics at all doses tested and also substantially reduced plasma levels of 2HG, which is produced by the mutant IDH1 protein, to the level observed in healthy volunteers. The mechanism of response is consistent with differentiation, as evidenced by the maturation of the leukemic cells into infection fighting white blood cells, or neutrophils. Based on these findings, we plan to initiate multiple expansion cohorts in the first half of 2015. We intend to initiate a global registration program for AG-120 in IDH1-mutant positive hematologic malignancies by early 2016.

In January 2015, Celgene agreed to exercise its exclusive option to license development and commercialization rights to AG-120 outside the United States, subject to receipt of any required regulatory approvals, including any applicable clearance under the Hart-Scott-Rodino Act. We had previously elected to exercise our option to retain development and commercialization rights to AG-120 in the United States in January 2014. Upon Celgene s exercise of its exclusive option under the terms of our agreement, Celgene would lead development and commercialization outside the United States, and we would lead development and commercialization in the United States. Celgene would be responsible for future development and commercialization costs specific to countries outside the United States, we would be responsible for future development and commercialization costs specific to the United States, and we and Celgene would equally fund the future global development costs of AG-120 that are not specific to any particular region or country. Celgene would be eligible to receive tiered royalties on any net sales in the U.S. We would be eligible to receive tiered royalties on any net sales outside the U.S. and up to $120 million in payments on achievement of certain milestones.

***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 that is present in red blood cells. Mutations in PKR cause defects in red cell glycolysis and lead to a hematological RGD 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-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 genetic disorder and disease understanding is still evolving. Several published epidemiology studies estimated prevalence of PK deficiency between three to nine affected patients per million. We estimate that there are approximately 2,400 diagnosed patients in the U.S. and EU5 countries (United Kingdom, France, Germany, Italy, Spain), 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.

*AG-348*: *lead pyruvate kinase (PK) deficiency program*

AG-348 is an orally available small molecule and a potent activator of the PKR enzyme. We have previously reported in nonclinical studies that AG-348 is a potent activator of the wild-type (normal) and mutated PKR enzymes, resulting

in restoration of ATP levels and a decrease in 2,3-DPG levels in blood sampled from patients with PK deficiency. The wild-type PKR activity of AG-348 allows the study of enzyme activation in healthy volunteers, providing an opportunity to understand the safety, dosing and pharmacodynamic activity of AG-348 prior to entering a proof-of-concept study in patients.

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In April 2014, we initiated a single ascending dose, or SAD, escalation phase 1 clinical trial for AG-348 in healthy volunteers and in June 2014, we initiated a multiple ascending dose, or MAD, escalation phase 1 clinical trial for healthy volunteers. In late 2014, we reported the SAD trial was completed and met its primary endpoint. The MAD trial completed dosing in early 2015 and has also met its primary endpoint. The primary endpoint is defined in the protocol to identify a safe and pharmacodynamically active dose and dosing schedule for AG-348 to be used in subsequent clinical studies in patients with pyruvate kinase deficiency.

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

We have worldwide development and commercial rights to AG-348 and expect to fund the future development and commercialization costs related to this program.

**Collaboration with Celgene**

In April 2010, we entered into a discovery and development collaboration and license agreement with Celgene, focused on targeting cancer metabolism. The goal of the collaboration is to discover, develop and commercialize disease-altering therapies in oncology arising out of our cancer metabolism research platform that have achieved development candidate status. On December 8, 2014, Celgene elected to extend the period of its exclusivity for an additional year to April 2016. The extension marks the final year for the discovery phase of the collaboration. We will receive a $20.0 million payment as a result of the extension, which we expect to receive in the second quarter of 2015.

Following this extension, the discovery portion of the collaboration will expire on April 14, 2016. Under the terms of the agreement, we lead research, preclinical and early development efforts through phase 1, while Celgene receives an option to obtain exclusive rights either upon investigational new drug, or IND, acceptance or at the end of phase 1, to further develop and commercialize certain medicines emerging from our cancer metabolism research platform through April 14, 2016. Celgene would lead and fund global development and commercialization of development candidates for which they exercise their option to obtain a co-commercialization license, and we would retain development and commercialization in the United States for development candidates for which we exercise our option to retain a split license. For each of these programs, we are eligible to receive up to $120 million in milestone-based payments as well as royalties on any net sales.

AG-221 and AG-120 are two development candidates that we have nominated to date during the discovery phase of the collaboration. Primarily all of our revenues for the years ended December 31, 2014, 2013, and 2012 are from payments received under our agreement with Celgene.

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*Discovery programs with development candidates*. Celgene may elect to progress into preclinical development each discovery program for which we nominate and the joint research committee, or 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 $5.0 million upon the earlier of the determination of the maximum tolerated dose or Celgene s election to license the program, 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. 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. Our IDH2 program is a co-commercialized licensed program and not a split licensed program. In June 2014, Celgene exercised its option to an exclusive global license for the development and commercialization of our IDH2 program, AG-221. We continue to conduct early clinical development activities within the AG-221 development program in collaboration with Celgene. We elected to retain U.S. rights to our IDH1 program, AG-120, in January 2014. In January 2015, Celgene agreed to exercise its exclusive option to license development and commercialization rights to AG-120 outside the United States, subject to receipt of any required regulatory approvals including any applicable clearance under the Hart-Scott-Rodino Act. If the regulatory approvals are obtained, and Celgene s license of its rights to AG-120 outside the United States is effective, the program will become a split licensed program.

We will retain our rights to the development candidates and certain other compounds from any discovery program for which we nominate and the JRC confirms a development candidate but 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 to independently 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, upon completion of such phase 1 study, will fund global development and commercialization of each co-commercialized licensed program. We have the right to participate in a portion of commercialization 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.

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*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 Celgene and us. 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 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. In connection with the 1-for-2.75 reverse stock split of our common stock, the shares of these series B preferred stock converted into 1,887,473 shares of common stock upon the closing of our initial public offering in July 2013. 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 elected to extend the discovery phase of the strategic collaboration by one year, extending the initial period of exclusivity from four years to five years, until April 2015. As a result of the December 2013 extension, we received a $20.0 million extension payment from Celgene in May 2014. In December 2014, Celgene elected to extend the discovery phase of the strategic collaboration by one additional year, extending the period of exclusivity from five years to six years, until April 2016. As a result of the December 2014 extension, we will receive a $20.0 million extension payment from Celgene, which payment is expected in the second quarter of 2015.

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

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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.

In addition to the milestone payments described above, for each co-commercialized licensed program that does not become a split licensed program, we will be reimbursed for all eligible development costs of the related phase 1 multiple ascending dose (MAD) study. The initial costs will be reimbursed as a milestone payment equal to the greater of $5.0 million or eligible development costs incurred by us upon the earlier of the determination of the maximum tolerated dose (MTD) or Celgene s election to license the program. Subsequent to the initial milestone payment, development costs will be reimbursed on a quarterly basis. During 2014, we received $20.1 million related to reimbursable development costs for our IDH2 program. As of December 31, 2014, we have recorded a collaboration receivable of $6.5 million related to reimbursable development costs for this program for activities performed during the fourth quarter of 2014.

In addition to the milestone payments described above, for each split licensed program, we are eligible for reimbursement of the costs of disease-specific expansion cohort(s) within a phase 1 clinical trial design that supports the initiation of a subsequent pivotal clinical trial. Costs will be reimbursed as a milestone payment equal to the lesser of $10.0 million or fifty percent of the eligible costs for the disease-specific expansion cohort(s) upon the first patient dosed under the corresponding pivotal clinical trial. The maximum amount for the milestone payment will be $10.0 million for each split program regardless of the number of disease-specific expansion cohorts and pivotal trials undertaken for each split program.

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,

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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, 2014, we had a portfolio of pending U.S. and foreign patent applications. A significant portion of our pending patent applications pertain to our key development programs, including AG-221, AG-120 and AG-348. Any patents that may issue from these applications would expire between 2027 and 2035.

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.

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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 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 RGDs. There are other companies working to develop therapies in the field of cancer metabolism and RGDs. 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, including immuno-cancer therapies. 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.

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*Rare genetic disorders of metabolism*. In the field of RGDs, our principal competitors include Alexion Pharmaceuticals, Inc., BioMarin Pharmaceutical, Inc., Genzyme, a Sanofi company, and Shire Biochem, Inc.

The most common methods for treating patients with RGDs 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 RGDs. 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 RGDs. 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 and planned clinical testing from third party manufacturers. We obtain our supplies from these manufacturers on a purchase order basis and do not have any long-term supply arrangements 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.

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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 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, 2014, 2013, and 2012, company-sponsored research and development expenses were $100.4 million, $54.5 million, and $41.0 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.

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*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 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

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labeling, among other things, are submitted to the FDA as part of an NDA requesting approval to market the 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 $2.3 million, and the sponsor of an approved NDA is also subject to annual product and establishment user fees, currently exceeding $110,000 per product and $560,000 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.

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*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.

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*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.

***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.

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FDA officials issued guidance in 2014 that addresses 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 guidance 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 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 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

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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 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.

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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.

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.

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***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 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

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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 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

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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.

**Segment Reporting**

We are engaged solely in the discovery and development of medicines for the treatment of cancer and rare genetic disorders of metabolism. Accordingly, we have determined that we operate in one operating segment.

**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.

*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;

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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.

| Name | Primary affiliation |
|---|---|
| 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 |
| Charles Sawyers, M.D. | Memorial Sloan-Kettering Cancer Center |
| Matthew Vander Heiden, M.D., Ph.D. | Koch Institute for Integrative Cancer Research at MIT |
| Ralph Deberardinis, M.D., Ph.D. | University of Texas Southwestern Medical Center |

**Employees**

As of December 31, 2014, we had 128 full-time employees, including 58 employees with M.D. or Ph.D. degrees. Of these full-time employees, 95 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.

**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. References to our website are inactive textual references only and the content of our website should not be deemed incorporated by reference into this Form 10-K.

**Available Information**

Our Annual Reports on Form 10-K, Quarterly Reports on Form 10-Q, Current Reports on Form 8-K and any amendments to these reports filed or furnished pursuant to Section 13(a) or 15(d) of the Securities Exchange Act of 1934, as amended, are available free of charge on our website located at www.agios.com as soon as reasonably

practicable after they are filed with or furnished to the Securities and Exchange Commission (the SEC ). These reports are also available at the SEC s Internet website at www.sec.gov. The public may also read and copy any materials filed with the SEC at the SEC s Public Reference Room at 100 F Street, N.E., Washington D.C. 20549. Information on the operation of the Public Reference Room may be obtained by calling the SEC at 1-800-SEC-0330.

A copy of our Corporate Governance Guidelines, Code of Business Conduct and Ethics and the charters of the Audit Committee, Compensation Committee and Nominating and Corporate Governance Committee are posted

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on our website, www.agios.com, under Corporate Governance and are available in print to any person who requests copies by contacting us by calling (617) 649-8600 or by writing to Agios Pharmaceuticals, Inc., 38 Sidney Street, 2nd Floor, Cambridge, Massachusetts 02139.

## Item 1A. Risk Factors

*The following risk factors and other information included in this Annual Report on Form 10-K should be carefully considered. The risks and uncertainties described below are not the only risks and uncertainties we face. Additional risks and uncertainties not presently known to us or that we presently deem less significant may also impair our business operations. Please see page 2 of this Annual Report on Form 10-K for a discussion of some of the forward-looking statements that are qualified by these risk factors. If any of the following risks occur, our business, financial condition, results of operations and future growth prospects could be materially and adversely affected.*

### Risks Related to Our Financial Position and Need for Additional Capital

***We have incurred significant losses since inception. We expect to incur losses for the foreseeable future and may never achieve or maintain profitability.***

Since inception, we have incurred significant operating losses. Our net losses were $53.5 million, $39.4 million and $20.1 million for the years ended December 31, 2014, 2013 and 2012, respectively. As of December 31, 2014, we had an accumulated deficit of $166.9 million. We have financed our operations primarily through private placements of our preferred stock, our initial public offering and the concurrent private placement, our follow-on public offerings and our collaboration with Celgene focused on cancer metabolism. We have devoted substantially all of our efforts to research and development. We are in early stages of clinical development of our product candidates and expect that it will be many years, if ever, before we have a product candidate ready for commercialization. Although we may from time to time report profitable results, such as during the three months ended September 30, 2014, which was the result of the recognition of previously deferred collaboration revenue upon the amendment of our agreement with Celgene, we generally expect to continue to incur significant expenses and increasing operating losses for the foreseeable future. The net losses we incur may fluctuate significantly from quarter to quarter. We anticipate that our expenses will increase substantially if and as we:

- continue our research and preclinical development of our product candidates;
- seek to identify additional product candidates;
- initiate and continue clinical trials for our product candidates;
- seek marketing approvals for our product candidates that successfully complete clinical trials;
- ultimately establish a sales, marketing and distribution infrastructure to commercialize any medicines for which we may obtain marketing approval;

maintain, expand and protect our intellectual property portfolio;

hire additional clinical, quality control and scientific personnel;

add operational, financial and management information systems and personnel, including personnel to support our product development and planned future commercialization efforts; and

acquire or in-license other medicines and technologies.

To become and remain profitable, we must develop and eventually commercialize a medicine or medicines with significant market potential. This will require us to be successful in a range of challenging activities, including completing preclinical testing and clinical trials of our product candidates, obtaining marketing approval for these product candidates, manufacturing, marketing and selling those medicines for which we may obtain marketing approval and satisfying any post-marketing requirements. We may never succeed in these activities and, even if we do, may never generate revenues that are significant or large enough to achieve profitability. We

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are currently in early clinical testing stages for our product candidates. If we do achieve profitability, we may not be able to sustain or increase profitability on a quarterly or annual basis. Our failure to become and remain profitable would decrease the value of the company and could impair our ability to raise capital, maintain our research and development efforts, expand our business or continue our operations. A decline in the value of our company could also cause our stockholders to lose all or part of their investment.

***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.***

We expect our expenses to increase in connection with our ongoing activities, particularly as we continue the research and development of, initiate and continue clinical trials of, and seek marketing approval for, our product candidates. In addition, if we obtain marketing approval for any of our product candidates, we expect to incur significant commercialization expenses related to product sales, marketing, manufacturing and distribution to the extent that such sales, marketing, manufacturing and distribution are not the responsibility of Celgene or other collaborators. Furthermore, we will continue to incur increased costs associated with operating as a public company. Accordingly, we will need to obtain substantial additional funding in connection with our continuing operations. If we are unable to raise capital when needed or on attractive terms, we would be forced to delay, reduce or eliminate our research and development programs or future commercialization efforts.

We expect that our existing cash, cash equivalents and marketable securities as of December 31, 2014, together with $3.8 million in anticipated refundable income taxes, anticipated interest income, the $20.0 million anticipated from Celgene as a result of its exercise in December 2014 of its option to extend the discovery term of our agreement for an additional year and anticipated expense reimbursements under our collaboration agreement with Celgene, will fund our operating expenses and capital expenditure requirements until at least late 2017. Our future capital requirements will depend on many factors, including:

- the scope, progress, results and costs of drug discovery, preclinical development, laboratory testing and clinical trials for our product candidates;
- the success of our collaboration with Celgene;
- the costs, timing and outcome of regulatory review of our product candidates;
- the costs of preparing, filing and prosecuting patent applications, maintaining and enforcing our intellectual property rights and defending intellectual property-related claims;
- our ability to establish and maintain additional collaborations on favorable terms, if at all; and
- the extent to which we acquire or in-license other medicines and technologies.

Identifying potential product candidates and conducting preclinical testing and clinical trials is a time-consuming, expensive and uncertain process that takes years to complete, and we may never generate the necessary data or results

required to obtain marketing approval and achieve product sales. In addition, our product candidates, if approved, may not achieve commercial success. Our commercial revenues, if any, will be derived from sales of medicines that we do not expect to be commercially available for many years, if at all. Accordingly, we will need to continue to rely on additional financing to achieve our business objectives. Adequate additional financing may not be available to us on acceptable terms, or at all.

***Raising additional capital may cause dilution to our stockholders, restrict our operations or require us to relinquish rights to our technologies or product candidates.***

Until such time, if ever, as we can generate substantial product revenues, we expect to finance our cash needs through a combination of equity offerings, debt financings, collaborations, strategic alliances and licensing arrangements. We do not have any committed external source of funds, other than our collaboration with Celgene, which is limited in scope and duration. To the extent that we raise additional capital through the sale of equity or convertible debt securities, ownership interests will be diluted, and the terms of these securities may

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include liquidation or other preferences that adversely affect the rights of our common stockholders. Debt financing, if available, may involve agreements that include covenants limiting or restricting our ability to take specific actions, such as incurring additional debt, making capital expenditures or declaring dividends.

If we raise funds through additional collaborations, strategic alliances or licensing arrangements with third parties, we may have to relinquish valuable rights to our technologies, future revenue streams, research programs or product candidates or to grant licenses on terms that may not be favorable to us. If we are unable to raise additional funds through equity or debt financings when needed, we may be required to delay, limit, reduce or terminate our product development or future commercialization efforts or grant rights to develop and market product candidates that we would otherwise prefer to develop and market ourselves.

***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.***

We are a clinical-stage company. We were founded in the second half of 2007 and commenced operations in late 2008. Our operations to date have been limited to organizing and staffing our company, business planning, raising capital, acquiring and developing our technology, identifying potential product candidates and undertaking preclinical and early clinical studies of our product candidates. All of our product candidates are still in preclinical and early clinical development. We have not yet demonstrated our ability to successfully complete any clinical trials, including large-scale, pivotal clinical trials, obtain marketing approvals, manufacture a commercial scale medicine, or arrange for a third party to do so on our behalf, or conduct sales and marketing activities necessary for successful commercialization. Typically, it takes about 10 to 15 years to develop one new medicine from the time it is discovered to when it is available for treating patients. Consequently, any predictions you make about our future success or viability may not be as accurate as they could be if we had a longer operating history.

In addition, as a new business, we may encounter unforeseen expenses, difficulties, complications, delays and other known and unknown factors. We will need to transition from a company with a research focus to a company capable of supporting commercial activities. We may not be successful in such a transition.

**Risks Related to Our Operations**

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

Our scientific approach focuses on using our proprietary technology to identify key metabolic enzymes in cancer, RGDs or other diseased cells in the laboratory and then using these key enzymes to screen for and identify product candidates targeting cellular metabolism.

Any medicines that we develop may not effectively correct metabolic pathways. Even if we are able to develop a product candidate that targets cellular metabolism in preclinical studies, we may not succeed in demonstrating safety and efficacy of the product candidate in human clinical trials. Our focus on using our proprietary technology to screen for and identify product candidates targeting cellular metabolism may not result in the discovery and development of commercially viable medicines to treat cancer or RGDs.

***We may not be successful in our efforts to identify or discover potential product candidates.***

A key element of our strategy is to identify and test compounds that target cellular metabolism in a variety of different types of cancer and RGDs. A significant portion of the research that we are conducting involves new compounds and

drug discovery methods, including our proprietary technology. The drug discovery that we are conducting using our proprietary technology may not be successful in identifying compounds that are useful in

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treating cancer or RGDs. Our research programs may initially show promise in identifying potential product candidates, yet fail to yield product candidates for clinical development for a number of reasons, including:

- the research methodology used may not be successful in identifying appropriate biomarkers or potential product candidates; or
- potential product candidates may, on further study, be shown to have harmful side effects or other characteristics that indicate that they are unlikely to be medicines that will receive marketing approval and achieve market acceptance.

Research programs to identify new product candidates require substantial technical, financial and human resources. We may choose to focus our efforts and resources on a potential product candidate that ultimately proves to be unsuccessful.

If we are unable to identify suitable compounds for preclinical and clinical development, we will not be able to obtain product revenues in future periods, which likely would result in significant harm to our financial position and adversely impact our stock price.

***We depend heavily on the success of our most advanced product candidates. All of our product candidates are still in early clinical development. Clinical trials of our product candidates may not be successful. If we are unable to commercialize our product candidates or experience significant delays in doing so, our business will be materially harmed.***

We have invested a significant portion of our efforts and financial resources in the identification of our most advanced product candidates, AG-221 and AG-120 for the treatment of hematological and solid tumors and AG-348 for the treatment of PK deficiency. We initiated phase 1 studies for our most advanced product candidates. We have not commenced clinical trials for any of our other product candidates. Our ability to generate product revenues, which we do not expect will occur for many years, if ever, will depend heavily on the successful development and eventual commercialization of these product candidates by us and our collaborators. The success of our product candidates will depend on many factors, including the following:

- successful enrollment in, and completion of, clinical trials;
- receipt of marketing approvals from applicable regulatory authorities;
- establishing commercial manufacturing capabilities or making arrangements with third-party manufacturers;
- obtaining and maintaining patent and trade secret protection and non-patent exclusivity for our medicines;

launching commercial sales of the medicines, if and when approved, whether alone or in collaboration with others;

acceptance of the medicines, if and when approved, by patients, the medical community and third-party payors;

effectively competing with other therapies;

continuing acceptable safety profile for the medicines following approval;

enforcing and defending intellectual property rights and claims; and

achieving desirable medicinal properties for the intended indications.

If we or our collaborators do not achieve one or more of these factors in a timely manner or at all, we or our collaborators could experience significant delays or an inability to successfully commercialize our most advanced product candidates, which would materially harm our business.

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***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.***

Before obtaining marketing approval from regulatory authorities for the sale of our product candidates, we must complete preclinical development and then conduct extensive clinical trials to demonstrate the safety and efficacy of our product candidates in humans. Clinical testing is expensive, difficult to design and implement, can take many years to complete and is uncertain as to outcome. A failure of one or more clinical trials can occur at any stage of testing. The outcome of preclinical testing and early clinical trials may not be predictive of the success of later clinical trials, and interim results of a clinical trial do not necessarily predict final results.

Moreover, preclinical and clinical data are often susceptible to varying interpretations and analyses. Many companies that have believed their product candidates performed satisfactorily in preclinical studies and clinical trials have nonetheless failed to obtain marketing approval of their products.

We or our collaborators may experience numerous unforeseen events during, or as a result of, clinical trials that could delay or prevent our ability to receive marketing approval or commercialize our product candidates, including:

- regulators or institutional review boards may not authorize us, our collaborators or our investigators to commence a clinical trial or conduct a clinical trial at a prospective trial site;
- we or our collaborators may have delays in reaching or fail to reach agreement on acceptable clinical trial contracts or clinical trial protocols with prospective trial sites;
- clinical trials of our product candidates may produce negative or inconclusive results, and we or our collaborators may decide, or regulators may require us, to conduct additional clinical trials or abandon product development programs;
- the number of patients required for clinical trials of our product candidates may be larger than we anticipate; enrollment in these clinical trials, which may be particularly challenging for some of the orphan diseases we target in our RGD programs, may be slower than we anticipate; or participants may drop out of these clinical trials at a higher rate than we anticipate;
- third-party contractors used by us or our collaborators may fail to comply with regulatory requirements or meet their contractual obligations in a timely manner, or at all;
- we or our collaborators might have to suspend or terminate clinical trials of our product candidates for various reasons, including a finding that the participants are being exposed to unacceptable health risks;

regulators, institutional review boards, or the data safety monitoring board, or DSMB, for such trials may require that we, our collaborators or our investigators suspend or terminate clinical research for various reasons, including noncompliance with regulatory requirements or a finding that the participants are being exposed to unacceptable health risks;

the cost of clinical trials of our product candidates may be greater than anticipated;

the supply or quality of our product candidates or other materials necessary to conduct clinical trials of our product candidates may be insufficient or inadequate; and

our product candidates may have undesirable side effects or other unexpected characteristics, causing us, our collaborators or our investigators, regulators or institutional review boards to suspend or terminate the trials.

If we or our collaborators are required to conduct additional clinical trials or other testing of our product candidates beyond those that we currently contemplate, if we or our collaborators are unable to successfully complete clinical trials of our product candidates or other testing, if the results of these trials or tests are not positive or are only modestly positive or if there are safety concerns, we or our collaborators may:

be delayed in obtaining marketing approval for our product candidates;

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not obtain marketing approval at all;

obtain approval for indications or patient populations that are not as broad as intended or desired;